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4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride: An Efficient Condensing Agent Leading to the Formation of Amides and Esters

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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 (CDMT) and *N*-methylmorpholine (NMM) in THF, and characterized. Condensation of carboxylic acids and amines by DMTMM proceeded effectively in THF to give the corresponding amides in good yields. The corresponding esters can be obtained by esterification of carboxylic acids with DMTMM in methanol, ethanol, isopropyl alcohol, or *t*-butyl alcohol in the presence of NMM. The amount of alcohols can be reduced to a stoichiometric amount by conducting the reaction in THF. Since the reactions proceed under atmospheric conditions without drying of the solvent, and the co-product (4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one) arising from DMTMM after condensation can be readily removed by extraction, this method is a very practical one.

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

Among various condensing agents for the preparation of amides or esters by coupling between carboxylic acids and amines or alcohols,[1,2] 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) has been shown to be a useful non-carbodiimide reagent, in terms of stability, mild reaction conditions, and cost.[3,4] The disadvantage of CDMT is, however, that it is irritating to the eye and nose. In addition, reactions using it are generally conducted under dry conditions by a two-step procedure in which a carboxylic acid is first treated with CDMT in the presence of *N*-methylmorpholine (NMM) to activate the acid, then an amine or an alcohol is added to obtain the product.[3,4] This requires confirmation of the completion of the first step for successful results. To resolve these issues, a more convenient one-step approach is desired, involving activation of carboxylic acids in the presence of amines or alcohols, by use of a less irritating condensing agent.

One promising candidate agent as a triazine derivative is 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-

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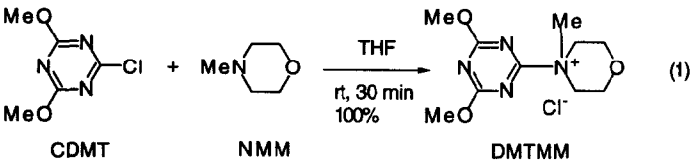
methylmorpholinium chloride (DMTMM), which was reported to have been prepared in another laboratory.[5] Unfortunately, the condensation of carboxylic acids and amines with DMTMM under the conditions employed was found to proceed in yields lower than those observed in reactions using the standard CDMT–NMM system.[3a] In addition, the carboxylic acids undergoing coupling seem to be limited to either sterically hindered trimethylacetic 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 (for demethylation: see below).[6] Independently, we have found that DMTMM can be quantitatively formed by the reaction of CDMT with NMM in THF and can be used as an efficient and convenient condensing agent leading to the formation of amides and esters.[7] In this paper, we report on our work with DMTMM.

Results and Discussion

Synthesis of DMTMM Treatment of CDMT and NMM in THF at room temperature quantitatively afforded DMTMM as a white precipitate within 30 min (eq 1). All the spectral data of DMTMM support its structure (Table 1).[8] DMTMM can be stored in the solid state for one month at room temperature or for at least several months in a refrigerator without any detectable decomposition. An attempt to prepare DMTMM in CH_2Cl_2 under similar conditions (rt, 30 min) afforded a yield (78%) lower than that in THF due to its decomposition by demethylation at the morpholinium nitrogen to give 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine (DMTM, 21%).[9] In fact, complete decomposition to DMTM was observed when DMTMM was suspended in CH_2Cl_2 for 3 h at room temperature[10] whereas it was found to be stable in THF even after stirring at room temperature for 13 h (Table 2, runs 1, 4, 5). In addition to this stability, DMTMM is insoluble in THF while both CDMT and DMTM are soluble. This makes isolation of DMTMM



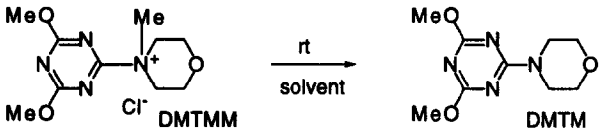
(1)

Table 1. Physical and spectral data for DMTMM

mp (°C)	Formula	Anal. (%) Calcd (Found) C	H	^{1}H-NMR (solvent) δ	^{13}C-NMR (methanol-d4) δ	IR (cm^{-1})
116–117	$C_{10}H_{17}ClN_4O_3$	43.40 (43.22)	6.19 (6.07)	(methanol-d4) 3.54 (s, 3 H), 3.80-3.94 (m, 4 H), 4.07 (m, 2 H), 4.18 (s, 6 H), 4.53 (m, 2 H)	56.5, 57.6, 61.4, 63.2, 172.0, 175.5	1621, 1538, 1373, 1130
				(DMSO-d_6) 3.49 (s, 3 H), 3.74-3.83 (m, 2 H), 3.88-3.98 (m, 2 H), 4.01 (m, 2 H), 4.10 (s, 6 H), 4.35 (m, 2 H)		

simple when it is prepared in THF. Studies on the stability of DMTMM toward demethylation in several solvents are shown in Table 2. Demethylation was found to occur almost completely within 3 h in $CHCl_3$, and partially in DMSO or acetonitrile while DMTMM was stable in Et_2O or AcOEt as well as THF. Neither demethylation nor solvolysis (hydrolysis, alcoholysis) occurred when DMTMM was dissolved in water or methanol. What should be noted is that no allergic properties of DMTMM including irritation of the eye and nose were observed in our laboratory.

