Study of 1,3,5-Triazine-Based Catalytic Amide-Forming Reactions: Effect of Solvents and Basicity of Reactants

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Effect of the basic property of reactants (tertiary amine catalysts, a substrate amine, and acid neutralizers) on catalytic dehydrocondensation between a carboxylic acid and an amine by using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was studied. The reaction yield was affected by the acid–base equilibrium among reactants. In dichloromethane, a representative aprotic solvent, a strongly basic catalyst gave amides in higher yields than weakly basic catalysts, regardless of the basicity of the acid neutralizer, which is called the proton capture agent (PCA). In contrast, in protic solvents, such as methanol or aqueous methanol, weakly basic catalysts gave amides in somewhat better yields than the strongly basic catalysts. In general, PCAs with weakly basic properties are favorable, because those with strongly basic properties tend to give byproducts arising from the reaction between CDMT and the substrate amine.

Key words amide; dehydrocondensation; 1,3,5-triazine; catalytic reaction; solvent effect

Dehydrocondensation to form amides and esters is an essential tool for organic and medicinal chemists, and various dehydrocondensing reagents have been developed for the past several decades.[1,2] Among them, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM, Fig. 1), has proven to be useful because of its stability, reactivities, and low synthetic cost.[3–5] In particular, it selectively produces amides from carboxylic acids and amines even in alcoholic or aqueous media.[6–8] Related triazine-based compounds, *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*,*N*,*N*-trialkylammonium chloride (DMT-Ams), which consist of tertiary amines (*tert*-amine) instead of *N*-methylmorpholine (NMM), have a similar reactivity for dehydrocondensation.[9–12]

We found catalytic dehydrocondensation involving the *in situ* generation of DMT-Am from a stoichiometric amount of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and a catalytic amount of a *tert*-amine, as summarized in Chart 1.[13] In this system, the addition of a base, proton capture agent (PCA),[14] which is inert toward CDMT, is essential for the regeneration of the *tert*-amine from its hydrochloride.

From this understanding, we have developed catalytic dehydrocondensing reactions using a *tert*-amine with a specific functional property, such as molecular recognition.[13,15–19] As functionalized catalysts, we employed an *N*,*N*-dimethylglycine ester as a catalytic *tert*-amine part because of its facile introduction into functional molecules *via* the ester group and also because of its potent catalytic activity in a protic solvent. However, the details of the choice of catalytic *tert*-amine parts depending on the reaction conditions have not been described.

Very recently, we have studied the structure–reactivity relationship of *tert*-amines reacting with CDMT for the generation of DMT-Am, and proposed the *gauche* β-alkyl group effect.[12] This effect indicates that a steric environment around the nitrogen atom rather than the basicity of the *tert*-amines is predominantly correlated with their reactivity. However, we have not investigated the effect of the basicity of *tert*-amines in a similar steric environment. In addition, because all the reactants (carboxylates, amines, and *tert*-amines) can exist in an acid–base equilibrium with each other, the reaction can be affected by solvent properties. Here, we report the effects of the basicity of *tert*-amines and PCAs on the catalytic dehydrocondensations for the preparation of amides in protic and aprotic solvents.

Results and Discussion

Effect of *tert*-Amine Catalysts and PCAs on the Catalytic Amide-Forming Reaction in Dichloromethane To examine the effect of catalysts and PCAs on the catalytic amide-forming reaction, we chose 2-phenylpropionic acid (**1a**) and 2-phenethylamine (**2a**) as model reactants, both of which possess a primary aliphatic substituent and allow their detection by UV absorption of the phenyl group. Since we were concerned with the side reaction between **2a** and CDMT (Chart 1), we determined yields of the resulting amine-substituted product (**4a**) in addition to the desired amide (**3a**). On the basis of the reactivity of *tert*-amines toward CDMT caused by the *gauche* β-alkyl group,[12] we employed NMM, *N*,*N*-dimethylglycine ethyl ester (DMGE), and *N*,*N*-dimethylbutylamine (Me_2NBu) as catalysts, and triethylamine (Et_3N), *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), *N*-cyclohexylmorpholine (NCHM), *N*,*N*-diethylaniline ($PhNEt_2$), and sodium bicarbonate ($NaHCO_3$) as PCAs. DMGE and Me_2NBu would be suitable catalysts for investigation of the effect of their basicity, because they have different basicities and have similar steric

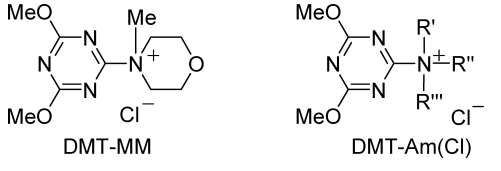

Fig. 1. Structure of DMT-MM and DMT-Am

The authors declare no conflict of interest.

