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Comparison of the thermal stability of diazonium salts and their corresponding triazenes

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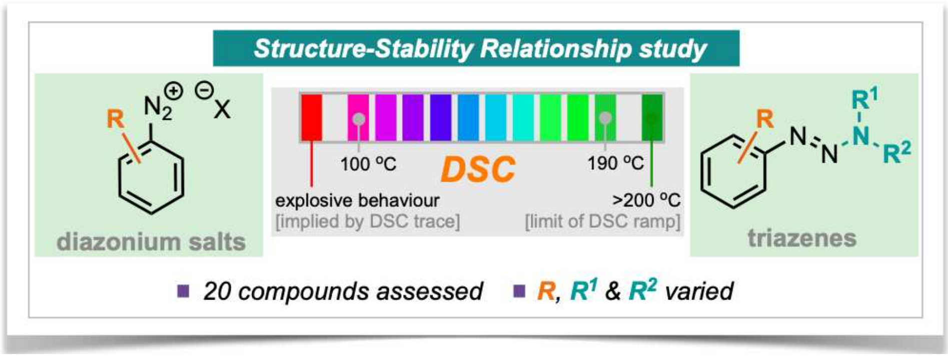

ABSTRACT A range of diazonium salts and their corresponding triazenes have been prepared in order to directly compare their relative thermal stabilities (via initial decomposition temperature) from differential scanning calorimetry (DSC) data. A structure-stability relationship (SSR) has been explored to investigate trends in stability, depending on the aromatic substituent and the structure of the secondary amine component of the diazonium salts and triazenes. All triazenes investigated show significantly greater stability (in many cases stable above 200 °C) compared to the corresponding diazonium salts, which show varying stabilities.

KEYWORDS triazene, diazonium salt, thermal stability, DSC, continuous processing

INTRODUCTION Diazonium salts are important intermediates in synthetic chemistry as they permit functionalization or transformation at the attached aromatic carbon. Consequently, many transformations utilizing diazonium salts have been developed.[1-3] However, variability in the stability of diazonium salts renders their use at large scale problematic.[4, 5] The stability of diazonium salts ranges from excellent to explosive, though very few are in the latter category. Nonetheless, the existence of some explosive compounds raises caution and concern, which provides motivation for the development of alternative synthetic route design to avoid diazonium salt chemistry. The isolation of some diazonium salts can be especially hazardous as they are shock sensitive and decompose readily, while aryl diazonium tetrafluoroborate, tosylate, disulfonimide or carboxylate salts are often deemed stable for isolation, depending on the substituents on the aromatic ring.[6-10] The thermal instability of diazonium salts and the evolution of large volumes of nitrogen gas upon decomposition is a particular issue for industrial scale syntheses and it is important to understand and control these reactive intermediates.[11] This issue has led to the development of a number of continuous flow procedures in which diazonium salts are made and consumed *in situ*.[12, 13] The increased temperature control and presence of only small amounts of reactive diazonium salt at any one time makes this way of processing inherently safer.

