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Imido-substituted triazines as dehydrative condensing reagents for the chemoselective formation of amides in the presence of free hydroxy groups†

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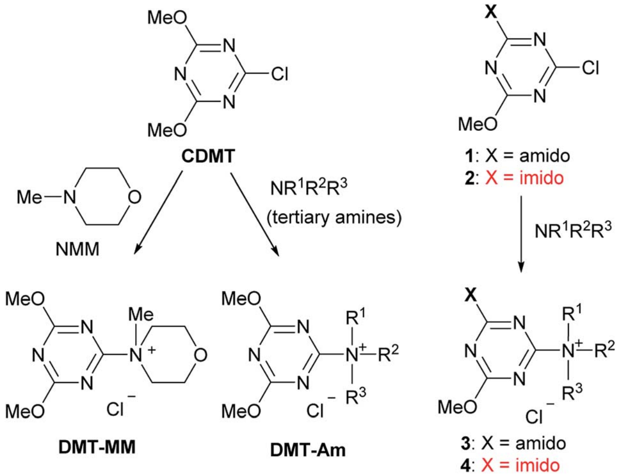
In this paper, we discuss the synthesis of imido-substituted chlorotriazines and demonstrate their use in dehydrative condensation reactions. Chemoselective amide-forming reactions of amino alcohols using succinimido-substituted chlorotriazine (**2A**) proceeded smoothly. Occasionally, nonselectivity was problematic during the synthesis of hydroxy-substituted amides. Moreover, it was noteworthy that this method was applicable to hydroxy-substituted carboxylic acids that could have formed a lactone or an ester during the carboxylic acid activation step. The imido-substituted chlorotriazine (**2A**) was superior to the amido-substituted chlorotriazine and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in terms of reaction rates and yields.

Introduction

Amides are important functional groups that can be found in many materials, pharmaceuticals, and natural products. Therefore, they are routinely synthesized from carboxylic acids and amines in both the laboratory and industry.[1] Chemoselective amide-forming reactions of amino alcohols have long been investigated[2–4] because many important compounds contain this combination of functional groups, including anti-inflammatory drugs such as acetaminophen,[2] cosmetics,[5] and surfactants.[6] However, nonselective *N*- and *O*-acylation of amino alcohols is often problematic during amide synthesis.[2,3,7] In addition, the activation of a hydroxy-substituted carboxylic acid is difficult using conventional methods because lactone or ester formation is possible during carboxylic acid activation.

We have developed a class of trizaine-based dehydrative condensing reagents [(4,6-dimethoxy-1,3,5-triazin-2-yl)trialkylammonium salts, DMT-Ams], including 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), which can be employed in aqueous or alcoholic solvents (Scheme 1. See the ESI† for the detailed reaction mechanism).[8,9] These reagents were prepared from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) or tertiary amines (*tert*-amines).[9] For the preparation of functional DMT-Ams that selectively activate carboxylic acids, various *tert*-amines were studied.[10,11] However, in most cases, the substituents on the triazine ring were limited to dimethoxy groups. Considering that substituents on the triazine would be important for the development of a diverse family of dehydrative condensing reagents, we studied chlorotriazines and their ammonium salts. As part of this project, we have recently reported that electron-withdrawing amido-substituted triazines (**1** and **3**) showed a higher reactivity for dehydrative condensing reactions.[12] According to the Hammett substituent constants,[13] imido-substituents ($\sigma_m = 0.34$ for the succinimido group) are more electron-withdrawing than methoxy- ($\sigma_m = 0.12$) and



Scheme 1 Triazine-based condensing reagents.

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amido-substituents ($\sigma_m = 0.21$ for the acetamido group); therefore, a higher reactivity for condensation was expected. In this study, triazines with even more electron-withdrawing imido-substituents (**2** and **4**) were investigated, including the chemoselective acylation of amino alcohols and activation of hydroxy-substituted carboxylic acids.

Results and discussion

Rapidly available imides, such as succinimide, phthalimide, maleimide, and glutarimide, as substituents for triazine, were studied because condensing reagents should be inexpensive, especially if they are to be used in large-scale syntheses (**2A–2D** in Fig. 1). Moreover, instead of cyclic imides, linear diacetamide was also considered (**2E** in Fig. 1). For simplification, only one methoxy group on CDMT was replaced with an imido-substituent (Fig. 1).

It was difficult to determine the general reaction conditions for the synthesis of the above-mentioned imido-substituted chlorotriazines because the different imides possessed unequal reactivities (Scheme 2). The succinimido-substituted compound **2A** was obtained from the reaction of 2,4-dichloro-6-methoxy-1,3,5-triazine (DCMT) with the succinimide anion in tetrahydrofuran (THF) at 55 °C (55% isolated yield). **2B** was prepared in a 58% isolated yield using the commercially available phthalimide potassium salt and DCMT in the presence of 18-crown-6 at ambient temperature. However, **2C** could not be obtained under similar reaction conditions using DCMT in the presence of various bases. Compared to the five-membered ring succinimide, the nucleophilicity of the six-membered glutarimide anion toward DCMT was unexpectedly low. Despite the decreased delocalization of the negative charge for the glutarimide anion as expected from their pK_a values (11.4 for glutarimide and 9.6 for succinimide), the yield of **2D** was low.[14] Shielding of the nitrogen lone pairs of the imide anion by the two adjacent carbonyl oxygen groups, as expected from X-ray crystal structure analysis of glutarimide[15] and succinimide,[16] may explain the reduced reactivity. Glutarimide had a smaller O=C–N bond angle (119.60° for glutarimide and 123.86° for succinimide) and larger C–N–C bond angle (126.90° for glutarimide and 112.62° for succinimide). **2D** was successfully crystalized and the structure was confirmed by X-ray single crystal structure analysis (see the ESI†). In the case of the linear diacetamide, **2E** was difficult to prepare. Despite the consumption of DCMT, only side products were detected.