Table 2. Stability of DMTMM in several solvents



run	solvent		conditions		DMTMM[a] (recovery)	DMTM[a]
1	CH_2Cl_2	suspended	rt,	3h	0%	96%
2	CH_2Cl_2	suspended	0°C,	18h	83%	17%
3	$CHCl_3$	suspended	rt,	3h	11%	83%
4	THF	suspended	rt,	3h	95%	2%
5	THF	suspended	rt,	13h	85%	13%
6	hexane	suspended	rt,	3h	85%	<1%
7	Et_2O	suspended	rt,	3h	96%	<1%
8	AcOEt	suspended	rt,	3h	95%	2%
9	DMSO-d_6	dissolved	rt,	3h	57%[b]	43%[b]
10	acetonitrile-d_3	dissolved	rt,	3h	38%[b]	62%[b]
11	methanol-d_4	dissolved	rt,	3h	100%[b]	0%[b]
12	D_2O	dissolved	rt,	3h	100%[b]	0%[b]

[a] Isolated yields. [b] Determined by NMR

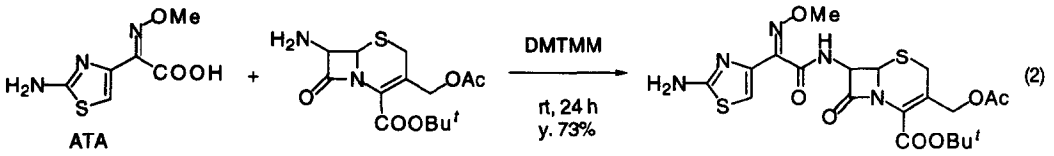
Amide Synthesis by Dehydration of Ammonium Carboxylates We have found that DMTMM is a very efficient agent for condensing a variety of carboxylic acids and amines. Addition of DMTMM powder to a mixture of 3-phenylpropionic acid (**1a**) and 2-phenylethanamine (**2a**) in THF at room temperature followed by stirring for 3 h gave the corresponding amide (**3a**) in 84% yield (Table 3, run 1). All the reactions summarized in Table 3 were conducted in a flask open to the atmosphere by using commercial THF without further purification or drying. The method is applicable to aliphatic (**1a**, **1b**, **1f**), aromatic (**1g–i**), sterically hindered (**1e**), and α,β-unsaturated acids (**1c**, **1d**). Benzoic acids with either an electron-donating or an electron-withdrawing group gave the amides in good yields (runs 7–9, 12). Both primary and secondary amines can be condensed to give the corresponding amide. *N*-Acetylation of phenylalanine methyl ester hydrochloride readily proceeded on simply mixing it with sodium acetate and DMTMM (run 14).

Table 3. Condensation of carboxylic acids with amines by DMTMM in THF[a]

$$R^1COOH\ (\mathbf{1}) + R^2R^3NH\ (\mathbf{2}) \xrightarrow[THF]{DMTMM} R^1CONR^2R^3\ (\mathbf{3})$$

run	carboxylic acid	amine	product	time	yield (%)[b]
1	$Ph(CH_2)_2COOH$ (1a)	$Ph(CH_2)_2NH_2$ (2a)	$Ph(CH_2)_2CONH(CH_2)_2Ph$ (3a)	4 h	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 h	70
4	HC≡CCOOH (1d)	2a	HC≡CCOCONH$(CH_2)_2$Ph (3d)	3 h	67
5	*t*-BuCOOH (1e)	2a	*t*-BuCONH$(CH_2)_2$Ph (3e)	3 h	62
6	*p*-MeO-$C_6H_4CH_2COOH$ (1f)	2a	*p*-MeO-$C_6H_4CH_2CONH(CH_2)_2Ph$ (3f)	4 h	82
7	PhCOOH (1g)	2a	PhCONH$(CH_2)_2$Ph (3g)	4 h	81
8	*p*-O_2N-C_6H_4COOH (1h)	2a	*p*-O_2N-$C_6H_4CONH(CH_2)_2Ph$ (3h)	3 h	82
9	*p*-MeO-C_6H_4COOH (1i)	2a	*p*-MeO-$C_6H_4CONH(CH_2)_2Ph$ (3i)	3 h	95
10	1a	$PhCH_2NH_2$ (2b)	$Ph(CH_2)_2CONHCH_2Ph$ (3j)	3 h	77
11	1a	Et_2NH (2c)	$Ph(CH_2)_2CONEt_2$ (3k)	4 h	68
12	1g	*cyclo*-$C_6H_{11}NH_2$ (2d)	PhCONH-*cyclo*-C_6H_{11} (3l)	3 h	92
13[c]	1h	$PhNH_2$ (2e)	*p*-O_2N-$C_6H_4CONHPh$ (3m)	20 h	92
14[d]	CH_3COONa (1j)	HCl•H_2N-Phe-OMe (2f)	CH_3CONH-Phe-OMe (3n)	12 h	71

[a] The reactions were perfomed using carboxylic acid, amine, and DMTMM in the ratio of 1.0 : 1.1 : 1.1 in THF at rt. [b] Isolated yield. [c] The ratio of 1h/2e/DMTMM is 1.0 : 1.0 : 1.1. [d] The ratio of 1j/2f/DMTMM is 1.2 : 1.0 : 1.2.



