JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX Article pubs.acs.org/joc

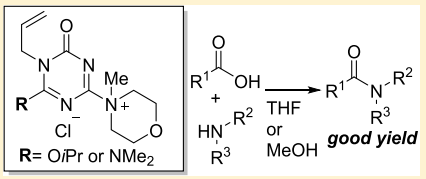
Development of Triazinone-Based Condensing Reagents for Amide Formation

Kohei Yamada, Mika Kota, Kensuke Takahashi, Hikaru Fujita, Masanori Kitamura, and Munetaka Kunishima*

Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

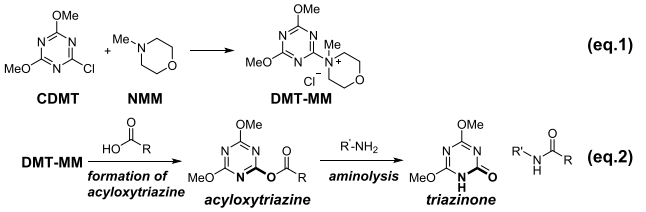
Supporting Information

ABSTRACT: Novel triazinone-based condensing reagents have been developed. The palladium-catalyzed O−N allylic rearrangement of 2-(allyloxy)-4,6-dichloro-1,3,5-triazine and subsequent regioselective substitution using alcohols and an amine afforded chlorotriazinones, which can be readily converted using *N*-methylmorpholine into the corresponding condensing reagents. The condensation of carboxylic acids and amines using these reagents proceeded to afford the desired amides in good yields. In comparison with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, the newly synthesized triazinone-based condensing reagents exhibited higher reactivity.



INTRODUCTION

A triazine-based condensing reagent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), which is synthesized from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM), has been widely used for the synthesis of amides from carboxylic acids and amines in alcohols or water (eqs 1 and 2).[1] *N*-



Methylmorpholino group of DMT-MM can be replaced by other trialkylammonio groups using alternative *tert*-amines as long as they satisfy the steric and electronic requirements for the formation of triazinylammonium salts.[2] Therefore, using functionalized *tert*-amines, we previously developed substrate-selective amidations via molecular recognition.[3] Moreover, the synthesis of several chlorotriazines possessing substituents, such as phenoxy, trifluoroethoxy, *N*-ethylamino, amido, and imido was reported for the control of reactivity.[4] It appears reasonable that the replacement of the methoxy group at the triazine ring by more electron-withdrawing functionality would result in more reactive condensing reagents. However, a strong electron-withdrawing group bonded to triazine via a heteroatom, such as oxygen or nitrogen, may also serve as an eliminating group, which makes the corresponding condensing reagent unstable. Therefore, new highly reactive stable triazine derivatives devoid of a strong electron-withdrawing group are required to address this issue.

Previously, we reported a triazine-based acid-catalyzed benzylating reagent, 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT), and its derivatives (Figure 1A).[5] Additionally, we have also developed highly reactive triazinedione-based benzylating reagents, 6-(benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (MonoBOT) and *N*,*N*′-dimethylated 6-(benzyloxy)-1,3,5-triazine-2,4-(1*H*,3*H*)-dione (DMBOT).[6] DMBOT is more reactive than TriBOT and can thus benzylate alcohols in the presence of 2,6-di-*tert*-butylpyridinium trifluoromethanesulfonate, a relatively weak acid catalyst, which is not effective for the benzylation using TriBOT. With regard to the calculation study of the sequential tautomerization of cyanuric acid to isocyanuric acid,[7] the difference in the reactivity of these benzylating reagents can be explained as follows: the enthalpy change from MonoBOT (DMBOT) to isocyanuric acid is considered to be larger than that from TriBOT to 4,6-bis-(benzyloxy)-1,3,5-triazin-2(1*H*)-one.[5c] Accordingly, the triazinedione- and triazinone-based condensing reagents **1** and **2**, respectively, are also expected to be highly reactive despite the absence of a strong electron-withdrawing group (Figure 1B). Indeed, the lowest unoccupied molecular orbital (LUMO) energy levels of CDMT, chlorotriazinone **3**, and chlorotriazinedione **4** were calculated as −1.13, −1.54, and −1.55 eV, respectively (B3LYP/6-31G* level of theory, Figure 1C). These results indicate that with regard to the formation of acyloxytriazines, which is the rate-determining step in the condensation,[3g] the triazinone- and triazinedione-based condensing reagents **1** and **2**, respectively, are more reactive than DMT-MM.

Herein, we report the synthesis and reactivity of new condensing reagents possessing these promising core skeletons.

Received: May 25, 2019

   DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

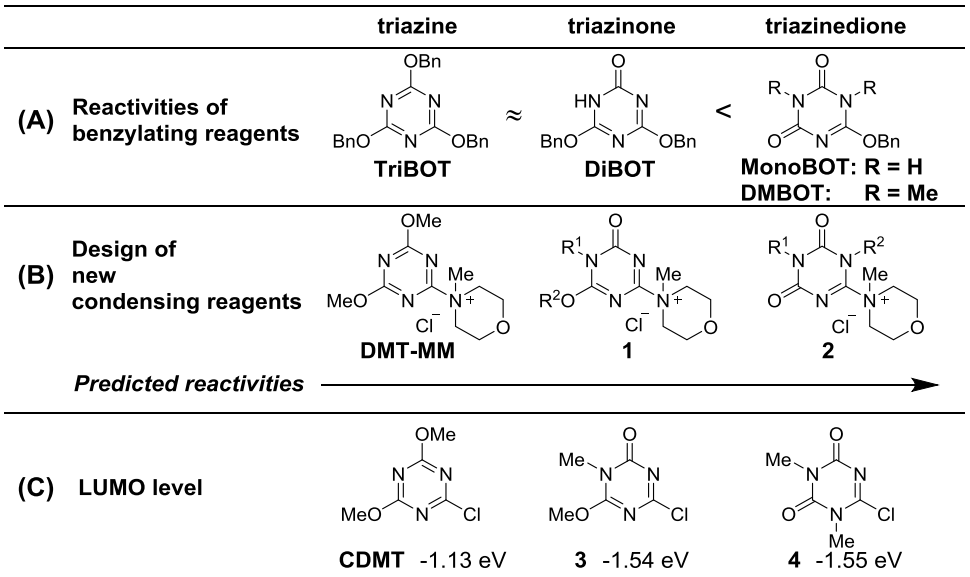
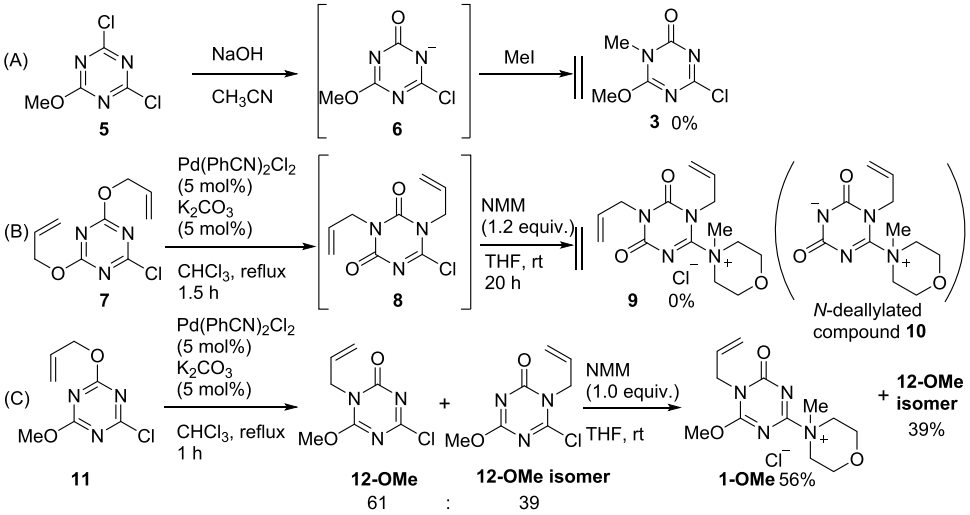