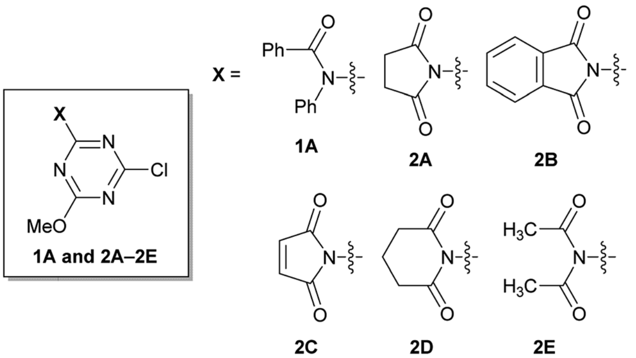
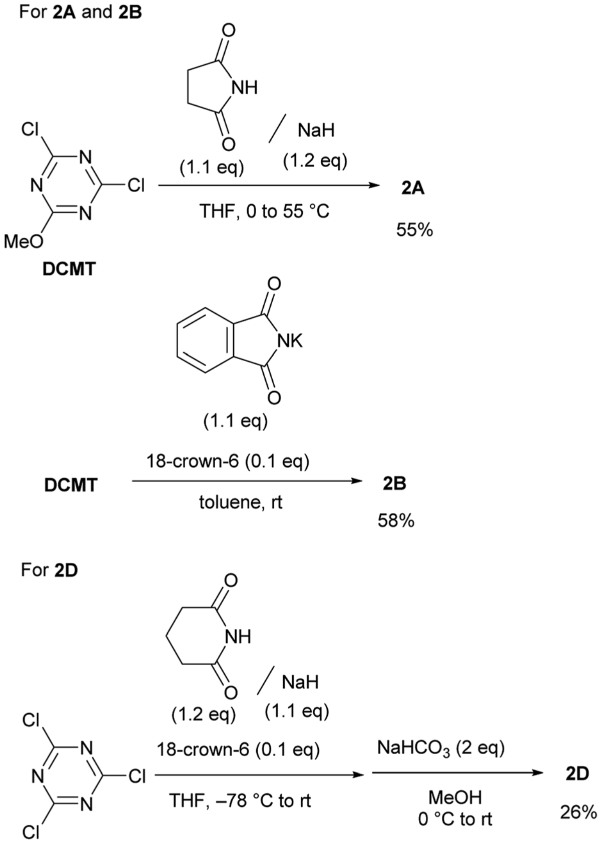


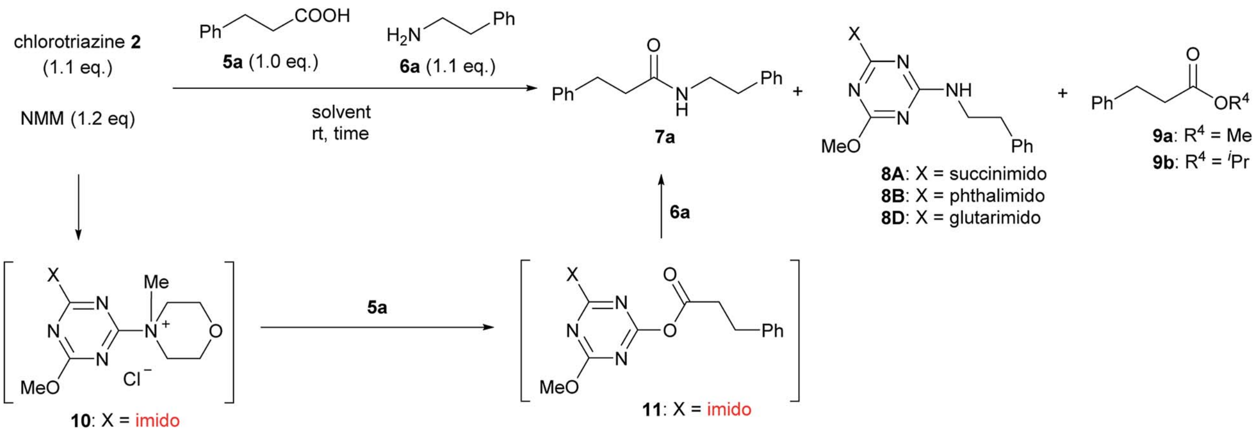
Fig. 1 Structures of amido- or imido-substituted chlorotriazines.



Scheme 2 Synthesis of chlorotriazines (2A, 2B, and 2D).