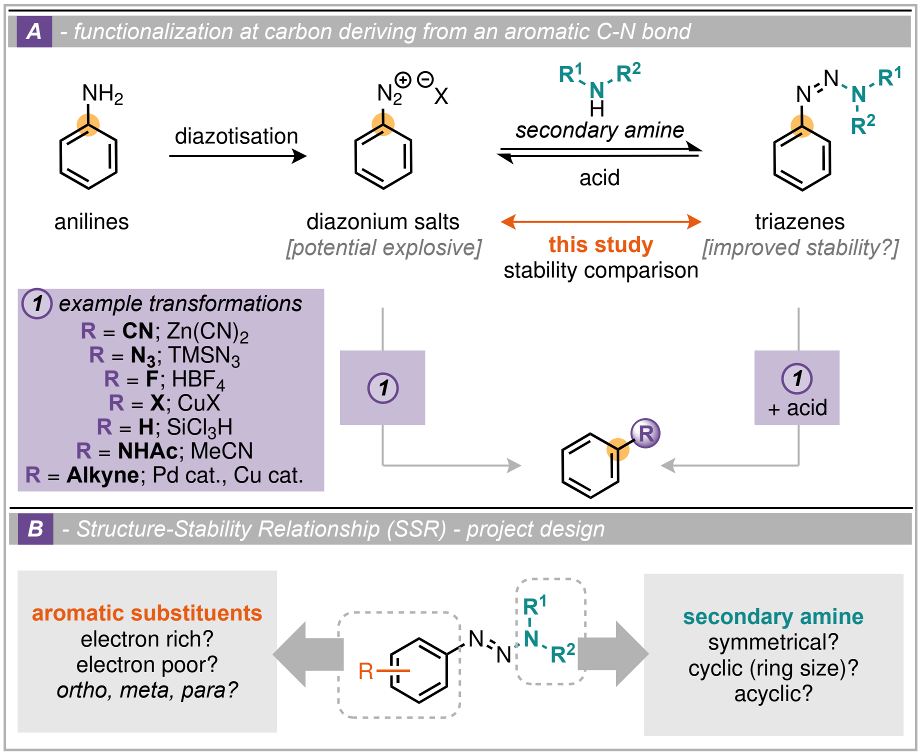

Figure 1 Overview of the reactivity of diazonium salts and triazenes and the structure-stability relationship project design

Another tactic for manipulating diazonium salts is to protect them in the form of a triazene (Figure 1).[14-20] Triazenes can be prepared by protecting diazonium salts with a secondary amine, leading to products which exhibit very similar reactivity to diazonium salts.[21] Typically, under acidic conditions, triazenes re-establish the reactivity exhibited by the parent diazonium salt through an on-off equilibrium. While the diazonium compound is still present in this situation, it is never isolated in dry form and thus no shock sensitivity is encountered. Hence, triazenes participate in much of the reactivity already established for diazonium salts, as long as a Lewis or Brønsted acid is present, but with reduced risk and hence greater safety. Triazenes have also been used as directing groups for metalation reactions and as linkers in solid-phase synthesis as they are usually stable towards alkylating agents, strong bases, oxidation and reduction. Furthermore, most importantly, they are bench stable.[8, 15, 17, 18, 22-29]

Whilst it is widely accepted that triazenes offer improved thermal and shock sensitivity compared to the corresponding diazonium salts, we have been unable to find any systematic studies of structure-stability relationship trends between these two species. Herein, we report a preliminary study towards establishing such structure-stability relationships. Our project design features the preparation of a set of tetrafluoroborate diazonium salts bearing electron rich, electron poor and *ortho*, *meta* and *para*-substituents, together with the corresponding triazenes. In the triazene series, the secondary amine component could also impact the stability of these materials, so a range of secondary amines has been designed, encompassing examples that are cyclic (with different ring sizes), acyclic, and with different symmetries. A few reports have measured decomposition energies and decomposition temperatures of triazenes but have not compared them directly to those of the corresponding diazonium salts in a systematic manner. Lippert *et al.* showed that the decomposition temperature of triazenes decreases with the electron withdrawing capacity of the substituents on the aromatic ring, whereas the steric properties of the amine do not have a strong influence.[30] Döbele *et al.* used triazenes for the formation of aryl fluorides via the Wallach reaction and measured DSC data for one of their triazene precursors to demonstrate the high stability of triazenes.[31] Although the stability of triazenes compared to their diazonium salts is mentioned in most publications, no direct comparison of their relative stabilities has been established.

