Tetrahedron Letters, Vol.32, No.49, pp 7165-7166, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A SIMPLE METHOD FOR THE MICROSCALE PREPARATION OF MOSHER'S ACID CHLORIDE

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Key Words: Mosher's acid; Mosher's acid chloride; Mosher's esters; preparation of acid chlorides; microscale

Abstract : *Mosher's acid is treated with oxalyl chloride in the presence of DMF in hexane. Filtration and concentration provide the acid chloride which is suitable for use without further purification. The procedure is amenable to microscale.*

Mosher's acid[1] [α-methoxy-α-(trifluoromethyl)phenylacetic acid, MTPA] continues to be a popular chiral derivatizing agent for the determination of the enantiomeric purity[2] of alcohols and amines. Typical procedures for the derivatization of alcohols or amines require Mosher's acid chloride (MTPACl) which is prepared[1a,3] from MTPA by prolonged refluxing with $SOCl_2$ followed by distillation.[4] The reaction of MTPA with $SOCl_2$ can lead to varying amounts of the anhydride and α-chloro-α-methoxy-α-trifluoromethyltoluene depending on the reaction conditions.[1a,3] Because of the relatively high cost of MTPA and the small amounts of derivative typically required for high field NMR analysis (also GC or HPLC) we became interested in developing a protocol for the preparation of MTPACl which would be amenable to microscale (i.e. ≤ 5 mg, ≤ 0.02 mmol). Thus we required a method which would produce MTPACl in high yield free from contaminants without the need for distillation or chromatographic purification.

The reaction of carboxylic acids with oxalyl chloride gives acid chlorides with CO, CO_2, and HCl as the only byproducts. This reaction is efficiently catalyzed by DMF,[5] presumably[5a,5c,6] involving the intermediacy of N-(chloromethylene)-N-methylmethanaminium chloride (DMFCl). In our hands, MTPA is quantitatively converted into MTPACl (by ^1H NMR) within 1 hour at room temperature by treatment with excess oxalyl chloride in the presence of DMF. Concentration of the reaction mixture (to remove excess oxalyl chloride and HCl) gives MTPACl contaminated only by DMFCl.[7] If only a small amount (< 0.1 equivalents) of DMF is used to catalyze the reaction, the resulting "crude" MTPACl can be used directly to prepare Mosher's acid derivatives. However, DMFCl is more reactive than MTPACl and reacts with alcohols to produce alkyl halides and/or formate esters[8] (after workup). Thus the yield of Mosher's acid derivatives obtained from "crude" MTPACl decreases as the amount of DMF used in the preparation increases.[9]

The efficacy of several experimental conditions to produce MTPACl in suitable yield and purity from 0.01 mmol of MTPA was evaluated. We have found that the offending DMFCl can be conveniently removed from MTPACl by filtering if the reaction is conducted in hexane. Concentration of the resulting filtrate gives essentially homogeneous MTPACl (85-95% yield by ^1H NMR using an internal standard) which is suitable for use without further purification. The choice of hexane as solvent is crucial. Although the formation of MTPACl proceeds smoothly in other solvents (e.g. CH_2Cl_2, $CDCl_3$, C_6H_6), the DMFCl is not efficiently removed by filtration.[10]

The procedure works equally well on larger scale and is applicable to other acid chlorides.[11] The preparation of the Mosher's ester of (±)-1-phenylethanol on 0.01 mmol scale is illustrated.

Acknowledgement: Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Procedure: Oxalyl chloride (5 μL, 0.057 mmol)[12] was added to a solution of (*R*)-(+)-MTPA (2.8 mg, 0.012 mmol) and DMF (0.9 mg, 0.012 mmol)[12] in hexane (0.5 mL) at room temperature. A white precipitate formed immediately. After 1 h the mixture was filtered and concentrated (water aspirator). A solution of (±)-1-phenylethanol (1.3 mg, 0.01 mmol), Et_3N (4 μL, 0.03 mmol), and DMAP (a small crystal, ca. 1 mg) in $CDCl_3$ (100 μL) was added to the residue.[13] After 1 h, ^1H NMR of the mixture revealed complete[14] conversion into the diastereomeric Mosher's esters [δ for (*R,R*)-isomer: 6.14 (q, *J* = 6.5 Hz, CHOR), 3.46 (brs, OMe), 1.57 (d, *J* = 6.5 Hz, CMe); for (*S,R*)-isomer: 6.08 (q, *J* = 6.5 Hz, CHOR), 3.54 (brs, OMe), 1.63 (d, *J* = 6.5 Hz, CMe)] along with the presence of various amounts of MTPACl (δ 3.71, OMe), MTPA (δ 3.62, OMe), and MTPA anhydride (δ 3.37, OMe).

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7. The reaction of DMF with oxalyl chloride is known[5a,5c,6] to produce N-(chloromethylene)-N-methylmethanaminium chloride. The ^1H NMR spectrum ($CDCl_3$) of DMF with excess oxalyl chloride shows signals at δ 10.75 (s, 1H) and δ 3.96 (s, 6H). After addition of MTPA, the same signals are observed along with those attributed to MTPACl [δ: 7.4-7.6 (5H, m), 3.77 (3H, q, *J* = 2 Hz)]. However, after concentration of the mixture (water aspirator) the ^1H NMR spectrum shows signals for MTPACl, various amounts of MTPA [δ 3.57 (3H, q)] and singlets at δ 8.05, 3.01, 2.93, and 1.93. For a discussion of the NMR spectrum of DMFCl and its hydrolysis products see: Paasivirta, J.; Ahonen, I.; Hakli, H. *Magn. Reson. Relat. Phenom. Proc. Congr. AMPERE, 20th*, **1978**, 478; (*Chem. Abstr.*, **93**: 238638j)
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9. Using small amounts of DMF presents several added problems: i) The amount of DMF used affects the reaction time. ii) We have observed the formation of varying amounts of anhydride[1a] [δ 3.41 (3H, q, OCH_3)] when using < 0.01 equivalents of DMF. iii) On a 0.02 mmol scale, 0.15 mg or 0.16 μL = 0.002 mmol of DMF; adding this amount reliably presents additional experimental difficulty.
10. Concentration of the filtered reaction mixture shows (^1H NMR) the presence of products derived[7] from DMFCl. The contaminated MTPACl thus obtained is highly prone to hydrolysis. Alternatively, if the reaction mixture is first concentrated and then filtered from hexane, a variable yield of MTPACl contaminated with varying amounts of MTPA is obtained (^1H NMR).
11. We have prepared up to 50 mg of MTPACl using this procedure. Similarly, phenylacetyl chloride was prepared in 95% yield on a 1 mmol scale.
12. The procedure tolerates wide variation in stoichiometry. As long as oxalyl chloride is present in excess, analogous results were obtained using 0.1, 0.25, 1.0 or 10 equivalents of DMF.
13. Pyridine or pyridine with DMAP can also be used as base, however, the reaction is slower. Success on this scale requires dry solvent, reagents, and glassware.
14. Obviously, complete conversion is important for accurate measurement of ee. The rate constant for formation of the (*R,R*) diastereomer is ca. 1.5-2 times that for the (*S,R*) diastereomer.

(Received in USA 5 September 1991)