Figure 1. Concept and design of new condensing reagents.

Scheme 1. Attempt for the Synthesis of the Triazinedione- and Triazinone-type Condensing Reagents



RESULTS AND DISCUSSION

Preliminary studies have revealed that the synthesis of *N*-methylated cholorotriazinone **3** by *N*-alkylation using methyl iodide was unsuccessful possibly because of the low nucleophilicity of the anion intermediate **6** (Scheme 1A). After extensive efforts, the formation of *N*,*N*-dialkylated cholorotriazinedione and *N*-alkylated cholorotriazinone structures was achieved via the O−N allylic rearrangement of allyloxytriazines.[8] The reaction of 2,4-diallyloxy-6-chloro-1,3,5-triazine (**7**) in the presence of a palladium catalyst smoothly proceeded to afford the corresponding 1,3-diallyl-6-chloro-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**8**) (Scheme 1B). However, when compound **8** was treated with NMM for 24 h, the corresponding triazinylammonium salt (**9**) was not obtained. Instead, the unreacted compound **8** and several decomposed compounds, such as *N*-deallylated compound **10**, were formed as a result of the nucleophilic attack of the chloride counteranion. The reaction of 2-(allyloxy)-4-chloro-6-methoxy-1,3,5-triazine (**11**) with a palladium catalyst afforded a mixture of regioisomeric chlorotriazinones **12-OMe** and **12-OMe** isomer in a 61:39 ratio (Scheme 1C). The reaction of this regioisomeric mixture with NMM selectively produced triazinylammonium salt **1-OMe**; the **12-OMe** isomer was inert to the reaction with NMM due to the steric hindrance of the adjacent *N*-allyl group.[9]

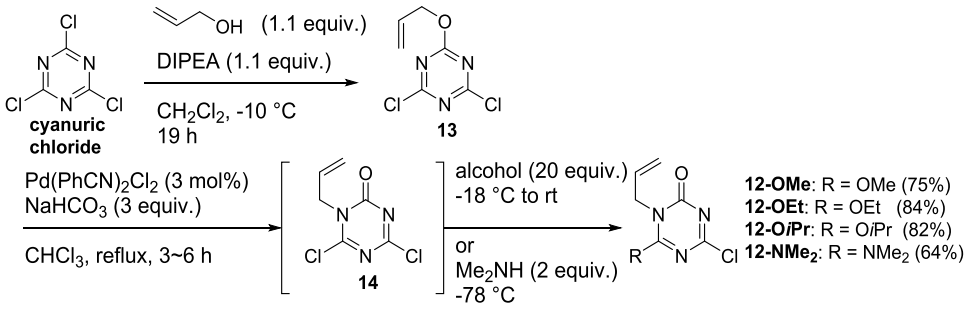
Further efforts led to the regioselective synthesis of **12-OMe** in 75% (three steps from cyanuric chloride; Scheme 2A) via the O−N rearrangement of 2-(allyloxy)-4,6-dichloro-1,3,5-triazine (**13**), followed by regioselective substitution at the sixth position of the resulting 1-allyl-4,6-dichloro-1,3,5-triazin-2(1*H*)-one (**14**) with MeOH.[10] With a reliable procedure in hand, we prepared the alkoxy derivatives **12-OEt** and **12-O*i*Pr** using EtOH and *i*-PrOH, respectively. Moreover, the amino-substituted triazinone **12-NMe$_2$** can be synthesized by employing dimethylamine as a nucleophile. The treatment of these synthesized chlorotriazinones with NMM afforded the corresponding condensing reagents **1-OMe**, **1-OEt**, **1-O*i*Pr**, and **1-NMe$_2$** in good yields (Scheme 2B).[11]

We previously reported that DMT-MM in CH_2Cl_2 is decomposed by demethylation at the morphonium nitrogen. To investigate the stability of the new condensing reagents in

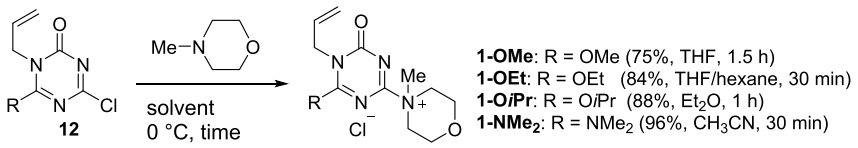
DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Successful Synthesis of Triazinone-type Condensing Reagents

(A) Regioselective synthesis of chlorotriazinones

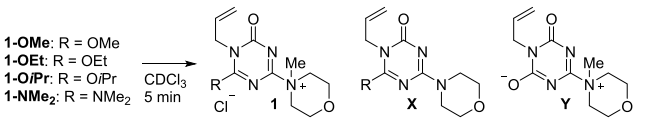


(B) Synthesis of condensing reagents



an aprotic solvent, NMR experiments were performed in $CDCl_3$. Demethylation at the nitrogen atom and/or dealkylation at the oxygen atom occurred to generate **X** and **Y**, respectively (Table 1). From the viewpoint of stability of these

Table 1. Stability of the Condensing Reagents in $CDCl_3$



	1 (%)	X (%)	Y (%)
1-OMe	25	19	56
1-OEt	69	24	7
1-O*i*Pr	78	21	1
1-NMe_2	95	5	

condensing reagents in a nonpolar solvent, **1-O*i*Pr** and **1-NMe_2** were found to be relatively stable; thus, they were used for further investigation.

