Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7337-7340, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01782-6

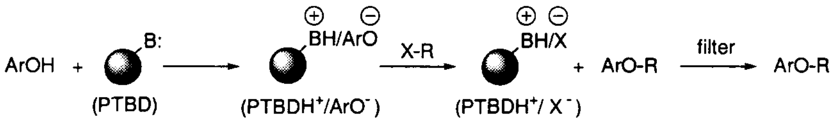
Polymer Supported Bases in Combinatorial Chemistry: Synthesis of Aryl Ethers from Phenols and Alkyl Halides and Aryl Halides

Wei Xu*, Raju Mohan, and Michael M. Morrissey

Department of Pharmaceuticals Discovery, Berlex Biosciences
15049 San Pablo Avenue, Richmond, CA 94804, USA

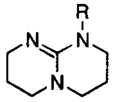
Abstract: Polymer supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD) was used as a base and a reagent scavenger for rapid synthesis of aryl ethers from phenols and alkyl or aryl halides. This method provides a simple reaction operation, and generally high purity of reaction product in good yield.

Combinatorial chemistry has emerged as an important methodology for the rapid synthesis of a large number of structurally diverse small molecules libraries and in recent years become an increasingly important approach for expediting the drug discovery process.[1] Our synthetic efforts in the area of both lead generation and lead optimization have led to the exploration of a practical process for the high throughput synthesis of structurally diverse compound libraries. Alkylation of phenol building blocks is a versatile approach to large libraries of aryl ethers, a functionality that is an important constituent in the structures of many pharmaceutically important chemical templates. Herein, we report solution phase O- and N-alkylations and O-arylation of phenols utilizing a polymer supported base that serves a dual purpose in its role as a base for deprotonation of phenols and as a "scavenger"[2] for trapping the unreacted excess starting phenol. This methodology utilizes excess phenol to drive the reactions to completion and products are isolated in high yields and purity after simple filtration and solvent evaporation (Scheme 1).

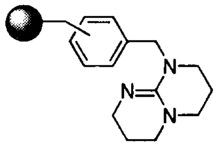


Scheme 1

The polymer bound base that has been utilized in this sequence is polystyrene supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD).[3-4] The monomeric bicyclic guanidines, such as 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD)[5] and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[6] are known as strong organic bases for organic synthesis.[7-8] PTBD has been recently reported as an effective reagent for the esterification of carboxylic acids and for the alkylation of active methylene compounds.[4, 9-10] Because of its high basicity, high steric hindrance and low quaternizablity we decided to explore the synthetic application of PTBD in various types of O- and N-alkylation reactions.



TBD (R = H)
MTBD (R = Me)



PTBD

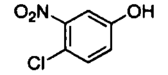
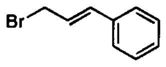
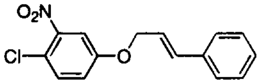
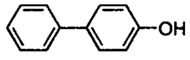
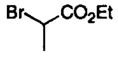
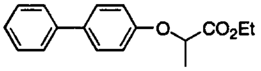
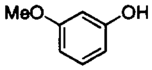
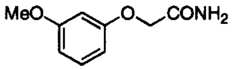
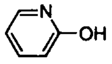
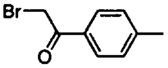
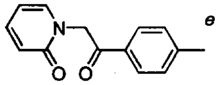
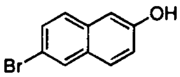
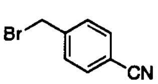
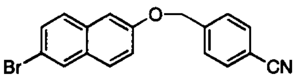
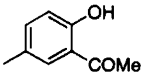
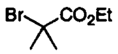
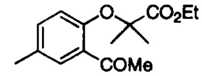
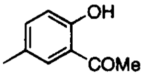
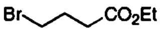
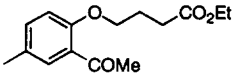
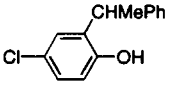
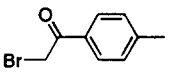
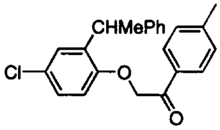
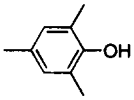
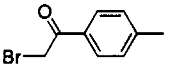
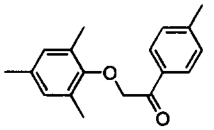
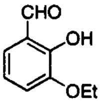
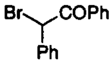
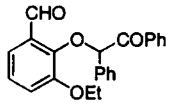
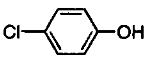
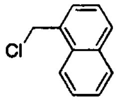
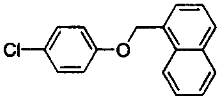
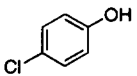
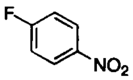
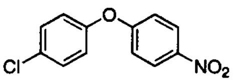
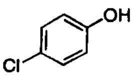
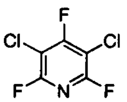
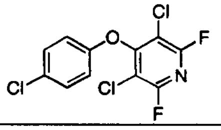
We examined the reaction between 6-bromo-2-naphthol and 4-cyanobenzyl bromide utilizing a PTBD resin in a control experiment[11] wherein the phenol was first adsorbed on the polymeric base in acetonitrile. HPLC analysis of the supernatant after 36 h indicated the total absence of the phenolic chromophore. On subsequent treatment with the benzylic bromide, a time-course analysis of the supernatant shows the emergence of the aryl benzyl ether product. This result indicates that the phenol is first deprotonated by the polymeric base to form the polymeric species PTBDH$^+$/ArO$^-$ (Scheme 1). The phenoxide then undergoes a S$_N$2 reaction with the benzylic bromide R-Br to generate the aryl ether ArOR with PTBD scavenging the resulting HBr. More significantly, this result demonstrates that PTBD not only acts as a base to deprotonate phenols, but also a polymeric repository for the phenolic anion. In solvents such as acetonitrile, excess unreactive phenol is thereby simply bound to PTBD in its anionic form.[12]

