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Pd-catalyzed kinetic resolution of benzylic alcohols: a practical synthesis of (*R*)-tomoxetine and (*S*)-fluoxetine hydrochlorides

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Abstract—A convenient synthetic route to (*R*)-tomoxetine hydrochloride (90% ee) and (*S*)-fluoxetine hydrochloride (84% ee) is described. (*S*)-3-Phenyl-3-hydroxypropyl *p*-toluenesulphonate, the key intermediate, is obtained by the oxidative kinetic resolution of the corresponding racemic 3-phenyl-3-hydroxypropyl *p*-toluenesulphonate using (−)-sparteine/Pd(II)/O_2 (1 atm) catalytic system. © 2002 Published by Elsevier Science Ltd.

(*R*)-Tomoxetine **1** is the first norepinephrine reuptake-inhibiting anti-depressant which does not possess strong affinity for either α or β adrenergic receptors.[1] (*S*)-Fluoxetine **2** is also a potent and highly selective inhibitor of neural serotonin-reuptake and is among the most important drugs for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity, bulimia).[2] In view of their pharmaceutical importance, several methods of enantioselective synthesis of both **1** and **2** have received growing interest in recent years.[3] However, these methods suffer from disadvantages such as the use of expensive reagents or reagents in stoichiometric quantities often resulting in low yields and selectivity.

The use of molecular oxygen as a stoichiometric reoxidant in combination with a catalytic metal has exceptional practical advantages for applications in organic synthesis.[4] Recently, Pd-catalyzed oxidative kinetic resolution of secondary alcohols has been reported employing molecular oxygen as the terminal oxidant in conjunction with the naturally occurring diamine ligands such as (−)-sparteine.[5] In this paper, we describe the five-step synthesis of (*R*)-tomoxetine hydrochloride **1** and (*S*)-fluoxetine hydrochloride **2** by employing a kinetic resolution of benzylic alcohol **7**, with a Pd(II)-(−)-sparteine/O_2 catalytic system as the key step in introducing the stereogenic center into the molecule (Scheme 1).

β-Hydroxyester **3** prepared readily by the Reformatsky reaction of benzaldehyde with ethyl bromoacetate, was subjected to oxidative kinetic resolution [5 mol% $Pd(OAc)_2$/20 mol% (−)-sparteine/O_2 (1 atm)/toluene at 80°C] to produce the chiral alcohol **4** in low ee (12%) along with β-keto ester **5** in 15% yield. Hence, it was of interest to subject the 1,3-diol **6**, obtained by the lithium aluminum hydride reduction of **3**, to oxidative kinetic resolution but this resulted in mixtures of products which were difficult to separate. However, the corresponding tosylate **7** underwent oxidative kinetic resolution [5 mol% $Pd(OAc)_2$, 20 mol% (−)-sparteine/O_2, 3 Å sieves, $PhCH_3$, 80°C, 36 h] smoothly to afford (*S*)-3-phenyl-3-hydroxypropyl *p*-toluenesulphonate **8**[6] in 95% ee and 47% yield along with its oxidized product **9**. The optical purity of **8** {$[\alpha]_D = -15.15$ (*c* 1, $CHCl_3$)} was determined by recording the ^1H NMR (300 MHz) spectrum of its acetate in the presence of Eu(III)-shift reagent. Chiral alcohol **8** was readily separated from its side product **9** by a simple column chromatographic purification (EtOAc:pet. ether, 1:3). We also observed that the kinetic resolution of **7** also works well with 5 mol% of $Pd(CH_3CN)_2Cl_2$ as catalyst. The mechanism of oxidative kinetic resolution of alcohol **7** probably occurs by the in situ formation of a chiral Pd(II)-(−)-sparteine complex assisted by the presence of 10 mol% excess of (−)-sparteine.[5] Subsequently, displacement of tosylate **8** with $MeNH_2$ was achieved to produce the common intermediate **10** in 95% yield and in high enantiomeric excess {$[\alpha]_D = -49.18$ (*c* 1, $CHCl_3$); lit.[2,7] $[\alpha]_D = -33.5$ (*c* 0.5, $CHCl_3$)}. Finally, amino alcohol **10** was transformed to (*R*)-tomoxetine hydrochloride **1** in 90% ee {$[\alpha]_D = -36.3$ (*c* 1, EtOH); lit.[7] $[\alpha]_D = -40.3$ (*c* 0.94, EtOH)} and (*S*)-fluoxetine hydrochloride **2** in 84% ee {$[\alpha]_D = -9.1$ (*c* 1, H_2O); lit.[7] $[\alpha]_D = -10.85$ (*c* 1, H_2O)} by following the literature procedures.[7]

Keywords: resolution; oxidation; asymmetric synthesis; alcohols.

