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Solvent Affected Facile Synthesis of Hydroxynaphthyl Ketones: Lewis Acids Promoted Friedel–Crafts and Demethylation Reaction

Wan-mei Li, Hu-qin Lai, Zhong-hua Ge, Cheng-rong Ding, and Ying Zhou

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, China

Abstract: Hydroxynaphthyl ketones were obtained with high yields under very mild conditions in the presence of $AlCl_3$ via Friedel–Crafts acylation and demethylation from naphthyl ethers. Several Lewis acids were tested, and $AlCl_3$ was the most efficient catalyst.

Keywords: demethylation, Friedel–Crafts, hydroxynaphthyl ketones, Lewis acids

Hydroxynaphthyl ketones (**2**) were usually prepared from the corresponding naphthyl esters via a Fries-rearrangement reaction in the presence of Lewis acid[1] (Scheme 1). Although the yields were good, the deacylation product (**3**) inevitably was formed. The by-products (**3**) were difficult to isolate from the desired products.

The direct acylation of naphthol in the presence of catalyst was possible,[1a,1f,1g,2] but in fact the reactions proceeded with acylation of hydroxyl followed by Fries rearrangement in many cases. Herein we report a facile and efficient method for the preparation of hydroxynaphthyl ketones from naphthyl ethers with acylating reagents catalyzed by Lewis acid.

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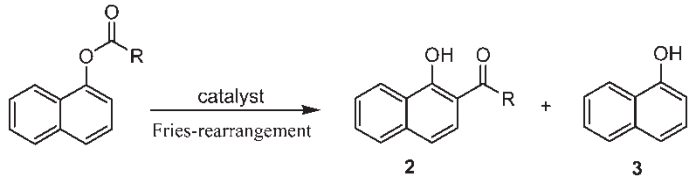
Address correspondence to Hu-qin Lai, College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China. E-mail: laihuqin@zjut.edu.cn

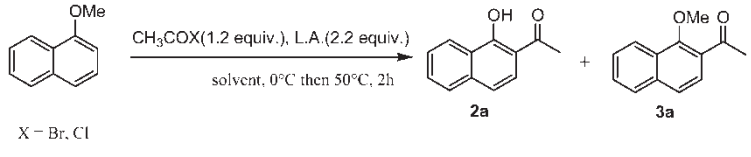


Scheme 1.

Initially, several Lewis acids were investigated in the reaction (Scheme 2), and the results are shown in Table 1. Data showed that anhydrous $AlCl_3$ (entry 1), $TiCl_4$ (entry 11), and BF_3 (entry 8) were the better catalysts. In these cases, the acetylated and demethylated product (**2a**) was isolated in good yield. Acetylation product (**3a**) was formed in about 20% yields. Other Lewis acids such as $SnCl_4$, $ZnCl_2$, and $FeCl_3$ showed low activity in terms of demethylating. The acylating reagent obviously affected the results; when active acetyl bromide was used instead of acetyl chloride in the presence of $AlCl_3$ or BF_3, only a trace of **3a** was detected, and **2a** was obtained in very high yields (entry 2 and 8). $AlBr_3$ showed excellent reactivity in this reaction when acetyl chloride was used as the acylating reagent (entry 7); the same results were obtained with the use of $AlCl_3$ and acetyl bromide. In this reaction condition, we suppose that the halogen would be transformed between the catalyst and acetylating reagent (Scheme 3).

However, we found the solvent affected the results greatly. The ratio of two products could be reversed in different solvents. CS_2 and hexane were suitable for demethylation reaction to obtain **2a**. Product **3a** was formed in 40% yield when CH_3NO_2 was used as the solvent. If the reaction was carried out in CH_2Cl_2 as well as $CHCl_3$, **3a** was the main product, contaminated with a very small amount of **2a**. In addition, the amount of $AlCl_3$ should not be fewer than 2.0 equiv.; otherwise the demethylation reaction would not proceed thoroughly, and acetylated product **3a** was the major product.

Thus in the presence of $AlCl_3$ and acetyl bromide, several hydroxynaphthyl ketones were prepared from naphthyl ethers (Scheme 4, Table 2). Obviously, α-ethers as well as β-ethers could be converted to corresponding



Scheme 2.

