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Isocyanide Insertion: De Novo Synthesis of Trifluoromethylated Phenanthridine Derivatives

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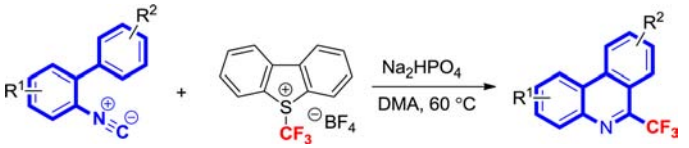
ABSTRACT



A mechanistically new strategy has been described for the simple, practical, and environmentally friendly preparation of 6-(trifluoromethyl)phenanthridine derivatives using ionic isocyanide insertion from biphenyl isocyanide derivatives and Umemoto's reagent. These reactions were promoted only by inorganic base in good-to-excellent chemical yields without any external stoichiometric oxidants and radical initiators.

The phenanthridines are an important group of natural alkaloids,[1] typified by trisphaeridine[2] and nitidine[3] (Figure 1). Many of them show a wide range of pharmacological properties including antitumor, antileukemic, antifungal, and antiviral activities.[4] It is well-known that the introduction of a trifluoromethyl group can lead to a change in the physical, chemical, and biological properties of a compound.[5] Therefore it is of interest to prepare trifluoromethylated phenanthridine derivatives.[6] Herein, we present our efforts in the de novo synthesis of 6-(trifluoromethyl)-phenanthridine derivatives.

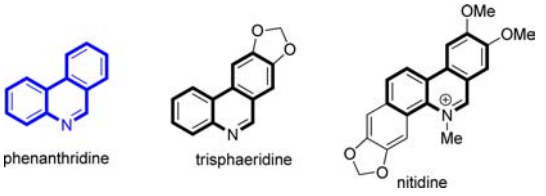


Figure 1. Typical phenanthridine alkaloids.

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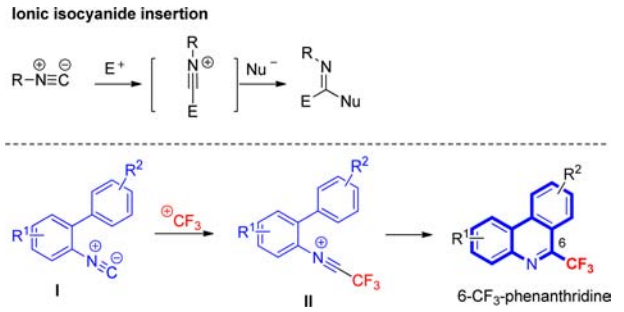
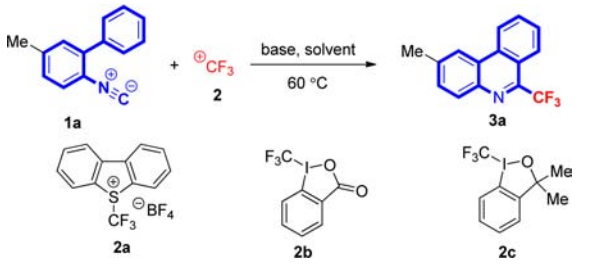


Figure 2. Rationale for synthesis of 6-(trifluoromethyl)-phenanthridine using ionic isocyanide insertion.

Typically, phenanthridine derivatives are constructed by inter- or intramolecular biaryl couplings,[7] which, however, are not suitable for the preparation of 6-(trifluoromethyl)-phenanthridines. Direct trifluoromethylation of phenanthridines leads to mixtures of regioisomers.[8] Trifluoromethylation of 6-prefunctionalized phenanthridines,[9] such as 6-halophenanthridines,[10] is also not convenient because 6-halophenanthridines are not readily available.[11] We envisaged that 6-(trifluoromethyl)phenanthridines could be accessed via ionic isocyanide insertion[12] from biphenyl isocyanide derivatives and electrophilic trifluoromethylating reagents.[13] As shown in Figure 2, 6-(trifluoromethyl)-phenanthridines can potentially be constructed through an intramolecular Friedel–Crafts-type reaction from the trifluoromethylated nitrilium **II**, which can in principle be generated from isocyanide **I** and an electrophilic trfluoromethylating reagent.[14,15]

This idea was first examined using isocyanide **1a**, which is an odorless solid, and Umemoto's reagent **2a**[13] as reaction partners (Table 1). When a solution of **1a** and **2a** in DMF was stirred at room temperature in the presence of Na_2HPO_4 for 24 h, the desired phenanthridine **3a** was isolated in 40% yield (entry 1). When the reaction was heated to 60 °C, the yield was improved to 85% (entry 2). Solvent screening (entries 2–10) showed that aprotic polar solvents, such as DMF, NMP, and DMA, were suitable reaction media while nonpolar solvents, such as DCE and

