Pergamon

Tetrahedron Letters 43 (2002) 7333–7335

TETRAHEDRON LETTERS

An azetidinium ion approach to 3-aryloxy-3-aryl-1-propanamines

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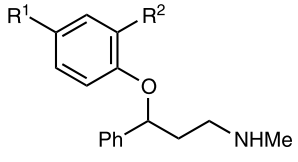
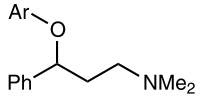
Received 26 July 2002; accepted 16 August 2002

Abstract—Treatment of 3-(dimethylamino)-1-phenyl-propan-1-ol with mesyl chloride and then different phenols generates a range of *N*,*N*-dimethyl-3-aryloxy-3-aryl-1-propanamines via regiospecific opening of a proposed azetidinium ion intermediate. During the rearrangement process, there was some leakage of stereochemical integrity.

3-Aryloxy-3-aryl-1-propanamines such as fluoxetine **1a**, tomoxetine **1b**, nisoxetine **1c** and thiotomoxetine **1d** are potent and selective inhibitors of neuronal norepinephrine and serotonin uptake.[1] Thus, they have been widely exploited in the treatment of a wide range of disorders including depression and the most famous compound in this class is fluoxetine **1a** which is better known by its trade name Prozac®.[2] Although the synthesis of **1a**–**d** has been widely studied, the development of new routes (in particular for the synthesis of enantiomerically pure compounds) continues to attract recent interest.[3–6] In this paper, we describe the development of a convenient procedure for the synthesis of *N*,*N*-dimethyl-3-aryloxy-3-aryl-1-propanamines **2**, which are precursors[4] to biologically active amino ethers such as **1a**–**d**.



1a: $R^1 = CF_3$, $R^2 = H$
1b: $R^1 = H$, $R^2 = Me$
1c: $R^1 = H$, $R^2 = OMe$
1d: $R^1 = H$, $R^2 = SMe$



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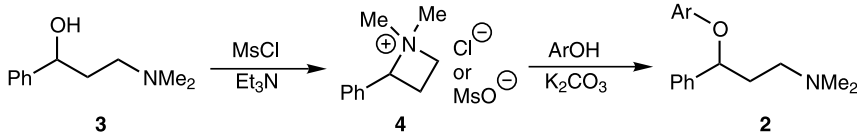
Following our successful development of an aziridinium ion strategy for the synthesis of chiral diamines,[7–9] we envisaged extending the methodology to the higher homologues, namely azetidinium ions (e.g. **4**). Our plan was to investigate the direct conversion of amino alcohol **3** into a range of amino ethers **2** and to establish the intermediacy of azetidinium ion **4** in this sequence (Scheme 1). This flexible approach to amino ethers **2** would proceed via in situ generation of azetidinium ion **4** (by mesylation of amino alcohol **3**) and subsequent trapping with a variety of phenols at the benzylic position.

Although aziridinium ions are now well established as useful and versatile intermediates in organic synthesis,[7–10] there are only a few examples of the synthetic utilisation of azetidinium ions.[11–13] Of these, Kane and Szumuszovicz reported the conversion of an amino alcohol into a diamine upon mesylation and subsequent reaction with an aniline, a result that could only be explained in terms of an azetidinium ion intermediate.[12] More recently, Overman et al. noted that use of a polar solvent and high temperatures favoured the in situ generation of an azetidinium ion.[13] Given the limited examples of synthetic protocols using azetidinium ions, we decided to explore an azetidinium ion route to amino ethers **2**.



3 **4** **2**

Scheme 1.

Keywords: amino alcohols; phenols; neighbouring group effects; azetidinium ions; 3-aryloxy-3-aryl-1-propanamines.
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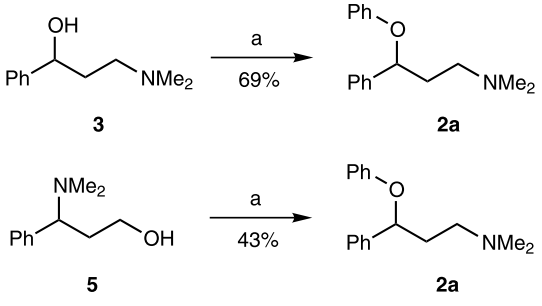
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01724-0

