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Three-component reaction of small-ring cyclic amines with arynes and acetonitrile†

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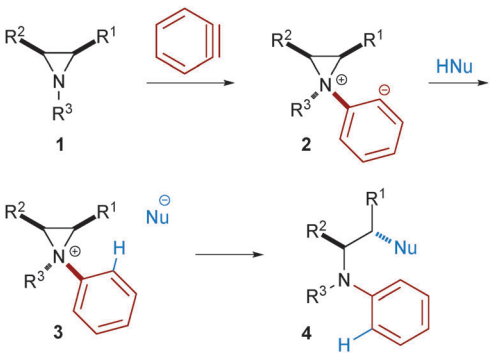
A novel stereospecific three-component reaction of aziridines and azetidines with arynes and acetonitrile has been developed. The reaction affords *N*-aryl γ-aminobutyronitriles and δ-aminovaleronitriles that can be used as precursors and congeners of a number of bioactive compounds, such as pregabalin and lergotrile.

Arynes have emerged as versatile and highly reactive intermediates *en route* to diverse aromatic and heteroaromatic compounds.[1] Recently, multicomponent reactions of arynes have attracted significant attention due to the ability of arynes to react with a variety of functional groups.[2] In particular, the ability of arynes to engage both electrophilic and nucleophilic reagents in a consecutive fashion has led to a number of efficient syntheses of polycyclic (hetero)aromatic frameworks, such as xanthenes,[3] benzisoxazoles,[4] isoquinolines,[5] and coumarins.[6]

We envisaged that the reaction of benzyne with aziridines **1** would give rise to the corresponding zwitterionic intermediates **2** (Scheme 1). The anionic residue in **2** could be sufficiently basic to generate a carbon nucleophile that would otherwise be inaccessible under these mild conditions. Subsequent nucleophilic attack would produce *N*-arylated amines **4**. We report herein the first example of such a three-component reaction with acetonitrile as a pronucleophile.

Nitriles are versatile synthetic intermediates. They can be readily transformed into carboxylic acids,[7] amides,[8] amines[9] and ketones.[10] Furthermore, the cyano group is present in a number of natural products[11] and pharmaceuticals,[12] including antiparkinsonian lergotrile[13] and antidiabetic drug vildagliptin.[14]

Nucleophilic activation of alkyl nitriles remains a challenging task due to their low acidity (pK_a 31.1 in DMSO for CH_3CN[15]) and reduced stability of the carbanion in the presence of strong bases.[16] Several methods have been developed that rely on activation of nitriles by transition metals,[17] as well as strong non-nucleophilic bases (Vercade's proazaphosphatrane[18] or cesium and potassium *tert*-butoxides[19]). Despite this progress, generation and use of alkyl nitriles in the context of multicomponent reactions have been limited. Recently, Cheng and co-workers have reported a three-component coupling of arynes, *N*-heteroaromatics and acetonitrile that involves deprotonation of acetonitrile by a zwitterionic intermediate.[20] Similarly, benzyne-initiated ring-opening reactions of cyclic ethers by acidic methines have been observed by Okuma and co-workers.[21] On the other hand, reactions of arynes with allylamines have been shown to give rise to the products of aza-Claisen reaction.[22] Reactions of arynes with aziridines and azetidines have not been described, but related azirines are known to give rise to substituted indoles upon reaction with benzyne.[23]



Scheme 1 General mechanistic proposal for the dual activation of aziridines and pronucleophiles by arynes.

Substituted aziridines and azetidines react sluggishly with carbon nucleophiles.[24] Recent approaches for activation of aziridines have focused on *N*-methylation with toxic methyl triflate,[25] use of electron deficient *N*-acyl and *N*-arylsulfonylaziridines,[26] and activation with stoichiometric amounts of Lewis acid.[27] In addition to diminished reactivity, control of the regioselectivity of the nucleophilic ring-opening reactions of substituted aziridines remains a challenge.[28]

Reaction with arynes represents a new mode of activation of *N*-alkylaziridines. Thus, aryne plays a dual role by activating both the aziridine and the pronucleophile.

