Protected Diazonium Salts: A Continuous-Flow Preparation of Triazenes Including the Anticancer Compounds Dacarbazine and Mitozolomide

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Received: 20 May 2016; accepted: 13 June 2016

Herein, we report a continuous-flow process for the preparation of triazenes, whereby diazonium salts are generated and converted into their masked or protected triazene derivatives. Key to realizing the process, which is applicable to a wide range of substrates, is the identification of solvent and reagent parameters that avoid fouling and clogging in the tubing used in these studies. The process has also been applied to prepare the antineoplastic agents mitozolomide and dacarbazine. We also report isolation and differential scanning calorimetry (DSC) analysis of an anthranilic acid-derived triazene whose related diazonium salt is a contact explosive. The data highlights improved stability but also suggests that an exothermic process does occur with an onset temperature of 118 °C. Finally, an 18-hour continuous operation of the reaction procedure using high-performance liquid chromatography (HPLC) pumps is reported.

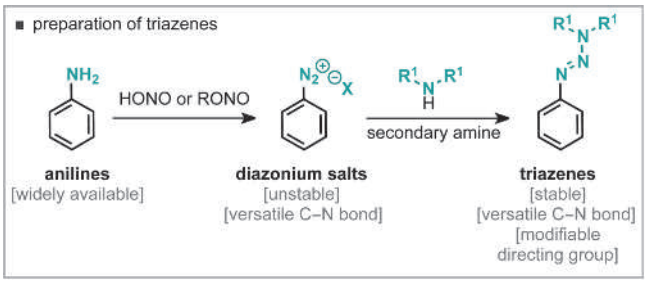
Keywords: triazenes, diazonium, salts, anti-cancer, compounds

1. Introduction

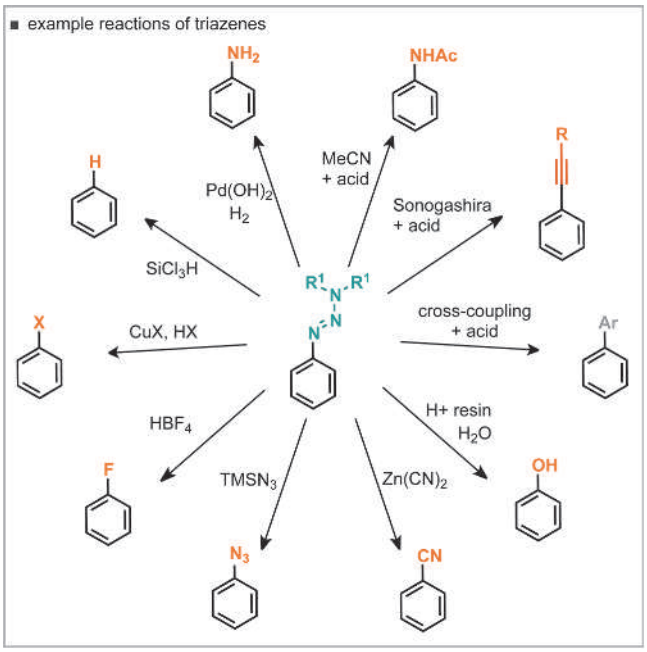
Chemical functional groups containing nitrogen are ubiquitous across the physical and biological sciences. Indeed, nitrogen and the amine functional group in particular are present in a large number of products from commercial suppliers of fine chemicals. However, it is notable that there are still very few methods for the activation and use of a C–N bond as a tool for the construction of more complex molecules, with the formation and use of diazo- and diazonium compounds being the most widely adopted process to achieve this goal [1]. However, there are several drawbacks to the use of diazonium compounds, not the least of which include the associated safety hazards that are well documented particularly with isolating these intermediates [2]. Unsurprisingly then, the formation and use of diazo- and diazonium compounds have been well explored under continuous-flow conditions, and indeed, this research continues to produce exciting results and is clearly a rich seam which will be further explored [3, 4]. An alternative method for the safe handling of diazonium compounds is to trap them as their more stable and protected triazene forms by reaction with a secondary amine (Scheme 1) [5].

Triazenes themselves are an exciting class of compounds displaying much of the reactivity of diazonium salts, but in recent years also being demonstrated to direct catalytic or stoichiometric metalation reactions [6, 7]. Under acidic conditions, triazenes exist in equilibrium with their diazonium congeners; thus, their use as a protecting group is reversible to unveil the latent reactivity of a diazonium compound. Thus, triazenes can be converted to the corresponding azides by treatment with a Lewis acid and $TMSN_3$ (Scheme 2) [6a]. Alternatively, the diazonium can be unveiled and then participate in palladium coupling chemistries such as Sonogashira, Suzuki, and amino-carbonylation reactions — with all of these processes occurring in one-pot operations from the triazene material [6b–e]. Traditional Sandmeyer chemistry can be conducted using the appropriate copper salt with addition of acid [6f]. The Balz–Schiemann fluorination reaction is also applicable where treatment with HBF_4 provides the desired transformation [6g]. With regards to directing metalation reactions, triazenes have been successfully used to guide *ortho*-deprotonation using *sec*- or *tert*-butyllithium (Scheme 3). In the former case, carbon dioxide was used as a quench, leading indirectly to anthranilic acid-derived triazenes, whereas, in the latter case, the lithium was transmetalated to magnesium and then added to a cyclobutanone intermediate on the way towards the synthesis of welwitindolinone A isonitrile [7a]. More recently, Hafner and Bräse demonstrated that a silver-mediated trifluoromethylation reaction was directed to the *ortho* position by the triazene handle

