



Cite this: *Chem. Commun.*, 2022, 58, 3681

Received 27th December 2021,
 Accepted 11th February 2022

DOI: 10.1039/d1cc07213g

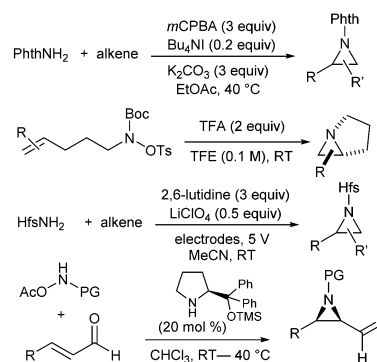
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Expedient metal-free preparation of aryl aziridines via thermal cycloaddition reactions†

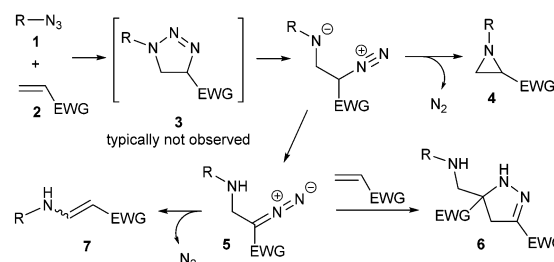
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A straightforward synthesis of aryl aziridines is reported from readily available azides and alkenes and using technical solvents in the presence of air. This methodology does not require any additives and the obtained compounds can be employed in ring-opening and ring-expansion reactions.

Aziridines, the smallest nitrogen-containing heterocycle, are found in biologically active natural products and are key intermediates in the synthesis of a wide array of nitrogenated derivatives.¹ A range of methodologies have been developed for the stereoselective synthesis of these valuable heterocycles,² but arguably metal-mediated transfer reactions (either of a nitrogen source to olefins or a carbon source to imines) remain the most prevalent options. Chemists' fascination for this motif is far from waning and new, elegant alternative metal-free methodologies continue to appear in the literature,³ such as the hypoidite mediated aziridination of alkenes with *N*-aminophthalimide,⁴ an aza-Prilezhaev reaction,⁵ or the electrochemical coupling of amines and alkenes,⁶ just to name a few (Scheme 1). While most of these reactions are limited to electron-rich alkenes, amine organocatalysis is a good alternative for α,β -unsaturated aldehydes.⁷ In this context, decades before aziridines gained their current popularity as nitrogen sources for the addition of the corresponding nitrenes to alkenes,⁸ pioneer work by Huisgen showed that electron-deficient alkenes deliver 1,4-disubstituted triazolines regioselectively when reacted with azides,⁹ which might deliver the corresponding aziridines upon nitrogen extrusion (Scheme 2).¹⁰ Subsequent reports of thermolysis¹¹ or photolysis¹² of triazolines to access aziridines have since emerged in the literature, however, these remain anecdotal in comparison to other methodologies due to selectivity issues. While the presence of electron-withdrawing substituents in triazoline 3 facilitates the cycloaddition step, it also increases the stability



Scheme 1 Selected metal-free syntheses of aziridines. PhthNH₂ = *N*-aminophthalimide; TFE = tetrafluoroethylene; HfsNH₂ = 1,1,1,3,3,3-hexafluoropropan-2-yl sulfamate.



Scheme 2 Evolution of 1,4-disubstituted 1,2,3-triazolines.

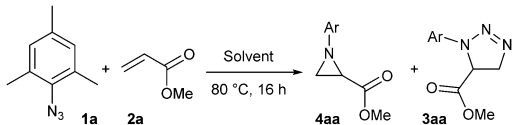
of its open-ring isomer that might evolve into aziridine 4, or a diazo compound 5. The latter can further react with an alkene to form after tautomerisation 2-pyrazoline 6,^{10,11} or undergo elimination to form an aminoalkane 7.¹³ The fate of these transient 1,4-disubstituted triazolines is strongly dependent on the substituents on either starting material and substantial decomposition is also often observed. More recently, the reaction of alkyl azides and alkenes with an electron-withdrawing group in the presence of an excess of triflic acid at low temperatures has been reported to produce aziridines in good to excellent yields.¹⁴ However, aryl azides only led to moderate yields due to azide decomposition under the optimal conditions.