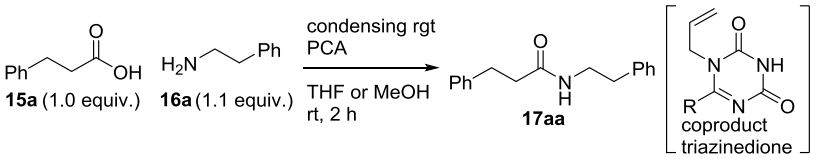
The treatment of 3-phenylpropionic acid **15a** and phenethylamine **16a** with the condensing reagent **1-O*i*Pr** in tetrahydrofuran (THF) at room temperature for 2 h afforded the corresponding amide **17aa** in a modest yield (78%, entry 1, Table 2). Since the protonation of **16a** by an imide proton of the coproduct, triazinedione, was considered responsible for this moderate yield, we investigated the effect of the addition of a proton capture agent. The addition of 1.1 equiv of triethylamine was effective for the reaction (entries 3 and 4), while the addition of NMM moderately increased the yield (85%, entry 2). When MeOH was used as a solvent, amide **17aa** was obtained in 87% yield (entry 5). The reaction in MeOH in the presence of NMM increased the yield to 93% (entry 6). The yields were maintained even at shortened reaction time (10 min, entries 7 and 8). Similarly, in the case of **1-NMe_2**, the reaction in the presence of triethylamine in THF and that in the presence of NMM in MeOH afforded the amide in excellent yields (entries 9−13).

The substrate scope of a series of carboxylic acids **15** and amines **16** was evaluated (Table 3). While the reactions of the secondary amine **16b** using either **1-O*i*Pr** or **1-NMe_2** in MeOH resulted in moderate yields (56 and 59% yields, respectively, entries 1 and 3), the reactions in THF afforded the product **17ab** in good yields (86 and 88% yields, respectively, entries 2 and 4). On the contrary, dibenzylamine **16c** in either MeOH or THF afforded a tertiary amide **17ac** in excellent yields (entries 5 and 6). The coupling of sterically bulky pivalic acid **15b** with **16a** produced **17ba** in moderate yields (entries 7−10). Next, several aromatic acids were used as starting materials. Similar to the reaction using aliphatic acid **15a**, the reaction of benzoic acid **15c** with **16a** using **1-O*i*Pr** for 10 min afforded benzamide **17ca** in excellent yields (entries 11 and 12). The condensation between **15c** and **16a** using **1-NMe_2** also gave good yields (91%, entries 13 and 14), although prolonged reaction times (7 h in MeOH, and 3 h in THF) were required. The reaction was amenable to both electron-rich (entries 15−18) and electron-poor benzoic acids (entries 19−22). As in the case of the reactions of aliphatic acids and secondary amines (entries 1−6), the coupling of benzoic acid **15c** with secondary amines **16b** and **16c** in THF afforded the corresponding products in high yields (entries 24, 26, and 28), while the reaction in MeOH exhibited inferior results when **1-O*i*Pr** was used (entries 23 and 27). Compared to DMT-MM, **1-O*i*Pr** and/or **1-NMe_2** gave higher yields in THF, although DMT-MM often afforded good yields in MeOH. Users can select from these reagents depending on the purpose.

To evaluate the utility of the reagent, we conducted the peptide synthesis. Amidations of Cbz-L-Phe-OH (**15f**) and Cbz-D,L-Phe-OH (D,L-**15f**) with L-Ala-OMe (**16d**) using **1-O*i*Pr** proceeded to give **17fd** and D,L-**17fd** in 91 and 89% yields, respectively (Scheme 3). Racemization at α-position of phenylalanine moiety of **17fd** was not observed (Supporting Information, Figure S1). These results indicate that **1-O*i*Pr** is superior to a triazine-type condensing reagent, DMT-MM-(TsO) (77, 98% de),[12] and comparable with other recently reported Oxyma-type condensing reagents, such as HOTU

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Screening of Reaction Conditions



entry	condensing reagent	solvent	proton capture agent	yield (%)[a]
1	**1-O*i*Pr**	THF	none	78
2	**1-O*i*Pr**	THF	NMM (1.1 equiv)	85
3	**1-O*i*Pr**	THF	Et_3N (1.1 equiv)	95 (95%)[c]
4	**1-O*i*Pr**	THF	Et_3N (0.5 equiv)	84
5	**1-O*i*Pr**	MeOH	none	87
6	**1-O*i*Pr**	MeOH	NMM (1.1 equiv)	93
7[b]	**1-O*i*Pr**	THF	Et_3N (1.1 equiv)	91
8[b]	**1-O*i*Pr**	MeOH	NMM (1.1 equiv)	95
9	**1-NMe_2**	THF	none	67
10	**1-NMe_2**	THF	NMM (1.1 equiv)	86
11	**1-NMe_2**	THF	Et_3N (1.1 equiv)	95
12	**1-NMe_2**	MeOH	none	64
13	**1-NMe_2**	MeOH	NMM (1.1 equiv)	87

[a]NMR yield. [b]Reaction time: 10 min. [c]Isolated yield.

(100, >99% de),[13] *o*-NosylOXY (91, >99% de),[14] and TsOXY (93, 97% de).[15]

Based on the comparison of the reaction times for synthesizing aromatic amide **17ca** using **1-O*i*Pr** (10 min, entry 11 in Table 2), **1-NMe_2** (7 h, entry 13 in Table 2), and DMT-MM (2 h),[1c] the order of reactivity of these condensing reagents was **1-O*i*Pr** > DMT-MM > **1-NMe_2**. As in the case of DMT-MM,[3g] the rate-determining step of the reaction using **1-O*i*Pr** and **1-NMe_2** was expected to be the formation of acyloxytriazinone intermediates. To compare the relative electrophilicity among these condensing reagents, substitution reaction experiments were conducted (Scheme 4). Upon treatment of the condensing reagents **1-O*i*Pr**, **1-NMe_2**, and DMT-MM with triethylamine (1.0 equiv) in CD_3OD for 10 min, the substitutions of the *N*-methylmorpholino group with the deuterated methoxy group proceeded to afford **18-O*i*Pr**, **18-NMe_2**, and **19** in 89, 45, and 78% yields, respectively. These results revealed that **1-O*i*Pr** is a more reactive condensing reagent than DMT-MM and that the reactivity of triazinone-type reagents can be modulated by replacement of the substituent at the triazinone ring.