(2)

Coupling of 2-(2-amino-4-thiazolyl)-2-*syn*-methoxyimino acetic acid (ATA), having an unprotected 2-amino group, with *t*-butyl 7-aminocephalosporanate[11] was effectively achieved to give a cephalosporin derivative in 73% yield (eq 2).[12] The formation of a small amount of DMTM, which can be separated from the amides by TLC, was observed in most of reactions.

Esterification of Carboxylic Acid in an Alcohol The esterification of carboxylic acids by DMTMM readily proceeds in alcohols. NMM was added to a mixture of **1a** and DMTMM in dry methanol at room temperature, followed by stirring for 4 h at rt under nitrogen, which gave methyl 3-phenylpropionate (**4a**) in 75% yield as seen in Table 4 (run 1). Addition of NMM as a tertiary amine to form a morpholinium carboxylate is essential to the reaction. Thus, the esterification proceeded with a catalytic amount (0.1 eq) of NMM in 85% yield whereas only a low yield (32%) of the ester was formed with recovery of **1a** (49%) without NMM (runs 2, 3). The best yield was obtained by using 2 eq of DMTMM with 1.2 eq of NMM (93%, run 5). It is noteworthy that the reaction also proceeds under atmospheric conditions by using commercial MeOH without drying (run 6). Aliphatic (**1a**), α,β-unsaturated (**1c**), and α-branched (**1k**, **1l**) carboxylic acids were found to undergo esterification. In contrast to aromatic carboxylic acids with an electron-withdrawing group (**1h**, **1m**), which underwent esterification smoothly, those without an electron-withdrawing group (**1g**, **1i**) required either prolonged reaction time at rt or an elevated temperature (50°C)

Table 4. Condensation of carboxylic acids with alcohols by DMTMM[a]

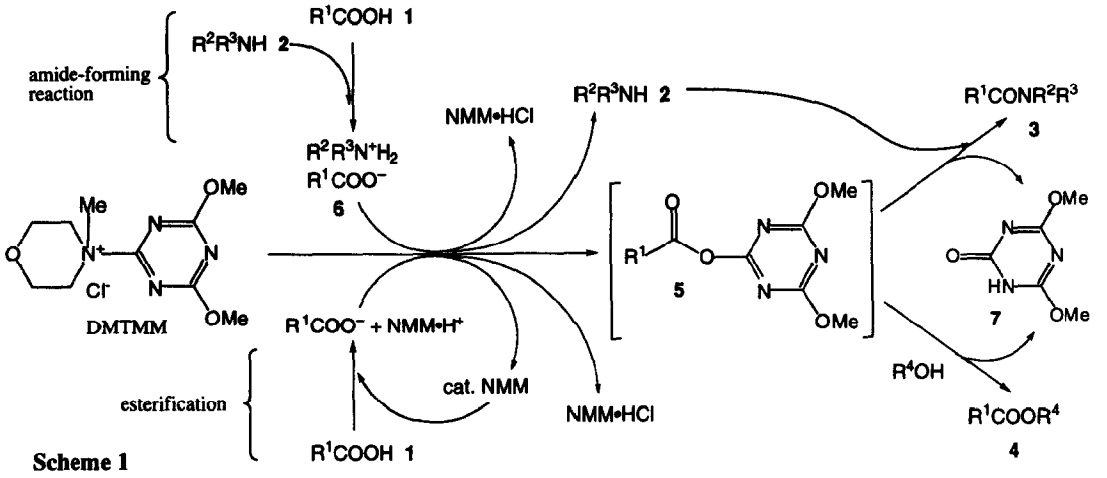
R^1COOH (1) —DMTMM, R^4OH→ R^1COOR^4 (4)

