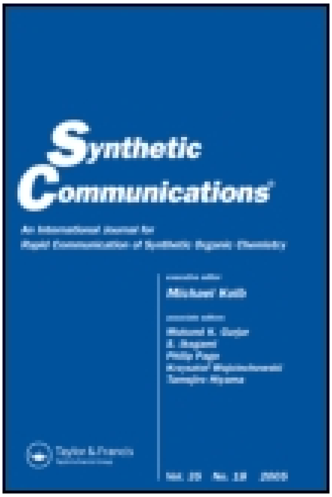


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Preparation of (±)-α-Methoxy-α-trifluoromethylphenylacetic Acid (Mosher's Acid)

J. Michael Chong [a] & Rob Loewith [a]
[a] Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada, N2L 3G1

To cite this article: J. Michael Chong & Rob Loewith (1993) A Convenient Preparation of (±)-α-Methoxy-α-trifluoromethylphenylacetic Acid (Mosher's Acid), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:15, 2145-2150, DOI: 10.1080/00397919308018609

To link to this article: http://dx.doi.org/10.1080/00397919308018609

SYNTHETIC COMMUNICATIONS, 23(15), 2145-2150 (1993)

A CONVENIENT PREPARATION OF (±)-α-METHOXY-α-TRIFLUOROMETHYLPHENYLACETIC ACID (MOSHER'S ACID)

J. Michael Chong* and Rob Loewith

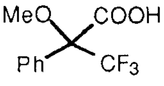
Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada
N2L 3G1

ABSTRACT: Mosher's Acid can be prepared from PhC(O)CF_3 via a vinylation, methylation, ozonolysis/oxidation sequence in >80% overall yield.

One of the reagents most widely used for the determination of enantiomeric purity of alcohols and amines is α-methoxy-α-trifluoromethylphenylacetic acid (**1**) (MTPA), commonly known as Mosher's acid.[1-3] This acid is easily resolved via crystallization of its α-methylbenzylamine salts, and both antipodes are commercially available. Diastereomeric esters or amides are typically prepared via the acid chloride (MTPA-Cl), and diastereomer ratios may be determined by ^1H or ^{19}F NMR, GC or HPLC analysis. One disadvantage of MTPA is that it is relatively expensive.

---

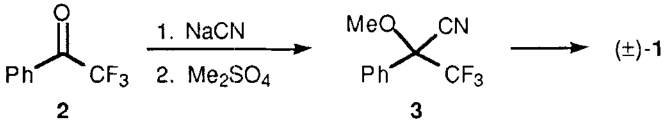
* To whom correspondence should be addressed.



1

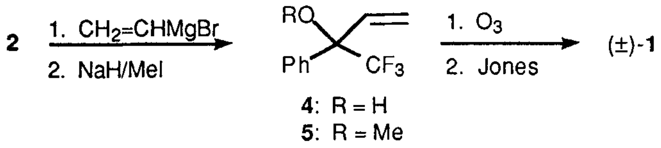
A search of the literature revealed that the only routes to (±)-MTPA reported involve formation of methylated cyanohydrin **3** followed by hydrolysis (Figure 1).[1,4,5] The original 3-step sequence described by Mosher[1] starts from $PhC(O)CF_3$ (**2**) and affords (±)-MTPA in 58% overall yield. In our hands, hydrolysis of nitrile **3** using 17 M H_2SO_4 followed by 7 M NaOH, the procedure used by Mosher, was extremely capricious, sometimes affording very low (10-20%) isolated yields of acid. Hall has shown that hydrolysis of nitrile **3** with alkaline H_2O_2 proceeds in much better (85%) yield.[4] However, we also had difficulties in reproducibly forming the cyanohydrin of **2** and methylating it to form **3**. Thus we sought to develop a route to (±)-MTPA which does not involve nitrile **3**.

FIG 1



Since there are many ways to oxidize a vinyl group to a carboxylic acid,[6] the route shown in Scheme 1 was envisaged. In practice, both alcohol **4** (96% yield) and methyl ether **5** (91% yield) were easily obtained via well-precedented procedures. Oxidation of **5** to **1** was not quite as straight-forward, with many of the "standard" oxidation procedures (*e.g.* $KMnO_4$, $NaIO_4$;[7] $RuCl_3$, $NaIO_4$,[8] n-Bu_4NMnO_4[9]) affording only trace quantities of the desired acid. Eventually, it was found that **5** could be very efficiently converted to **1** by ozonolysis in acetone (-78°C) followed by oxidation of the ozonide with Jones reagent (-78°C → rt, 94%) in situ.[10] Thus the 3-step sequence described in Scheme 1 proceeds in >80% overall yield. This sequence compares very favourably with the established route to (±)-MTPA and should be useful for the preparation of (±)-MTPA.

SCHEME 1



Experimental Section

2-Phenyl-1,1,1-trifluoro-3-buten-2-ol (4) was prepared essentially as described by Gassman[11] except that the reagents were mixed at -78 °C (instead of 0 °C), allowed to warm to rt, and stirred at rt for 12 h. From 50.1 g (0.288 mol) of 2, 2, 2-trifluoroacetophenone in THF (500 mL) and 346 mL of vinylmagnesium bromide (1.0 M in THF, 0.346 mol) there was obtained, after kugelrohr distillation (air-bath temperature 85-105°C/15 mm Hg), 55.8 g (96%) of alcohol **5** as a colorless oil: ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.55-7.60 (m, 2 H), 7.32-7.45 (m, 3 H), 6.42 (dd, J = 10.9, 17.2 Hz, 1 H), 5.60 (d, J = 17.2 Hz, 1 H), 5.49 (d, J = 10.9 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 137.1, 135.4, 128.6, 128.1, 126.7, 124.9 (q, $^{1}J_{CF}$ = 268 Hz), 118.3, 77.2 (q, $^{2}J_{CF}$ = 19 Hz).