As a starting point, an optimised procedure for the conversion of amino alcohol **3**[14] into amino ether **2a** was developed (Scheme 2). We elected to use the polar acetonitrile as the solvent in a one-pot process and found that excess phenol in the second step was optimal. Thus, mesylation of amino alcohol **3** using triethylamine and mesyl chloride at room temperature for 3 h was followed by refluxing the solution with potassium carbonate and excess phenol for 65 h. After work-up and chromatography, a good 69% yield of amino ether **2a** was obtained.[15] The appearance of a 1H double doublet (J 5.0 and 8.0 Hz) at δ_H 5.21 ppm for the PhC*H*O resonance confirmed that the phenol had substituted adjacent to the phenyl group, which is in line with previous observations on ring opening of aziridinium ions.[7–10]

The full mechanistic details for the generation of amino ether **2a** via the sequence described in Scheme 2 have not been firmly established. At the end of the mesylation step, it is likely that an equilibrium mixture of amino mesylate, amino chloride and azetidinium ion **4** is set up. However, we believe that subsequent regiospecific substitution proceeds via azetidinium ion **4** since treatment of the regioisomeric amino ether **5**[16] under identical reaction conditions furnished a 43% isolated yield of amino ether **2a** (Scheme 2). This 'rearranged' substitution product could only have been generated by reaction of an azetidinium ion intermediate at the activated benzylic position.

Whatever the exact mechanistic pathway, the conversion of amino alcohol **3** into amino ether **2a** is a useful addition to the synthetic literature on the preparation of 3-aryloxy-3-aryl-1-propanamines and the scope of the reaction was briefly explored. For comparative purposes, reaction with a range of phenols was carried out in refluxing acetonitrile for 16 h and the results are presented in Table 1. In all cases, regiospecific formation of amino ethers **2** was observed: the PhC*H*O resonance appeared as a 1H double doublet (J 5.0 and 8.0 Hz) at δ_H 5.10–5.25 ppm in the ^{1}H NMR spectra of amino ethers **2a–d**. More electron rich phenols gave the best yields (entries 3 and 4); somewhat disappointing yields were obtained with phenol (entry 1) and with *p*-trifluoromethylphenol (entry 2), although these can



Scheme 2. *Reagents and conditions*: a (i) 1.2 equiv. Et_3N, 1.1 equiv. MsCl, MeCN, rt, 3 h; (ii) 2.0 equiv. K_2CO_3, 5.0 equiv. PhOH, reflux, 65 h.

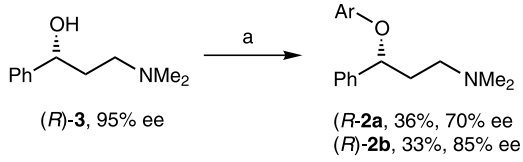
Table 1. Synthesis of amino ethers **2a–d** from amino alcohol **3**

Entry	Ar	Product	Yield (%)[a,b]
1	Ph	**2a**	42 (69[c])
2	4-$CF_3C_6H_4$	**2b**	35
3	4-$MeOC_6H_4$	**2c**	46
4	3,4-$(MeO)_2C_6H_3$	**2d**	67

[a] *Conditions*: (i) amino alcohol **3**, 1.2 equiv. Et_3N, 1.1 equiv. MsCl, MeCN, rt, 3 h; (ii) 2.0 equiv. K_2CO_3, 5.0 equiv. ArOH, reflux, 16 h.
[b] Isolated yield of product after chromatography.
[c] Yield obtained when 65 h was employed for the second step (instead of 16 h).

be improved with longer reaction times (see Scheme 2 and entry 1).

Finally, we have also explored the stereospecificity of our new route to amino ethers **2**. Amino ether (*R*)-**3** of 95% ee[17] {$[\alpha]_D$ +22.6 (*c* 1.05 in $CHCl_3$)} was prepared using a known[4] resolution method with (*R*)-mandelic acid. Reaction of (*R*)-**3** with mesyl chloride and then refluxing with phenol in acetonitrile for 16 h produced amino ether (*R*)-**2a** in 36% yield and with 70% ee[17] {$[\alpha]_D$ +12.3 (*c* 1.06 in $CHCl_3$)}. In an analogous fashion, amino ether (*R*)-**2b** was obtained in 33% yield and with 85% ee[17] {$[\alpha]_D$ +6.5 (*c* 1.09 in $CHCl_3$)} (Scheme 3). The (*R*) configuration of amino ether **2b** obtained in this way was established unequivocally by independent synthesis[18] and (*R*)-**2a** was assigned by analogy. Thus, the conversion of amino alcohol (*R*)-**3** into amino ethers (*R*)-**2a** and (*R*)-**2b** proceeds with predominantly overall retention of configuration (almost certainly via azetidinium ion (*S*)-**4**). However, there is a small proportion of stereochemical leakage presumably via an open chain carbocation intermediate.



