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Bromine azide (BrN_3), a useful but extremely toxic and explosive reagent for the preparation of vicinal 1,2-bromine azide compounds, was safely generated and reacted *in situ* with alkenes in a continuous flow photoreactor. BrN_3 was generated by a novel procedure from NaBr and NaN_3 in water, and efficiently extracted into an organic phase containing the alkene thus avoiding decomposition. The resulting addition products have been used for the preparation of several useful building blocks.

Halogen azides XN_3 ($\text{X} = \text{F, Cl, Br, I}$) are, together with hydrazoic acid ($\text{X} = \text{H}$), the simplest possible azide compounds and among the few covalent inorganic azides that have been studied in the last decades. They have been investigated in great depth experimentally and theoretically to clarify their structure and bonding situation.^{1–3} However, the extraordinary tendency toward explosion and the considerable toxicity presents a significant challenge to the experimental chemist. These materials are thus commonly regarded as high energy species rather than as genuinely valuable synthetic reagents. For instance, bromine azide (BrN_3) is extremely explosive and only little is known about its physical and chemical properties. In fact, until recently, iodine azide was the only halogen azide, for which a crystal structure was available. The other halogen azides are extremely sensitive to even smallest variations in temperature and pressure, with explosions occurring at pressure variations of $\Delta p \geq 67 \text{ }\mu\text{bar}$.¹ The reaction energy for the disintegration of BrN_3 to Br_2 and N_2 is very large (404 kJ mol^{–1}), and the decomposition is accompanied by the formation of large amounts of toxic and corrosive gases.¹ The $\text{Br}-\text{N}_3$ bond in this molecule is particularly weak, with a thermodynamic strength near zero.² Only very recently, Schulz and coworkers succeeded in obtaining BrN_3 crystals using a miniature zone-melting procedure and the crystal structure of

bromine azide could be elucidated.³ The chemistry of the halogen azides was systematically explored by the group of Hassner.⁴ Hassner and co-workers for the first time demonstrated the direct addition of halogen azides to olefins in the 1960s. This reaction has finally provided broad access to synthetically highly valuable vicinally functionalized azides and vinyl azides. The addition of IN_3 to alkenes usually proceeds by an ionic mechanism in a Markovnikov fashion and with anti-selectivity, whereas ClN_3 predominantly reacts by a radical pathway. This reflects the increasing tendency for homolytic cleavage in the order $\text{IN}_3 < \text{BrN}_3 < \text{ClN}_3$. Accordingly, for BrN_3 both radical and ionic reactions have been reported depending on the reaction conditions (Fig. 1).^{4,5}

Early syntheses of bromine azide started from Br_2 gas and solid NaN_3 .⁶ Combinations with *N*-bromosuccinimide and NaN_3 or TMSN_3 allow the generation of BrN_3 *in situ* and have become popular for the preparation of vicinal bromoazides from olefins.⁷ Very recently the group of Finn described an elegant procedure for the *in situ* generation and trapping of chlorine azide in a biphasic system in batch.⁸ Chlorine azide was generated from NaN_3 , NaOCl , and AcOH in aqueous solution and immediately reacted with olefinic compounds in the organic phase. This methodology significantly increases the safety during the laboratory scale generation and use of ClN_3 .

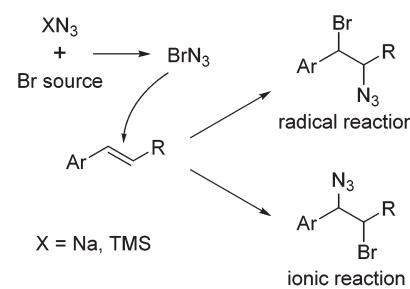


Fig. 1 Generation of BrN_3 and addition to an alkene. Homolytic or heterolytic cleavage of the $\text{Br}-\text{N}_3$ bond leads to the radical reaction or the ionic reaction products, respectively.



