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A One-Pot Access to 6-Substituted Phenanthridines from Fluoroarenes and Nitriles via 1,2-Arynes

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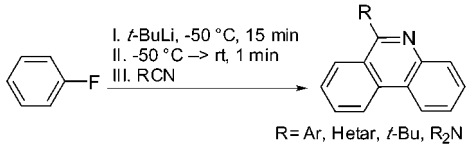
ABSTRACT



A one-pot, *t*-BuLi-induced synthesis of 6-substituted phenanthridines from fluoroarenes and nitriles via 1,2-arynes is reported. Aryl- and hetaryl nitriles, cyanamides, and trimethylacetonitrile gave phenanthridine products. The method was extended to provide bisphenanthridine 10 by a one-pot bis-cyclization, using 1,3-dicyanobenzene and PhF in 1:5 ratio. Reaction of 1-fluoronaphthalene and 4-chlorofluorobenzene with benzonitrile afforded the regioisomerically pure products 11 and 12, respectively.

Chemistry of arynes provides a robust tool for synthetic design and methodology.[1] The recent reports concerned with formation,[2] reactivity,[3] and in particular synthetic applications[4] of arynes illustrate the continued interest in the area. Biehl and others have shown that arynes can be employed with outstanding success for the synthesis of various nitrogen heterocycles.[1c,5] Yet, despite apparent practical advantages of such a strategy (see below), we are not aware of a route to dibenzo-fused pyridine systems simply by reacting a nitrile with two aryne molecules in a 2 + 2 + 2 fashion.[6,7] Herein, this goal is formally accomplished: we report a *t*-BuLi-induced synthesis of 6-substituted phenanthridines (6SPs) from nitriles and fluoroarenes, which presumably proceeds via 1,2-aryne intermediates.

6SPs have recently found interesting applications,[8] but even the contemporary methods for their construction rely on multistep syntheses and often require harsh conditions.[9] We reasoned that 6SPs (**1**) could be obtained by *timely addition of a nitrile* to reactive 2-fluoro-2′-lithiobiphenyl **2** (Scheme 1).[10] By this method, **1** would be formed by addition of **2** to a nitrile, followed by an intramolecular S_NAr reaction. The salient aryllithium **2** would be generated by attack of a

(1) For reviews, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427−498. (c) Biehl, E. R.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, *22*, 275−281. (d) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 2.3.

(2) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674−11679.

(3) (a) Clark, A. E.; Davidson, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 10691−10698. (b) Liu, H.-C.; Wang, C.-S.; Guo, W.; Wu, Y.-D.; Yang, S. *J. Am. Chem. Soc.* **2002**, *124*, 3794−3798.

(4) (a) Escudero, S.; Pérez, D.; Guitian, E.; Castedo, L. *Tetrahedron Lett.* **1997**, *38*, 5375−5378. (b) Cobas, A.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 4896−4897. (c) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1998**, *63*, 6742−6744. (d) Bailey, W. F.; Longstaff, S. C. *J. Org. Chem.* **1998**, *63*, 432−433. (e) Frid, M.; Pérez, D.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9469−9470. (f) Tripathy, S.; LeBlanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973−1975. (h) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334−5341. (i) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280−7286. (j) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403−1412. (k) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686−12687. (l) Rayabarapu, D. K.; Majumdar, K. K.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 3646−3649. (m) Rao, U. N.; Biehl, E. *J. Org. Chem.* **2002**, *67*, 3409−3411. (n) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem. Eur. J.* **2002**, *8*, 2034−2045.

(5) Biehl, E. R. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press Inc: New York, 2000; Vol. 4, pp 251−293 and references therein.

(6) (a) For a leading reference on metal-catalyzed pyridine formation from two alkynes and a nitrile, see: Takahashi, T.; Tsai, F.-Y.; Li, Z.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059−5067. (b) For a novel method to construct pyridines from lithiobutadienes and nitriles, see: (1) Cheng, J.; Song, Q.; Wang, C.-S.; Xi, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6238−6239.

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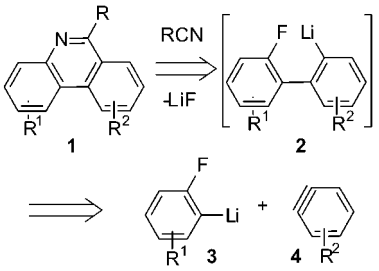
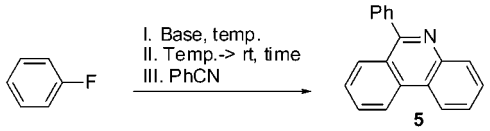
Scheme 1