Initial experiments with aziridine **5**, benzyne precursor **6** and cesium fluoride in acetonitrile afforded the three-component reaction product **7** in 34% yield, asserting feasibility of the process (Table 1). Subsequent attempts to identify a better fluoride source have led to suboptimal results, as neither of the other salts provided an

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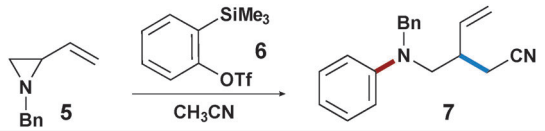
Table 1 Optimization study of the reaction of aziridine **5** with benzyne precursor **6** and acetonitrile[a]



Entry	Fluoride source	Solvent	Temperature (°C)	Yield (%)
1	CsF	CH_3CN	80	34
2	NaF	CH_3CN	80	10
3	TBAF	CH_3CN	80	7
4	TAS-F	CH_3CN	80	5
5	KF	CH_3CN	65	24
6	CsF	$PhCH_3$–CH_3CN[b]	65	86
7	CsF	THF–CH_3CN[b]	65	31
8[c]	—	$PhCH_3$–CH_3CN[b]	65	25
9	CsF	DME–CH_3CN[b]	65	16

[a] Reaction conditions: aziridine **5** (0.25 mmol), fluoride (6 equiv.), **6** (3 equiv.), solvent (2 mL), 3 Å molecular sieves (30 mg). [b] Solvent/CH_3CN ratio: 3 : 1. [c] Benzenediazonium-2-carboxylate was used as a benzyne precursor instead of **5** and CsF.

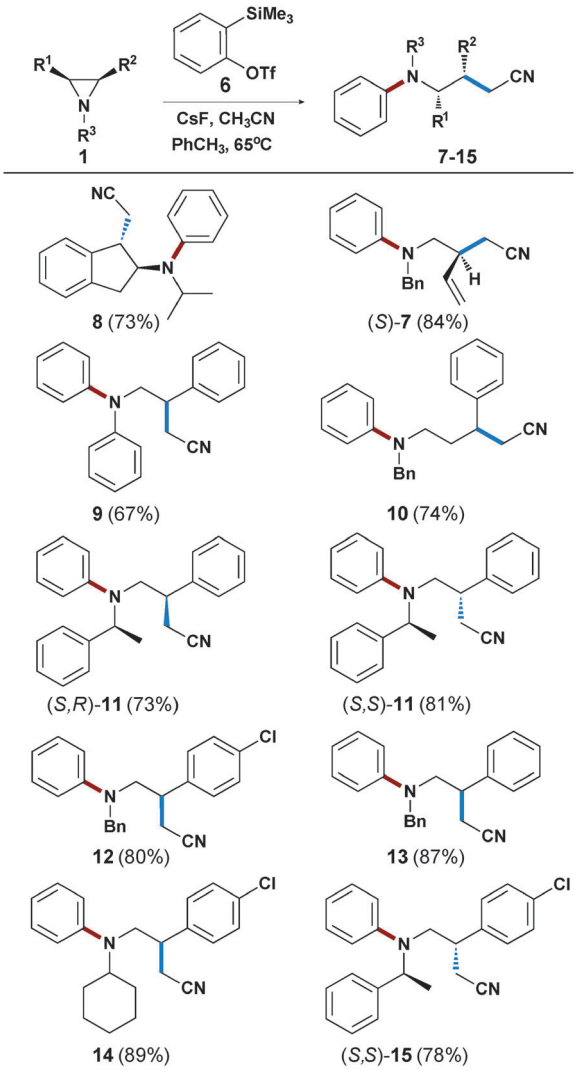


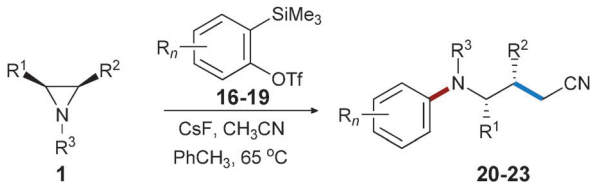
Fig. 1 *N*-Aryl-γ-amino nitriles prepared from aziridines or azetidines, acetonitrile and triflate **6**.

