Pergamon

Tetrahedron Letters 40 (1999) 5327–5330

TETRAHEDRON LETTERS

Synthesis and Characterization of 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride

Munetaka Kunishima,*[a] Chiho Kawachi,[a] Fumiaki Iwasaki,[b] Keiji Terao,*[c] and Shohei Tani[a]

[a]Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Nishi-ku, Kobe 651-2180, Japan, [b]Tokuyama Corp., 40 Wadai, Tsukuba-City, Ibaraki 300-4247, Japan, and [c]Wacker Chemicals East Asia Ltd., 2-14-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan.

Received 23 March 1999; revised 10 May 1999; accepted 14 May 1999

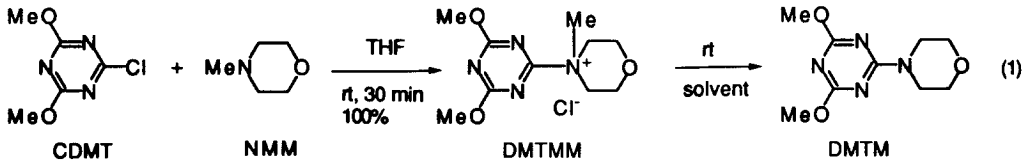
Abstract. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) was quantitatively synthesized by the coupling of 2-chloro-4,6-dimethoxy-1,3,5-triazine and *N*-methylmorpholine in THF, and fully characterized. Condensation of carboxylic acids and amines by DMTMM proceeded effectively in THF to give the corresponding amides in good yield.

Keywords: *Triazines; Condensations; Amides; Carboxylic acids and derivatives*

2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) is a useful non-carbodiimide condensing agent for the synthesis of amides, esters, and acid anhydrides.[1,2] During our study of amide synthesis,[3] we found that 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) was formed by the reaction of CDMT with *N*-methylmorpholine (NMM).[4] The preparation and characterization of DMTMM was reported very recently from another laboratory.[5] However, the condensation of carboxylic acids and amines with DMTMM under the conditions employed was found to proceed in yields lower than those observed in the reactions using the standard CDMT–NMM system.[1a] In addition, carboxylic acids undergoing coupling seem to be limited to either sterically hindered pivalic acid or benzoic acids, especially those with an electron-withdrawing group. These results can be attributed to decomposition of DMTMM before or during condensation reactions (see below). In this paper, we report the quantitative synthesis, characterization, and utilization of DMTMM as a good condensing agent leading to the formation of amides.

Treatment of CDMT and NMM in THF at room temperature afforded DMTMM as a white precipitate in 100% yield within 30 min (eq 1), which can be stored in the solid state for one month at room temperature without any detectable decomposition. DMTMM completely decomposed (96%) into 4-(4,6-dimethoxy-

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00968-5



solvent	time	DMTMM	DMTM
THF	13 h	85%	13%
CH_2Cl_2	3 h	0%	96%

1,3,5-triazin-2-yl)morpholine (DMTM) by demethylation at the morpholinium nitrogen when it was suspended in CH_2Cl_2 for 3 h at room temperature,[6] whereas it was found to be stable in THF (suspension) even after stirring for 13 h (85% recovery and 13% demethylation) (eq 1). Interestingly, no methanolysis was observed when it was dissolved in MeOH although it is a dehydrating condensing agent.

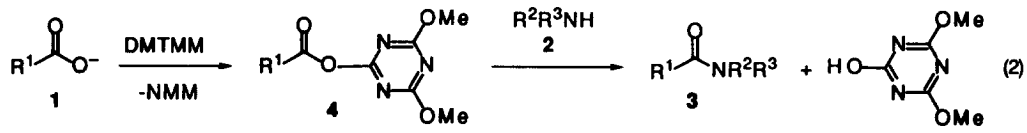
^1H and ^{13}C NMR data of both DMTMM and DMTM are given in Table 1.[7] The data of DMTMM (entries 3 and 6) reported by Kaminski *et al.* agree better with those of DMTM (entries 2 and 5) rather than DMTMM (entries 1 and 4). The signals at δ 27.0 in the carbon spectrum and at δ 3.03 in the proton spectrum, which were assigned to the morpholinium methyl group by Kaminski *et al.*, should be assigned to chloromethane arising from demethylation of DMTMM. In fact, ^1H-NMR analysis of DMTMM in $CDCl_3$ indicated the disappearance of DMTMM with the appearance of the signals of DMTM and chloromethne (singlet at δ 3.03). The latter signal disappeared after evaporation of the solvent. Based on ^{13}C-^1H COSY spectrum of DMTMM, we assigned the signal at δ 56.5 to N^+-CH_3 and that at δ 61.4 to N^+-CH_2-, respectively. These chemical shifts agree well with those for methylmorpholinium salts given in literature.[8]

