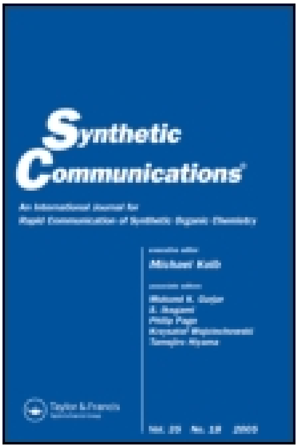

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 10 Jan 2011.

To cite this article: Weike Su & Can Jin (2004): One-Step Reaction of Friedel-Crafts Acylation and Demethylation of Aryl-Methyl Ethers Catalyzed by Ytterbium(III) Triflate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:22, 4199-4205

To link to this article: http://dx.doi.org/10.1081/SCC-200036628

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 22, pp. 4199–4205, 2004

One-Step Reaction of Friedel–Crafts Acylation and Demethylation of Aryl-Methyl Ethers Catalyzed by Ytterbium(III) Triflate

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ABSTRACT

Catalytic amount of ytterbium(III) triflate [$Yb(OTf)_3$] has been used to catalyze Friedel–Crafts acylation and demethylation of aryl-methyl ethers in one-step reaction to produce hydroxyacylphenones with moderate yields under mild conditions.

Key Words: Demethylation; Ethers; Friedel–Crafts acylation; Ytterbium(III) triflate.

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DOI: 10.1081/SCC-200036628
0039-7911 (Print); 1532-2432 (Online)

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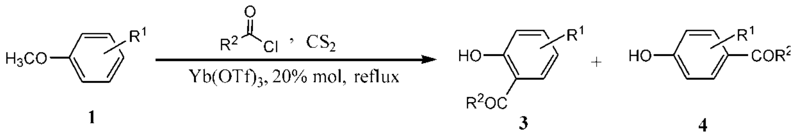
Lanthanide trifluoromethanesulfonate [lanthanide triflates; $Ln(OTf)_3$], especially ytterbium triflate [$Yb(OTf)_3$], as a new versatile Lewis acid has been used in Friedel–Crafts reactions with a catalytic amount of catalyst,[1] which can be reused easily.[2] For example, Friedel–Crafts reactions of aromatic compounds with ethyl α-chloro-α-(ethylthio)acetate promoted by ytterbium triflate can proceed smoothly.[3] Methylation is a very important method to protect hydroxy group in organic chemistry, which can be regenerated via demethylation. Deprotecting of methoxy group can proceed with nucleophilic reagents under acidic or basic condition. There are several methods[4] that have been used in deprotection of alkoxyl group. Recently, Lisa et al.[5] reported demethylation of aryl-methyl ethers using no-odorous thiolate. However, some methods need drastic conditions, which usually bring about the structural and stereochemical changes or have low yields because aryl-methyl ether is difficult to be demethylated under mild conditions.[6] As a very strong Lewis acid, $Yb(OTf)_3$ can catalyze Friedel–Crafts acylation as well as demethylation.

Herein, we report demethylation of aryl-methyl ethers using acyl chloride as acylation and demethylation reagents by one-step reaction to obtain hydroxyacylphenones catalyzed by $Yb(OTf)_3$ (Scheme 1) and the results are shown in Table 1.

From Table 1, it was found that the aryl-methyl ethers can be deprotected by acyl chloride in the presence of catalytic amount of $Yb(OTf)_3$ with moderate yields except that when the substrate is *o*-nitroanisole (entry 2). When, *o*-nitroanisole reacts with acylation reagents for longer time, unfortunately, none of the desired product was detected (entry 2). Furthermore, the highly chemselective products was obtained in our experiment and 0.2 equivalents of $Yb(OTf)_3$ is enough to complete the reaction. It is of interest that the main product **3e** was obtained when 2 equivalents of acetyl chloride was used to react with *m*-methyl-anisole for 10 hr in the presence of $Yb(OTf)_3$.

