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Formation of carboxamides by direct condensation of carboxylic acids and amines in *alcohols* using a new alcohol- and water-soluble condensing agent: DMT-MM

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Abstract—Selective formation of carboxamides in an alcohol or water by an exceptionally convenient one-step procedure in which a condensing agent is simply added to a mixture of acids and amines has been achieved successfully by using a new condensing agent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). Activation of carboxylic acids by DMT-MM in the presence of amines and subsequent aminolysis of the resulting acyloxytriazine in alcoholic solvents occurred selectively and led to the formation of carboxamides in excellent yields. The rate of aminolysis of the acyloxytriazine intermediate can be estimated to be about 2×10^4 times greater than that of methanolysis. The amide/ester selectivity observed using DMT-MM was much larger than that obtained with DCC or EDC. Condensation of polar substrates, such as amino acid esters and their hydrochlorides, glucosamine hydrochloride, sodium acetate and dicarboxylic acids, proceeded successfully in MeOH, water or aqueous MeOH in good yields. The present reaction is technically quite simple and easy to achieve. It proceeds by simple mixing of acids, amines and DMT-MM without any additives, and the MeOH is readily removable by a rotary evaporator after completion of the reaction.

The carboxamide groups (–CONR–) occur in many drugs, natural products and peptides; therefore, over the past century, we have seen development of many methods for synthesizing this important functional group.[1] Among these procedures, those that have been adopted as most generalizable and useful are condensations of carboxylic acids and amines via activation of the acid moiety. These reactions involve either isolation or in situ formation of the activated acid-derivatives.

The former case is represented by acid halides,[2] acid anhydrides,[3] activated amides,[4] acyl azides,[5] and activated esters.[6,7] The acylation of amines using these activated compounds usually occurs easily and cleanly, and many kinds of solvents, including water and alcohols, can be employed when the compounds are stable in the solvents.[8] Isolation of the resulting carboxamides is usually easy. However, unless the compounds are commercially available, a separate step is still required for preparation of the activated acid-derivatives. Condensing agents such as carbodiimides[9] or other activating agents are generally employed for this purpose. Many such reactions must be conducted under dry conditions[1–7] and, furthermore, purification and isolation of the activated acid-derivatives is tedious, especially when they are unstable.

In situ formation of the activated acid-derivative is more convenient and more advantageous, especially when carboxylic acids are valuable. In some methods, however, where activation of acids needs to be completed prior to the addition of amines,[1–7] completion of the first step must be confirmed if the reaction is to proceed successfully. By contrast, carbodiimides, and many kinds of phosphorous agents[10] such as phosphoniums, phosphonates, or phosphoramides, enable the activation of acids in the presence of amines, and therefore, serve as useful and convenient agents. Reactions using these reagents are generally conducted in less polar solvents, such as CH_2Cl_2, Et_2O, THF and MeCN, but when substrates are insoluble in these solvents, a more polar solvent like DMF and DMSO needs to be used. Removing polar solvents that have high boiling points and are water-soluble, however, is particularly troublesome, and these problems plague other condensation methods as well. In the case of dicyclohexylcarbodiimide (DCC), a side reaction that forms an *N*-acylurea as a byproduct becomes serious in THF, DMF, acetone.[9c,d,11]

Since the nucleophilicity of water is weaker than that of amines, a condensation between more polar components can be effected in water, which, in fact, is now recognized to be the cleanest solvent and one that is compatible with the environment. Several reactions have been reported to

Keywords: solvents and solvent effects; amides; condensations; triazines.

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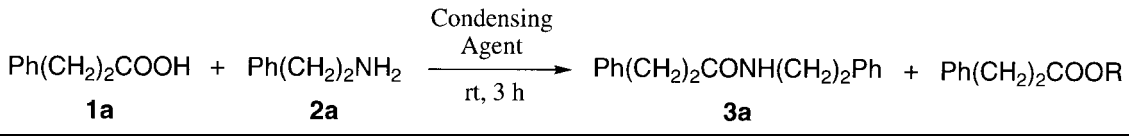
Table 1. Preparation of an amide in alcohols using DMT-MM, DCC or EDC



