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Efficient synthesis of β-aminonitriles from arynes and imines in acetonitrile†

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Multicomponent reactions are powerful strategies for synthesizing complex molecules in an efficient manner. In this work, we investigate a novel multicomponent reaction involving arynes, imines, and nitriles, leading to chiral β-aminonitriles. Notably, two new bonds (C–C and C–N) are formed in one step without the use of metal catalysts, showing the great potential of this transformation. We demonstrate that this synthetic methodology is compatible with different arynes and imines, and propose a reasonable reaction mechanism initiated by the nucleophilic addition of the imine to the aryne.

Introduction

(5 + 2) Cycloadditions are useful tools for the synthesis of seven-membered rings,[1] which are relevant building blocks in natural products and pharmaceuticals. One of the synthetic protocols to this aim involves the reaction between a vinylcyclopropane derivative and an alkyne.[2] Due to our long-standing interest in aryne cycloadditions,[3] we wonder if a similar (5 + 2) cycloaddition could be carried out by reacting a cyclopropyl imine **I** with an aryne **II** (Scheme 1). Beyond its theoretical interest, this question has practical importance, since the potential (5 + 2) cycloadduct would be a benzazepine **III**, a very important building block in pharmaceuticals.[4] Although most (5 + 2) reactions involving vinylcyclopropanes are catalyzed by transition metals,[2] considering the nucleophilicity of imines and the high electrophilicity of benzyne,[5] we decided to attempt the cycloaddition without catalysis. However, when this reaction was performed, the expected benzazepine **III** was not obtained. Instead, a β-aminonitrile **IV** was isolated as a major product. Apparently, a three-component reaction involving the imine, the aryne and acetonitrile took place. Similar multicomponent reactions involving arynes have been reported previously.[6,7] Recent developments in multicomponent reactions have demonstrated various strategies for complex molecular synthesis. For instance, a radical cascade reaction for β-amino acids using Ni/diboron catalysis,[8] or an efficient spirocyclization of *N*-benzylacrylamides with *N*-halosuccinimides under metal-free condition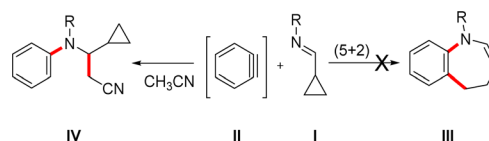s.[9] Additionally, a photoinduced coupling reaction for C–H heteroarylation of enamines,[10] and a radical-polar crossover method for fluoropyrazoles, both utilizing CF_2Br_2 as a new carbon source, have been introduced.[11] Unlike these approaches that often involve metals or specific reagents, our research presents a novel, metal-free multicomponent reaction using arynes, imines, and nitriles to efficiently synthesize chiral β-aminonitriles, offering improved scope and yield.

β-Aminonitriles are privileged skeletons that can be found in many bioactive compounds, such as ruxolitinib,[12] nitroquinoline and isoindole derivatives.[13,14] Moreover, the nitrile group presented in β-aminonitriles can be reduced to an amine or hydrolyzed to the corresponding amide, adding extra value in the field of the synthesis of natural products and bioactive compounds.[15,16] For instance, β-amino acids are part of Taxol®,[17] one of the most worldwide studied chemotherapeutic drug and protease inhibitor of different retroviruses, such as HIV.[18,19]

The novelty of this multicomponent reaction and the interest of β-aminonitriles prompted us to investigate the scope and the mechanism of this transformation.

Results and discussion

Initially, as imine we choose the cyclopropyl derivative **1a** while for the generation of benzyne **3a** we choose the method based on the fluoride-induced decomposition of *o*-(trimethylsilyl)

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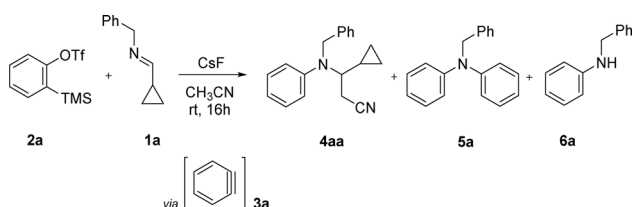*bCentro Interdisciplinar de Química e Bioloxía (CICA), Universidade da Coruña, 15071 A Coruña, Spain*

Scheme 1 Reaction of benzyne with a cyclopropyl imine.

