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Convergent Synthesis of 6-Substituted Phenanthridines via Anionic Ring Closure

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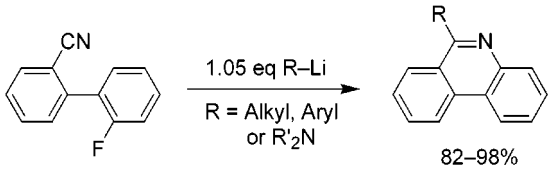
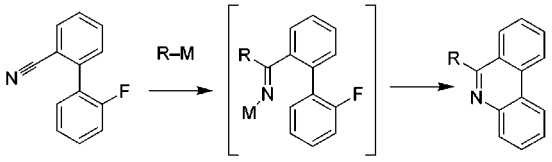
ABSTRACT



The addition of organometallic derivatives to the cyano group of 2-(2-fluorophenyl)benzonitrile followed by intramolecular nucleophilic substitution produces 6-substituted phenanthridines. Alkyllithiums, aryllithiums, and sterically nondemanding lithium amides reacted at −78 °C to produce the 6-substituted phenanthridines in 82−98% yield upon warming to room temperature. The addition of the corresponding Grignard reagents requires an excess of the organometallic reagent and extented reaction times at elevated temperature.

The addition of organometallic species to cyano groups is a fundamental transformation in organic synthesis.[1] The resulting imine intermediates can be protonated and isolated at the imine-stage or hydrolyzed to yield the corresponding ketones.[2] Alternatively, the intermediate imine anions can be trapped with electrophiles.[3] Protocols for the intramolecular trapping of imine-anions have also been developed. Thus, addition of Grignard reagents to the cyano group of 4-chlorobutyronitriles and subsequent intramolecular displacement of the chloride produces substituted pyrrolines.[4] We now wish to report a new variant of this reaction, see Scheme 1.[5] Addition of an organometallic reagent to the cyano group of 2-(2-fluorophenyl)benzonitrile (**1**) gives the intermediate imine-anion (**2**). Subsequent intramolecular nucleophilic aromatic substitution gives 6-substituted phenanthridines (**3**).

Scheme 1. 6-Substituted Phenanthridines via Anionic Ring Closure



1 **2** **3**

Substituted phenanthridines are of great interest for medicinal chemistry applications and have a broad range of biological activities.[6] The Bischler−Napieralski cyclization

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(1) Kharash, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice Hall: New York, 1954; Chapter 10.

(2) (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press Ltd.: Oxford, 1974; pp 116−121. (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press Limited: London, 1995; pp 101−108.

(3) (a) Chan, L. H.; Rochow, E. G. *J. Organomet. Chem.* **1967**, *9*, 231−250. (b) Padwa, A.; Koehn, W. P. *J. Org. Chem.* **1975**, *40*, 1896−1902. (c) Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 691−703. (d) Ortiz-Marciales, M.; Tirado, L. M.; Colón, R.; Ufret, M. L.; Figueroa, R.; Lebrón, M.; DeJesús, M.; Martínez, J.; Malavé, T. *Synth. Commun.* **1998**, *28*, 4067−4075.

(4) Demoen, P. J. A.; Janssen, P. A. *J. Chem. Soc.* **1959**, 6281−6285 and references therein.

(5) We recently reported a similar approach to the synthesis of substituted pyrazoloquinolines; see: Pawlas, J.; Vedsø, P.; Jakobsen, P.; Huusfeldt, P. O.; Begtrup, M. *J. Org. Chem.* **2001**, *66*, 4214−4219.

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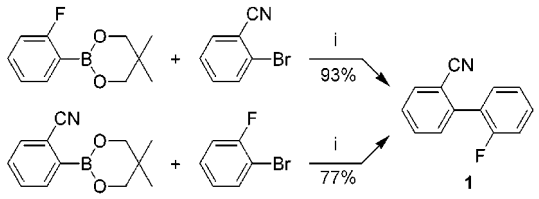
has been used extensively to synthesize phenanthridine derivatives.[7] It is usually performed in the presence of P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperature, thereby limiting the kind of functional groups that can be tolerated. Many other synthetic routes to phenanthridines have been developed.[8]

The key starting compound **1** required for the anionic ring closure was accessed via a Suzuki cross-coupling reaction.[9] The biphenyl could be prepared in two ways, see Scheme 2.

Scheme 2. Dual Synthesis of **1**[a]

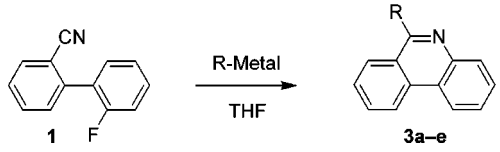


[a] Key: (i) 3% $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O 6:1:1, 85 °C, 7 h.

This dual approach should offer the possibility of preparing a wide selection of substituted derivatives of **1** using readily available aryl halides and arylboronic acids and esters. The arylboronic esters in Scheme 2 were prepared as previously reported.[10]

In our initial experiment we focused on the Cu(I)-catalyzed addition of Grignard reagents to **1**.[11] The reactions were very sluggish and required heating for extended time (Table 1, entries 1−5). Furthermore, 3 equiv of Grignard reagent was needed. Refluxing **1** with 1 equiv of *i*-PrMgCl in the presence of 3% CuI for 20 h gave a 3:2 mixture of unchanged **1** and the desired 6-substituted phenanthridine **3b**. When 3 equiv of *i*-PrMgCl was used, the desired product **3b** was isolated in 74% yield. MeMgCl and *n*-BuMgCl gave **3a** and **3c** in 59% and 49% yields under similar conditions, whereas *p*-tolylMgCl gave the desired product **3e** in 81% yield after 3 h at 70 °C. The reaction with *t*-BuMgCl (entry 4) gave complicated mixtures under several different conditions and none of the desired product **3d** could be isolated.