On the other hand, the amounts of acyl chloride was studied in our experiment, and it was found that when 2 equivalents of acylation reagent are used, a by-product is obtained from esterification of phenol (Scheme 2). However, there are no by-products under the condition that 1 or 1.5 equivalents of acyl chloride are used. In addition, when aroyl chloride is used, the reaction needs longer time, and the yield is not so high as using alkyl acyl chloride (entries 6 and 7).



Scheme 1.

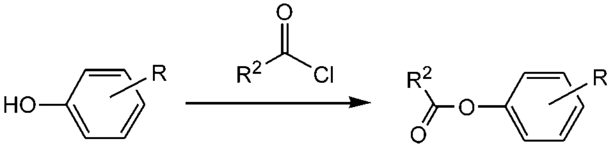
Table 1. Friedel–Crafts acylation and demethylation of aryl-methyl ethers catalyzed by $Yb(OTf)_3$.[a]

Entry	R^1	R^2	Time (hr)	Product	Yield[b] (%)
1	H	Me	6	4-$HOC_6H_4COCH_3$	75 (**4a**)
2	*o*-NO_2	Me	18	None	
3	*p*-NO_2	Me	6	5-NO_2-2-$HOC_6H_3COCH_3$	66 (**3c**)
4	*o*-OCH_3	Me	6	4-HO-3-$CH_3OC_6H_3COCH_3$	79 (**4d**)
5	*m*-CH_3	Me	10	2-OH-4-CH_3-5-$CH_3COC_6H_2COCH_3$	65 (**3e**)[c]
6	H	C_6H_5	10	4-$HOC_6H_4COC_6H_5$	66 (**4f**)
7	*p*-NO_2	C_6H_5	10	5-NO_2-2-$HOC_6H_3COC_6H_5$	56 (**3g**)
8	*p*-$NHCOCH_3$	Me	6	5-CH_3CONH-2-$HOC_6H_3COCH_3$	64 (**3h**)

[a] 1.5 equivalents of acyl chloride are used.

[b] Isolated yields based on aryl-methyl ethers purified by TLC and determined by 400M ^1H NMR.

[c] 2.0 equivalents of acetyl chloride are used.



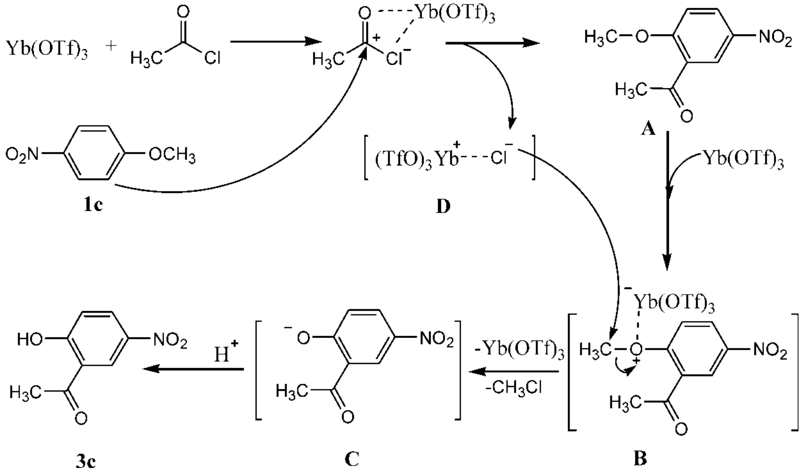
Scheme 2.

The mechanism of this reaction has not been clarified yet, according to literature 4f and considering Friedel–Crafts acylation, a possible mechanism is postulated in Scheme 3 (when R^1 is *para*-NO_2 and R^2 is CH_3). In Scheme 3 we suppose that the presence of catalyst is propitious to not only Friedel–Crafts acylation but also demethylation.

In conclusion, with moderate yields, simple operation and mild conditions, the work described gives a useful method for deprotecting of aryl-methyl ethers to obtain hydroxyacylphenones by one-step reaction. Further studies to the strong catalytic reactivity of ytterbium triflate are now in progress.

EXPERIMENTAL

All reagents used are commercially available. ^1H NMR spectra were recorded on a Varian-400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were recorded on a AVATAR-370



Scheme 3.