Scheme 1. Preparation of triazenes from diazonium compounds



Scheme 2. Examples of the conversion of triazenes to other functional groups



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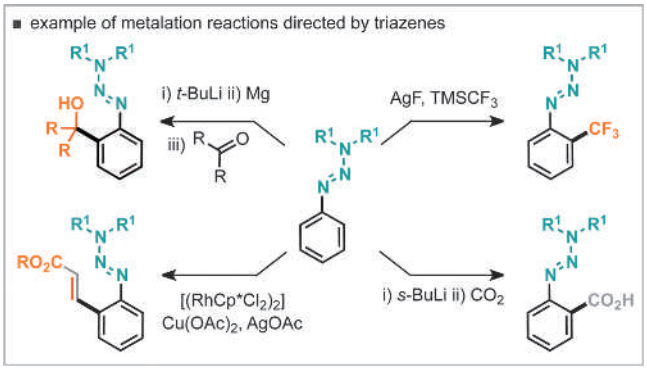
DOI: 10.1556/1846.2016.00025

First published online: 26 July 2016

Scheme 3. Examples of the use of triazenes to direct metalation reactions



[7b], while Huang showed that Rh (III) can be used to catalyze C–H olefination reactions *ortho* to a triazene directing group [7c].

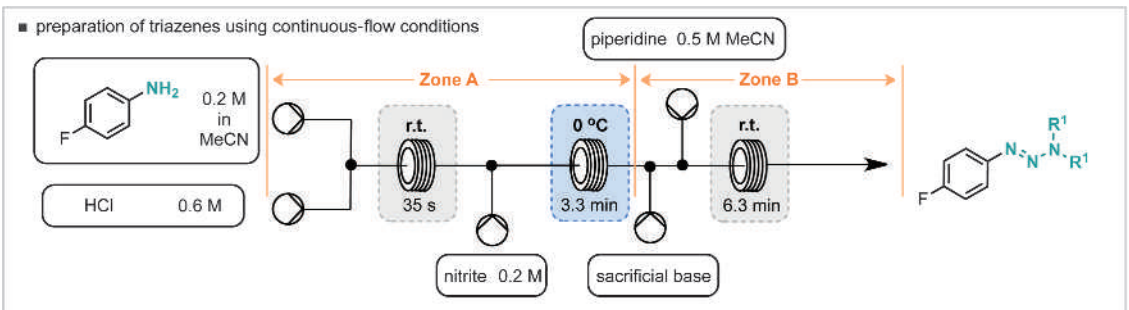
Therefore, the most exciting facet of the triazene functional group is the combination of these properties, whereby they can be installed starting from a wide variety of commercially available anilines and then used to direct controlled and selective catalytic C–H functionalization processes before being removed under acidic conditions to participate in diazonium type reactivity. Owing to this, they have been classified as a "functionalizable or modifiable directing group" [8].

Continuous-flow processing is suited for the preparation of hazardous intermediates such as diazonium compounds because they can be made and consumed within the same reactor series [9]. Thus, the total of hazardous material at any one point in time is very small. It is equal to the volume of the "hot-section" ("hot" being used to describe the section of tubing between the formation and consumption of the hazardous material) multiplied by the concentration. If the reactor is operating under segmented flow conditions where the segment volume is less than that of the "hot volume," the volume of hazardous material is just determined by the volume of the segment. In any case, the total volume of hazardous material is small. In batch mode, however, the quantity of hazardous material per unit time is directly related to the bulk reaction volume. At scale, therefore, the bulk preparation of a hazardous and potential explosive intermediate is a huge risk that could be mitigated by conducting the reaction under continuous conditions. While triazenes are protected forms of diazonium salts, they are most commonly accessed through a batch-wise preparation of the diazonium followed by quenching with a secondary amine; thus, the hazard still exists and has the opportunity to present itself during the process. We were therefore interested in establishing a multistep flow process [10] for the in situ diazotization of amines and subsequent trapping as a triazene functionality that could then be further manipulated or stored.

2. Results and Discussion

2.1. Initial Setup. From the outset, we were mindful that one of the key challenges for establishing a flow process for this chemistry would be identifying optimal solvent combination ratios to avoid precipitation and fouling of the tubular reactors [11]. This was especially true as there are some reports that highlight the possibility for diazonium salts to precipitate and behave as contact explosives [2a]. Specifically, a survey of the literature methods for the batch preparation of triazenes highlighted a common factor of the use of a mineral base in combination with the basic secondary amine of interest [6, 7]. The mineral base (such as K_2CO_3) is typically added to neutralize the acidic conditions necessary for the diazonium forming reaction with the amine and then present solely as a reactant to feature in the product. The mineral base is therefore sacrificial in nature. As shown in Scheme 4, our initial setup consequently consisted of the merging of five streams to a common flow line to effect two reactions: first, the diazotization of the aniline by combining with an acid and a nitrite followed by passage through a small cooled reaction coil (Scheme 4, zone A) and, second, neutralizing this with a sacrificial base and merging with the required amine and passing through another reaction coil (Scheme 4, zone B) to form a triazene. It was found that the use of isoamyl nitrite rather than sodium nitrite meant that acetonitrile instead of water could be incorporated as a solvent within our reactor and keep materials in solution (Scheme 4 cf. entries 1 and 2). We then explored the behavior in zone B and found that the addition of an aqueous solution of a mineral base (K_2CO_3) leads to rapid precipitation at the T-piece due to insolubility in the diluted organic solvent. We conducted some observational batch experiments to identify conditions that would lead to homogenous mixtures yet still afford good conversion (using ^{19}F nuclear magnetic resonance (NMR) as a conversion guide). It was found that the use of Et_3N as base avoided precipitate formation but also resulted in complex

