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Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents

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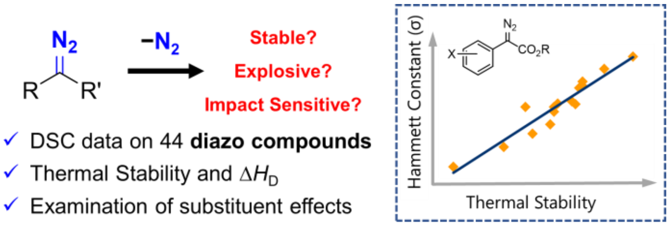


✓ DSC data on 44 **diazo compounds**

✓ Thermal Stability and ΔH_D

✓ Examination of substituent effects

ABSTRACT: Despite their wide use in academia as metal-carbene precursors, diazo compounds are often avoided in industry owing to concerns over their instability, exothermic decomposition and potential explosive behaviour. The stability of sulfonyl azides and other diazo-transfer reagents is relatively well understood, but there is little reliable data available for diazo compounds. This work firstly collates available sensitivity and thermal analysis data for diazo-transfer reagents and diazo compounds to act as an accessible reference resource. Thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and accelerating rate calorimetry (ARC) data for the model donor/acceptor diazo compound ethyl (phenyl)diazoacetate is presented. We also present a rigorous DSC dataset with 43 other diazo compounds, enabling direct comparison to other energetic materials to provide a clear reference work to the academic and industrial chemistry communities. Interestingly, there is a wide range of onset temperatures (T_{onset}) for this series of compounds which varied between 75 and 160 °C. The thermal stability variation depends on the electronic effect of substituents and the amount of charge delocalisation. A statistical model is demonstrated to predict the thermal stability of differently substituted phenyl diazoacetates. A maximum recommended process temperature (T_{D24}) to avoid decomposition is estimated for selected diazo compounds. Average enthalpy of decomposition (ΔH_D) for diazo compounds without other energetic functional groups is -102 kJ mol^{-1}. Several diazo transfer reagents are analyzed using the same DSC protocol and found to have higher thermal stability, which is in general agreement with reported values. For sulfonyl azide reagents an average ΔH_D of -201 kJ mol^{-1} is observed. High quality thermal data from ARC experiments shows the initiation of decomposition for ethyl (phenyl)diazoacetate to be 60 °C , compared to 100 °C for the common diazo transfer reagent *p*-ABSA. The Yoshida correlation is applied to DSC data for each diazo compound in order to provide an indication of both their impact sensitivity (IS) and explosivity. As a neat substance, none of the diazo compounds tested are predicted to be explosive but many (particularly donor/acceptor diazo compounds) are predicted to be impact sensitive. It is therefore recommended that manipulation, agitation, and other processing of neat diazo compounds is conducted with due care to avoid impacts, particularly with large quantities. The full dataset is presented to inform chemists of the nature and magnitude of hazards when using diazo compounds and diazo transfer reagents. Given the demonstrated potential for rapid heat generation and gas evolution, adequate temperature control and cautious addition of reagents which begin the reaction is strongly recommended when conducting reactions with diazo compounds.

KEYWORDS: differential scanning calorimetry, diazo compound, diazo transfer, sulfonyl azide, process safety.

INTRODUCTION

The choice of synthetic route in process development is multifactorial and often governed by reagent costs, product yield and purity, environmental impact, robustness and most importantly, safety.[1,2] Chemical transformations from commercial reagents to the desired product are evaluated holistically with these principles in mind, and a route devised using available synthetic methods. Certain classes of reagent are essentially excluded from a process chemist’s toolkit due to safety concerns. To determine whether reagents are acceptable to use in a scaled process requires practical assessment of specific hazardous properties.[3]

Energetic materials pose specific explosive hazards, resulting from the high quantities of heat and gas that can be released upon rapid decomposition. There are several metrics commonly used to assess a reagent.[4] These can be grouped into risk assessment categories determining the *likelihood* or *severity* of an unwanted decomposition. The *likelihood* will be proportional to the activation energy term of an Arrhenius equation for the decomposition reaction. Thermal stability is a measure of the temperature at which a compound pyrolyzes. Sensitivity to several stimuli can be exhibited by energetic materials, defined by specialist tests with results quoted in comparison to well-known sensitive materials. The cause of sensitive behaviour is a complex phenomenon and there is currently no theoretical way to predict sensitivity.[5] Impact (or shock) sensitivity (IS)[6] can be the most relevant for a chemical process, but friction, electrostatic discharge (ESD) or other sensitivities such as to light may also be relevant.[7] On the other hand, metrics related to *severity* will be primarily concerned with the magnitude of the heat produced in an exothermic process (ΔH_R). Other important considerations include whether a material can sustain a detonation[8] and the amount of pressure generated by evolved gases.

These concepts are defined from an experimental basis, with reference to well-studied materials so there is no *inherent* property to determine. RDX (1,3,5-trinitro-1,3,5-triazinane) is often used as a reference compound by explosive materials scientists;[9] for organic or process chemists 1,3-dinitrobenzene (*m*-DNB) is a more appropriate, conservative reference.[10] These tests are notorious for reproducibility as a large number of factors can alter the result: from test methodology to the presence of air bubbles in liquid samples,[10] or the crystal structure[5b] or particle morphology of a solid sample.[4] The measurement obtained will therefore depend upon the idiosyncrasies of the specific method used and as such, full and accurate reporting of all experimental aspects is vital. Ideally, measurements should be conducted on the same setup and performed at the same time. Such tests require specialist test equipment not commonly available outside energetic materials labs that consume decagram quantities of material.

Differential Scanning Calorimetry (DSC) is a valuable screening tool in process safety, providing information on both likelihood and severity characteristics related to a reaction or compound. The energy change of a sample crucible is monitored versus an inert reference crucible as the temperature is controlled, usually following a steady temperature ramp. Thermal stability and exotherm magnitude can be easily and rapidly obtained using this technique from small quantities of sample (~mg). However, DSC lacks the high sensitivity of other techniques and does not provide valuable pressure data, such as with Accelerating Rate Calorimetry (ARC). Energetic compounds which evolve gas upon decomposition must be analyzed in a sealed DSC crucible capable of withstanding the generated pressure to avoid misleading results.[11]

DSC results generally include the enthalpy of decomposition (ΔH_D) which indicates the energetic yield of the decomposition, as well as initiation (T_{init}) and/or extrapolated onset temperatures (T_{onset}) which represent thermal stability. T_{init} is defined by the temperature at which the heat flow is measured to be >0.01 W g^{-1} from the baseline. T_{onset} is defined by the intersection of the extrapolated maximum peak slope and the baseline, often determined by DSC software. Typically, for process safety purposes only T_{init} is used, and to complicate matters is often named T_{onset}. It is important to note that unlike melting points, decomposition reactions have a kinetic factor and decomposition will occur at lower temperatures than T_{init}, albeit at an exponentially slower rate.

Diazo compounds are energetic materials that find extensive application in chemical synthesis as versatile synthetic intermediates, but almost exclusively in academic labs.[12] Such compounds present powerful bond forming potential *via* the (catalytic) generation of metal carbenes, and offer important synthetic disconnections, relevant to the preparation of pharmaceutically relevant motifs. The most valuable transformation is arguably the reaction with alkenes to form cyclopropanes.[13,14] In a rare large scale example, a styryl-diazo ester was employed by Bristol-Myers Squibb in an enantioselective cyclopropanation in a multikilogram synthesis of Beclabuvir,[15] using the Rh_2(*S*-DOSP)$_4$ catalyst reported by Davies.[16] Carbene C–H insertion processes are becoming increasingly controlled, with potential to streamline synthetic routes.[17] Similarly, heteroatom X-H insertion reactions (X = O, N, S, and P),[18,19,20] and cycloaddition reactions[21] can install important pharmaceutically relevant functionality and heterocycles. Despite these available transformations the diazo functional group is essentially avoided for reactions at process scale, due to the potential explosion hazard.[22]

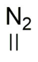
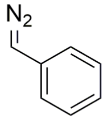
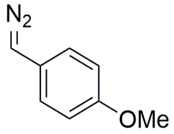
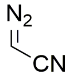
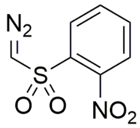
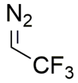
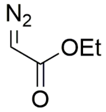
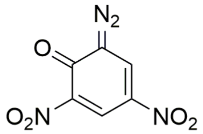
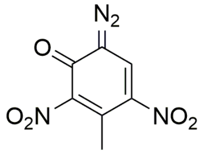
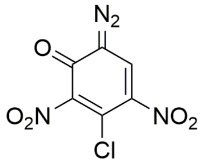
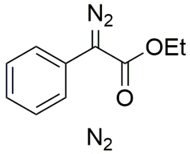
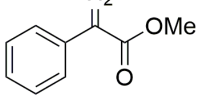
The available data on the thermal hazards of diazo compounds is limited and disparate. Rarely is thermal hazard data presented and it is common in the academic literature to make general comments as to the potential stability hazards, along the lines, of “Caution - while we never experienced any problems, diazo compounds are presumed to be potentially explosive”. Here, we have collated all available data on diazo compounds from the literature (Table 1). This data is largely from DSC experiments, though other results are quoted where this is not available. We have included ΔH_D in J g^{-1} and in kJ mol^{-1}. For process safety, the ΔH value is often reported in J g^{-1}, as this can be divided by the specific heat capacity (c_p in J g^{-1} K^{-1}) to gauge the adiabatic temperature rise (ΔT_{ad}) of a defined mixture to give an idea of the severity of a runaway exotherm.[2] Impact sensitivity (IS) is given where it is available. If an explosion has been reported it is noted though the root cause is often unclear and an absence of reports should not be interpreted as an absence of explosive behaviour. The data presented in Table 1 should be treated with caution as exact details of experimental methods are often not reported and there are inconsistencies in the use of terminology within the reported literature.