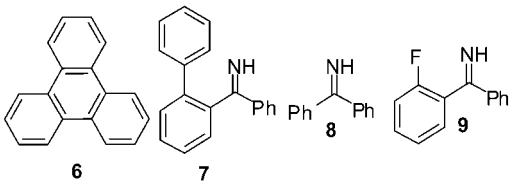
o-fluorophenyllithium **3**[11] on 1,2-aryne **4**, which could be formed either from **3** by loss of LiF ($R^1 = R^2$), or from another aryne precursor ($R^1 \neq R^2$). The latter approach would allow installation of different substituents onto phenyl rings in 6SPs. However, *o*-fluorophenyllithium is known to be stable only at or below −70 °C.[11] At higher temperatures—presumably needed for addition of **3** to benzyne **4** at sufficiently high rates—LiF elimination from **3** may occur faster than attack on benzyne, preventing formation of substantial amounts of aryllithium **2**. Gratifyingly, our initial attempt to prove the principle outlined in Scheme 1 did provide the phenanthridine product, though in a modest yield (Table 1, entry 1). Fluorobenzene, which served as the precursor for both **3** and **4**, was *ortho*-lithiated[12] using *t*-BuLi at −78 °C in dry THF. After 10 min at −78 °C, the reaction was warmed to room temperature to generate **2**, followed by addition of 1.5 equiv of PhCN, which gave **5**. Yet, the **3**:**4** ratio obtained under these conditions was not optimal: according to GC−MS analysis, a large amount of triphenylene **6** was formed, most likely by reaction of **2** with **4**.[13] Moreover, small amounts of imines **7** and **8** were also detected by GC−MS, indicating the presence of PhLi at the time PhCN was added.[14] After some experimentation, we found conditions that completely suppressed formation of **7** and **8** (entry 2). This in turn provided a slightly better yield of **5**, but **6** was again formed as the major product. In our next attempt, we added PhCN before warming the reaction to room temperature (entry 3). The yield of **5** was further increased, and the arene **6** was not formed at all. In fact, the only detectable byproduct was the imine **9**. Through a series of experiments varying temperature and timing of PhCN addition, we established that the isolated yield of **5** is highest when PhCN is added *while the reaction is being warmed to room temperature*, ca. 1 min after the acetone−dry ice bath keeping the reaction at low temperature is removed (entry 4). It is noteworthy that imine **9**, which was invariably obtained as a byproduct in these reactions, could be hydrolyzed to the corresponding ketone at an acidic pH. This ketone was in turn easily removed by extraction, circumventing use of chromatography during isolation of **5**.[15] Since unreacted PhCN was always detected in the crude product mixtures in the above experiments, we carried out reactions using less PhCN (entries 5 and 6). Nevertheless, this had a detrimental effect on the yield of **5**, and arene **6** emerged as a byproduct. Next, different lithium bases were screened (entries 7 and 8),[16] but these reactions provided **5** in lower yields than experiments using *t*-BuLi as the base.

Table 1. Base-Induced Formation of 6-Phenylphenanthridine from Fluorobenzene and Benzonitrile[a]



entry	base	time (min)	temp (°C)	equiv of PhCN[b]	% yield
1	*t*-BuLi[c]	10	−78	1.50	16[d]
2	*t*-BuLi[e]	10	−50	1.50	19[d]
3	*t*-BuLi[e]	0	−50	1.50	37[f]
4	*t*-BuLi[e]	1	−50	1.50	63[f]
5	*t*-BuLi[e]	1	−50	1.25	54[f]
6	*t*-BuLi[e]	1	−50	1.00	49[f]
7	*s*-BuLi[e]	1	−50	1.50	43[f]
8	LTMP[g]	1	−50	1.50	40[f]

[a] Reaction conditions: 3.2 mmol of PhF in 10 mL of THF under N_2 at temp, 3.2 mmol of base added. [b] Based on PhF being 2.0 equiv. [c] Added over 10 min. [d] Calibrated GC−MS yield. [e] Added over 5 min, kept at −50 °C a further 10 min. [f] Isolated yield. [g] PhF (neat) added over 1 min to premade LTMP in 10 mL of THF, kept at −50 °C a further 14 min.



With the optimized conditions for the one-pot formation of 6-phenylphenanthridine **5** (Table 1, entry 4),[17] we

(7) For a benzyne-mediated pyridine formation in benzo[*c*]phenanthridines, see: Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708−1713.

(8) (a) 6SPs as 5-HT_3 receptor ligands: Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Bruni, G.; Romeo, M. R.; Menziani, M. C.; De Benedetti, P. G.; Langer, T. *J. Med. Chem.* **1998**, *41*, 728−741. (b) As topoisomerase inhibitors: Lynch, M. A.; Duval, O.; Sukhanova, A.; Devy, J.; MacKey, S. P.; Waigh, R. D.; Nabiev, I. *Bioorg. Med. Chem.* **2001**, *11*, 2643−2646. (d) As a tether in enzyme-controlled cycloaddition: Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053−1056.

