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Me_2NSO_2Cl and *N*,*N*-dimethylamines; a novel and efficient agent for esterification, amidation between carboxylic acids, and equimolar amounts of alcohols and amines

Kazunori Wakasugi, Atsushi Nakamura and Yoo Tanabe*

School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662-8501, Japan

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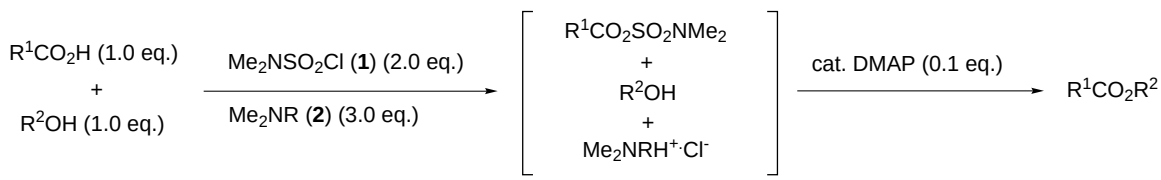
Abstract—Various carboxylic esters or amides were prepared in good to excellent yields between carboxylic acids and equimolar amounts of alcohols or amines under very mild conditions using dimethylsulfamoyl chloride (Me_2NSO_2Cl) combined with *N*,*N*-dimethylamines. The choice of the sulfamoyl chloride and the amine is crucial for the reactions.

Mild and effective esterification or amidation of carboxylic acids with alcohols or amines has been extensively examined due to their wide utility in organic, bioorganic, and related fine-chemical syntheses.[1] There are many methods for esterification and/or amidation using specific dehydrating reagents under mild liquid-phase conditions; DCC,[2] halopyridinium salts,[3] 2,4,6-trichlorobenzoyl chloride,[4] *N*,*N*-carbonyldiimidazaole,[5] BOP-Cl,[6] DPC,[7] DPTC,[8] and several other condensation agents.[9]

From the recent standpoint of a green chemical requirement, there still exists the request of a simpler, more convenient, inexpensive, and less toxic agent, particularly between carboxylic acids and equimolar amounts of alcohols or amines. Consistent with our interest in green chemical esterification,[10] we introduce here a novel efficient condensation agent, dimethylsulfamoyl chloride (Me_2NSO_2Cl; **1**) together with *N*,*N*-dimethylamines (Me_2NR: **2a**; R = Me **2b**; R = Bu) (Scheme 1).

First, we focused our attention on the use of commercially available sulfonyl chlorides and tertiary amines. Methanesulfonyl chloride ($MeSO_2Cl$) is the most obvious candidate, and indeed a study using $MeSO_2Cl$ together with Et_3N has been reported,[9g] this method, however, has two serious problems. Reexamination in our hands revealed that high yields reported were not reproducible; over 4 equiv. of each $MeSO_2Cl$ and Et_3N were required to complete the esterification (reported account; 1 equiv. of $MeSO_2Cl$ and 2 equiv. of Et_3N). We assume that the first step for a mixed-anhydride formation does not proceed smoothly, i.e. concomitant loss of Me_2SO_2Cl considerably occurs due to the undesirable side sulfene-dimerization.[11] Moreover, there was an unavoidable critical side reaction of mesylation of alcohols.

To overcome the problem, we planned the use of Me_2NSO_2Cl (**1**) instead of $MeSO_2Cl$, because **1** lacks α-hydrogens, which causes the undesirable sulfene-dimerization. The initial trial of esterification of 3-phenylpropanoic acid with an equimolar amount of 1-octanol resulted in 34% yield using **1** (2.0 equiv.)



Scheme 1.

Keywords: esterification; amidation; sulfamoyl chloride; tertiary amine; chemoselective.

* Corresponding author.