We have found that DMTMM is efficient for condensing carboxylic acids and amines (eq 2). Addition

Table 1. ^1H and ^{13}C NMR data of DMTMM and DMTM[a]

entry	material	nucleus	solvent	N-CH_2-CH_2-O		triazine	O-CH_3	N^+-CH_3	CH_3-Cl
1	DMTMM	^{13}C	methanol-d_4	61.4	63.2	172.0, 175.5	57.6	56.5	
2	DMTM	^{13}C	DMSO-d_6	43.5	65.7	166.2, 171.8	54.1		(25.6)[c]
3[b]	DMTMM	^{13}C	DMSO-d_6	44.4	66.6	167.1, 172.8	55.0	27.0	
4	DMTMM	^1H	DMSO-d_6	3.78, 3.93, 4.01, 4.35			4.10	3.49	
5	DMTM	^1H	DMSO-d_6	3.64, 3.74			3.85		3.06[d]
6[b]	DMTMM	^1H	DMSO-d_6	3.60, 3.70			3.81	3.03	

[a] Chemical shits (δ in ppm). [b] Reported by Kaminski's group, ref.5. [c] The chemical shift reported in a literture: Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-resolution methods and applications in organic chemistry and biochemistry*, 3rd, completely rev. ed., VCH; Weinheim, 1987. No signal corresponding to chloromethane was observed. [d] The signal appeared along with DMTM when ^1H-NMR of DMTMM was measured in DMSO-d_6.



of DMTMM powder to a mixture of 2-phenylpropionic acid **1a** and phenethylamine **2a** in THF at room temperature followed by stirring for 3 h gave the corresponding amide **3a** in 84% yield. The reaction is thought to involve an activated ester **4** as illustrated in eq 2.[1a,9] All the reactions, summarized in Table 2, were conducted in a flask open to the atmosphere, not under nitrogen flow, by using commercial THF without further purification or drying. The method is applicable to aromatic, aliphatic, and α,β-unsaturated acids. Both primary and secondary amines can be condensed to give the corresponding amides.

It was reported that the condensation using DMTMM performed in CH_2Cl_2 resulted in a lower yield of product probably due to a prolonged activation time and the formation of a carboxylic anhydride as a byproduct.[5] However, we found that when **1a** was treated with DMTMM for 17 h in THF in the presence of 1% water followed by addition of **2a**, **3a** was formed in 70% yield. It is unlikely that **4**, if it is present, can survive as a major intermediate without significant hydrolysis under the conditions including water because the activated ester **4** undergoes attack by alcohols, carboxylic acids, and probably water as well as amines.[1a,10] Thus, it is reasonable to assume that almost no reaction took place between **1a** and DMTMM until the addition of amine **2a** in THF because of the poor nucleophilicity of free carboxylic acids. Low yields observed in CH_2Cl_2 were probably due to decomposition of DMTMM during the reactions. Otherwise, DMTMM had been already decomposed before the condensation reaction.