Scheme 4. Initial reactor setup and optimization of conditions



Entry	Setup	Nitrite Source/Solvent	Sacrificial Base/Solvent	Observations
1	zone A only	$NaNO_2$ in H_2O	–	precipitate formed
2	zone A only	isoamyl nitrite in MeCN	–	no precipitate formed
3	zone A + B	isoamyl nitrite in MeCN	K_2CO_3 in H_2O	precipitate formed in zone B
4	batch flask	isoamyl nitrite in MeCN	$NaHCO_3$ in H_2O	precipitate formed - triazene formed
5	batch flask	isoamyl nitrite in MeCN	Et_3N in MeCN	no precipitate formed - complex mixture
6	batch flask	isoamyl nitrite in MeCN	DMAP in MeCN	no precipitate formed - triazene formed
7	batch flask	isoamyl nitrite in MeCN	piperidine in MeCN	no precipitate formed - triazene formed
8	**zone A + B**	**isoamyl nitrite in MeCN**	**piperidine in MeCN**	**no precipitate formed - triazene formed - 48% yield**

mixtures as observed by ^{19}F NMR of the crude reaction material. Conversely, both dimethylaminopurine (DMAP) and piperidine provided positive results in both homogeneity and NMR analysis. Therefore, piperidine was chosen as both the sacrificial base and the amine nucleophile and, thus, delivered via a single pump in a total of 4.5 equivalents. Under continuous conditions, this afforded a 48% isolated yield of the triazene product without any solids formation (**2**). The sub-optimal yield in this particular case is due to a competing nucleophilic aromatic substitution reaction where the triazene is acting as a *para*-electron-withdrawing group to the fluorine leaving group with a piperidine nucleophile.

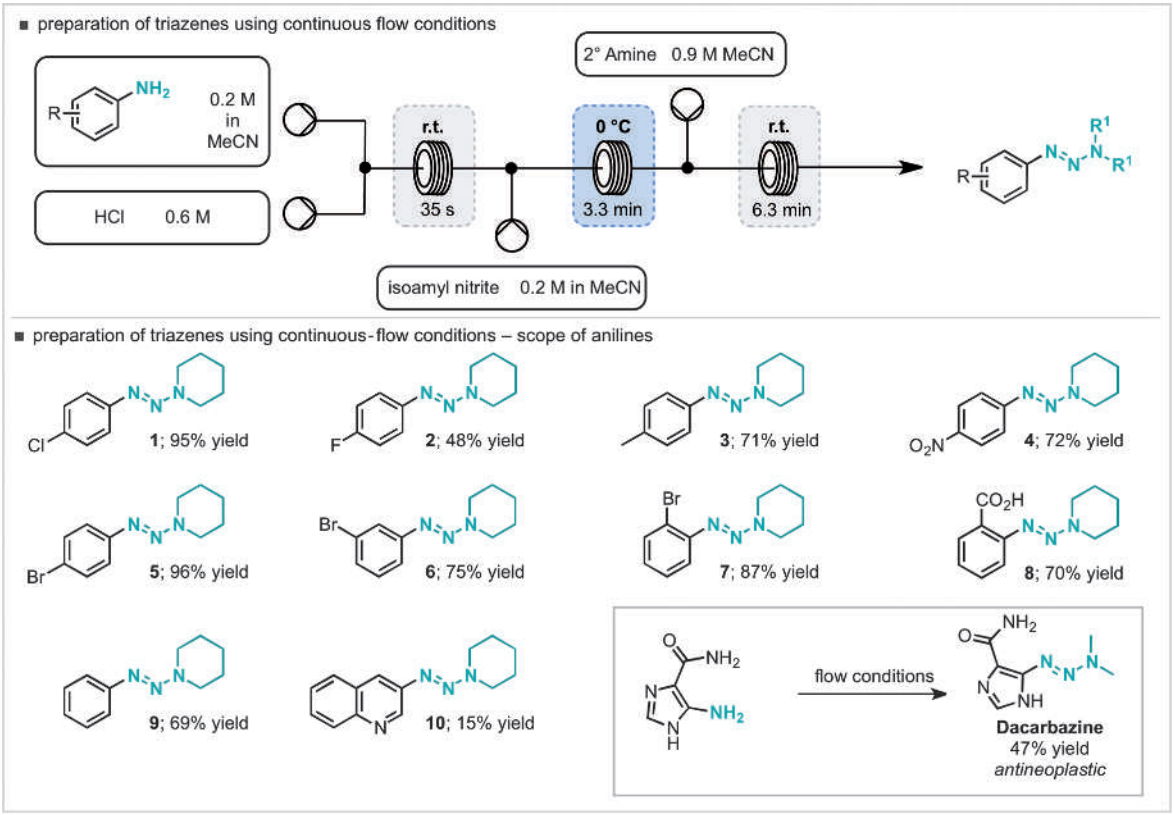
2.2. Aniline Scope. With these conditions in hand, the setup was used next to investigate the scope of the process with respect to aniline — paying particular attention to problems associated with fouling or clogging arising from covering a cross-section of substrates (Scheme 5). Initially, it was found that the *para*-chloroaniline underwent the continuous process without incident, and indeed, in this case, an improved yield of 95% (**1**) was isolated, supporting the notion of a competing S_NAr process for the fluoro derivative. It was found that a range of halogen bearing anilines all proceeded in good isolated yield without incident in the reactor, including *ortho*-, *meta*-, and *para*-bromo-anilines (**5**, **6**, and **7**). Notably, the workup of the products is very straightforward with a simple liquid–liquid extraction affording products that were typically greater than 90% purity. *para*-Nitro aniline did not proceed as straightforwardly as other examples, also likely arising from S_NAr type reactivity but, this time, with N_2 gas as the leaving group of the diazonium intermediate. Indeed, outgassing, leading to segments of gas and liquid, was visible in this example. However, an isolated yield of 72% of the desired triazene (**4**) could be achieved following column chromatography.