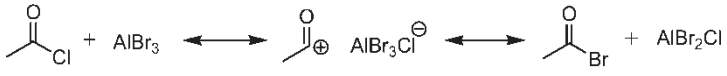
Table 1. Lewis acid–catalyzed reactions of naphthyl ethers with acylating reagents

Entry	LA	X	Solvent	**2a** (yield %)[a]	**3a** (yield %)[a]
1	$AlCl_3$	Cl	CS_2	75	19
2	$AlCl_3$	Br	CS_2	94	trace
3	$AlCl_3$	Cl	Hexane	71	20
4	$AlCl_3$	Cl	CH_3NO_2	58	40
5	$AlCl_3$	Cl	$CHCl_3$	8	89
6	$AlCl_3$	Cl	CH_2Cl_2	5	93
7	$AlBr_3$	Cl	CS_2	95	Trace
8	BF_3	Cl (Br[b])	CS_2	68 (93[b])	23 (2[b])
9	$SnCl_4$	Cl	CS_2	33	58
10	$ZnCl_2$	Cl	CS_2	38	55
11	$TiCl_4$	Cl	CS_2	73	22
12	$FeCl_3$	Cl	CS_2	31	62
13	$AlCl_3$[c]	Br	CS_2	22	71

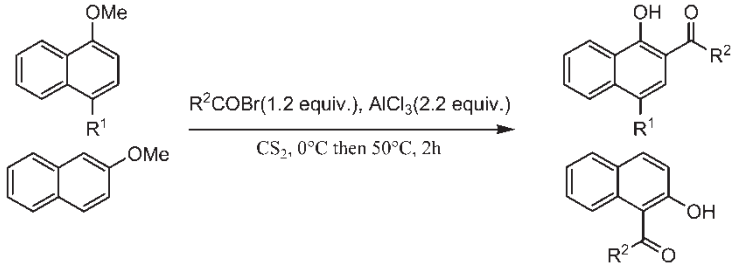
[a]Isolated yields based on ethers.
[b]Acetyl bromide was used instead of acetyl chloride.
[c]1.0 equiv. of $AlCl_3$ was used.

products in high yields. Furthermore, the reaction also proceeded well when diether was the substrate (Scheme 5). It was clear that both HBr and $AlCl_3$ were reacted as mild demethylation reagents.[3]

In contrast, the preparation of compound **2i** by normal Fries-rearrangement reaction from the corresponding ester was unsuccessful. An unidentified

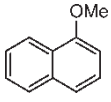
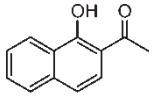
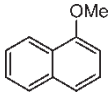
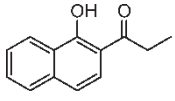
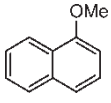
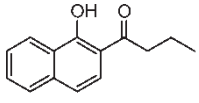
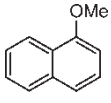
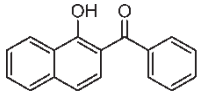
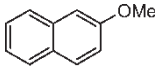
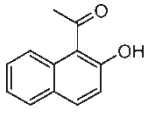
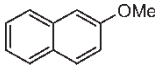
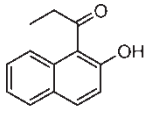
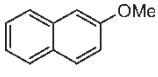
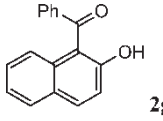
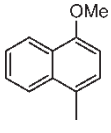
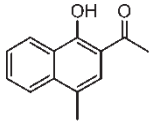


Scheme 3.



Scheme 4.

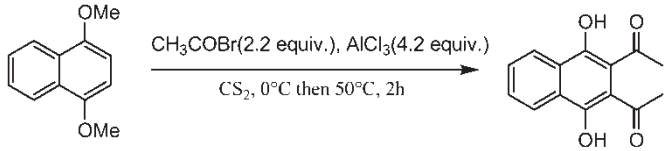
Table 2. Synthesis of hydroxynaphthyl ketones in carbon disulfide

Entry	Ether	R^2	Product	Yield (%)[a]
1		CH_3	 **2a**	94
2		CH_3CH_2	 **2b**	93
3		$CH_3CH_2CH_2$	 **2c**	94
4		Ph	 **2d**	90
5		CH_3	 **2e**	96
6		CH_3CH_2	 **2f**	95
7		Ph	 **2g**	89
8		CH_3	 **2h**	97

[a]Isolated yields based on naphthyl ethers.

complex was obtained (Scheme 6). Thus the present work has an advantage compared with the normal synthetic route.

In conclusion, with high yields, simple operation, and mild reaction conditions, the work described gives a useful method for the preparation of hydroxynaphthyl ketones. The preparation and procedure would be suitable for a large scale, too.



2i, 51%

Scheme 5.

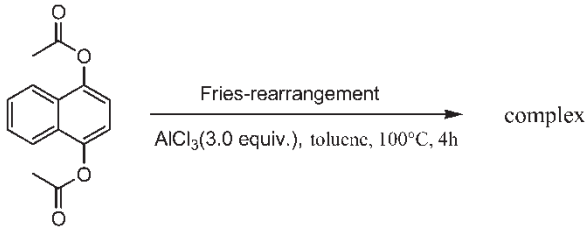
EXPERIMENTAL

All reagents used are commercially available. Melting points were uncorrected. ^{1}H NMR spectra was recorded on a Varian 400-MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were recorded on an Avatar-370. Mass spectra were test by a Thermo Finnagan LCQ Advantage instrument. Microanalysis was carried out on a Carlo-Erba 1106 instrument.

