Synthetic Methods

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A Multicomponent Reaction of Arynes, Isocyanides, and Terminal Alkynes: Highly Chemo- and Regioselective Synthesis of Polysubstituted Pyridines and Isoquinolines**

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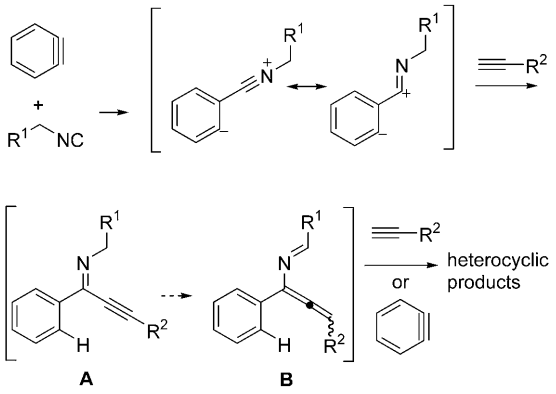
Pyridine, a class of important heterocycles, is not only the fundamental motif found in the core of numerous alkaloids[1] but is also a pivotal building block for pharmaceutical compounds[2] and chiral ligands.[3] Although many methods have been developed for their synthesis, lengthy or complicated procedures as well as harsh reaction conditions are usually applied.[4–5] Thus, it is still important to develop direct and efficient routes that afford pyridine derivatives under mild conditions. Arynes are an important intermediate in organic synthesis and have received attention over the past decades.[6] Because of their low-lying LUMO, arynes exhibit highly electrophilic character; even neutral nucleophiles can easily add to arynes to produce zwitterions, which act as key intermediates in the subsequent transformation that can lead to a variety of benzoannulated compounds.[7] This feature has been successfully explored by Yoshida et al. in the three-component reaction of arynes, isocyanides, and aldehydes, ketones, or imines for the direct synthesis of benzoannulated iminofurans and 2-iminoisoindolines.[8] However, examples of multicomponent reactions (MCR) containing both arynes and isocyanides are still limited owing to the obvious difficulty in regulating the reactivity of the aryne component;[8,9] especially the control of chemo- and regioselectivity remain challenging. We envisioned that an adduct of benzyne and isocyanide (generated in situ) may be trapped by a terminal alkyne to form a reactive imide intermediate **A**,[10] which may further undergo a 1,5-hydride shift to produce an allenyl imine intermediate **B** (Scheme 1).[11b] Then a consecutive cycloaddition reaction of **B** with another molecule of benzyne or terminal alkyne may occur to afford useful heterocyclic compounds.[11] Herein we reported our results on this novel multicomponent reaction, which provides a direct and mild synthesis of polysubstituted pyridines and isoquinolines with high chemo- and regioselectivity. An attractive feature of this protocol is that four molecules could be directly assembled into the desired azacyclic compounds in a highly efficient and atom-economic manner.



Scheme 1. MCR strategy for the synthesis of heterocyclic products.

We initially examined the reaction of 2-(trimethylsilyl)-phenyl triflate (**1a**),[12a] benzyl isocyanide (**2a**), and phenyl ethyne (**3a**) in MeCN at room temperature (Table 1, entry 1). Interestingly, *N*-benzyl alkynyl imine **4a** was formed in 81% yield together with isoquinoline **5a** and pyridine **6a** in 6% and 2% yields, respectively. Efforts were made to optimize the reaction conditions to afford predominantly one product. The reaction with 2.5 equivalents of **1a** at 40 °C afforded **5a** in 49% yield (Table 1, entry 3). The reaction in toluene/MeCN (1:3) afforded **5a** in 74% yield (Table 1, entry 5).[13] Likewise, with 3.0 equivalents of **3a**, the yield of **6a** was increased to 76% (compare Table 1, entries 6 and 7 with entry 8) after 48 h at 75 °C.

Under the optimized reaction conditions, we then employed a variety of aryne precursors **1**,[12] isocyanides **2**, and terminal alkynes **3** to examine the scope of the reaction. As shown in Table 2, the reaction proceeded smoothly to give the corresponding polysubstituted pyridines **6** in good yields.