The alkylation reactions of a number of representative phenols and alkyl halides in the presence of PTBD have been studied and the results are shown in Table 1. In a typical reaction procedure, the phenol (0.060 mmol) and alkyl halide (0.050 mmol) were added to the reaction vessel containing the PTBD resin (0.10 mequiv) in 0.6 mL of acetonitrile. The reaction mixture was vortexed at room temperature until the halide was completely consumed, as determined by HPLC analysis. The reaction mixture was then filtered free of the polymeric material and after removal of the solvent in vacuo, the product was analyzed by HPLC and ^{1}H NMR. As shown in Table 1, the products obtained exhibit high chemical purity (70-99%), and moderate to high chemical yields (32-99%).[13] Even for sterically hindered phenols, the O-alkylation affords moderate yields (entries 9 and 10). This method has also been found to be quite general for electron-rich and electron-deficient phenols and for alkyl halides exhibiting a wide range of reactivity (entries 1, 3, 6, 7 and 11). For 2-hydroxypyridine, the N-alkylation takes place exclusively to produce the pyridinone product (entry 4).

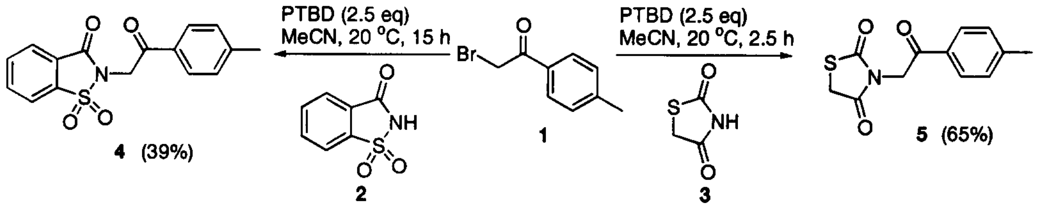
To further expand the scope of this methodology, we also examined the nucleophilic aromatic substitution reaction of activated aryl halides with the phenolic nucleophiles utilizing PTBD. In a protocol similar to that for the alkyl halides, the fluoro-substituted aromatic compounds react with the phenols in the presence of polymer bound base PTBD, to form aryl ether products of high purity and in good yields (Table 1, entries 12-13).[14]

We also found that this method can be utilized in the N-alkylation reactions of various sulfimide and imide derivatives. For example, when 2,4-thiazolidinedione (**3**, 1.2 eq) was treated with PTBD (2.5 eq) in acetonitrile at 25 °C, it underwent a S$_N$2 reaction with 2-bromo-4'-methylacetophenone (**1**, 1.0 eq) to produce the N-alkylation product **5** in 65% yield and 99% purity (Scheme 2). Similarly, treating saccharin (**2**) with PTBD in the presence of **1** afforded the N-alkylation product **4** in a moderate yield (39%) with high chemical purity (87%).