phenyl triflate (**2a**).[20,21] When a solution of imine **1a** (1 equiv.) and benzyne precursor **2a** (1 equiv.) in acetonitrile was treated with CsF (3 equiv.) and stirred at room temperature for 16 h, a mixture of products was obtained. The chromatographic separation led to the isolation of products **4aa** as a racemic mixture, **5a** and **6a** in 41, 12 and 11% yield, which were confirmed by NMR and mass spectra (Fig. S1–S11†), ruling out the formation of a benzazepine by (5 + 2) cycloaddition. Increasing the ratio of reactants **1a** : **2a** to 1.5 : 1 and raising the temperature to 60 °C for 16 h improved the yield of isolated racemic mixture **4aa** to 88% (Scheme 2).

Encouraged by the high yield of the unexpected product **4aa**, we decided to explore the scope of this multicomponent reaction with different arynes. Therefore, we performed the reaction of imine **1a** and the arynes **3b–d**, generated from the corresponding easily accessible *o*-(trimethylsilyl)aryl triflates **2b–d** (see ESI for details†), obtaining the results shown in Table 1. Symmetrically substituted aryne **3b** (Table 1, entry 1) reacted with imine **1a** to give the corresponding nitrile **4ab** (50%). Asymmetric aryne **3c** reacted with imine **1a** to give a 1 : 1 mixture of regioisomers **4ac** in 58% yield (Table 1, entry 2). When asymmetric aryne **3d** was generated in the presence of imine **1a** compound **4ad** was obtained regioselectively in 48% yield (Table 1, entry 3). It is well known that substitution in position 4 of benzyne (*i.e.* **3c**) has little influence in the regioselectivity of an aryne nucleophilic addition, while a methoxy substituent in position 3 (*i.e.* **3d**) orientates the nucleophilic attack to position 1.[5–7] Therefore, the isolation of compounds **4ac** and **4ad** strongly supports a mechanism initiated by the nucleophilic addition of the imine to the aryne.

The next step was to investigate the scope of the reaction with several imines. In particular, we proposed experiments to test whether the cyclopropyl or the benzyl group are necessary moieties in **1a** for the course of the reaction. Thus, the reaction of imine **1b** (R$_2$ = C$_8$H$_{17}$) with benzyne precursor **2a** in the presence of acetonitrile led to the formation of compound **4ba** in 64% yield (Table 2, entry 1), confirming that the benzyl group in **1a** can be replace by an alkyl group in **1b**. On the other hand, the multicomponent reaction of imine **1c** (R$_2$ = Ph) and aryne precursor **2a** in the presence of acetonitrile led to aminonitrile **4ca**, isolated in 47% yield (Table 2, entry 2). The substitution of the cyclopropyl group in **1a** by a butyl in **1d** (R$_1$ = C$_4$H$_9$) led to the corresponding product **4da** in 20% yield (Table 2, entry 3). Finally, benzylidene imines **1e,f** react with benzyne precursor **2a** to afford the aminonitriles **4ea** and **4fa**, in 40 and 68% yields, respectively (Table 2, entries 4 and 5).

Table 1 Reaction of imine **1a** and aryne precursors **2b–d**[a]

Entry	Aryne precursor	Aryne	β-aminonitrile	Yield (%)
1	**2b**	**3b**	**4ab**	50
2	**2c**	**3c**	**4ac**	58
3	**2d**	**3d**	**4ad**	48

[a] Reaction conditions: imine **1a** (1.5 equiv.), aryne precursor **2** (1 equiv.), CsF (3 equiv.) in CH$_3$CN (0.05 M) at 60 °C, 16 h.

Then, considering these findings and the reaction conditions employed in this multicomponent reaction, we proposed the mechanism depicted in Scheme 3. First, fluoride-induced decomposition of triflate **2** afforded aryne **3**, which is highly electrophilic species.[20,21] Then, the nucleophilic addition of the imine **1** to the aryne **3**, should give the zwitterionic structure **7**, which would act as a base against acetonitrile, thus generating iminium cation **8** and the conjugated base of acetonitrile. Nucleophilic attack of this base to the electrophilic position of iminium **8**, would afford β-aminonitrile **4**. Previous works in which the conjugated base of acetonitrile was added to aziridinium,[22] isoquinolinium or pyridazinium ions support this mechanistic proposal.[23,24]