In addition to symmetric arynes (Table 2, entries 1–5), various unsymmetrical arynes could also undergo the reaction smoothly. For example, when *o*-methyl aryne (Table 2, entry 6) was employed, the reaction occurred with high regioselectivity, probably as a result of an electronic effect from the methyl substituent, which generated the thermodynamically stable intermediate and introduced the imino moiety *ortho* to the methyl group.[6b,8b,c] A similar result was also observed using **1d** as the aryne precursor (Table 2,

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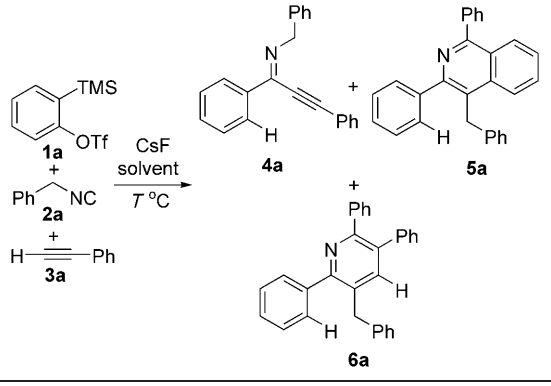
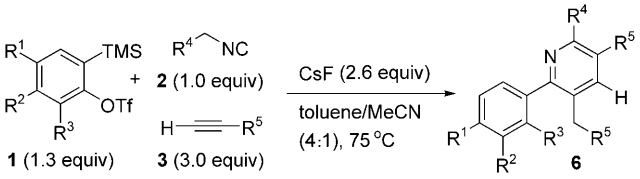
Table 1: Optimization of the reaction conditions for the multicomponent reactions.[a]



Entry	1a/2a/3a [mmol]	Toluene/MeCN [v/v]	t [h]	T [°C]	Yield [%][b] 4a	5a	6a
1	**1.3:1.0:1.0**	**0:1**	**37**	**RT**	**81**	**6**	**2**
2	2.5:1.0:1.0	0:1	37	RT	72	13	3
3	2.5:1.0:1.0	0:1	10	40	26	49	3
4	2.5:1.0:1.0	1:5	13	40	12	68	1
5	**2.5:1.0:1.0**	**1:3**	**18**	**40**	**2**	**74**	**0.6**
6	1.3:1.0:2.0	1:1	22	75	0	16	57
7	1.3:1.0:2.5	4:1	48	75	0	6	69
8	**1.3:1.0:3.0**	**4:1**	**48**	**75**	**0**	**0.4**	**76**
9	1.3:1.0:3.0	5:1	40	85	0	0.3	70

[a] The reactions were conducted using **1a**, **2a**, **3a**, and CsF (2.0 equiv, based on **1a**) in 5 mL of solvent (toluene/MeCN). [b] Yield of isolated product was based on the isocyanide **2a**. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

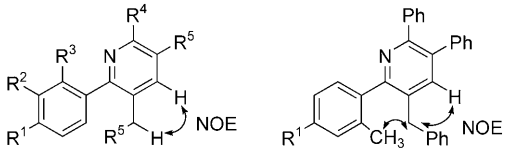
Table 2: Multicomponent reactions for the synthesis of pyridines **6**.[a]



Entry	Aryne 1	R1	R2	R3	Isocyanide 2	R4	Ethyne 3	R5	Yield [%][b]	Prod. 6
1	**1a**	H	H	H	**2a**	Ph	**3b**	*p*-EtC_6H_4	65	**6b**
2	**1a**				**2b**	*p*-Tol	**3a**	Ph	73	**6c**
3	**1a**				**2b**		**3c**	*p*-ClC_6H_4	81	**6d**
4	**1b**	Me	Me	H	**2b**		**3c**		70	**6e**
5	**1b**				**2c**	*p*-FC_6H_4	**3c**		77	**6f**
6	**1c**	H	H	Me	**2a**		**3a**		69	**6g**
7	**1d**	Br	H	Me	**2a**		**3a**		78	**6h**
8	**1e**	F	H	H	**2a**		**3a**		82	**6i**
9[c]	**1a**				**2a**		**3d**	*n*-C_6H_{13}	31	**6j**
10[d]	**1a**				**2a**		**3e**	*c*-C_3H_5	43	**6k**
11[e]	**1a**				**2a**		**3f**	*p*-FC_6H_4CO	53	**6l**

