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Base catalyzed [1, 2] wittig rearrangement of ethers: Preparation of regiospecific diaryl methanols

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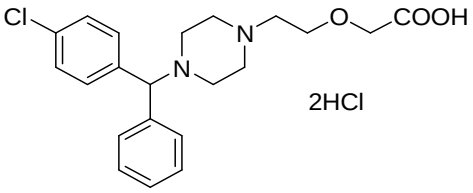
ABSTRACT

Base catalyzed [1,2] Wittig rearrangement of ethers is studied to give diaryl methanols. A method is developed to prepare regiospecific (1 and 2) aryl naphthyl ketones.

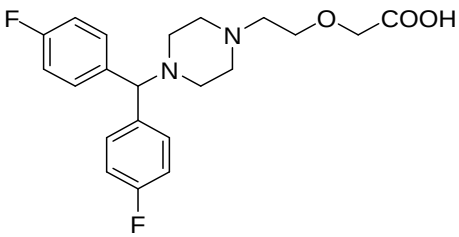
Key words: Sodium hydride, Naphthyl benzyl ethers, Wittig rearrangement.

INTRODUCTION

The 1, 2, diaryl methanols are important intermediates in the preparation of biologically active compounds such as cetirizine.2HCl **1,** Efletirizine **2** as antihistamine drugs.



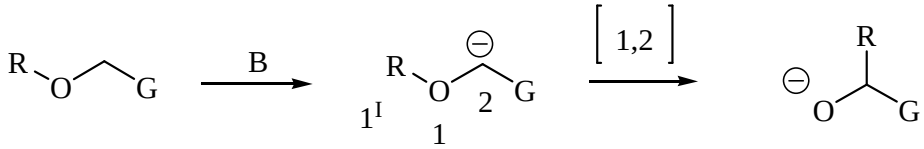
1.Cetirizine.2HCl



2. Efletirizine

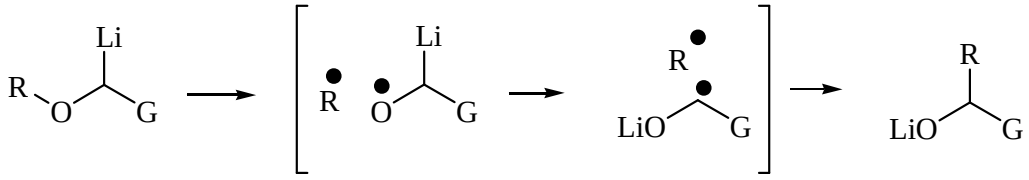
Figure 1: cetirizine.2HCl and Efletirizine

We followed [1,2] Wittig rearrangement methodology for the preparation of 1,2-diaryl methanols. The [1,2] Wittig rearrangement is a carbanion rearrangement of ethers which involves a 1,2-alkyl shift onto the α-oxy carbanion. George wittig[1] who carried out definitive work on this rearrangement.



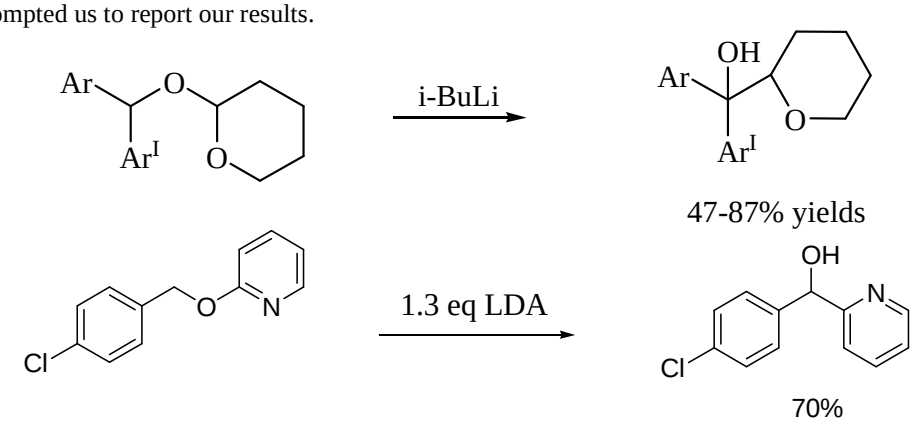
Scheme 1: Anionic type of rearrangement

Of the several mechanisms proposed, the radical cleavage recombination mechanism appears to be explaining the results obtained.[2, 3] It is now recognized as a special class of intramolecular radical process.