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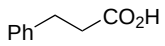
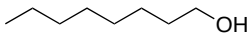
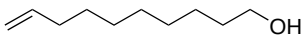
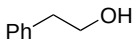
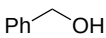
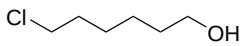
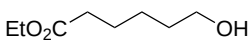
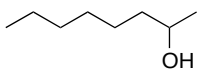
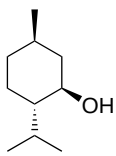
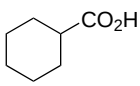
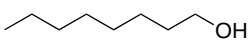
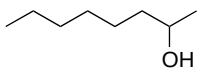
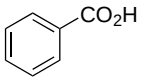
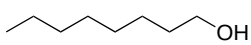
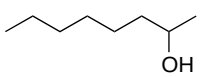
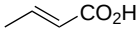
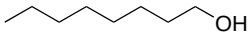
combined with Et_3N (3.0 equiv.) in MeCN at 0–5°C. To activate **1**, Me_3N·HCl (3.0 equiv.) was added for in situ generation of Me_3N (**2a**; bp 2.9°C). Thus, the yield markedly increased up to 86%.[12] DMAP (0.1 equiv.) should be added in order to enhance the second acylation step (up to 93%, Table 1, entry 1). The only amine used during the first step, *N*,*N*-dimethylbutylamine ($BuNMe_2$, **2b**) also promoted the esterification at 45–50°C (92%).

Based on these results, esterifications between several carboxylic acids and alcohols were performed.[13] The esters of primary and secondary alcohols were prepared in good to excellent yields under the two unified conditions. Several functionalities on alcohols such as a double and a triple bond, a halogen, and an ester were tolerated (entries 2, 3, 7, and 8). Higher yields were generally obtained compared with the report using halopyridinium salts method.[3a] Unfortunately, sterically crowded substrates such as pivalic acid and *t*-butyl alcohol did not produce high yields.[14] *E*-Crotonic acid, a base sensitive substrate (leading to easy isomerization) underwent this esterification with keeping good stereochemistry.

Table 1. Esterification between carboxylic acids and equimolar amounts of alcohols

Entry	R^1CO_2H	R^2OH	Method[a)]	Yield / %
1			A	93
			B	92
2			A	95
			B	92
3			A	91
			B	93
4			A	90
			B	94
5			A	86
			B	86
6		PhOH	A	80
			B	80
7			A	91
			B	90
8			A	90
			B	88
9			A	95[b)]
			B	94[b)]
10			A	96[b,c)]
			B	94[b,c)]
11			A	93
			B	92
12			A	90[b)]
			B	94[b)]
13			A	92
			B	92
14			A	91[b)]
			B	92[b)]
15			A	73 (*E* : *Z* = 10 : 1)
			B	71 (*E* : *Z* = 7 : 1)

[a] A: Use of Me_3N·HCl (**2a**·HCl)/Et_3N, 0–5°C, 3 h, MeCN solvent. B: Use of $BuNMe_2$ (**2b**), 40–45°C, 1 h, MeCN solvent.
[b] DMAP (1.0 equiv.) was used.
[c] $[\alpha]_D^{23}$ −59.5 (*c* 1.47, $CHCl_3$).

The salient features are as follows. (1) Me_2NSO_2Cl (**1**) and the amines used are relatively cheap and commercially available, structurally simple (atom-economic), and **1** is less hygroscopic among sulfonyl chlorides. (2) *N*,*N*-Dimethyl structure in **2a** and **2b** is crucial, except for the case of DABCO, because our previous studies of green chemical sulfonylations suggest that such less hindered amines significantly activate the sulfonyl chlorides during the first mixed-anhydride formation.[15] (3) This agent had very high chemoselectivity toward the carboxyl group versus the hydroxyl group, namely, the experiment could be performed with the addition of both carboxylic acids and alcohols. This chemoselectivity was rarely observed using other sulfonyl chloride reagents. Thus, the experimental procedure is simple and convenient, and, moreover, would ensure the lactonization reaction of ω-hydroxyl carboxylic acids.

This protocol could be also extended to an amidation reaction between carboxylic acids and equimolar amounts of primary or secondary amines (Table 2).[16] The present reaction proceeded with good to excellent yields in every case examined. It should be noted that no substantial isomerization occurs in the case using *E*-crotonic acid (entries 6 and 7). Synthetic application to the synthesis of a certain biologically active natural product is now in progress.

