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Convenient preparation of aryl ether derivatives using a sequence of functionalized polymers

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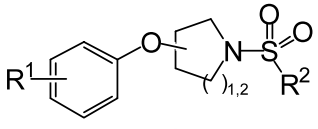
Abstract—A four-step synthesis to aryl ether derivatives, three of which utilize polymer-supported reagents, has been developed. Supported triphenylphosphine was successfully utilized in two distinct synthetic processes in the first step, whilst supported base and ionic and covalent scavengers were employed to complete the synthesis and purification of the target compounds. © 2003 Elsevier Science Ltd. All rights reserved.

Current synthetic approaches in organic chemistry have benefited greatly from the pioneering work conducted in the area of functionalized polymers during the 1970s and 80s.[1] In particular, multi-step synthesis using supported reagents has become a common approach in synthetic organic chemistry and has been the subject of steady literature attention from both academic and industrial laboratories over the past 10 years.[2,3] In a previous communication we outlined an optimized procedure for the construction of aryl ethers from aminoalcohols and phenols using polymer-supported triphenylphosphine.[4] That chemistry was carried out as part of a larger exercise focused towards the development of a four-step synthesis of functionalised aryl ether derivatives; details of this exercise are outlined below (Fig. 1).

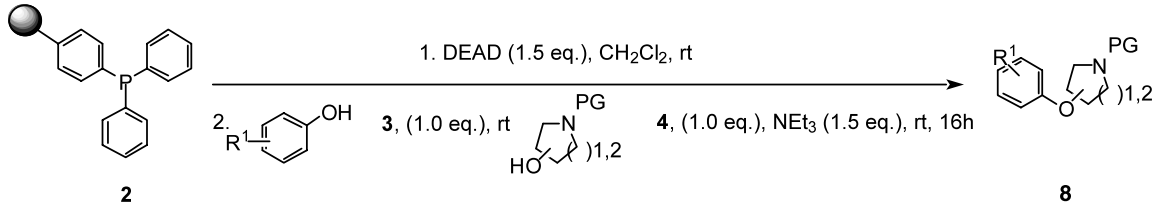


1

Figure 1.

Aryl ethers **1** were designed using a pharmacophore model as putative ligands for a family of cellular receptors, and we chose to synthesize a targeted combinatorial library of derivatives using a sequence of supported reagents. For the first step, we examined two distinct uses of supported triphenylphosphine **2**.[5] As outlined previously,[4] the Mitsunobu coupling of phenols **3** with *N*-protected aminoalcohols **4** using **2** in the presence of triethylamine served as a successful route to the intermediate compounds **8** (Scheme 1), and several derivatives prepared using this approach were used in the subsequent steps in the compound library synthesis.

In addition to the Mitsunobu route, we also developed an alternative approach to **8** by using **2** to mediate chlorination of *N*-protected aminoalcohol substrates.[6] In a typical procedure, **4** was first dissolved in an equal volume mixture of carbon tetrachloride and dichloromethane, and the resulting solution was treated with **2**. After 12 h stirring at reflux the corresponding



2 8

Scheme 1.

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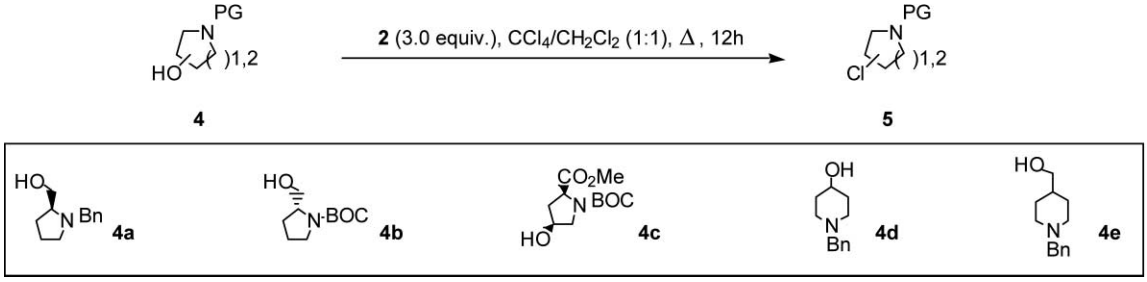
alkyl chlorides were isolated in high yields. This procedure was successful for the production of both primary and secondary alkyl chlorides **5**, as illustrated by the representative examples shown in Table 1.

To complement the set of protected aminoalcohols previously synthesized using the Mitsunobu reaction,[4] alkyl chloride **5a** was treated with phenolates, generated by treating the phenol substrates **3** with polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **6** in chloroform.[7] These nucleophilic displacements were conducted over the course of 12 h at reflux in the presence of a catalytic quantity of potassium iodide. Upon completion of the reactions, the crude product mixtures were poured onto sulfonic acid resin **7**;[8] after 10 min, the suspensions were filtered, and the resins washed extensively with methanol and dried. The resins were then treated with a methanolic ammonia solution, and the products **8** were subsequently isolated following evaporation of the filtrate in vacuo. A representative set of data for this step, illustrating the use of substrate **5a**, is shown in Table 2.

