

Development of a Simple System for Dehydrocondensation Using Solid-Phase Adsorption of a Water-Soluble Dehydrocondensing Reagent (DMT-MM)

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It has been indicated that hydrophilic solid powder to which aqueous solution of a novel dehydrocondensing reagent DMT-MM is adsorbed becomes a simple solid-phase dehydrocondensing reagent of low cost. Reaction in a liquid–liquid biphasic system on the surface of a solid phase with a large area was accelerated by suspending this powder in a dichloromethane solution of a carboxylic acid and an amine to be condensed. The reaction was rapid with a high yield despite the heterogeneity of the system. Like general solid-phase reagents, a hydrophobic carboxamide alone could be isolated at a relatively high purity only by filtration of the resulting suspension of reaction mixture.

Key words carboxamide; heterogeneous system; condensing agent; solid-supported reagent

A novel triazine type dehydrocondensing reagent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), developed in our laboratory is a quaternary ammonium compound with 1,3,5-triazino residue bound to 4-methylmorpholine.¹⁾ This compound dissolves very well in water and alcohol, but is almost insoluble in general aprotic organic solvents.²⁾ It is characteristic of DMT-MM to synthesize carboxamides at high yields only by addition of it to mixtures of carboxylic acids and amines. The reaction proceeds not only in general neutral aprotic solvents but also in protic solvents, such as water and alcohol, independent of the solubility of DMT-MM.³⁾ Automation and simplification of the dehydrocondensation for combinatorial synthesis is expected because of the simple and efficient reaction characteristics of DMT-MM, for which it is most common to obtain insolubility by binding the basic structure of DMT-MM to solid-phase carriers.⁴⁾ However, in general, there are problems in the synthesis of polymer-support reagent, such as reduction of the reaction efficiency and increases in cost and waste.^{5,6)} Since the dehydrocondensation using a solid-support reagent must be carried out in heterogeneous systems with the solid and liquid phases,⁷⁾ reduction of the reaction rate is also a problem. We developed a simple, efficient, and economic method using monomeric DMT-MM, which solved the problems of solid-phase reagents.

The major compounds generated by synthesis of carboxamides using DMT-MM are the target compounds, 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT),⁸⁾ and methylmorpholine hydrochloride derived from the condensing reagent. Since the latter two compounds are water-soluble, they can be separated from the hydrophobic carboxamides by extraction. Based on the solubility of DMT-MM in water and organic solvents described above, we examined the reaction in the heterogeneous system with a suspension of solid-phase carriers adsorbed with an aqueous solution of DMT-MM in an organic solvent that is immiscible with water. Carboxylic acids and amines as the reaction substrates were dissolved in the organic solvent, and then mixed with the solid phase. The reaction system is apparently a solid–liquid biphasic system,

but actually, it is a liquid–liquid biphasic system on the surface of the solid phase. Since the interface area should be equivalent to the surface area of the solid phase, the contact area of the two phases is markedly larger than that in simple liquid–liquid biphasic systems, suggesting that the reaction between DMT-MM in the aqueous phase and carboxylic acid in the organic phase proceeds rapidly. Since HO-DMT and methylmorpholine hydrochloride generated by the reaction should remain in the aqueous phase adsorbed to the solid phase, hydrophobic carboxamides alone may be obtained by filtration of the suspension followed by rinsing the solid with an organic solvent (Fig. 1).

We performed a dehydrocondensation of 3-phenylpropionic acid and benzylamine. The solid-phase material we employed was Extrelut[®], which is often used for extraction. Extrelut[®], with high water retentivity, is widely used as a liquid–liquid extraction column filler,^{10–12)} and has been reported to be used for organic chemical reaction in columns.^{13,14)} Dichloromethane solution of the carboxylic acid and amine was added to the solid phase adsorbed with an aqueous solution of two equivalents of DMT-MM, and a reaction was performed at room temperature by standing after 5 min of stirring. The reaction suspension was filtered with suction, and the solid material was washed with dichloromethane. The yield of carboxamides was 91% and 100% with a reaction at room temperature for 10 min and 30 min, respectively, indicating that the reaction was sufficiently rapid compared to that in the simple homogeneous system with methanol (Table 1, runs 1, 2, 6). As the control,

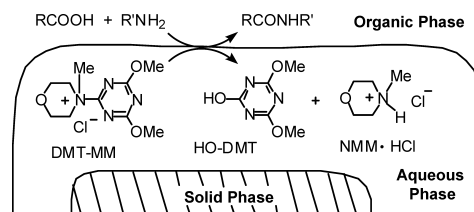


Fig. 1. Dehydrocondensation by DMT-MM in a Liquid–Liquid Biphasic System on a Solid Surface

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an amidation was performed in a simple water–dichloromethane biphasic system without the solid phase by the same procedures, and the yield at room temperature for 30 min was markedly low (61%) (run 3). These results indicated that the reaction was accelerated by adsorption of the aqueous phase to the solid phase. In the system without the solid phase, the yield was 76% with dichloromethane alone and 31% with water alone. This may be because DMT-MM is only sparsely soluble in dichloromethane and because self-decomposition of DMT-MM occurs by an intramolecular nucleophilic demethylation caused by chlorine ions.²⁾ In water, since 3-phenylpropionic acid as the substrate is hardly soluble, the reaction at room temperature for 30 min may have been insufficient (runs 4, 5).