Scheme 2: Biradical mechanism

Recent studies by Xu et al[4b] and Yang et al[4d] on preparation of tertiary alcohols and diaryl methanols as shown in Scheme 3 prompted us to report our results.



Scheme 3: Preparation of tertiary alcohol and diaryl methanols

MATERIALS AND METHODS

General: All chemicals were purchased from Merch and Sigma-Aldrich as 'synthesis grade' and used without further purification. ^{1}H (400 MHz) & ^{13}C (100 MHz) NMR spectra were recorded using a Bruker 400 Spectrometer with TMS as internal standard. IR spectra were recorded on Perkin Elmer Spectrophotometer as KBr pellets or neat. Microanalysis was performed on a Perkin Elmer-240CHN elemental analyzer. Analytical TLC was conducted on E-Merck 60F254 aluminum-packed silica gel plates (0.2mm). Developed plates were visualized using UV light or Iodine chamber. HPLC spectra were recorded on shimadzu 2010.

General Procedure for the synthesis of 1-Naphthalen-1-yl-1-phenyl-ethanol 4a

Sodium hydride (2.41 gm, 0.060 moles 60%) was added to a stirred solution of 1-(1-Phenyl-ethoxy)-naphthalene **3a** (5.0 gm, 0.020 moles) in DMSO(20ml), and the reaction mixture was heated to 80-90°C for 2h to complete the reaction (monitored by TLC) and then allowed to cool to room temperature. The reaction mass was quenched into chilled water (20ml) and the resulting precipitate was filtered and washed with water(10ml) to obtain crude product. The crude product was purified on silica gel column to obtained 1-Naphthalen-1-yl-1-phenyl-ethanol **4a** as white solid.

Characterization Data for the Respective Compounds.

1-Naphthalen-1-yl-1-phenyl-ethanol (4a): White solid; m.p. 64.1-68.4°C; IR (KBr, cm^{-1}): 3377, 3043, 1065, 780, 703; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.09 (s, 3H, CH_3), 2.44 (s, 1H, OH), 7.24-7.29 (m, 4H, ArH), 7.36-7.40 (t, 3H, ArH, *J* = 7.5 Hz), 7.5 (s, 1H, ArH), 7.82-7.90 (m, 4H, ArH); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 32.76, 76.68, 124.02, 124.60, 125.11, 125.16, 125.35, 126.68, 127.25, 128.25, 128.71, 129.01, 130.61, 134.82, 141.96, 148.47.

1-(3-Methoxy-phenyl)-1-naphthalen-1-yl-ethanol(4b): White solid; m.p. 113.5-114.6°C; IR (KBr, cm^{-1}): 3445, 2965, 1591, 1242, 1150, 1025, 782; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.07 (s, 3H, CH_3), 2.45 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 6.74-6.76 (d, 1H, ArH, *J* = 7.7 Hz), 6.88-6.90 (d, 1H, ArH, *J* = 7.60 Hz), 7.04 (s, 1H, ArH), 7.15-7.19 (t,

1H, ArH, *J* = 7.8 Hz), 7.24-7.25 (d, 1H, ArH, *J* = 7.14 Hz), 7.35-7.37 (d, 1H, ArH, *J* = 7.54 Hz), 7.48-7.52 (t, 1H, ArH, *J* = 7.64 Hz), 7.82-7.85 (t, 3H, ArH, *J* = 6.8 Hz), 7.94-7.96 (d, 1H, ArH, *J* = 8.61 Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 32.71, 55.06, 76.96, 111.30, 111.62, 117.74, 123.94, 124.55, 125.09, 125.37, 127.11, 128.67, 129.00, 129.23, 130.62, 134.77, 141.83, 150.31, 159.50.

Naphthalen-2-yl-phenyl-methanol (4c): White solid; m.p. 85.9-86.5°C; IR(KBr,cm^{-1}): 3238, 3083, 3057, 1598, 1492, 1453, 1035, 1023, 814, 745; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.74 (s, 1H, OH), 5.96 (s, 1H, CH), 7.30-7.39 (m, 3H, ArH), 7.43-7.45 (d, 3H, ArH, *J* = 6.71 Hz), 7.52-7.53 (t, 2H, ArH, *J* = 3.69 Hz), 7.81-7.90 (m, 4H); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 76.26, 124.77, 125.00, 125.94, 126.15, 126.69, 127.61, 127.65, 128.06, 128.28, 128.49, 132.83, 133.21, 141.09, 143.58.