Next, we examined the preparation of the imido-substituted condensing reagents (**4**). Although the desired **4** would be formed using NMM and *N*-methylpiperidine (NMP) as the *tert*-amines, the purities of **4** were low because demethylation (by the chloride anion) and hydrolysis occurred during the isolation steps. To prevent demethylation, the synthesis of **4** was attempted in the presence of nonnucleophilic perchlorate anions; however, hydrolysis was still problematic. It was assumed that the strong electron-withdrawing effect of the imido group made isolation difficult.

For convenient evaluation of the reactivity of these prepared chlorotriazines (**2A**, **2B**, and **2D**), the corresponding DMT-Ams (**10**) were generated *in situ* and used for coupling of carboxylic acid **5a** and amine **6a** (Scheme 3 and Table 1).[9] Chlorotriazine **2A** was added to a mixture of **5a**, **6a**, and NMM at ambient temperature in MeOH (Table 1, entry 1).[17] Amide **7a** was only obtained in a 69% yield. The formation of side product **8A** (3%) and methyl ester **9a** (11%) was also observed. The yield of **9a** using **2A** was larger than that using CDMT (2% for CDMT), indicating that the electrophilicity of triazinyl ester **11** toward methanol was increased because of the succinimido group on the triazine ring. In THF, the increased yield of the side product **8A** (35% for **2A**) was observed, in contrast to CDMT (18% for CDMT), implying a similar electron-withdrawing effect of the



Scheme 3 Amide-forming reactions of carboxylic acid **5a** and amine **6a** using imido-substituted chlorotriazines **2**.

Table 1 Amide-forming reactions using the imido-substituted chlorotriazines/NMM system

		Yield[a] (%)										
		In MeOH				In THF			In ^{i}PrOH			
Entry	Chlorotriazine	**7a**	**8**	**9a**	Time	**7a**	**8**	Time	**7a**	**8**	**9b**	Time
1	**2A**	69	3	11	3 h	62	35	3 h	84	2	Trace	30 min
2	**2B**	67	—[b]	15	3 h	53	—[b]	3 h	—[c]	—[c]	—[c]	—[c]
3	**2D**	72	4	5	2 h	58	41	3 h	83	8	2	3 h

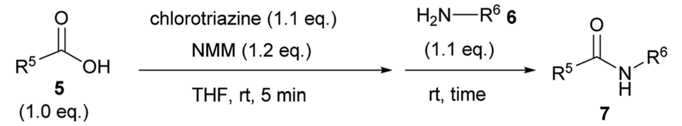
[a] Based on ^{1}H NMR. [b] Not determined. [c] Not conducted.

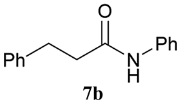
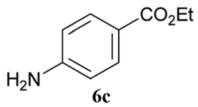
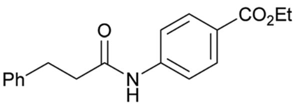
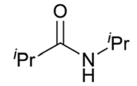
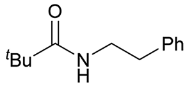
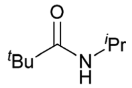
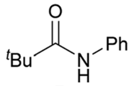
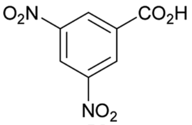
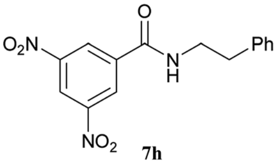
succinimido group.[18] To prevent the alcoholysis of **11**, the reaction was conducted in ^{i}PrOH and the yield of **7a** was improved to 84% (Table 1, entry 1). Due to the fact that similar results were obtained for **2B** and **2D** (Table 1, entries 2 and 3), the influence from the kind of imido-structures was thought to be small for the condensing reactions. Moreover, the phthalimido-substituted chlorotriazine (**2B**) was not very soluble in THF and alcohol; therefore, only succinimido-substituted chlorotriazine **2A** and glutarimido-substituted chlorotriazine **2D** were selected for further studies.

The formation of the side product **8** was assumed to result from chlorotriazine **2** being more electrophilic than **10** or **11**. Thus, the addition of amine **6** after the formation of **11** should prevent the formation of **8** (Table 2). Accordingly, amine **6** was added to the preformed mixture of chlorotriazine, NMM, and carboxylic acid **5** in THF. In this solvent, ester **9** would never be formed. In the amide-forming reactions of 2-phenylpropionic acid (**5a**) with 2-phenethylamine (**6a**), aniline (**6b**), or 4-(ethoxycarbonyl)aniline (**6c**) (the nucleophilicity of these amines decreases in this order), imido-substituted **2A** and **2D** afforded better yields than CDMT (Table 2, entries 1–9). From the viewpoints of atom economy, starting material costs, and synthetic yields, **2A** was selected for further studies. In the case of sterically hindered isobutyric acid (**5b**, entries 10 and 11), **2A** also afforded amide **7d** in a better yield than that using CDMT. When the more sterically hindered pivalic acid (**5c**) was used (entries 12–17), different reactivities between **2A** and CDMT were observed for aniline **6b** (entry 16 *versus* 17). Although it was thought that the benzoic acid derivative (**5d**, with electron-withdrawing nitro groups) might form intermediate **11** slowly, **2A** afforded product **7h** in an excellent yield compared to CDMT (Table 2, entry 18 *versus* 19). This method is also effective for formation of a peptide bond, *i.e.*, condensation of Boc-Leu-OH (**5e**) and H-Phe-OMe (**6e**) afforded the corresponding dipeptide (**7i**) in 94% NMR yield as a single diastereomer (Table 2, entry 20). As indicated in entry 18 of Table 2, purification by only extraction and recrystallization without column chromatography was also possible.