Table 1. Reaction Condition Optimization[a]



entry	2	base	solvent	yield[b] (%)
1[c]	**2a**	Na_2HPO_4	DMA	40
2	**2a**	Na_2HPO_4	DMF	85
3	**2a**	Na_2HPO_4	CH_3OH	61
4	**2a**	Na_2HPO_4	DMSO	54
5	**2a**	Na_2HPO_4	CH_3CN	0
6	**2a**	Na_2HPO_4	THF	55
7	**2a**	Na_2HPO_4	DCE	trace
8	**2a**	**Na_2HPO_4**	**DMA**	**89**
9	**2a**	Na_2HPO_4	NMP	85
10	**2a**	Na_2HPO_4	$PhCH_3$	trace
11	**2a**	Na_2CO_3	DMA	84
12	**2a**	$NaHCO_3$	DMA	81
13	**2a**	AcONa	DMA	79
14	**2a**	K_3PO_4	DMA	39
15	**2a**	K_2HPO_4	DMA	78
16	**2a**	Cs_2CO_3	DMA	57
17	**2a**	NaOH	DMA	44
18	**2b**	Na_2HPO_4	DMA	trace
19	**2c**	Na_2HPO_4	DMA	50
20	**2a**	none	DMA	26
21	**2a**[d]	Na_2HPO_4	DMA	75

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), and base (0.2 mmol) in indicated solvent (1.0 mL) at 60 °C for 24 h. [b] Isolated yield. [c] Room temperature. [d] 1.2 equiv of **2a** was used.

(7) For selected examples, see: (a) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 5558. (b) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2007**, 4041. (c) Budén, M. E.; Dorn, V. B.; Gamba, M.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **2010**, *75*, 2206. (d) Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2008**, *73*, 4721. (e) Portela-Cubillo, F.; Scanlan, E. M.; Scottb, J. S.; Walton, J. C. *Chem. Commun.* **2008**, 4189. (f) Alonso, R.; Campos, P. J.; García, B.; Rodrlguez, M. A. *Org. Lett.* **2006**, *8*, 16. (g) Read, M. L.; Gundersen, L. L. *J. Org. Chem.* **2013**, *78*, 1311. (h) Linsenmeier, A. M.; Williams, C. M.; Bräse, S. *J. Org. Chem.* **2011**, *76*, 9127. (i) Fox, M. A.; Chandler, D. A.; Lee, C. *J. Org. Chem.* **1991**, *56*, 3246. (j) Murahashi, S. I.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, 1745. (k) Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933.

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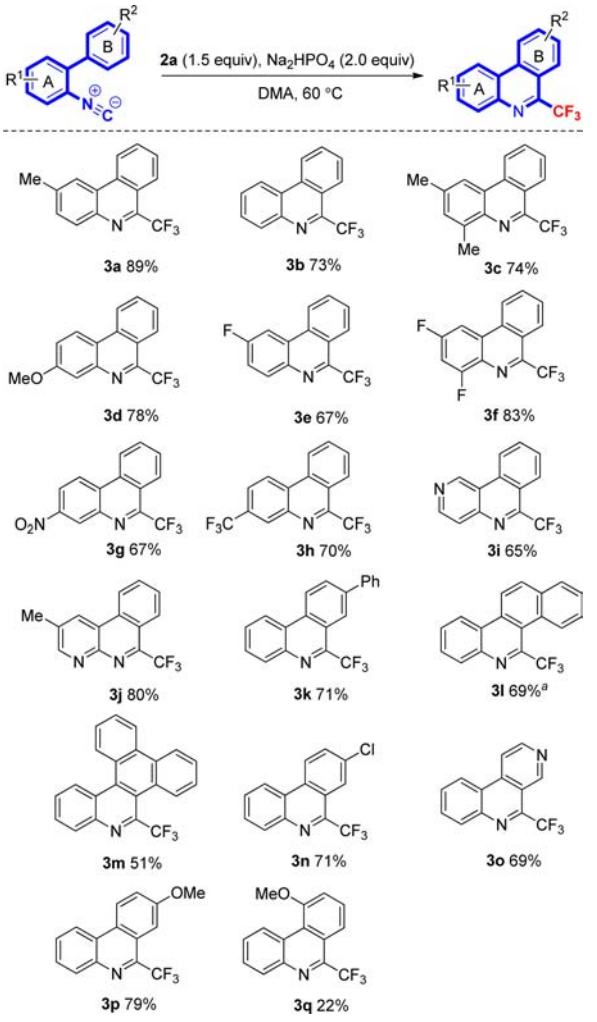

Figure 3. Scope of coupling of bromides with alkynes. All reactions carried out under the optimized conditions. The yields were isolated yields. [a]The ratio of regioisomers is 13:1 based on ^{19}F NMR analysis.

toluene, were not effective at all. A variety of bases were then examined (entries 11−17), and none of them was better than Na_2HPO_4. Alterative electrophilic trifluoromethylating reagents, such as Togni's reagents **2b** and **2c**, were not superior to Umemoto's reagent **2a** (entries 18 and 19). The yield dropped to 26% without base (entry 20), and the yield was slightly decreased to 75% when less **2a** (1.2 equiv) was used (entry 21).