Naphthalen-1-yl-phenyl-methanol (4d): White solid; m.p. 84.8-85.8°C; IR (KBr, cm^{-1}): 3256, 3057, 2849, 1455, 1058, 989, 800, 782, 697; ^{1}HNMR(400 MHz, DMSO, δ/ppm): 6.06-6.07 (s, 1H, OH), 6.38-6.39 (d, 1H, CH, J=3.18 Hz) 7.18-7.20 (d, 1H, ArH, *J* = 7.03 Hz), 7.25-7.29 (t, 2H, ArH, *J* = 7.20 Hz), 7.38-7.43 (m, 4H, ArH), 7.52-7.54 (t, 1H, ArH, *J* = 7.49 Hz), 7.69-7.71 (d, 1H, ArH, *J* = 6.80 Hz), 7.82-7.84 (d, 1H, ArH, *J* = 7.98 Hz), 7.89-7.91 (d, 1H, ArH, *J* = 7.25 Hz), 8.14-8.16 (d, 1H, ArH, *J* = 7.39 Hz); ^{13}C NMR(100MHz, DMSO, δ/ppm): 72.24, 124.69, 124.81, 125.71, 125.74, 126.05, 127.17, 127.88, 128.38, 128.82, 130.57, 133.83, 140.94, 145.19.

1-(3,4-Dimethoxy-phenyl)-1-naphthalen-1-yl-ethanol(4e): Off White solid; m.p. 120.2-122.0°C; IR (KBr, cm^{-1}): 3490, 2971, 1508, 1257, 1138, 1025, 781; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.08 (s, 3H, CH_3), 2.41 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.70-6.77 (m, 2H, ArH), 7.07 (s, 1H, ArH), 7.22-7.25 (t, 1H, ArH, *J* = 7.79 Hz), 7.35-7.39 (t, 1H, ArH, *J* = 7.1Hz), 7.48-7.52 (q, 1H, ArH), 7.82-7.86 (t, 3H, ArH, *J* = 8.28Hz), 7.91-7.93 (d, 1H, ArH, *J* = 8.44Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 32.56, 55.67, 55.75, 77.29, 108.72, 110.66, 117.65, 123.90, 124.56, 125.05, 125.28, 127.17, 128.65, 128.90, 130.61, 134.73, 141.24, 142.07, 147.61, 148.67.

1-(4-Fluoro-phenyl)-1-naphthalen-1-yl-ethanol(4f): White solid; m.p. 80.2-82.7°C; IR (KBr, cm^{-1}): 3380, 1600, 1505, 1219, 783, 590 ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.06 (s, 3H, CH_3), 2.45 (s, 1H, OH), 6.92-6.96 (t, 2H, ArH, *J* = 7.24 Hz), 7.24-7.25 (d, 2H, ArH, *J* = 5.82 Hz), 7.34-7.38 (t, 2H, ArH, *J* = 7.4 Hz), 7.51-7.52 (d, 1H, ArH, *J* = 7.01 Hz), 7.84-7.89 (m, 4H, ArH). ^{13}C NMR (100MHz, $CDCl_3$, δ/ppm): 33.02, 76.61, 114.83, 115.03, 123.98, 124.54, 125.16, 125.38, 126.80, 126.88, 128.74, 130.47, 134.83, 141.54, 144.26, 160.71.

1-(3-Fluoro-4-methoxy-phenyl)-1-naphthalen-1-yl-ethanol (4g): White solid; m.p. 55.1-56.8°; IR (KBr, cm^{-1}): 3391, 2932, 1510, 1272, 782, 644; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.04 (s, 3H, CH_3), 2.43 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 6.79-6.83 (t, 1H, ArH, *J* = 7.95 Hz),6.99-7.01 (d, 1H, ArH, *J* = 7.49 Hz), 7.15-7.18 (d, 1H, ArH, *J* = 12.4 Hz), 7.36-7.38 (d, 1H, ArH, *J* = 6.56 Hz), 7.48-7.51 (m, 1H, ArH), 7.62 (m, 1H, ArH), 7.83 (s, 3H, ArH), 7.90-7.92 (d, 1H, ArH, *J* = 8.2 Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 32.73, 56.08, 76.41, 112.93, 113.47, 120.85, 123.97, 124.54, 125.05, 125.14, 127.06, 128.75, 129.75, 130.48, 134.80, 141.40, 141.84, 146.16, 150.82.