run	carboxylic acid	alcohol[b]	DMTMM (eq)	NMM (eq)	product	time	yield (%)[c]
1	$Ph(CH_2)_2COOH$ (**1a**)	MeOH (solvent)	1.1	1.1	$Ph(CH_2)_2COOMe$ (**4a**)	4 h	75
2	**1a**	MeOH (solvent)	1.2	0.1	**4a**	5 h	85
3	**1a**	MeOH (solvent)	1.2	0	**4a**	5 h	32
4	**1a**	MeOH (solvent)	1.2	1.2	**4a**	2 h	90
5	**1a**	MeOH (solvent)	2.0	1.2	**4a**	1.5 h	93
6	**1a**	MeOH (solvent)[d]	2.0	1.2	**4a**	1.5 h	87
7	**1a**	MeOH (2.0 eq)[e]	2.0	2.0	**4a**	22 h	67
8	**1a**	EtOH (solvent)	1.2	0.1	$Ph(CH_2)_2COOEt$ (**4b**)	4 h	60
9	**1a**	EtOH (solvent)	2.0	1.2	**4b**	1.5 h	95
10	**1a**	*i*-PrOH (solvent)	2.0	1.2	$Ph(CH_2)_2COOPr^i$ (**4c**)	5 h	72
11	**1a**	*t*-BuOH (solvent)[f]	2.0	1.2	$Ph(CH_2)_2COOBu^t$ (**4d**)	21 h	72
12	PhCH=CHCOOH (**1c**)	MeOH (solvent)	2.0	1.2	PhCH=CHCOOMe (**4e**)	2 h	99
13	**1c**	$PhCH_2OH$ (1.1 eq)[e]	3.0	3.0	$PhCH=CHCOOCH_2Ph$ (**4f**)	22 h	89
14	PhCOOH (**1g**)	MeOH (solvent)	2.0	1.2	PhCOOMe (**4g**)	18 h	76
15	*p*-O_2N-C_6H_4COOH (**1h**)	MeOH (solvent)	1.2	1.2	*p*-O_2N-C_6H_4COOMe (**4h**)	2.5 h	94
16	*p*-$MeOC_6H_4COOH$ (**1i**)	MeOH (solvent)	2.0	1.2	*p*-$MeOC_6H_4COOMe$ (**4i**)	21 h	86
17	**1i**	MeOH (solvent)[f]	2.0	1.2	**4i**	6 h	88
18	$Ph_2CHCOOH$ (**1k**)	EtOH (solvent)	2.0	1.2	$Ph_2CHCOOEt$ (**4j**)	2 h	96
19	Boc-Leu-OH (**1l**)	MeOH (solvent)	1.2	1.2	Boc-Leu-OMe (**4k**)	5 h	83
20	*p*-$HOOCC_6H_4COOH$ (**1m**)	MeOH (solvent)	2.4	2.2	*p*-$MeOOCC_6H_4COOMe$ (**4l**)	4 h	64
21	*t*-BuCOOH (**1e**)	$PhCH_2OH$ (3.0 eq)[e]	3.0	3.0	*t*-$BuCOOCH_2Ph$ (**4m**)	25 h[g]	34
22	*p*-CH_2=CH-C_6H_4COOH (**1n**)	MeOH (solvent)[f]	2.0	1.2	*p*-CH_2=CH-C_6H_4COOMe (**4n**)	2 h	88

[a] All reactions were conducted at room temperature. [b] The alcohol was used as a solvent. [c] Isolated yield. [d] Reaction was conducted in commercial MeOH without drying, see the text. [e] Reaction was conducted in THF as a solvent. [f] The reaction was conducted at 50°C. [g] After treatment of the acid with DMTMM and NMM for 1 h, benzyl alcohol was added, and the resulting solution was stirred for 24 h.

(runs 15, 20 vs. 14, 16, 17). Trimethylacetic acid (**1e**) was allowed to couple with benzyl alcohol (3 eq) in a moderate yield by a two-step procedure, where an acid was treated with DMTMM and NMM for 1 h, followed by addition of an alcohol (run 21). When the reaction was conducted in either EtOH (runs 8, 9, 18) or *i*-PrOH (run 10), the corresponding ethyl esters (**4b**, **4j**) or the isopropyl ester (**4c**) was formed, respectively. The *t*-butyl ester (**4d**) was also obtained in 72% yield by conducting the reaction in *t*-BuOH at 50 °C (run 11).[13] The reaction can be used on a styryl group that is sensitive to strong acids (run 22). The amount of alcohols was allowed to decrease to a stoichiometric amount by using THF as a solvent (run 13).

Mechanistic Considerations The reaction is thought to be initiated by addition of a carboxylate anion to DMTMM to give an activated ester (**5**),[14] which undergoes attack by an amine or an alcohol to give the corresponding amide or ester as illustrated in Scheme 1. Mixing of a carboxylic acid and an amine to form an ammonium carboxylate (**6**) prior to treatment with DMTMM was found to be important in this reaction. When **1a** was treated with DMTMM for 17 h in THF followed by addition of **2a**, the yield of **3a** was somewhat low (73%) (two-step procedure). A similar yield (70%) was obtained by conducting the reaction even with 1% water whereas a higher yield (83%), which is comparable to that obtained by the standard



Scheme 1

method (Table 3, run 1: 84%), was obtained under dry conditions using the two-step procedure. Thus, the hydrolysis of either **5** or DMTMM would cause problems in the two-step procedure unless the reaction was conducted under the dry conditions. On the other hand, when **2a** was first treated with DMTMM for 1 h followed by addition of **1a**, the yield of **3a** dropped to 47% with the formation of *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-2-phenylethanamine (18%) and DMTM (22%).