CONCLUSIONS

We successfully developed new triazinone-type reagents. The formation of a triazinone skeleton via the palladium-catalyzed O−N allylic rearrangement of allyloxytriazine, followed by regioselective substitution using nucleophiles, such as alcohols and an amine, provided the desired chlorotriazinones **12-OMe**, **12-OEt**, **12-O*i*Pr**, and **12-NMe_2**. The corresponding condensing reagents **1-OMe**, **1-OEt**, **1-O*i*Pr**, and **1-NMe_2** were readily prepared. The condensations of several carboxylic acids and amines including protected amino acids using **1-O*i*Pr** and **1-NMe_2** proceeded to give the desired amides in good yields. The comparison of electrophilicity measured via substitution reaction with CD_3OD and calculation of LUMO energy levels revealed that **1-O*i*Pr** is more reactive than DMT-MM.

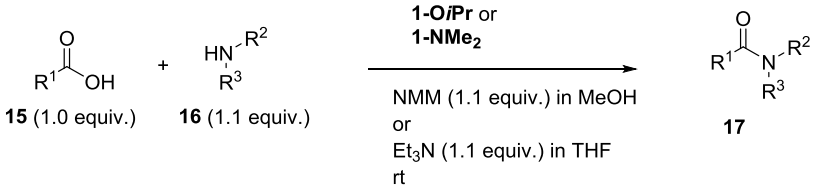
EXPERIMENTAL SECTION

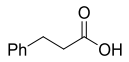
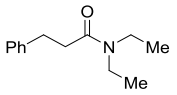
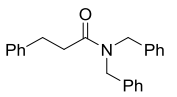
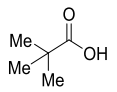
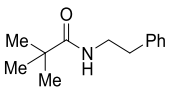
General Methods. Nuclear magnetic resonance (^1H NMR (400 MHz), ^{13}C NMR (100 MHz)) spectra or nuclear magnetic resonance (^1H NMR (600 MHz), ^{13}C NMR (150 MHz)) spectra were determined on a JEOL JNM-ECS400 spectrometer or a JEOL JNM-ECA600 spectrometer. Chemical shifts for ^1H NMR are reported as δ values relative to tetramethylsilane as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of a triplet at 77.16 ppm for deuteriochloroform and 49.00 ppm for CD_3OD. Mass spectra were measured on JMS-T100TD, JMS−SX102A. Analytical thin-layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F_{254}. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 N (spherical, neutral, 40−100 mesh) unless otherwise noted. Reagents were commercial grades and were used without any purification unless otherwise noted. All reactions sensitive to oxygen or moisture were conducted under a N_2 atmosphere. All calculations were performed using Spartan'14. LUMO energy was obtained by density functional theory calculations with the B3LYP/6-31G* basis set in vacuum.

General Procedure for the Synthesis of Chlorotriazinones. To a solution of cyanuric chloride (461 mg, 2.5 mmol) in CH_2Cl_2 (5 mL) was added a mixture of diisopropylethylamine (479 μL, 2.75 mmol) and allylalcohol (187 μL, 2.75 mmol) at −10 °C. After stirring for 18 h, reaction mixture was warmed up to room temperature. After 6 h, the reaction mixture was washed with 1 M HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude allyloxytriazine **13**, which was used in the next reaction without further purification. A solution of allyloxytriazine **13**, $NaHCO_3$ (630 mg, 7.5 mmol), and $Pd(PhCN)_2Cl_2$ (29 mg, 0.075 mmol) in chloroform (10.5 mL) was heated at reflux. After 3 h, the reaction mixture was cooled to −20 °C and added MS3A (1.35 g). *i*PrOH (3.8 mL, 50 mmol) was added dropwise over 40 min. After 1.5 h, the reaction mixture was warmed to −10 °C. After 2 h, reaction mixture was gradually wormed to rt. After 36 h, reaction mixture was filtered through celite pad and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt = 4:1) to give chlorotriazinone **12-O*i*Pr** (470 mg, 82% yield) as a white solid.

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. Substrate Scope for Condensation Using 1-O*i*Pr and 1-NMe_2[a]



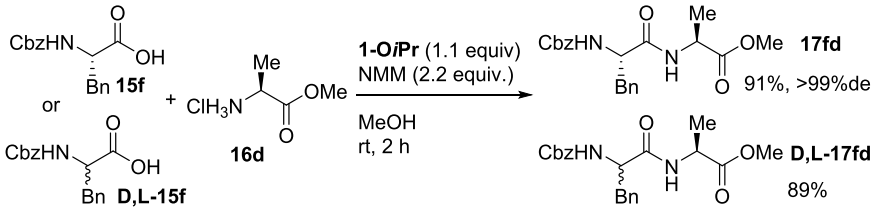
entry	Carboxylic acid	Amine	Amide	1	Solvent/ time	yield (%)	Using DMT-MM [a,b]
1	 15a	 16b	 17ab	1-O*i*Pr	MeOH 2h	56	2h 98%[a]
2				1-O*i*Pr	THF 1 h	86	4h 68%[b]
3				1-NMe_2	MeOH 3 h	59	2h 98%[a]
4				1-NMe_2	THF 3 h	88	4h 68%[b]
5	15a	 16c	 17ac	1-O*i*Pr	MeOH 1 h	91	
6				1-O*i*Pr	THF 1 h	91	
7	 15b	16a	 17ba	1-O*i*Pr	MeOH 2 h	52	3h 84%[a]
8				1-O*i*Pr	THF	59	3h
					2 h		62%[b]
9				1-NMe_2	MeOH 24 h	63	3h 84%[a]
10				1-NMe_2	THF 24 h	81	3h 62%[b]

[a]From ref 1c. [b]From ref 1b.

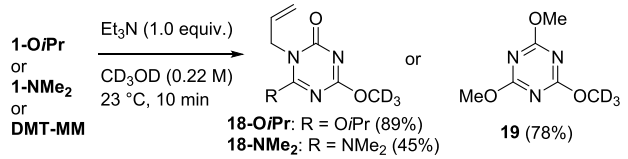
*1-Allyl-4-chloro-6-methoxy-1,3,5-triazin-2(1H)-one (**12-OMe**).* White solid (380 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (ddt, J = 17, 11, 6.0 Hz, 1H), 5.29 (ddt, J = 17, 1.4, 1.4 Hz, 1H), 5.29 (ddt, J = 11, 1.4, 1.4 Hz, 1H), 4.55 (ddd, J = 6.0, 1.4, 1.4 Hz, 2H),

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Dipeptides Using 1-O*i*Pr



Scheme 4. Substitution Reaction of the Condensing Reagents Using Triethylamine in CD_3OD



4.16 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 162.8, 153.8, 129.4, 120.0, 57.9, 45.0; HRMS (DART-TOF) calcd for $C_7H_9ClN_3O_2$ ($[M + H]^+$): 202.0383, found: 202.0400; anal. calcd for $C_7H_8ClN_3O_2$: C, 41.70; H, 4.00; N, 20.84. Found: C, 41.62; H, 4.01; N, 20.83.