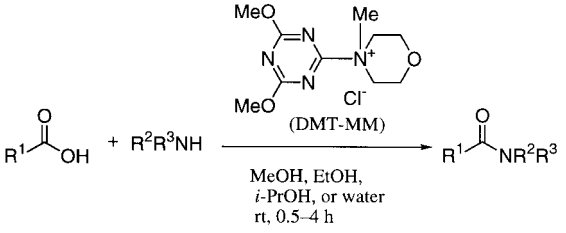
Run	Condensing agent	Solvent	Amide (**3a**)[a] (%)	Ester[a] (%)	Amide/Ester
1	DMT-MM	MeOH	98	1.0 (R=Me)	98
2	DMT-MM	EtOH	99	0.7 (R=Et)	141
3	DMT-MM	*i*-PrOH	96	0.7 (R=*i*-Pr)	137
4	DCC	MeOH	27[b]	7.0 (R=Me)	4
5	EDC[a]	MeOH	53	16.0 (R=Me)	3.3

[a] Isolated yield.
[b] *N*-Acylurea was isolated in 21%

proceed successfully in an aqueous solvent.[12,13] However, most such reactions employ a two-step procedure in which an acid moiety is first activated, then followed by addition of an amine.[12] Some reactions require dry conditions for the first step, and some are simply conducted in the presence of a *small* amount of water. Reagents allowing a one-step condensation of acids and amines via in situ activation of acids *in water* are virtually limited to water-soluble carbodiimides, which are quite expensive.[13a–c]

Water is not a suitable solvent if even one of the starting compounds (acids, amines, and condensing agents) is insoluble in it. MeOH, EtOH and *i*-PrOH are ideal polar solvents in terms of their cost, their low-boiling points (allowing them to be removed by a rotary evaporator), and their ability to solubilize many kinds of polar or non-polar compounds. Interestingly, the use of alcohols as solvents rather than co-solvents in the direct condensation of stoichiometric amounts of carboxylic acids and amines to give carboxamides[14] has, to the best of our knowledge, received little attention. Reaction of activated carboxylic acid-derivatives with water results in the formation of the starting carboxylic acids, which undergo reactivation in the presence of an excess of a condensing agent. Reaction of the acid-derivatives with alcohols, on the other hand, results in the formation of the corresponding esters, which are no longer converted into carboxamides under normal conditions. Thus, the activated carboxylic acid-derivatives must react with only a stoichiometric amount of amine much more quickly than with the large excess of alcohol. This might account for the lack of systematic studies focused on the one-step amide-forming reaction in alcohols.

In this paper we report the formation of carboxamides by direct condensation of carboxylic acids and amines using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in an alcohol or in water (Eq. (1)).



(1)

Table 2. Condensation of carboxylic acids and amines by DMT-MM in MeOH

Run	Carboxylic acid	Amine	Product	Time	Yield (%)[a]
1	$Ph(CH_2)_2COOH$ (**1a**)	$Ph(CH_2)_2NH_2$ (**2a**)	$Ph(CH_2)_2CONH(CH_2)_2Ph$ (**3a**)	3 h	98
2[b]	$CH_3(CH_2)_4COOH$ (**1b**)	**2a**	$CH_3(CH_2)_4CONH(CH_2)_2Ph$ (**3b**)	Overnight	96
3	PhCH=CHCOOH (**1c**)	**2a**	$PhCH{=}CHCONH(CH_2)_2Ph$ (**3c**)	4 h	92
4[c]	**1c**	**2a**	**3c**	2.5 h	87
5	*t*-BuCOOH (**1d**)	**2a**	*t*-$BuCONH(CH_2)_2Ph$ (**3d**)	3 h	84
6	*p*-MeO–$C_6H_4CH_2COOH$ (**1e**)	**2a**	*p*-MeO–$C_6H_4CH_2CONH(CH_2)_2Ph$ (**3e**)	4 h	85
7	*p*-Me–$C_6H_4CH_2COOH$ (**1f**)	**2a**	*p*-Me–$C_6H_4CH_2CONH(CH_2)_2Ph$ (**3f**)	3 h	99
8[d]	PhCOOH (**1g**)	**2a**	$PhCONH(CH_2)_2Ph$ (**3g**)	2 h	97
9[d]	*p*-O_2N–C_6H_4COOH (**1h**)	**2a**	*p*-O_2N–$C_6H_4CONH(CH_2)_2Ph$ (**3h**)	2 h	93
10	*p*-MeO–C_6H_4COOH (**1i**)	**2a**	*p*-MeO–$C_6H_4CONH(CH_2)_2Ph$ (**3i**)	3 h	100
11	**1a**	$PhCH_2NH_2$ (**2b**)	$Ph(CH_2)_2CONHCH_2Ph$ (**3j**)	3 h	96
12[e]	**1a**	Et_2NH (**2c**)	$Ph(CH_2)_2CONHEt_2$ (**3k**)	2 h	98
13	**1a**	$PhCH_2NMeH$ (**2d**)	$Ph(CH_2)_2CONMeCH_2Ph$ (**3l**)	3 h	100
14	**1a**	$HO(CH_2)_2NH_2$ (**2e**)	$Ph(CH_2)_2CONH(CH_2)_2OH$ (**3m**)	0.5 h	96
15	**1g**	*cyclo*-$C_6H_{11}NH_2$ (**2f**)	PhCONH-*cyclo*-C_6H_{11} (**3n**)	3 h	91
16	**1h**	$PhNH_2$ (**2g**)	*p*-O_2N-$C_6H_4CONHPh$ (**3o**)	3 h	82