(the reactions were carried out in a 0.6 mmol scale). On the other hand, operation with larger reaction volumes clearly would become problematic.

Recently, continuous flow processing has emerged as an important tool which enables to safely perform chemistries typically “forbidden” in batch.^{9,10} In a microreactor, highly reactive and/or toxic intermediates can be generated *in situ* within a closed system and converted directly to nonhazardous intermediates or products by combining multiple reagent streams.¹¹ Moreover, the outstanding heat and mass transfer characteristics of microreactors, together with the fact that the reaction is resolved along the length of the reaction channel, enables a precise control of the residence time of intermediates or products, sometimes down to the microsecond level, by a thermal or chemical quench of the solution. Since the actual reaction volumes in a microreactor/flow device are very small, safety concerns associated with hazardous reagents are further minimized.¹¹ An example of the generation of a halogen azide generated in a microreactor was recently described by the group of Wirth. IN₃ was generated from iodine monochloride (ICl) and tetrabutylammonium azide and was reacted with aldehydes yielding carbamoyl azides.¹²

To overcome the problems associated with BrN₃ we envisaged a continuous flow protocol for its safe generation and utilization. Herein we report the generation of BrN₃ by a novel route starting from inexpensive NaBr and NaN₃ as halogen and azide sources, and Oxone as oxidizing agent. Photolysis in a subsequent continuous flow photoreactor in the presence of an alkene afforded vicinal bromo azides with good yields and essentially complete anti-Markovinkov selectivity.

The continuous flow setup consisted of three feeds (Fig. 2) containing the olefin in an organic solvent (dichloromethane or ethyl acetate) (Feed A), an aqueous solution of NaBr and NaN₃ (Feed B), and an excess of Oxone in water (Feed C). The

three feeds were introduced in the reactor using sample loops (2 mmol substrate scale, see ESI† for details), and mixed using a PEEK cross-assembly (0.5 mm i.d.). BrN₃ is rapidly formed upon mixing of NaN₃/NaBr and oxone in the water phase. A reddish color develops in the aqueous phase upon mixing of the feeds, indicating the formation of BrN₃, and the colored compound is immediately extracted into the organic phase. BrN₃ is highly water sensitive and reacts with water to form toxic and explosive hydrazoic acid (HN₃) and HOBr. HN₃ and HOBr then further react to ultimately form dinitrogen gas, hydrogen bromide and water. Therefore a rapid extraction of BrN₃ into the organic phase is essential to prevent excessive decomposition in the aqueous phase. This efficient extraction was achieved by the segmented flow regime obtained within the tubing. In the organic phase the bromine azides reacts with the olefin (Fig. 2). A 20% excess of NaBr/NaN₃ was used to ensure complete conversion of the olefin and thus facilitate the isolation of the 1,2-bromine azide product. Addition of the halogen azide to electron rich alkenes is a fast process with selectivity (ionic vs. radical addition) dependent on the solvent polarity.^{4a} However, when electron withdrawing groups are attached to the olefin, the addition becomes slower, and partial decomposition of the halogen azide can lead to poor yields for the desired addition products. Thus, the continuous flow setup for the generation and extraction of BrN₃ was coupled with a flow photoreactor to enhance the radical addition for electron-poor substrates. The photochemical reactor¹³ simply consisted of a transparent FEP tubing (i.d. 0.8 mm, 18 mL volume) wrapped around a compact fluorescent lamp (max. 365 nm) (see ESI† for details). The system was pressurized using a 7 bar back-pressure regulator to properly control the residence time (nitrogen gas is formed due to partial decomposition of BrN₃). The reaction mixture was immediately quenched after the photoreactor with an aqueous solution containing an excess of Na₂S₂O₃ after a residence time of approximately 10 min. Using this continuous flow setup large amounts of material can be processed by simply running the flow setup for longer periods of time. Yet, even in case that no addition to the olefin would occur a maximum quantity of 3 mmol of BrN₃ would be present in the reactor at any time.