1-Allyl-4-chloro-6-ethoxy-1,3,5-triazin-2(1H)-one ***(12-OEt)***. Colorless oil (451 mg, 84%); ^1H NMR (600 MHz, $CDCl_3$): δ 5.85 (ddt, J = 17, 10, 6.2 Hz, 1H), 5.29 (ddt, J = 17, 1.0, 1.0 Hz, 1H), 5.29 (ddt, J = 10, 1.0, 1.0 Hz, 1H), 4.61 (q, J = 7.2 Hz, 2H), 4.55 (ddd, J = 6.2, 1.0, 1.0 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 162.1, 153.8, 129.5, 119.8, 67.9, 44.8, 14.0; HRMS (DART-TOF) calcd for $C_8H_{11}ClN_3O_2$ ($[M + H]^+$): 216.0540, found: 216.0527; anal. calcd for $C_8H_{10}ClN_3O_2$: C, 44.56; H, 4.67; N, 19.49. Found: C, 44.73; H, 4.71; N, 19.41.

1-Allyl-4-chloro-6-isopropoxy-1,3,5-triazin-2(1H)-one ***(12-OiPr)***. White solid (470 mg, 82%); ^1H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddt, J = 17, 11, 6.0 Hz, 1H), 5.48 (sep, J = 6.4 Hz, 1H), 5.28 (ddt, J = 16, 1.4, 1.4 Hz, 1H), 5.28 (ddt, J = 11, 1.4, 1.4 Hz, 1H), 4.53 (ddd, J = 6.0, 1.4, 1.4 Hz, 1H), 1.43 (d, J = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 161.8, 154.1, 129.7, 120.0, 77.0, 44.9, 21.8; HRMS (DART-TOF) calcd for $C_9H_{13}ClN_3O_2$ ($[M + H]^+$): 230.0696; found: 230.0713; anal. calcd for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.30. Found: C, 46.97; H, 5.30; N, 18.50.

1-Allyl-4-chloro-6-(dimethylamino)-1,3,5-triazin-2(1H)-one ***(12-NMe$_2$)***. White solid (1.38 g, 64%); ^1H NMR (600 MHz, $CDCl_3$): δ 6.02 (ddt, J = 17, 11, 5.2 Hz, 1H), 5.31–5.37 (m, 1H), 5.20–5.26 (m, 1H), 4.51–4.55 (m, 2H), 3.17 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 162.5, 156.2, 131.9, 118.3, 50.3, 41.5; HRMS (ESI^+-TOF) calcd for $C_8H_{12}ClN_4O$ ($[M + H]^+$): 215.0700, found: 215.0703; anal. calcd for $C_8H_{11}N_4OCl$: C, 44.76; H, 5.17; N, 26.10. Found: C, 44.67; H, 5.15; N, 25.98.

General Procedure for the Synthesis of Condensing Reagents. To a solution of chlorotriazinone **12-O*i*Pr** (689 mg, 3.0 mmol) in Et_2O was added *N*-methylmorpholine (495 μL, 4.5 mmol) dropwise at 0 °C. After stirring for 1 h, a precipitate was filtered and washed with Et_2O to give **1-O*i*Pr** (876 mg, 88% yield) as a white solid.

4-(5-Allyl-6-methoxy-4-oxo-4,5-dihydro-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride ***(1-OMe)***. White solid (225 mg, 75%); ^1H NMR (400 MHz, CD_3OD): δ 5.92 (ddt, J = 17, 11, 6.0 Hz, 1H), 5.41 (ddt, J = 17, 1.4, 1.4 Hz, 1H), 5.32 (ddt, J = 11, 1.4, 1.4 Hz, 1H), 4.62 (ddd, J = 6.0, 1.4, 1.4 Hz, 2H), 4.50–4.40 (m, 2H), 4.26 (s, 3H), 4.10–4.01 (m, 2H), 3.95–3.86 (m, 2H), 3.86–3.76 (m, 2H), 3.51 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 168.5, 167.4, 156.2, 130.8, 120.4, 63.3, 61.2, 59.7, 55.9, 47.0; HRMS (ESI-TOF) calcd for $C_{12}H_{19}N_4O_3$ ($[M - Cl]^+$): 267.1457, found: 267.1442.

4-(5-Allyl-6-ethoxy-4-oxo-4,5-dihydro-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride ***(1-OEt)***. White solid (138 mg, 84%); ^1H NMR (400 MHz, CD_3OD): δ 5.93 (ddt, J = 17, 11, 6.4 Hz, 1H), 5.41 (d, J = 17 Hz, 1H), 5.32 (d, J = 11 Hz, 1H), 4.87 (s, 3H), 4.72 (q, J = 6.9 Hz, 2H), 4.62 (d, J = 6.4 Hz, 2H), 4.48–4.40 (m, 2H), 4.10–4.02 (m, 2H), 3.96–3.86 (m, 2H), 3.87–3.77 (m, 2H), 3.52 (s, 3H), 1.49 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 168.5, 166.7, 156.3, 130.8, 120.5, 70.7, 63.3, 61.2, 55.8, 46.9, 14.3; HRMS (ESI-TOF) calcd for $C_{13}H_{21}N_4O_3$ ($M - Cl^+$): 281.1614, found: 281.1629.

4-(5-Allyl-6-isopropoxy-4-oxo-4,5-dihydro-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride ***(1-OiPr)***. White solid (876 mg, 88%); ^1H NMR (400 MHz, CD_3OD): δ 5.92 (ddt, J = 17, 10, 6.0 Hz, 1H), 5.52 (sep, J = 6.4 Hz, 1H), 5.40 (dd, J = 17, 1.4 Hz, 1H), 5.32 (dd, J = 10, 1.4 Hz, 1H), 4.89 (s, 3H), 4.61 (ddd, J = 6.0, 1.4, 1.4 Hz, 2H), 4.47–4.38 (m, 2H), 4.11–4.01 (m, 2H), 3.96–3.86 (m, 2H), 3.86–3.76 (m, 2H), 3.51 (s, 3H), 1.48 (d, J = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 168.6, 166.2, 156.4, 130.8, 120.4, 80.4, 63.3, 61.2, 55.7, 46.9, 21.9; HRMS (ESI-TOF) calcd for $C_{14}H_{23}N_4O_3$ ($M - Cl^+$): 295.1770, found: 295.1788.

