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Ionic hydrogenation of naphthyl tetrafluoropyridin-4-yl ethers as a new route to 5,6,7,8-tetrahydronaphthols

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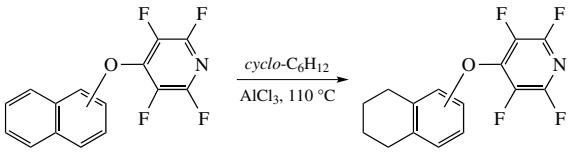
***O*-Tetrafluoropyridin-4-yl-protected naphthols undergo regioselective reduction with cyclohexane in the presence of aluminium chloride to afford the corresponding 5,6,7,8-tetrahydronaphthyl ethers.**

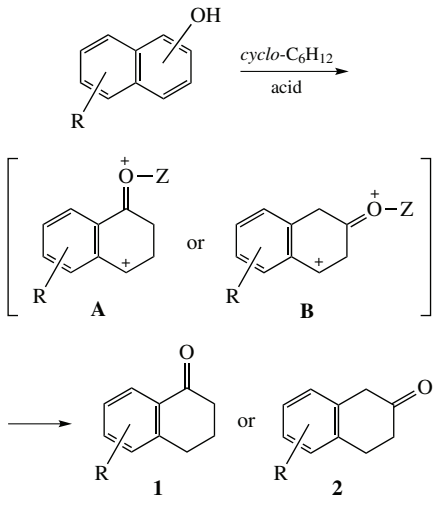


Keywords: polyfluoropyridines, naphthyl ethers, ionic hydrogenation, 5,6,7,8-tetrahydronaphthols, organofluorine compounds, cyclohexane.

Naphthols and naphthalenediols undergo selective reduction with cyclohexane in the presence of aluminium halides or HUSY zeolites to afford tetralones **1** and **2** through the formation of intermediate dicationic superelectrophiles **A** or **B**, respectively (Scheme 1).[1] Obviously, the regioselectivity of these reactions is determined by the strongly electron donating hydroxy group playing a decisive role in stabilizing of intermediates **A** and **B**. Hence, one would expect that protection of the hydroxy group with an electron withdrawing substituent should have an effect on the reactivity of naphthols. In this connection, it is important to note that the tetrafluoropyridine moiety is a rare example of an easily installable and removable phenol protecting group[2] also being resistant to drastic acidic conditions.[3]

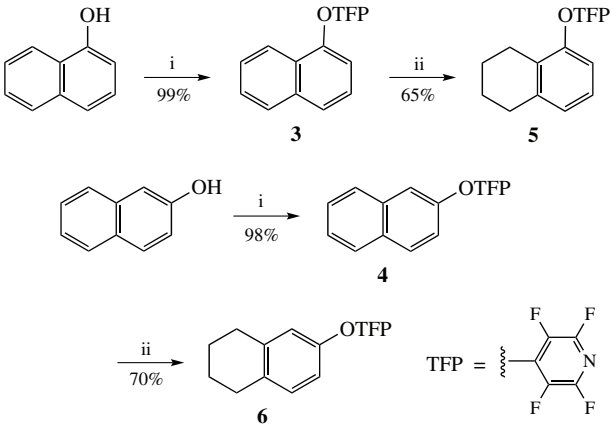
Herein, we report that the use of tetrafluoropyridin-4-yl protecting group completely changes the regioselectivity of the reduction of 1- and 2-naphthols with cyclohexane producing 5,6,7,8-tetrahydronaphthol core (Scheme 2).†

Apparently, the reduction of ethers **3** and **4** into products **5** and **6**, respectively, involves protonation on the benzene moiety of the starting ethers leading to generation of electrophilic



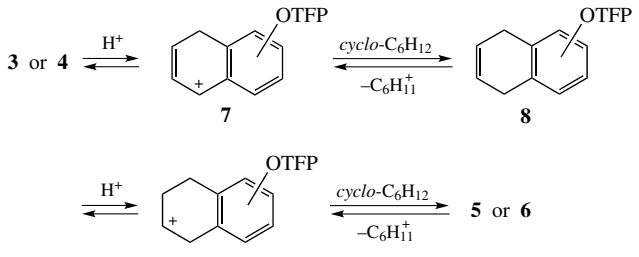
R = H or OH
Z = H, $Al_nHal_{3n}^-$ or Lewis acid site

Scheme 1



Scheme 2 *Reagents and conditions*: i, pentafluoropyridine (PFP), K_2CO_3, DMF, 20 °C, 1 h; ii, $AlCl_3$, cyclohexane, pressure tube, 110 °C, 0.5 h.