The reactions were performed by using carboxylic acid, amine and DMT-MM in the ratio of 1:1.1:1.1 in MeOH at rt.
[a] Isolated yield.
[b] Carboxylic acid/amine/DMT-MM=1:1:1.
[c] Performed in 0.1 mol scale.
[d] Carboxylic acid/amine/DMT-MM=1.5:1:1.5.
[e] Carboxylic acid/amine/DMT-MM=1:1.5:1.5.

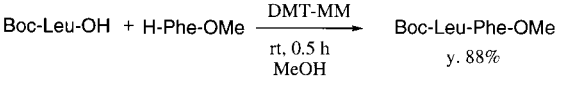
1. Results and discussion

To successfully facilitate a one-step condensation of acids and amines to give amides in water or in alcohols, the condensing agent should be both stable and soluble in the solvents. In addition, the reagent needs to react selectively with a carboxyl group to give activated acid-derivatives more quickly than with the solvents or with the amine in the first stage of the reaction. In the second stage, the reaction of the resulting activated acid-derivative with the amine to give an amide must be faster than its solvolysis. DMT-MM, developed by us very recently,[15,16] is highly suitable for this purpose because it is soluble in water, MeOH and EtOH without any detectable decomposition (stable for at least one day).

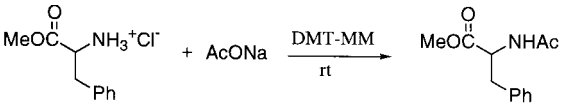
1.1. Condensation in alcohols

Treatment of 3-phenylpropionic acid **1a** and 2-phenylethanamine **2a** dissolved in MeOH with DMT-MM at room temperature for 3 h gave the corresponding amide **3a** in 98% yield (Table 1). The formation of methyl ester was observed only in a trace amount (1%). Similar reactions proceeded in EtOH or *i*-PrOH in excellent yields with a high amide/ester selectivity. In contrast, when DCC or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was used instead of DMT-MM, yields and selectivity were found to be poor.

As shown in Table 2, condensation of **1b**–**1i** and **2a**–**2g** by DMT-MM in MeOH proceeded with good yields. The system was applicable to aliphatic, aromatic, sterically hindered and α,β-unsaturated acids. Benzoic acids with either an electron-donating or an electron-withdrawing group gave the amides in good yield. Aniline as well as both primary and secondary aliphatic amines could be condensed to give the corresponding amide. A hydroxyl group on an amine moiety does not need to be protected, as shown in run 14. Reaction of Boc-Leu-OH and H-Phe-OMe gave the corresponding dipeptide in 88% yield as a single stereoisomer (Eq. (2)). Although many reactions listed in Table 2 were stopped after several hours, TLC monitoring indicated that most of them had been almost completed within 30 min.

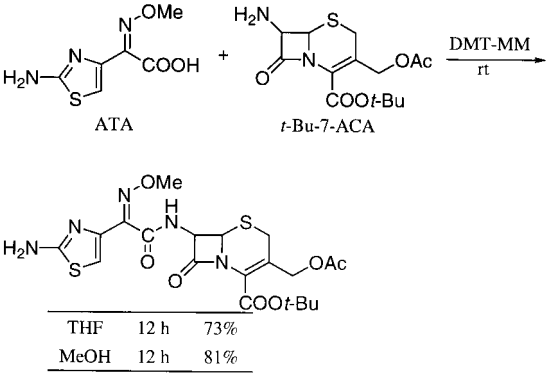


(2)



(3)

