Preparation of Weinreb Amides Using 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride (DMT-MM)

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Weinreb amides were successfully prepared from the corresponding carboxylic acids using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in the solvents, methanol, isopropyl alcohol, and acetonitrile, which can solubilize DMT-MM. A variety of carboxylic acids were converted to the corresponding Weinreb amides in excellent yields by simply mixing with DMT-MM and *N*,*O*-dimethylhydroxylamine hydrochloride.

Key words Weinreb amide; dehydrating condensation; polar solvent; carboxylic acid

Weinreb amides have been widely utilized in the synthesis of natural products and biologically active substances,[1—4] since such carboxylic acid derivatives can be readily converted to the corresponding ketones or aldehydes and not to alcohols.[5—8] Moreover, the method is applicable for the reaction using chiral sources such as amino acids without racemization. Among the various methods for the preparation of Weinreb amides,[9—11] it is reasonable to assume that the technique involving the activated ester from the carboxylic acid using coupling reagents is the most convenient.

We have recently reported that the formation of amides using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) can be conducted in protic solvents, such as water, methanol, ethanol, and 2-propanol[12,13] as well as in aprotic solvents;[14] in general, reactions in methanol proceeded more rapidly and with better yields than those in THF. Independently, Giacomelli and his colleagues reported on a simple method for the synthesis of Weinreb amides using condensing agents based on [1,3,5]triazine.[15] Their studies demonstrated that, in THF, 2-chloro-4,6-dimethoxy[1,3,5]triazine (CDMT) outperformed DMT-MM in terms of reaction time and yields. However, since DMT-MM is insoluble in THF, the resulting heterogeneous conditions were attributed to their poor results using this substance. Consequently, we reasoned that the reaction can be improved by selecting a suitable solvent that can solubilize DMT-MM. In this note, we report the efficient use of DMT-MM for the preparation of Weinreb amides using such solvents.

In accordance with our previously reported method using DMT-MM in methanol,[12] dehydrocondensation between various carboxylic acids and *N*,*O*-dimethylhydoxylamine was examined. The results are shown in Table 1 along with those recently reported by other groups using CDMT, DMT-MM,[15] 2-chloro- and 2-bromo-1-methylpyridinium iodide (CMPI and BMPI),[9] [bis(2-methoxyethyl)amino]sulfur trifluoride (DFF),[10] *S*-(1-oxido-2-pyridinyl)-1,3-dimethylpropyleneuronium tetrafluoroborate (TODT), and *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HOTT)[11] as coupling reagents. As expected, the reaction using DMT-MM improved significantly when the solvent was switched from THF to methanol. It is noteworthy that, in general, Weinreb amides were afforded in higher yields using DMT-MM than other coupling agents. In the case of benzoylformic acid, the Weinreb amide was formed in only 39% yield, along with 21% of the corresponding methyl ester. The acyloxytriazine intermediate, which possesses an electron withdrawing α-keto group at the acyl carbonyl, should be reactive toward alcohols, and accordingly, the activated ester was subjected to a certain extent of methanolysis (Chart 1).[16] To minimize the formation of the methyl ester, the reactions were examined using the solvents ethanol and acetonitrile, which are less nucleophilic while still able to dissolve DMT-MM. Increases in the yield of the desired amide were observed with decreasing nucleophilicity of the solvents. Using acetonitrile, ethyl adipate and Boc-proline were also effectively converted to the corresponding Weinreb amides.

In summary, when carried out in methanol or acetonitrile, DMT-MM was shown to be an excellent condensing agent for the preparation of Weinreb amides. The benefits of DMT-MM include: i) a convenient one-step reaction: DMT-MM is simply added to a mixture of acids and amines in the solvents, ii) based on our laboratory use, reagents that are non-irritating to the eyes and nose and non-allergenic, and iii) low cost: DMT-MM can be obtained from inexpensive cyanuric chloride.