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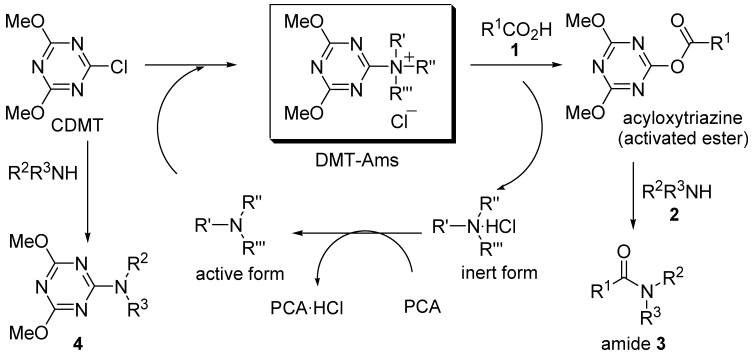


Chart 1. Catalytic Amide-Forming Reaction Involving DMT-Am

environments around the nitrogen atom.[20] We confirmed that the *tert*-amines moiety of PCAs cannot serve as a catalyst because of two or more unavoidable *β-gauche* alkyl groups (see, Supplemental Table S2).

Table 1 shows the influence of the basicity of the catalysts and PCAs[20–23] on the distribution of the products (**3a**, **4a**) in dichloromethane (CH_2Cl_2), which was chosen as a representative aprotic solvent because it produced the highest yield of **3a** among aprotic solvents under stoichiometric conditions (Supplemental Table S1). Me_2NBu gave the highest yield of **3a** and the lowest yield of **4a** in the presence of every PCA except $PhNEt_2$. On the other hand, in the case of the NMM or DMGE catalyst, the yield of **4a** increased with increasing the basicity of PCAs, whereas the yield of **3a** remained moderate regardless of the basicity of the PCAs.

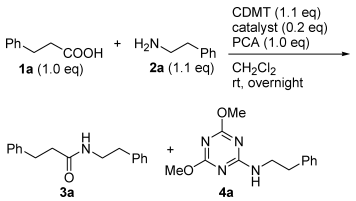
Because the precipitation of DMT-Am, which is insoluble in CH_2Cl_2, was not observed during the reactions, the rate of generation of DMT-Am would be slower than that of its consumption.[24] Therefore, we believe that the key step in the catalytic amide-forming reaction is the *S*$_N$Ar substitution of CDMT by *tert*-amine producing DMT-Am. Me_2NBu having a large pK_a value would have a higher nucleophilicity than **2a**, as we empirically know that *tert*-amines generally react with CDMT faster than primary or secondary amines.[25] Thus, CDMT is quickly converted into the acyloxytriazine by Me_2NBu catalyst regardless of the basicity of the PCAs (Chart 2a).

In the case of NMM and DMGE having lower basicities than Me_2NBu, the direct reaction of **2a** toward CDMT to give **4a** competes with the production of DMT-Am because of the lower nucleophilicities of these catalysts. Hydrogen chloride arising from the reaction of CDMT with either **2a** or *tert*-amines followed by **1a** should be captured by unreacted **2a** or PCA rather than DMGE and NMM. The use of $NaHCO_3$, $PhNEt_2$, or NCHM, whose basicities are sufficiently lower than that of **2a**,[26] primarily results in the protonation of **2a**. The resulting ammonium salt is unreactive with CDMT; therefore, a lesser amount of **4a** is produced (Chart 2b). When using Et_3N and *i*-Pr_2NEt with the basicities comparable with that of **2a**, the amount of the reactive non-protonated form of **2a** should increase, causing an increased yield of **4a**.

Therefore, Me_2NBu with stronger basicity was found to be superior to weakly basic *tert*-amine catalysts such as NMM and DMGE for the catalytic amide-forming reaction in aprotic solvents. Consequently, the catalytic amide-forming reaction using a combination of Me_2NBu and NCHM proceeds in good yields in common aprotic solvents (Table 2). The yields were comparable to those obtained under stoichiometric conditions, as shown in Supplemental Table S1.

