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S_NAr Reactions of Benzaldimines: A Concise Synthesis of Substituted Phenanthridines$^{\Phi}$

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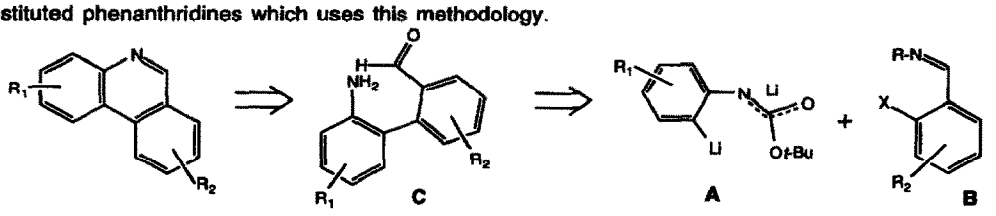
Key Words: *Nucleophilic aromatic substitution; aromatic aldimines; organolithium reagents*

Abstract: Halogenated benzaldimines react with dilithiated N-Boc-aniline derivatives to yield biaryl imines *via* a S_NAr reaction. Mild hydroysis of this imine then allows cyclization to the substituted phenanthridine. Extension of this reaction to a variety of N-Boc-anilines and imines was explored.

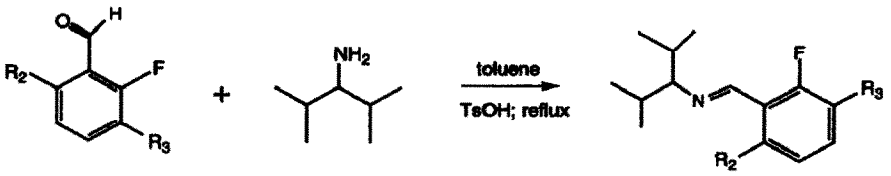
The phenanthridine ring system is an integral part of many synthetic dyestuffs, antibacterial and antileukemic agents, and diverse metabolites of the plant families Fumariaceae, Papaveraceae, and Rutaceae.[1] Several diverse synthetic routes are available for the construction of substituted phenanthridines; however, most of the known procedures[2] suffer from limited generality or poor yields. In this Letter we describe a concise synthesis of substituted phenanthridines that proceeds via S_NAr coupling of o-fluorobenzaldimines with ortho-lithiated N-Boc-aniline derivatives. This novel synthesis appears to complement the extant methodology inasmuch as several previously undescribed phenanthridines are now readily available.

Nucleophilic substitution with a carbon nucleophile at an aromatic center (S_NAr) has played an increasingly important role in organic synthesis over the past two decades.[3] Although activating groups on the electrophilic component of S_NAr reactions with carbon nucleophiles have classically been limited to substituted oxazolines (carboxylic acid oxidation state), it has been demonstrated recently that the 2,4-dimethylpent-3-ylimine moiety (aldehyde oxidation state) also activates aromatic electrophiles toward S_NAr reaction with organolithium reagents.[4] Herein, we describe a new synthetic route to substituted phenanthridines which uses this methodology.



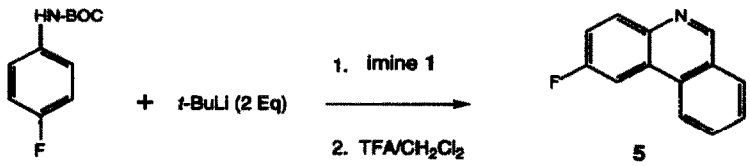
Our approach to the phenanthridine ring system included an ortho-lithiated, protected aniline (**A**) and an aromatic aldimine (**B**). We envisaged that S_NAr coupling of the dianion and the aldimine followed by hydrolytic deprotection would provide a biphenyl aldehyde (**C**). This intermediate should then be poised for cyclization to the phenanthridine ring system.

Synthesis of the requisite N-Boc aniline derivatives was straightforward following standard procedures.[5] Benzaldimines **1-4** were prepared readily in $\geq$ 90% yield through 3-amino-2,4-dimethylpentane addition to the appropriate aldehyde with removal of water *via* a Dean-Stark trap.[4]