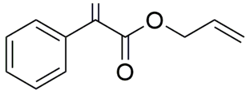
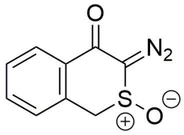
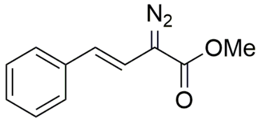
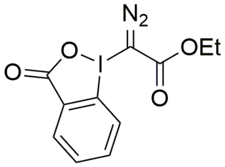
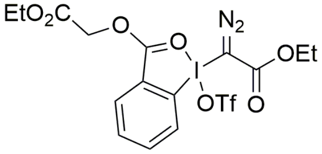
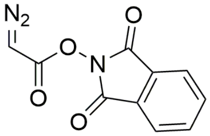
The extremely unstable and explosive nature of alkyl diazo compounds has been evident since their discovery in the late 1890s[23] and they are rarely isolated as a result. Diazomethane **1** is the simplest diazo compound and is a highly sensitive, explosive gas.[24] Widely known to explode at the slightest provocation, including exposure to direct sunlight, chipped glassware or ground-glass joints,[25] its extreme sensitivity and gaseous nature is a barrier to precisely investigating the initiation of the decomposition using standard techniques. While generally agreed to decompose above 100 °C,[26] the difficulty in ensuring the reaction is triggered thermally makes accurate determination of the thermal stability impractical.[27] Given the well-known hazards, the spectre of diazomethane is perhaps one reason that diazo compounds are often avoided in the pharmaceutical industry. There are a few examples of industrial interest in diazomethane, leveraging continuous flow processes to generate and consume the reagent *in situ* with increased safety.[28]

Pure phenyl diazomethane **2**,[29] the 4-methoxyphenyl-analogue **3**[30] and diazoacetonitrile **4**[31,32] are reported to explode spontaneously. When required, these mono-substituted, low molecular weight diazo compounds are generally prepared *in situ* for immediate use in one-pot protocols or continuous flow processes.[33] Due to their violently short-lived nature, isolation of quantities sufficient for stability or sensitivity testing is impractical. So-called “semi-stabilized” diazo compounds with a conjugated aryl or alkenyl π-system are similarly handled in solution for brief periods of time.[34]

EDA (ethyl diazoacetate) is the most commonly used diazo compound and DSC data is available on a dilute solution[35] and neat sample.[36] DDNP (diazodinitrophenol) is a well-studied primary explosive[37] which, along with its derivatives (**7** and **8**) are less appropriate for fine chemical synthesis. Disubstituted donor-acceptor diazo compounds are often isolated, depending on the structure, but there remains very little data on their stability in the literature. Data were reported for aryl diazoacetates **9**, **10**, **11** and α-diazo-β-keto sulfoxide **12**, however in each case full experimental details of the thermal analysis were not reported.[38,39,40,41,42] Recently, hypervalent iodine diazoacetates **14** and **15** for photoredox chemistry and redox-active *N*-hydroxyphthalimidoyl diazoacetate (NHPI-DA) **16** were reported with accompanying DSC data.[43,36]

Table 1. Impact Sensitivity (IS), Thermal Stability and Exotherm Data Previously Reported for Diazo Compounds

entry		diazo compound	IS (J)	explosion reported?	thermal analysis[44]				ref
					heating rate (°C min^{-1})	T_{init} (°C) [a]	T_{onset} (°C) [a]	ΔH_D (kJ mol^{-1}) [a]	
1	**1**		very sensitive	25, 26, 45, 46	n.a. [b]	>100		est. −180 to −297	45
2	**2**		very sensitive	yes					29
3	**3**		very sensitive	yes	reported to slowly decompose at −80 °C				30
	4		very sensitive	yes					31,32
5	**5**			yes					47
6	**6**			yes					48
7	**EDA**			cannot sustain detonation[49]	5 n.a. [d] n.a. [b]	 55 [d] 65 [e]	101[c] 85 [e]	−171 [c] −178 [d] −155	35 35 36
8	**DDNP**		1.5[37]	primary explosive[37]	5 10		178 [f] 155	 −436	50 10
9	**7**				5		201 [f]		50
10	**8**				5		203 [f]		50
11	**9**				n.a. [b]	90 [e]	120 [e]		38
12	**10**				n.a. [b] 5	86 [e] 77 [e]	115 [e] 108[e]	−124 −152	39 40

13	**11**		n.a. [b]		77 [g]	−182	41
14	**12**		n.a. [b]	108 [h]			42
15	**13** [i]		n.a. [b]		42 [g]	−176	15
16	**14**		10	90 [e]	91	−255	43
17	**15**		10	76 [e] 190 [e, j]	102 194 [j]	−175 −67 [j]	43
18	**16**		n.a. [b]	125 [e] 205 [e, j]	152 [e] 220 [e, j]	−186 −115 [j]	36

[a] Measured by DSC unless otherwise noted. [b] Heating rate not given. [c] DSC of 40% weight EDA in toluene. ΔH_D reported was −602 J g^{-1} which was extrapolated to 100% weight EDA assuming a linear relationship. [d] Measured by ARC on neat EDA – a much more sensitive instrument and slower heating rate and so T_{onset} is lower and ΔH_D is higher than a typical DSC experiment. [e] Estimated from DSC plot given in SI. [f] DSC peak maxima temperatures. [g] Distinction between T_{init} and T_{onset} was unclear, so we have assumed T_{init} as defined in this work. [h] Measured by TGA. [i] Interestingly, this compound is reported to cyclize into a pyrazole rather than evolving N_2 gas. [j] Distinct second decomposition is observed.

There are several possible routes for the preparation of diazo compounds which themselves involve energetic reagents (Figure 1). Diazotisation is limited to simple diazo compounds.[51] Aryl or alkyl diazo compounds can be prepared from *N*-sulfonylhydrazones which are cleaved with base,[52] thermolytically or photolytically[53] though forcing conditions may decompose of the diazo product. Unsubstituted hydrazones can be dehydrogenated using oxidizers.[54] Regitz diazo transfer to an activated methylene compound is the most widely used method to access complex diazo compounds with at least one electron withdrawing group. The N_2 transfer is typically effected by sulfonyl azide reagents, though recently other azides have been developed that effect the same reaction.[55,56]

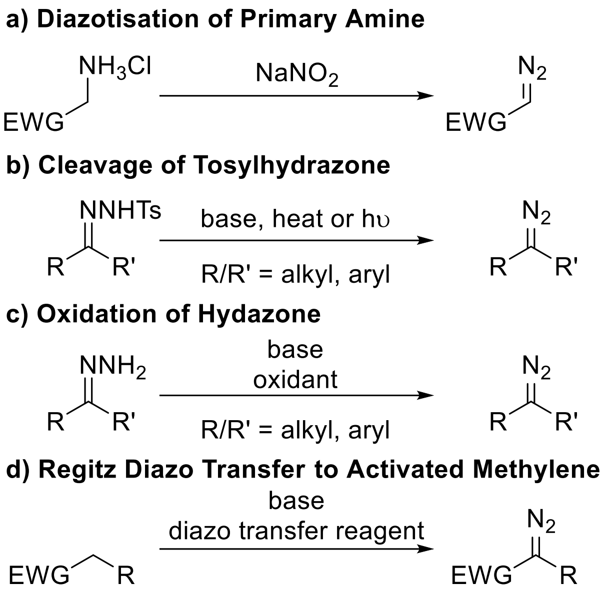
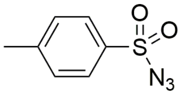
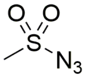
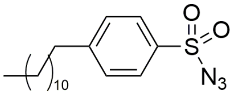
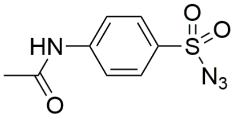
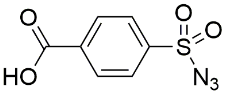
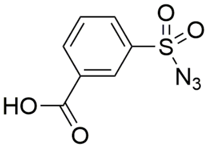
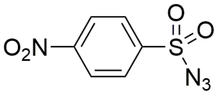
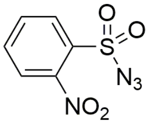
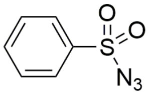
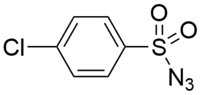
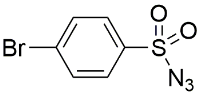
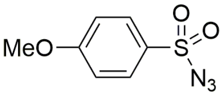
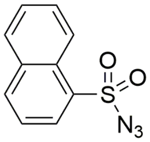
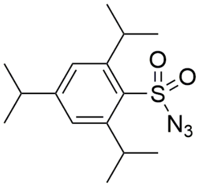
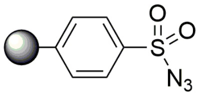
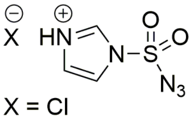
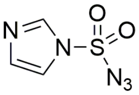
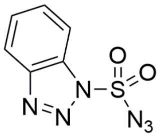
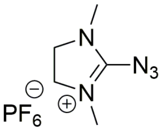
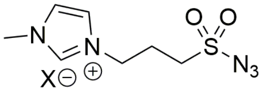
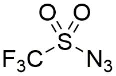
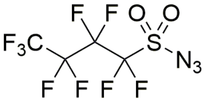
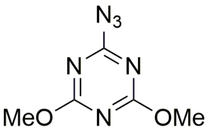


Figure 1. General synthetic methods to prepare diazo compounds.

Sulfonyl azides are commonly used diazo transfer reagents that have known hazardous properties.[57] Several explosions have been reported[58-62] and so these compounds have been relatively well-studied. Available literature thermal analysis and sensitivity data for sulfonyl azide and other diazo transfer reagents is collated in Table 2. Though generally more thermally stable than diazo compounds, the sulfonyl azide functional group confers significantly higher energetic yield than diazo compounds. Sulfonyl azides have been reported to be impact sensitive,[63,64,65] however, another report claimed that impurities were the cause i.e. pure MsN_3 was not impact sensitive but a slightly impure sample was highly sensitive.[66] Pure TsN_3 has been reported to explode,[58,59] but the root cause of these incidents was not conclusively demonstrated to be the azide and the only report of explosive power comes from unpublished private correspondence.[63] It has been noted that preparations of sulfonyl azide using an alcohol as solvent lead to impurities which may be the cause of the observed impact sensitivity, and so preparation of sulfonyl azides in acetone/water is recommended to avoid this possibility.[67]

Table 2. Impact Sensitivity, Thermal Stability and Exotherm Data Previously Reported for Sulfonyl Azide and Other Diazo Transfer Reagents

entry		diazo transfer reagent	IS (J)	explosion reported?	thermal analysis[44]				ref
					heating rate (°C min^{-1})	T_{init} (°C) [a]	T_{onset} (°C) [a]	ΔH_D (kJ mol^{-1})	
1	**TsN_3**		4.9	yes[58,59]	10	120		−334	63, 64, 65
					5	121	156	−312	68
					5	128	158	−209	11
2	**MsN_3**		4.9	yes[69], no	10	125		−282	63, 64, 65
3	***p*-DBSA**		>14.7 [b]		10	151		−246	63, 64, 65
4	***p*-ABSA**		25 (3/25)		n.a. [c]	180 [d]			70
			>13.4 [b]		10	120		−173	71, 65
					n.a. [c]	125	148	−219	38
5	***p*-CBSA**		29.4 (3/6)		10	163		−224	63, 64, 65
					10	148 [e]	167	−259	72
6	***m*-CBSA**				10	122 [e]	157	−251	72
7	***p*-NBSA**		25 (9/25)		n.a. [c]	166 [d]			70
8	***o*-NBSA**		4.9		10	118		−477	65
9	**17**		25 (9/25)	yes[69] [f] no[73] [g]	n.a. [c]	162 [d]			70
10	**18**		>25 [b]	yes[74] [h]	n.a. [c]	166 [d]			70
			29.4 (4/6)		10	139		−327	64, 65
11	**19**		29.4 (6/6)		10	127		−310	64, 65
12	**20**		25 (2/25)	yes[f]	n.a. [c]	173 [d]			70
13	**21**		29.4 (5/6)		10	146		−270	63, 64, 65