RESULTS AND DISCUSSION The designed compounds were synthesized using known methods. The diazonium salts (**2a** to **8a**) were prepared on small scale in batch by first treating the corresponding anilines to boron trifluoride diethyletherate followed by addition of isoamyl nitrite. Diazonium salt **1a**, derived from anthranilic acid, was not prepared as it is known to be a contact explosive.[32-38] The triazene compound series was prepared using a telescoped continuous flow process optimized to generate and consume the diazonium salt *in situ* while avoiding precipitation of the intermediate diazonium salt (Figure 3).[39-41]

The degradation temperature of each compound has been assessed using Differential Scanning Calorimetry (DSC). DSC is a thermo-analytical technique in which a sample and a reference (typically an empty sample holder) are heated or cooled at constant rate. The mode of operation differs for different types of DSC instrument (e.g., power-compensated DSC or heat-flux DSC), but the basic principle is that the instrument attempts to maintain the sample and reference at the same temperature throughout the heating/cooling process by varying the amount of heat that the instrument exchanges with the sample and with the reference, or by allowing heat exchange to occur between the sample and the reference. As the present work is focused on studying sample degradation at high temperature, the DSC experiments involved heating the sample (and reference) from 20 °C to a temperature in the range of 160 - 250 °C at a rate of 20 °C min^{-1}. If an endothermic or exothermic process occurs in the sample, the amount of energy required to heat the sample differs from the amount of energy required to heat the reference. For example, during an endothermic process in the sample (e.g., melting), the energy supplied to the sample must increase in order to maintain the sample and reference at the same temperature; conversely, during an exothermic process in the sample (e.g., decomposition), the energy supplied to the sample must decrease in order to maintain the sample and the reference at the same temperature. In the DSC data shown here and in Supporting Information, endothermic processes appear as negative peaks (increased heat flow to the sample) while exothermic processes appear as positive peaks (decreased heat flow to the sample). In the present work, significant exothermic events are assigned as compound degradation.[30, 42] For some of the samples studied, the DSC data exhibit overlapping peaks due to the occurrence of different thermal events, which complicates the extraction of peak onset temperatures. For this reason, our analysis of exothermic peaks assigned as decomposition is focused on the initial decomposition temperature rather than the onset temperature (see Figure 2). It is important to note that, for a given sample, the initial decomposition temperature will vary depending on the heating rate used in the DSC measurement. However, as the DSC data for all samples studied here were recorded at the same heating rate (20 °C min^{-1}), differences in the initial decomposition temperature between different samples provide a reliable qualitative indication of their relative thermal stabilities.

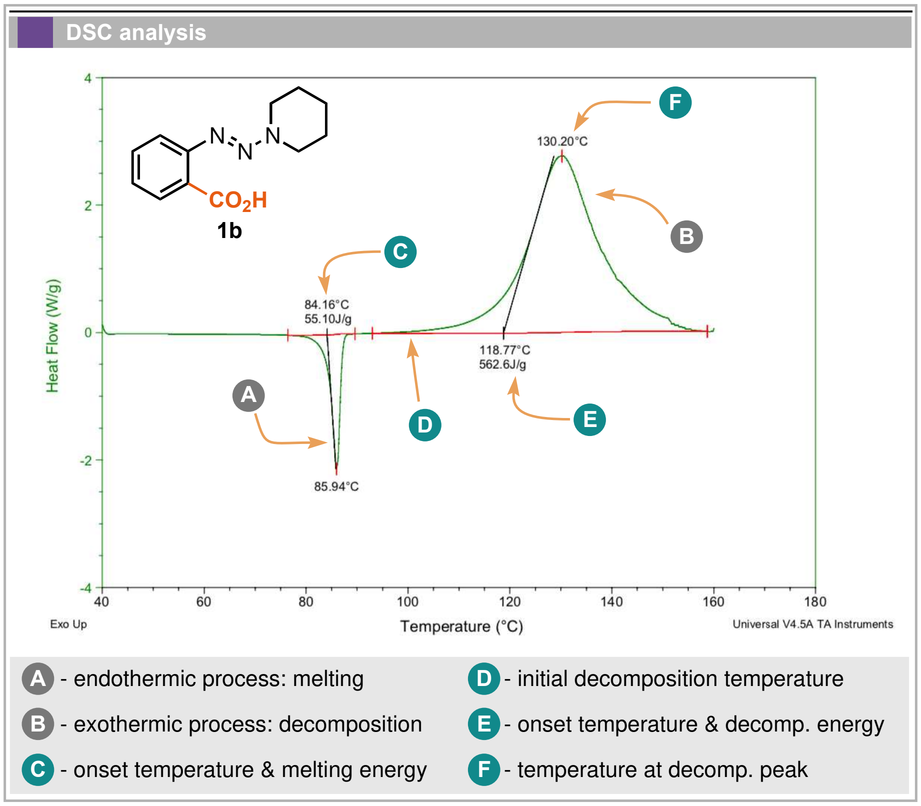

Figure 2 Representative DSC data for the anthranilic acid derived triazene **1b**