An initial set of experiments using styrene (**1a**) and ethyl cinnamate (**1b**) as model substrates was carried out with the continuous flow setup (Table 1). A 0.5 M solution of substrate in the organic solvent, 1.2 equivalents of NaBr and NaN₃, and 2 equivalents of Oxone were introduced in the flow reactor (Fig. 2). The fast addition of BrN₃ to styrene did not require irradiation, and full conversion of the substrate was achieved independently of the use of the lamp. Yet, improved selectivity towards the radical process was attained under irradiation (entries 1–4). As expected the solvent had an important influence on the selectivity, with the product of the radical pathway favored when the less polar DCM was used (entries 3–4). In the case of ethyl cinnamate (**1b**) poor conversions were observed in the absence of light (entries 6 and 8). Prolonged reaction times (>1 h) did not significantly improve the results due to

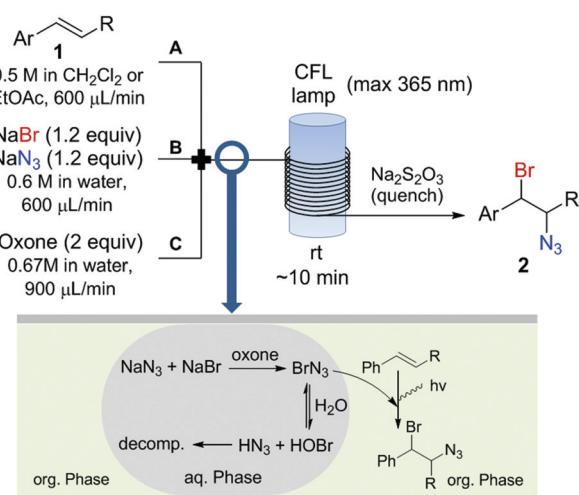


Fig. 2 Continuous flow setup utilized for the generation and use of BrN₃. The halogen azide is formed in the aqueous phase and rapidly extracted to the organic solvent reacting with the alkene. R = H, Aryl, COOEt.



Table 1 Effect of solvent and light irradiation on the 1,2-bromoazidation of styrene (**1a**) and ethyl cinnamate (**1b**)^a

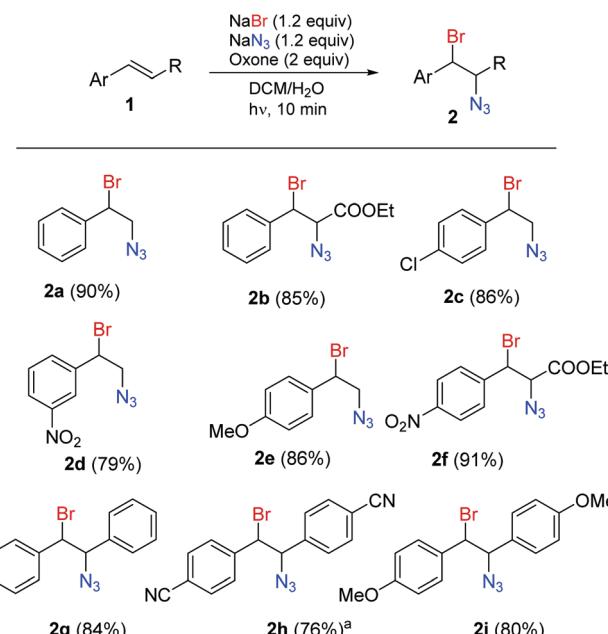
| Entry | Substrate | Solvent | Light irradiation | Conv. (selectivity) ^b (%) |
|-------|---|---------|-------------------|--------------------------------------|
| 1 |  | EtOAc | On | 99(43) |
| 2 |  | EtOAc | Off | 99(10) |
| 3 |  | DCM | On | 99(82) |
| 4 |  | DCM | Off | 99(74) |
| 5 |  | EtOAc | On | 99(94) |
| 6 |  | EtOAc | Off | 43(83) |
| 7 |  | DCM | On | 98(96) |
| 8 |  | DCM | Off | 41(96) |

^a Conditions: reactions were carried out using the conditions depicted in Fig. 2 on a 2 mmol scale. ^b Conversions and selectivity were determined by GC-MS for **1a**, and HPLC (215 nm) for **1b**. Selectivity refers to the proportion of the desired 1,2-bromine azide addition product resulting from the radical pathway (cf. Fig. 1).