1-(4-Chloro-phenyl)-1-naphthalen-1-yl-ethanol (4h): White solid; m.p. 89.5-91.5°C; IR (KBr, cm^{-1}): 3419, 1489, 1091, 1066, 782, 573; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.05 (s, 3H, CH_3), 2.47 (s, 1H, OH), 7.21-7.25 (m, 3H, ArH), 7.30-7.32 (d, 2H, ArH, *J* = 8.37Hz), 7.36-7.38 (d, 1H, ArH, *J* = 7.53Hz), 7.48-7.52 (t, 1H, ArH, *J* = 7.72 Hz), 7.82-7.89 (m, 4H, ArH); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 33.03, 76.65, 114.84, 115.05, 124.00, 124.56, 125.19, 125.41, 126.81, 126.89, 127.16, 128.76, 129.18, 134.84, 141.55, 144.30.

1-(2-Methoxy-phenyl)-1-naphthalen-1-yl-ethanol(4i): White solid; m.p. 100.5-105.0°C; IR (KBr, cm^{-1}): 3520, 1960, 1232, 1024, 781, 477; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.10 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.91 (s, 1H, OH), 6.96 (m, 2H, ArH), 7.13 (d, 1H, ArH, *J* = 7.42 Hz), 7.30 (m, 2H, ArH), 7.53 (d, 2H, ArH, *J* = 7.1 Hz), 7.80 (d, 1H, ArH, *J* = 8.04 Hz), 7.84 (d, 2H, ArH, *J* = 8.02 Hz),8.4 (d, 1H, ArH, *J* = 8.6 Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 29.49, 55.44, 77.89, 111.98, 120.94, 123.90, 124.52, 124.77, 124.81, 127.57, 127.68, 128.39, 128.40, 128.53, 131.00, 134.73, 135.86, 142.65, 156.73.

1-Furan-2-yl-1-naphthalen-1-yl-ethanol (4j): IR (Neat, cm^{-1}): 3429, 3049, 1509, 1154, 778, 739; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 2.14 (s, 3H, CH_3), 2.66 (s, 1H, OH), 6.27-6.29 (d, 1H, ArH, *J* = 2.6 Hz), 6.30-6.37 (s, 1H, ArH), 7.39-7.48 (m, 4H, ArH), 7.69-7.70 (d, 1H, ArH, *J* = 7.21 Hz), 7.82-7.87 (m, 2H, ArH), 8.10-8.12 (d, 1H, ArH, *J* = 8.56 Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 28.25, 73.32, 106.35, 110.30, 123.66, 124.85, 125.03, 125.39, 125.79, 128.85, 128.92, 130.43, 134.47, 140.52, 141.78, 159.27.

General Procedure for the synthesis of Naphthalen-2-yl-phenyl-methanone (5)

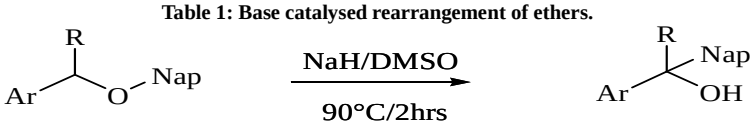
Naphthalen-2-yl-phenyl-methanol **(4C)** (6.6 gm, 0.0282 moles) was added to a stirred solution of MnO_2 (12.26 gm, 0.1410 moles) in DCE (35 ml), and the mixture was heated to 80-85°C for 1h then the reaction mixture was filtered through hyflobed and washed with DCE (5 ml). The organic layer was washed with sat. $NaHCO_3$ sol (20 ml) and water (20 ml). The solvent was evaporated under vaccum at 40°C, and the crude was mixed with hexane (20 ml) at 20-25°C. The product was isolated by filtration and washed with hexane (5 ml) to give Naphthalen-2-yl-phenyl-methanone **(5)** as a white solid, yield: 5.2 gm (80%) m.p. 81.2-82.7°C (Rep: 80-82°C Alfa Aesar); IR (KBr, cm^{-1}): 3055, 1658, 1623, 1277, 1236, 819, 754, 717, 698; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 7.50-7.57 (m, 3H, ArH), 7.59-7.64 (m, 2H, ArH), 7.87-7.92 (m, 4H, ArH), 7.95-7.98 (m, 2H, ArH), 8.28 (s, 1H, ArH); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 125.70, 126.73, 127.74, 128.23, 128.25, 128.27, 129.33, 130.02, 131.79, 132.17, 132.31, 134.73, 135.18, 137.82, 196.64.

