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# Base catalyzed Mitsunobu reactions as a tool for the synthesis of aryl *sec*-alkyl ethers

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**Abstract**—A facile and versatile method for the synthesis of aryl *sec*-alkyl ethers from phenols with alcohols in the presence of base via a Mitsunobu reaction is described.


## 1. Introduction

As part of our recent research work we were in need of synthesizing alkoxyaryl ethers. A search of the literature showed that a number of methods exist for the synthesis of alkylaryl ethers which are complementary to the traditional Williamson ether synthesis.[1] These include methods such as the direct nucleophilic substitution of activated aryl halides,[2] Cu(I)-catalyzed cross-coupling of alkoxides with aryl halides[3] and palladium-catalyzed intra- and intermolecular cross-coupling reactions of aryl halides with alcohols.[4–6] Recently, Zong et al. reported the condensation of diols with 3,4-dihydroxypyrroles to afford 3,4-alkylenedioxypyrroles.[7] Besides these reactions the Mitsunobu reaction is often used as a tool for the condensation of alcohols with active methylene compounds such as malononitrile,[8] and with molecules exhibiting Brønsted acidity such as tosyl- and Boc-hydrazones[9] and dithiocarbamates.[10] Recently, a report in the literature described the synthesis of bis-*N*-heterocyclic alkyl substituted ethers through Mitsunobu reaction under heating.[11] A thorough search of the literature showed that the Mitsunobu reaction is quite a common protocol for the synthesis of esters and other related derivatives[12,13] but not so common for synthesizing ethers if the alcohols involved are secondary where the yields are often low.[7] Although, the reaction of primary alkanols with phenols to afford alkoxyaryl ethers via the Mitsunobu reaction is well documented.[14] Recent reports in the literature have described the synthesis of arylalkyl ethers with phenols and *sec*-alcohols via Mitsunobu reactions in high yields. They used cyclotriphosphazene core derived polymers[15] or phosphinated poly dendrimers.[16] Besides these methods, sonication conditions have also been reported for the synthesis of aryl *sec*-alkyl ethers.[17] These observations led us to focus on the reactions of *sec*-alcohols with phenols using standard Mitsunobu conditions for synthesizing aryl *sec*-alkyl ethers. When we attempted the reactions of *sec*-alcohols with phenols under normal Mitsunobu conditions either no product or exceptionally low yields were obtained. Analyzing the mechanism of the Mitsunobu reaction[18] between carboxylic acids and alcohols led us to try some modifications, presented herein, which have hitherto not been reported in the literature for synthesizing aryl *sec*-alkyl ethers. We report on the condensation of phenols with secondary alcohols which proceed in good to moderate yields in the presence of triethylamine. We also carried out a set of parallel reactions without triethylamine.

When 4-bromophenol and 3-pentanol were subjected to a Mitsunobu reaction, the corresponding ether was obtained in only 24% yield after 96 h at rt. We carried out the same reaction in the presence of 1 equiv of triethylamine and obtained a 68% yield of 3-(4-bromophenyloxy)pentane after 48 h. Prolonging the reaction time or increasing the equivalents of the base did not lead to any appreciable increase in yield. Other bases such as

*Keywords*: Phenols; *sec*-Alcohols; Triethylamine; Triphenylphosphine; Diisopropyl azodicarboxylate (DIAD); Aryl *sec*-alkyl ether; Mitsunobu reaction.
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**Table 1.** Base catalyzed synthesis of arylalkyl ethers