4-(5-Allyl-6-(dimethylamino)-4-oxo-4,5-dihydro-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride ***(1-NMe$_2$)***. White solid (709 mg, 96%); ^1H NMR (400 MHz, CD_3OD): δ 6.11 (ddt, J = 17, 11, 5.0 Hz, 1H), 5.28–5.41 (m, 2H), 4.56–4.64 (m, 2H), 3.64–4.47 (m, 8H), 3.46 (s, 3H), 3.28 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 166.8, 164.8, 159.6, 133.8, 118.4, 63.5, 60.8, 56.1, 52.2, 42.3; HRMS (FAB-TOF) calcd for $C_{19}H_{19}N_4O_3$ ($[M + H]^+$): 351.1457, found: 351.1456.

General Procedure for Amidation. To the solution of acid **15c** (48.8 mg, 0.4 mmol), amine **16a** (55 μL, 0.44 mmol), and *N*-methylmorpholine (48 μL, 0.44 mmol) in MeOH (2 mL) was added **1-O*i*Pr** (146 mg, 0.44 mmol) at room temperature. After stirring for 10 min, the reaction mixture was quenched with 1 M aq. $KHSO_4$ and was concentrated under reduced pressure. The mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 7:3) to afford **17ca** (87.5 mg, 97%) as a white solid.

N-Phenethyl-3-phenylpropanamide ***(17aa)***.[1b,4a] White solid (96.4 mg, 95%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.26 (m, 4H), 7.24–7.17 (m, 4H), 7.09 (d, J = 1.8 Hz, 2H), 5.30 (s, 1H), 3.48 (q, J = 4.6 Hz, 2H), 2.95 (t, J = 5.0 Hz, 2H), 2.74 (t, J = 4.6 Hz, 2H), 2.42 (t, J = 5.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 140.9, 140.0, 139.0, 128.8, 128.7, 128.6, 128.5, 126.6, 126.3, 40.7, 38.6, 35.7, 31.8; LRMS (DART-TOF): 254 ($[M + H]^+$).

N,N-Diethyl-3-phenylpropanamide ***(17ab)***.[1b,4a] Colorless oil (70.3 mg, 86%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.16 (m, 5H), 3.38 (q, J = 7.3 Hz, 2H), 3.22 (q, J = 7.3 Hz, 2H), 2.98 (t, J = 8.3 Hz, 2H), 2.59 (t, J = 8.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H), 1.10 (t, J = 7.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 141.7, 128.5, 126.1, 42.0, 40.3, 35.2, 31.7, 14.3, 13.2; LRMS (DART-TOF): 206 ($[M + H]^+$).

N,N-Dibenzyl-3-phenylpropanamide ***(17ac)***.[16] White solid (120 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.14 (m, 13H), 7.07 (d, J = 7.4 Hz, 2H), 4.60 (s, 2H), 4.37 (s, 2H), 3.05 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.8, 141.3, 137.4, 136.5, 129.0, 128.7, 128.6, 128.6, 128.4, 127.7, 127.5, 126.4, 126.2, 49.9, 48.4, 35.1, 31.7; LRMS (DART-TOF): 330 ($[M + H]^+$).

N-Phenethylpivalamide ***(17ba)***.[4a] White solid (66.4 mg, 81%); ^1H NMR (600 MHz, $CDCl_3$): δ 7.33–7.16 (m, 5H), 5.66 (brs, 1H),

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX–XXX

3.50 (dt, J = 6.9, 7.8 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H), 1.14 (s, 9H); $^{13}C\{^1H\}$ NMR (600 MHz, $CDCl_3$): δ 178.4, 139.2, 128.9, 128.7, 126.6, 40.7, 38.7, 35.8, 27.6.

N-Phenethylbenzamide (17ca).[1,4] White solid (87.5 mg, 97%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.71−7.66 (m, 2H), 7.53−7.45 (m, 1H), 7.45−7.7.38 (m, 2H), 7.37−7.30 (m, 2H), 7.29−7.22 (m, 3H), 6.10 (s, 1H), 3.73 (q, J = 6.9 Hz, 2H), 2.95 (t, J = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 139.0, 134.7, 131.5, 128.9, 128.8, 128.6, 126.9, 126.6, 41.3, 35.8; LRMS (DART-TOF): 226 ($[M + H]^+$).

N-Phenethyl-4-methoxybenzamide (17da).[1b] White solid (95.6 mg, 94%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.69−7.62 (m, 2H), 7.36−7.30 (m, 2H), 7.28−7.22 (m, 3H), 6.93−6.87 (m, 2H), 6.02 (s, 1H), 3.84 (s, 3H), 3.71 (q, J = 6.9 Hz, 2H), 2.93 (t, J = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.1, 162.2, 139.1, 128.9, 128.8, 128.7, 127.0, 126.6, 113.8, 55.5, 41.2, 35.9; LRMS (DART-TOF): 256 ($[M + H]^+$).

N-Phenethyl-4-nitrobenzamide (17ea).[1,4] White solid (101 mg, 94%); ^1H NMR (400 MHz, $CDCl_3$): δ 8.29−8.25 (m, 2H), 7.85−7.81 (m, 2H), 7.37−7.33 (m, 2H), 7.30−7.23 (m, 3H), 6.13 (s, 1H), 3.76 (q, J = 4.4 Hz, 2H), 2.97 (t, J = 4.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 149.6, 140.3, 138.6, 128.9, 128.9, 128.1, 126.9, 123.9, 41.5, 35.6; LRMS (DART-TOF): 271 ($[M + H]^+$).

N,N-Diethyl-benzamide (17cb).[17] Colorless oil (67.9 mg, 96%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.34 (m, 5H), 3.62−3.47 (m, 2H), 3.32−3.18 (m, 2H), 1.30−1.18 (m, 3H), 1.17−1.03 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 137.4, 129.1, 128.4, 126.3, 43.3, 39.3, 14.3, 13.0; LRMS (DART-TOF): 178 ($[M + H]^+$).

N,N-Dibenzyl-benzamide (17cc).[18] White solid (117 mg, 97%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.46 (m, 2H), 7.42−7.26 (m, 11H), 7.19−7.09 (m, 2H), 4.70 (s, 2H), 4.40 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.4, 137.0, 136.5, 136.3, 129.8, 129.0, 128.8, 128.7, 128.5, 127.8, 127.6, 127.1, 126.8, 51.6, 46.9; LRMS (DART-TOF): 302 ($[M + H]^+$).