Because the reaction rate of carboxylate anions is likely to be much faster than that of carboxylic acids, pre-treatment of the carboxylic acid and the amine, to be condensed, to form the ammonium carboxylate salt (**6**) would promote the generation of **5**. In addition, the formation of **6** efficiently prevents the direct addition of the amine to DMTMM. The amine will be regenerated from the ammonium by the action of NMM liberated from DMTMM by substitution with the carboxylate, and then, will react with **5** affording **3** and its co-product (**7**).[16] Thus, in the first stage of the amide-forming reaction, amines would act as a specific base catalyst for coupling of acids with DMTMM leading to the formation of **5** with itself would be deactivated, and in the second stage, as a nucleophile to **5** to give the products.

In the case of esterification, the addition of NMM should promote the formation of **5** by increasing the amount of carboxylate anions. Since NMM is liberated from DMTMM in the formation of **5** (Scheme 1), only a catalytic amount of NMM is sufficient to cause the reaction (Table 4, run 2 vs. run 3). The slow reaction rate of the aromatic acids (**1g**, **1i**) and the sterically hindered acid (**1e**) can be ascribed to the stability of their activated esters (**5**) toward alcoholysis.[18] Very recently, Kaminska et al. have reported the esterification of carboxylic acids using CDMT by a two-step procedure involving **5**.[4m] Comparison of their method with ours using DMTMM shows the advantage of our method in which the reaction proceeds within several hours even for an isopropyl ester by a convenient one-step reaction.

In summary, we prepared DMTMM quantitatively from CDMT and NMM in THF, characterized it, and demonstrated its stability and efficiency in acting as an agent for condensation of carboxylic acids with amines or alcohols. The reactions generally proceed by the one-step procedure within a few hours under almost neutral or weak basic conditions. Since neither predrying of the solvent nor conducting the reaction under

nitrogen is required even for esterification, the present condensation reaction is simple, easy, and therefore, very practical. The co-product (**7**) formed after condensation can be easily removed by extraction, thus facilitating the purification of products. As a large-scale preparation of CDMT from inexpensive cyanuric chloride is possible,[19] the present reaction is also economically advantageous.

Experimental Section

General Methods. All solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Dry THF was prepared by distillation from sodium/benzophenone prior to use. MeOH, EtOH, *i*-PrOH, and *t*-BuOH were dried over molecular sieves. Chemical shifts of ^{1}H (400 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from TMS as an internal standard using Brüker DPX 400 spectrometer. Preparative thin-layer chromatography (TLC) was performed on Merck precoated silica gel plates. Melting points are uncorrected.

Preparation of 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride (DMTMM). NMM (2.02 g,.20 mmol) was added to a solution of CDMT (3.86 g, 22 mmol) in THF (60 mL) at room temperature. A white solid appeared within several minutes. After stirring for 30 min at rt, the solid was collected by suction and washed with THF and dried to give DMTMM (5.52 g, 100%). Although the purity of DMTMM is good enough for condensation at this point, it can be recrystallized from methanol and ether: a white solid; FAB MS *m/z* 241 [(M-Cl)$^+$].

Demethylation of (DMTMM). A suspension of DMTMM (70 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was stirred for 3 h at room temperature. The solid gradually disappeared to give a clear solution, which is filtered and the filtrate was concentrated to give 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine (DMTM) in 96% (48 mg): colorless crystals; mp 129–130 °C; IR (KBr) 1579, 1467, 1353, 1128, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.72 (m, 4 H), 3.85 (m, 4 H), 3.96 (s, 6 H); ^{1}H NMR (DMSO-d_6) δ 3.64 (m, 4 H), 3.74 (m, 4 H), 3.85 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 43.5 (N$\underline{C}H_2$C), 54.1 (O$\underline{C}H_3$), 65.7 (O$\underline{C}H_2$C), 166.2, 171.8; MS *m/z* 226 (M$^+$); HRMS calcd for $C_9H_{14}N_4O_3$ (M$^+$) 226.1066, found 226.1072.

General Procedure for the Condensation of Carboxylic Acids and Amines. *N*-Phenethyl-3-phenylpropanamide (3a). A mixture of 3-Phenylpropionic acid **1a** (30.0 mg, 0.20 mmol) and 2-phenylethanamine **2a** (26.7 mg, 0.22 mmol) in THF (1.0 mL) was stirred at room temperature for 10 min. DMTMM (60.9 mg, 0.22 mmol) was added to the mixture and stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with ether. The organic phase was combined and washed successively with saturated sodium carbonate, water, 1N HCl, water, and brine and dried over $MgSO_4$. The crude product was purified by preparative TLC (hexane : AcOEt = 1 : 1) to give 42.4 mg of **3a** (84%): colorless crystals; mp 94.5–95.5 °C (CH_2Cl_2/hexane); IR (KBr) 3299, 1635, 1544 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.41 (t, *J* = 7.7 Hz, 3 H), 2.73 (t, *J* = 6.9 Hz, 2 H), 2.94 (t, *J* = 7.7 Hz, 2 H), 3.47 (td, *J* = 6.9, 6.0 Hz, 2 H), 5.37 (br. s, 1 H), 7.16-7.30 (m, 5 H); HRMS calcd for $C_{17}H_{19}NO$ (M$^+$) 253.1467, found 253.1477 (M$^+$). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56. Found C, 80.65; H, 7.53.