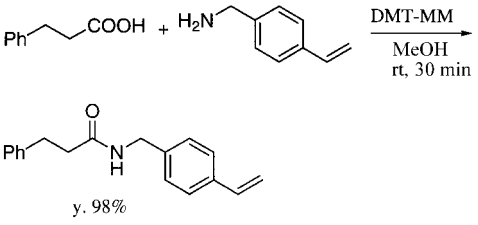
THF	12 h	71%
MeOH	0.5 h	91%



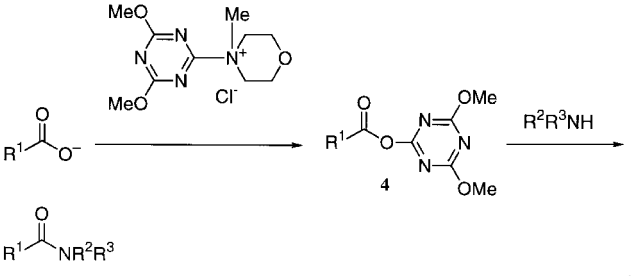
(4)

It is noteworthy that in this system, acetylation takes place effectively using sodium acetate, which is easier to treat, and therefore, more practical than the common acetylating agents, acetyl chloride or acetic anhydride. *N*-Acetylation of phenylalanine methyl ester hydrochloride proceeded readily upon simple mixture with sodium acetate and DMT-MM (Eq. (3)). Since both starting compounds are soluble in MeOH but not in THF, the reaction proceeded faster and the yield was higher than seen in THF. Similarly, coupling of 2-(2-amino-4-thiazolyl)-2-*syn*-methoxyimino acetic acid (ATA)—for which the 2-amino group was unprotected—with *t*-butyl 7-aminocephalosporanate[17] to give a cephalosporin derivative was improved by using MeOH instead of THF (Eq. (4)).[15c] Methylamine possessing a styryl group that tends to polymerize under acidic, strong basic, or radical conditions underwent coupling with carboxylic acids in an excellent yield (Eq. (5)).

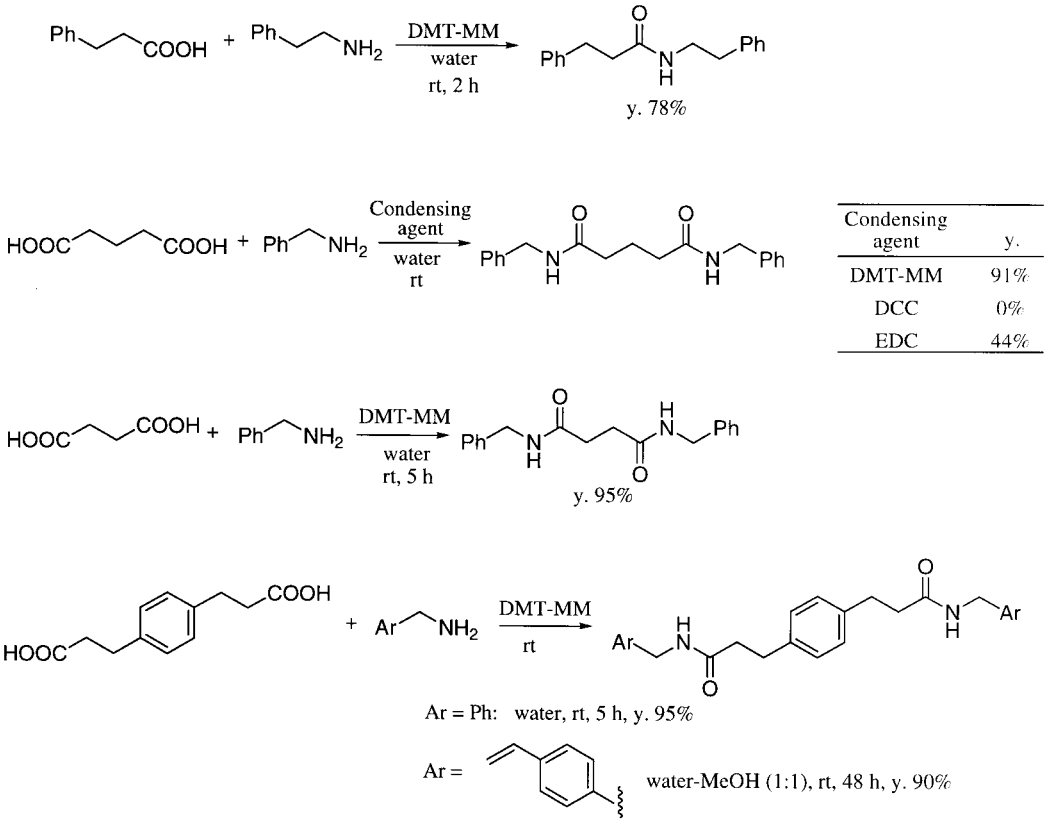
The reaction involves an acyloxytriazine **4**, which undergoes attack by an amine to give an amide (Eq. (6)).[18] As the initial concentration of amine **2a** was 0.11 mol/L in the reaction of Table 1, run 1, the rate of nucleophilic addition of the amine to the acyloxytriazine was estimated to be greater than that of MeOH by a factor of about 2×10^4.