[a] Unless otherwise specified, the reactions were conducted using **1** (0.65 mmol), **2** (0.5 mmol), **3** (1.5 mmol), and CsF (1.3 mmol) in MeCN (0.5 mL) and toluene (2 mL) at 75 °C for 48 hours. [b] Yield of isolated product was based on the isocyanide **2**. [c] The reaction was conducted in MeCN (0.25 mL) and toluene (2.25 mL) for 91 h. [d] The reaction was carried out in a sealed tube with a screw cap. [e] The reaction was conducted in MeCN (2.5 mL) at room temperature overnight. Tol = tolyl.

entry 7). The reaction of *p*-fluorobenzyne precursor **1e** produced regioisomer **6i** exclusively. This outcome could be rationalized by the strong electron-withdrawing effect of the fluoro substituent, which causes the negative charge at the *meta* position to be greater than at the *para* position (in the transition state for the addition of an isocyanide to *p*-fluorobenzyne), thus facilitating the introduction of the imino moiety at the *para* position (Table 2, entry 8).[8a,14] Our results demonstrated that aromatic alkynes, including *p*-C_2H_5- and *p*-Cl-substituted phenyl ethynes, could be successfully applied to the reactions (Table 2, entries 1, 3–5). However, when alkyl alkynes were employed the reaction gave the corresponding products in lower yields (Table 2, entries 9 and 10). In addition, the reaction of the electron-deficient alkyne **3f** afforded the corresponding product **6l** in modest yield (Table 2, entry 11). It should be noted that the reactions showed excellent regioselectivity with respect to the alkyne to give 3-aryl-substituted pyridines **6**, whose structures were confirmed by NOESY experiments (Scheme 2).



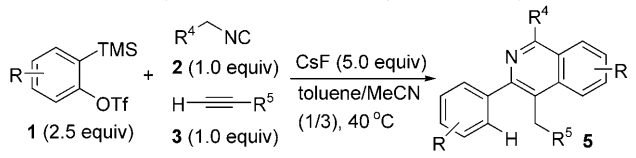
Scheme 2. NOE interactions were used to confirm the configuration of pyridines **6**.

Further experiments under the optimized reaction conditions (Table 1, entry 5) demonstrated that the multicomponent reaction could be extended to generate substituted isoquinolines in good yields (Table 3). The phenyl ethyne derivatives that are substituted with either an electron-withdrawing or -donating group could be smoothly transformed into the corresponding products (Table 3, entries 1–5). In addition to benzyl and *p*-methyl benzyl isocyanides, naphthalen-1-yl methyl and *p*-fluoro benzyl isocyanides participated in the reaction to afford the desired products in 72% and 76%, respectively (Table 3, entries 4 and 5). Furthermore, the reaction of unsymmetrical aryne precursor **1c** afforded two regioisomers **5ia** and **5ib** with good selectivity (Table 3, entry 8). The structure of the product **5g** was confirmed by X-ray diffraction studies (Figure 1).[15]

Interestingly, when an alkyl isocyanide substrate was used the reaction stopped at the alkynyl imine **4b** (Scheme 3), thus indicating the importance of the phenyl group (R^1) in the isomerization from **A** to **B** (Scheme 1). In fact, mechanistic experiments demonstrated that the treatment of alkynyl imine **4a** with 2-(trimethylsilyl)phenyl triflate (**1a**) or alkyne **3a** in the presence of CsF could furnish isoquinoline **5a** and pyridine **6a** in 75% and 77% yields, respectively (Scheme 3). This result further proved that **4** is an intermediate for this type of transformation.