Experimental

DMT-MM was prepared according to our procedures, as previously described.[14] Other chemicals and solvents were obtained from commercial sources and used without further purifications. Analytical and preparative TLC plates were Merck 5715 and 5744, respectively. ^{1}H-NMR spectra were taken on a Bruker DPX-400 spectrometer. Mass spectra were recorded on a Waters Micromass ZQ 2000 spectrometer. Optical rotations were measured by JASCO DIP-1000 digital polarimeter.

Typical Procedures for the Preparation of the Weinreb Amide To a solution of benzoic acid (0.4 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.6 mmol), and *N*-methylmorpholine (0.8 mmol) in methanol (4 ml), was added DMT-MM (0.48 mmol) at room temperature. The reaction mixture was stirred until disappearance of the acid, as determined using TLC. After removal of the solvent under reduced pressure, the residue was extracted with ethyl acetate (20 ml). The organic layer was washed successively with saturated $NaHCO_3$ solution (10 ml), 1 N HCl (10 ml), water (10 ml), and brine (5 ml), then dried over $MgSO_4$ and concentrated. The resulting product was purified by preparative TLC (hexane/EtOAc=7 : 3) to give *N*-methoxy-*N*-methylbenzamide (88% yield). ^{1}H-NMR ($CDCl_3$) δ: 7.63—7.70 (2H, m), 7.36—7.47 (3H, m), 3.55 (3H, S), 3.35 (3H, S). IR (film) cm^{-1}: 1647, 1417, 1363, 979, 788. ESI-MS *m*/*z*: 166 $[M+H]^+$.

4-Chloro-*N*-methoxy-*N*-methylbenzamide ^{1}H-NMR ($CDCl_3$) δ: 7.66 (2H, d, J=9.0 Hz), 7.38 (2H, d, J=9.0 Hz), 3.54 (3H, s), 3.36 (3H, s). IR

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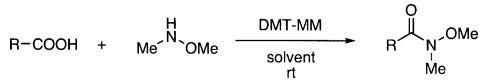
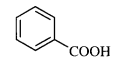
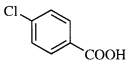
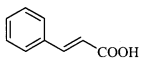
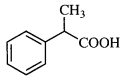
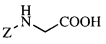
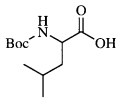
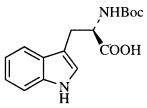
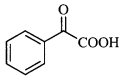
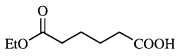
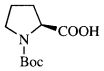
Table 1. Preparation of Weinreb Amides from Carboxylic Acids



Run	Substrate	Yield (%)[a]	Solvent		Reported yield (%)	
1		88	MeOH	1 h	56[b] 85[c]	80 (CMPI)[d] 86 (TODT)[e]
2		99	MeOH	30 min	—	83 (BMPI)[d]
3		93	MeOH	2 h	80[b] 97[c]	91 (HOTT)[e]
4		92	MeOH	30 min	80[b] 97[c]	—
5		99	MeOH	2 h	—	70 (CMPI)[d]
6		97	MeOH	1 h	67[b] 97[c]	91 (DFF)[f]
7		91	MeOH	1 h	—	59 (CMPI)[d]
8		39[g]	MeOH	3.5 h	—	53 (CMPI)[d]
9		75	EtOH	2 h		
10		99	CH_3CN	1.5 h		
11		51	MeOH	1 h	—	82 (BMPI)[d]
12		69	iso-PrOH	30 min		
13		82	CH_3CN	1.5 h		
14		98	CH_3CN	30 min	53[b] 95[c]	84 (CMPI)[d] 86 (DFF)[f]

a) Isolated yield. *b*) Using DMT-MM; ref. 15. *c*) Using CDMT; ref. 15. *d*) ref. 9. *e*) ref. 11. *f*) ref. 10. *g*) The corresponding ester (21%) was obtained along with the desired amide. Other products were obtained as a complexed mixture.