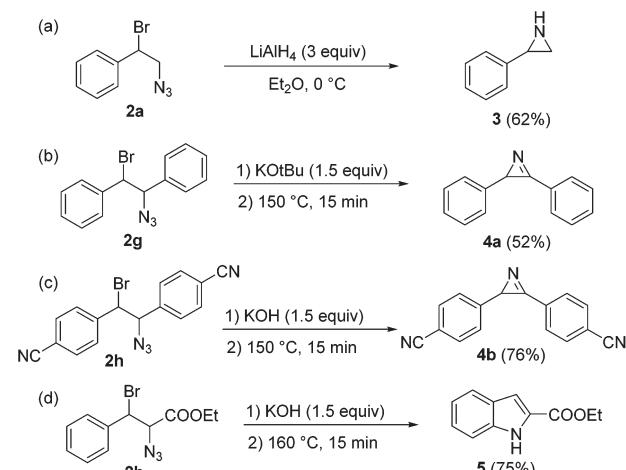
decomposition of BrN_3 . Gratifyingly, the addition reaction was considerably enhanced under light irradiation and full conversion was obtained both in DCM and EtOAc as solvents (entries 5 and 7). Product resulting from the ionic addition pathway was not observed for this substrate, probably inhibited by the presence of the carboxylate group, and the main side product observed was the 1,2-dibromide (*ca.* 4%). DCM as solvent and light irradiation were chosen as general conditions for the continuous flow 1,2-bromoazidation of alkenes. GC-MS and HPLC analyses of the crude reaction mixtures demonstrated extremely clean reaction profiles (see Fig. S2 in the ESI†). Thus, the pure 1,2-bromine azide adducts could be isolated in very good yields by simple separation of the organic phase and evaporation of the solvent after washing with brine.

A series of aromatic alkenes were converted into the corresponding bromine azide adducts using the continuous flow setup (Scheme 1). Styrenes (**2a**, **2c–e**) and cinnamates (**2b**, **2f**) decorated with electron withdrawing and electron donating groups gave the corresponding 1,2-bromine azide adducts with very good to excellent yields. Stilbenes (**2g–i**) were also reacted under the same conditions.‡ It should be noted that the radical addition is not an anti-selective process and resulted in mixtures of products that could not be separated. In the case of the cinnamates **2b**, **2f** and stilbenes **2g–i** mixtures of two pairs of diastereomers showing separated sets of NMR signals were isolated.

The high purity profiles with which the 1,2-bromine azide reaction mixtures were obtained allowed us to directly use the crude products without purification for exploring several follow-up reactions (Scheme 2). Compound **2a** could be transformed to 2-phenyl aziridine **3** by simply adding LiAlH_4 in dry diethyl ether solution.¹⁴ Aziridines are typically prepared from haloamines and aminoalcohols¹⁵ or oximes.¹⁶ Aziridination of alkenes is possible *via* nitrene addition.¹⁷ The current method provides an efficient two-step procedure for the aziridination of alkenes. Compound **3** was obtained in a overall yield of 62% (with respect to the starting styrene) (Scheme 2a).