Our ^{13}C NMR data for the triazene series suggest that these molecules undergo restricted rotation, as previously reported for such materials (i.e., variable temperature ^{13}C NMR experiments demonstrate temperature-dependent coalescence behaviour).[30, 43-50] There is inconsistency in the manner in which this issue is reported in the literature – in some cases, the observation of fewer ^{13}C environments than expected is not even addressed, while other cases simply note that the NMR data are inconsistent with the proposed structure (with reference to the restricted rotation phenomenon). To address this issue more rigorously, the present paper reports ^{13}C NMR data at three different temperatures for each triazene studied (see Supporting Information), and we also demonstrate how these temperature-dependent ^{13}C NMR data can be used to calculate the rotational energy barrier in the case of triazene **8b**.

Initial decomposition temperatures derived from the DSC measurements are presented in Figure 3 (with further analysis discussed in the Supporting Information), revealing some key observations both within and between the different compound series. To aid interpretation, the results in Figure 3 are colour coded on a scale from red (low decomposition temperatures or explosive behaviour) *via* blue to green (higher decomposition temperatures). We note that, instead of degradation, the diazonium salts may undergo a Balz-Schiemann reaction with the release of nitrogen gas, boron trifluoride and formation of the corresponding aryl fluoride.[51] In the present study, the occurrence of the Balz-Schiemann transformation is regarded as a decomposition pathway. Among the seven diazonium salts studied by DSC analysis, the results in two cases (**2a** and **8a**) are considered as potentially indicative of Balz-Schiemann processes; on heating these materials, a melting endotherm is followed by an exothermic or an endothermic Balz-Schiemann reaction, which is followed by an endothermic phase change (boiling) of the product aryl fluoride at higher temperature (we note that the boiling points of the corresponding aryl fluorides are below the temperatures at which the Balz-Schiemann process occurs, congruent with this interpretation). Three of the other five diazonium salts (**3a**, **4a** and **6a**) undergo a melting endotherm, which is quickly followed by an exothermic decomposition; this sequence of thermal events is consistent with the melting behaviour of those previously studied, which are reported to exhibit "decomposition on melting".[52] Of the remaining two diazonium salts, one (**5a**) does not decompose below 200 °C and the other (**7a**) decomposes in a manner congruent with a "thermal runaway".

Some general observations can also be made with regard to the triazene series. The triazenes that are solid at room temperature all exhibit a melting endotherm below 100 °C, and in most cases below 60 °C; in contrast, the triazenes that are liquids at room temperature do not show this endothermic transition in the DSC data. Typically, the triazenes do not decompose below 200 °C. However, some of the triazenes exhibit broad exotherms below 200 °C that are assigned as degradation, including compound **1b** (initial decomposition temperature *ca.* 100 °C) and compounds **3c** and **3f** (initial decomposition temperatures *ca.* 150 °C). The actual decomposition pathways for these triazenes are not yet assigned; however, the Balz-Schiemann reaction can be ruled out as no fluoride source is present in the preparation of these materials. For five of the triazenes (**2b**, **4b**, **5b**, **6b** and **3e**) a broad endothermic event is observed, which is consistent with evaporation of a liquid phase. In three of these cases (**2b**, **4b** and **6b**), the material is a solid at room temperature; on heating the solid, a sharp endotherm is observed due to melting, followed by the broad endothermic event. In the other two cases (**5b** and

3e), the material is already a liquid/oil at room temperature, and the broad endotherm is the only thermal event observed below 200 °C.