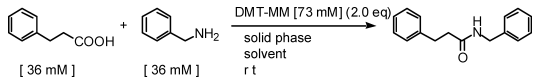
Experiments were performed with solid powder materials¹⁵⁾ shown in Table 2 by the same procedures. To evaluate the characteristics of these solid phases accurately, 1.1 eq of DMT-MM was used. The reaction with Alumina N or Celite[®] proceeded almost quantitatively at room temperature for 30 min. The yield by the reaction with diatomaceous earth was 90%, while that with silica gel 60N was very low (35%).

The relationship between the yield and specific surface area S (m^2/g) was examined for each solid phase. The reactions with Celite[®], of the smallest specific surface area of $0.93 \text{ m}^2/\text{g}$, and with Alumina N, of a more than 200-fold larger specific surface area than that of Celite[®], proceeded quantitatively, while the yield with silica gel 60N, of the largest specific surface area of $650 \pm 50 \text{ m}^2/\text{g}$, was lowest, indicating that there was no correlation between the specific surface area and yield. However, the results shown in Table 1 demonstrated that the solid-phase carriers were clearly effective, indicating that solid substances with a specific surface area of at least $1 \text{ m}^2/\text{g}$ have sufficient acceleration effects. Since there was no correlation between the specific surface area and the yield, the relationship between the yield and pH of the solid phases was examined. Silica gel was weakly acidic, and the remaining solid phases were weakly basic. To evaluate the effects of pH, experiments using Alumina A (pH 4.5) and Alumina B (pH 10) with the same specific surface area were performed using the same procedures, and the yield was 78% and 99%, respectively. The yield by the reaction with Extrelut[®] in phosphate buffer at pH 5, even when performed with two equivalents of DMT-MM, was reduced to 79%, showing that the yield was reduced at an acidic pH as predicted. The correlation between pH and the yield agreed well with the acidification of the solution by generation of morpholine hydrochloride as the dehydrocondensation with DMT-MM proceeded. In other words, the dissocia-

tion of carboxylic acids and amine-conjugated acids as the substrates was suppressed, and both the rate of addition of carboxylic acid to DMT-MM and the rate of aminolysis of activated ester intermediates were reduced, resulting in the reduction of the yield. However, since the yield remained at 39% with silica gel 60N even when using Et_3N /hydrochloride buffer at pH 9, it was suggested that the nature of solid-phase materials are also an important factor, though the details are unknown.

Based on these results, syntheses of other hydrophobic carboxamides were examined. As shown in Table 3, an aqueous solution of 1.1 eq of DMT-MM was adsorbed to Alumina B, and a reaction was performed in dichloromethane. After addition of ether to the reaction mixture, filtration, and rinsing of the solid substances with ether were performed, and the mixture of the filtrate and rinsing solution was condensed, providing carboxamides with a sufficiently high

Table 1. Reaction Acceleration in a Liquid–Liquid Biphasic System on the Surface of Extrelut[®]

				
Run	Solvent	Time	Solid phase	Yield (%) ^{a)}
1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	10 min	Extrelut [®]	91
2	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	30 min	Extrelut [®]	100
3	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	30 min	none	61
4	CH_2Cl_2	30 min	none	76
5	H_2O	30 min	none	31
6 ^{b)}	MeOH	3 h	none	96

a) Determined by GC. b) Data cited from ref. 3.

Table 2. Relationship of the Yield of Dehydrocondensation on a Solid Surface to Specific Surface Area and pH of the Solid

Solid phase	Yield (%)	Specific surface area S (m^2/g)	pH
Extrelut [®]	88	$1.18^{\text{a)}$	$10^{\text{a)}$
Diatomaceous Earth	90	$1.54^{\text{b)}$	$10.11^{\text{c)}$
Molecular Sieves 3A, Powder	83	$2.02^{\text{b)}$	$11.93^{\text{c)}$
Molecular Sieves 4A, Powder	86	—	$12.19^{\text{c)}$
Alumina A	78	$200^{\text{a)}$	$4.5^{\text{a)}$
Alumina N	99	$200^{\text{a)}$	$7.5^{\text{a)}$
Alumina B	99	$200^{\text{a)}$	$10^{\text{a)}$
Celite [®]	98	$0.93^{\text{b)}$	$9.43^{\text{c)}$
Silica Gel 60N	35	$650^{\text{a)}$	$6.37^{\text{c)}$
Silica Gel 60N	$43^{\text{d)}$	$650^{\text{a)}$	$6.37^{\text{c)}$

a) The value described in the catalog. b) Measured by BET method. c) The pH of 10% suspension of the solid. d) Two equivalent of DMT-MM was used.