Most notably, the triazene of anthranilic acid (**8**) was directly made using flow conditions. The diazonium salt of which is known to lose nitrogen and carbon dioxide gas to generate benzyne in situ which can react exothermically if adequate temperature control is not provided. During the course of this work, we have been unable to find experimental literature evidence as to the stability of triazenes compared to diazonium counterparts. Much literature cites that these materials are stable, and we have not found reports of them being explosive. While a lack of data suggests that they are inherently more stable (literature is available on this topic for diazonium salts), it does not afford hard evidence. We therefore decided to run differential scanning calorimetry (DSC) of the anthranilic acid-derived triazene (**8**). This material was found to be readily isolated with a workup procedure following that of the other triazene examples prepared. The DSC data (Scheme 6) show that this triazene has an endothermic phase transition (melting) with an onset temperature of 84 °C; this is followed by a strongly exothermic process that is 10 times bigger than the melting phase change with an onset temperature of 118 °C. Notably, this exotherm is broad in shape and heating does not accelerate which signifies that this is not a runaway or sudden energy release.

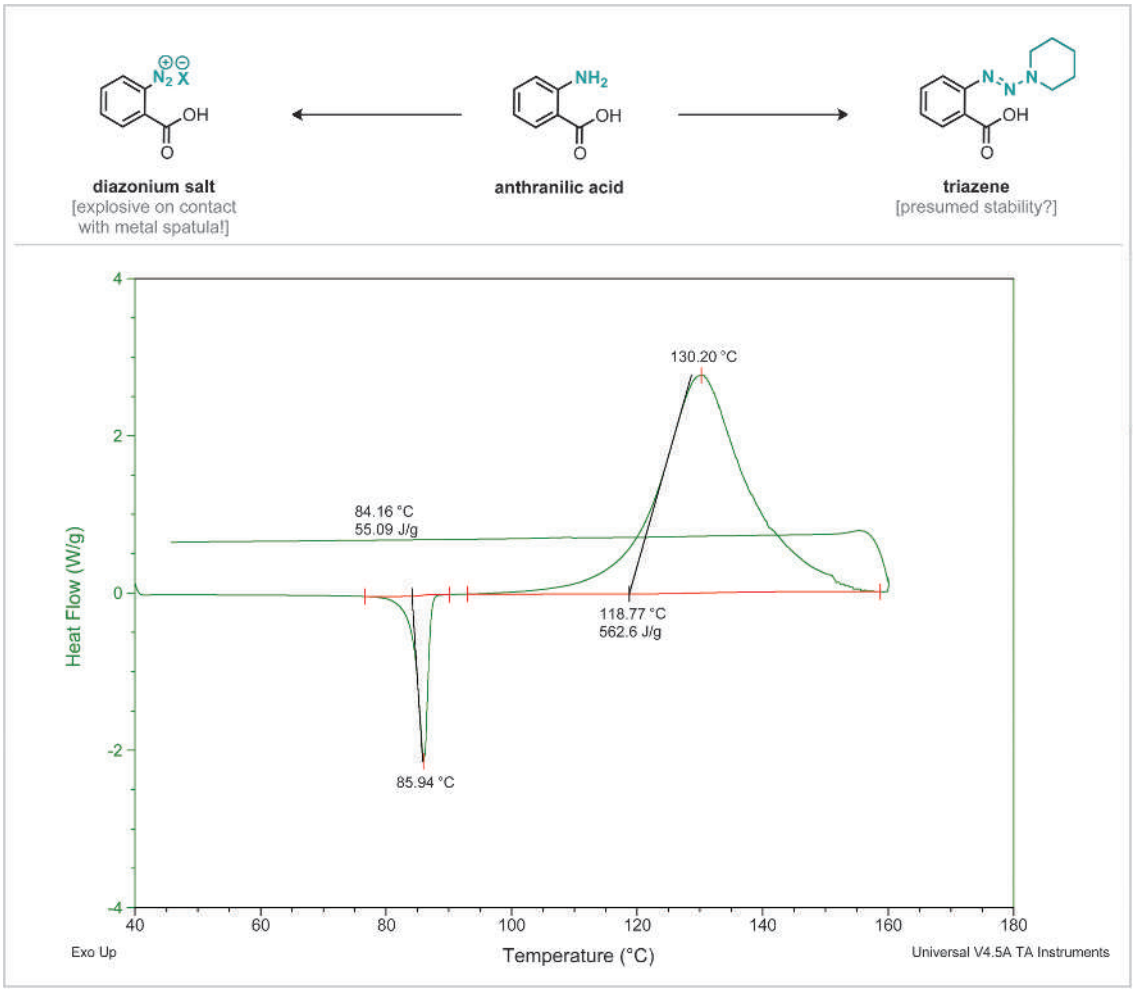
This data fully supports the notion that triazenes are more stable than diazonium salts, but one should demonstrate caution if heating the neat solid materials.

