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Synthesis of Highly Oxygenated Dinaphthyl Ethers via S_NAr Reactions Promoted by Barton's Base

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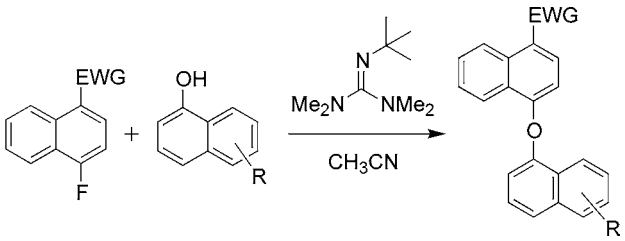
ABSTRACT



Electron-rich dinaphthyl ethers were synthesized by S_NAr reactions between naphthols and activated fluoronaphthalenes. 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (Barton's base) was found to be an excellent, mild alternative to traditional inorganic bases for promoting the coupling reaction.

The diaryl ether moiety has become an increasingly important structural feature in the realm of biologically active natural product synthesis.[1] Construction of diaryl ethers has classically involved the Ullmann coupling procedure in which a phenol and an aryl halide are reacted at high temperature in the presence of a copper catalyst.[2] During our recent syntheses of the naphthalene spiroketal natural products palmarumycin CP_1 (**1**)[3] and diepoxin σ (**2**),[4] an Ullmann reaction between phenol **5** (R^1 = H, $(OCH_2)_2$; R^2 = H, OH) and iodide **6** was employed to prepare the key diaryl ether **4** in good yield (Figure 1). In an attempt to extend this methodology toward the synthesis of the related natural product spiroxin A (**3**),[5] a strategy was devised in which more highly oxygenated derivatives of iodide **6** were subjected to

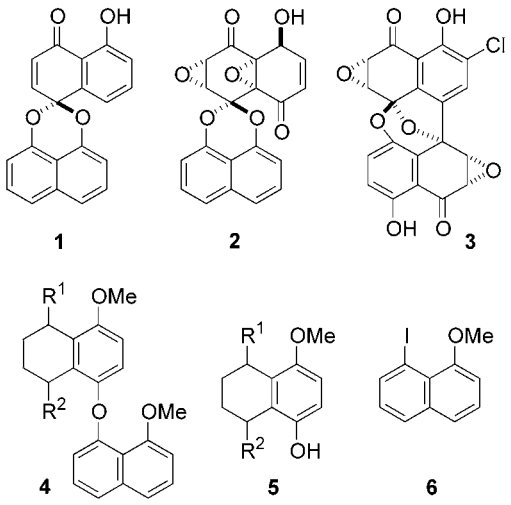


Figure 1. Naphthalenediol spiroketal natural products and intermediates.

(1) For examples of biologically active natural products containing diaryl ethers, see: (a) Rama Rao, A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135. (b) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2097. (c) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455. (d) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.

(2) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345. (c) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.

(3) (a) Wipf, P.; Jung, J.-K.; Rodriguez, S.; Lazo, J. S. *Tetrahedron* **2001**, *57*, 283. (b) Wipf, P.; Hopkins, T. D.; Jung, J.-K.; Rodriguez, S.; Birmingham, A.; Southwick, E. C.; Lazo, J. S.; Powis, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2637.

(4) (a) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319. (b) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **1999**, *64*, 1092.

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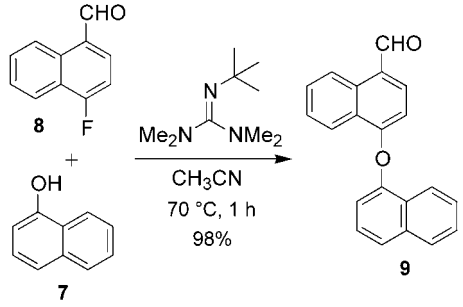
similar Ullmann conditions. Unfortunately, the yields of these reactions proved unsatisfactory.

The harsh conditions usually required for Ullmann etherification reactions have prompted many alternative approaches for the preparation of diaryl ethers.[6] Prevalent among these has been the nucleophilic aromatic substitution (S_NAr) which generally allows for both intermolecular[7] and intramolecular[8] ether synthesis under comparatively mild conditions.

While the S_NAr reaction of activated aryl fluorides with phenols is an established protocol for the synthesis of diaryl ethers, harsh reaction conditions sometimes render this method unattractive when dealing with sensitive substrates. In an attempt to develop a milder set of conditions for diaryl ether formation, we decided to explore alternatives to inorganic bases such as K_2CO_3 and NaH which represent the standard for S_NAr reactions. The guanidine bases, particularly the sterically hindered derivatives developed by Barton, have been used in a variety of applications and are known to effectively generate phenolate anions.[9] Recent reports of the utility of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base) in combinatorial synthesis highlight its strength, volatility, and ease of use and rate it superior in nature to traditional hindered organic bases such as DBU.[10] Therefore, we decided to screen Barton's base for its potential to promote S_NAr reactions of activated aryl fluorides.