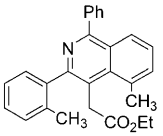
In conclusion, we have developed a new multicomponent reaction of arynes, isocyanides, and terminal alkynes with good selectivity. The different reaction pathways could be

Table 3: Multicomponent reactions for the synthesis of isoquinolines **5**.[a]

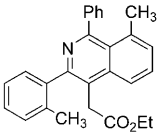


Entry	Aryne **1**	Isocyanide **2** R^4		Ethyne **3** R^5		Yield [%][c]	Prod. **5**
1	**1a**	**2a**		**3c**		75	**5b**
2	**1a**	**2a**		**3b**		67	**5c**
3	**1a**	**2b**		**3a**		79	**5d**
4	**1a**	**2d**	1-naphthyl	**3c**		72	**5e**
5	**1b**	**2c**		**3c**		76	**5f**
6[b]	**1a**	**2a**		**3g**	CO_2Et	71	**5g**
7[b]	**1b**	**2b**		**3g**		64	**5h**
8[b]	**1c**	**2a**		**3g**		55	**5ia/5ib** (7:1)[d]

[a] Unless otherwise specified, the reactions were conducted using **1** (1.25 mmol), **2** (0.5 mmol), **3** (0.5 mmol), and CsF (2.5 mmol) in MeCN (1.88 mL) and toluene (0.63 mL) at 40 °C overnight. [b] The reactions were conducted using **1** (1.25 mmol), **2** (0.5 mmol), **3g** (0.5 mmol), [18]crown-6 (3.0 mmol), and KF (2.5 mmol) in THF (2.5 mL) at 0 °C overnight. [c] Yield of isolated product was based on the isocyanide **2**. [d] Determined by isolation of the products. The configuration of **5ia** was confirmed by NOESY experiments.



5ia



5ib

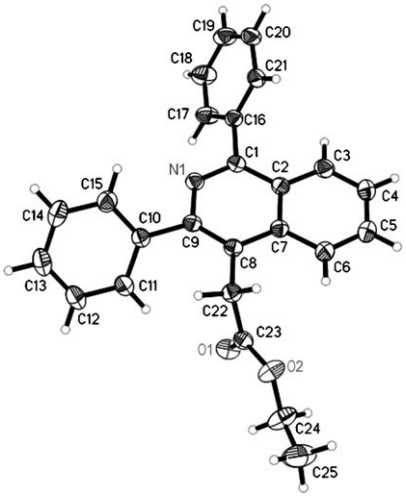
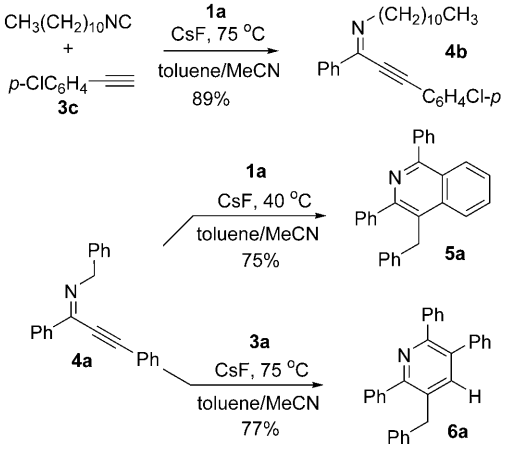


Figure 1. An ORTEP plot of isoquinoline **5g**. The thermal ellipsoids are drawn at the 30% probability level.

controlled well by choosing the appropriate reaction conditions, thus providing one-pot, highly efficient methods for the regioselective synthesis of polysubstituted pyridines and isoquinolines, which are difficult to obtain through conventional methods. Further studies of our MCR and understanding of its mechanism are currently in progress.



Scheme 3. MCR using alkyl isocyanide and experiments that confirm **4** as the intermediate for the MCR.

Experimental Section

Synthesis of **6a–i**: CsF (1.3 mmol, 198 mg) was added to a stirred solution of 2-(trimethylsilyl)aryl triflate **1** (0.65 mmol), isocyanide **2** (0.5 mmol), and aryl ethyne **3** (1.5 mmol) in dry MeCN (0.5 mL) and dry toluene (2 mL) under nitrogen. The reaction mixture was stirred at 75 °C for 48 hours. When the reaction was judged to be complete (as evident by TLC), the mixture was filtered through a layer of silica gel and eluted with Et_2O. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 35:1) to afford **6**.

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[15] CCDC 715782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