(9) (a) For a recent three-step protocol, see: Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257−259. (b) Katritzky, A. R.; Yang, B.; Dalal, N. S. *J. Org. Chem.* **1998**, *63*, 1467−1472. (c) Patra, P. K.; Suresh, J. R.; H., I.; Junjappa, H. *Tetrahedron* **1998**, *54*, 10167−10178; see also references therein for listing of earlier methods.

(10) For a route to pyrazoloquinolines by adding nitriles to a 2-fluorophenylpyrazolyllithium, see: Pawlas, J.; Vedsø, P.; Jakobsen, P.; Huusfeldt, P. O.; Begtrup, M. *J. Org. Chem.* **2001**, *66*, 4214−4219.

(11) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1955**, *77*, 3919−3920.

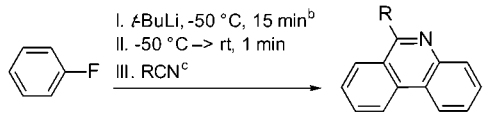
(12) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

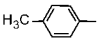
(13) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217−2222.

(14) PhLi can be formed from an alkylithium and benzyne: Franzen, V.; Joschek, H.-I. *Angew. Chem.* **1960**, *72*, 564.

examined the scope of the cyclization using different nitriles (Table 2). Arylnitriles with different steric and electronic properties participated in this cyclization (entries 1−11), although the substitution pattern on the benzene moiety had a profound effect on the yield of phenanthridine products. For example, tolunitriles (entries 2, 4, and 6) and both 4- and 2-chlorobenzonitrile (entries 3 and 7) provided 6SPs in yields comparable to reactions using benzonitrile, but the yield of phenanthridine product was substantially lower when 3-chlorobenzonitrile was employed (entry 5). Presumably, this was due to competitive proton abstraction from the nitrile by aryllithium **2**.[18] Furthermore, moderately congested 2-substituted benzonitriles afforded reasonable yields of cyclized products (entries 6 and 7), but when the highly hindered nitriles in entries 8 and 9 were used, the yields dropped significantly. On the other hand, some base-sensitive substituents were tolerated (entries 10 and 11).[19] Also hetarylnitriles could be incorporated (entries 12−15). As was the case with arylnitriles, large differences in yields were observed. For example 2-cyanopyridine afforded the cyclized product in much higher yield than the 3-isomer (entries 12 and 13). Again, the lower yield with the latter is possibly due to abstraction of an acidic proton from the nitrile by **2**.[18] In addition, by utilizing the bulky trimethylacetonitrile in entry 16, we extended our method beyond aromatic substrates. The lower yield in this case was primarily due to preferential formation of **6**, which was formed as the major product.[20] The extension to cyanamides is important despite the modest yields obtained in these reactions (entries 17 and 18). This process constitutes a one-step entry to a medicinally relevant structural class[7a] from readily available materials.

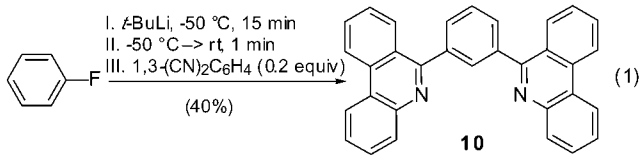
Table 2. *t*-BuLi-Induced Synthesis of 6-Substituted Phenanthridines from Fluorobenzene and Nitriles[a]



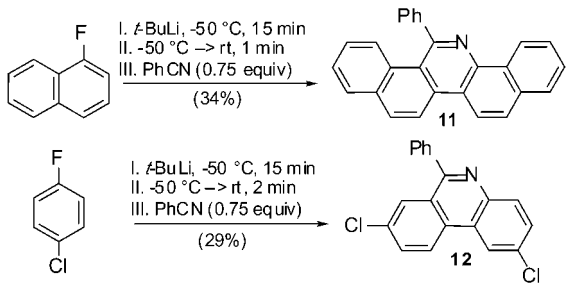
Entry	R	% Yield[d]	Entry	R	% Yield[d]
1[e]		63	10		43
2		56	11		43[f]
3		45	12		36
4		56	13		19
5		31	14		46
6		48	15		31
7		42	16	*t*-Bu–	29
8		27	17	Et_2N–	35
9		30	18		26

[a] Reaction conditions: 3.2 mmol of PhF in 10 mL THF at −50 °C under N_2, 3.2 mmol of *t*-BuLi added. [b] *t*-BuLi added over 5 min. [c] 1.5 equiv, based on PhF being 2.0 equiv. [d] Isolated yield, average of two runs. [e] Table 1, entry 4. [f] Isolated as free amine.