1 $R_2 = R_3 = H$
2 $R_2 = Cl; R_3 = H$
3 $R_2 = H; R_3 = F$
4 $R_2 = F; R_3 = H$

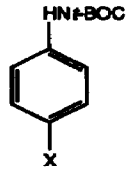
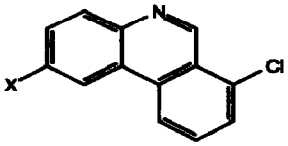
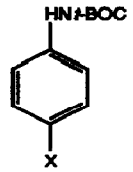
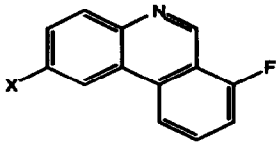
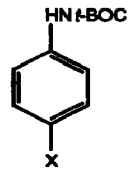
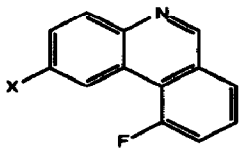
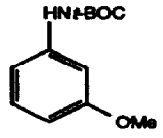
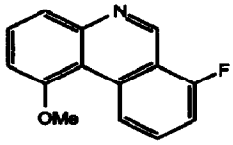
Treatment of N-Boc *p*-fluoroaniline with two equivalents of *tert*-butyllithium in ether at -30 °C resulted in clean formation of the dianion (determined by benzaldyhyde quench and isolation of the product). Transfer of the dianion solution slowly into an ethereal solution of imine **1**[6] with a cannula provided a primary adduct which was hydrolyzed without purification (TFA/CH_2Cl_2) to yield 20% of phenanthridine **5**.



5

This protocol was extended to several other imine/N-Boc-aniline pairs to give substituted phenanthridines in fair to good yield (Table).[7] The reaction appeared to be sensitive to steric hindrance in either the aniline or the imine derivative[8] and additional electronegative substituents on the imine component led to increased S_NAr reactivity.[9]

In conclusion, we have described a novel, concise synthesis of substituted phenanthridines utilizing S_NAr methodology. Future directions include extending the methodology to phenanthridine-containing natural products as well as the construction of other heterocyclic ring systems.

Carbamate	Imine	Product	Yield
	2		
		5 X = H	65%
		6 X = OMe	62%
		7 X = F	40%
		8 X = CH_3	52%
		9 X = Cl	62%
	4		
		10 X = H	63%
		11 X = OMe	74%
		12 X = CH_3	49%
	3		
		13 X = F	21%
		14 X = OMe	32%
	4		
		15	15%

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Φ Contribution #894 from the Institute of Organic Chemistry. This paper is dedicated to Dr. John Edwards on the occasion of his retirement from Syntex Discovery Research.

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4. Flippin, L. A., Carter, D. S., Dubree, N., *Tetrahedron Lett.*, **1993**, *34*, 3255.

5. Muchowski, J. M., Venuti, M. C., *J. Org. Chem.*, **1980**, *45*, 4798.

6. Originally, we attempted utilizing the *o*-methoxyaldimine; however none of the desired product could be obtained. Other references incorporating the use of halogenated imines and oxazolines are as follows: Meyers, A.I., Williams, B., *Tetrahedron Lett.*, **1978**, *19*, 223; Shindo, M., Koga, K., Tomioka, K., *J. Am. Chem. Soc.*, **1992**, *114*, 8732.

7. All products were completely characterized by NMR, IR, mass spectrometry, and elemental analysis.

8. Steric hindrance in the imine component may be responsible for the low yields of phenanthridines **13** and **14**. Steric hindrance in the N-Boc-aniline component may have caused the low yield of **15**.

9. A typical procedure of **10** is as follows: To a dry 3-neck 100 mL round bottom flask under a nitrogen atmosphere was added 0.87 g (4.50 mmol) of the aniline followed by 30 mL of Et_2O. This solution was cooled to -70 °C and 5.2 mL (8.84 mmol) of *t*-BuLi was added slowly. The resulting mixture was allowed to warm to 0 °C for 90 minutes and then recooled to -70 °C. This homogeneous solution was then transferred *via* a cannula to the imine (0.79 g, 3.3 mmol) in 15 mL of Et_2O at -30 °C over 5 minutes. The reaction was allowed to stir at this temperature for one hour. The reaction was quenched *via* addition of 5 mL of saturated NH_4Cl solution and this mixture was washed with EtOAc (2X). The organic solution was evaporated and transferred to a round bottom where TFA (5 mL) was added and this mixture was allowed to stir 14 hours. Following this period, CH_2Cl_2 was added and the reaction was cooled to 0 °C. Slowly the pH was adjusted to 9 with 20% NaOH and the organic phase was isolated and dried. Flash chromatography (SiO_2, 8% EtOAc/hexane) provided a solid (0.41 g, 63%): mp 110-112 °C; ^1H NMR ($CDCl_3$) δ 9.61 (s, 1H), 8.58 - 8.54 (dd, 1H, J = 8Hz, J = 1.5Hz), 8.40 (d, 1H, J = 8Hz), 8.25 - 8.21 (dd, 1H, J = 8Hz, J = 1.5Hz), 7.84 - 7.69 (m, 3H), 7.39 - 7.35 (t, 1H, J = 8Hz); IR (KBr) 3051, 720; LRMS (EI) 197 (M+, 100); Anal. Calcd for C_{13} H_8 N F: C 79.15, H 4.1, N 7.11. Found: C 79.51, H 4.17, N 7.01.

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