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† Electronic supplementary information (ESI) available: FAIR data for NMR spectra and crystallographic data, see ref. 29. CCDC 2129406. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc07213g

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Table 1 Solvent screening^a


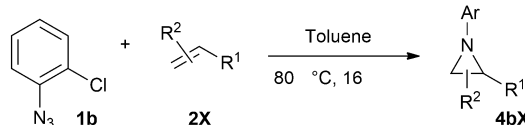
Entry	Solvent	4aa (%) ^b	3aa (%) ^b
1	Toluene	90	10
2	1,4-Dioxane	92	8
3	THF	75	11
4	EtOAc	84	12
5	EtOH	71	12
6	Brine	65	12
7	Water	73	—
8	Neat	77	12

^a Reaction conditions: Azide **1a** (1 mmol), alkene **2a** (2.2 mmol) in 2 mL of solvent. ^b ¹H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

During our previous work on the preparation of pyrazolines from aryl azides and alkenes with an electron-withdrawing group,¹⁵ we noticed the significant formation of aziridines in some reactions involving *ortho*-substituted aryl azides. Since the formation of pyrazolines was facilitated by using DES (Deep Eutectic Solvent, choline chloride/urea 1:2) as solvent, we tested alternative technical grade solvents with mesityl azide **1a** and methyl acrylate **2a** as model substrates (Table 1). The desired aziridine **4aa** was the major product in all cases, and 1,5-disubstituted triazoline **3aa** was the only other product identified in these reactions. Such product distribution indicates that all the originally formed 1,4-disubstituted triazoline evolved selectively into the corresponding aziridine. Remarkably, the reaction proceeded well even on water or in the absence of any solvent (Table 1, entries 7 and 8). Overall, either toluene or 1,4-dioxane provided the best results (Table 1, entries 1 and 2), and toluene was selected for further studies due to its relatively lower environmental impact.¹⁶

We then screened a range of mono- and di-substituted alkenes with 2-chlorophenyl azide **1b** as model substrate (Table 2). The reaction tolerated a range of functional groups such as esters, amides, aldehydes and nitriles. Only in the case of diethyl vinyl phosphonate **2h** a low yield was obtained and it could not be significantly improved by changing the reaction time or temperature (Table 2, entry 8). Pyrazoline formation was only detected with dimethyl fumarate **2o** as starting alkene (Table 2, entry 15), but small quantities of aminoalkenes **7** were often observed. By-products **7** were obtained as *Z*-isomers only, as favoured by the formation of a hydrogen bond between the amine and the different carbonyl groups.

Disubstituted alkenes required higher reaction temperatures (90–110 °C) but both geminal and vicinal substitution patterns were possible (Table 2, entries 9–15). As expected, the reaction was completely stereospecific with (*E*)-3-penten-2-one **2n** and dimethyl fumarate **2o** (Table 2, entries 14 and 15) as confirmed by ¹H NMR and X-ray diffraction (Fig. 1).¹⁷ In contrast, the reaction of **1b** and dimethyl maleate **2p** at 100 °C led to the formation of at least five different products, including both *cis*- and *trans*-**4bp**.¹⁸ The starting maleate was geometrically pure, so most probably the originally formed *cis*-**4bp** partially interconverted into its *trans* isomer at the

Table 2 Alkene scope in the preparation of aziridines **4a**^a


Entry	Alkene	4bX ^b (%)	Additional products
1 ^c	2a	83 (89)	3ba (6%)
2	2b	99 (>95) dr = 55:45	—
3 ^c	2c	55 (64)	7bc (24%)
4	2d	90 (87)	7bd 7% (8%)
5 ^c	2e	86 (93)	—
6 ^d	2f	51 (63)	Decomposition
7 ^{ee}	2g	90 (>95)	—
8	2h	(28)	Decomposition and 1b recovered (34%)
9 ^{ee}	2i	60 (63)	3bi (6%) and decomposition
10 ^{ee}	2j	72 (73)	7bj (15%)
11 ^{cf}	2k	70 (76)	Decomposition
12 ^e	2l	49 (57)	7bl 6% (29%) and 1b recovered (27%)
13 ^{ee}	2m	39 (40)	Decomposition
14 ^e	2n	36 (61)	7bn (5%) and 1b recovered (20%)
15 ^g	2o	68 (69)	6bo 5% (9%)

^a Reaction conditions: Azide **1b** (2 mmol), alkene **2X** (4 mmol) in 4 mL of technical toluene. ^b Isolated yields. ^c ¹H NMR yields are given in brackets and were calculated using 1,3,5-trimethoxybenzene as internal standard and are the average of at least two independent experiments. ^d 6.5 mmol of azide **1b**. ^e 9.8 mmol of azide **1b**. ^f 90 °C. ^g 110 °C.