Table 3. Convenient Synthesis of Lipophilic Amides in a Biphasic System on Alumina B^{a)}

Carboxylic acid	Amine	Product	Yield ^{b)}
$\text{Ph}(\text{CH}_2)_2\text{CO}_2\text{H}$	PhCH_2NH_2	$\text{Ph}(\text{CH}_2)_2\text{CONHCH}_2\text{Ph}$	99%
$\text{PhCH}=\text{CHCO}_2\text{H}$	$\text{Ph}(\text{CH}_2)_2\text{NH}_2$	$\text{PhCH}=\text{CHCONH}(\text{CH}_2)_2\text{Ph}$	94%
PhCO_2H	$c\text{-C}_6\text{H}_{11}\text{NH}_2$	$\text{PhCONH-c-C}_6\text{H}_{11}$	87%
$\text{Ph}(\text{CH}_2)_2\text{CO}_2\text{H}$	Et_3NH	$\text{Ph}(\text{CH}_2)_2\text{CONEt}_2$	$93\%^{\text{c)}$
$\text{Ph}(\text{CH}_2)_2\text{CO}_2\text{H}$	$\text{HO}(\text{CH}_2)_2\text{NH}_2$	$\text{Ph}(\text{CH}_2)_2\text{CONH}(\text{CH}_2)_2\text{OH}$	$94\%^{\text{d)}$
PhCO_2H	$\text{H-Ser-OMe} \cdot \text{HCl}$	PhCO-Ser-OMe	$100\%^{\text{e)}$
PhCO_2H	$\text{H-Ser-OMe} \cdot \text{HCl}$	PhCO-Ser-OMe	$83\%^{\text{f)}$

a) The reaction procedure: see the typical experiment. b) Isolated yield. c) Two equivalent of DMT-MM was used. d) Carboxylic acid/amine/DMT-MM = 1 : 3 : 2. e) Carboxylic acid/amine/DMT-MM = 1 : 5 : 2. NMM was used as a neutralizer. The reaction was performed for 3 h. f) Carboxylic acid/amine/DMT-MM = 1 : 3 : 2. NMM was used as a neutralizer. The reaction was performed for 24 h.

purity by NMR.

In general, marked reduction of the reaction rate is the major problem in heterogeneous reaction systems. To solve this problem, use of a phase transfer catalyst,^{16–18} use of an excessive amount of reagents,^{19–23} and improvement of stirring efficiency^{24,25} are performed. In this study, the interface area of two phases was increased by performing reactions in the water–dichloromethane biphasic system on the surface of solid phases, and reaction acceleration and improvement of the yield were achieved. We also succeeded in simplification of purification procedures utilizing the solubility of the reaction products in water and dichloromethane. Thus, the usefulness of our system is comparable to that of polymer reagents even though a simple monomer reagent is used. In other words, since the system is liquid–liquid biphasic in reaction but solid–liquid biphasic in operation, highly pure carboxamides could be obtained only by filtration. Although carboxamides must be lipophilic in order that this method is effective, it will be applicable to various compounds because the amide residue is originally hydrophobic. DMT-MM can be synthesized at low cost,^{1,26} and the solid materials used in this study can be purchased at low cost and are reusable.²⁷ Therefore, the present method is considered economic and practical.

Reactions in the heterogeneous system have synthetic advantages, such as simplification of purification procedures,^{28,29} recycling of expensive catalysts,^{30,31} and expression of a novel reaction selectivity,³² which is not observed in the homogeneous system. For example, we are developing a substrate-specific amidation using a cyclodextrin as an inverse phase transfer catalyst.³³ The major problem of this reaction is also reduction of the reaction rate in the heterogeneous system. We are further evaluating the acceleration of this substrate-specific reaction by the present solid-phase adsorption system.

Experimental

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.² CDMT was prepared from 2,4,6-trichloro-1,3,5-triazine.²⁶ All other solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Chemical shifts of ¹H- (400 MHz) and ¹³C-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.