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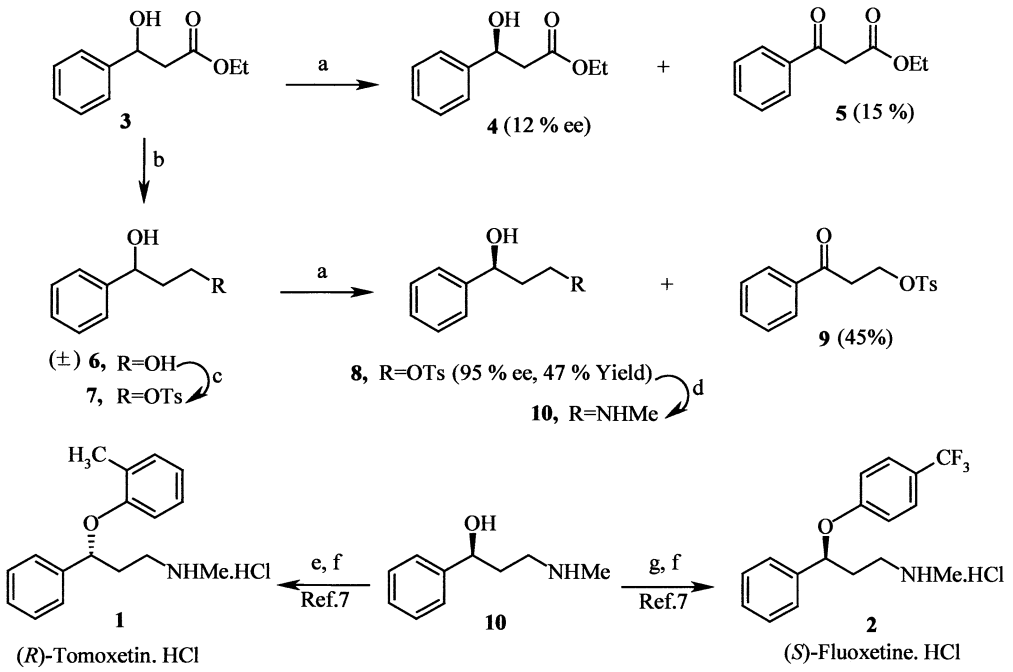

Scheme 1. (a) 5 mol% $Pd(OAc)_2$, 20 mol% (−)-sparteine/O_2 (1 atm), 3 Å sieves, $PhCH_3$, 80°C, 36 h; (b) $LiAlH_4$, THF, 2 h, 85%; (c) TsCl, Et_3N, DCM, −10 to 0°C, 95%; (d) 40% aq. $MeNH_2$, THF, 65°C; (e) *o*-cresol, PPh_3, DEAD, ether, −10 to 0°C; (f) HCl (gas), ether; (g) NaH, DMAC, 90°C, *p*-chlorobenzotrifluoride, 100–105°C.

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6. Spectral data of (*S*)-3-phenyl-3-hydroxypropyl *p*-toluenesulphonate **8**:
   IR ($CHCl_3$): 3541, 3056, 2985, 2962, 2925, 2306, 1731, 1598, 1494, 1454, 1357, 1265, 1188, 1097, 968, 815 cm^{-1}; ^1H NMR: (200 MHz, $CDCl_3$): δ 7.70–7.80 (d, $J=8.0$ Hz, 2H), 7.15–7.60 (m, 7H), 4.70–4.85 (dd, $J=4.0$ Hz each, 1H), 4.20–4.35 (m, 1H), 3.95–4.10 (m, 1H), 2.46 (s, 3H), 2.24 (bs, 1H), 1.90–2.05 (m, 2H); ^{13}C NMR: ($CDCl_3$): δ 144.7, 143.4, 132.8, 129.7, 128.3, 127.7, 127.5, 125.5, 69.9, 67.5, 37.9, 21.4; MS: 306 [(M^+) 13], 305 (16), 278 (3), 215 (5), 200(7), 172 (45), 155(17), 134(85), 118(18), 107(80), 92(20), 91(100), 77(60), 65(45); $[\alpha]_D=-15.15$ (*c* 1, $CHCl_3$).
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