Methyl ((Benzyloxy)carbonyl)-L-phenylalanyl-L-alaninate (17fd).[14] White solid (35 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.13 (m, 10H), 6.49−6.31 (m, 1H), 5.44−5.31 (m, 1H), 5.08 (s, 2H), 4.50 (dq, J = 7.3, 7.3 Hz, 1H), 4.38−4.50 (m, 1H), 3.70 (s, 3H), 3.10 (dd, J = 6.4, 13.8 Hz, 1H), 3.05 (dd, J = 6.9, 13.8 Hz, 1H), 1.32 (d, J = 7.3 Hz, 3H).

Methyl ((Benzyloxy)carbonyl)-L-phenylalanyl-L-alaninate (D,L-17fd).[14] White solid (34 mg, 89%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.13 (m, 10H), 6.56−6.41 (m, 0.5H), 6.41−6.25 (m, 1H), 5.59−5.48 (m, 0.5H), 5.48−5.32 (m, 10.5), 5.07 (s, 2H), 4.50 (dq, J = 7.3, 7.3 Hz, 0.5H), 4.49 (dq, J = 7.3, 7.3 Hz, 0.5H), 4.52−4.39 (m, 1H), 3.70 (s, 1.5H), 3.68 (s, 1.5H), 3.15−2.96 (m, 2H), 1.32 (d, J = 7.3 Hz, 1.5H), 1.21 (d, J = 7.3 Hz, 1.5H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01261.

Amidation using **12-OiPr** in the presence of diisopropylethylamine: racemization test of **17fd**; calculations; ^1H and ^{13}C NMR spectra for compounds **12-OMe**, **12-OEt**, **12-OiPr**, **12-NMe$_2$**, **1-OMe**, **1-OEt**, **1-OiPr**, and **1-NMe$_2$**; ^1H NMR spectra for compounds **17aa**−**17fd** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kunisima@p.kanazawa-u.ac.jp.

ORCID

Kohei Yamada: 0000-0002-7857-1474

Hikaru Fujita: 0000-0002-0430-9705

Masanori Kitamura: 0000-0002-8087-1855

Munetaka Kunishima: 0000-0002-3296-490X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by JSPS KAKENHI Grant Nos. 17H03970, 26293003, and 16K08160.

■ REFERENCES

(1) (a) Kunishima, M.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. Synthesis and characterization of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride. *Tetrahedron Lett.* **1999**, *40*, 5327−5330. (b) Kunishima, M.; Kawachi, C.; Monta, J.; Terao, K.; Iwasaki, F.; Tani, S. 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride: an efficient condensing agent leading to the formation of amides and esters. *Tetrahedron* **1999**, *55*, 13159−13170. (c) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Tani, S. Formation of carboxamides by direct condensation of carboxylic acids and amines in alcohols using a new alcohol- and water-soluble condensing agent: DMT-MM. *Tetrahedron* **2001**, *57*, 1551−1558. (d) Kitamura, M.; Kunishima, M. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride. In *e-EROS (Encyclopedia of Reagents for Organic Synthesis) [Online]*; Crich, D., Charette, A. B., Fuchs, P. L., Eds.; John Wiley & Sons, Ltd: West Sussex, 2013. (e) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20*, 140−177. See for a recent review for other coupling reagents; and references are therein

(2) We previously reported that a β-alkyl group kept in a gauche relationship with the nitrogen lone pair of *tert*-amines blocks the approach of CDMT to nitrogen (*gauche* β-alkyl effect): Kunishima, M.; Ujigawa, T.; Nagaoka, Y.; Kawachi, C.; Hioki, K.; Shiro, M. Study on 1,3,5-Triazine Chemistry in Dehydrocondensation: Gauche Effect on the Generation of Active Triazinylammonium Species. *Chem. - Eur. J.* **2012**, *18*, 15856−15867.

(3) (a) Kunishima, M.; Yoshimura, K.; Morigaki, H.; Kawamata, R.; Terao, K.; Tani, S. Cyclodextrin-Based Artificial Acyltransferase: Substrate-Specific Catalytic Amidation of Carboxylic Acids in Aqueous Solvent. *J. Am. Chem. Soc.* **2001**, *123*, 10760−10761. (b) Kunishima, M.; Hioki, K.; Moriya, T.; Morita, J.; Ikuta, T.; Tani, S. Primary-Amine-Specific Lactamization of ω-Amino Acids by an Artificial Cyclotransferase Based on [18]Crown-6. *Angew. Chem., Int. Ed.* **2006**, *45*, 1252−1255. (c) Kunishima, M.; Tokaji, M.; Matsuoka, K.; Nishida, J.; Kanamori, M.; Hioki, K.; Tani, S. Spontaneous Membrane Fusion Induced by Chemical Formation of Ceramides in a Lipid Bilayer. *J. Am. Chem. Soc.* **2006**, *128*, 14452−14453. (d) Kunishima, M.; Nakanishi, S.; Nishida, J.; Tanaka, H.; Morisaki, D.; Hioki, K.; Nomoto, H. Convenient modular method for affinity labeling (MoAL method) based on a catalytic amidation. *Chem. Commun.* **2009**, 5597−5599. (e) Nakanishi, S.; Tanaka, H.; Hioki, K.; Yamada, K.; Kunishima, M. Labeling study of avidin by modular method for affinity labeling (MoAL). *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7050−7053. (f) Kitamura, M.; Kawasaki, F.; Ogawa, K.; Nakanishi, S.; Tanaka, H.; Yamada, K.; Kunishima, M. Role of Linkers in Tertiary Amines That Mediate or Catalyze 1,3,5-Triazine-Based Amide-Forming Reactions. *J. Org. Chem.* **2014**, *79*, 3709−3714. (g) Kunishima, M.; Imada, H.; Kikuchi, K.; Hioki, K.; Nishida, J.; Tani, S. Unusual Rate Enhancement of Bimolecular Dehydrocondensation To Form Amides at the Interface of Micelles of Fatty Acid Salt. *Angew. Chem., Int. Ed.* **2005**, *44*, 7254−7257. (h) Kunishima, M.; Kikuchi, K.; Kawai, Y.; Hioki, K. Substrate-Selective Dehydrocondensation at the Interface of Micelles and Emulsions of Common Surfactants. *Angew. Chem., Int. Ed.* **2012**, *51*, 2080−2083. (i) Kunishima, M.; Kato, D.; Nakanishi, S.; Kitamura, M.; Yamada, K.; Terao, K.; Asano, T. Specific Labeling of Streptavidin for Better Understanding of Ligand Modification in Modular Method for Affinity Labeling (MoAL). *Chem. Pharm. Bull.* **2014**, *62*, 1146−1150. (j) Kunishima, M.; Watanabe, Y.; Terao, K.; Tani, S. Substrate-

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX

Specific Amidation of Carboxylic Acids in a Liquid-Liquid Two-Phase System Using Cyclodextrins as Inverse Phase-Transfer Catalysts. *Eur. J. Org. Chem.* **2004**, *2004*, 4535−4540.