Catalytic Amide-Forming Reaction in Protic Solvents We examined the catalytic amide-forming reaction in neutral protic solvents, such as methanol or a 50% aqueous methanol solution (Table 3). In general, the absolute methanol produced higher yields of **3a** and lower yields of **4a**, than the 50% aqueous methanol solution. In contrast to the reaction in dichloromethane, in an aqueous solvent, weakly basic *tert*-amine catalysts such as DMGE and NMM produced higher yields of the amide (**3a**) to some extent compared with Me_2NBu with strong

Table 1. Effect of *tert*-Amine Catalysts and PCAs on the Reaction between **1a** and **2a** in CH_2Cl_2[a]



PCA	DMGE pK_a=7.2[b]		NMM pK_a=7.4[b]		Me_2NBu pK_a=10.0[b]	
	3a (%)	**4a** (%)	**3a** (%)	**4a** (%)	**3a** (%)	**4a** (%)
$NaHCO_3$ pK_a=6.4[b]	69	9	76	13	76	3
$PhNEt_2$ pK_a=6.6[b]	63	8	56	21	56	2
NCHM pK_a=8.3[b]	76	14	68	26	91	5
Et_3N pK_a=10.7[b]	57	23	53	32	79	5
i-Pr_2NEt pK_a=11.4[b]	63	28	63	27	82	4

a) Yields were determined by ^{1}H-NMR of the mixture of **3a** and **4a** after PTLC. *b*) The pK_a indicates the values of their conjugated acids (refs. 20–23).

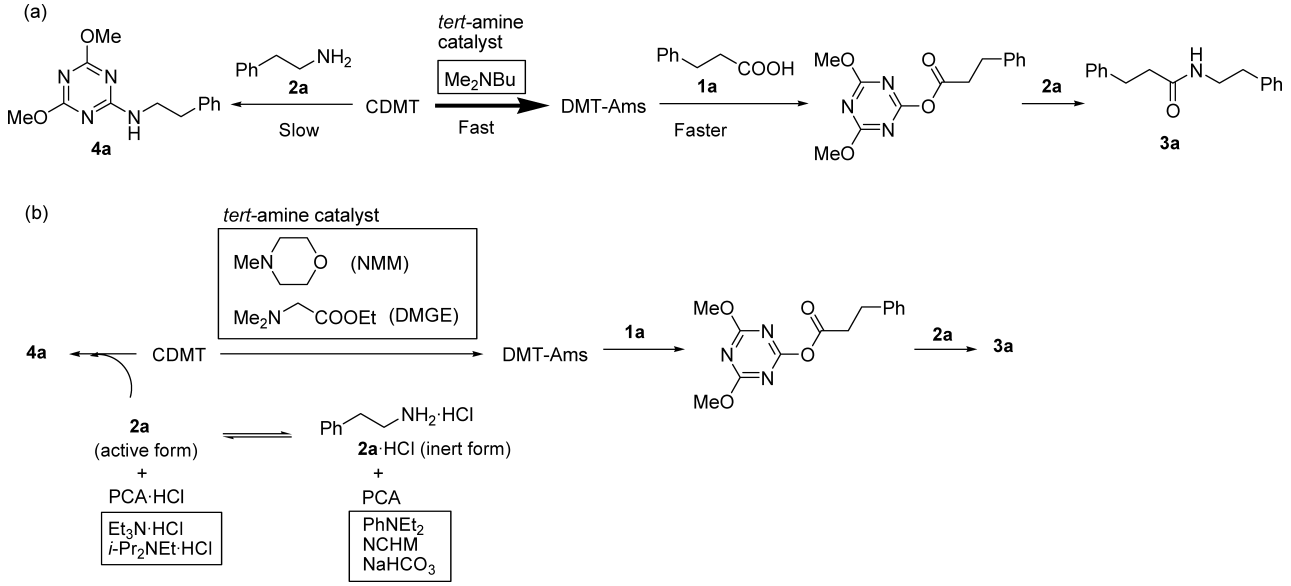
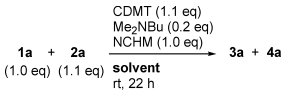


Chart 2. Mechanistic Consideration for the Effect of Acid–Base Equilibrium of Reactants on the Products Distribution in CH_2Cl_2

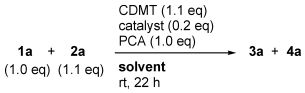
Table 2. Catalytic Amide-Formation Using Me_2NBu and NCHM in Aprotic Solvents[a)]



Solvent	CH_2Cl_2[b)]	AcOEt	THF	DMSO	CH_3CN
3a	91%	89%	84%	87%	80%
4a	5%	2%	8%	8%	6%

a) Yields were determined by ^{1}H-NMR of the mixture of **3a** and **4a** after PTLC. *b*) The data was cited from Table 1.