Infrared Spectrophotometer. Mass spectra were tested by a Thermo Finnagan LCQ Advantage instrument. Microanalysis was carried out on a Carlo-Erba 1106 instrument. Melting points were determined on a Digital Melting Point Apparatus WRS-1B and uncorrected. $Yb(OTf)_3$ was prepared from Ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[7]

General Experimental Procedure

Acyl chloride (3 mmol) was added to a solution of substrate (2 mmol) in carbon bisulfide (10 mL) in a 25-mL dry flask. The mixture was refluxed for 5 min, cooled to room temperature, and $Yb(OTf)_3$ (0.4 mmol, 0.248 g) was added. The solution was refluxed for the given time (see Table 1) after being cooled to room temperature, and then quenched by 5 mL ice water. The organic layer was washed by 5% sodium bicarbonate (10 mL) and extracted by chloroform, and then the combined organic layer was dried over anhydrous Na_2SO_4. After concentrated in vacuo, the residue was purified by TLC to yield corresponding products.

Compound **4a**

Mp 107°C (Lit[8] 106–107°C). IR υ_{max}/cm^{-1}: 3288, 1644; NMR δ_H: 8.71 (1H, s, ArOH), 7.95 (2H, d, J = 8.4 Hz, ArH), 6.99 (2H, d, J = 8.4 Hz, ArH), 2.54 (3H, s, CH_3).

Compound **3c**

Mp 102.5–103.0°C (Lit[9] 102–103°C). IR υ_{max}/cm^{-1}: 3364, 1668; NMRδ_H: 7.71 (1H, s, ArOH), 7.75 (1H, s, ArH), 7.73 (1H, d, J = 8.0 Hz, ArH), 6.84 (1H, d, J = 8.0 Hz, ArH), 2.56 (3H, s, CH_3).

Compound **4d**

Mp 114–115°C (Lit[10] 115°C). IR υ_{max}/cm^{-1}: 3328, 1648; NMR δ_H: 10.12 (1H, s, ArOH), 7.58–7.48 (2H, m, ArH), 6.99–6.81 (1H, s, ArH), 3.93 (3H, s, CH_3), 2.54 (3H, s, CH_3); (ESI) MS (m/z): 165.2 $(M\text{-}H)^-$.

Compound **3e**

Mp 102–104°C. IR υ_{max}/cm^{-1}: 3314, 1678, 1665; NMR δ_H: 12.53 (1H, s, ArOH), 8.16 (1H, s, ArH), 6.81 (1H, s, ArH), 2.66 (3H, s, CH_3), 2.59 (3H, s, CH_3), 2.57 (3H, s, CH_3); (ESI) MS (m/z): 191.1 $(M\text{-}H)^-$; Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.77; H, 6.33.

Compound **4f**

Mp 133.8–134.3°C (Lit[11] 133.8–133.9°C). IR υ_{max}/cm^{-1}: 3221, 1637; NMR δ_H: 12.25 (1H, s, ArOH), 7.79–7.74 (3H, m, ArH), 7.62–7.56 (2H, m, ArH), 7.48 (2H, d, J = 8.2 Hz, ArH), 6.95 (2H, d, J = 8.2 Hz, ArH).

Compound **3g**

Mp 122–124°C (Lit[12] 122–124°C). IR υ_{max}/cm^{-1}: 3228, 1641; NMR δ_H: 8.14–8.11 (3H, m, ArH), 7.64–7.60 (2H, m, ArH), 7.50–7.47 (3H, m, ArH), 4.85 (1H, s, ArOH).

Compound **3h**

Mp 163–164°C. IR υ_{max}/cm^{-1}: 3418, 3302, 1668, 1647; NMR δ_H: 12.08 (1H, s, ArOH), 8.18 (1H, s, NH), 8.08 (1H, s, ArH) 7.42 (1H, m, ArH), 6.97 (1H, m, ArH), 2.62 (3H, s, CH_3), 2.17 (3H, s, CH_3). (ESI) MS (m/z): 194.1 $(M+H)^+$; 192.2 $(M\text{-}H)^-$; Anal. calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.19; H, 5.78; N, 7.26.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China [20276072] for financial support.

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Received in UK December 15, 2003