General Experimental Procedure

To solution of naphthyl ether (0.1 mol) and acetyl bromide (0.12 mol, 14.6 g) in CS_2 (50 mL) at 0°C, anhydrous $AlCl_3$ (29.3 g) was added in several portions, very carefully holding the temperature under 5°C. After completion, the mixture was heated to reflux and stirred for additional 2 h. Then the solvent was evaporated, and a gummy mixture was obtained. The ice water was poured into the mixture, and then concentrated HCl (50 mL) was added subsequently. The suspension was stirred vigorously for 10 min. The crude desired products were obtained as straw-yellow solids after filtration; in most cases the purity was higher than 95%.

Further purification should be carried out as following: The crude product obtained was treated with an appropriate volume of 20% NaOH to obtain a yellow aqueous solution, then filtered. The filtrate was neutralized with HCl



Scheme 6.

to pH = 5, and white solid precipitated. The pure (99% by HPLC) product was collected.

Data

2-Acetyl-1-naphthol (2a):[1a] IR (ν_{max}/cm^{-1}): 3310, 1678; ^1H NMR (δ, $CDCl_3$): 2.61 (s, 3H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.50–7.57 (m, 1H), 7.62–7.69 (m, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 8.44 (d, $J = 8.4$ Hz, 1H), 15.12 (s, 1H).

2-Propionyl-1-naphthol (2b):[4] IR (ν_{max}/cm^{-1}): 3358, 1698; ^1H NMR (δ, $CDCl_3$): 1.24 (t, $J = 7.2$ Hz, 3H), 2.85 (q, $J = 7.2$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.52–7.62 (m, 1H), 7.64–7.69 (m, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 8.45 (d, $J = 8.4$ Hz, 1 H), 11.48 (s, 1H).

2-Butyryl-1-naphthol (2c):[5] IR (ν_{max}/cm^{-1}): 3338, 1686; ^1H NMR (δ, $CDCl_3$): 1.11 (t, $J = 7.6$ Hz, 3H), 1.77 (m, 2H), 2.91 (t, $J = 7.6$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.51–7.60 (m, 1H), 7.64–7.68 (m, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 8.46 (d, $J = 8.4$ Hz, 1 H), 12.41 (s, 1H).

2-Benzoyl-1-naphthol (2d):[1e] IR (ν_{max}/cm^{-1}): 3402, 1656; ^1H NMR (δ, $CDCl_3$): 7.21 (d, 1H, $J = 8.8$ Hz), 7.61–7.49 (m, 5H), 7.64 (t, 1H, $J = 8$ Hz), 7.71 (d, 2H, $J = 8$ Hz), 7.75 (d, 1H, $J = 8$ Hz), 8.52 (d, 1H, $J = 8$ Hz), 14.55 (s, 1H).

1-Acetyl-2-naphthol (2e):[1b] IR (ν_{max}/cm^{-1}): 3322, 1706; ^1H NMR (δ, $CDCl_3$): 2.83 (s, 3H), 7.11 (d, $J = 8.4$ Hz, 1H), 7.35–7.39 (m, 1H), 7.52–7.56 (m, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 13.1 (s, 1H).

1-Propionyl-2-naphthol (2f):[5] IR (ν_{max}/cm^{-1}): 3398, 1712; ^1H NMR (δ, $CDCl_3$): 1.28 (t, $J = 7.6$ Hz), 2.88 (m, 2H), 7.11 (d, $J = 8.4$ Hz, 1H), 7.35–7.39 (m, 1H), 7.52–7.56 (m, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 13.1 (s, 1H).

1-Benzoyl-2-naphthol (2g):[6] IR (ν_{max}/cm^{-1}): 3350, 1647; ^1H NMR (δ, $CDCl_3$): 7.15 (t, $J = 8.0$ Hz, 1H), 7.31–7.22 (m, 3H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 13.10 (s, 1H).

4-Methyl-2-acetyl-1-naphthol (2h):[7] IR (ν_{max}/cm^{-1}): 3408, 1689; ^1H NMR (δ, $CDCl_3$): 2.61 (s, 3H), 2.65 (s, 3H), 7.55–7.58 (m, 1H), 7.64–7.69

(m, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 8.41 (d, $J = 8.4$ Hz, 1H), 10.56 (s, 1H).

2,3-Diacetyl-4-hydroxyl-1-naphthol (2i): mp: 201–202°C, gray powder (will turn dark after long exposure in moist air); IR (ν_{max}/cm^{-1}): 3398, 1697; ^{1}H NMR (δ, $CDCl_3$): 2.66 (s, 6H), 7.95–7.99 (m, 2H), 8.26–8.30 (m, 2H), 11.02 (s, 2H); ^{13}C NMR (δ, $CDCl_3$): 211.3, 154.8, 134.8, 130.7, 125.4, 119.1, 31.1; ESI- MS (m/z): 243.1 $(M\text{-}H)^-$. Anal. calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; found: C, 68.78; H, 4.89.

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