Furthermore, we were able to extend the method herein to a facile one-pot bis-cyclization. Thus, bisphenanthridine **10** was obtained simply by changing the PhF to 1,3-dicyanobenzene ratio from 4:3 (as in Table 2, entry 10) to 5:1 (eq 1).[21] The phenanthridine shown in Table 2 was present as a minor byproduct, and could be easily separated by chromatography. Finally, we initiated studies using substituted fluorobenzenes. Not surprisingly,[22] using 4-fluorotoluene, benzonitrile, and the conditions optimized in Table 1 afforded an inseparable, ca. 1:1 mixture of dimethylated 6-phenylphenanthridines in 41% overall yield.[23] On the contrary, both 1-fluoronaphthalene and 4-chlorofluorobenzene provided the phenanthridine products as single regioisomers (Scheme 2).[24] In the latter case, to obtain **12**, slightly modified conditions had to be employed.



Scheme 2



In summary, a one-pot, *t*-BuLi-induced process to construct 6SPs from fluoroarenes and nitriles was developed.

(15) **Typical Procedure**. **6-Phenylphenanthridine (Table 2, entry 1).** To a stirred solution of fluorobenzene (316 μL, 3.20 mmol) in 10.0 mL of THF at −50 °C was added over 5 min dropwise 1.7 M *t*-BuLi in pentane (1.88 mL, 3.20 mmol). After an additional 10 min at −50 °C, the acetone−dry ice bath was removed. Exactly 1 min after removal of the acetone−dry ice bath, benzonitrile (248 μL, 2.40 mmol) was added. The reaction was allowed to warm to room temperature, 15 mL of 4 M HCl was added, and the crude mixture was vigorously stirred overnight. The reaction was then extracted with diethyl ether (3 × 150 mL), the pH of the aqueous phase was adjusted to ca. pH 10 using 2 M NaOH, and the basic aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), ca. 50 mL EtOAc was added, and filtration through a pad of silica gel (ca. 4 g) followed by evaporation afforded 257 mg (63%) of the title compound as yellow crystals, mp 100−101 °C (EtOAc/heptane).

(16) According to GC−MS, *n*-BuLi, MeLi, PhLi, and LDA gave only traces of **5**.

(17) Using DME, Et_2O, or THF/dioxane as solvent gave <20% of **5**, while the reactions performed at concentrations higher than those given in Table 1 provided **6** as the main product. Phenanthridine **5** was not obtained when PhCl was used instead of PhF.

The scope of the method was examined using a variety of nitriles. This chemistry also set up a one-pot formation of a bis-cyclized product **10**. A few substituted fluoroarenes were examined, which in some cases afforded 6SPs as single regioisomers. Experimental simplicity,[15] abundance of inexpensive readily available building blocks, and easy access to diverse structural motifs compensate for the moderate yields generally delivered by this method. Future studies will focus on providing access to unsymmetrically substituted 6SPs (Scheme 1, $R^1 \neq R^2$), as well as on utilizing hetarynes[1b] in the herein disclosed cyclization.

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Supporting Information Available: Experimental details, characterization of all products, and NMR spectral data of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Large amounts of 2-fluorobiphenyl were detected in the crude reaction mixture by GC−MS.

(19) Free amino, nitro, and ester groups are not compatible with this chemistry.

(20) Expectedly, CH_3CN did not give 6-methylphenanthridine. An α-proton was abstracted by **2** instead to give 2-fluorobiphenyl as the major product. See ref 9a for a method enabling introduction of α-hydrogen-containing alkyl groups.

(21) Bisphenanthridines of type **10** are unknown, and the potential uses of such systems are thus unexplored. On the other hand, the related terpyridines are well-known and have been used, e.g., in Ru-based cyclometalated complexes. See for example: (a) Beley, M.; Collin, J.-P.; Louis, R.; Metz, B.; Sauvage, J.-P. *J. Am. Chem. Soc*. **1991**, *113*, 8521−8522. (b) Beley, M.; Chodorowski, S.; Collin, J.-P.; Sauvage, J.-P. *Tetrahedron Lett.* **1993**, 2933−2936. (c) Chavarot, M.; Pikramenou, Z. *Tetrahedron Lett.* **1999**, 6865−6868.

(22) For a general discussion on addition of nucleophiles to unsymmetrically substituted arynes, see ref 1a, pp 134−150.

(23) Both 3- and 2-fluorotoluenes also provided ca. 1:1 mixtures of regioisomers, but in much lower yields than 4-fluorotoluene.

(24) While it is known that additions of nucleophiles to 1-naphthyne and 4-chlorobenzyne may lead to mixtures of regioisomers, additions to the 2-position of the former and the 4-position of the latter are generally favored for a variety of nucleophiles.[22]