We also used our reactor system to prepare the antineoplastic compound dacarbazine, which features on the World Health Organization (WHO) model list of essential medicines [12]. Dacarbazine is active against metastatic melanoma by a DNA alkylating mode of action [13]. Here, it was prepared starting from the requisite amino imidazole and using a solution of dimethylamine in THF as the secondary amine nucleophile (Scheme 5). By delivering the amine in a changed solvent system, this may have had a knock-on effect on the isolation of the product which is also more aqueous soluble than the other materials prepared; nonetheless, dacarbazine was isolated in 47% yield.

Scheme 5. Reaction scope with respect to aniline component

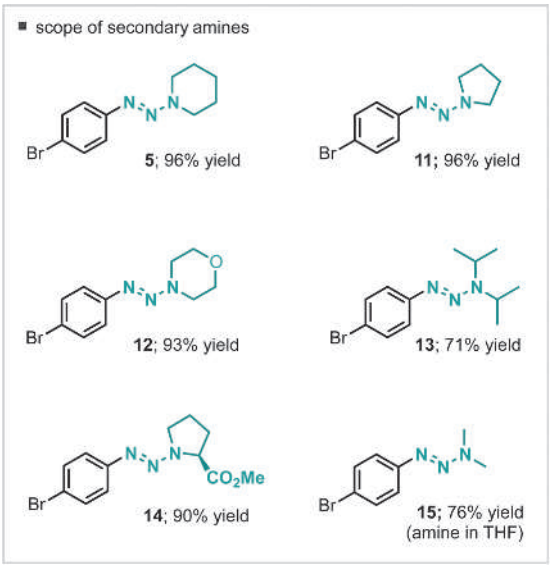


Scheme 6. Differential scanning calorimetry plot of the anthranilic acid-derived triazene



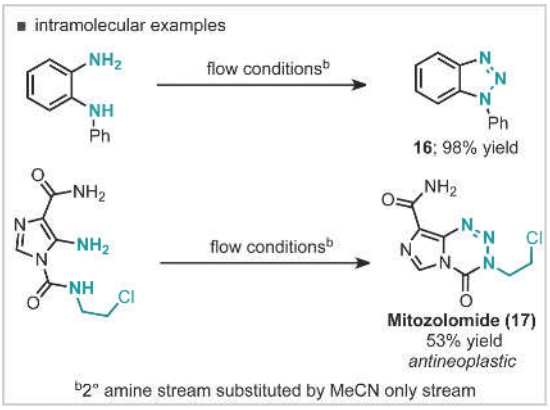
2.3. Secondary Amine Scope. Next, the scope with respect to secondary amine was explored, again, paying attention to any precipitate or fouling of the tubes across a variety of substrates. In addition to piperidine, it was also found that pyrrolidine (**11**), morpholine (**12**), diisopropylamine (**13**), and dimethylamine (**15**) were functional in the flow process without precipitate formation (Scheme 7). The resulting products were all formed in good to excellent yields. In addition, we have prepared the *S*-proline-methylester-derived triazene (**14**) in 90% isolated yield (Scheme 7). It is noteworthy that all triazenes reported here exhibit restricted rotation type behavior. This leads to temperature-dependent coalescence. Importantly, for the default room temperature ^{13}C NMR spectra of these compounds, the signals corresponding to the alpha carbons to nitrogen (of the amine component) are extremely broad and not readily discernible from the baseline. This appears to be congruent with supporting data files in other literature that concerns the preparation of triazenes but is not mentioned or noted as a general observation or phenomena [14]. We are actively exploring the rotation barriers and variable temperature NMR behavior of these materials. In addition to this, the signals of the attached protons also appear unexpectedly broad and do not show the expected (any) coupling patterns in the ^{1}H NMR spectra (see electronic Supporting Information for a brief account of this). X-ray crystallography has been used to verify and confirm the prepared material as a triazene, and variable temperature studies of the same molecule show a coalescence effect.

Scheme 7. Reaction scope with respect to secondary amine component



In addition to intermolecular examples, we also briefly explored intramolecular triazene formation where the amine component is tethered to the formed diazonium (Scheme 8). Indeed, treatment of *N*-phenyl-*o*-phenylenediamine to the flow reactor system furnished the benzotriazole product (**16**) in excellent isolated yield [15]. It was at this juncture that we were also able to prepare the antineoplastic agent mitozolomide (**17**) [16]. Treatment of the previously used dacarbazine aminoimidazole with the appropriate alkylisocyanate furnished the starting material for the flow reactor process. Application of this