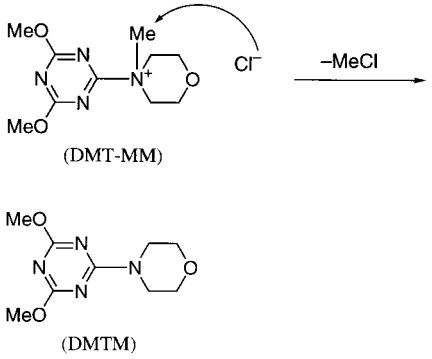
(5)



(6)



Scheme 1.



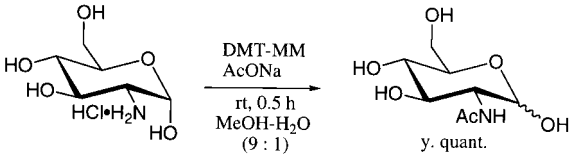
(7)

DMT-MM is susceptible to demethylation at the morpholinium nitrogen to give chloromethane and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine (DMTM) when it is suspended in chloroform or dichloromethane (Eq. (7)).[15a,c] The formation of a small amount of DMTM, generally observed during the course of the reaction in THF, is almost negligible in MeOH. This can be attributed to total separation of the morpholinium cation and the chloride ion that results from the complete dissociation of DMT-MM when dissolved in the polar protic solvent like MeOH or water. The attack of the solvated chloride to the methyl group at the solvated morpholinium nitrogen would become very slow.

1.2. Condensation in water

Reaction of **1a** and **2a** in water also proceeded well, giving **3a** in 78% yield, as shown in Scheme 1. Reaction of glutaric acid that is very soluble in water and benzylamine **2b** took place using DMT-MM in 91% yield whereas DCC and EDC afforded 0 and 44% yield, respectively. Similarly, succinic acid and 1,4-phenylenedipropionic acid underwent coupling with **2b** in very good yields. Reaction with methylamine possessing the unstable styryl group afforded the corresponding diamide in good yields. When the amide products are insoluble in water, isolation and purification are facilitated by precipitation of the amides during the course of the reaction. In fact, in our example, all other materials such as the starting acids, amines, DMT-MM, 4-methylmorpholine hydrochloride, and co-produced 4,6-dimethoxy-1,3,5-triazin-2-one are soluble in water.[19]

Finally, chemoselective acetylation of glucosamine, which is soluble in aqueous MeOH, with sodium acetate proceeded quantitatively in MeOH–water (9:1) within 30 min (Eq. (8)).[20]



(8)

2. Conclusions

In summary, condensation of carboxylic acids with amines by DMT-MM was found to occur effectively in MeOH, EtOH, *i*-PrOH, water, and a mixture of these solvents leading to the formation of amides in excellent yields. In comparison with the use of common aprotic polar solvents like DMF and DMSO, alcohols and water as solvents have the following advantages:

1. they are inexpensive and clean;
2. because of the low boiling points of alcohols, they are readily removable by a rotary evaporator;
3. when water is used for condensation, insoluble amide products can be easily separated by suction or extraction with organic solvent from the reaction mixture.

Further practical features of DMT-MM include: (1) the reaction proceeds by a convenient one-step procedure in which DMT-MM is simply added to a mixture of acids and amines in a solvent; (2) no additives are required; (3) DMT-MM is a stable but not hygroscopic solid; (4) neither irritating properties to the eye and nose nor allergenic properties were observed in our laboratory; (5) the co-product is highly water-soluble and can be readily removed by washing with water; and (6) DMT-MM can be prepared at a low cost from inexpensive cyanuric chloride.[15,21]

3. Experimental

3.1. General methods

DMT-MM was prepared from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine according to the method reported previously.[15c] CDMT was prepared from 2,4,6-trichloro-1,3,5-triazine.[21] All other solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Chemical shifts of ^{1}H (400 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from TMS as an internal standard. Preparative thin-layer chromatography (TLC) was performed on Merck precoated silica gel plates.