Comparison between the whole diazonium salt series and the whole triazene series highlights that the triazenes are more stable than the corresponding diazonium salts with respect to thermally induced degradation (i.e. more compounds in the triazene series are colour coded green). This difference is particularly notable between **1a** and **1b**, for which the anthranilic acid derived triazene (**1b**) is isolable and not shock sensitive, and degrades in a controlled exothermic process with initial decomposition temperature *ca*. 100 °C; in contrast, the corresponding diazonium salt (**1a**) is explosive, as noted above. Direct comparison between the set of 'a' compounds (diazonium salts) and the corresponding 'b' compounds (triazenes) highlights the greater stability of the triazene molecules.

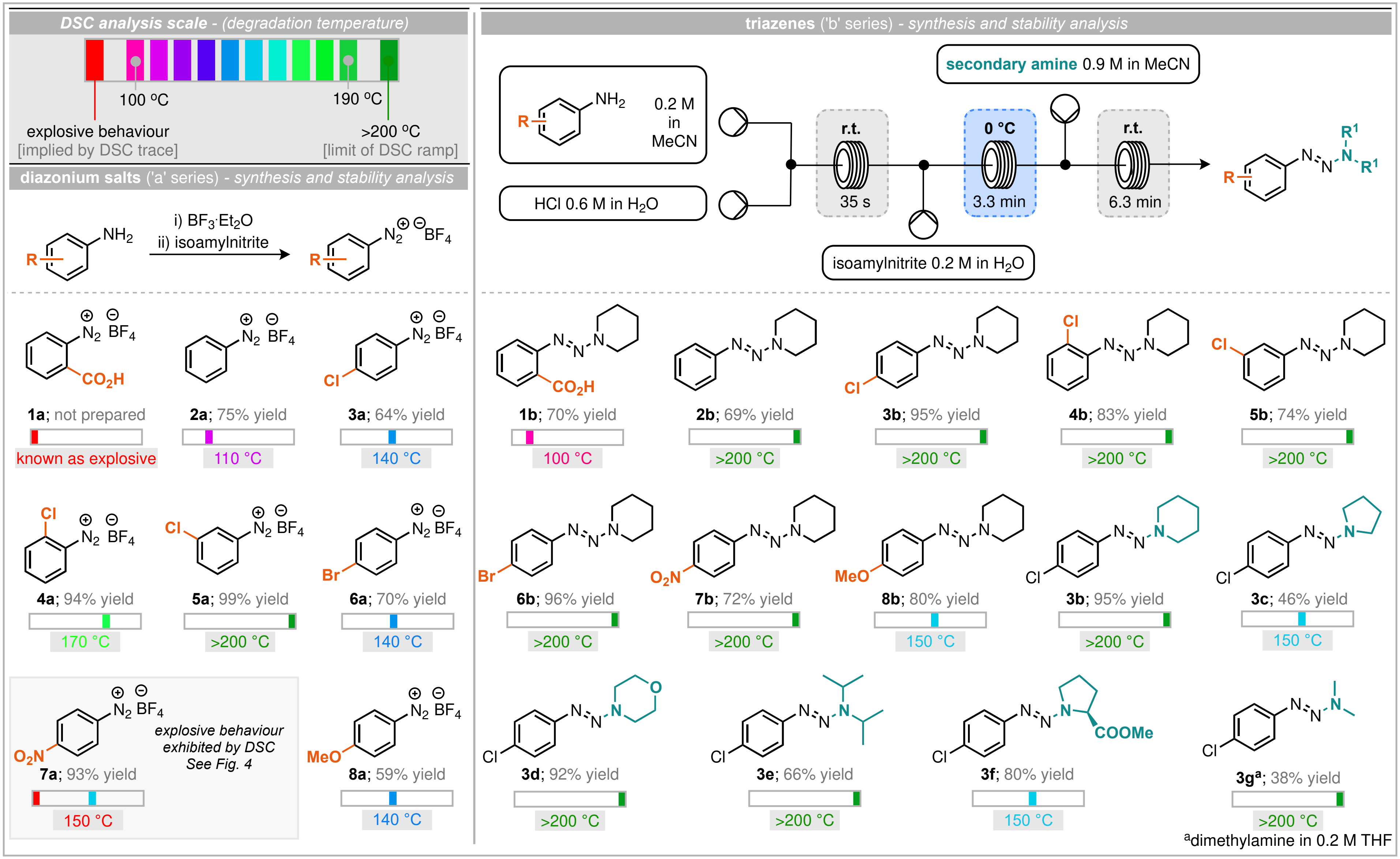

Figure 3 Synthesis and initial decomposition temperature (assigned from DSC data) for the diazonium salt ('a') series and the triazene ('b') series. Accuracy of temperature = ±5°C

With regard to aromatic substituents, the sample set is too small to draw firm conclusions, but comparison of the results for the three mono-chloro anilines (*para-, ortho-* and *meta-*; **3a**, **4a** and **5a**, respectively) points towards increased stability within the diazonium series for *meta*-substitution, with thermal stability above 200 °C for **5a**. The corresponding triazenes (**3b**, **4b** and **5b** respectively; with piperidine as secondary amine) show increased stabilities (decomposition >200 °C). The same trend in relative stability is observed for the *para*-bromo substituted diazonium salt (**6a**, initial decomposition temperature of 140 °C) *versus* the corresponding piperidine triazene (**6b**, decomposition temperature above 