Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8981–8982

Synthesis of soft alkyl phenolic ether prodrugs using Mitsunobu chemistry

Susruta Majumdar, Juha Juntunen, Sashi Sivendran, Neelam Bharti and K. B. Sloan*

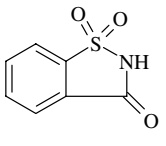
Department of Medicinal Chemistry, University of Florida, Gainesville, FL 32608, United States

Received 17 August 2006; revised 28 September 2006; accepted 29 September 2006

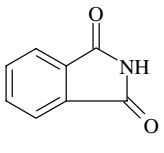
Abstract—The synthesis of soft alkyl phenolic ether prodrugs in excellent yields has been reported by coupling a phenol with a hydroxymethylimide using Mitsunobu chemistry. The imides used in this study include saccharin, phthalimide, succinimide and two other compounds containing acidic imide-like N–H groups, benzotriazole, and imidazole.

The oral bioavailability of phenolic drugs like morphine, estradiol, and acetaminophen is compromised by premature metabolism. The medicinal chemistry approach to transiently mask the phenolic functional group as a prodrug so that the degree of first pass metabolism by sulfation or glucuronidation is reduced has proved useful in numerous cases.[1,2] The oral bioavailability of estradiol was increased 8-fold by using imidomethyl prodrugs where saccharin was the imide (compounds containing an acidic NH functional group).[3,4] The hydrolysis of imidomethyl prodrugs of phenols has been extensively studied by Sloan and co-workers.[5] These types of prodrugs rely on simple chemical hydrolysis rather than enzymatic hydrolysis to revert to the parent drug as shown in Scheme 1.

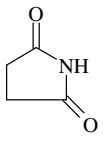
Structures of imide-like promoieties investigated in this study.



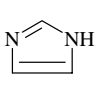
Saccharin



Pthalimide

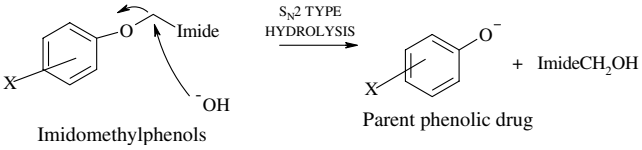


Succinimide



Imidazole

Benzotriazole



Scheme 1.

These prodrugs were synthesized in three steps. The imide was first reacted with HCHO to give hydroxymethylimide which was subsequently converted to chloromethylimides using $PCl_5/SOCl_2$. The alkylation of phenols with chloromethylimides in the presence of NaI and K_2CO_3 gave the soft alkyl phenolic ether prodrugs (Protocol A).[5] The synthesis involved three steps, harsh reaction conditions, long reaction times and gave poor yields (Table 1). We therefore decided to investigate the synthesis of these derivatives using an alternate route (Protocol B).

Our new protocol relies on converting the imide to its corresponding hydroxymethylimide by reacting it with formaldehyde/paraformaldehyde and coupling it directly to a phenol in the presence of PPh_3 and DIAD using Mitsunobu chemistry.[6] Briefly, 1 equiv of phenol (0.01 mmol) and PPh_3 (0.011 mmol) was stirred, while cooling with an ice bath, in 25 ml dry THF for 5 min. Hydroxymethylimide (0.011 mmol) and DIAD (0.011 mmol) were subsequently added. The reaction was allowed to equilibrate to room temperature and the yellow colored solution was stirred overnight. The desired products were then purified by column chromatography using ethyl acetate:hexanes as the eluent.[7] All

Keywords: Mitsunobu coupling; Imide; Phenolic ethers; Prodrugs.
* Corresponding author. Tel.: +1 352 846 1957; fax: +1 352 392 9455; e-mail: sloan@cop.ufl.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.162

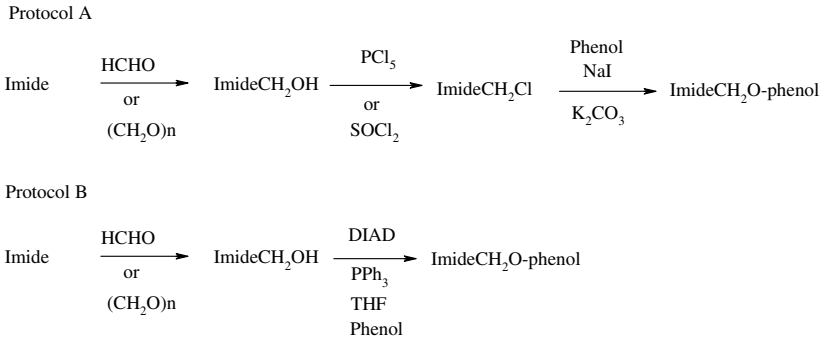


Table 1. A comparison of yields obtained using protocol A and protocol B

X[a]	Imide	Yields (%)	
		Protocol A	Protocol B
$-NO_2$	Saccharin	26[b]	58
$-NHCOCH_3$	Saccharin	11[b]	57
$-NO_2$	Phthalimide	13[b]	25
$-NHCOCH_3$	Phthalimide	12[b]	25
$-NO_2$	Succinimide	11[b]	83
$-NHCOCH_3$	Succinimide	14[b]	58
$-NO_2$	Benzotriazole	63	64
$-NHCOCH_3$	Benzotriazole	48	75
$-NO_2$	Imidazole	[c]	56
$-NHCOCH_3$	Imidazole	[c]	60