Table 1. Synthesis of 6-Substituted Phenanthridines via the Addition of Grignard and Organolithium Reagents to **1**



Entry	R	Product	Yield (%)[a] MgCl[b]	Li[c]
1	Methyl	**3a**	59	87
2	*i*-propyl	**3b**	74	-[d]
3	*n*-butyl	**3c**	49	87
4	*tert*-butyl	**3d**	-[e]	85
5	*p*-tolyl	**3e**	81[f]	90

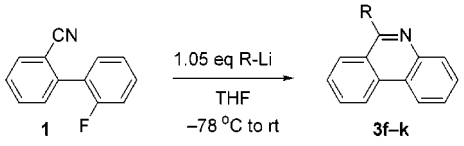
[a] Yields of chromatographically pure product. [b] 3 equiv of RMgCl, 3% CuI, reflux 20 h. [c] 1.05 equiv of RLi, −78 °C to room temperature. [d] Experiment not performed. [e] Complex mixture. [f] Reflux for 3 h.

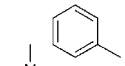
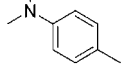
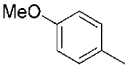
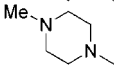
The addition to the cyano group appears to be the rate-limiting step, as the imine-intermediate was not observed at any time. In an attempt to speed up the reaction, the use of the corresponding lithium reagents was investigated. The addition to the cyano group proceeded at −78 °C, and subsequent warming of the reaction mixture to room temperature produced the desired 6-substituted phenanthridines; see Table 1.

Yields were higher than with Grignard reagents, and only 1.05 equiv of the organolithium reagent was required to obtain full conversion of **1**. Notably, *tert*-butyllithium produced the desired product **3d** in 85% yield (entry 4). Furthermore, higher yields were obtained when **1** was added to a solution containing the lithium reagents. 6-Butylphenanthridine (**3c**) was isolated in 87% yield when **1** was added to *n*-butyllithium at −78 °C, compared to 77% when the order of addition was reversed.

The protocol was extended to other aryllithium reagents; see Table 2. The 6-aryl-substituted phenathridinines **3f**−**h** were isolated in 82−92% yield. 6-Aryl-substituted phenanthridines have been reported as potent DNA-intercalating antitumor agents.[6a] Furthermore, sterically nondemanding lithium amides reacted smoothly to give the corresponding 6-aminophenanthridines **3i**−**k** in 88−98% yield.[12] Recently,

Table 2. Synthesis of 6-Substituted Phenanthridines via the Addition of Aryllithium Reagents and Lithium Amides to **1**



Entry	R	Product	Yield (%)[a]
1		**3f**	92
2		**3g**	82
3		**3h**	85
4		**3i**	88
5		**3j**	94
6		**3k**	98

[a] Yields of chromatographically pure product.

(6) DNA-Intercalating antitumor agents: (a) Atwell, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1988**, *31*, 774−779. 5-HT_3 receptor ligands: (b) Cappelli, A.; Anzini, M.; Vomero, S.; Mannuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Bruni, G.; Romeo, M. R.; Menziani, M. C.;

3k and analogues thereof were reported to have high affinity for the 5-HT_3 receptor.[6b] Our approach provides a rapid and convergent access to this class of compounds.

In conclusion, we have developed a rapid and convergent synthesis of 6-substituted phenanthridines proceeding in two steps from readily available starting materials. The addition of alkyllithiums, aryllithiums and lithium amides to 2-(2-fluorophenyl)benzonitrile (**1**) produces the corresponding 6-substituted phenanthridines **3a**−**k** via an intramolecular anionic ring closure.[13] We are currently exploring the scope of the reaction with respect to substituted derivatives of **1** and the application of other nucleophiles.

Supporting Information Available: Detailed experimental procedures and characterization for compounds **1** and **3a**−**k**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Mamalis, P.; Petrow, V. *J. Chem. Soc.* **1950**, 703−711. (b) Buu-Hoï, N. P.; Jaquignon, P.; Long, C. T. *J. Chem. Soc.* **1957**, 505−509.

(8) For a comprehensive list of references see Patra, P. K.; Suresh, J. R.; Ila, H.; Junjappa, H. *Tetrahedron* **1998**, *54*, 10167−10178.

(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(10) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437.

(11) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901−3904.

(12) Attempted addition of lithium diisopropylamide to **1** led to a complex mixture, presumably due to competing ortho-lithiation.

(13) **Representative Procedure. 6-Piperidyl-phenanthridine (3j).** Piperidine (91 mg, 1.05 mmol) was dissolved in THF (4 mL) under N_2 and cooled to −10 °C. *n*-Butyllithium (1.6 M in hexanes, 1.05 mmol) was added, and stirring was continued for 10 min. The mixture was cooled to −78 °C before 2-(2-fluorophenyl)benzonitrile (**1**) (1.00 mmol) dissolved in THF (2 mL) was added dropwise, and stirring was continued for 15 min. The dry ice bath was removed, and the mixture was stirred at room temperature for 20 min. The reaction was quenched with saturated NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried (Na_2SO_4), and the solvent was evaporated giving the crude product, which was purified by flash chromatography yielding 246 mg (94%) of **3j** as colorless crystals, mp 86 °C, reported mp 82−83 °C. Keene, B. R. T.; Turner, G. L. *Tetrahedron* **1971**, *27*, 3405−3416.