From these results, it is unambiguous that the succinimido-substituted chlorotriazine **2A** was more reactive than CDMT, and less sterically hindered alcoholic solvents (especially methanol) are unsuitable for carrying out the condensing reactions because of alcoholysis of **11**. However, we anticipated that the competing alcoholysis against aminolysis would be reduced when lower concentrations of alcohols were used. Namely, chemoselective amide forming reactions could be effective even using carboxylic acids **5** and amines **6** having free hydroxy groups. Thus, we tested 6-hydroxyhexanoic acid (**5f**) as it would be susceptible to an intramolecular lactone-formation or an intermolecular ester-formation during the carboxylic acid activation step (Table 3, entries 1 and 2). The desired amide **7j** was obtained in a good yield compared to CDMT under the reaction conditions used in Table 2. When amino alcohols such as benzyl(2-hydroxyethyl)amine (**6f**, Table 3, entries 3 and 4) and *N*-(2-hydroxyethyl)aniline (**6g**, Table 3, entries 5 and 6) were employed, better yields of amide products (**7k** and **7l**) were

Table 2 The scope of amide-forming reactions of carboxylic acids **5** with amines **6**



Entry	Chlorotriazine	Carboxylic acid **5**	Amine **6**	Amide **7**	Time	Yield[a] (%)
1	**2A**	**5a**	**6a**	**7a**	40 min	91 (83)
2	CDMT				40 min	86
3	**2A**	**5a**	H_2N–Ph **6b**	 **7b**	30 min	91 (90)
4	**2D**				20 min	91
5	CDMT				30 min	65
6	**2A**	**5a**	 **6c**	 **7c**	2 h	92 (90)
7	**2D**				2 h	71
8	**2D**				7 h	93
9	CDMT				2 h	34
10	**2A**	^{i}Pr–CO_2H **5b**	H_2N–^{i}Pr **6d**	 **7d**	5 h	91 (69)
11	CDMT				5 h	82
12	**2A**	^{t}Bu–CO_2H **5c**	**6a**	 **7e**	5 h	78 (63)
13	CDMT				5 h	79
14[b]	**2A**	**5c**	**6d**	 **7f**	24 h	77 (75)
15[b]	CDMT				24 h	84
16[b]	**2A**	**5c**	**6b**	 **7g**	8 h	69 (60)
17[b]	CDMT				8 h	25
18	**2A**	 **5d**	**6a**	 **7h**	5 h	96 (94[c])
19	CDMT				5 h	86
20[d]	**2A**	Boc-Leu-OH **5e**	H-Phe-OMe **6e**	Boc-Leu-Phe-OMe **7i**	1 h	94 (90)

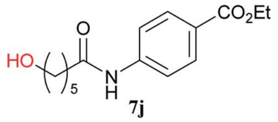
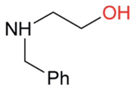
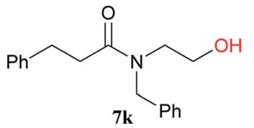
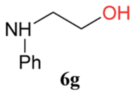
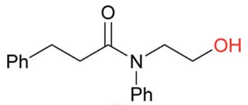
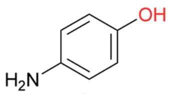
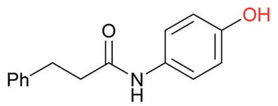
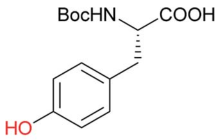
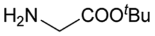
[a] NMR yields. Isolated yields are given in the parentheses. [b] Reaction time of the first step was 15 min. [c] The desired product was isolated in 81% yield only by extraction and recrystallization without column chromatography. [d] Boc-Leu-OH (1.0 eq.), **2A** (1.05 eq.), NMM (1.2 eq.), H-Phe-OMe·HCl (1.2 eq.), and EtN^iPr_2 (1.2 eq.) were used.

observed, even in the presence of the competing free hydroxy groups. Although the chemoselective acylation of 4-aminophenol (**6h**) using EDC and HOBt in the presence of a surfactant was insufficient,[2] **2A** afforded the desired product **7m** chemoselectively. Even though Boc-Tyr-OH having the phenolic hydroxy group was used as the starting material, the desired dipeptide (**7n**) was obtained in 80% NMR yield and 71% isolated yield (Table 3, entry 9).

To clarify the reactivity of **2A** compared with the amido-substituted chlorotriazine **1A** and CDMT, the formation of **7l** under similar conditions used in Tables 2 and 3 was investigated kinetically with ^1H NMR spectroscopy (Fig. 2). The reaction rate with **2A** was faster than that with **1A** or CDMT.