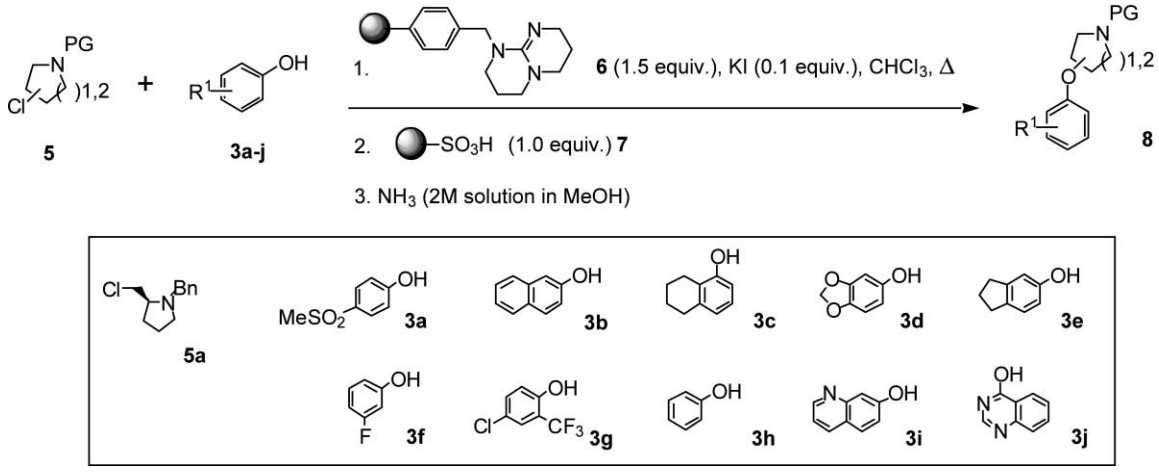
Removal of the *N*-benzyl or *N*-BOC protecting groups from intermediates **8** was then accomplished using 10% trifluoroacetic acid in dichloromethane or transfer

Table 1.



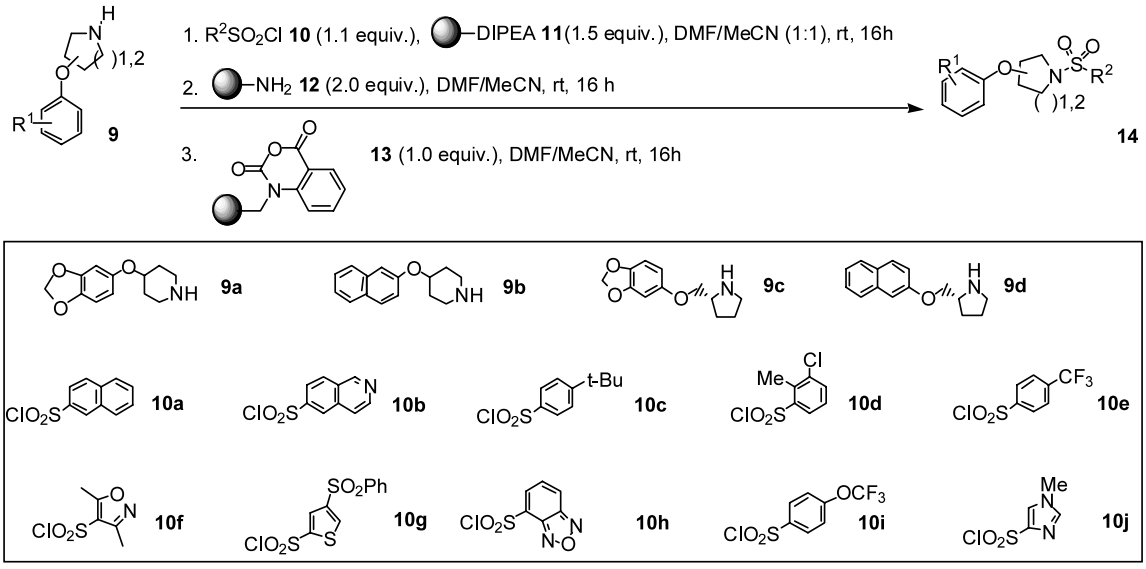
Entry	1	2	3	4	5
Substrate	**4a**	**4b**	**4c**	**4d**	**4e**
Isolated yield of **5** (%)	88	80	94	80	45

Table 2.



Entry	Phenol	Alkyl halide	Conversion to **8** (%)[9]
1	**3a**	**5a**	99
2	**3b**	**5a**	95
3	**3c**	**5a**	95
4	**3d**	**5a**	85
5	**3e**	**5a**	95
6	**3f**	**5a**	95
7	**3g**	**5a**	95
8	**3h**	**5a**	95
9	**3i**	**5a**	85
10	**3j**	**5a**	60

Table 3.