In conclusion, useful esterification and amidation were achieved using the combined reagents, Me_2NSO_2Cl (**1**) and Me_2NR (**2a**; R = Me **2b**; R = Bu). This method has merits of the operational simplicity, economy in use of reagents and substrates, and reactivities, which rival those reported for related condensation agents.

Acknowledgements

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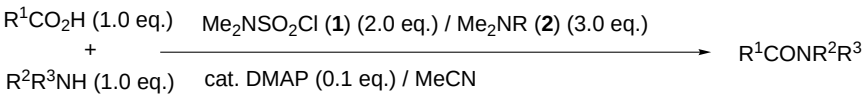
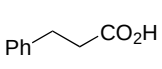
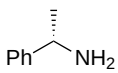
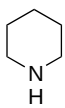
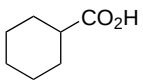
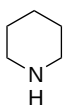
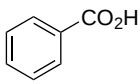
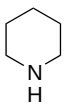
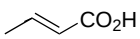
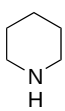
Table 2. Amidation between carboxylic acids and equimolar amounts of amines



Entry	R^1CO_2H	R^2R^3NH	Method[a]	Yield / %
1			A	95[b]
			B	96[b]
2		$^tBuNH_2$	A	96
			B	97
3			A	92
			B	93
4			A	92
			B	92
5			A	90
			B	94
6		$^tBuNH_2$	A	88[c] (*E* only)
			B	92[c] (*E* only)
7			A	90[c] (*E* only)
			B	93[c] (*E* only)

[a] A: Use of $Me_3N{\cdot}HCl$ (**2a**·HCl)/Et_3N, 0–5°C, 3 h, MeCN solvent. B: Use of $BuNMe_2$ (**2b**), 40–45°C, 1 h, MeCN solvent.
[b] $[\alpha]_D^{24}$ −54.0 (*c* 1.01, $CHCl_3$).
[c] DMAP (1.0 equiv.) was used.

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12. Screening of amines: DABCO (82%), $BuNMe_2$ (79%), TMEDA (63%), DBU (42%), $BnNMe_2$ (31%). The reaction using toluene or THF solvent resulted in low yields. Concerning the reactivity of DABCO; Wong, Z.; Campaguna, S.; Yang, K. H.; Xu, G. Y.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *J. Org. Chem*. **2000**, *65*, 927.
13. Attention: It is important to dry up $Me_3N{\cdot}HCl$ (**2a**·HCl) under reduced pressure before use. General procedure of method A: $Me_3N{\cdot}HCl$ (2.00 mmol) was added to a stirred solution of a carboxylic acid (1.00 mmol), an alcohol (1.00 mmol), Et_3N (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) at 0–5°C under an Ar atmosphere, and the mixture was stirred for 10 min. Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) was added to the mixture at 0–5°C, and the mixture was stirred at that temperature for 3 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane:ether = 40:1–10:1) to give the desired ester.
    Method B: Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1 ml) was added to a stirred solution of a carboxylic acid (1.00 mmol), an alcohol (1.00 mmol), $BuNMe_2$ (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) at 45–50°C under an Ar atmosphere, and the mixture was stirred at that temperature for 1 h. A similar work-up procedure as described above gave the desired ester.
14. 40%; between pivalic acid and 1-octanol. Trace; between 3-phenylpropanoic acid and *t*-butyl alcohol.
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16. General procedure of method A: An amine (1.00 mmol), Et_3N (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) was added to a stirred solution of a carboxylic acid (1.00 mmol), $Me_3N{\cdot}HCl$ (2.00 mmol), and Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) at 0–5°C under an Ar atmosphere, and the mixture was stirred at that temperature for 3 h. A similar work-up procedure as described above gave the desired amide.
    Method B: Amines (1.00 mmol), $BuNMe_2$ (3.00 mmol) and DMAP (0.10 mmol) in MeCN (1.0 ml) was added to the stirred solution of a carboxylic acid (1.00 mmol) and Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) at 45–50°C under an Ar atmosphere, and the mixture was stirred at that temperature for 3 h. A similar work-up procedure as described above gave the desired amide.