^a Reaction conditions: Azide **1b** (2 mmol), alkene **2X** (4 mmol) in 4 mL of technical toluene. ^b Isolated yields. ^c ¹H NMR yields are given in brackets and were calculated using 1,3,5-trimethoxybenzene as internal standard and are the average of at least two independent experiments. ^d 6.5 mmol of azide **1b**. ^e 9.8 mmol of azide **1b**. ^f 90 °C. ^g 110 °C.



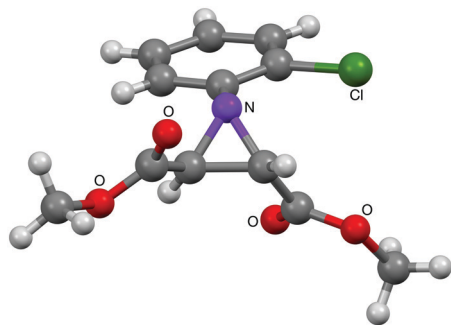


Fig. 1 Structure of aziridine **trans-4bo** (CCDC 2129406†).

Table 3 Azide scope in the preparation of aziridines **4**^a

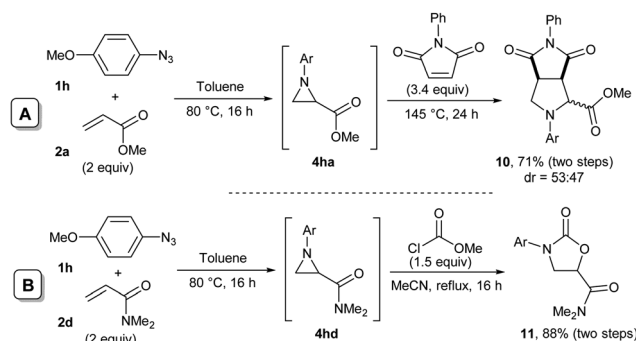
Entry	Azide	4Xd ^b (%)	7Xd ^b (%)
1		1b 90 (87)	7 (9)
2		1c 89 (88)	(6)
3		1d 95 (92)	(4)
4		1e 66 (74)	10 (14)
5		1f 70 (82)	(4)
6		1g 90 (86)	—
7 ^c		1h 88 (>95)	—
8		1i 74 (91)	(4)
9		1j 71 (84)	(<5)
10		1k 94 (95)	(<5)
11		1l 98 (>95)	—
12		1m 83 (n.d.)	(8)
13 ^d		1n (19)	(8)

^a Reaction conditions: Azide **1X** (2 mmol), alkene **2d** (4 mmol) in 4 mL of technical toluene. ^b Isolated yields. ¹H NMR yields are given in brackets and were calculated using 1,3,5-trimethoxybenzene as internal standard and are the average of at least two independent experiments. ^c 10 mmol of azide **1h**. ^d 48% (58%) of pyrazoline **6nd** was obtained in this reaction.

Table 4 Reactions of **4hd** with nucleophiles

Entry	Conditions	Yield (%) ^a	8 : 9
1	PhSH (7 equiv), neat, RT, 18 h	A 99 (>95)	80 : 20
2	PhSH (2 equiv), neat, RT, 18 h	(>95)	91 : 9
3	PhNH ₂ (1.2 equiv), bas. silica gel, neat, RT, 48 h	B 75 (84)	80 : 20
4	TMSN ₃ (2 equiv), MeCN, reflux, 18 h	C 37 (46) ^b	82 : 12
5	TMSN ₃ (4 equiv), neat, RT, 18 h	51 (63)	94 : 6

^a Isolated yields. ¹H NMR yields are given in brackets and were calculated using 1,3,5-trimethoxybenzene as internal standard and are the average of at least two independent experiments. ^b 42% (50%) of unreacted **4hd** was also recovered.