3.2. General procedure for condensation of carboxylic acids and amines in alcohols

3.2.1. *N*-Phenethyl-3-phenylpropanamide (3a).[15c] DMT-MM (182.6 mg, 0.66 mmol) was added to a mixture of 3-Phenylpropionic acid **1a** (90.1 mg, 0.6 mmol) and 2-phenylethanamine **2a** (80.0 mg, 0.66 mmol) in MeOH (6.0 mL) at room temperature. After 3 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, 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=1:2) to give 148.8 mg of **3a** (98%) and 1.0 mg of the methyl ester (1%). **3a**: colorless crystals; mp 94.5–95.5°C (CH_2Cl_2/hexane); IR (KBr) 3299, 1635, 1544 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (t, *J*=7.7 Hz, 3H), 2.73 (t, *J*=6.9 Hz, 2H), 2.94 (t, *J*=7.7 Hz, 2H), 3.47 (td, *J*=6.9, 6.0 Hz, 2H), 5.37 (br s, 1H), 7.16–7.30 (m, 5H); HRMS calcd for $C_{17}H_{19}NO$ (M^+) 253.1467, found 253.1477 (M^+).

3.2.2. *N*-Phenethylhexanamide (3b).[15c] 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, 3H), 1.21–1.36 (m, 4H), 1.59 (quint, *J*=7.4 Hz, 2H), 2.11 (t, *J*=7.4 Hz, 2H), 2.82 (t, *J*=6.9 Hz, 2H), 3.52 (td, *J*=6.9, 5.9 Hz, 2H), 5.42 (br s, 1H), 7.17–7.34 (m, 5H); MS *m/z* 219 (M^+).

3.2.3. *N*-Phenethylcinnamamide (3c).[15c] Colorless needles; mp 126–127°C (CH_2Cl_2/hexane); IR (KBr) 3299, 1650, 1614, 1544 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.89 (t, *J*=6.9 Hz, 2H), 3.66 (td, *J*=6.9, 6.0 Hz, 2H), 5.73 (br s, 1H), 6.33 (d, *J*=15.6 Hz, 1H), 7.21–7.37 (m, 8H), 7.45–7.50 (m, 2H), 7.62 (d, *J*=15.6 Hz, 1H); MS *m/z* 251 (M^+).

3.2.4. *N*-Phenethyl-2,2-dimethylpropanamide (3d).[15c] Colorless crystals; mp 81–82°C (CH_2Cl_2/hexane); IR (KBr) 3340, 1633, 1533 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9H), 2.81 (t, *J*=6.9 Hz, 2H), 3.50 (td, *J*=6.9, 5.9 Hz, 2H), 5.65 (br s, 1H), 7.17–7.34 (m, 5H); MS *m/z* 205 (M^+).

3.2.5. *N*-Phenethyl-(4-methoxyphenyl)acetamide (3e).[15c] Colorless crystals; mp 98–98.5°C (CH_2Cl_2/hexane); IR (KBr) 3286, 1643, 1544, 1241, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.71 (t, *J*=6.8 Hz, 2H), 3.45 (td, *J*=6.8, 6.1 Hz, 2H), 3.46 (s, 2H), 5.39 (br s, 1H), 6.82–6.87 (m, 2H), 7.02–7.10 (m, 4H), 7.18–7.26 (m, 3H); MS *m/z* 269 (M^+).

3.2.6. *N*-Phenethyl-(4-methylphenyl)acetamide (3f).[22] Colorless crystals; mp 98.5–99°C (CH_2Cl_2/hexane); IR (KBr) 3295, 1648, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.71 (t, *J*=6.8 Hz, 2H), 3.45 (m, 2H), 3.49 (s, 2H), 5.32 (br s, 1H), 7.00–7.07 (m, 4H), 7.09–7.14 (m, 2H), 7.16–7.26 (m, 3H); MS *m/z* 253 (M^+).

3.2.7. *N*-Phenethylbenzamide (3g).[15c] Colorless crystals; mp 113–114°C (CH_2Cl_2/hexane); IR (KBr) 3345, 1639, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.93 (t, *J*=6.9 Hz, 2H), 3.71 (td, *J*=6.9, 5.9 Hz, 2H), 6.24 (br s, 1H), 7.21–7.27 (m, 3H) 7.29–7.35 (m, 2H), 7.36–7.42 (m, 2H), 7.44–7.50 (m, 1H), 7.67–7.71 (m, 2H); MS *m/z* 225 (M^+).