From the study of the DMT-Ams, we previously elucidated that the reactivity of *tert*-amines toward CDMT was strongly influenced by their steric hinderance;[9] that is, a β-alkyl group toward the nitrogen lone pair in a *gauche* relationship remarkably hampers the nucleophilic attack on CDMT. Because of this effect, *N*-ethylmorpholine, *N*-ethylpiperidine, and triethylamine are unable to react with CDMT to afford DMT-Ams at ambient temperature. Contrastingly, the imido-

Table 3 Amide-forming reactions in the presence of free hydroxy groups

Entry	Chlorotriazine	Carboxylic acid 5	Amine 6	Amide 7	Time	Yield[a] (%)
1	**2A**	 **5f**	**6c**	 **7j**	4 h	81 (75)
2	CDMT				4 h	30
3	**2A**	**5a**	 **6f**	 **7k**	15 min	88 (84)
4	CDMT				15 min	71
5	**2A**	**5a**	 **6g**	 **7l**	6 h	97 (85)
6	CDMT				6 h	73
7[b]	**2A**	**5a**	 **6h**	 **7m**	15 min	90 (73)
8[b]	CDMT				15 min	54
9[c]	**2A**	 **Boc-Tyr-OH** **5g**	 **H-Gly-O^{t}Bu** **6i**	Boc-Tyr-Gly-O^{t}Bu **7n**	1 h	80 (71)

[a] NMR yields. Isolated yields are given in the parentheses. [b] 3-Phenylpropionic acid (1.1 eq.), **2A** or CDMT (1.0 eq.), NMM (1.05 eq.), and 4-aminophenol (1.0 eq.) were used. [c] Boc-Tyr-OH (1.0 eq.), **2A** (1.0 eq.), NMM (1.2 eq.), H-Gly-O^{t}Bu·HCl (2.0 eq.), and EtN^{i}Pr$_2$ (2.0 eq.) were used.

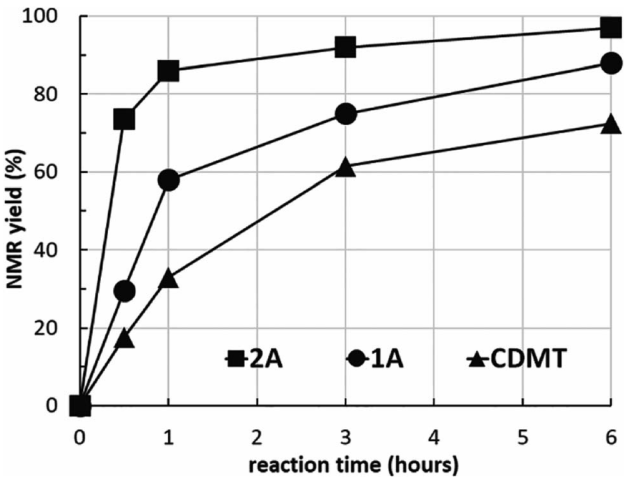
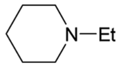
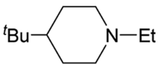
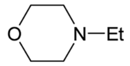


Fig. 2 Kinetic study of amide **7l** formation using **2A**, **1A**, and CDMT.

substituted chlorotriazine **2A** reacted with these *tert*-amines, resulting in the formation of **7a** (Table 4). The strong electron-withdrawing ability of the succinimido group was thought to be responsible for overcoming this difficulty, thus enabling the use of various *tert*-amines for condensing reagents.[10,11]

Table 4 Amide-forming reactions using sterically hindered *tert*-amines that were incapable of reacting with CDMT

$$\underset{(1.0\text{ eq.})}{\mathbf{5a}} \xrightarrow[\text{THF, rt, time}]{\mathbf{2A}\text{ (1.1 eq.)},\ \textit{tert}\text{-amine (1.2 eq.)}} \xrightarrow[\text{rt, 1 h}]{\mathbf{6a}\text{ (1.1 eq.)}} \mathbf{7a}$$

Entry	*tert*-Amine	Time (min)	Yield[a] (%)
1		30	78
2		30	77
3		60	62
4	Et$_3$N	60	63

[a] NMR yields.

Conclusion

We have developed imido-substituted chlorotriazines (**2**) and demonstrated their use in efficient dehydrative condensing reactions between carboxylic acids and amines. Chemoselective amide-forming reactions using amino alcohols with succinimido-substituted **2A** were successfully achieved. In addition, we demonstrated that **2A** was an effective reagent for the chemoselective condensing reaction of hydroxy-substituted carboxylic acids that could form a lactone or an ester during the activation step. In terms of reaction rates and amide yields, **2A** was superior to the amido-substituted chlorotriazine **1A** and CDMT. Sterically hindered *tert*-amines that would never react with CDMT at ambient temperature, such as *N*-ethylmorpholine, *N*-ethylpiperidine, and triethylamine, were successfully employed in the formation of DMT-Ams with **2A**. These results will contribute to the development of novel functionalized triazine-based condensing reagents and *tert*-amine-catalyzed amide-forming reactions.