14	**22**		>29.4 [b]		10	136		−261	63, 64, 65
15	**23**		>40 [b]		n.a. [c]	130	166	−183	75
16	**24**	 X = Cl	6	yes [60]	5		102		76
17	**25**	X = H_2SO_4	40		5		131		76
18	**26**	X = OMs	40		5		88		76
19	**27**	X = OTs	30		5		114		76
20	**28**	X = ClO_4	<1		5		140		76
21	**29**	X = BF_4	40		5		146		76
22	**30**		<1		5		112		76
23	**31**			yes [62 i]	n.a. [c]	112 [j]			77
24	**ADMP**		>25 [b]		10	200			55
25	**32**	 X = SO_3CF_3			n.a. [c]	160			78
26	**TfN_3**		very sensitive [k]	yes [61]					79
27	**NfN_3**		>25.5 [b]		n.a. [c]	120 [d]			80
					10		141	−136	81
28	**ADT**		>100 [b]		n.a. [c]		195 [d]		82
					5	159	150 [l]		56
					5		187	−207	11

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[a] Measured by DSC unless otherwise noted. [b] Sample reached the upper test limit with no reaction. [c] Heating rate not given. [d] Method not clear from report. [e] Estimated from DSC plot given in the report. [f] Explosion judged by report[70] of audible sound effect on thermal decomposition, indicative of a supersonic detonation. [g] Pure **17** reported to decompose ‘quietly’ approx. 105 °C but crude product exploded. [h] Explosion occurred on addition of a spiro azepanoindole species to neat azide. [i] The root cause of this explosion is unclear. [j] Reported from TGA as DSC was not run to decomposition. [k] No data has been published but the pure form is reported to spontaneously

explode so testing would be difficult. [l] Initially reported as +30 kJ mol^{-1} endothermic decomposition due to DSC measurement in open crucibles.

p-ABSA is considered to be a ‘safer’ diazo transfer reagent and is generally preferred over mesyl (MsN_3) or tosyl azide (TsN_3) for batch diazo preparation. The key reasons for this can be seen in Table 2; while the thermal stability (T_{init} and T_{onset}) is similar, it is significantly less sensitive to impact and has an apparently lower ΔH_D. It has not been demonstrated that *p*-ABSA can sustain a detonation, as the only result is unclear.[70] *p*-DBSA and ADT have been demonstrated to be non-impact sensitive alternative diazo transfer reagents.[63–65,56] Polystyrene-supported benzenesulfonyl azide **23** has been suggested as another safer, if costly option.[75] Both TsN_3 and MsN_3 have been prepared and used in flow[83] where the sulfonyl azide is maintained in solution throughout the protocol and thus the explosive properties of the neat material are avoided.[84] Among the more reactive diazo transfer reagents, NfN_3,[81] ADMP[55] and **25**[76] have been demonstrated to be insensitive alternatives to the explosive TfN_3. The only friction and ESD sensitivity data available is for the imidazole-1-sulfonyl azide salts **24** to **29**.[75]

Diazo compounds and diazo transfer reagents are valuable synthetic tools but the question of explosive potential discourages their use. Table 2 compiles a large amount of thermal and explosive hazard data on diazo transfer reagents available in the literature. It is apparent that similar information is scarce for diazo compounds, which are generally regarded to pose similar hazards in the chemical laboratory. Here we present a rigorous DSC dataset of diazo compounds and offer direct comparison to diazo transfer reagents and other energetic materials to provide a clear reference work to the academic and industrial chemistry communities. Thermal stability data on 44 diazo compounds using DSC is reported and the effects of various substituents on these properties is explored. Onset temperatures were found to be 75-160 °C, with electron-rich substituents generally giving lower thermal stability. Energetic yields were around 102 kJ mol^{-1} unless other energetic functional groups were included. Furthermore, the Yoshida correlation is applied to the DSC data to predict the impact sensitivity and explosivity of the tested diazo compounds. None are predicted to be explosive, but many are predicted to exhibit impact sensitivity with exothermic decomposition. The implications of these results is that scale up of reactions using sulfonyl azides or diazo compounds should be undertaken with caution, ensuring adequate thermal control and overpressure relief mechanisms are in place; and that the initiating reagent is added at an appropriate rate.

RESULTS & DISCUSSION

DSC Analysis of Diazo Compounds

In this study, the thermal stability and energetic yield of 44 diazo compounds was measured using DSC. In a typical measurement, 5 mg of diazo compound was weighed into a high-pressure crucible, sealed and equilibrated at 25 °C. The sample was then heated at 5 °C min^{-1} while the heat flow was monitored versus an empty reference crucible. The use of high pressure crucibles ensured containment of all gaseous decomposition products, which otherwise led to erroneous endothermic peaks.[85,11] The results for T_{init}, T_{onset}, and ΔH_D were measured for two samples and averaged (Table **3**). For selected results, this analysis was repeated on different DSC equipment at GlaxoSmithKline (GSK) using a slightly different method with a 2 °C min^{-1} temperature ramp, which resulted in lower T_{init} and T_{onset} due to the higher resolution. Repeatability criteria were 2% for T_{init} and T_{onset}

and 10% for ΔH_D,[3a] though the majority of results were well within this range; any results falling outside this range were repeated.

The DSC plots for the donor/acceptor diazo compound ethyl (phenyl)diazoacetate **9** and analogous ethyl (phenyl)acetate **33** are shown in Figure 2.[86] Both compounds are liquid at 25 °C and thus do not exhibit melting points typically observed as a sharp endothermic peak for solids. A clear exothermic decomposition is observed in the DSC plot of **9** which corresponds to the dissociation of the diazo to form N_2 gas and a highly reactive carbene. This decomposition is also evident in the thermogravimetric analysis (TGA) plot of **9** (Figure 3) which clearly shows a sharp mass loss initiating around 85 °C (99.6% of starting mass) and corresponding to a 14.8% mass loss by 126 °C. The molecular mass of N_2 (28.01 g mol^{-1}) is exactly 14.73% of the molecular mass of **9** (190.2 g mol^{-1}). The average DSC for **9** (Table 3, entry 1) shows agreement with both our result (Table 3, entry 2) and existing literature report (Table 1, entry 10; heating rate and ΔH_D were not reported).

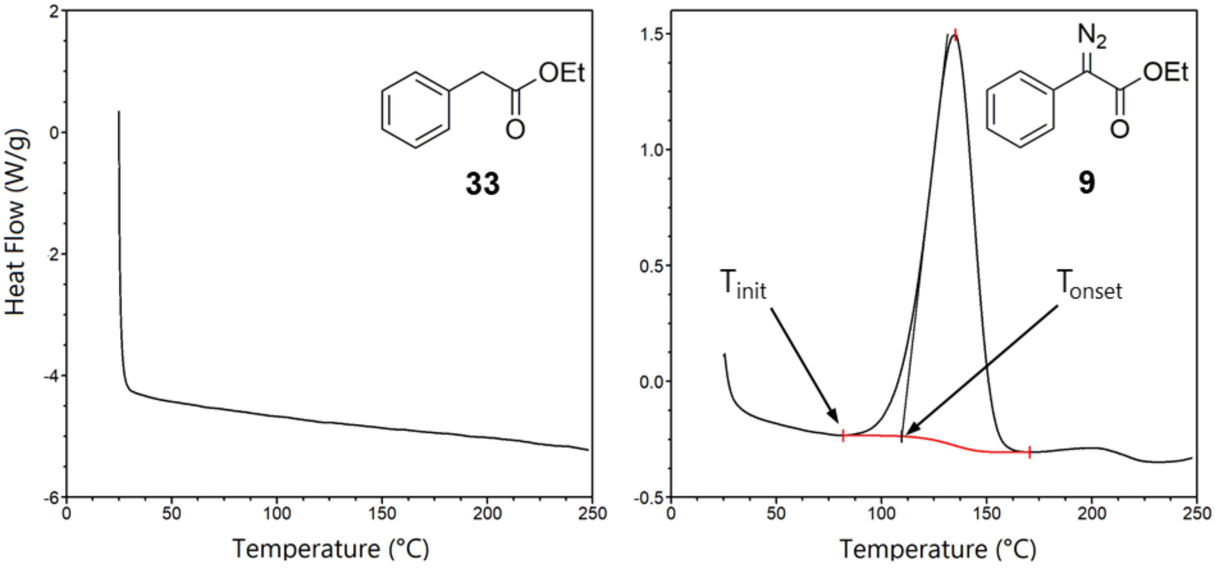


Figure 2. Comparison of DSC plot for ethyl (phenyl)acetate 33 and ethyl (phenyl)diazoacetate 9.

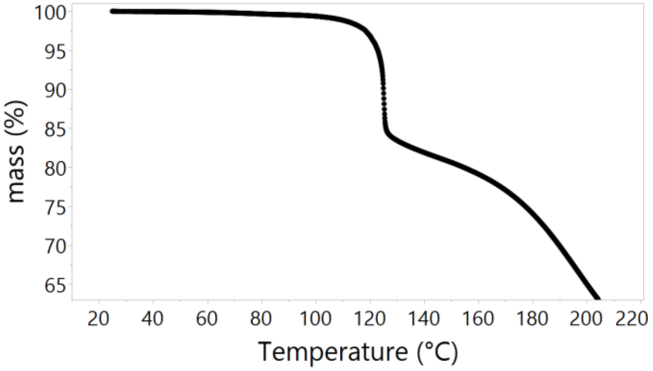
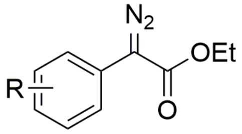
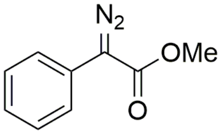
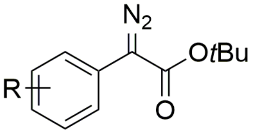
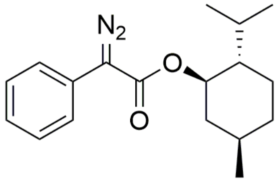
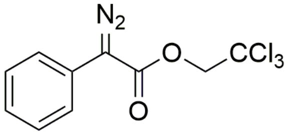
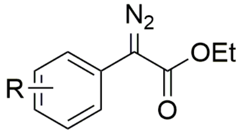
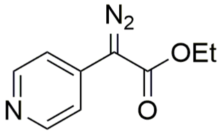
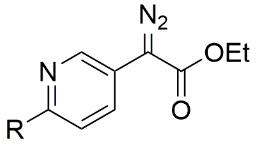
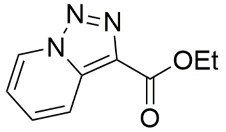
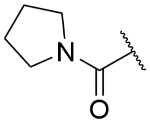
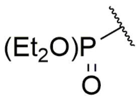
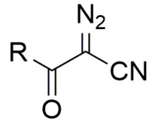
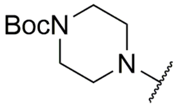
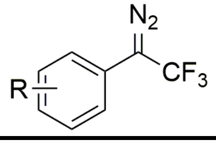


Figure 3. TGA plot for ethyl (phenyl)diazoacetate 9.