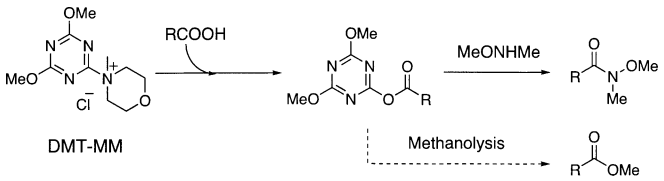


Chart 1

(film) cm^{-1}: 1644, 1592, 1468, 1416, 1364, 1091, 840, 746. ESI-MS *m/z*: 200, 202 $[M+H]^-$.

***N*-Methoxy-*N*-methylcinnamoylamide** ^{1}H-NMR ($CDCl_3$) δ: 7.70 (1H, d, J=16.0 Hz), 7.56—7.50 (2H, m), 7.42—7.36 (3H, m), 6.44 (1H, d, J=16.0 Hz), 3.77 (3H, s), 3.31 (3H, s). IR (film) cm^{-1}: 1655, 1618, 1451, 1415, 1379, 1364, 1201, 1098, 997, 762, 702. ESI-MS *m/z*: 192 $[M+H]^+$.

***N*-Methoxy-*N*-methyl-2-phenylpropionamide** ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.27 (4H, m), 7.26—7.18 (1H, m), 4.21—4.05 (1H, m), 3.41 (3H, s), 3.16 (3H, s). IR (film) cm^{-1}: 2973, 2935, 1663, 1453, 1382, 1176, 999, 754, 701. ESI-MS *m/z*: 194 $[M+H]^+$.

***N*-Benzyloxycarbonyl-L-glycine-*N*′-methoxy-*N*′-methylamide** mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.28 (5H, m), 5.55 (1H, br s), 5.13 (2H, s), 4.15 (2H, d, J=4.4 Hz), 3.72 (3H, s), 3.20 (3H, s). IR (KBr) cm^{-1}: 3291, 3067, 2947, 1725, 1661, 1541, 1281, 1253, 1172, 979 741, 698. ESI-MS *m/z*: 253 $[M+H]^+$.

***N*-*t*-Butoxycarbonyl-L-leucine-*N*′-methoxy-*N*′-methylamide** ^{1}H-NMR ($CDCl_3$) δ: 5.04 (1H, d, J=8.4 Hz), 4.72 (1H, m), 3.79 (3H, s), 3.20 (3H, s), 1.72 (1H, m), 1.43 (9H, s), 0.97 (3H, d, J=6.5 Hz), 0.93 (3H, d, J=6.7 Hz). IR (film) cm^{-1}: 3326, 2959, 1712, 1663, 1506, 1390, 1367, 1251, 1171. ESI-MS *m/z*: 275 $[M+H]^+$. $[\alpha]_D^{28}$ −24.9° (c=1.0, MeOH); lit[9] $[\alpha]_D^{26}$ −24.3° (c=1.0, MeOH).

***N*-α-*t*-Butoxycarbonyl-L-tryptophane-*N*′-methoxy-*N*′-methylamide** mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.02 (1H, s), 7.60 (1H, d, J=7.8 Hz), 7.34 (1H, d, J=8.0 Hz), 7.20—7.08 (2H, m), 7.05 (1H, d, J=2.4 Hz), 5.23 (1H, br s), 5.01 (1H, br s), 3.64 (3H, s), 3.27—3.20 (2H, m), 3.14 (3H, s), 1.40 (9H, s). IR (KBr) cm^{-1}: 1695, 1655, 1508, 1458, 1280, 1168, 992, 749. ESI-MS *m/z*: 348 $[M+H]^+$. $[\alpha]_D^{27}$ −24.3° (c=1.0, DMF); lit[9] $[\alpha]_D^{26}$ −24.2° (c=1.0, DMF).

***N*-Methoxy-*N*-methyl-2-oxo-2-phenylacetamide** mp 67 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.94—7.88 (2H, m), 7.66—7.60 (1H, m), 7.54—7.48 (1H, m), 3.65 (3H, s), 3.36 (3H, s). IR (KBr) cm^{-1}: 2943, 1684, 1653, 1450, 1396, 1260, 1180, 1008, 959, 718, 693. ESI-MS *m/z*: 194 $[M+H]^+$.