Experimental

General methods

Nuclear magnetic resonance [^{1}H NMR (400 or 600 MHz) and ^{13}C NMR (100 or 150 MHz)] spectroscopy was carried out on JEOL JNM-ECS400 and JEOL JNM-ECA600 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ values relative to tetramethylsilane (TMS). The coupling constants for ^{1}H NMR were reported in hertz (Hz). The following abbreviations were used for reporting the spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR were reported as δ values relative to the center line of the deuterochloroform triplet at 77.16 ppm. Mass spectra were measured on a JEOL JMS-T100TD spectrometer (DART- and ESI-MS). Analytical thin-layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Flash chromatography separation was performed using Kanto Chemical silica gel 60 N (spherical, neutral, 40–100 mesh) unless otherwise noted. All Reagents were of commercial grade and were used without further purification unless otherwise noted. Anhydrous THF and toluene were purchased from commercial sources. All reactions that are sensitive to oxygen or moisture were conducted under a N_2 atmosphere. The ^{1}H NMR spectral data for 2-methoxy-4-phenethylamino-6-succinimido-1,3,5-triazine (**8A**) and 2-glutarimido-4-methoxy-6-phenethylamino-1,3,5-triazine (**8D**) were consistent with those of authentic samples prepared from **2A** and **2D** (see the ESI† for synthetic details). ^{1}H NMR spectral data for methyl 3-phenylpropanoate (**9a**)[19,20] and 2-propyl 3-phenylpropanoate (**9b**)[20,21] were consistent with the referenced chemical shift values. ^{1}H NMR spectral data of the isolated amide products **7a**,[22] **7b**,[23,24] **7d**,[25] **7e**,[26] **7f**,[27] **7g**,[28] **7i**,[29] **7m**,[30] and **7n** (ref. 31) were identical to known literature values (see the ESI†).

Experimental procedure and characterization data

2-Chloro-4-methoxy-6-succinimido-1,3,5-triazine (2A). To a THF solution (70 mL) of sodium hydride (60%, 1.44 g, 36.0 mmol), succinimide (3.27 g, 33.0 mmol) was added at 0 °C. To this reaction mixture, a THF solution (30 mL) of 2,4-dichloro-6-methoxy-1,3,5-triazine (5.40 g, 30.0 mmol) was added dropwise at ambient temperature. After stirring for 30 h at 55 °C, the reaction mixture was quenched with 1 M $KHSO_4$ and extracted with AcOEt. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 1 : 1) to afford **2A** (4.00 g, 55% yield) as a white solid. Mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (s, 3H), 2.94 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.63, 173.27, 172.71, 163.20, 56.96, 28.92; IR (KBr): 2956, 1736, 1560, 1415, 1369, 1288, 1163, 991, 918, 812 cm^{-1}; HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_8H_8ClN_4O_3$ 243.0285; found: 243.0301; anal. calcd for $C_8H_7ClN_4O_3$: C, 39.60; H, 2.91; N, 23.09. Found: C, 39.43; H, 2.95; N, 22.89.

2-Chloro-4-methoxy-6-phthalimido-1,3,5-triazine (2B). To a toluene solution (100 mL) of 2,4-dichloro-6-methoxy-1,3,5-triazine (2.70 g, 15.0 mmol), potassium phthalimide (2.78 g, 15.0 mmol) and 18-crown-6 (0.39 g, 1.5 mmol) were added at ambient temperature. After stirring for 12 h, the reaction mixture was filtered and washed with AcOEt. After concentrating the filtrate under reduced pressure, the residue was purified by flash column chromatography (hexane/AcOEt = 2 : 1) to afford **2B** (1.68 g, 58% yield) as a white solid. Mp 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.19, 172.40, 163.94, 162.76, 135.46, 131.29, 124.67, 56.74; IR (KBr): 3095, 3064, 2958, 1797, 1739, 1558, 1419, 1353, 1271, 1082, 935 cm^{-1}; HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_8ClN_4O_3$ 291.0285; found: 291.0282; anal. calcd for $C_{12}H_7ClN_4O_3$: C, 49.59; H, 2.43; N, 19.28. Found: C, 49.41; H, 2.50; N, 19.23.

2-Chloro-4-glutarimido-6-methoxy-1,3,5-triazine (2D). To a THF solution (1 mL) of sodium hydride (88 mg, 2.2 mmol), glutarimide (272 mg, 2.4 mmol) in THF (5.5 mL) was added at ambient temperature. To this mixture, a THF solution (0.3 mL) of 18-crown-6 (53 mg, 0.20 mmol) and a THF solution (2.4 mL) of cyanuric chloride (369 mg, 2.0 mmol) were sequentially added dropwise at −78 °C. After stirring for 7 h at ambient temperature, methanol (10 mL) and $NaHCO_3$ (336 mg, 4.0 mmol) were added at 0 °C. After stirring for 13 h at ambient temperature, the reaction mixture was quenched with 1 M $KHSO_4$ (2 mL) at 0 °C and extracted with CH_2Cl_2. The organic phase was washed with 1 M $KHSO_4$ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 9 : 1) to afford **2D** (135 mg, 26% yield) as a white solid. Mp 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (s, 3H), 2.79 (t, *J* = 6.4 Hz, 4H), 2.14 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.85, 173.13, 171.19, 167.12, 57.00, 32.35, 17.11; IR (KBr): 3016, 2970, 1743, 1697, 1560, 1539, 1498, 1408, 1358, 1282, 1248, 1144, 1016, 920, 760, 561, 442 cm^{-1}; HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{10}ClN_4O_3$ 257.0441; found: 257.0444; anal. calcd for $C_9H_9ClN_4O_3$: C, 42.12; H, 3.53; N, 21.83. Found: C, 42.05; H, 3.47; N, 21.83.