***N*-Phenethylhexanamide (3b):**[20] colorless crystals; mp 37.5–38.5 °C (CH_2Cl_2/hexane); IR (KBr) 3305, 1639, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.21-1.36 (m, 4 H), 1.59 (quint, *J* = 7.4 Hz, 2 H), 2.11 (t, *J* = 7.4 Hz, 2 H), 2.82 (t, *J* = 6.9 Hz, 2 H), 3.52 (td, *J* = 6.9, 5.9 Hz, 2 H), 5.42 (br. s, 1 H), 7.17-

7.34 (m, 5 H) ; MS *m/z* 219 (M^+).

***N*-Phenethylcinnamamide (3c):**[21] colorless needles; mp 126–127 °C (CH_2Cl_2/hexane); IR (KBr) 3299, 1650, 1614, 1544 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.89 (t, *J* = 6.9 Hz, 2 H), 3.66 (td, *J* = 6.9, 6.0 Hz, 2 H), 5.73 (br. s, 1 H), 6.33 (d, *J* = 15.6 Hz, 1 H), 7.21-7.37 (m, 8 H), 7.45-7.50 (m, 2 H), 7.62 (d, *J* = 15.6 Hz, 1 H); MS *m/z* 251 (M^+). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82. Found C, 81.39; H, 6.75.

***N*-Phenethylpropiolamide (3d):** colorless crystals; mp 53–54 °C (CH_2Cl_2/hexane); IR (KBr) 3257, 2107, 1627, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (s, 1 H), 2.85 (t, *J* = 7.0 Hz, 2 H), 3.57 (td, *J* = 7.0, 6.1 Hz, 2 H), 6.03 (br. s, 1 H), 7.18-7.27 (m, 3 H), 7.30-7.35 (m, 2 H); MS *m/z* 173 (M^+); HRMS calcd for $C_{11}H_{11}NO$ (M^+) 173.0841, found 173.0824.

***N*-Phenethyl-2,2-dimethylpropanamide (3e):** colorless crystals; mp 81–82 °C (CH_2Cl_2/hexane); IR (KBr) 3340, 1633, 1533 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 9 H), 2.81 (t, *J* = 6.9 Hz, 2 H), 3.50 (td, *J* = 6.9, 5.9 Hz, 2 H), 5.65 (br. s, 1 H), 7.17-7.34 (m, 5 H); MS *m/z* 205 (M^+); HRMS calcd for $C_{13}H_{19}NO$ (M^+) 205.1467, found 205.1464.

***N*-Phenethyl-(4-methoxyphenyl)acetamide (3f):**[22] colorless crystals; mp 98–98.5 °C (CH_2Cl_2/hexane); IR (KBr) 3286, 1643, 1544, 1241, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71 (t, *J* = 6.8 Hz, 2 H), 3.45 (td, *J* = 6.8, 6.1 Hz, 2 H), 3.46 (s, 2 H), 5.39 (br. s, 1 H), 6.82-6.87 (m, 2 H), 7.02-7.10 (m, 4 H), 7.18-7.26 (m, 3 H); MS *m/z* 269 (M^+).

***N*-Phenethylbenzamide (3g):**[23] colorless crystals; mp 113–114 °C (CH_2Cl_2/hexane); IR (KBr) 3345, 1639, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (t, *J* = 6.9 Hz, 2 H), 3.71 (td, *J* = 6.9, 5.9 Hz, 2 H), 6.24 (br. s, 1 H), 7.21-7.27 (m, 3 H) 7.29-7.35 (m, 2 H), 7.36-7.42 (m, 2 H), 7.44-7.50 (m, 1 H), 7.67-7.71 (m, 2 H); MS *m/z* 225 (M^+). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found C, 79.71; H, 6.60.

***N*-Phenethyl-4-nitrobenzamide (3h):**[23,24] colorless crystals; mp 149.5–150.5 °C (CH_2Cl_2/hexane); IR (KBr) 3328, 1643, 1538, 1517, 1353 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, *J* = 6.9 Hz, 2 H), 3.74 (td, *J* = 6.9, 6.0 Hz, 2 H), 6.36 (br. s, 1 H), 7.20-7.28 (m, 3 H), 7.30-7.36 (m, 2 H), 7.83 (d, *J* = 8.9 Hz, 2 H), 8.23 (d, *J* = 8.9 Hz, 2 H); LCMS *m/z* 271 [$(M+1)^+$].