Treatment of a CH_3CN solution containing 1-naphthol (**7**) and 4-fluoro-1-naphthalenecarbaldeyde (**8**) with a slight excess of Barton's base[11] showed only a modest rate of etherification at room temperature (Scheme 1). However,

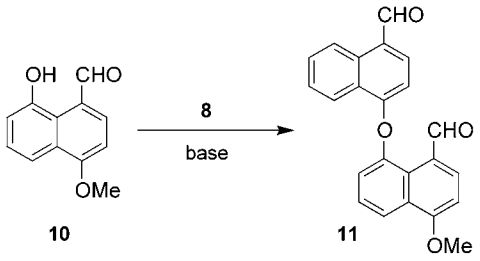
Scheme 1. S_NAr Reaction Promoted by Barton's Base



gentle heating dramatically increased the reactivity such that all of the starting material was consumed after 1 h at 70 °C. Evaporation and trituration of the reaction mixture led to a nearly quantitative yield of dinaphthyl ether **9** that was pure enough for further synthetic purposes.

In the desired S_NAr coupling reaction of fluoronaphthalene **8** with the highly functionalized naphthol **10**, Barton's base provided indeed both higher yields and cleaner reaction mixtures than other hindered organic bases such as tetramethylguanidine (TMG) and DBU (Table 1). Barton's base

Table 1. Base Dependence in the S_NAr Reaction of Naphthol **10** and Fluoronaphthalene **8**



entry	conditons	yield (%)
1	NaH, DMSO, 25 °C	49
2	K_2CO_3, DMAC, 150 °C	54
3	DBU, CH_3CN, 70 °C	46
4	TMG, CH_3CN, 70 °C	59
5	Barton's base, CH_3CN, 70 °C	85

also proved considerably superior to the inorganic bases K_2CO_3 and NaH, which promoted the desired transformation only in moderate yields.

To explore the general scope of this methodology, naphthols possessing various degrees of oxygenation and substitution patterns were reacted with fluoronaphthalene **8** in the presence of Barton's base. As summarized in Table 2, the yields of the resulting dinaphthyl ethers ranged from 41 to 98%.[12] Most products were isolated as analytically pure crystalline solids by simple trituration of the crude reaction mixture. As shown in entry 4, the reaction is tolerant of ortho-functionalization of the naphthol component. Couplings with **20** and **22** (entries 5 and 6) were found to proceed at a sluggish pace, however, presumably due to steric hindrance imparted by substitution at the peri-position of the naphthols. An increase in the amount of base and an extension of the reaction time afforded the predicted dinaphthyl ethers in acceptable yields.

(5) (a) McDonald, L. A.; Abbanat, D. R.; Barbieri, L. R.; Bernan, V. S.; Discafani, C. M.; Greenstein, M.; Janota, K.; Korshalla, J. D.; Lassota, P.; Tischler, M.; Carter, G. T. *Tetrahedron Lett.* **1999**, *40*, 2489. (b) Wang, T.; Shirota, O.; Nakanishi, K.; Berova, N.; McDonald, L. A.; Barbieri, L. R.; Carter, G. T. *Can. J. Chem.* **2001**, *79*, 1786.

(6) For a recent review, see: Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045.

(7) (a) Perez-Gonzalez, M.; Jackson, R. F. *Chem. Commun.* **2000**, 2423. (b) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III. *J. Org. Chem.* **1998**, *63*, 6338. (c) Keseru, G. M.; Dienes, Z.; Nogradi, M.; Kajtar-Peredy, M. *J. Org. Chem.* **1993**, *58*, 6725.

(8) (a) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004. (b) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700. (c) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488. (d) Zhu, J. *Synlett* **1997**, 133.

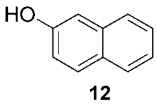
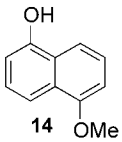
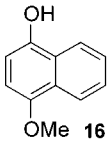
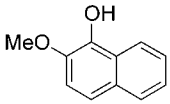
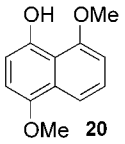
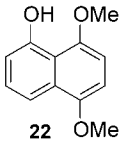
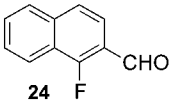
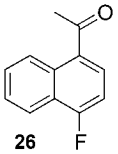
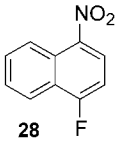
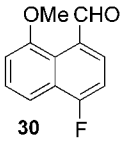
(9) (a) Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085. (b) Barton, D. H. R.; Charpiot, B.; Motherwell, W. B. *Tetrahedron Lett.* **1982**, 3365.

(10) (a) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **1999**, *1*, 579. (b) Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett.* **2001**, *3*, 271.

(11) Barton's base is commercially available from Fluka or may be prepared: Barton, D. H. R.; Chen, M.; Jaszberenyi, J. C.; Taylor, D. K. *Org. Synth.* **1996**, *74*, 101.