General procedure for the amide-forming reactions (Tables 2, 3, and Fig. 2). To a THF solution (2 mL) of carboxylic acid **5** (0.4 mmol) and NMM (53 μL, 0.48 mmol), chlorotriazine **2** or CDMT (0.44 mmol) was added. After stirring for 5 min at ambient temperature, amine **6** (0.44 mmol) was added to the reaction mixture. The reaction was monitored for completion using TLC and quenched with 1 M $KHSO_4$ (4 mL). The mixture was extracted with $CHCl_3$ (10 mL × 3), and the combined organic layers were washed with 1 N HCl, sat. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was analyzed by quantitative NMR using coumarin or 1,3,5-trimethoxybenzene as an internal standard. After concentration under reduced pressure, the residue was purified by flash column chromatography with the appropriate eluent to afford amide **7**.

***N*-(4-Ethoxycarbonylphenyl)-3-phenylpropionamide (7c).** The title compound (107 mg, 90% yield) was obtained by flash column chromatography (hexane/AcOEt = 8 : 2) as a white solid. Mp 136–137 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.52 (br, 1H), 7.30–7.20 (m, 5H), 4.34 (q, J = 7.2 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.85, 166.32, 142.03, 140.49, 130.85, 128.81, 128.47, 126.60, 125.97, 118.93, 61.03, 39.60, 31.50, 14.45; IR (KBr): 3317, 3060, 3030, 2983, 2904, 1709, 1670, 1608, 1593, 1523, 1454, 1410, 1363, 1315, 1277 cm^{-1}; HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443; found: 298.1464; anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.41; H, 6.34; N, 4.70.

3,5-Dinitro-*N*-(2-phenethyl)benzamide (7h). The title compound (119 mg, 94% yield) was obtained by flash column chromatography (hexane/AcOEt = 9 : 1 to $CHCl_3$, $CHCl_3$/AcOEt = 7 : 3) as a white solid. Mp 155–156 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.14 (t, J = 2.0 Hz, 1H), 8.86 (d, J = 2.0 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29–7.24 (m, 3H), 6.43 (br, 1H), 3.80 (td, J = 6.9, 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.91, 148.76, 138.24, 138.16, 129.09, 128.89, 127.22, 127.16, 121.19, 41.83, 35.50; IR (KBr): 3415, 3097, 2945, 1672, 1630, 1603, 1541, 1527, 1487, 1452, 1435, 1346, 1327, 1306, 1282 cm^{-1}; HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_5$ 316.0934; found: 316.0936; anal. calcd for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 56.92; H, 4.15; N, 13.31.

***N*-(4-Ethoxycarbonylphenyl)-6-hydroxyhexanamide (7j).** The title compound (80 mg, 75% yield) was obtained by flash column chromatography ($CHCl_3$/MeOH = 99 : 1 to 95 : 5) as a white solid. ^1H NMR (400 MHz, $CDCl_3/CD_3OD$ = 1 : 1): δ 7.98 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.59 (t, J = 6.6 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H), 1.75 (quin, J = 7.6 Hz, 2H), 1.60 (quin, J = 7.1 Hz, 2H), 1.45 (quin, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$ = 1 : 1): δ 173.20, 166.53, 142.76, 130.16, 124.79, 118.62, 61.40, 60.63, 36.70, 31.70, 25.02, 24.99, 13.64; IR (KBr) 3315, 2935, 2868, 1712, 1657, 1610, 1535, 1462, 1439, 1408, 1367, 1282, 1259, 1176, 1103, 1074, 1024, 962, 858, 769, 725, 694, 501 cm^{-1}; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{21}NNaO_4$ 302.1368; found: 302.1350.

***N*-Benzyl-*N*-(2-hydroxyethyl)-3-phenylpropanamide (7k).** The title compound (95 mg, 84% yield) was obtained by flash column chromatography (hexane/AcOEt = 1 : 1) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.05 (m, 10H, major and minor), 4.65 (s, 0.6H, minor), 4.49 (s, 1.4H, major), 3.71 (t, J = 5.0 Hz, 1.4H, major), 3.63 (t, J = 5.6 Hz, 0.6H, minor), 3.53 (t, J = 5.0 Hz, 1.4H, major), 3.32 (t, J = 5.6 Hz, 0.6H, minor), 3.01 (t, J = 7.8 Hz, 0.6H, minor), 2.98 (t, J = 7.8 Hz, 1.4H, major), 2.79 (t, J = 7.8 Hz, 0.6H, minor), 2.66 (t, J = 7.8 Hz, 1.4H, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.88, 173.29, 141.31, 140.95, 137.63, 136.29, 129.03, 128.65, 128.57, 128.51, 127.94, 127.77, 127.37, 126.31, 126.26, 126.17, 61.87, 59.93, 52.54, 49.95, 48.97, 48.70, 35.17, 35.06, 31.68, 31.56; IR (KBr) 3400, 3086, 3060, 3028, 2931, 2875, 1623, 1496, 1473, 1452, 1421, 1363, 1209, 1076, 1030, 733, 700 cm^{-1}; HRMS (DART) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{21}NNaO_2$ 306.1470; found: 306.1463.