Scheme 3 Ring-expansion reactions of aryl aziridines.

reaction temperature.¹⁹ Next, we explored the azide scope and pleasingly these reaction conditions do not require an *ortho*-substituted aryl azide, which indicates that steric factors are not dominant when determining the fate of the 1,4-disubstituted triazoline. With *N,N*-dimethyl acrylamide **2d** as model alkene, differently substituted aryl and heteroaryl azides were successfully converted into aziridines **4** (Table 3). Both electron-withdrawing and electron-donating groups led to good results with aryl azides but interestingly, very different reaction outcomes were obtained with pyridine derivatives (Table 3, entries 12 and 13). While aziridine **4md** was obtained in good yield from 3-pyridylazide **1m**, only low conversion into 4-pyridylaziridine **4nd** was observed as the corresponding pyrazoline **6nd** was obtained as the major reaction product instead.

In order to establish the synthetic practicality of these reactions, different aryl aziridines were prepared from 6.5 mmol, or more, of the starting azide **1** and several of the corresponding aziridines were obtained in the gram-scale, such as **4ba** (1.15 g), **4be** (1.09 g), **4bg** (1.16 g), **4bo** (1.20 g) or **4hd** (1.94 g) (see Tables 2 and 3). Also, we adapted several protocols reported in the literature to exploit well-established reactivity of aziridines, namely nucleophilic ring-opening reactions as well as the generation of larger heterocycles. These transformations have been largely developed with activated aziridines bearing strongly electron-withdrawing groups on the nitrogen atom,²⁰ possibly due to the lack of accessible methods for the preparation of *N*-alkyl- or *N*-aryl aziridines, often termed



non-activated aziridines. Hence, we purposely used aziridine **4hd**, bearing an electron rich *N*-aryl group to test the reactivity with three different nucleophiles, thiophenol,²¹ aniline,²² and trimethylsilylazide²³ while avoiding any additional harsh additives (Table 4). In all cases the best results were obtained at room temperature in the absence of solvent to obtain a linear product, issue of a nucleophilic attack on the more hindered side of the starting aziridine, as the major reaction product. Excellent yields were obtained in the reaction with thiophenol and a smaller excess of nucleophile led to a slight improvement in regioselectivity (Table 4, entries 1 and 2). Compounds **8–9B** were formed in good yields, but only in the presence of silica gel basified with 2% w/w aniline (Table 4, entry 3). No products were formed with either standard or NEt₃-basified silica. As expected, reactions with TMSN₃, the weakest nucleophile of the three, resulted in moderate conversions into **8–9C** either in refluxing acetonitrile or at room temperature under neat conditions (Table 4, entries 4 and 5). Larger nucleophile excess, or increased reaction temperatures did not improve the overall results, but in all these reactions the unreacted aziridine could be recovered and no significant decomposition was observed.

Next, we used this methodology as starting point to easily access larger cyclic molecules. The synthesis of pyrrolidine **10** from **4ha** and *N*-phenylmaleimide in anhydrous and degassed refluxing toluene had been previously reported in 48% yield.²⁴ Gratifyingly, both cycloaddition steps could be carried out in one pot in technical toluene and in the presence of air, by simply adding the maleimide and raising the temperature after 16 h to generate the corresponding azomethine ylide. Pyrrolidine **10** was then isolated in an overall 71% yield for both steps (Scheme 3A).²⁵ Finally, 2-oxazolidone **11** was prepared by reacting aziridine **4hd** with methyl chloroformate, conditions previously reported for *N*-benzyl aziridines.²⁶ In this case different solvents had to be used for each step as the one-pot reaction in toluene led to the formation of an uncyclised α -chlorocarboxylate intermediate as final product.¹⁸ Switching to refluxing acetonitrile for the reaction with chloroformate cleanly led to oxazolidone **11** in an excellent yield (Scheme 3B).

In conclusion, the present methodology is convenient, user friendly, and easily scalable. It does not require a metal catalyst or additional reagents such as strong Brønsted acids. Furthermore, it offers a complementary approach to other established reactions since it does not require an electron-poor nitrogen source and it allows the introduction of a range of polar functional groups, which makes the resulting aziridines particularly useful as building blocks.²⁷ Except for highly activated alkenes, the reaction remains stereospecific and the geometry of the starting alkene is preserved in the final heterocycle. The sheer simplicity of these reactions together with the known asymmetric transformations of racemic aziridines²⁸ makes them an attractive alternative for the broader synthetic community.

EPSRC and the Royal Thai Government are acknowledged for studentships to F. S. and L. R., respectively.

Conflicts of interest

There are no conflicts to declare.

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