(12) **Typical Procedure.** To a solution of 5-methoxy-1-naphthol (**14**, 191 mg, 1.10 mmol) and 4-fluoro-1-naphthalenecarbaldehyde (**8**, 174 mg, 1.00 mmol) in CH_3CN (3 mL) at room temperature was added 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (0.24 mL, 1.2 mmol). The reaction mixture was heated at 70 °C for 1 h, cooled to room temperature, poured into 1.0 M HCl, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Trituration of the residue with cold hexanes/EtOAc (4:1) afforded 275 mg (84%) of **15** as a beige solid: mp 132−133 °C (EtOAc/hexanes).

Table 2. S_NAr Reactions with Fluoronaphthalenes[a]

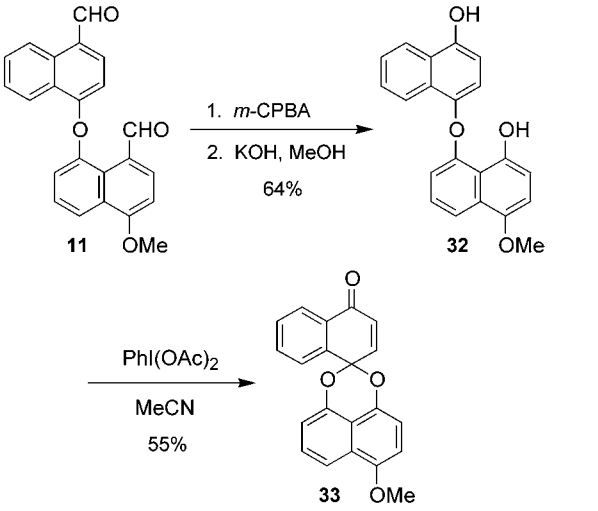
entry	naphthol	fluoride	binaphthyl ether	yield
1	 **12**	**8**	**13**	97%
2	 **14**	**8**	**15**	84%
3	 **16**	**8**	**17**	77%
4	 **18**	**8**	**19**	79%
5	 **20**	**8**	**21**[b]	56%
6	 **22**	**8**	**23**[b]	41%
7	**7**	 **24**	**25**[b]	81%
8	**7**	 **26**	**27**[b]	80%
9	**7**	 **28**	**29**[c]	88%
10	**7**	 **30**	**31**	87%

[a] Unless indicated otherwise, 1.0 equiv of fluoronaphthalene, 1.1 equiv of naphthol, and 1.2 equiv of Barton's base were used at a reaction temperature of 70 °C for 1 h. [b] 1.7 equiv of Barton's base was used, and the reaction time was 3 h. [c] Reaction was run at room temperature.

Electron-withdrawing groups other than formyl could be used to activate fluoronaphthalenes in this S_NAr methodology. 4-Nitro-1-fluoronaphthalene **28** (entry 9) was found to be the most reactive substrate tested, participating in substitution with 1-naphthol at room temperature in 1 h. Both the ortho-substituted aldehyde **24** and ketone **26** (entries 7 and 8) proved to be slightly less reactive than aldehyde **8**, but still underwent smooth substitution when treated with an additional 0.5 equivalent of base concurrant with longer reaction times. Also notable was the participation of the methoxy-substituted, electron-rich fluorobenzene **30** in the S_NAr reaction with no significant decline in yield.

After establishing the use of Barton's base for the preparation of dinaphthyl ethers, we turned our attention to their further elaboration toward the spiroketal scaffold. Electron-rich aryl aldehydes are prone to undergo a Dakin reaction to produce aryl formate esters which can, in turn, be easily hydrolyzed to phenols.[13] The bis-formylated dinaphthyl ether **11** was of particular interest to us since it might allow for the introduction of further oxygenation onto the naphthalene scaffold using the Dakin methodology.[14] Thus, treatment of **11** with excess *m*-CPBA at room temperature, followed by addition of cold methanolic KOH, afforded bisnaphthol **32** in 64% yield (Scheme 2). This

Scheme 2. Synthesis of a Palmarumycin Analogue



compound participated in the oxidative spirocyclization in the presence of $PhI(OAc)_2$ in MeCN at room temperature to afford the palmarumycin analogue **33** in 55% yield.[15]

In conclusion, Barton's base provides a mild alternative to heterogeneous, inorganic bases as well as amidines and less sterically hindered guanidines for the synthesis of highly oxygenated dinaphthyl ethers via nucleophilic aromatic

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(14) (a) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 764. (b) Boswell, G. E.; Licause, J. F. *J. Org. Chem.* **1995**, *60*, 6592. (c) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63.
(15) (a) Akai, S.; Kita, Y. *Org. Prep. Proc. Int.* **1998**, *30*, 603. (b) Coutts, I. G. C.; Allcock, R. W.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 9105. (c) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

substitution reactions. Products of these S_NAr couplings are well-suited for Dakin reactions followed by oxidative cyclization to afford naphthalenediol spiroketals. Applications of this methodology toward the total synthesis of members of the spiroxin family of marine natural products will be reported in due time.

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Supporting Information Available: Experimental procedures and spectral data for compounds **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27**, and **29**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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