To confirm the mechanistic hypothesis, we designed new reactions using propionitrile and benzonitrile as solvents. According to the proposal, zwitterion **7** should react with propionitrile to form a carbanion in the α position to the CN group, which would attack the iminium ion **8** to give **9** (Scheme 4). In fact, when this reaction was performed under the standard conditions, **9** was obtained in 35% yield. This lower yield can be due to the lower acidity of propionitrile and to its mayor steric hindrance.
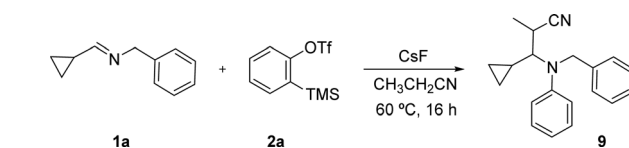
On the other hand, as expected, when the reaction was carried out with benzonitrile, the formation of the β-aminonitrile was not detected. Lacking hydrogen in α to the CN group, it is not possible to carry out the proton abstraction, preventing the evolution of the reaction towards the corresponding β-

Scheme 2 Reaction of imine **1a** with triflate **2a**.

Table 2 Reaction of imines **1b–f** and aryne precursor **2**[a]

Entry	Imine	β-aminonitrile	Yield (%)
1	**1b**	**4ba**	64
2	**1c**	**4ca**	47
3	**1d**	**4da**	20
4	**1e**	**4ea**	40
5	**1f**	**4fa**	68

[a] Reaction conditions: imine (1.5 equiv.), aryne precursor **2** (1 equiv.), CsF (3 equiv.) in CH_3CN (0.05 M) at 60 °C, 16 h.

Scheme 3 Proposed mechanism for the formation of the β-aminonitriles.

Scheme 4 Reaction of imine **1a** with triflate **2a** in propionitrile.

aminonitrile. These results are in good accordance with the mechanism proposed above (Scheme 3).

Finally, we focus our attention into minor products **5** and **6**. It is known that imines **1a–f** react with benzyne to give diarylamines.[25] According to this precedent, compound **5** could be formed by the reaction of β-aminonitrile **4** with benzyne. However, we proved that **4** does not react with benzyne under the reaction conditions. Probably **5** was formed in the reaction mixture by arylation of amine **6**, which in turn could be formed by hydrolysis of **1**.

Conclusions

Overall, we have studied a new multicomponent transformation based on the reaction of imines, nitriles and arynes to obtain chiral β-aminonitriles. It was found that the reaction is compatible with species of different electronic richness. In particular, the reaction with an *ortho*-substituted aryne, such as 3-methoxybenzyne **3d**, is regioselective, while a *meta*-substituted aryne, such as 4-chlorobenzyne **3c**, leads to a mixture of regioisomers. On the other hand, regarding the use of imines, the reaction is compatible with aromatic and aliphatic imines. It is worth to mention that a structural requirement should be maintained, that is, the nitrile group must present α hydrogens to the CN group to obtain the β-aminonitrile.

Data availability

Detailed experimental procedures and characterization data for all novel compounds are included in ESI.†
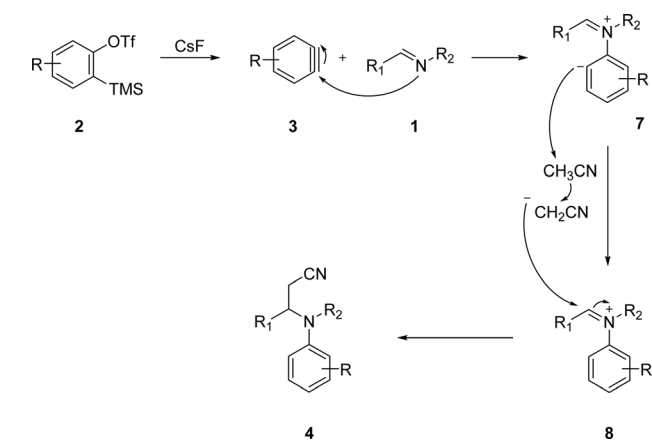
Author contributions

I. J. G. and C. M. performed the experiments and characterized the novel compounds. I. J. G. wrote the original draft. Di. P. designed and supervised the study. Do. P., E. G., and Di. P. reviewed and edited the original draft and obtained funding.

Conflicts of interest

There are no conflicts to declare.

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