Scheme 8. Intramolecular triazene examples including mitozolomide



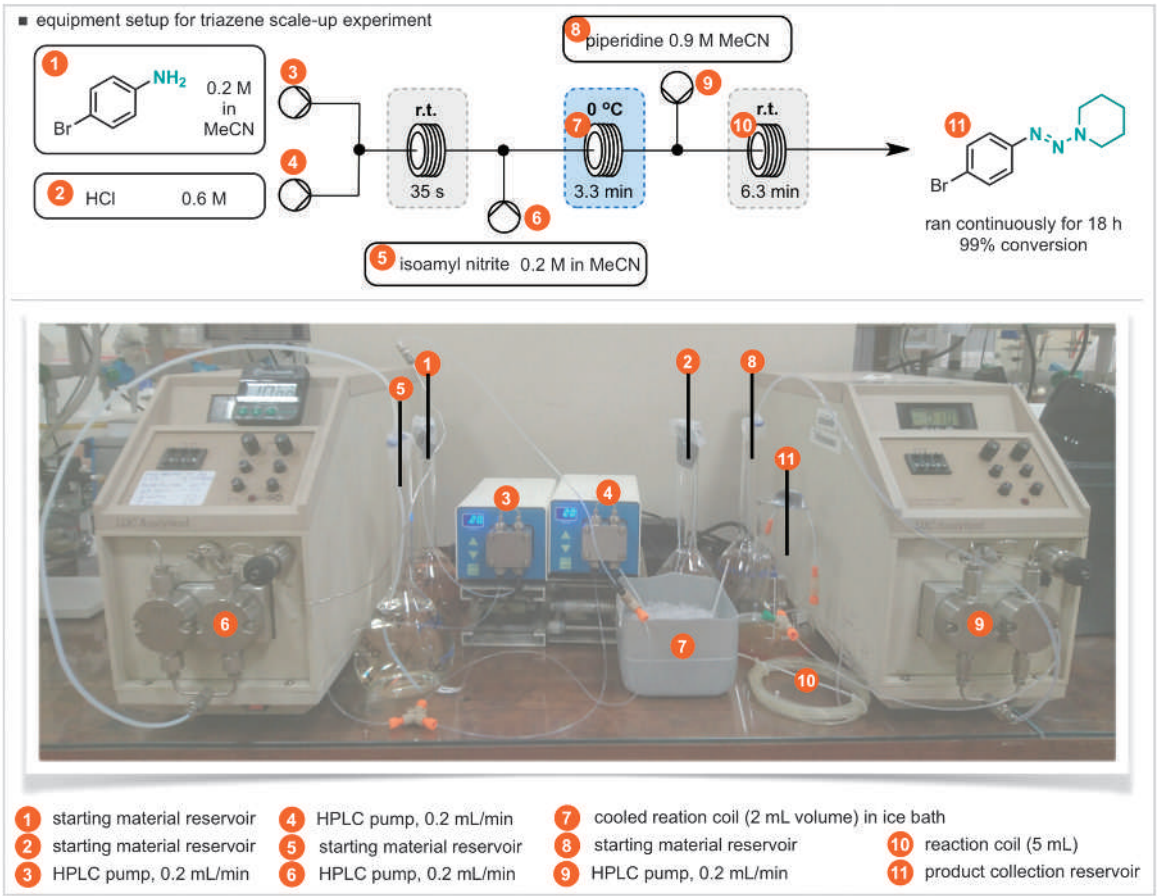
material to the flow conditions provided mitozolomide in 53% isolated yield. Again, in this instance, we suspect that the isolated yield is relatively low due to partition coefficients during the workup phase.

2.4. Large-Scale Experiment. Finally, we were mindful that, until now, the triazene materials had been prepared on relatively small scales (1–2 mmol) due to the use of single-shot syringe pumps delivering the reagents to the reactor in relatively low concentrations (these were necessary to avoid precipitation). We therefore switched our reactor setup to incorporate the use of high-performance liquid chromatography (HPLC) pumps that could continually process directly from solvent reservoir bottles. Our setup is shown in Scheme 9 and comprises of four 2-piston HPLC pumps, the reactor coils, and solvent reservoirs. We chose 4-bromoaniline and piperidine as the substrates for this process demonstration. In the normal fashion, low dilution leads then to a bottleneck in the downstream processing of the product solution which becomes laborious, unless an inline workup method is incorporated [17]. For the first hour of processing, the sample was collected and extracted in the usual batch-way to afford 92% isolated yield of the desired product (**5**). We proceeded to "spot-check" at time points beyond this and analyzed material by NMR spectroscopy. This highlighted that the pump flow rates deviated from the desired set point and, thus, led to less pure samples and drew our attention to the issues such as low reagent levels, pump priming, and back-washing of the pumps to get the process back on track and within the defined specification. In the event, the material was processed continuously for 18 hours without fouling or clogging of the reactor.

3. Conclusion

In summary, we have reported a continuous-flow process for the preparation of triazenes with the *in situ* generation and consumption of diazonium salts. Key to realizing a process was the identification of solvent and reagent parameters that would avoid fouling and clogging in the 0.8 mm ID tubing used in these studies. The process has also been applied to a wide range of substrates and the preparation of intramolecular examples including the antineoplastic mitozolomide and the dimethylamine intermolecular adduct dacarbazine. We also report isolation and DSC analysis of an anthranilic acid-derived triazene whose related diazonium salt is a contact explosive highlighting improved stability. Finally, we demonstrated an 18 hour continuous operation of the reaction procedure using HPLC pumps to deliver the material.

Scheme 9. Setup for continuous experiment using HPLC pumps in place of single-shot syringe systems



4. Experimental

4.1. General Methods. All reagents and solvents were commercially available and were used without further purification if not stated otherwise. Petroleum ether refers to the 40–60 °C fraction.

For the measurement of ^{1}H, ^{13}C, and ^{19}F NMR spectra, a Bruker Fourier^{300} (300 MHz), 400 UltraShield™ (400 MHz), or Ascend™ 500 (500 MHz) was used. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal or to the standard trifluorotoluene (−63.72 ppm) in ^{19}F NMR. Spin–spin coupling constants J are given in Hz. ^{13}C spectra are reported as obtained at default temperature (room temperature about 18 °C).

The flow setup consisted of perfluoroalkoxy (PFA) tubing of 0.8 mm ID and two pumps. The residence coils were made from the tubing by taking the appropriate length for the desired volume.