Entry	1	2	3	4	5	6	7	8	9	10
Amine	**9a**	**9a**	**9a**	**9a**	**9a**	**9a**	**9a**	**9a**	**9a**	**9a**
Sulfonyl chloride	**10a**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**	**10h**	**10i**	**10j**
Conversion to **14** (%)[9]	90	90	90	90	85	85	85	90	90	85
Entry	11	12	13	14	15	16	17	18	19	20
Amine	**9b**	**9b**	**9b**	**9b**	**9b**	**9b**	**9b**	**9b**	**9b**	**9b**
Sulfonyl chloride	**10a**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**	**10h**	**10i**	**10j**
% Conversion to **14**[9]	60	80	80	80	85	90	75	60	85	60
Entry	21	22	23	24	25	26	27	28	29	30
Amine	**9c**	**9c**	**9c**	**9c**	**9c**	**9c**	**9c**	**9c**	**9c**	**9c**
Sulfonyl chloride	**10a**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**	**10h**	**10i**	**10j**
% Conversion to **14**[9]	90	50	90	90	90	90	90	85	90	90
Entry	31	32	33	34	35	36	37	38	39	40
Amine	**9d**	**9d**	**9d**	**9d**	**9d**	**9d**	**9d**	**9d**	**9d**	**9d**
Sulfonyl chloride	**10a**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**	**10h**	**10i**	**10j**
% Conversion to **14**[9]	85	85	85	85	85	85	80	85	85	90

hydrogenation,[10] respectively, to furnish the desired secondary amines **9**. Finally, these products were treated with a structurally diverse set of sulfonyl chlorides **10** in the presence of polymer-supported Hünig's base **11**[11] using an equal volume mixture of *N*,*N*-dimethylformamide and acetonitrile as solvent. After 16 h stirring at room temperature, the suspensions were filtered into a bed of aminomethyl polystyrene **12**[12] to remove excess sulfonyl chloride. Finally, following filtration, the product solutions were treated with supported mesatoic anhydride **13**[13] to remove any unreacted amine **9** and to furnish the desired target compounds **14**. Table 3 depicts examples of products isolated in this exercise.[14]

In summary, a convenient multi-step sequence to functionalised aryl ether derivatives using a series of polymer supported reagents has been developed, in which supported triphenylphosphine was utilized efficiently in both Mitsunobu coupling and chlorination, and functionalized covalent and ionic scavengers were used for purification. This method enabled us to rapidly produce several hundred structurally diverse aryl ether analogues in high conversion.

Acknowledgements

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5. Commercially-available from Sigma-Aldrich Inc., catalogue #36,645-5.
6. For examples of halogenation mediated by supported triphenylphosphine, see: (a) Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. *J. Org. Chem.* **1983**, *48*, 3721; (b) Dabbagh, A.-H.; Mallakpour, S. E.; Faghihi, K. *Ir. Polym. J.* **1998**, *7*, 149.
7. Commercially-available from Polymer Laboratories Ltd., catalogue #3414-1679.
8. Commercially-available from Polymer Laboratories Ltd., catalogue # 3404-4679.
9. Percentage conversion to the desired products was determined by HPLC at 220 nm and 254 nm using an Agilent 1100 LC/MSD VL ESI system.
10. Typical protocol involved treating a methanolic solution of the substrate with wet palladium on carbon (Aldrich catalogue # 33,010-8, 3 weight equivalents) with 5% formic acid over a 12 h period. Following removal of the inorganic residue by filtration, the product was isolated following evaporation of the filtrate under reduced pressure.
11. Commercially-available from Polymer Laboratories Ltd., catalogue # 3413-4679.
12. Commercially available from Novabiochem Inc.; catalogue # 01-64-0177.
13. Commercially available from Novabiochem Inc.; catalogue # 01-64-0317.
14. Data for selected examples: Table 3 entry 3: δ_H (400 MHz, $CDCl_3$) 7.8 (2H, d), 7.60 (2H, d), 6.65 (1H, d), 6.40 (1H, s), 6.25 (1H, d), 5.90 (2H, s), 4.15 (1H, m), 3.20–3.15 (4H, m), 2.10–1.80 (4H, m) 1.10 (9H, s); M+1 found 418.1; $C_{22}H_{27}NO_5S$ exact mass: 417.16. Table 3 entry 30: δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d), 6.7 (1H, s), 6.50 (1H, s), 6.35 (1H, s), 5.90 (2H, s), 4.20 (2H, d), 3.75 (3H, s), 3.20 (1H, m), 2.10-1.40 (6H, m); M+1 found 366.1; $C_{16}H_{19}N_3O_5S$ requires 365.10.