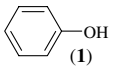
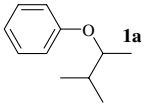
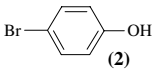
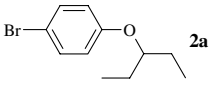
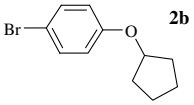
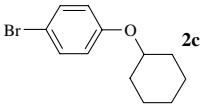
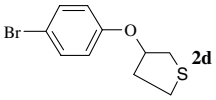
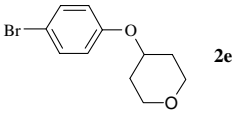
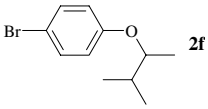
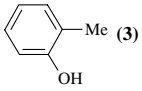
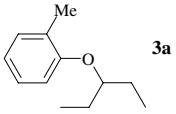
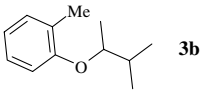
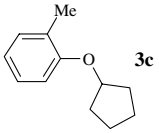
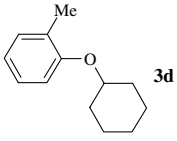
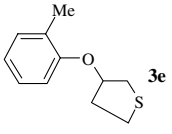
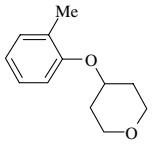
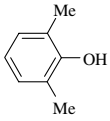
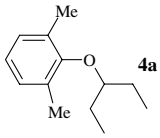
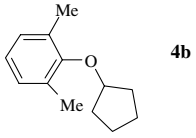
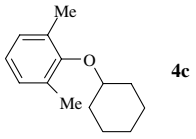
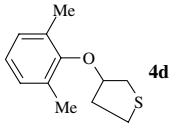
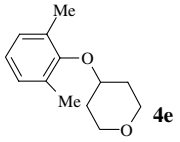
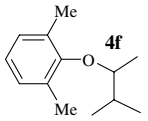
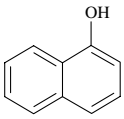
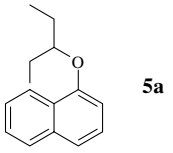
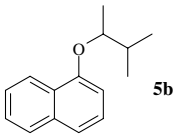
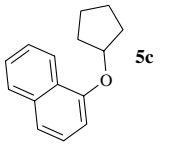
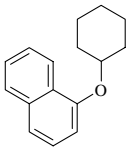
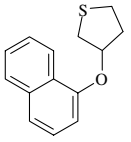
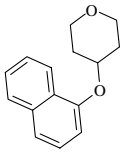
| Entry | Phenol | *sec*-Alcohol | Product | Yield[a,b,c] (%) |
|---|---|---|---|---|
| 1 |  (**1**) | 3-Methylbutan-2-ol (**a**) |  **1a** | 72 (16) |
| 2 |  (**2**) | 3-Pentanol (**a**) |  **2a** | 68 (24) |
| 3 | (**2**) | Cyclopentanol (**b**) |  **2b** | 81 (31) |
| 4 | (**2**) | Cyclohexanol (**c**) |  **2c** | 65 (27) |
| 5 | (**2**) | 3-Hydroxy-tetrahydrothiophene (**d**) |  **2d** | 72 (NR) |
| 6 | (**2**) | 4-Hydroxy-tetrahydropyran (**e**) |  **2e** | 86 (NR) |
| 7 | (**2**) | 3-Methylbutan-2-ol (**f**) |  **2f** | 74 (18) |
| 8 |  (**3**) | 3-Pentanol (**a**) |  **3a** | 67 (<15) |
| 9 | (**3**) | 3-Methylbutan-2-ol (**b**) |  **3b** | 68 (16) |
| 10 | (**3**) | Cyclopentanol (**c**) |  **3c** | 55 (25) |
| 11 | (**3**) | Cyclohexanol (**d**) |  **3d** | 61 (37) |
| 12 | (**3**) | 3-Hydroxy-tetrahydrothiophene (**e**) |  **3e** | 50 (NR) |