Scheme 3. *Reagents and conditions*: a (i) 1.2 equiv. Et_3N, 1.1 equiv. MsCl, MeCN, rt, 3 h; (ii) 2.0 equiv. K_2CO_3, 5.0 equiv. PhOH, reflux, 65 h.

In summary, we report a synthetically useful way of converting amino alcohol **3** into a range of 3-aryloxy-3-aryl-1-propanamines **2** (which are precursors to antidepressants such as fluoxetine **1a** and related compounds **1b–d**). The sequence involves mesylation followed by reaction with a phenol and almost certainly involves the intermediacy of an azetidinium ion **4** with regiospecific nucleophilic attack at the benzylic position. In addition, using an enantiomerically enriched starting material, we have demonstrated that the overall process does not proceed with complete stereospecificity. This is in contrast to substitution of aziridinium ions under similar conditions[10] and merits further investigation.

Acknowledgements

We thank the EPSRC and Lancaster Synthesis for a CASE award (to T.D.T.) and The Nuffield Foundation for the award of an undergraduate research bursary (to D.W.P.).

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14. Amino alcohol **3** was obtained by sodium borohydride reduction of the corresponding amino ketone according to the procedure described in Ref. 4.
15. Representative experimental procedure: MsCl (0.08 cm^3, 1.0 mmol) was added dropwise to a stirred solution of amino alcohol **3** (160 mg, 0.9 mmol) and Et_3N (0.15 cm^3, 1.1 mmol) in MeCN (7.5 cm^3) at 0°C under N_2. After stirring at 0°C for 10 min, the mixture was stirred at rt for 3 h. Then, K_2CO_3 (250 mg, 1.8 mmol) and phenol (430 mg, 4.6 mmol) were added and the resulting mixture heated at reflux for 65 h. After cooling to rt, the precipitate was removed by filtration and was washed with Et_2O (25 cm^3). The organic layer was washed with 2 M $NaOH_{(aq)}$ (5 cm^3) and water (5 cm^3), dried (Na_2SO_4) and evaporated to give the crude product. Purification by chromatography on silica with CH_2Cl_2–MeOH (10:1) as eluent gave *N*,*N*-dimethyl-3-phenoxy-3-phenyl-1-propanamine **2a** (160 mg, 69%) as a colourless oil, R_F (10:1 CH_2Cl_2–MeOH) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1599 and 1495; δ_H (270 MHz; $CDCl_3$) 7.38–7.12 (7H, m), 6.89–6.82 (3H, m), 5.21 (1H, dd, *J* 5.0 and 8.0), 2.43 (2H, t, *J* 7.5), 2.23 (6H, s), 2.20–2.11 (1H, m) and 2.02–1.89 (1H, m); δ_C (67.5 MHz; $CDCl_3$) 158.2, 142.0, 129.2, 128.5, 127.4, 125.9, 120.6, 115.9, 78.2, 55.9, 45.5 and 36.9; *m*/*z* (CI, NH_3). Found: $(M+H)^+$, 256.1710. $C_{17}H_{21}NO$ requires *M*+H, 256.1701.
16. Amino alcohol **5** was synthesised via a two-step sequence: (i) conjugate addition of lithium dimethylamide to ethyl cinnamate furnished the *N*,*N*-dimethylamino ester in 33% yield; (ii) lithium aluminium hydride reduction of the ester then gave amino alcohol **5** in quantitative crude yield. For a representative procedure for the conjugate addition step, see: O'Brien, P.; Porter, D. W.; Smith, N. M. *Synlett* **2000**, 1336.
17. The enantiomeric excess was established using ^1H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
18. Reaction of amino alcohol (*R*)-**3** of 95% ee with sodium hydride and 4-chlorobenzotrifluoride in DMSO according to a literature procedure (see Ref. 4) generated amino ether (*R*)-**2b** with retention of configuration via a nucleophilic aromatic substitution reaction. Amino ether (*R*)-**2b** of 95% ee generated in this way exhibited $[\alpha]_D$ +7.2 (*c* 1.2 in $CHCl_3$).