Table 3. Effect of *tert*-Amine Catalysts and PCAs on the Reaction between **1a** and **2a** in Aqueous and Non-aqueous Methanolic Solvents[a)]



Solvent	PCA	DMGE		NMM		Me_2NBu	
		3a (%)	**4a** (%)	**3a** (%)	**4a** (%)	**3a** (%)	**4a** (%)
MeOH	$NaHCO_3$	81	2	77	4	79	3
MeOH	NCHM	74	13	59	9	52	8
MeOH	Et_3N	55	19	59	22	55	15
50% aq MeOH	$NaHCO_3$	61	5	72	13	50	8
50% aq MeOH	NCHM	60	14	54	15	47	22
50% aq MeOH	Et_3N	38	28	35	28	26	31

a) Yields were determined by ^{1}H-NMR of the crude product after PTLC.

basicity. Again, the basicity of the PCA affected the product yield; in particular, a lower yield of **3a** and a significantly higher yield of **4a** were obtained when using Et_3N.

In protic solvents, particularly in aqueous solvents, the substrates (**1a**, **2a**) should be present as salts such as the ammonium carboxylate because of the stabilization of the ionized structures by solvation (Chart 3a). The resultant ammonium salt of **2a** will be in an acid–base dissociation equilibrium with the catalysts and PCAs, and therefore, affects the product distribution. When Et_3N, which has strong basicity, was used as the PCA, the ammonium of **2a** can be significantly deprotonated to form the amine, which is reactive toward CDMT. Therefore, the amine-substituted product **4a** was produced in a significantly high yield (Chart 3b). In contrast, when weakly basic PCAs, such as NCHM and $NaHCO_3$, were used, **2a** having the strongest basicity among the species in the reaction media should be presents in an ionized state (as the ammonium salt), which causes a decrease in the yield of **4a** (Chart 3c).

With respect to the *tert*-amine catalysts, NMM and DMGE should be present in a reactive non-protonated form, which results in the smooth formation of DMT-Am whereas Me_2NBu should be present significantly in the protonated form within the reaction mixture (Charts 3d, e). Owing to a smaller population of the reactive non-protonated species of Me_2NBu, a

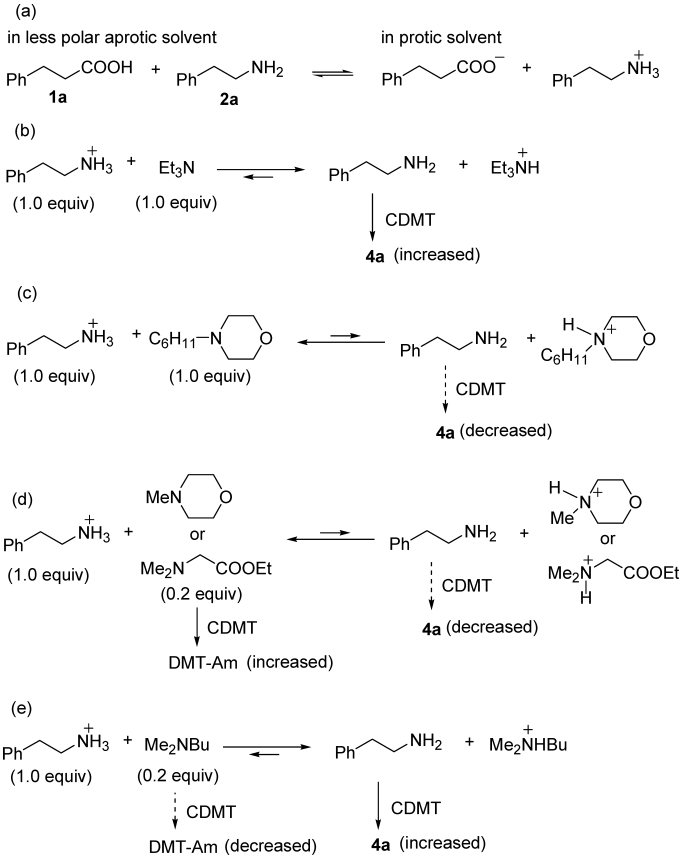


Chart 3. Mechanistic Consideration for the Effect of Acid–Base Equilibrium of Reactants on the Products Distribution in Aqueous Solvents

retarded formation of DMT-Am may cause a lower yield of the amide. Thus, a combination of weakly basic catalysts and PCAs was found to be desirable in aqueous methanol. The observed better results in absolute methanol, which were not affected by the basicity of *tert*-amine catalyst, may be due to the somewhat intermediate polarity of methanol between aprotic and aqueous solvents.