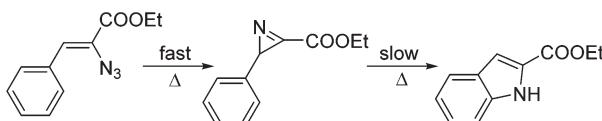
Scheme 1 Continuous-flow light-enhanced 1,2-bromoazidation of alkenes (isolated yields). For Experimental details, see the ESI.† ^a Compound **2h** was prepared in batch.



Scheme 2 Transformations of 1,2-bromine azides.

One of the most useful applications of 1,2-bromine azides is their transformation into vinyl azides, followed by thermolysis to lead azirines.¹⁸ Azirines are found in some natural products, and can be used for the generation of nitrile ylides under UV irradiation.¹⁹ Treatment of compounds **2g** and **2h** with base and thermolysis in toluene at 150 °C§ (Scheme 2b and c) resulted in the corresponding pure azirines. Interestingly, different bases were required for the elimination of HBr from **2g** and **2h**. While KOtBu was needed for the elimination in the case of **2g**, KOH sufficed for substrates bearing electron withdrawing groups (**2h**). Notably, treatment of **2h** with KOtBu





Scheme 3 Mechanism of the Hemetsberger–Knittel indole synthesis.

provoked partial, undesired elimination of hydrazoic acid from the substrate.

Azirines can be transformed into indoles using rhodium catalysts under suitable conditions.²⁰ A special case is the Hemetsberger–Knittel indole synthesis, which enables the preparation of indole-2-carboxylic esters from the corresponding 3-aryl-2-azido-propenoic esters.²¹ The continuous flow protocol presented herein when applied to substituted alkyl cinnamate substrates thus results in a facile and convenient route for the preparation of indole-2-carboxylic esters. 1,2-Bromine azide **2b** was treated with KOH (1.5 equiv.), washed with water, and heated in toluene at 160 °C for 15 min. Notably, the HPLC analysis of the crude reaction mixture revealed that indole **5** had been formed in very high purity. Evaporation of the solvent and crystallization from cyclohexane yielded the pure ethyl indole-2-carboxylate **5** with 75% yield.

The mechanism of the Hemetsberger–Knittel indole synthesis is not very well understood, but stable azirine intermediates have been proposed as well as transient nitrene species (Scheme 3).^{22,23} In order to shed light on the mechanism, heating of the vinyl azide formed after addition of the base to **2b** was repeated at lower temperature (120 °C) and monitored by HPLC analysis. The results revealed very rapid formation of the azirine intermediate *via* thermal extrusion of N₂ and a subsequent, slow transformation of the azirine into the final indole product. Indeed, the azirine intermediate could be detected by HPLC analysis (see ESI† for details). Preliminary DFT calculations on the azide thermolysis and indole formation suggest concerted transition states instead of nitrene intermediates as previously suggested (see ESI† for details).

In summary, we have developed a continuous flow protocol for the safe generation and use of BrN₃. The procedure is based on a biphasic system. The hazardous reagent is generated in aqueous solution using a novel protocol from NaBr and NaN₃, and Oxone as oxidizing agent. Upon formation, BrN₃ is rapidly extracted to an organic solvent containing the alkene substrate using a segmented flow regime. The 1,2-bromoazidation can be significantly enhanced by light irradiation. Therefore, a continuous flow photochemical reactor has been integrated in our setup. Addition of BrN₃ to electron-poor alkenes takes place efficiently avoiding undesired decomposition of the reagent. The 1,2-bromine azide adducts are obtained in high purity, and can be directly used for the generation of several building blocks such as aziridines, azirines, and indoles using facile, literature known procedures.

Notes and references

‡ 4,4'-Dicyanostilbene was poorly soluble in organic solvents and the reaction could not be performed in continuous flow. In this case, the 1,2-bromoazidation was carefully performed in batch adding the solution of Oxone to a biphasic mixture of the alkyne in DCM and NaBr/NaN₃ in water.

§ Thermolysis in DCM and ethyl acetate also gave the desired compounds. However, higher purity was obtained in toluene as solvent.

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