Methyl 2-phenyl-1,1,1-trifluoro-3-buten-2-yl ether (5) To a suspension of NaH (20.6 g of a 60% dispersion in oil previously washed with 3 x 10 mL of hexanes, 0.52 mol) in THF (300 mL) was added MeI (64 mL, 147 g, 1.03 mol),and the mixture was warmed to 45°C. Alcohol **4** (49.4 g in 50 mL of THF, 244 mmol) was then added dropwise over 30 min while maintaining the reaction temperature at 45-50°C.[12] The grey slurry became a thick white slurry after stirring at gentle reflux for 15 h. The mixture was cooled to 0°C and quenched by the dropwise addition of water. It was then diluted with ether (1 L) and washed successively with water, saturated NH_4Cl, 5% $Na_2S_2O_3$, and brine. The organic layer was dried (Na_2SO_4), concentrated and distilled (bp 81-84°C/ 15 mm Hg) to afford 48.2 g (91%) of methyl ether **5** as a colorless liquid: IR (film) 3065, 1280, 1166, 1088, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50-7.58 (m, 2 H), 7.35-7.42 (m, 3 H), 6.10 (dd, J = 10.1, 17.6 Hz, 1 H), 5.68 (d, J = 10.1 Hz, 1 H), 5.57 (d, J = 17.6 Hz, 1 H), 3.30 (s, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 134.6, 131.9, 128.7, 128.5, 128.1, 124.9 (q, $^1J_{CF}$ = 287 Hz), 121.9, 82.5 (q, $^2J_{CF}$ = 27 Hz), 52.5; MS m/z (relative intensity): 216 (M^+, 9), 184 (11), 165 (20), 147 (100), 115 (57). Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 60.95; H, 4.92.

(±)-α-Methoxy-α-trifluoromethylphenylacetic acid (1) Ozone (as a ~2% stream in O_2) was bubbled through a solution of **5** (21.6 g, 100 mmol) in acetone (500 mL) at -78°C until the blue color of excess O_3 was evident. Nitrogen was then bubbled through the solution for 30 min to purge the excess O_3. Jones reagent[13,14] [80 mL, 2.67 M in Cr(VI), 214 mmol] was then added dropwise and the resulting dark mixture was allowed to slowly warm to rt, then stirred at rt for 2 h. Excess Cr (VI) was destroyed by the dropwise addition of 2-propanol (10 mL). Acetone was then removed by rotoevaporation and the resulting dark green mixture was partitioned between Et_2O (1 L) and H_2O (200 mL). The organic layer was washed with 1 M HCl (3 x 100 mL), dried ($MgSO_4$) and concentrated. Distillation (kugelrohr air-bath temperature 120-130°C/ 0.2 mm Hg) of the residual material provided 22.1 g (94%) of (±)-MTPA (**1**) as a colorless thick oil which slowly crystallized to a white solid. mp 43-45°C (lit.[15] mp 43-45°C) This material exhibited only the expected ^1H and ^{13}C NMR signals.[4]

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada for financial support and the University of Waterloo for a WATSEARCH studentship (to R. L.).

References

1. Dull, D. L. and Mosher, H. S., J. Am. Chem. Soc., 1967, 89, 4230; Dale, J. H., Dull, D. L. and Mosher, H. S., J. Org. Chem., 1969, 34, 2543.
2. Yamaguchi, S. in "Asymmetric Synthesis, Vol. 1", Morrison, J. D., Ed; Academic Press, New York, 1984, chapter 7.
3. Parker, D., Chem. Rev. 1991, 91, 1441.
4. Hall, W. E., Seeholzer, K, Baumeister, M. and Ugi, I., Tetrahedron, 1986, 42, 547.
5. Very recently an alternative preparation involving addition of $Cl_3CCOOSiMe_3$ to **2** followed by hydrolysis was published: Goldberg, Y. and Alper, H., J. Org. Chem. 1992, 57, 3731.
6. See, for example: Larock, R. C. "Comprehensive Organic

Transformations," VCH, New York, 1989; pp. 828-829.

7. Lemieux, R. U. and von Rudloff, E., Can. J. Chem., 1955, 33, 1701.
8. Wolfe, S., Hasan, S. K. and Campbell, J. R., J. Chem. Soc., Chem. Commun., 1970, 1420; Carlsen, P. H. J., Katsuki, T., Martin, V. S. and Sharpless, K. B., J. Org. Chem., 1981, 46, 3936.
9. Sala, T. and Sargent, M. V., J. Chem. Soc., Chem. Commun., 1978, 253.
10. Patel, D. V., VanMiddlesworth, F., Donaubauer, J., Gannett, P. and Sih, C. J., J. Am. Chem. Soc., 1986, 108, 4603.
11. Gassman, P. G., Ray, J. A., Wenthold, P. G. and Mickelson, J. W., J. Org. Chem., 1991, 56, 5143.
12. Brown, C. A. and Barton, D., Synthesis, 1974, 434.
13. Jones reagent was prepared by mixing 133.5 g of CrO_3 in 200 mL of water, adding 115 mL of 98% H_2SO_4 with cooling, and diluting to a total volume of 500 mL with water: Hudlicky, M., "Oxidations in Organic Chemistry," American Chemical Society, Washington, 1990; p. 273.
14. Bowers, A., Halsall, T. G., Jones, E. R. H.and Lemin, A. J., J. Chem. Soc., 1953, 2548.
15. Fluka Chemika-Biochemika catalogue, 1993-94, product #65371.

(Received in USA 4 March 1993)