Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7171-7172, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01617-6

Expeditious Synthesis of Mosher Amides using a Solid Supported Carbodiimide

Maciej Adamczyk* and Jeffrey R. Fishpaugh

Abbott Laboratories, 100 Abbott Park Road, D-9NM AP-20, Abbott Park, IL 60064

Abstract: *A novel method of Mosher amide synthesis using a solid supported carbodiimide in $CDCl_3$ is described. Estimation of optical purity can be promptly achieved by direct NMR analysis of the reaction solvent.* Copyright © 1996 Elsevier Science Ltd

Determination of optical purity is an integral step in the synthesis of chiral compounds.[1] Mosher's amides[2] play a significant role in measuring enantiomeric purity of amines by NMR[3] (^1H and ^{19}F), gas chromatography[4] and high-performance liquid chromatography,[5] additionally NMR can be used to determine absolute configuration.[6]

Frequently, Mosher amides are prepared from amines by carbodiimide mediated coupling[6,7] of Mosher's acid [α-methoxy-α-trifluoromethyl-phenylacetic acid] or via Mosher's acid chloride[8] employing a variety of bases.[2,9] Evaluation of enantiomeric purity can only be performed after workup of the reaction mixture and purification of the amide.

Now we report a novel method for the synthesis of Mosher amides in deuterochloroform ($CDCl_3$) from a variety of amines using ethyl 3-(dimethylaminopropyl)-carbodiimide on a polystyrene solid support[10] (SS-EDAC). This reagent has recently been employed in the synthesis of active esters (hydroxysuccinimidyl, pentafluorophenyl)[11] and thiol esters.[12] Coupling of an amine with Mosher's acid mediated by SS-EDAC gave the desired amides in 4 hours and in good to high yield, see Table 1.[13,14] *Direct analysis of the $CDCl_3$ reaction mixture detected only the presence of the amide* with no starting amine or Mosher acid. No formation of the Mosher ester was observed for the coupling of isoleucinol (entries 12-14) using this method, thus the coupling is chemoselective for the amine in the presence of an alcohol.[6] A series of experiments to examine the scope of this method were performed including coupling of a racemic amine with enantiopure Mosher's acid and racemic Mosher's acid with enantiopure amines, no notable differences in the rate of reactivity of either racemic α-methylbenzyl amine with (R) or (S)-Mosher's acid (entries 4,5) or racemic Mosher's acid with several enantiopure amines (entries 3,8,11,14,17) as demonstrated by equal formation of the two amide diastereomers. Transformation of amino ester hydrochloride salts was readily accomplished for both a monosubstituted amine, L-valine methyl ester (entries 9-11), and a disubstituted amine, L-proline methyl ester (entries 15-17), to produce the corresponding amides.[6]

In conclusion, amide derivatives of Mosher's acid were readily prepared in high yield and high purity using the solid supported coupling reagent SS-EDAC. Our method combines the ease and convenience of solid supported reagents, thus offering expeditious NMR analysis of the resulting deuterochloroform/amide solution. This new procedure should enhance the use of Mosher amides for the determination of enantiomeric purity of chiral amines.

Table 1. Facile Synthesis of Mosher Amides from Mosher's Acid in Deuterochloroform Using SS-EDAC

Entry	Amine	Acid Configuration	Mosher Amide	Yield[a]	δ(-OCH_3)	Ref.[b]
1	(R)-α-Methyl benzylamine	R		80	3.37	3a
2		S		89	3.41	3a
3		Racemic		83	3.37,3.41	3a
4	(±)-α-Methyl benzylamine	R		81	3.37,3.41	3a
5		S		89	3.37,3.41	3a
6	(S)-α-Methyl benzylamine	R		82	3.41	3a
7		S		80	3.37	3a
8		Racemic		85	3.37,3.41	3a
9	*L*-Valine methyl ester HCl salt	R		90	3.39	7
10		S		95	3.55	7
11		Racemic		80	3.39,3.55	7
12	*L*-Isoleucinol	R		85	3.40	7
13		S		80	3.46	7
14		Racemic		70	3.40,3.46	7
15	*L*-Proline methyl ester HCl salt	R		71	3.65	16
16		S		75	3.82	16
17		Racemic		74	3.65,3.82	16

[a] Yields were not optimized and were determined by removal of deuterochloroform *in vacuo*.

[b] Literature references to ^1H NMR spectra of Mosher amide.

References

1. a) Stinson, S.C. *Chemistry & Engineering News* **1995**, 73(41), 44.
   b) Cannarsa, M.J. *Chem. Ind.* **1996**, 374.
2. a) Dale, J.A., Dull, D.L. and Mosher H.S. *J. Org. Chem.* **1969**, *34*, 2543.
   b) Yamaguchi, S. in *Asymmetric Synthesis* (Morrison, J. ed.), 1983, Vol. 1, Ch. 7, 125-142.
3. a) For ^1H NMR, see Dale, J.A. and Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
   b) For ^{19}F NMR, see Sullivan, G.R.; Dale, J.A. and Mosher, H.S. *J. Org. Chem.* **1973**, *38*, 2143.
4. LeBelle, M.J.; Savard, C.; Dawson, B.A.; Black, D.B.; Katyal, L.K.; Zrcek, F. and By, A.W. *Forensic Sci. Int.* **1995**, *71*, 215.
5. Balani, S. et al. *J. Chem. Soc., Perkin Trans. I.* **1983**, 2751.
6. Kusumi, T.; Fukushima, T.; Ohtani, I. and Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939.
7. Erikson, S.D.; Simon, J.A. and Still, W.C. *J. Org. Chem.* **1993**, *58*, 1305.
8. Ward, D.E. and Rhee, C.K. *Tetrahedron Lett.* **1991**, *32*, 7165.
9. a) Kabuto, K.; Yasuhara, F. and Yamaguchi, S. *Tetrahedron Lett.* **1981**, *22*, 659.
   b) Evans, D.A.; Britton, T.C.; Durow, R.L. and Dellaria, J.F. *Tetrahedron* **1988**, *44*, 5525.
10. Desai, M. and Stramiello, L. *Tetrahedron Lett.* **1993**, *34*, 7685.
11. Adamczyk, M.; Fishpaugh, J. and Mattingly, P. *Tetrahedron Lett.* **1995**, *36*, 8345.
12. Adamczyk, M. and Fishpaugh, J. *Tetrahedron Lett.* **1996**, *37*, 0000.
13. Deuterochloroform [$CDCl_3$, 4 mL] was added to SS-EDAC[15] (600 mg) in a 10 mL flask under N_2, stirred 5 minutes to swell the polymer then added a solution of Mosher's acid (0.12 mmol) in 1.0 mL $CDCl_3$ to the heterogeneous mixture. The amine (0.06 mmol) in $CDCl_3$ (1.0 mL) was added 5 minutes later and the mixture was stirred for 4 hours. Filtration through cotton in a glass pipette afforded the desired amide which could be directly analyzed by ^1H NMR.
14. Coupling of a chiral secondary alcohol under these conditions gave only the starting alcohol and none of the desired ester. Additives employed afforded only mixtures of desired ester and starting alcohol.
15. SS-EDAC was washed with $CDCl_3$, filtered and vacuum dried to remove any residual non-deuterated solvents prior to use.
16. All amides had correct molecular weight by MS and were >97% purity by analytical HPLC (analytical μporasil column eluted with ethyl acetate/hexanes).

(*Received in USA* 25 *July* 1996; *accepted* 12 *August* 1996)