Naphthalen-1-yl-phenyl-methanone (6): m.p. 75.5-76.9°C (Rep: 75-76°C Alfa Aesar); IR (KBr, cm^{-1}):3065, 1658, 1287, 1248, 916, 797, 789, 720, 693; ^{1}HNMR(400 MHz, $CDCl_3$, δ/ppm): 7.450-7.60 (m, 7H, ArH), 7.88-7.90 (d, 2H, ArH, *J* = 7.10 Hz), 7.92-7.94 (d, 1H, ArH, *J* = 7.34 Hz), 8.00-8.02 (d, 1H, ArH, *J* = 7.74 Hz), 8.11-8.13 (d, 1H, ArH, *J* = 7.45Hz); ^{13}C NMR(100MHz, $CDCl_3$, δ/ppm): 124.26, 125.61, 126.38, 127.18, 127.69, 128.33, 128.37, 130.32, 130.87, 131.19, 133.15, 133.64, 136.26, 138.23, 197.93.

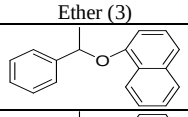
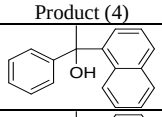
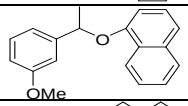
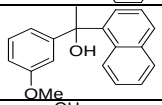
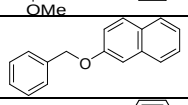
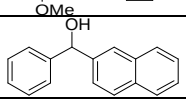
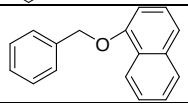
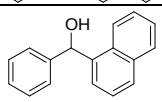
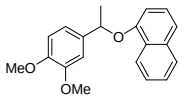
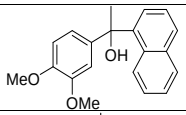
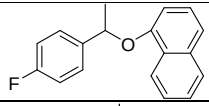
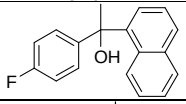
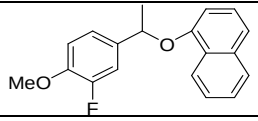
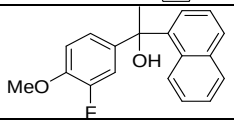
RESULTS AND DISCURSION

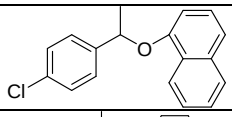
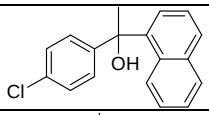
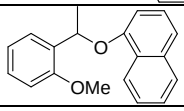
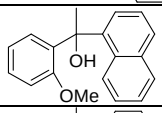
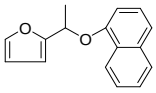
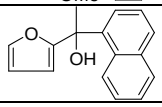
In our earlier studies on acid catalyzed rearrangement of ethers we synthesized tolterodine[5] and mimosofoliol[6] analogues. The base catalyzed rearrangement of ethers is reported by witting[1] as early as 1942, and mechanistic studies were reported during 1950-1970. Later studies[4] are also done with very strong bases like BuLi, t-BuLi, i-BuLi etc. We studied the same rearrangement with cheaper bases like NaH (60%oil). Our results are tabulated in the Table 1.

Table 1: Base catalysed rearrangement of ethers.

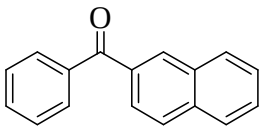


3 **4**

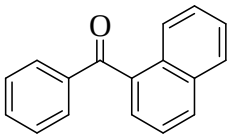
Entry	Ether (3)	Product (4)	MP°C	Yield(%)
a			64.1-68.4	90.0[7]
b			113.5-114.6	70.0
c			85.9-86.5	40.0[7b]
d			84.8-85.8	40.0[7b]
e			120.2-122.0	13.3
f			80.2-82.7	10.0
g			55.1-56.8	10.0

h			89.5-91.5	6.0
i			100.5-105.0	4.0
j			--	10.0

The products **4c** and **4d** are oxidized to give regiospecific ketones **5** and **6**, which are others, wise difficult to get in pure form.



5



6

Scheme 4: Ketones prepared

CONCLUSION

In conclusion we have developed sodium hydride induced rearrangement of ethers to give diaryl methanols in good yields.

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