Table 3. Averaged DSC Results for Diazo Compounds.

entry	compound [a]	structure	R	T_{init} (°C)	T_{onset} (°C)	ΔH_D ($J\ g^{-1}$)	ΔH_D ($kJ\ mol^{-1}$)
1	**9** [b]		H	87	109	−539	−103
2	**9** [c]			80	107	−562	−107
3	**10**		-	85	108	−574	−101
4	**10** [c]			80	98	−554	−98
5	**34**		H	76	108	−479	−105
6	**35**		4-Br	98	115	−344	−102
7	**36**		-	87	110	−360	−106
8	**37**		-	84	100	−395	−116
9	**38**		4-OMe	63	81	−467	−103
10	**39**		4-Me	79	103	−486	−99
11	**40**		4-F	72	101	−503	−105
12	**41**		4-Cl	97	115	−448	−101
13	**42**		4-Br	98	114	−380	−102
14	**43**		4-CF_3	96	123	−416	−107
15	**44**		4-NO_2	113	131	−578	−136
16	**45**		3-OMe	86	110	−472	−104
17	**46**		3-Me	82	109	−485	−99
18	**47**		3-F	88	116	−451	−94
19	**48**		3-Cl	95	117	−464	−104
20	**49**		3-CF_3	92	117	−394	−102
21	**50**		2-OMe	61	84	−521	−115
22	**50** [c]		2-OMe	57	75	−443	−98
23	**51**		2-F	72	98	−503	−105
24	**52**		2-Cl	71	94	−464	−104
25	**53**		2-CF_3	79	104	−407	−105
26	**54**		3,4-Cl	97	116	−376	−97
27	**55**		3,4-Me	82	101	−465	−101
28	**56**		3,4-OMe	71 [d]	84 [e]	−437 [e]	−109 [e]
29	**57**		3,4,5-OMe	72 [d]	97 [e]	−323 [e]	−90 [e]
30	**57** [c]		3,4,5-OMe			−225	−63

31	**58**		4-OPh	81	95	−385	−109
32	**59**		4-Ph	80[f]	108	−396	−105
33	**60**		-	110	133	−435	−83[f]
34	**61**		H	88	108	−494	−94
35	**62**		Cl	100	114	−468	−106
36	**63**		-	205	223	−539	−103
37	**EDA**[g]		H−	60	110	−1143	−130
38						−1283[h]	−146[h]
38	**64**		O_2N-	85	111	−729	−116
39	**65**		PhO_2S-	89	121	−536	−136
40	**66**		H_3COC-	89	132	−690	−108
41	**66**[c]			101	139	−691	−108
42	**67**			114	133	−473	−100
43	**68**		EtO_2C-	120	156[f]	−460[f]	−86[f]
44	**69**			134	161	−379	−95
45	**70**		Et_2N-	84	101	−471	−78
46	**71**		BnO−	98	114	−497	−100
47	**72**			46[d]	101	−357	−100
48	**73**		H	70	97	−492	−92
49	**74**		4-Br	63	96	−377	−100

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[a] Results using DSC method A and average results where $n = 2$ unless otherwise noted. [b] $n = 6$. [c] Using DSC method B and $n = 1$. [d] T_{init} given as start of endothermic melting point which overlapped the exothermic decomposition. This makes calorimetric data less reliable as more than one transition is being measured. [e] Data reported was obtained by excluding endothermic melting to more accurately determine calorimetric data, which shifts T_{onset} slightly. See Experimental Section for more details. [f] Result altered by overlapping transition. [g] EDA in 13% wt. CH_2Cl_2. [h] ΔH_D divided by 0.87 to exclude the unreactive mass of CH_2Cl_2.

Diazo compound **9** was then compared to a variety of other aryl diazoacetates to investigate the effect of substituents on thermal stability. T_{onset} was used for this comparison, as it was found to give more consistent results. Changing the ester alkyl group did not have a significant effect on

T_{onset}, which represents thermal stability. *tert*-Butyl (phenyl)diazoacetate **34** and *tert*-butyl (4-bromophenyl)diazoacetate **35** have almost identical DSC results to their ethyl ester analogues **9** and ethyl (4-bromophenyl)diazoacetate **42**. A bulkier alkyl ester such as menthol derivative **36** did not significantly impact thermal stability. A small reduction in thermal stability was observed for trichloroethyl ester **37**.

The effect of different aryl substituents was also explored with ethyl (phenyl) diazoacetates **38−59** (Table 3, entries 9-35). It was apparent that the more electron donating substituents led to lower T_{init} and T_{onset}. Indeed there was a correlation of thermal stability with the Hammett substitution constants (Figure 4): σ_m is used for *meta* substituents and σ_p^+ for *para* substituents.[87] Chlorine at the 4-position **41** resulted in almost identical T_{onset} to 4-bromo **42**; these substituents have very similar σ_p^+ constants (4-Cl = 0.11, 4-Br = 0.15). For chloro-substituted ethyl (phenyl)diazoacetates, T_{onset} is similar for 4-Cl **42** and 3-Cl **48**. Fluorine has a greater difference between σ_m and σ_p^+ (0.41 vs. 0.26) as it is significantly more electronegative and so for fluoro-substituted ethyl (phenyl)diazoacetates we observed a more exaggerated difference between the electron poor 3-F **47**, and 4-F **40**, which is destabilized by π-donation into the conjugated aryl-diazo system. The methoxy group is a strong π-donor and PMP **38** gave the lowest T_{onset}. 3-OMe **45** had lower T_{onset} than 3-Cl or 3-F, indicating that the weaker σ-withdrawing effect confers a smaller benefit to the diazo compound thermal stability. Both strong σ-acceptor (such as CF_3 **43**, **49**) and π-acceptor substituents such as NO_2 (**44**) serve to stabilize the diazo compound leading to T_{onset} of approx 120 °C and 130 °C respectively.

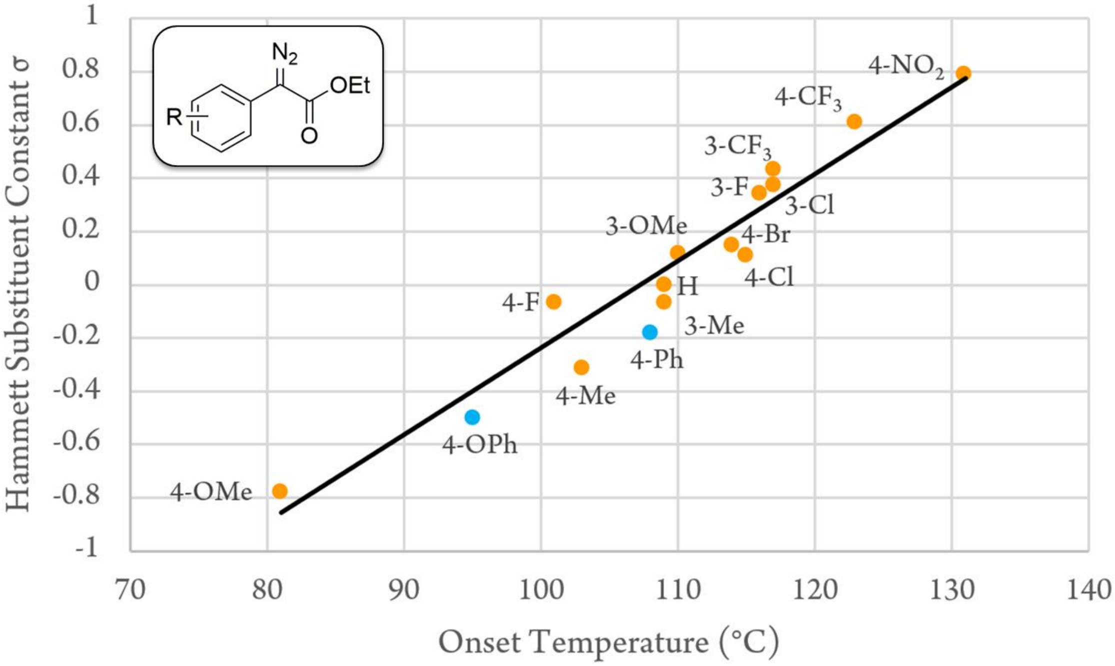

Figure 4. Plot of σ_m/σ_p^+ against onset temperature for compounds 38–49 (from Table 3), detailing correlation. Compounds 58–59 included in blue are described later.

Using the data from Table 3, we developed a statistical model to predict the thermal stability of novel diazo compounds of the substructure shown in Figure 5, using only the Hammett parameter of substituent R_1 or R_2 (eq 1). We propose that this model could be used as a prediction of stability (as T_{onset} on a 5 °C min^{-1} ramp) on novel diazo compounds of this type, in order to provide an estimate of the thermal stability before synthesis. The model was tested by synthesis of previously unknown phenoxyaryl-substituted diazo compound **58**, which was predicted by eq 1 to have a T_{onset} of 93 °C ($\sigma_p^+ = -0.50$, experimental result 95 °C; Table 1, entry 31) and biphenyl diazoacetate **59**, with a predicted T_{onset} of 102 °C ($\sigma_p^+ = -0.18$, experimental result 108 °C; Table 1, entry 32). While phenoxy **58** had excellent predictive accuracy, biphenyl **59** was slightly more stable than expected. This data is also plotted in Figure 4 for comparison. It is possible that this difference is due to the resonance stabilization of the diazo moiety, as the enhanced delocalization of charge is not captured in the Hammett parameter.

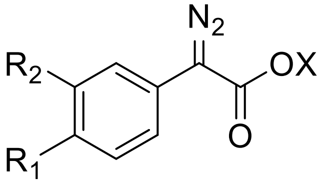

Figure 5. Model diazo compound.

$$T_{onset}\ (°C) = (28.69 \times \sigma_m \text{ or } \sigma_p^+) + 107.5 \qquad \mathbf{1}$$

ortho-Substituted examples were found to be less thermally stable than *meta* or *para* analogues, depending on the steric bulk of the substituent. Chlorophenyl diazo **52** and trifluoromethylphenyl diazo **53** gave a significant reduction in T_{init} and T_{onset}, with onset temperatures approximately 20 °C lower - whereas less bulky substituents such as methoxyphenyl diazo **50** and fluorophenyl diazo **51** had comparable thermal stability to *para*-substituted **38** and **40** respectively. This suggests a steric clash with the larger functional groups, reducing conjugation of the aryl ring with the diazoester due to out-of-plane twisting of the aromatic ring despite the proximity of electron withdrawing substituents.