In summary, we prepared DMTMM quantitatively from CDMT and NMM in THF, correctly characterized it, and showed it to be an efficient agent for condensation of carboxylic acids with amines. Our method is simpler and easier, and seems to proceed faster than the CDMT–NMM system.[1,2] In addition,

Table 2. Condensation of carboxylic acids with amines by DMTMM in THF[a]

run	carboxylic acid	amine	product	time	yield (%)
1	$Ph(CH_2)_2COOH$ (1a)	$Ph(CH_2)_2NH_2$ (2a)	$Ph(CH_2)_2CONH(CH_2)_2Ph$ (3a)	4 hr	84
2	$CH_3(CH_2)_4COOH$ (1b)	2a	$CH_3(CH_2)_4CONH(CH_2)_2Ph$ (3b)	overnight	83
3	PhCH=CHCOOH (1c)	2a	PhCH=CHCONH$(CH_2)_2$Ph (3c)	4 hr	70
4	1a	Et_2NH (2b)	$Ph(CH_2)_2CONEt_2$ (3d)	4 hr	68
5	PhCOOH (1d)	*cyclo*-$C_6H_{11}NH_2$ (2c)	PhCONH-*cyclo*-C_6H_{11} (3e)	3 hr	92

[a] The reactions were performed using carboxylic acid, amine, and DMTMM in the ratio of 1 : 1.1 : 1.1 in THF at rt.

because the solvent need not be predried and the reaction need not be conducted under nitrogen, the reaction is very practical. Since CDMT can be prepared on a large scale from inexpensive cyanuric chloride,[11] the present reaction is economically advantageous.

References and Notes

1 (a) Kaminski, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901–2904. (b) Kaminski, Z. J. *Synthesis* **1987**, 917–920.

2 For recent paper using CDMT: (a) Taylor, E. C.; Dowling, J. E. *J. Org. Chem.* **1997**, *62*, 1599–1603. (b) Svete, J.; Aljaz-Rozic, M.; Stanovnik, B. *J. Heterocycl. Chem.* **1997**, *34*, 177–193. (c) Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982–991. (d) Kuciauskas, D.; Liddell, P. A.; Hung, S.- C.; Lin , S.; Stone, S.; Seely, G. R.; Moore, A. L.; Moore, T. A.; Gust, D. *J. Phys. Chem. B* **1997**, *101*, 429–440. (e) Lee, H.-W.; Kang, T. W.; Cha, K. H.; Kim, E.-N.; Choi, N.-H.; Kim, J.-W.; Hong, C. I. *Synth. Commun.* **1998**, *28*, 1339–1349.

3 Unpublished result.

4 After we developed our method for the preparation and utilization of DMTMM that we reported here, a paper appeared describing the synthesis and characterization of DMTMM by Kaminski et al; see ref. 5.

5 Kaminski, Z. J.; Paneth, P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248–4255.

6 Most of the solid disappeared within 30 min to give a clear or a slightly turbid solution. Similar decomposition was also found to occur in either $CHCl_3$ or DMSO at room temperature.

7 DMTMM: a white solid; mp 116-117 °C; IR (KBr) 1621, 1538, 1486, 1373, 1130 cm^{-1}; ^1H NMR (methanol-d_4) δ 3.54 (s, 3 H, $NC\underline{H}_3$), 3.80-3.94 (m, 4 H), 4.07 (m, 2 H), 4.18 (s, 6 H), 4.53 (m, 2 H); Anal. Calcd for $C_{10}H_{17}ClN_4O_3$: C, 43.40; H, 6.19. Found C, 43.22; H, 6.04.
DMTM: colorless crystals; mp 129-130 °C; IR (KBr) 1579, 1467, 1353, 1128, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (m, 4 H), 3.85 (m, 4 H), 3.96 (s, 6 H); MS *m/z* 226 (M^+); HRMS calcd for $C_9H_{14}N_4O_3$ (M^+) 226.1066, found 226.1072. The structure of DMTM was confirmed by comparison with the compounds obtained from CDMT and morpholine.

8 Jones, A. J.; Beeman, C. P.; Hasan, M. U.; Casy, A. F.; Hassan, M. M. A. *Can J. Chem.* **1976**, *54*, 126-135.

9 Kaminski, Z. J.; Paneth, P.; O'Leary, M. H. *J. Org. Chem.* **1991**, *56*, 5716–5718. Kaminski, Z. J. *Int. J. Peptide Protein Res.* **1994**, *43*, 312–319.

10 This consideration is also applicable to an acid anhydride, an alternative intermediate, arising from **4** and an acid.

11 Cronin, J. S.; Ginah, F. O.; Murray, A. R.; Copp, J. D. *Synth. Commun.* **1996**, *26*, 3491–3494. CDMT is commercially available.