3.2.8. *N*-Phenethyl-4-nitrobenzamide (3h).[15c] Colorless crystals; mp 149.5–150.5°C (CH_2Cl_2/hexane); IR (KBr) 3328, 1643, 1538, 1517, 1353 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95 (t, *J*=6.9 Hz, 2H), 3.74 (td, *J*=6.9, 6.0 Hz, 2H), 6.36 (br s, 1H), 7.20–7.28 (m, 3H), 7.30–7.36 (m, 2H), 7.83 (d, *J*=8.9 Hz, 2H), 8.23 (d, *J*=8.9 Hz, 2H); LC/MS *m/z* 271 [$(M+1)^+$].

3.2.9. *N*-Phenethyl-4-methoxybenzamide (3i).[15c] Colorless crystals; mp 117.5–118.5°C (CH_2Cl_2/hexane); IR (KBr) 3351, 1637, 1544, 1255, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.92 (t, *J*=6.9 Hz, 2H), 3.70 (td, *J*=6.9, 5.9 Hz, 2H), 3.83 (s, 3H), 6.08 (br s, 1H), 6.89 (d, *J*=8.9 Hz, 2H), 7.21–7.27 (m, 3H), 7.29–7.35 (m, 2H), 7.65 (d, *J*=8.9 Hz, 2H); MS *m/z* 255 (M^+).

3.2.10. *N*-Benzyl-3-phenylpropanamide (3j).[15c] 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, 2H), 2.98 (t, J=7.6 Hz, 2H), 4.37 (d, J=5.7 Hz, 2H), 5.75 (br s, 1H), 7.11–7.31 (m, 10H); MS m/z 239 (M^+).

3.2.11. *N*,*N*-Diethyl-3-phenylpropanamide (3k).[15c] Colorless oil; IR (neat) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.1 Hz, 3H), 2.59 (t, J=7.9 Hz, 2H), 2.99 (t, J=7.9 Hz, 2H), 3.22 (q, J=7.1 Hz, 2H), 3.38 (q, J=7.1 Hz, 2H), 7.17–7.31 (m, 5H); MS m/z 205 (M^+).

3.2.12. *N*-Benzyl-*N*-methyl-3-phenylpropanamide (3l).[23] Colorless oil; IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) for major conformational isomer: δ 2.64–2.71 (m, 2H), 2.84 (s, 3H), 2.97–3.06 (m, 2H), 4.59 (s, 2H), 7.15–7.35 (m, 10H); for minor conformational isomer: δ 2.64–2.71 (m, 2H), 2.94 (s, 3H), 2.97–3.06 (m, 2H), 4.45 (s, 2H), 7.06–7.10 (m, 2H), 7.15–7.35 (m, 8H); MS m/z 253 (M^+).

3.2.13. *N*-(2-Hydroxyethyl)-3-phenylpropanamide (3m).[24] Colorless needles; mp 72.5–73.5°C (AcOEt/hexane); IR (KBr) 3293, 1646, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (br s, 1H), 2.50 (t, J=7.6 Hz, 2H), 2.98 (t, J=7.6 Hz, 2H), 3.33–3.39 (m, 2H), 3.63 (d, J=5.0 Hz, 2H), 5.58 (br s, 1H), 5.72 (dd, J=17.6, 0.9 Hz, 1H), 7.18–7.24 (m, 3H), 7.27–7.32 (m, 2H); Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found C, 68.19; H, 7.82.

3.2.14. *N*-Cyclohexylbenzamide (3n).[15c] 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, 3H), 1.36–1.50 (m, 2H), 1.61–1.82 (m, 3H), 1.99–2.08 (m, 2H), 3.93–4.05 (m, 1H), 6.04 (br s, 1H), 7.38–7.50 (m, 3H), 7.73–7.79 (m, 2H).

3.2.15. *N*-Phenyl-4-nitrobenzamide (3o).[15c] 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, 1H), 7.38–7.44 (m, 2H), 7.61–7.67 (m, 2H), 7.79 (br s, 1H), 8.02–8.07 (m, 2H), 8.33–8.38 (m, 2H); LC/MS (ESI) m/z 243 [$(M+1)^+$].

3.2.16. Boc-Leu-Phe-OMe.[25] Colorless crystals; mp 83.5–84°C (CH_2Cl_2/hexane); IR (KBr) 3342, 3307, 1743, 1666, 1523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, J=6.2 Hz, 3H), 0.92 (d, J=6.4 Hz, 3H), 1.24–1.31 (m, 1H), 1.44 (s, 9H), 1.57–1.69 (m, 2H), 3.09 (dd, J=5.9, 13.7 Hz, 1H), 3.14 (dd, J=5.8, 13.7 Hz, 1H), 3.71 (s, 3H), 4.07 (br s, 1H), 4.77 (br s, 1H), 4.84 (td, J=5.9, 7.8 Hz, 1H), 6.44 (br d, J=7.5 Hz, 1H), 7.08–7.13 (m, 2H), 7.21–7.31 (m, 3H); MS m/z 392 (M^+).