Column chromatography was performed using 60 A (40–64 μm) silica and solvent mixtures of petroleum ether and ethyl acetate or dichloromethane.

High resolution mass spectral (HRMS) data were obtained on a Waters MALDI-TOF mx at Cardiff University or on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Infrared (IR) spectra were obtained from a Shimadzu IR-Affinity-1S FTIR and melting points using a Gallenkamp apparatus and are reported uncorrected.

DSC measurements were performed using a TA instruments Q100. The sample was heated to 160 °C from 40 °C using a 5 °C/min gradient.

References to spectroscopic data are given for known compounds.

4.2. General Method for the Preparation of Triazenes 1–10 in Flow (Scheme 5). Solutions of the aniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3 × 20 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If necessary, the crude product was further purified by column chromatography.

1-((4-Chlorophenyl)diazenyl)piperidine (**1**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.24–7.19 (m, 2H), 3.77–3.63 (m, 4H), 1.71–1.54 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 131.0, 129.0, 122.0, 25.5, 24.5.

1-((4-Fluorophenyl)diazenyl)piperidine (**2**) [18]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.37 (m, 1H), 7.05–6.98 (m, 1H), 3.81–3.69 (m, 2H), 1.77–1.64 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 160.0, 147.5 (d, J = 2.9 Hz), 129.0, 122.0 (d, J = 8.1 Hz), 116.5, 115.5 (d, J = 22.4 Hz), 48.5, 25.5, 24.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.01 (s, 1F).

1-((4-Methylphenyl)diazenyl)piperidine (**3**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.17–7.10 (m, 2H), 3.81–3.67 (m, 4H), 2.34 (s, 4H), 1.79–1.61 (m, 6H). HRMS (EI+): $[C_{12}H_{17}N_3]$ calc. 203.1422, found 203.1423.

1-((4-Nitrophenyl)diazenyl)piperidine (**4**) [6h]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.14 (m, 1H), 7.54–7.46 (m, 1H), 4.03–3.73 (m, 2H), 1.93–1.58 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 145.0, 125.0, 120.5, 53.5, 44.0, 26.5, 24.5, 24.5.

1-((4-Bromophenyl)diazenyl)piperidine (**5**) [14]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 3.77 (d, J = 5.6 Hz, 2H), 1.70 (d, J = 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.5, 25.5, 24.5.

1-((3-Bromophenyl)diazenyl)piperidine (**6**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 1H), 7.38–7.33 (m, 1H), 7.31–7.25 (m, 1H), 7.24–7.18 (m, 1H), 3.86–3.76 (m, 4H), 1.83–1.65 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 130.0, 128.0, 123.0, 123.0, 120.0, 25.5, 24.5.

1-((2-Bromophenyl)diazenyl)piperidine (**7**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 1H), 7.–7.39 (m, 1H), 7.29–7.20 (m, 1H), 7.02–6.94 (m, 1H), 3.98–3.70 (m, 4H), 1.81–1.64 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 133.0, 128.0, 126.5, 120.0, 118.5, 25.0, 24.5.

2-(Piperidin-1-yldiazenyl)benzoic acid (**8**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.99 (s, 1H), 8.28–8.22 (m, 1H), 7.72–7.68 (m, 1H), 7.53–7.47 (m, 1H), 7.31–7.25 (m, 1H), 3.98–3.90 (m, 2H), 3.88–3.78 (m, 2H), 1.91–1.74 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 148.5, 133.5, 132.5, 126.5, 122.0, 116.0, 54.0, 45.5, 26.0, 24.0, 23.5. HRMS (EI+): $[C_{12}H_{15}O_2N_3]$ calc. 233.1164, found 233.1162. m.p. (acetone): 88–89 °C. IR: 2945, 1703, 1704, 1593, 1410, 1109, 766, 692, 608 cm^{-1}.

1-(Phenyldiazenyl)piperidine (**9**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.37–7.30 (m, 2H), 7.19–7.12 (m, 1H), 3.84–3.71 (m, 4H), 1.77–1.64 (m, 6H). HRMS (EI+): $[C_{11}H_{15}N_3]$ calc. 189.1266, found 189.1263.

· 3-(Piperidin-1-yldiazenyl)quinoline (**10**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14–9.07 (m, J = 2.2 Hz, 1H), 8.09–8.04 (m, J = 8.8 Hz, 1H), 8.04–7.99 (m, J = 2.2 Hz, 1H), 7.80–7.75 (m, J = 8.5 Hz, 1H), 7.62–7.56 (m, J = 11.3, 4.0 Hz, 1H), 7.51–7.45 (m, J = 7.5 Hz, 1H), 3.94–3.78 (m, J = 5.5 Hz, 4H), 1.80–1.66 (m, 6H). HRMS (EI+): $[C_{14}H_{16}N_4]$ calc. 240.1375, found 240.1373.

4.3. General Method for the Preparation of Triazenes 11–15 in Flow (Scheme 6). Solutions of the *p*-bromoaniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and a secondary amine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3 × 20 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If the purity of the product did not exceed 90%, the crude product was further purified by column chromatography.

1-((4-Bromophenyl)diazenyl)pyrrolidine (**11**) [19]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.31–7.26 (m, 2H), 3.77 (bs, 4H), 2.14–1.88 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 132.0, 122.0, 118.0, 51.0, 46.5, 24.0.