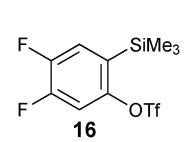
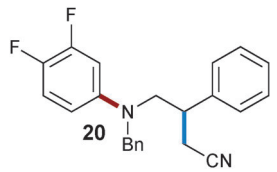
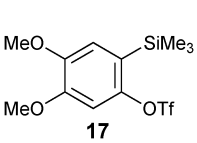
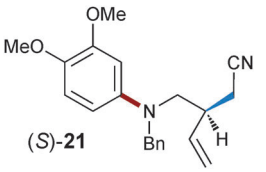
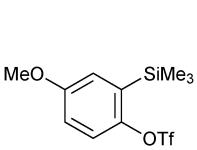
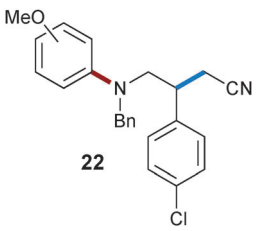
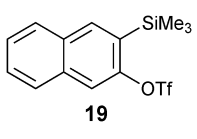
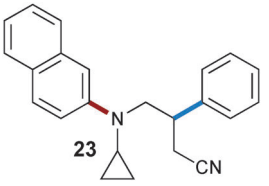
improvement over CsF. On the other hand, use of toluene as a co-solvent at a lower temperature has led to a cleaner reaction with a much improved yield of 86%.

Less promising results have been observed with other co-solvents, including tetrahydrofuran, 1,2-dimethoxyethane and dioxane. Attempts to replace triflate **6** and cesium fluoride as a source of benzyne with benzenediazonium-2-carboxylate[29] have produced the desired γ-amino-nitrile **7** in 25% yield. Although synthetically less attractive, this experiment supports our hypothesis that the nitrile carbanion is generated *via* proton abstraction by zwitterionic intermediate **2** and not by the fluoride, in line with the deuterium-labelling experiments performed by Cheng *et al.*[20] and Greaney *et al.*[22] for their systems.

After completion of the optimization study we sought to explore the scope of the new three-component reaction with respect to the structure of the amine component. A number of *N*-substituents in the aziridine ring are well tolerated, including primary and secondary alkyl, and phenyl groups (Fig. 1). The yields of γ-aminonitriles **7–9** and **11–15** are generally high. Bicyclic aziridines are also viable substrates, as exemplified by the indene-derived product **8**. The reaction proceeds in a stereoselective fashion and affords **7** with >95 : 5 dr. The nucleophilic attack by the nitrile carbanion generally occurred at the benzylic or allylic position of the aziridines, placing the substituent at the β-position in the corresponding products. Azetidines[30] readily undergo the

Table 2 Scope of the aryne precursors



Entry	Aryne precursor	*N*-aryl-γ-amino nitrile	Yield (%)
1			81
2			86
3			75
4			93

ring-opening reaction as well. In this case, δ-aminovaleronitrile **10** was isolated in 74% yield. Five- and six-membered cyclic amines, on the other hand, gave mixtures of unidentified products under these conditions.

In an effort to determine the stereochemical outcome of the reaction, several chiral aziridines were prepared from (1*S*)-phenylethylamine, and the absolute configuration of one of the diastereomers has been established by single-crystal X-ray crystallography.[31] These chiral aziridines afforded corresponding products (*S*,*R*)-**11** and (*S*,*S*)-**11**, as well as (*S*,*S*)-**15** with >95 : 5 dr.

In addition, we have also explored the influence of the aryne structure on the reaction. Substituted aryne precursors **16–19** have been subjected to the reaction with aziridines and nitrile products **20–23** have been isolated in good yields (Table 2). Both *m*- and *p*-isomers of nitrile **22** have been formed in equal amounts with triflate **18** as an aryne precursor. Other substituted alkyl nitriles have yielded complex mixtures of products, highlighting the importance of steric and electronic factors in this reaction. Work is underway to expand the scope of the reaction to other carbon and heteroatom pronucleophiles, as well as non-benzylic/allylic aziridines and azetidines. The γ-aminobutyronitrile framework that is readily accessed by this three-component reaction is widely observed among molecules of biomedical interest. In addition, hydrolysis of the nitrile products to the corresponding carboxylic acids can afford chiral β-substituted γ-aminobutyric acids. This class of compounds has recently yielded a number of new psychoactive small-molecule therapeutics, including the blockbuster drug pregabalin (Lyrica™), as well as vigabatrin,[32] gabapentin,[33] and atagabalin, currently in clinical development for treatment of insomnia.[34]

In conclusion, we have developed a new three-component reaction between aziridines and azetidines, arynes and acetonitrile that leads to *N*-aryl-γ-amino nitriles. The reaction proceeds with a high degree of stereoselectivity and allows for transfer of chirality from aziridine to the product. The aryne plays a crucial role by effecting dual activation of the small-ring tertiary amine and the nitrile in a stepwise fashion *via* zwitterionic intermediate **2**.

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