In multi-substituted systems, similar trends in thermal stability are observed. Ethyl (3,4-dichlorophenyl)diazoacetate **54** and ethyl (3,4-dimethylphenyl)diazoacetate **55** have a similar T_{onset} to their 3- and 4- substituted analogues. Ethyl (3,4-dimethoxyphenyl) diazoacetate **56** is significantly stabilized compared to 4-OMe **38**, due to *meta*-methoxy being σ-electron withdrawing. Indeed, the presence of another methoxy-group in 3,4,5-trimethoxyphenyl example **57** conferred another improvement to thermal stability.[88]

Ethyl (pyridin-4-yl)diazo acetate **60** was more thermally stable due to the electron-poor 4-pyridyl substituent. On the other hand ethyl (pyridin-3-yl)diazo acetate **61** and 6-chloropyridin-3-yl **62**, which cannot delocalise a negative charge of a potential carbene onto the nitrogen atom, displayed no significant difference versus benzo-analogues **9** and **41**. Interestingly, the pyridin-2-yl diazo compound **63** adopts the triazolo tautomer, and has a thermal stability far surpassing the diazo compounds in this study.

Acceptor/acceptor-type diazo compounds can be contrasted to the donor/acceptor compounds. ethyl diazoacetate (EDA) has comparable thermal stability to ethyl (phenyl)diazoacetate **9**, though the initiation is observed at lower temperature. While another electron withdrawing substituent clearly increases the thermal stability of the diazo compound for diazoesters (**64**–**69**), cyanodiazo compounds (**70-72**) have comparable or lower onset temperatures even with an α-carbonyl. The onset temperature for benzyl ester **71** is comparable to ethyl esters with electron poor aromatics such as **62**. Donor/acceptor aryl trifluoromethyldiazo compounds **73** and **74** also have lower onset temperatures than their aryl ester analogues **9** and **42**.

The mean ΔH_D for diazo compounds **9**, **10** and **34−74** (excluding EDA, **44**, **64** and **65**) is -102 kJ mol^{-1} which confirms that diazo compound energetic yield is significantly lower than sulfonyl azides. Sulfone **65** and nitro containing **44** and **64** are exceptions, where adding additional energetic functional groups clearly increases the enthalpy of decomposition of the single main transition, indicating the other energetic functional groups concurrently or sequentially pyrolyze during the diazo decomposition, increasing the measured enthalpy. This average value is on the order of 50 kJ mol^{-1} lower than previous reports of similar diazo compounds **9**, **10**, which could be attributed to differences in equipment and methodology, particularly the heating rate and how the exothermic peak is integrated; and in the case of α-vinyl diazo compound **13** a different decomposition pathway. EDA has a significantly higher ΔH_D than the average diazo compound, as was also previously reported, indicating that the decomposition involves both loss of N_2 and additional processes.

DSC Analysis of Sulfonyl Azides and other Diazo Transfer Reagents

DSC data for thermal stability and energetics of decomposition were also collected for several common diazo transfer reagents (Table 4). They are generally more thermally stable than diazo compounds, but the decomposition has a larger energetic yield. The data were broadly similar to previous reports (cf. Table 2) although both TsN_3 and *o*-NBSA were found to be almost 30% less energetic. For the same decomposition of an energetic functional group, the ΔH_D per mole might be expected to be quite similar, which is not seen in the broad range of sulfonyl azide results in the literature (Table 2, -334 to -136 kJ mol^{-1}). With DSC data, it is important to make comparisons between compounds using the same technique, ideally on the same machine. The sulfonyl azide data in Table 4 has an average -201 kJ mol^{-1} (excluding *o*-NBSA, ADMP and ADT) ,similar to all the literature sulfonyl azide DSC data (average -226 kJ mol^{-1}), however the literature ΔH_D data has a much broader range and higher sample standard deviation (139.6 vs. 10.7 for the data in Table 4) which is likely to be a reflection of the different methods and equipment used. This dataset therefore provides a more standardized set of measurements for comparison of the thermal stability of these reagents.

Table 4. DSC Analysis of Selected Diazo Transfer Reagents

entry	compound [a]	T_{init} (°C)	T_{onset} (°C)	ΔH_D (J g^{-1})	ΔH_D (kJ mol^{-1})
1	**TsN_3**	128	158	−1057	−208
2	***p*-ABSA**	130	156	−790	−190
3	***p*-ABSA** [b]	120	138	−928	−223
4	***p*-CBSA**	148	167	−923	−210
5	***m*-CBSA**	93 [c]	155	−920	−209
6	***o*-NBSA**	123	151	−1541	−352
7	**ADMP**	167	202	−793	−226
8	**NfN_3**	102	136	−582	−189
9	**ADT**	159	186	−1135	−207

[a] Results using DSC method A unless otherwise noted. [b] Using DSC method B. [c] Reported as initiation of melting point which obscures exotherm initiation.

Prediction of Sensitivity and Explosion Hazards – Yoshida Correlation

In a seminal work, Yoshida conducted impact sensitivity and explosive propagation experiments on a number of energetic materials and developed a correlation to predict these properties from DSC results.[89,10] The Yoshida correlations (eq 2 and 3) use T_{onset} (in °C) and ΔH_D (as Q, an inverse value in cal g^{-1} representing energy output) and give a dimensionless number. A value >0 predicts that a material will exhibit impact sensitivity (IS) and/or explosive propagation (EP) whilst a value <0 predicts it will not. Additionally, even a sample that gives a null prediction could still result in a safety incident if the exothermic decomposition is not respected.

$$\text{Impact Sensitivity (IS)} = \log_{10}(Q) - 0.72[\log(T_{onset} - 25)] - 0.98 \qquad \textbf{2}$$
$$\text{Explosive Propagation (EP)} = \log_{10}(Q) - 0.38[\log(T_{onset} - 25)] - 1.67 \qquad \textbf{3}$$

Process safety scientists at Pfizer recently published an assessment of peptide coupling reagents, where the authors used a more conservative version of this correlation (eq 4 and 5) where the Q term was reduced by 25% and T_{init} was used instead of T_{onset}.[3a]

$$\text{Impact Sensitivity (IS)} = \log_{10}(Q) - 0.72[\log(T_{onset} - 25)] - 0.98 \qquad \textbf{4}$$
$$\text{Explosive Propagation (EP)} = \log_{10}(Q) - 0.38[\log(T_{onset} - 25)] - 1.67 \qquad \textbf{5}$$

We applied both correlations to the literature DSC data for diazo transfer reagents from Table 2 to predict impact sensitivity and explosive properties, which will give an indication of sensitivity and explosivity hazards for compounds for which DSC is reported but the specialist tests have not been undertaken. For those with specialist data reported, the IS and EP predictions were compared with those reports (Table S2).

The Yoshida correlation correctly flags all diazo transfer reagents which are reported to be impact sensitive with the exception of naphthalene-2-sulfonyl azide **21**. The more conservative Pfizer-modified correlation on the other hand flags NfN_3 and ADT; both of which have been experimentally demonstrated to be insensitive to impact.[56,81] *p*-CBSA and *p*-ABSA are predicted to be insensitive to impact; however there are reports of some impact sensitivity and they are categorized as ‘less sensitive’ and infrequently react to impact loadings of almost 30 J.[65,70]

Both correlations correctly predict explosivity for those reagents which are known to detonate; the Pfizer-modified correlation may be overly conservative as it flags several commonly used compounds that do not appear to be explosive, such as *p*-ABSA. Any reagent flagged by the less conservative Yoshida EP correlation, which from the literature data is only *p*-bromobenezenesulfonyl azide **19**, should be regarded as explosive unless further testing is undertaken. *p*-DBSA, *m*-CBSA, naphthalene-2-sulfonyl azide **21**, triisopropylbenzenesulfonyl azide **22**, polystyrene-supported benzenesulfonyl azide **23** and ADT are predicted to be non-explosive.[90]

Application of the correlations to literature DSC data for diazo compounds highlighted both allyl (phenyl)diazoacetate **11** and vinyl diazoester **13** are both predicted to be both impact sensitive and explosive by the Yoshida correlation, primarily due to the low reported onset temperatures.

Hypervalent iodine diazoacetates **14** and **15** and NHPI-DA **16** are not predicted to be impact sensitive or explosive.

Prediction of the Sensitivity and Explosion Hazards of Diazo Compounds

Both correlations were applied to all diazo compound DSC results from Table 3 to predict impact sensitivity or explosive properties (see Table S3 for data). Figure 6 plots the DSC results and compares the Yoshida correlation and the more conservative Pfizer-modified prediction. While the Yoshida correlation predicts none of the tested compounds are impact sensitive, when the Pfizer-modified prediction is applied many of the diazo compounds are predicted to be impact sensitive. Only **35**, **36**, **42**, **54**, triazolo **63** and **69** are predicted to be insensitive using the Pfizer-modified IS correlation. Interestingly, the compounds flagged as insensitive contain more ‘molecular ballast’, i.e. bromo, dichloro, phosphonyl or menthyl substituted compounds with a lower proportion of the overall molecular weight being due to the energetic functional group. This reduces the energetic yield per unit mass while the energetic yield per unit mole remains the same. Triazolo **63** is significantly stabilized in the dominant aromatic tautomer. None of the peptide-coupling reagents assessed by Sperry *et al* were flagged by the Yoshida IS correlation whilst six were flagged by the Pfizer-modified IS correlation.[3a] Of these, four compounds exhibited IS. Based on this, we suggest the Yoshida correlation may not flag some impact sensitive materials and the Pfizer-modified prediction more accurately predicts impact sensitivity for diazo compounds.