200 °C). The electron rich *para*-methoxy substituted diazonium salt (**8a**) degrades at a lower temperature (140 °C) than its triazene congener, although in this case it appears that the *para*-electron donating group present in **8b** leads to increased instability leading to a broad exothermic decomposition with an initial temperature of 150 °C. The electron poor *para*-nitro substituted diazonium salt **7a** is rendered significantly more thermally stable in its piperidine triazene form, **7b**. In the case of **7a**, the initial decomposition temperature is 150 °C (Figure 4); however, the exothermic peak in the DSC data in this case is sharp and leans towards higher temperatures, indicative of an uncontrollable exothermic event corresponding to thermal runaway during decomposition. Although a different DSC heating ramp may mask this behaviour, for ease of comparison, all compounds in this study were assessed using an identical DSC ramp protocol (with heating at 20 °C/min) and **7a** was the only compound to show such behaviour. Notably, the corresponding triazene (**7b**) exhibits two endothermic events (Figure 4), probably arising from residual solvent evaporation followed by a phase transition (melting), with no decomposition exotherm observed up to the highest temperature (200 °C) studied. For the triazene series bearing different secondary amines (**3b-3g**; Figure 3), pyrrolidines (**3c** and **3f**) appear to have reduced stability compared to other secondary amines, including both acyclic and cyclic examples. Nonetheless, when compared to the parent diazonium salts, the triazenes have greater stability. Clearly, a larger data set would allow the dependence of stability on the specific nature of the substituents to be explored in greater depth.