Table 1. Reactions of Phenols and Alkyl Halides/Aryl Halides in the Presence of PTBD[a]

Entry	Phenol	Halide	PTBD eq.	Reaction Time	Product[b]	Yield[c]	Purity[d]
1			2.0	64 h		92%	92%
2			2.0	64 h		79%	91%
3			2.8	2.5 h		70%	95%
4			2.5	19 h	 [e]	65%	71%[f]
5			2.5	22 h		79%	91%
6			1.8	168 h		32%	95%
7			1.8	168 h		65%	94%
8			2.5	24 h		98%	98%
9			2.5	24 h		64%	90%
10			2.0	64 h		47%	93%
11			2.5	60 h		51%	92%
12	 (1.5 eq.)		3.0	144 h		73%	99%
13	 (1.0 eq.)		2.0	1 h		75%	79%

a. Reaction conditions: phenol (1.2 eq.) and halide (1.0 eq.) with indicated eq. of PTBD in MeCN at 25 °C; *b.* All products obtained were characterized by ^1H NMR; *c.* Isolated yield; *d.* Determined by HPLC; *e.* The N-alkylation product was confirmed by NOESY experiment; *f.* In this case the starting 2-hydroxypyridine was present in the crude mixture (28%).



Scheme 2

In summary, we have demonstrated a general method for the rapid synthesis of compound libraries containing aryl alkyl and biaryl ether functionality utilizing a polymer supported guanidine base (PTBD). These libraries are derived from the vast array of commercially available phenol, alkyl halides and aryl halide building blocks via a protocol that can be easily adapted for parallel and automated chemical synthesis. Further studies on the application of PTBD and other polymer supported bases are in progress and will be reported in due course.

REFERENCES AND NOTES

1. Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
2. For literature precedence using solid supported scavenging agents in solution phase reactions see: Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.
3. The polymer supported base PTBD used in this work was purchased from Aldrich/Fluka.
4. Iijima, K.; Fukuda, W.; Tomoi, M. *J. Macromol. Sci. Pure Appl. Chem.* **1992**, *A29*, 249.
5. McKay, A. F.; Kreling, M. E. *Can. J. Chem.* **1957**, *35*, 1438-1445. Schmidtchan, F. P. *Chem. Ber.* **1981**, *93*, 273.
6. Angst, C.; Kratky, C.; Eschenmoser, A. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 263.
7. Schwesinger, R. *Chimia*, **1985**, *39*, 269.
8. Hilpert, K.; Leumann, C.; Davis, A. P.; Eschenmoser, A. *J. Chem. Soc. Chem. Commun.* **1983**, 1401.
9. Schuchardt, U.; Vargas, R. M.; Gelbard, G. *J. Mol. Catal. A: Chem.* **1996**, *109(1)*, 37.
10. Tamura, Y.; Fukuda, W.; Tomoi, M. *Synth. Commun.* **1994**, *24(20)*, 2907.
11. A mixture of 6-bromo-2-naphthol (0.060 mmol), PTBD (0.125 mequiv), 2-methylnaphthalene (0.060 mmol, as HPLC internal standard), and MeCN (0.6 mL) was vortexed at 25 °C for 36 h. HPLC detected <1% of 6-bromo-2-naphthol remaining in the supernatant solution. Then 4-cyanobenzyl bromide (0.050 mmol) was added. The mixture was vortexed at 25 °C until the bromide was completely consumed (20 h), and filtered. After removal of MeCN and 2-methylnaphthalene in vacuo, the aryl benzyl ether product (13 mg, 77% yield) was obtained in 92% purity (HPLC). The product is identical to the standard prepared from a direct reaction of the bromonaphthol and the bromide with PTBD in MeCN.
12. For a discussion of a related ionic form in resin beads, see Ref. 4.
13. In some cases where the phenol alkylation reaction is relatively slow, the alkylation of PTBD with alkyl halide may become competitive, thus results in a moderate yield of the phenol alkylation product.
14. The following experiment exemplifies the nucleophilic substitution reaction of activated aryl halides with phenols utilizing PTBD: A mixture of 4-chlorophenol (58 mg, 0.45 mmol), 1-fluoro-4-nitrobenzene (42 mg, 0.30 mmol), PTBD (320 mg, 0.90 mequiv) and MeCN (1 mL) was vortexed at 25 °C until the conversion of 1-fluoro-4-nitrobenzene was completed, as determined by HPLC (144 h). After filtration and evaporation in vacuo, 4-chlorophenyl-4'-nitrophenol ether (55 mg, 73% yield) was obtained as the sole product in 99% purity as determined by HPLC. ^{1}H NMR ($CDCl_3$): 8.22 (d, J-9.3 Hz, 2H), 7.40 (d, J-9.3 Hz, 2H), 7.05 (d, J-6.6 Hz, 2H), 7.02 (d, J-6.6 Hz, 2H) ppm.

(*Received in USA* 16 *July* 1997; *revised* 14 *August* 1997; *accepted* 15 *August* 1997)