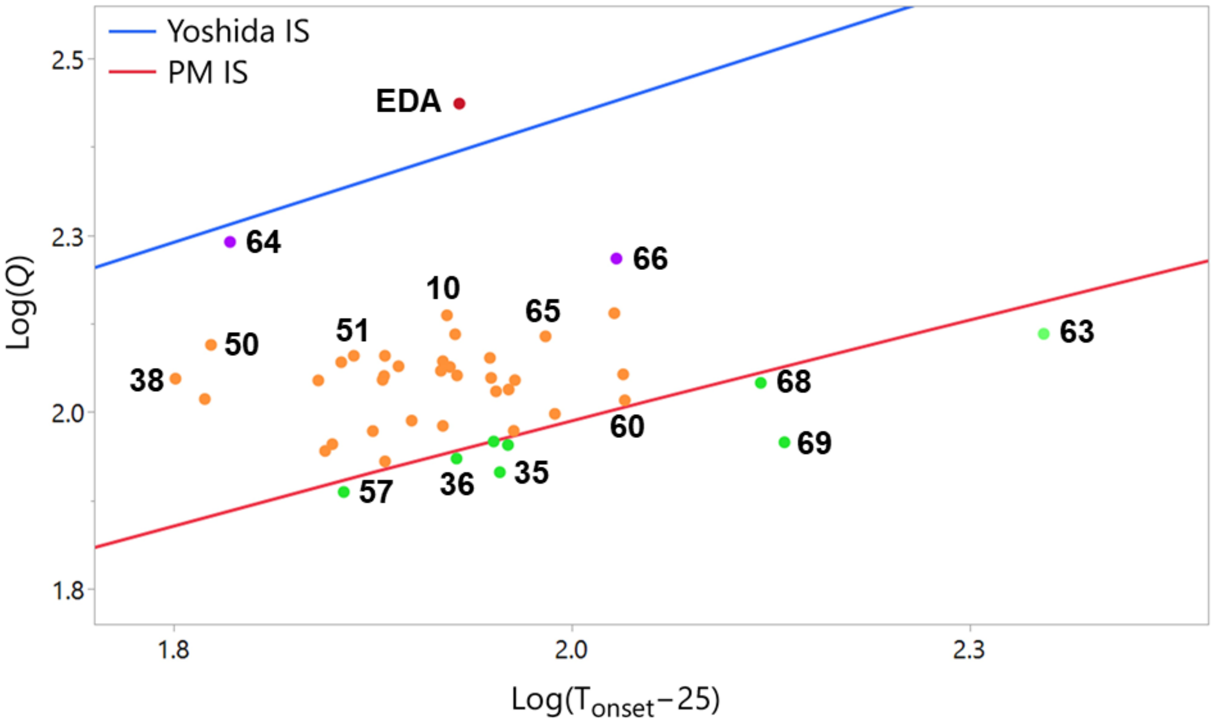

Figure 6. Plot of log(Q) vs. log(T_{onset}−25) for diazo compounds 9, 10 and 34-74 compared to the IS correlation limits, with selected compounds highlighted. See SI for further details.

Figure 7 plots the same DSC results with both Yoshida and Pfizer-modified EP predictions (see SI) and highlights that only ketodiazoacetate **66** is predicted to be capable of detonation by only the more conservative PM correlation. The Pfizer study determined that all compounds flagged by the modified EP correlation and not the Yoshida correlation were not considered explosive. We therefore do not predict explosivity for any of the tested diazo compounds.

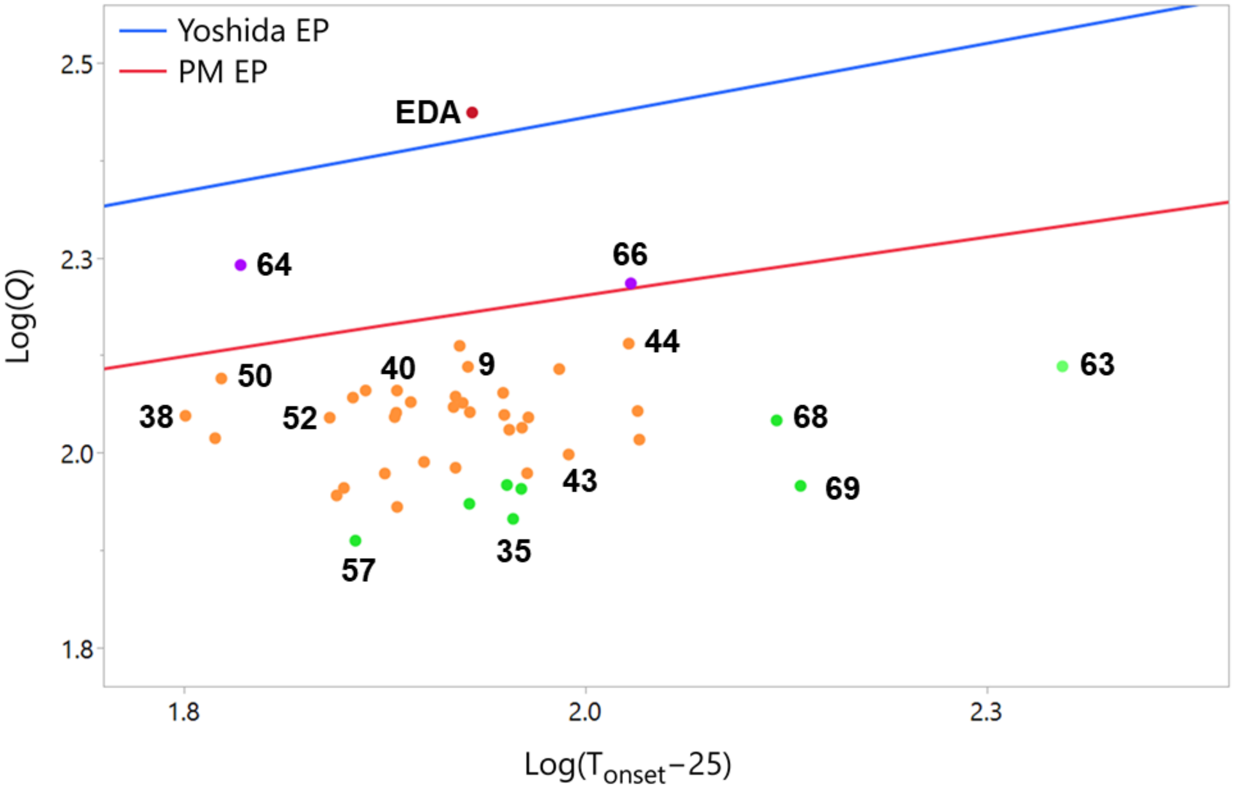

Figure 7. Plot of log(*Q*) vs. log(T_{onset}−25) for diazo compounds 9, 10 and 34-74 compared to the EP correlation limits, with selected compounds highlighted. See SI for further details.

Estimation of Maximum Recommended Process Temperature to Avoid Hazardous Thermal Decomposition

Exotherms of the magnitude typically observed for diazo compounds and sulfonyl azides are a cause for concern. To initially determine safe process operating conditions at GSK, the formula given in eq 6 is used,[2] with T_{init} (in °C) from a DSC experiment collected at a 2 °C min^{-1} heating rate. This allows for a conservative first approximation of safe operating temperature with a reasonable margin of safety, from a simple experiment using readily available DSC equipment.

$$T_{D24} = 0.7 \times T_{init} - 46 \qquad \textbf{6}$$

T_{D24} is the temperature at which the time to maximum rate under adiabatic conditions (TMR_{ad}) becomes >24 h. This equation relies on the assumptions that at the detection limit of an exotherm in the DSC experiment (T_{init}), the conversion is close to zero and thus the heat release rate is equal to the detection limit; as well as the conservative assumptions of a relatively low activation energy (50 kJ mol^{-1}) and zero-order kinetics for the decomposition. Because of the limited sensitivity of the DSC test, values are given to the nearest 5 °C.

T_{D24} was determined for selected diazo compounds using DSC data generated by Method B (Table 5). For the donor/acceptor diazo compounds **9**, **10**, **50**, and **57**, the T_{D24} was found to be below 20 °C which means these compounds should not be processed above ambient temperature as some amount of decomposition may occur. If temperature control is not applied it could lead to a thermal runaway and explosion, depending on the quantity of diazo compound. Acceptor/acceptor diazo compound **66** (Table 5 entry 5) had a T_{D24} of 25 °C, indicative of its higher thermal stability.

Though the formula is not directly applicable to DSC data using a 5 °C min^{-1} heating rate, which gives higher T_{init} than the 2 °C min, it can be used to give an indication of a safe operating window. We found that despite the higher T_{D24} using this data, most diazo compounds in Table 3 had a value below 25 °C, so it is not recommended to prepare or use these compounds with heating and that additional cooling measures should be considered. Only triazolo **63**, ethyl (4-nitrophenyl)diazoacetate **44** and acceptor/acceptor amide/ester **67**, malonate **68** and phosphonyl/ester **69** were found to have a T_{D24} above ambient temperature using the 5 °C min^{-1} data.

Table 5. Estimated Maximum Recommended Process Temperatures for selected diazo compounds.

entry	compound	T_{D24} (°C)
1	**9**	10
2	**10**	10
3	**50**	−5
4	**57**	0
5	**66**	25

It is important to note that for a process scale reaction, more complex and reliable thermal safety assessments may be conducted. For example, using ARC or reaction calorimeters on a case-by-case basis, which would seek to understand other process and reaction parameters and interactions. This enables a suitable Basis of Safety to be defined for the process to be scaled up safely.

Accelerating Rate Calorimetry (ARC)

DSC is used as an initial screening test by Process Safety at GSK when considering a reaction that is intended to be undertaken on a laboratory scale. Any sample exhibiting an exotherm above 300 J g^{-1} may be classed as self reactive as defined by the United Nations Globally Harmonised System of Classification and Labelling of Chemicals and would therefore be submitted for further testing. ARC gives an approximately tenfold more sensitive determination of T_{init} by operating in a heat-wait-search mode: a sample is heated in predefined temperature steps (typically 5 °C), stabilised at each temperature where the ARC searches for an exotherm at a predefined sensitivity. When the sample begins exothermic decomposition, the ARC heating matches the self-heating rate of the sample to simulate adiabatic conditions. The rate of pressure and temperature rise is measured. Compared to DSC, the technique is more sensitive but requires significantly more time and sample (typically between 3 and 7 g).

To provide highly accurate thermal stability data, ethyl (phenyl)diazoacetate **9** (3.355 g) was tested in an ARC using the heat-wait-search mode and the temperature and pressure plots recorded (Figure 8). The decomposition initiated at 60 °C which was followed by a long incubation time where the temperature rise rate remained below 0.1 °C min^{-1}; the TMR$_{ad}$ was calculated to be 183 min. The maximum rate of temperature rise was 4110 °C min^{-1} and maximum rate of pressure rise was 3094 bar min^{-1}.[91] The maximum temperature was 340 °C and the maximum pressure was 202 bar. Sperry suggests that materials exhibiting a rate of pressure rise of >17,000 bar min^{-1} should be considered for further explosivity testing, albeit using the faster modified 'ScanARC' method.[3a,8a] This adds further evidence that diazo compound **9** is not predicted to be explosive, but the significant rate of heat and pressure generation must be respected.