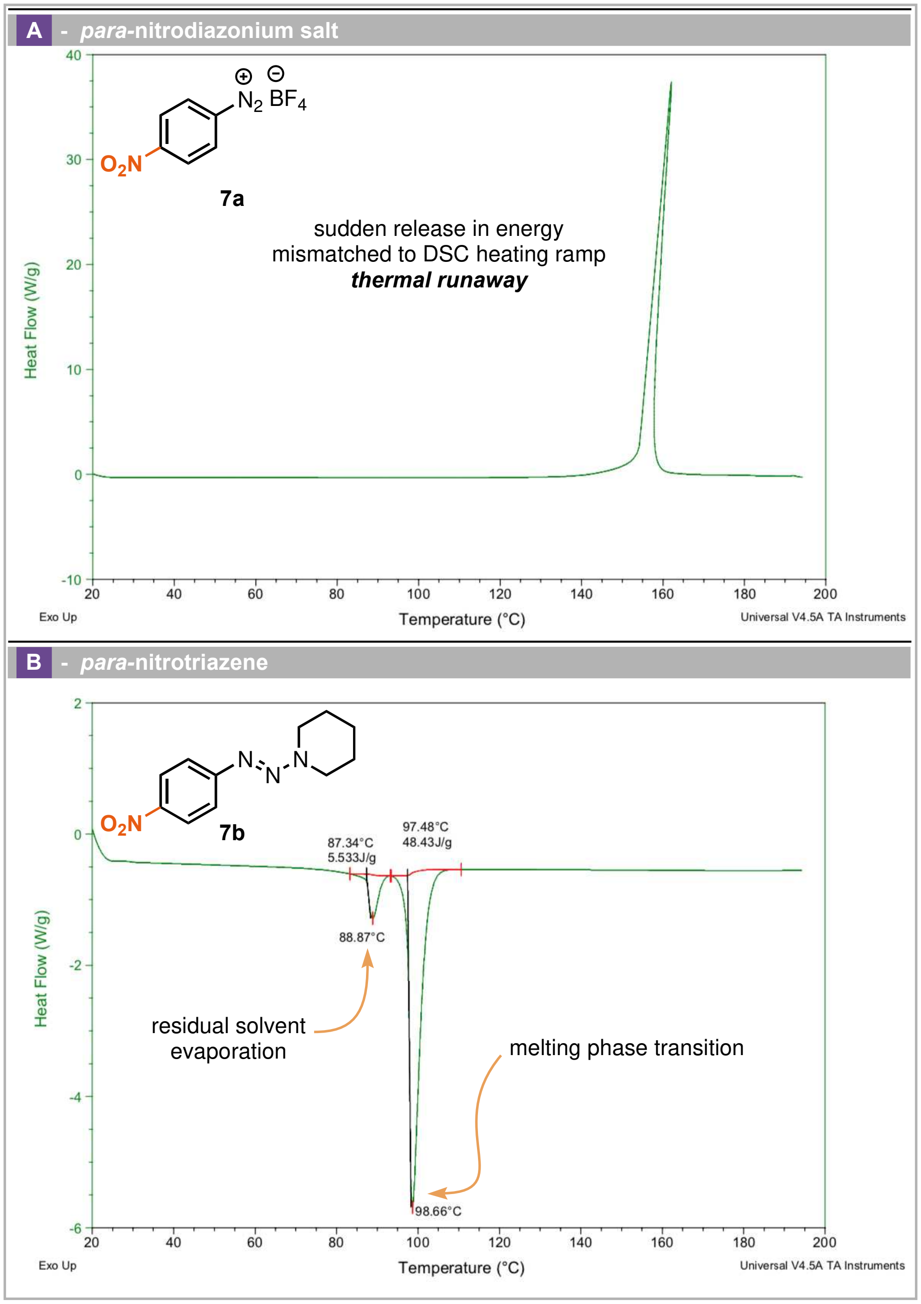

Figure 4 DSC data for the *para*-nitrodiazonium salt (**7a**) and the *para*-nitrotriazene (**7b**)

CONCLUSION The structure-stability relationship study reported here has compared the decomposition of a series of diazonium salts *versus* the decomposition of the corresponding triazenes. We have demonstrated that triazenes derived from treatment of their diazonium salt congeners with piperidine leads to materials with enhanced stability, although preliminary studies suggest that this may not be true for electron-rich systems. Moreover, the improved stability appears applicable to a range of secondary amines, with those based on a pyrrolidine motif exhibiting reduced stability in comparison to other triazene systems. However, the number of materials studied here is insufficient to allow more precise conclusions on structure-stability relationships to be derived. The continuous flow method used to prepare the triazenes in this work obviates the requirement for large scale preparation of diazonium salts and thus delivers triazenes as worthy candidates when planning synthetic routes requiring functionalization at the carbon of an aromatic C-N bond. Future work will investigate a larger matrix of compounds with regard to both the aromatic substituents and the secondary amine components.

ASSOCIATED CONTENT

Supporting Information. Supporting Information Electronic Supplementary Material (ESM), including compound characterization and copies of NMR spectra, is available in the online version at doi: XX.

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AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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