Conclusion

In the catalytic amide-forming reaction using a combination of CDMT and a *tert*-amine catalyst, we have found that the polarity of solvents and the basicity of the catalysts and PCAs affect the distribution of the products (**3a**, **4a**). A strongly basic catalyst such as Me_2NBu was found to be the superior catalyst in aprotic solvents as compared with weakly basic catalysts such as NMM and DMGE. NMM and DMGE were found to be slightly better than Me_2NBu in protic solvents. Weakly basic PCAs such as NCHM or $NaHCO_3$ are found to be favorable, regardless of the solvents, because they help to avoid the side reaction between CDMT and substrate amine, which produces undesirable **4a**. In addition, controlling the ionization state of the substrates and catalyst was essential in an aqueous solution. In this regard, the advantages of *N*,*N*-dimethylglycine esters that we have utilized for *tert*-amine catalyst in variety of catalytic amide-forming reactions in aqueous solvents have now been well interpreted. Based on these findings, we are now searching for a more effective *tert*-amine catalysts that can be used in aqueous solvents.

Experimental

General Experimental Procedures ^{1}H-NMR spectra were recorded on BRUKER DPX400 spectrometer referenced with tetramethysilane (δ 0.00 ppm) as an internal standard. IR spectra were recorded on Nicolet FT-IR AVATAR360. Low- and high resolution mass spectra were recorded on a JEOL Ltd. the Mstation JMS-700 mass spectrometer and Micromass Zq2000 spectrometer. Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. pK_a values were determined with Metrohm 794 Basic Titrino. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with Kanto Chemical silica gel 60N (63–210 mm, spherical, neutral). Preparative thin layer chromatography (PTLC) was performed on silica gel 60 F_{254} (Merck). Reagents and solvents were purchased from TCI, Nacalai Tesque, Aldrich, and Wako Pure Chemical Industries, Ltd. and were used without further purification.

General Procedure for Catalytic Amidation To a solution (2.37 mL) of phenylpropionic acid (**1a**, 35.6 mg, 0.237 mmol), phenethylamine (**2a**, 31.6 mg, 0.261 mmol), *tert*-amine catalyst (0.047 mmol) and base (0.237 mmol) were added CDMT (45.8 mg, 0.261 mmol) at ambient temperature. After stirring overnight, the reaction mixture was poured into a mixture of water and diethyl ether. The organic layer was washed with saturated sodium bicarbonate, 1 M HCl, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by PTLC ($CHCl_3$/MeOH= 95/5) to obtain **3a** and **4a** mixture. The yields were determined by ^{1}H-NMR.

***N*-Phenethyl-3-phenylpropanamide (3a)**[3] Colorless crystals (CH_2Cl_2–hexane). mp 94.5–95.5 °C. IR (KBr) cm^{-1}: 3299, 1635, 1544. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (2H, t, J=7.7 Hz), 2.73 (2H, t, J=6.9 Hz), 2.94 (2H, t, J=7.7 Hz), 3.47 (2H, td, J=6.9, 6.0 Hz), 5.37 (1H, brs), 7.15–7.30 (10H, m). MS *m*/*z*: 253 (M^+).

2,4-Dimethoxy-6-(*N*-phenethylamino)-1,3,5-triazine (4a)[12] Colorless crystals mp 113.5–114 °C. IR (KBr) cm^{-1}: 3264, 3146, 3020, 2940, 2861, 1643, 1621, 1478, 1462, 1364, 1107, 815. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (2H, t, J=6.9 Hz), 3.72 (2H, q, J=6.9 Hz), 3.91 (3H, s), 3.98 (3H, s), 5.49 (1H, brs), 7.18–7.33 (5H, m). HR-MS *m*/*z*: Calcd for $C_{13}H_{16}N_4O_2$; 260.1273 (M^+), Found; 260.1269 (M^+).

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24) Our recent NMR study also supports this fact, see: ref. 12.
25) It has not been solved why *tert*-amines without the *gauche* β-alkyl group preferentially react with CDMT over primary amines.
26) The pK_a of the hydrochloride of **2a** is 9.83 (ref. 21).