

Expeditious Synthesis of Mosher Amides using a Solid Supported Carbodiimide

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Abstract: *A novel method of Mosher amide synthesis using a solid supported carbodiimide in CDCl₃ 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 amides² play a significant role in measuring enantiomeric purity of amines by NMR³ (¹H and ¹⁹F), gas chromatography⁴ 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 chloride⁸ 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 deuteriochloroform (CDCl₃) from a variety of amines using ethyl 3-(dimethylaminopropyl)-carbodiimide on a polystyrene solid support¹⁰ (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 CDCl₃ 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 deuteriochloroform/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 Deuteriochloroform Using SS-EDAC

Entry	Amine	Acid Configuration	Mosher Amide	Yield ^a	$\delta(-OCH_3)$	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	(\pm)- α -Methyl benzylamine	R		81	3.37,3.41	3a
5		S		89	3.37,3.41	3a
6		Racemic		82	3.41	3a
7	(S)- α -Methyl benzylamine	R		80	3.37	3a
8		S		85	3.37,3.41	3a
9		Racemic		85	3.37,3.41	3a
9	<i>L</i> -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	<i>L</i> -Isoleucinol	R		85	3.40	7
13		S		80	3.46	7
14		Racemic		70	3.40,3.46	7
15	<i>L</i> -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 deuteriochloroform *in vacuo*.

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

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13. Deuteriochloroform [CDCl₃, 4 mL] was added to SS-EDAC¹⁵ (600 mg) in a 10 mL flask under N₂, stirred 5 minutes to swell the polymer then added a solution of Mosher's acid (0.12 mmol) in 1.0 mL CDCl₃ to the heterogeneous mixture. The amine (0.06 mmol) in CDCl₃ (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 CDCl₃, 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 μ porasil column eluted with ethyl acetate/hexanes).

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