5-(Methoxy methylcarbamoyl) Ethyl Pentanoate ^{1}H-NMR ($CDCl_3$) δ: 4.12 (2H, q, J=7.1 Hz), 3.68 (3H, s), 3.17 (3H, s), 2.48—2.41 (2H, m), 2.37—2.30 (2H, m), 1.72—1.64 (4H, m), 1.25 (3H, t, J=7.1 Hz). IR (film) cm^{-1}: 2940, 1732, 1665, 1464, 1375, 1153, 1179, 1107, 1000. ESI-MS *m/z*: 218 $[M+H]^+$.

***N*-α-*t*-Butoxycarbonyl-L-proline-*N*′-methoxy-*N*′-methylamide** ^{1}H-NMR ($CDCl_3$) δ: 4.74—4.68, 4.64—4.57 (1H, m), 3.79, 3.72 (3H, s), 3.64—3.52, 3.52—3.36 (2H, m), 3.20 (3H, s), 2.30—2.10 (1H, m), 2.08—

1.77 (3H, m), 1.46, 1.42 (9H, s). The signals are doubled due to hindered rotation. IR (film) cm^{-1}: 2976, 1698, 1399, 1165, 1123, 999, 774. ESI-MS *m/z*: 259 $[M+H]^+$. $[\alpha]_D^{28}$ −37.7° (*c*=1.0, MeOH); lit[9] $[\alpha]_D^{26}$ −37.6° (*c*=1.0, MeOH).

References

1) Dias L. C., Sousa M. A., *Tetrahedron Lett.*, **44**, 5625—5628 (2003).
2) Shimizu T., Kusada J., Ishiyama H., Nakata T., *Tetrahedron Lett.*, **44**, 4965—4968 (2003).
3) Lygo B., Bhatia M., Cooke J. W. B., Hirst D. J., *Tetrahedron Lett.*, **44**, 2529—2532 (2003).
4) Suh Y., Jung J., Seo S., Min K., Shin D., Lee Y., Kim S., Park H., *J. Org. Chem.*, **67**, 4127—4137 (2002).
5) Nahm S., Weinreb S. M., *Tetrahedron Lett.*, **22**, 3815—3818 (1981).
6) Sibi M. P., *Org. Prep. Proc. Int.*, **25**, 15—40 (1993).
7) Singh J., Satyamurthi N., Aidhen I. S., *J. Prakt. Chem.*, **342**, 340—347 (2000).
8) Mentzel M., Hoffmann H. M. R., *J. Prakt. Chem.*, **339**, 517—524 (1997).
9) Sibi M. P., Stessman C. C., Schultz J. A., Christensen J. W., Lu J., Marvin M., *Synth. Commun.*, **25**, 1255—1264 (1995).
10) Tunoori A. R., White J. M., Georg G. I., *Org. Lett.*, **2**, 4091—4093 (2000).
11) Bailén M. A., Chinchilla R., Dodsworth D. J., Nájera C., *Tetrahedron Lett.*, **42**, 5013—5016 (2001).
12) Kunishima M., Kawachi C., Hioki K., Terao K., Iwasaki F., Tani S., *Tetrahedron*, **57**, 1551—1558 (2001).
13) Kunishima M., Kitao A., Kawachi C., Watanabe Y., Iguchi S., Hioki K., Tani S., *Chem. Pharm. Bull.*, **50**, 549—550 (2002).
14) Kunishima M., Kawachi C., Morita J., Terao K., Iwasaki F., Tani S., *Tetrahedron*, **55**, 13159—13170 (1999).
15) Luca L. D., Giacomelli G., Taddei M., *J. Org. Chem.*, **66**, 2534—2537 (2001).
16) Kunishima M., Morita J., Kawachi C., Iwasaki F., Terao K., Tani S., *Synlett*, **1999**, 1255—1256 (1999).