**Table 1** (*continued*)

| Entry | Phenol | *sec*-Alcohol | Product | Yield[a,b,c] (%) |
|---|---|---|---|---|
| 13 | (**3**) | 4-Hydroxy-tetrahydropyran (**f**) |  **3f** | 73 (NR) |
| 14 |  (**4**) | 3-Pentanol (**a**) |  **4a** | 44 (NR) |
| 15 | (**4**) | Cyclopentanol (**b**) |  **4b** | 68 (<15) |
| 16 | (**4**) | Cyclohexanol (**c**) |  **4c** | 51 (26) |
| 17 | (**4**) | 3-Hydroxy-tetrahydrothiophene (**d**) |  **4d** | 66 (NR) |
| 18 | (**4**) | 4-Hydroxy-tetrahydropyran (**e**) |  **4e** | 59 (NR) |
| 19 | (**4**) | 3-Methylbutan-2-ol (**f**) |  **4f** | 81 (<12) |
| 20 |  (**5**) | 3-Pentanol (**a**) |  **5a** | 75 (37) |
| 21 | (**5**) | 3-Methylbutan-2-ol (**b**) |  **5b** | 72 (18) |
| 22 | (**5**) | Cyclopentanol (**c**) |  **5c** | 71 (<15) |

(*continued on next page*)

**Table 1** (*continued*)

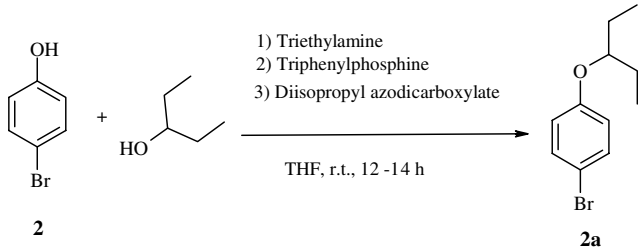
| Entry | Phenol | *sec*-Alcohol | Product | Yield[a,b,c] (%) |
|---|---|---|---|---|
| 23 | (**5**) | Cyclohexanol (**d**) |  **5d** | 61 (<15) |
| 24 | (**5**) | 3-Hydroxy-tetrahydrothiophene (**e**) |  **5e** | 70 (NR) |
| 25 | (**5**) | 4-Hydroxy-tetrahydropyran (**f**) |  **5f** | 51 (NR) |

[a] Isolated yield after column chromatography.
[b] Yield in the presence of triethylamine.
[c] Yields in parentheses correspond to reactions without base, NR—no reaction.

*N*-ethyldiisopropylamine or DBU were inferior. When we applied the same methodology to other secondary alcohols, all proceeded well to yield the corresponding ethers and in particular cases (**2d**, **2e**, **3e**, **3f**, **4a**, **4d**, **4e**, **5e**, and **5f**), ether formation was observed only in the presence of triethylamine (Table 1, Scheme 1).

It is reported in the literature that suitable alcohols and acids must have high p$K_a$ values in order to react. To this effect, for the reaction of *sec*-alcohols with weaker acids, special reagents such as cyanomethylenetributyl phosphorane have been developed[19] Herein, we visualize that the presence of a tertiary amine will help the reaction by favorably adjusting the p$K_a$ values.

In conclusion, $Et_3N$ has been employed as a mild and efficient base catalyst for the synthesis of aryl *sec*-alkyl ethers via Mitsunobu reaction in moderate to good yields from phenols and a wide variety of secondary alcohols.




**Scheme 1.**

## 2. Typical experimental procedure

In an oven dried three-necked round-bottomed flask, the phenol (10 mmol), secondary alcohol (12 mmol), triphenylphosphine (10 mmol) and triethylamine (10 mmol) were mixed under an argon atmosphere followed by the addition of dry THF (10 mL). The contents were cooled to 0 °C and DIAD (10 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred at that temperature until the reaction had proceeded to completion as judged by TLC or HPLC analysis. The reaction mixture was quenched with 5% HCl (10 mL) and extracted with ether ($3 \times 10$ mL) and concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel. All the products were colorless oils and were characterized by spectral analysis.

### 2.1. 2,6-Dimethylphenyl 1-ethylpropyl ether 4a

$^1$H NMR ($CDCl_3$, 300 MHz) $\delta = 7.1$ (m, 2H), 6.8 (m, 1H), 3.9 (m, 1H), 2.2 (m, 6H), 1.6 (m, 4H), 0.95 (t, 6H, $J$ 7.3 Hz ); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta = 154.4$, 131.3, 128.8, 122.9, 83.3, 25.5, 17.3, 9.6; MS ($M^+$) 192.6. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.12; H, 10.42.