[a] Scheme 1.
[b] Yields obtained from Ref. 5.
[c] Not determined.

synthesized compounds were characterized by NMR, melting points and elemental analysis.

The synthetic route uses less harsh reaction conditions, can be carried out in one less step, requires less time and labor and gives excellent yields. Sloan and co-workers[5] synthesized imidomethylphenols using three imides, saccharin, phthalimide, and succinimide. In the present letter we have synthesized imidomethylphenols using two other imide-like (because they contain acidic NH groups) promoieties: imidazole, and benzotriazole. The synthesis of imidazol-yl-methyl phenols has been reported by various groups.[8–10] The most practical route involves converting the phenol to its potassium salt and reacting it with CH_2I_2 and imidazole.[8] Use of a strong base like KOH to convert a drug to its potassium salt can be harsh on a drug molecule with sensitive functional groups like esters, which would cause their hydrolysis. The other methods rely on alkylation of phenol using chloromethylimidazole, similar to protocol A. Similarly, alkylation of phenol with chloromethylbenzotriazole has been used to synthesize benzotriazol-yl-methyl phenols.[11–15] Thus a novel, simple, efficient synthesis of imidomethylphenols under ambient conditions has been presented in present letter. The utility of this synthetic protocol is that it does not require the synthesis of chloromethylimide from hydroxymethylimide.

References and notes

1. Bundgaard, H. Design and Application of Prodrugs. In *A Textbook of Drug Design and Development*; Krogsgaard-Larsen, P., Bundgaard, H., Eds.; Harwood: Reading, UK, 1991; pp 113–191.
2. Ettmayer, P.; Amidon, G.; Clement, B.; Testa, B. *J. Med. Chem.* **2004**, *47*, 2393–2404.
3. Patel, J.; Prankerd, R.; Sloan, K. B. *J. Pharm. Sci.* **1994**, *83*, 1477–1481.
4. Patel, J.; Katovich, M. J.; Sloan, K. B.; Curry, S. H.; Prankerd, R. *J. Pharm. Sci.* **1995**, *84*, 174–178.
5. Getz, J. J.; Prankerd, R.; Sloan, K. B. *J. Org. Chem.* **1993**, *58*, 4913–4918.
6. Mitsunobu, O. *Synthesis* **1981**, 1.
7. Phthalimidomethyl-*p*-nitrophenol: The desired product was purified after silica gel column chromatography in ethyl acetate/hexane (50%) followed by recrystallization with acetone to give a white solid. Yield = 80%, mp = 160–161 °C. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, 2H), δ 7.95 (q, 2H), δ 7.81 (q, 2H), 7.19 (d, 2H), δ 7.05 (d, 2H), δ 5.76 (s, 2H). Elemental analysis (Found: C, 60.33; H, 3.43; N, 9.32. Calcd for $C_{15}H_{10}N_2O_5$: C, 60.2; H, 3.34; N, 9.36).
8. Khalafi-Nezhad, A.; Soltani Rad, A. M.; Hakimelahi, N. G. H.; Mokhtari, B. *Tetrahedron* **2002**, *58*, 10341–10344.
9. Leyendecker, J.; Neubauer, H. J.; Kardorff, U.; Kuenast, C.; Hofmeister, P.; Krieg, W. Ger. Offen. 3826681, **1990**, *25*.
10. Buerstinghaus, R.; Neubauer, H. J.; Hofmeister, P.; Kuenast, C.; Leyendecker, J.; Kardorff, U. Eur. Pat. Appl. 289919, **1988**, *27*.
11. Katritzky, A. R.; Kirichenko, K.; Hur, D.; Zhao, X.; Ji, Y.; Steel, P. J. *ARKIVOC* **2004**, *6*, 27–44.
12. Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613–5615.
13. Pleynet, D. P. M.; Dutton, J. K.; Johnson, A. P. *Tetrahedron* **1999**, *55*, 11903–11926.
14. Katritzky, A. R.; Serdyuk, L.; Xie, L. *J. Chem. Soc., Perkin Trans. 1* **1998**, *6*, 1059–1064.
15. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Org. Chem.* **1989**, *54*, 6022–6029.