***N*-(2-Hydroxyethyl)-*N*-phenyl-3-phenylpropanamide (7l).** The title compound (92 mg, 85% yield) was obtained by flash column chromatography (hexane/AcOEt = 4 : 1 to 2 : 3) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.30 (m, 3H), 7.26–7.15 (m, 3H), 7.05 (d, J = 7.3 Hz, 2H), 7.02 (d, J = 7.3 Hz, 2H), 3.86 (t, J = 5.3 Hz, 2H), 3.74 (d, J = 4.6 Hz, 2H), 3.38 (br s, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.37, 142.66, 140.99, 129.92, 128.52, 128.46, 128.26, 128.06, 126.21, 61.45, 52.92, 36.29, 31.78; IR (KBr) 3400, 3060, 3028, 2931, 2873, 1635, 1595, 1495, 1454, 1408, 1273, 1192, 1074, 1059, 1028, 858, 769, 752, 700, 552, 513 cm^{-1}; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{19}NNaO_2$ 292.1314; found: 292.1288.

Conflicts of interest

The authors declare no competing financial interest.

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Notes and references

1 P. D. Baily, I. D. Collier and K. M. Morgan, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon, Oxford, 1995, vol. 5, p. 264.
2 M. Parmentier, M. K. Wagner, K. Magra and F. Gallou, *Org. Process Res. Dev.*, 2016, **20**, 1104–1107.
3 D.-H. Kim, H.-S. Rho, J. W. You and J. C. Lee, *Tetrahedron Lett.*, 2002, **43**, 277–279.
4 A. R. Katritzky, S. K. Singh, C. Cai and S. Bobrov, *J. Org. Chem.*, 2006, **71**, 3364–3374.
5 H. Maag, *J. Am. Oil Chem. Soc.*, 1984, **61**, 259–267.
6 T. Maugard, M. Remaud-Simeon, D. Petre and P. Monsan, *Tetrahedron*, 1997, **53**, 5185–5194.
7 Y. Park, X. Fei, Y. Yuan, S. Lee, J. Hur, S. J. Park, J.-K. Jung and S.-Y. Seo, *RSC Adv.*, 2017, **7**, 41955–41961.
8 M. Kunishima, C. Kawachi, K. Hioki, K. Terao and S. Tani, *Tetrahedron*, 2001, **57**, 1551–1558.
9 M. Kunishima, T. Ujigawa, Y. Nagaoka, C. Kawachi, K. Hioki and M. Shiro, *Chem.–Eur. J.*, 2012, **18**, 15856–15867.

10 M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao and S. Tani, *J. Am. Chem. Soc.*, 2001, **123**, 10760–10761.

11 M. Kunishima, H. Imada, K. Kikuchi, K. Hioki, J. Nishida and S. Tani, *Angew. Chem., Int. Ed.*, 2005, **44**, 7254–7257.

12 M. Kunishima, D. Kato, N. Kimura, M. Kitamura, K. Yamada and K. Hioki, *Beilstein J. Org. Chem.*, 2016, **12**, 1897–1903.

13 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.

14 F. Milletti, L. Storchi, L. Goracci, S. Bendels, B. Wagner, M. Kansy and G. Cruciani, *Eur. J. Med. Chem.*, 2010, **45**, 4270–4279.

15 C. S. Petersen, *Acta Chem. Scand.*, 1971, **25**, 379–389.

16 R. Mason, *Acta Crystallogr.*, 1961, **14**, 720–724.

17 Without NMM, the reaction in MeOH did not proceed smoothly.

18 There is a possibility that **8** could be formed from **2**, **10**, or **11**.

19 P. J. Black, M. G. Edwards and J. M. J. Williams, *Eur. J. Org. Chem.*, 2006, **2006**, 4367–4378.

20 C. Salomé and H. Kohn, *Tetrahedron*, 2009, **65**, 456–460.

21 T. Takuwa, T. Minowa, H. Fujisawa and T. Mukaiyama, *Chem. Pharm. Bull.*, 2005, **53**, 476–480.

22 M. Kunishima, K. Yamamoto, Y. Watanabe, K. Hioki and S. Tani, *Chem. Commun.*, 2005, 2698–2700.

23 I. Shiina and Y. Kawakita, *Tetrahedron*, 2004, **60**, 4729–4733.

24 K. Hioki, S. Kameyama, S. Tani and M. Kunishima, *Chem. Pharm. Bull.*, 2007, **55**, 825–828.

25 V. P. Srivastava, A. K. Yadav and L. D. S. Yadav, *Synlett*, 2014, **25**, 665–670.

26 C. M. Boehner, D. M. Marsden, H. F. Sore, D. S. Norton and D. R. Spring, *Tetrahedron Lett.*, 2010, **51**, 5930–5932.

27 L. S. Baugh and J. A. Sissano, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 1633–1651.

28 K. Sasaki and D. Crich, *Org. Lett.*, 2011, **13**, 2256–2259.

29 R. A. Rodriguez, P.-S. Pan, C.-M. Pan, S. Ravula, S. Lapera, E. K. Singh, T. J. Styers, J. D. Brown, J. Cajica, E. Parry, K. Otrubova and S. R. McAlpine, *J. Org. Chem.*, 2007, **72**, 1980–2002.

30 T. Xu, F. Sha and H. Alper, *J. Am. Chem. Soc.*, 2016, **138**, 6629–6635.

31 L. Wang, B. P. Lieberman, K. Ploessl and H. F. Kung, *Nucl. Med. Biol.*, 2014, **41**, 58–67.