***N*-Phenethyl-4-methoxybenzamide (3i):** colorless crystals; mp 117.5–118.5 °C (CH_2Cl_2/hexane); IR (KBr) 3351, 1637, 1544, 1255, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (t, *J* = 6.9 Hz, 2 H), 3.70 (td, *J* = 6.9, 5.9 Hz, 2 H), 3.83 (s, 3 H), 6.08 (br. s, 1 H), 6.89 (d, *J* = 8.9 Hz, 2 H), 7.21-7.27 (m, 3 H), 7.29-7.35 (m, 2 H), 7.65 (d, *J* = 8.9 Hz, 2 H); MS *m/z* 255 (M^+). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found C, 74.48; H, 6.77; N, 5.77.

***N*-Benzyl-3-phenylpropanamide (3j):**[25,26] colorless crystals; mp 83–84 °C (CH_2Cl_2/hexane); IR (KBr) 3291, 1639, 1544 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (t, *J* = 7.6 Hz, 2 H), 2.98 (t, *J* = 7.6 Hz, 2 H), 4.37 (d, *J* = 5.7 Hz, 2 H), 5.75 (br. s, 1 H), 7.11-7.31 (m, 10 H); MS *m/z* 239 (M^+).

***N, N*-Diethyl-3-phenylpropanamide (3k):**[27] colorless oil; IR (neat) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, *J* = 7.1 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 2.59 (t, *J* = 7.9 Hz, 2 H), 2.99 (t, *J* = 7.9 Hz, 2 H), 3.22 (q, *J* = 7.1 Hz, 2 H), 3.38 (q, *J* = 7.1 Hz, 2 H), 7.17-7.31 (m, 5 H); MS *m/z* 205 (M^+). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found C, 75.58; H, 9.45.

***N*-Cyclohexylbenzamide (3l):**[23,28] colorless crystals; mp 145–146 °C (CH_2Cl_2/hexane); IR (KBr) 3328, 1627, 1533 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15-1.31 (m, 3 H), 1.36-1.50 (m, 2 H), 1.61-1.82 (m, 3 H), 1.99-

2.08 (m, 2 H), 3.93-4.05 (m, 1 H), 6.04 (br. s, 1 H), 7.38-7.50 (m, 3 H), 7.73-7.79 (m, 2 H).

***N*-Phenyl-4-nitrobenzamide (3m):**[25,29] colorless needles; mp 217.5–218.5 °C (CH_2Cl_2/hexane); IR (KBr) 1650, 1596, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18-7.24 (m, 1 H), 7.38-7.44 (m, 2 H), 7.61-7.67 (m, 2 H), 7.79 (br. s, 1 H), 8.02-8.07 (m, 2 H), 8.33-8.38 (m, 2 H); LC/MS (ESI) *m/z* 243 [$(M+1)^+$].

***N*-Acetylphenylalanine methyl ester (3n):**[30] colorless crystals; mp 89.5–90 °C (CH_2Cl_2/hexane); IR (KBr) 1752, 1648, 1537 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 3.09 (dd, J = 5.8, 13.9 Hz, 1 H), 3.14 (dd, J = 5.9, 13.9 Hz, 1 H), 3.72 (s, 3 H), 4.88 (td, J = 5.8, 7.9 Hz, 1 H), 6.00 (br. s, 1 H), 7.07-7.12 (m, 2 H), 7.22-7.32 (m, 3 H); LC/MS (ESI) *m/z* 222 [$(M+1)^+$]. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found C, 64.93; H, 6.73.

***t*-Butyl 7-[2-(amino-4-thiazolyl)-2-*syn*-(2-methoxyimino)acetamido]-3-acetoxymethyl-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylate:** colorless crystals; mp 104–105 °C (CH_2Cl_2/hexane); IR (KBr) 3430, 2979, 2935, 1781, 1722, 1675, 1627, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 2.08 (s, 3 H), 3.39 (d, J = 18.5 Hz, 1 H), 3.56 (d, J = 18.5 Hz, 1 H), 4.04 (s, 3 H), 4.81 (d, J = 13.3 Hz, 1 H), 5.07 (d, J = 4.9 Hz, 1 H), 5.08 (d, J = 13.3 Hz, 1 H), 5.69 (s, 2 H), 6.05 (dd, J = 4.9, 9.0 Hz, 1 H), 6.75 (s, 1 H), 7.98 (d, J = 9.0 Hz, 1 H); LC/MS (ESI) *m/z* 512 [$(M+1)^+$]. Anal. Calcd for $C_{20}H_{25}N_5O_7S_2$: C, 46.96; H, 4.93. Found C, 47.04; H, 4.92.