General Procedure for Condensation of Carboxylic Acids and Amines Using Solid-Phase Adsorption System *N*-Benzyl-3-phenylpropanamide³: Alumina B powder (3 g) was added to DMT-MM solution (220 mm, 1 ml), and mixed by shaking the reaction flask at intervals until all solution was adsorbed. A dichloromethane solution of a 3-phenylpropionic acid (100 mm, 2 ml) was added to the solid substance obtained, and a dichloromethane solution of a benzylamine (100 mm, 2 ml) was added. The mixture was stirred at room temperature for 30 min (when Extrelut[®] was used, the mixture was left standing for 25 min after 5 min of stirring because the material was crushed by stirring), and after addition of ether, filtration with suction was performed with a glass filter filled with a small amount of Celite[®]. Almost pure carboxamide was obtained by concentration of the filtrate.³⁴ Colorless crystals. mp 83–84 °C (CH₂Cl₂/hexane). IR (KBr) cm⁻¹: 3290, 1638, 1541. ¹H-NMR (CDCl₃) δ : 2.52 (2H, t, *J*=7.6 Hz), 3.00 (2H, t, *J*=7.6 Hz), 4.40 (2H, d, *J*=5.7 Hz), 5.60 (1H, brs), 7.13–7.32 (10H, m). MS *m/z*: 239 (M⁺).

N-Phenethylcinnamide³: Colorless needles. mp 126–127 °C (CH₂Cl₂/hexane). IR (KBr) cm⁻¹: 3301, 1651, 1615, 1544. ¹H-NMR (CDCl₃) δ : 2.89 (2H, t, *J*=6.9 Hz), 3.66 (2H, td, *J*=6.8, 6.1 Hz), 5.74 (1H, brs), 6.34 (1H, d, *J*=15.6 Hz), 7.22–7.35 (8H, m), 7.47–7.49 (2H, m), 7.62 (1H, d, *J*=15.6 Hz). MS *m/z*: 251 (M⁺).

N-Cyclohexylbenzamide³: Colorless crystals. mp 145–146 °C (CH₂Cl₂/hexane). IR (KBr) cm⁻¹: 3313, 1627, 1535. ¹H-NMR (CDCl₃) δ : 1.15–1.29 (3H, m), 1.38–1.49 (2H, m), 1.63–1.78 (3H, m), 2.02–2.06 (2H, m), 3.94–4.03 (1H, m), 5.94 (1H, brs), 7.40–7.50 (3H, m), 7.73–7.76 (2H, m).

N,N-Diethyl-3-phenylpropanamide³: Colorless oil. IR (neat) cm⁻¹: 1642. ¹H-NMR (CDCl₃) δ : 1.10 (3H, t, *J*=7.1 Hz), 1.11 (3H, t, *J*=7.1 Hz), 2.59 (2H, t, *J*=7.8 Hz), 2.98 (2H, t, *J*=7.7 Hz), 3.22 (2H, q, *J*=7.2 Hz), 3.37 (2H, q, *J*=7.1 Hz), 7.17–7.30 (5H, m). MS *m/z*: 205 (M⁺).

N-(2-Hydroxyethyl)-3-phenylpropanamide³: Colorless needles. mp 72.5–73.5 °C (AcOEt/hexane). IR (KBr) cm⁻¹: 3296, 1647, 1559. ¹H-NMR (CDCl₃) δ : 2.48 (2H, t, *J*=7.7 Hz), 2.94 (2H, t, *J*=7.6 Hz), 3.31–3.36 (2H, m), 3.61 (2H, t, *J*=5.0 Hz), 6.15 (1H, brs), 7.16–7.18 (3H, m), 7.21–7.27 (2H, m).

***N*-Benzoylserine Methyl Ester³⁵** Alumina B powder (3 g) was added to aqueous solution (1 ml) of DMT-MM (0.4 mmol, 2 eq) and H-Ser-OMe hydrochloride (1.0 mmol, 5 eq), *N*-methylmorpholine (1.0 mmol, 5 eq) and mixed by shaking the reaction flask at intervals until all solution was adsorbed. A dichloromethane solution of a benzoic acid (50 mm, 4 ml, 1 eq) was added to the solid substance obtained and the resulting mixture was stirred at room temperature for 3 h. After addition of 2 M HCl (1 ml) and ether, the mixture was filtered by suction through a glass filter filled with a small amount of Celite[®]. The organic layer was concentrated. The product was purified by preparative TLC. Colorless needles. mp 84–85 °C. IR (KBr) cm⁻¹: 3438, 3322, 1751, 1628. ¹H-NMR (CDCl₃) δ : 2.51 (1H, br), 3.83 (3H, s), 4.05–4.09 (2H, m), 4.88 (1H, dt, *J*=7.1, 3.6 Hz), 7.08 (1H, br), 7.43–7.47 (2H, m), 7.51–7.55 (1H, m), 7.82–7.85 (2H, m).

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