4-((4-Bromophenyl)diazenyl)morpholine (**12**) [20]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.42 (m, 2H), 7.37–7.28 (m, 2H), 3.89–3.82 (m, 4H), 3.82–3.75 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 132.0, 122.5, 120.0, 66.5.

1-(4-Bromophenyl)-3,3-diisopropyltriaz-1-ene (**13**) [21]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.31–7.26 (m, 2H), 5.27 (bs, 1H), 3.99 (bs, 1H), 1.30 (bs, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 132.0, 122.0, 117.5, 49.0, 46.0, 24.0, 19.5.

Methyl(4-bromophenyl)diazenyl)-L-prolinate (**14**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.31–7.25 (m, 2H), 4.66 (bs, 1H), 4.22–3.55 (m, 5H), 2.41–2.28 (m, 1H), 2.25–1.97 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 140.5, 131.5, 122.5, 119.0, 63.5, 59.5, 52.5, 51.0, 47.0, 29.0, 23.0. HRMS (EI+): $[C_{12}H_{14}N_3O_2Br+H]^+$ calc. 312.0348, found 312.0351. IR: 2951, 2876, 1740, 1479, 1427, 1392, 1323, 1148, 1067, 827 cm^{-1}.

1-(4-Bromophenyl)-3,3-dimethyltriaz-1-ene (**15**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 1H), 7.33–7.27 (m, 1H), 3.34 (bs, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.50.

4.4. Preparation of Internal Triazenes 16 and 17 in Flow (Scheme 8)

4.4.1. 1-Phenyl-1H-benzo[d][1,2,3]triazole (16) [22]. Solutions of the *N*-phenyl-*o*-phenylenediamine (0.2 M in acetonitrile), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3×20 mL), washed with brine, and dried over $MgSO_4$. After column chromatography (petroleum ether–DCM), the title compound (**16**) was obtained as a colorless solid in 98% yield (0.192 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.12 (m, 1H), 7.83–7.72 (m, 3H), 7.65–7.58 (m, 2H), 7.58–7.47 (m, 2H), 7.47–7.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 137.0, 132.5, 130.0, 129.0, 128.5, 124.5, 123.0, 120.5, 110.5.

4.4.2. 3-(2-Chloroethyl)-4-oxo-3,4-dihydroimidazo[5,1 d][1,2,3,5] tetrazine-8-carboxamide (17, Mitozolomide) [23]. To a solution of 5-aminoimidazole-4-carboxamide (0.631 g, 5.0 mmol) in dry acetonitrile (50 mL) at −7 °C, 2-chloroethyl isocyanate (0.530 g, 1.1 equiv.) in dry acetonitrile (10 mL) was added dropwise over 1 h. The mixture was stirred overnight at 25 °C and quenched with water (20 mL), and washed with ethyl acetate (3 × 10 mL) to yield 5-amino-N^1-(2-chloroethyl)-1*H*-imidazole-1,4-dicarboxamide as a white solid (72%, 0.838 g) [24].

^{1}H NMR (400 MHz, DMSO) δ 8.78 (t, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.03–6.66 (m, J = 36.2 Hz, 2H), 6.39 (s, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.60–3.50 (m, J = 5.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 150.5, 143.5, 126.0, 111.5, 43.0, 42.0.

Solutions of 5-amino-N^1-(2-chloroethyl)-1*H*-imidazole-1,4-dicarboxamide (0.2 M) in a mixture of DMSO and acetonitrile (1:4, *v*/*v*), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. The product was extracted with $CHCl_3$ (3×50 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was washed with petroleum ether–diethyl ether (50:50, *v*/*v*, 3×10 mL) and dried under reduced pressure to yield the product as a pale pink solid in 53% yield (0.128 g, **17**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.24 (s, 1H), 6.03 (s, 1H), 4.77 (t, J = 6.0 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 139.0, 134.0, 132.0, 128.5, 50.5, 41.0.

4.5. Method for the Preparation of 5-(3,3-Dimethyltriaz-1-en-1-yl)-1*H*-imidazole-4-carboxamide (Decarbazine) [25]. Solutions of 5-amino-1*H*-imidazole-4-carboxamide (0.2 M) in a mixture of aqueous HCl (0.6 M) and acetonitrile (3.5:6.5, *v*/*v*), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The product was extracted with $CHCl_3$ (3 × 50 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was washed with petroleum ether–diethyl ether (50:50, *v*/*v*, 3×10 mL) and dried under reduced pressure to yield the product as a pale yellow solid in 47% yield (0.855 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.91 (bs, 1H), 5.58 (bs, 1H), 2.17 (s, 6H). IR: 3279, 2193, 1709, 1524, 1449, 1371, 1343, 1261 cm^{-1}. HRMS (AP+): $C_6H_{10}N_6O+Na]^+$ calc. 205.0814, found 205.0796.

4.6. Large-Scale Experiment. Solutions of 4-bromoaniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 9) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), the reaction was run for 18 h. The first 50 mL (2.5 mmol, 62.5 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica to yield the clean compound **5** (92%, 0.587 g, 2.3 mmol).

Acknowledgments. We thank the Bolashak International Scholarship of the President of the Republic of Kazakhstan (YS), Cardiff University, and the Royal Society (DLB, award number RG150376) for financial support and EPSRC UK National Mass Spectrometry Facility at Swansea University for MS measurements. The authors are grateful to Prof. Kenneth D. M. Harris and Dr. Colan Hughes for support in obtaining the DSC results.

Supporting Information

Electronic Supplementary Material (ESM), including compound characterization and copies of NMR spectra, is available in the online version at doi: 10.1556/1846.2016.00025.

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