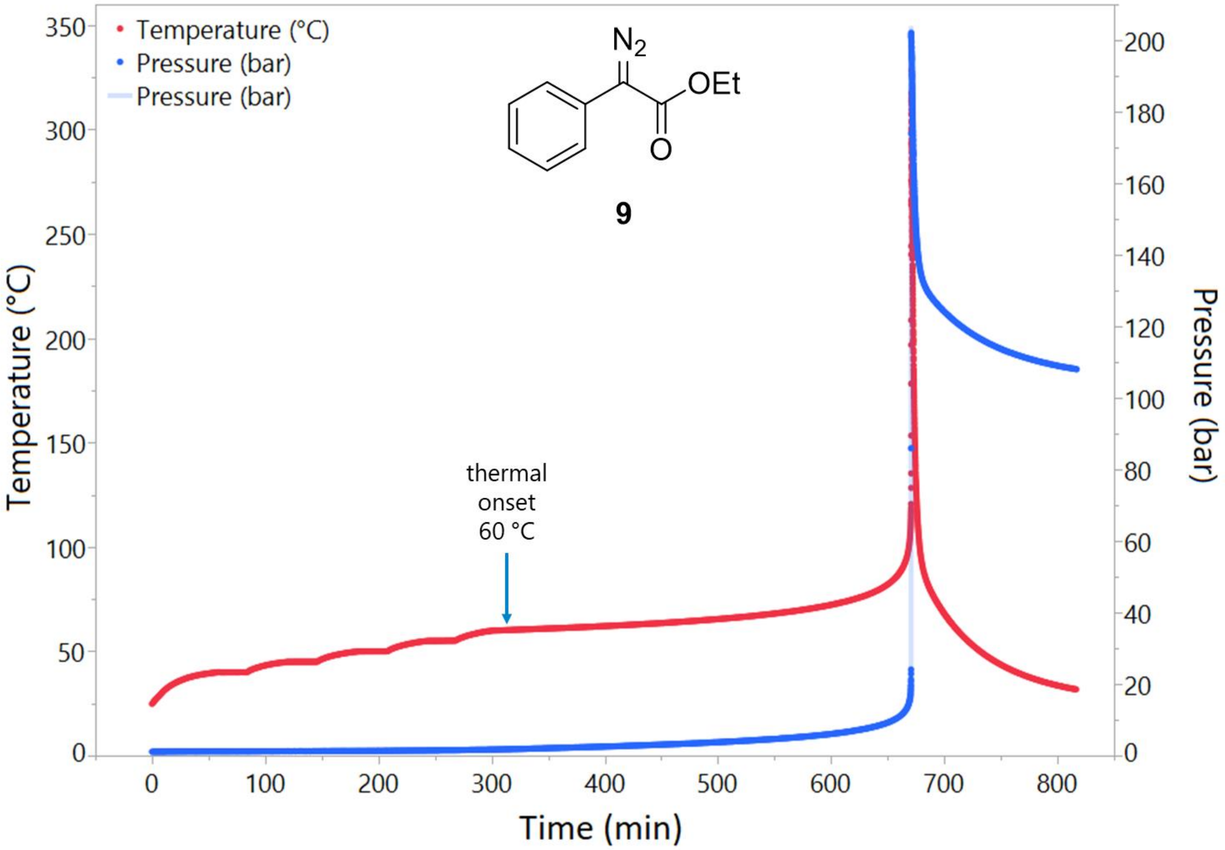

Figure 8. Plot of temperature and pressure during the ARC experiment with 9.

Diazo transfer reagent *p*-ABSA (3.699 g) was analyzed using the same ARC protocol (Figure 9). The decomposition initiated at 100 °C, and the initial decomposition was much less smooth than the diazo compound, exhibiting small jumps in temperature due to the initially very slow rate. The experiment had to be stopped as the decomposition developed to protect the ARC equipment and only the initial stages were measured. Using the same ARC protocol, another diazo transfer reagent ADT (2.107 g) was also analysed (Figure S104); the thermal onset was found to be 125 °C and the TMR$_{ad}$ was calculated to be 123 min; the maximum temperature was 350 °C, with a maximum rate of temperature rise of 2314 °C min^{-1} and the maximum pressure was 284 bar, with a maximum rate of pressure rise of 13,461 bar min^{-1}.[91]

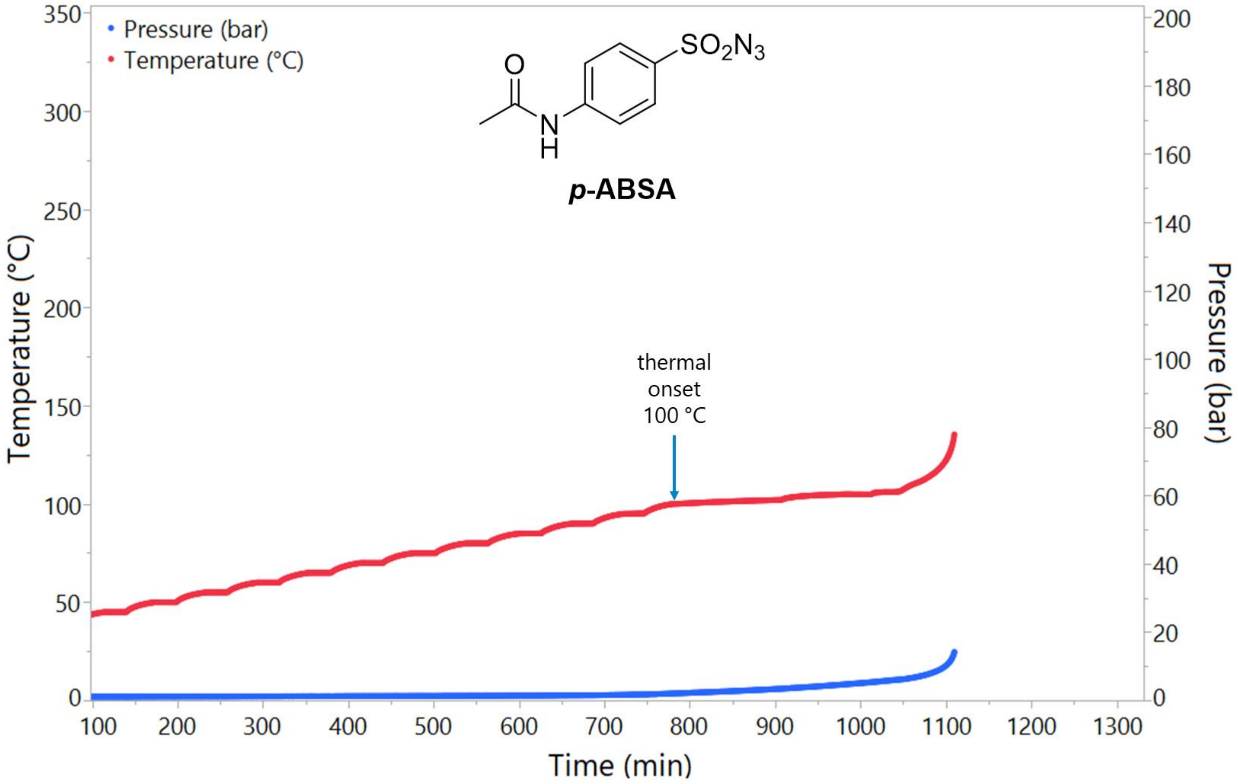

Figure 9. Plot of temperature and pressure during the ARC experiment with *p*-ABSA.

Contextualising the Hazards of Diazo Compounds

The energy release from an uncontrolled decomposition of sulfonyl azides or diazo compounds is typically rapid and results in thermal runaway and under adiabatic conditions. Sulfonyl azides are clearly more energetic than diazo compounds, which have a similar ΔH_D to the decomposition of hydrogen peroxide (See Figure 10 for comparisons).[3a,10,92,93,94] In the context of a reaction, any process which intends to decompose these compounds to effect the desired chemistry would be best conducted with adequate cooling and slow addition of initiator to manage exotherm development.

From the literature diazo transfer reagent IS data in Table 2, it can be seen that some reagents are classed as sensitive and should be handled with extreme care when neat (TsN_3, MsN_3, *o*-NBSA, TfN_3) if at all; most other reagents fall into the less sensitive category (including *p*-ABSA) or are insensitive to impact (ADMP, NfN_3, ADT). In the lab, impacts to neat reagent are most likely to be under manipulation during reaction preparation: handling with spatula or agitation with a stirrer or dropping a container. From our Yoshida correlation IS predictions, we recommend neat diazo compounds are handled with similar care as impact sensitivity is a strong possibility for all but the most stable examples. Some impact sensitivities of well-defined energetic materials are given in Table S4 for comparison.

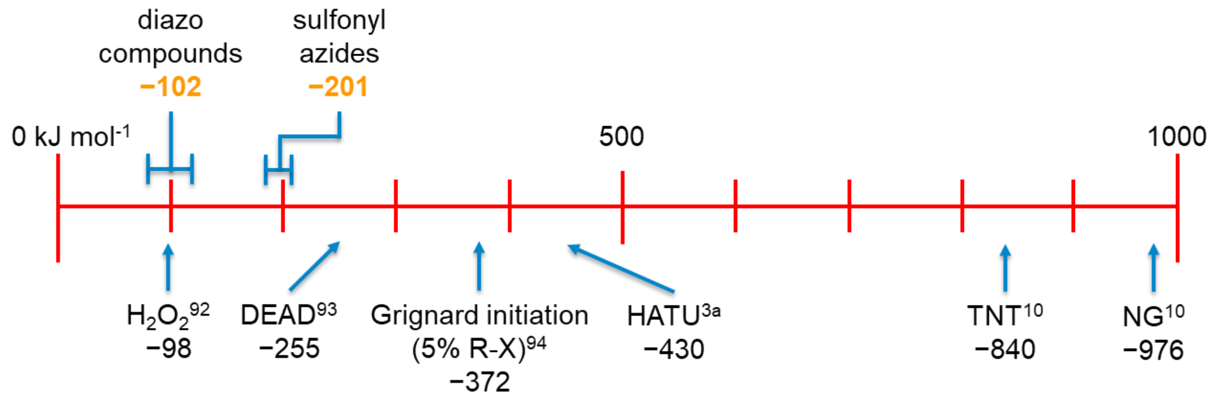

Figure 10. Indicative Scale of ΔH_D for known Exothermic Reagents.

The principal hazard of using diazo compounds (ignoring toxicity), sulfonyl azides and indeed many other exothermic reactions involving potentially unstable reagents is the risk of thermal runaway and pressure generation. Thermal runaway occurs because as the temperature of a reaction mixture increases, the rate of reaction (and thus heat output for exothermic processes) increases exponentially whereas the rate of cooling remains linear. For this reason, scale up should always be approached with appropriate caution. Metal-carbene chemistry relies upon decomposition of the diazo compound, which is similarly exothermic to decomposition and will evolve the same amount of N_2 gas. For exotherms of the magnitude observed, on small scales (for example <1 mmol), the likelihood of thermal runaway is low due to effective cooling. Furthermore, the heat and pressure generated from a runaway decomposition are unlikely to present a major hazard due to the small reaction mass. Additionally, at dilute concentrations (for example < 0.3 M), the solvent mass acts as a heatsink for the energy generated. At larger scales, although there maybe sufficient heatsink to prevent a hazard, there may be potential for serious consequences. More concentrated reaction mixtures present the possibility for the solvent mass to be heated rapidly and vaporised. Thus, any significant scale up would require its own detailed thermal hazard assessment to enable safe reaction design.

Any chemist conducting this type of reaction should pay careful attention to the scale, concentration, temperature control of reaction vessel and rate of addition when initiating the reaction, and to err on the side of caution if in doubt. Addition of the initiating reagent should be slow to allow effective management of the developing exotherm by the temperature control unit. Reaction vessel choice should seek to maximize surface-area-to-volume ratio and have an appropriate overpressure relief mechanism to manage the evolved N_2.