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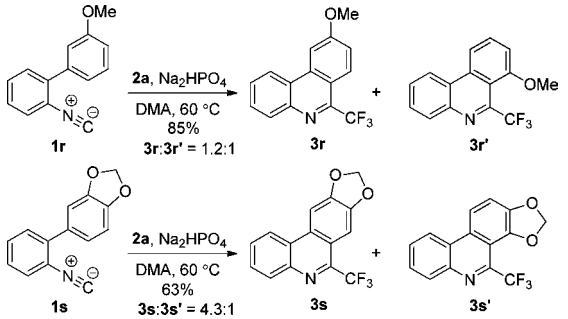
Scheme 1. Ionic Isocyanide Insertion of **1r** and **1s**



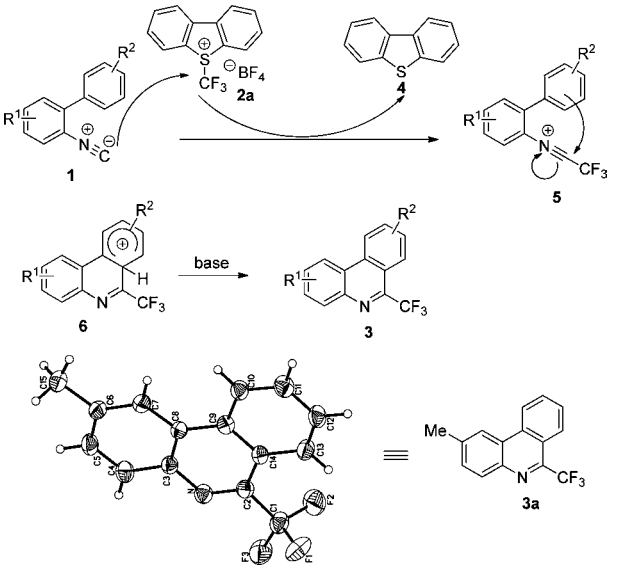


Figure 4. Proposed mechanism for the ionic isocyanide insertion of biphenyl isocyanides with Umemoto's reagent.

To find the scope of this transformation, a variety of isocyanides were explored, as shown in Figure 3. The substitutions on the benzene ring A did not affect this transformation significantly, and the desired 6-(trifluoromethyl)phenanthridines **3a**−**h** were isolated in good yields (70−89%). Pyridines were also compatible, and the trifluoromethylated heterocycles **3i** and **3j** were produced in satisfactory yields. Different substituted benzene rings B were then examined. All of them worked well to give trifluoromethylated heterocycles **3k**−**p** in 51−80% yields except *o*-substituted substrate **3q**, which was isolated in 22% yield.

When we attempted trifluoromethylation of isocyanides **1r** and **1s**, which bear *meta*-substitutions on benzene rings B, two regioisomers were isolated (Scheme 1). Trifluoromethylation

(15) During our preparation of this manuscript, two works on the synthesis of 6-(trifluoromethyl)phenanthridines via radical pathways have been reported; see: (a) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (b) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846.

of isocyanides **1r** gave phenanthridines **3r** and **3r′** in a 1.2:1 ratio based on ^{19}F NMR analysis and 85% overall yield. Isocyanides **1s** underwent this transformation to provide (trifluoromethyl)trisphaeridine **3s** and its regioisomer **3s′** in a ratio of 4.3:1 and 63% combined yield. The method presented here provides a convenient entry to trifluoromethylated natural phenanthridine alkaloids.

The reaction can go through ionic or radical pathways. Because of the lack of obvious radical initiator, the ionic pathway is the more preferred one, which is shown in Figure 4.[16] First, isocyanide **1** nucleophilically attacks Umemoto's reagent **2a** to give the trifluoromethylated nitrilium ion **5**. The nitrilium ion **5** undergoes intramolecular Bischler–Napieralski-type cyclization to give the final phenanthridine **3** after deprotonation. The structure of **3a** was established ambiguously by single-crystal X-ray diffraction analysis.

In summary, we have developed a concise and efficient synthetic approach to 6-(trifluoromethyl)phenanthridine derivatives through ionic isocyanide insertion from biphenyl isocyanide derivatives and Umemoto's reagent. The only reagent to promote this transformation is inorganic base Na_2HPO_4. The simple and environmentally friendly procedure should benefit the future development of potential industrial processes. Further exploration of mechanistic details and new isocyanide insertion is underway.

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Supporting Information Available. Full experimental procedures and characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) At this stage, the radical pathway cannot be excluded completely. For a possible radical pathway, see the Supporting Information.

The authors declare no competing financial interest.