3.2.17. *N*-Acetylphenylalanine methyl ester.[15c] 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, 3H), 3.09 (dd, J=5.8, 13.9 Hz, 1H), 3.14 (dd, J=5.9, 13.9 Hz, 1H), 3.72 (s, 3H), 4.88 (td, J=5.8, 7.9 Hz, 1H), 6.00 (br s, 1H), 7.07–7.12 (m, 2H), 7.22–7.32 (m, 3H); LC/MS (ESI) m/z 222 [$(M+1)^+$].

3.2.18. *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.[15c] 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, 9H), 2.08 (s, 3H), 3.39 (d, J=18.5 Hz, 1H), 3.56 (d, J=18.5 Hz, 1H), 4.04 (s, 3H), 4.81 (d, J=13.3 Hz, 1H), 5.07 (d, J=4.9 Hz, 1H), 5.08 (d, J=13.3 Hz, 1H), 5.69 (s, 2H), 6.05 (dd, J=4.9, 9.0 Hz, 1H), 6.75 (s, 1H), 7.98 (d, J=9.0 Hz, 1H); LC/MS (ESI) m/z 512 [$(M+1)^+$].

3.2.19. *N*-[(4-Vinylphenyl)methyl]-3-phenylpropanamide. Colorless crystals; mp 110–111°C (MeOH/water); IR (KBr) 3305, 1641, 1544 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (t, J=7.6 Hz, 2H), 3.00 (t, J=7.6 Hz, 2H), 4.38 (d, J=5.7 Hz, 2H), 5.24 (dd, J=10.9, 0.9 Hz, 1H), 5.57 (br s, 1H), 5.72 (dd, J=17.6, 0.9 Hz, 1H), 6.69 (dd, J=17.6, 10.9 Hz, 1H), 7.08–7.13 (m, 2H), 7.17–7.35 (m, 7H); Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found C, 81.50; H, 7.25.

3.2.20. *N*,*N*′-Dibenzylglutaramide. Colorless crystals; mp 169.5–170.5°C (CH_2Cl_2–MeOH/hexane); IR (KBr) 3241, 1652, 1623, 1564 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (quint, J=7.0 Hz, 2H), 2.30 (t, J=7.0 Hz, 4H), 4.42 (d, J=5.8 Hz, 4H), 5.96 (br s, 2H), 7.24–7.36 (m, 10H); Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found C, 73.31; H, 7.06.

3.2.21. *N*,*N*′-Dibenzylsuccinamide. Colorless crystals; mp 212.0–212.5°C (CH_2Cl_2–MeOH/hexane); IR (KBr) 3295, 1633, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 4H), 4.42 (d, J=5.7 Hz, 4H), 6.19 (br s, 2H), 7.24–7.35 (m, 10H); Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80. Found C, 72.70; H, 6.82.

3.2.22. *N*,*N*′-Dibenzyl-1,4-phenylenedipropanediamide. Colorless crystals; mp 198–199°C (CH_2Cl_2–MeOH/hexane); IR (KBr) 3299, 1639, 1552 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (t, J=7.5 Hz, 4H), 2.96 (t, J=7.5 Hz, 4H), 4.37 (d, J=5.7 Hz, 4H), 5.49 (br s, 2H), 7.10 (s, 4H), 7.14–7.33 (m, 10H); Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05. Found C, 78.05; H, 7.16.

3.2.23. *N*,*N*′-Bis[(4-vinylphenyl)methyl]-1,4-phenylenedipropanediamide. Colorless crystals; mp 204°C (decomposed) (CH_2Cl_2–MeOH/Et_2O); IR (KBr) 3295, 1641, 1550 cm^{-1}; ^1H NMR (CD_3OD–$CDCl_3$) δ 2.52 (t, J=7.7 Hz, 4H), 2.93 (t, J=7.6 Hz, 4H), 4.32 (s, 4H), 5.21 (dd, J=10.9, 0.9 Hz, 2H), 5.72 (dd, J=17.6, 0.9 Hz, 2H), 6.69 (dd, J=17.6, 10.9 Hz, 2H), 7.09–7.14 (m, 8H), 7.30–7.35 (m, 4H); Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13. Found C, 79.37; H, 7.14.

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