Conclusion

Diazo compounds offer powerful synthetic routes to complex molecules but are often avoided due to justifiable concerns about the potential hazards. Though the perils of diazomethane are well known, there is little data available to describe the hazards of more complex diazo compounds despite their frequent appearance in literature; when results are presented, vital experimental detail is often absent. We have presented consistent DSC data for 44 donor/acceptor and acceptor/acceptor diazo compounds. Onset temperatures were found to be in the range 75-160 °C and the thermal stability was significantly affected by substituents. Generally, electron withdrawing groups were found to improve thermal stability and increase T_{init} and T_{onset}, whereas electron donating groups have the opposite effect. More complex resonance effects were also noted, as steric clashes resulted in out-of-plane twisting and therefore reduced conjugation of the diazo functional group with the aryl ring, leading to a destabilising effect. A statistical model was demonstrated to reasonably predict T_{onset} for hypothetical alkyl (phenyl)diazoacetates based on the Hammett parameter σ_m or σ_p^+ of the aryl substituent.

A formula was used to estimate the maximum recommended process temperature to avoid unwanted decomposition; for most of the tested compounds, to avoid decomposition, it is not recommended to use above 20 °C or store above 0 °C; excepting particularly stabilized acceptor/acceptor diazo compounds. The diazo compounds were found to have a mean ΔH_D of -102 kJ mol^{-1}, and it is expected that a similar ΔH_D would be observed for similar compounds where the diazo functional group is the only source of exothermic decomposition. Several diazo transfer reagents were also tested using the same DSC method and found to have generally higher thermal stability in agreement with reported data and a mean ΔH_D of -201 kJ mol^{-1} for sulfonyl azides. Considerable variation in T_{onset} and ΔH_D results was found in the literature, likely due to different (and unreported) heating rates, highlighting the importance of exhaustive experimental detail in reporting DSC results. High quality thermal hazard data from the ARC is presented on ethyl (phenyl)diazoacetate **9**, which was found to initiate decomposition at 60 °C. The diazo transfer reagent *p*-ABSA was found to initiate decomposition at 100 °C. Significant pressure development was measured in addition to the exotherm and constitutes a considerable explosion hazard if the compounds are heated without an overpressure relief.

Yoshida's predictive correlation and a more conservative modified form from Pfizer were applied to the DSC data to screen for impact sensitivity and explosive propagation. Many of the diazo compounds tested are predicted to be impact sensitive as a neat substance – though all are predicted to be less sensitive than the borderline compound *m*-DNB. It is therefore recommended to treat diazo compounds with particular caution when neat, particularly to avoid impacts or physical processing at scale, especially for lower molecular weight examples. None of the diazo compounds tested are predicted to be explosive. All of the compounds still demonstrate a significant exothermic decomposition which must be respected, particularly when utilising the reaction of diazo compounds with metal catalyst for metal-carbene chemistry. As such, addition of the 'initiator' in the preparation and use of diazo compounds should always be conducted slowly and with adequate temperature control. While this observation may be in line with perceived knowledge, we believe this study will provide a valuable reference and standard set of experimental conditions for those working with these reagents. While on a small scale, diazo compounds will continue to be widely used, there are clear challenges to adapting these reagents to process scales. Part of the evaluation of the industrial viability and safety of any diazo transfer reagent or diazo compound should include DSC (and follow up ARC) to determine safe operating conditions.

Experimental Section

DSC Experimental Terminology: T_{init} is defined by the temperature at which the heat flow is measured to be > 0.01 W g^{-1} from the baseline. T_{onset} is defined by the intersection of the extrapolated maximum peak slope and the baseline. ΔH_D is obtained by integration of the peak.

Averaged DSC results reported where individual results have <2% difference from the average for T_{init} and T_{onset} and <10% difference from the average for ΔH_D. Where noted, if a melting point overlaps the decomposition, the melt endotherm was removed and blended with adjected data to allow T_{onset} and ΔH_D to be more accurately determined. In these cases, if T_{init} cannot be determined due to the melt endotherm, the temperature where the melt commences is used.

DSC Method A: DSC analysis was performed using a TA Instruments Q2000 DSC with Liquid Nitrogen Cooling System (LNCS). Approx 5 mg was accurately weighed to 1 d.p. into a reusable PerkinElmer B0182901 stainless steel high-pressure crucible with disposable gold-plated copper seal rated to 150 bar, and sealed under air with the appropriate B0182864 sealing tool. After equilibrating at 25 °C, samples were heated at 5 °C min^{-1} to a maximum temperature of 250 °C for diazo compounds and 300 °C for other compounds. Data analysis was conducted using TA Instruments Universal Analysis 2000 software version 4.5.0.5. Where noted, if a melting point overlaps the decomposition, the melt endotherm was removed and blended with adjected data to allow T_{onset} and ΔH_D to be more accurately determined. In these cases, if T_{init} cannot be determined due to the melt endotherm, the initiation temperature of the melt is used.

DSC Method B: DSC analysis was performed using a Mettler Toledo DSC 823e. Approx 5 mg was accurately weighed to 1 d.p. into a Mettler Toledo ME-26731 gold-plated 40 µl high-pressure crucible with seal insert and lid rated to 150 bar, and sealed under air with the appropriate sealing press. After equilibrating at 25 °C, samples were heated at 2 °C min^{-1} to a maximum temperature of 350 °C. Data analysis was conducted using Mettler Toledo STARe software version 12.00 build 5342.

TGA Method: TGA analysis was performed using a Mettler Toledo TGA/DSC 1LF/UMX. A tare weight was obtained for a Mettler Toledo 70 µl platinum crucible (open, medium, product no. 51119654) in the TGA before approx 30 mg was weighed into the crucible and reweighed in the TGA. A purge gas flow rate of 50 ml min^{-1} N_2 was used. After equilibrating at 25 °C, the sample was heated at 5 °C min^{-1} to a maximum temperature of 300 °C. The data was visualized with JMP Pro version 14.3.0.

ARC Method: Approx 3.5 g of sample was accurately weighed into a Hastelloy ARC test cell (or 'bomb'). The ARC test cell was placed in a Thermal Hazard Technology ES ARC and thermocouple attached by an equatorial clip. The experiment was performed using a heat-wait-search method starting at 40 °C and the test cell was heated in 5 °C increments to a maximum temperature of 280 °C, pressure of 35 bar or user intervention. At the end of the experiment, the ARC cools the test cell with compressed air. Data analysis was performed using Thermal Hazard Technology's ARCCal+ software v.1.6.2 which applies the Φ (phi) factor to correct the ARC thermal onset temperature and ATR results for the thermal inertia of the test cell using eq 7.

$$\Phi = 1 + (M_b \times C_b) + (M_{cl} \times C_{cl}) / (M_s \times C_s) \qquad \mathbf{7}$$

where M is mass (g); C is specific heat capacity (J kg^{-1} K^{-1}); b is the bomb (test cell); cl is the clip attached to the bomb and s is the sample. The TMR_{ad} (time to maximum rate under adiabatic conditions) was calculated from the ARC data at the exotherm onset using eq 8.

$$\mathrm{TMR_{ad}} = (t_{\max} - t_0) / \Phi \qquad \textbf{8}$$

where $t_{\max}$ is the time at the maximum self heat rate; and t_0 is the time at the start of the exotherm. The data was visualized with JMP Pro version 14.3.0.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

> DSC plots for all compounds, synthetic details, full table of Hammett σ parameters correlated to DSC results, abnormalities observed in DSC plots, full table of Yoshida correlation output for all compounds and ^{1}H and ^{13}C NMR spectra for **49** and **58**. (PDF)
> Full table of Yoshida and Pfizer-modified correlation output (Excel and JMP)

All characterization data for synthesized compounds, raw DSC data for all compounds, raw TGA data for **9** and raw ARC data for **9**, *p*-ABSA and ADT can be found at https://doi.org/10.14469/hpc/6274.

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Notes

The authors declare no competing financial interest.

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(7) Though thermal stability or impact sensitivity are most commonly used to define an unstable subtance, there are a number of other sensitivities which can be considered. Friction sensitivity is measured by placing the material between two plates and applying a defined load in a back-and-forth motion. Electrostatic discharge (ESD) sensitivity is measured with an applied electrical flow. Both tests are less common than impact sensitivity and suffer from more reproducibility issues.[4] Some energetic compounds can also exhibit instability to light. Experimental values will be

reported in the SI where they exist but due to the lack of available data and variability concerns will not be commented on further.

(8) If a combustion reaction is autocatalytic (or self-sustaining) a decomposition front is observed, where the energy released from exothermic decomposition of a molecule triggers decomposition of adjacent molecules, propagating through the material. Both TNT and wood can be considered materials with high energy content but differ in the velocity of a decomposition front. The decomposition is defined as deflagration (burning) if the front is subsonic, or detonation if the front moves faster than the speed of sound, creating a shockwave. This is measured by a variety of specialist tests, such as the Mk. III Ballistic Mortar; a sample of primary explosive such as PETN is placed in a shell containing the test material and detonated. If the shockwave can initiate detonation of the test material, it can be considered an explosive. As most chemists will not have access to this testing, Bodman and Chervin developed an alternative screening test using a modified ARC with ultra-fast pressure sensing in the sample capsule. [a) Bodman, G. T.; Chervin, S. Use of ARC in Screening for Explosive Properties. *J. Hazard. Mater.* **2004**, *115*, 101–105.] Upon decomposition, the maximum rate of pressure rise can be measured and considered versus known explosive samples: >20,000 bar/min would be considered worthy of further testing, specified in the UN Treaty on the Transport of Dangerous Goods.[3a,9]

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(84) Phlegmatization (or desensitization) is when a sensitive material is diluted in solvent or plasticizer to reduce the sensitivity. In this case, the sulfonyl azide is never handled out of solution and thus at far lesser risk of detonation.

(85) Distinct endotherms were observed from gas loss when the DSC experiment was conducted in an unsealed crucible.

(86) The initial drop in heat flow is an artefact from using the heavier high-pressure crucibles, which are required to avoid energy loss when gas is evolved. For more details, see: Thomas, L. C. *Interpreting Unexpected Events and Transitions in DSC Results*; TA039, 1-5. Retrieved from http://www.tainstruments.com/pdf/literature/TA039.pdf, August 2018.

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(89) The threshold was defined based on borderline sensitive *m*-DNB with a degree of conservatism. This plot was repeated for substances known to propagate an explosion (detonate) and those that cannot, defined by borderline explosives ammonium nitrate and 90% benzoyl peroxide in water.

(90) It is important to note this prediction only relates to the neat substance and does not preclude these compounds exploding if decomposition is trigged in a sealed vessel or reaction mixture, due to the significant amounts of heat and gas evolved.

(91) The rates of temperature and pressure rise are exponentially linked to sample size, so the rate data is only comparable to other ARC tests with the same sample size. For rates above 1,000 °C min^{-1}, there is a large margin of error due to the limits of detection speed. The same is true for large pressure rise rates.

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