General Procedure for the Condensation of Carboxylic Acids and Alcohols. Methyl 3-phenylpropionate (4a).[31] To a mixture of 3-Phenylpropionic acid **1a** (30.0 mg, 0.20 mmol) and NMM (24.3 mg, 0.24 mmol) in MeOH (1.0 mL) was added DMTMM (110.8 mg, 0.4 mmol) at room temperature. After stirring for 1.5 h at room temperature, the solvent was removed. The residue was dissolved in Et_2O, and the organic phase was washed successively with saturated sodium carbonate, water, and brine and dried over $MgSO_4$. The crude product was purified by preparative TLC (hexane : AcOEt = 2 : 1) to give 30.6 mg of **4a** (93%): colorless oil; IR (neat) 3023, 2952, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (t, J = 7.9 Hz, 2 H), 2.95 (t, J = 7.9 Hz, 2 H), 3.66 (s, 3 H), 7.17-7.22 (m, 3 H), 7.25-7.31 (m, 2 H); MS *m/z* 164 (M^+).

Ethyl 3-phenylpropionate (4b):[32] colorless oil; IR (neat) 3029, 2981,2931, 2871, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3 H), 2.61 (t, J = 7.8 Hz, 2 H), 2.95 (t, J = 7.8 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 3 H), 7.16-7.22 (m, 3 H), 7.25-7.31 (m, 2 H); MS *m/z* 178 (M^+).

Isopropyl 3-phenylpropionate (4c):[32] colorless oil; IR (neat) 3029, 2979, 2933, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6.3 Hz, 6 H), 2.59 (t, J = 7.8 Hz, 2 H), 2.94 (t, J = 7.8 Hz, 2 H), 5.00 (septet, J = 6.3 Hz, 3 H), 7.17-7.22 (m, 3 H), 7.24-7.31 (m, 2 H).

***t*-Butyl 3-phenylpropionate (4d):**[32] colorless oil; IR (neat) 3027, 2977, 2931, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 2.53 (t, J = 7.8 Hz, 2 H), 2.91 (t, J = 7.8 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 3 H), 7.16-7.21 (m, 3 H), 7.24-7.30 (m, 2 H).

Methyl *trans*-cinnamate (4e):[31] colorless crystals; mp 34–34.5 °C; IR (KBr) 3035, 2989, 2946, 1714, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 6.44 (d, J = 16.0 Hz, 1 H), 7.36-7.40 (m, 3 H), 7.50-7.54 (m, 2 H), 7.70 (d, J =16.0 Hz, 1 H); MS *m/z* 162 (M^+).

Benzyl *trans*-cinnamate (4f):[31] colorless crystals; mp 33–33.5 °C (hexane); IR (KBr) 3062, 3031, 2952, 1714, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (s, 2 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.30-7.43 (m, 8 H),

7.48-7.53 (m, 2 H), 7.73 (d, J = 16.0 Hz, 1 H); MS m/z 238 (M^+).

Methyl benzoate (4g):[31] colorless oil; IR (neat) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 7.41-7.46 (m, 2 H), 7.53-7.58 (m, 1 H), 8.02-8.06 (m, 2 H).

Methyl 4-nitrobenzoate (4h):[31] colorless crystals; mp 93.5–94.5 °C (CH_2Cl_2/hexane); IR (KBr) 1720, 1525, 1349 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (s, 3 H), 8.19-8.23 (m, 2 H), 8.27-8.31 (m, 2 H); MS m/z 181 (M^+).

Methyl 4-methoxybenzoate (4i):[31] colorless crystals; mp 48–49 °C (hexane); IR (KBr) 1714, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.88 (s, 3 H), 6.89-6.94 (m, 2 H), 7.97-8.01 (m, 2 H).

Ethyl diphenylacetate (4j):[33] colorless crystals; mp 56–57°C (hexane); IR (KBr) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 5.01 (s, 1 H), 7.22-7.33 (m, 10 H).

***N*-(*t*-Butoxycarbonyl)-L-leucine methyl ester (4k):**[34] colorless oil; IR (neat) 1750, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 1.44 (s, 9 H), 1.46-1.76 (m, 3 H), 3.73 (s, 3 H), 4.31 (m, 1 H), 4.91 (m, 1 H); MS m/z 144 [(M - Boc)$^+$].

Dimethyl telephtalate (4l):[31] colorless crystals; mp 140–141 °C (CH_2Cl_2/hexane); IR (KBr) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 6 H), 8.10 (s, 4 H); MS m/z 194 (M^+).

Benzyl trimethylacetate (4m):[33] colorless oil; IR (neat) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 5.11 (s, 2 H), 7.28-7.39 (m, 3 H).

Methyl 4-styrenecarboxylate (4n): colorless crystals; mp 34.5–35 °C (hexane); IR (KBr) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 5.37 (d, J = 10.9 Hz, 1 H), 5.85 (d, J = 17.6 Hz, 1 H), 6.74 (dd, J = 10.9, 17.6 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.96-8.01 (m, 2 H); MS m/z 162 (M^+); HRMS calcd for $C_{10}H_{10}O_2$ (M^+) 162.0681, found 162.0685.

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