### 2.2. 1-(Cyclopentyloxy)naphthalene 4c

$^1$H NMR ($CDCl_3$, 300 MHz) $\delta = 8.5$ (m, 1H), 7.9 (m, 1H), 7.6–7.5 (m, 4H), 6.9 (m, 1H), 5.0 (m, 1H), 2.1–2.0 (m, 6H), 1.8 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta = 153.6$, 134.6, 127.3, 126.1, 125.8, 125.2, 124.8,

122.2, 119.5, 105.8, 79.3, 32.8, 24.1; MS ($M^+$) 212.8. Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.79; H, 7.53.

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The authors thank Dr. Goutam Das, President, Syngene International Pvt. Ltd, for constant motivation and allocation of resources for this work.

## Supplementary data

Experimental and spectral data are available in supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.072.

## References and notes

1. Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498–2500.
2. (a) De Vries, V. G.; Moran, D. B.; Allen, G. R.; Riggi, S. J. *J. Med. Chem.* **1976**, *19*, 946–957; (b) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561–4570; (c) Zhao, G. L.; Shi, M. *Tetrahedron* **2005**, *61*, 7277–7288.
3. (a) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829–2835; (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456; (c) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565–5578.
4. (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; (b) Torraca, K. E.; Kuwabe, S. I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.
5. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396.
6. (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110; (b) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413–5418.
7. Zong, K.; Groenendaal, L. B.; Reynolds, J. R. *Tetrahedron Lett.* **2006**, *47*, 3521–3523.
8. Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *13*, 1279–1282.
9. Keith, J. M.; Gomez, L. *J. Org. Chem.* **2006**, *71*, 7113–7116.
10. Chaturvedi, D.; Ray, S. *Tetrahedron Lett.* **2006**, *47*, 1307–1309.
11. Chao, J.; Israiel, M.; Zheng, J.; Aki, C. *Tetrahedron Lett.* **2007**, *48*, 791–794.
12. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) *The Mitsunobu Reaction; Organic Reactions*; Paquette, L. A., Hughes, D., Eds.; John Wiley & Sons: New York, 1992; Vol. 42, p 335; (c) Kevin, J. H. *Tetrahedron* **2005**, *61*, 6860–6870; (d) Balint, A. M.; Bodor, A.; Gomory, A.; Vekey, K.; Szabo, D.; Rabai, J. *J. Fluorine Chem.* **2005**, *126*, 1524–1530; (e) Csokai, V.; Simon, A.; Balazs, B.; Toth, G.; Bitter, I. *Tetrahedron* **2006**, *62*, 2850–2856; (f) Hovinen, J. *Tetrahedron Lett.* **2004**, *45*, 5707–5709; (g) Zapf, C. W.; Valle, J. R. D.; Goodman, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4033–4036; (h) Hovinena, J.; Sillanpa, R. *Tetrahedron Lett.* **2005**, *46*, 4387–4389.
13. (a) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967–2971; (b) Csokai, V.; Balazs, B.; Toth, G.; Horvath, G.; Bitter, I. *Tetrahedron* **2004**, *60*, 12059–12066.
14. (a) Manhas, M. S.; Hoffman, W. H.; Lal, B.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461–463; (b) Girard, M.; Murphy, P.; Tsou, N. N. *Tetrahedron Lett.* **2005**, *46*, 2449–2452.
15. Reed, N. N.; Janda, K. D. *Org. Lett.* **2000**, *2*, 1311–1313.
16. Jayaraj, N.; Jayaraman, N. *Tetrahedron* **2005**, *61*, 11184–11191.
17. Lepore, S. D.; He, Y. *J. Org. Chem.* **2003**, *68*, 8261–8263.
18. Ahn, C.; Correia, R.; Deshong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753.
19. Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081–5082.