† *2,3,5,6-Tetrafluoro-4-(5,6,7,8-tetrahydronaphthalen-1-yloxy)pyridine* **5** *(typical procedure)*. A mixture of compound **3** (0.293 g, 1 mmol), $AlCl_3$ (0.8 g, 6 mmol) and cyclohexane (5 ml) was stirred at 110 °C (oil bath temperature) for 0.5 h in a 15 ml pressure tube. After cooling, the upper transparent layer (mixture of alkanes) was removed by decantation. The residue was carefully treated with ice (several grams), and the mixture was extracted with Et_2O. The organic phase was dried over anhydrous $MgSO_4$ to give a mixture consisting mainly of product **5** and isomeric alkanes $C_{12}H_{22}$.[1] Purification by flash chromatography (cyclohexane) afforded product **5** (0.193 g, 65%). HRMS, *m/z*: 297.0773 (calc. for $C_{15}H_{11}F_4NO$, *m/z*: 297.0774). ^{1}H NMR δ: 1.79–1.90 (m, 4H), 2.76–2.85 (m, 4H), 6.62 (d, 1H, *J* 8 Hz), 6.95 (d, 1H, *J* 8 Hz), 7.05 (t, 1H, *J* 8 Hz). ^{19}F NMR δ: 8.86 (m, 2F), 75.41 (m, 2F). ^{13}C NMR (selected data for tetraline moiety) δ: 22.4, 22.6, 23.0, 29.4 (CH_2), 112.5, 126.0, 126.1 (=CH), 127.4, 140.0 (=C), 154.1 (=C–O).



Scheme 3

species **7**, followed by hydride transfer from cyclohexane to a carbocation center of **7** (Scheme 3). The thus produced intermediates **8** undergo additional protonation and react with the second molecule of cyclohexane. All this explains the necessity to use an excess of $AlCl_3$ for performing these reactions. Indeed, a catalytic amount of protic superacid ($HCl–Al_nCl_{3n}$ or $H_2O–Al_nCl_{3n}$, $H_o \approx -18$) is normally present in such reaction media due to the *in situ* reaction between the excess of aluminium chloride and traces of water in the starting materials.[4] Overall, the mechanism suggested is similar to that for analogous reaction of 2,3-naphthalenediol.[5]

In conclusion, the protection of hydroxy group in 1- and 2-naphthols with tetrafluoropyridine moiety can affect the course of ionic hydrogenation with cyclohexane under superacidic conditions to reverse the reaction regioselectivity. This offers a new indirect method for regioselective reduction of naphthols to provide straightforward access to the 5,6,7,8-tetrahydro derivatives, which, in general, is not a trivial task.[6]

2,3,5,6-Tetrafluoro-4-(5,6,7,8-tetrahydronaphthalen-2-yloxy)pyridine **6** was prepared similarly from compound **4**. HRMS, *m*/*z*: 297.0772 (calc. for $C_{15}H_{11}F_4NO$, *m*/*z*: 297.0774). ^{1}H NMR δ: 1.75–1.83 (m, 4H), 2.7–2.77 (m, 4H), 6.73 (d, 1H, *J* 2.5 Hz), 6.78 (dd, 1H, *J* 2.5, 8 Hz), 7.04 (d, 1H, *J* 8 Hz). ^{19}F NMR δ: 9.94 (m, 2F), 75.51 (m, 2F). ^{13}C NMR (selected data for tetraline moiety) δ: 22.8, 23.0, 28.7, 29.5 (CH_2), 113.9, 116.8, 130.4 (=CH), 134.1, 139.2 (=C), 153.7 (=C–O).

For more details, see Online Supplementary Materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.020.

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