(4) (a) Kunishima, M.; Kato, D.; Kimura, N.; Kitamura, M.; Yamada, K.; Hioki, K. Potent triazine-based dehydrocondensing reagents substituted by an amido group. *Beilstein J. Org. Chem.* **2016**, *12*, 1897−1903. (b) Kamiński, Z. J. 2-chloro-4,6-disubstituted-1,3,5-triazines a novel group of condensing reagents. *Tetrahedron Lett.* **1985**, *26*, 2901−2904. (c) Jastrząbek, K.; Kolesińska, B.; Sabatino, G.; Rizzolo, F.; Papini, A. M.; Kamiński, Z. J. Benzyloxy Derivatives of Triazine-based Coupling Reagents Designed for an Efficient Solid Phase Peptide Synthesis on Polystyrene Resin. *Int. J. Pept. Res. Ther.* **2007**, *13*, 229−236. (d) Jastrzabek, K. G.; Subiros-Funosas, R.; Albericio, F.; Kolesinska, B.; Kamiński, Z. J. 4-(4,6-Di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium Tetrafluoroborate. Triazine-Based Coupling Reagents Designed for Coupling Sterically Hindered Substrates. *J. Org. Chem.* **2011**, *76*, 4506−4513. (e) Kunishima, M.; Yamamoto, K.; Hioki, K.; Kondo, T.; Hasegawa, M.; Tani, S. Development of chlorotriazine polymer dehydrocondensing reagents (Poly-Trzs). *Tetrahedron* **2007**, *63*, 2604−2612. (f) Kitamura, M.; Sasaki, S.; Nishikawa, R.; Yamada, K.; Kunishima, M. Imido-substituted triazines as dehydrative condensing reagents for the chemoselective formation of amides in the presence of free hydroxy groups. *RSC Adv.* **2018**, *8*, 22482−22489.

(5) (a) Yamada, K.; Fujita, H.; Kunishima, M. A Novel Acid-Catalyzed O-Benzylating Reagent with the Smallest Unit of Imidate Structure. *Org. Lett.* **2012**, *14*, 5026−5029. (b) Yamada, K.; Yoshida, S.; Fujita, H.; Kitamura, M.; Kunishima, M. *O*-Benzylation of Carboxylic Acids Using 2,4,6-Tris(benzyloxy)-1,3,5-triazine (TriBOT) under Acidic or Thermal Conditions. *Eur. J. Org. Chem.* **2015**, *2015*, 7997−8002. (c) Yamada, K.; Fujita, H.; Kitamura, M.; Kunishima, M. A Practical Method for *p*-Methoxybenzylation of Hydroxy Groups Using 2,4,6-Tris(p-methoxybenzyloxy)-1,3,5-triazine (TriBOT-PM). *Synthesis* **2013**, *45*, 2989−2997. (d) Yamada, K.; Hayakawa, N.; Fujita, H.; Kitamura, M.; Kunishima, M. Development of a Triazine-Based *tert*-Butylating Reagent, TriAT-*t*Bu. *Eur. J. Org. Chem.* **2016**, *2016*, 4093−4098. (e) Yamada, K.; Hayakawa, N.; Fujita, H.; Kitamura, M.; Kunishima, M. Study of *O*-Allylation Using Triazine-Based Reagents. *Chem. Pharm. Bull.* **2017**, *65*, 112−115.

(6) (a) Fujita, H.; Hayakawa, N.; Kunishima, M. Study of the Reactivities of Acid-Catalyzed *O*-Benzylating Reagents Based on Structural Isomers of 1,3,5-Triazine. *J. Org. Chem.* **2015**, *80*, 11200−11205. (b) Fujita, H.; Kakuyama, S.; Kunishima, M. *N,N′*-Dimethylated Benzyloxytriazinedione: A Stable Solid Reagent for Acid-Catalyzed *O*-Benzylation. *Eur. J. Org. Chem.* **2017**, *2017*, 833−839.

(7) (a) Liang, X.; Zheng, W.; Wong, N.-B.; Li, J.; Tian, A. Theoretical study on the mechanism of keto−enol isomerization for cyanuric acid and cyameluric acid. *J. Mol. Struct.: THEOCHEM* **2004**, *672*, 151−159. (b) Liang, X.; Pu, X.; Zhou, H.; Wong, N.-B.; Tian, A. Keto−enol tautomerization of cyanuric acid in the gas phase and in water and methanol. *J. Mol. Struct.: THEOCHEM* **2007**, *816*, 125−136.

(8) (a) Likhterov, V. R.; Klenovich, S. V.; Etlis, V. S.; Tsareva, L. A.; Pomerantseva, E. G.; Shmuilovich, S. M. Inter- and intramolecular rearrangements of cyanuric acid triallyl esters. *Chem. Heterocycl. Compd.* **1988**, *24*, 308−311. (b) Metz, P.; Mues, C.; Scboop, A. On the palladium(II)-catalyzed rearrangement of allyl imidates. *Tetrahedron* **1992**, *48*, 1071−1080.

(9) The steric hindrance of the *ortho-N*-allyl group of chlorotriazinedione and chlorotriazinone would affect the reactivity of nucleophilic aromatic substitution by NMM. See also ref 2.

(10) A similar regioselective substitution was reported for the aromatic nucleophilic substitution of 1-methyl-4,6-bis(methylthio)-1,3,5-triazin-2(1*H*)-one, which occurred at the ortho-position of nitrogen possessing a methyl group: Tosato, M. L.; Soccorsi, L. Regioselective reactions in heteroaromatic systems. Rules for methyl migration and nucleophilic substitution in methyl cyanurates and thiocyanurates. *J. Chem. Soc., Perkin Trans. 2* **1982**, *2*, 1321−1326.

(11) The reaction using **12-*Oi*Pr** and sterically bulky diisopropylethylamine resulted in the formation of trace amounts of the product. Therefore, the formation of the triazinylammonium salts is essential for the condensation (see Supporting Information, Scheme S1).

(12) Fraczyk, J.; Kaminski, Z. J.; Katarzynska, J.; Kolesinska, B. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Toluene-4-sulfonate (DMT/NMM/TsO) Universal Coupling Reagent for Synthesis in Solution. *Helv. Chim. Acta* **2018**, *101*, No. e1700187.

(13) Al-Warhi, T. I.; AL-Hazimi, H. M. A.; El-Faham, A.; Albericio, F. Synthesis of 2-(4,6-Dimethoxy-1,3,5-triazin-2-yloxyimino) Derivatives: Application in Solution Peptide Synthesis. *Molecules* **2010**, *15*, 9403−9417.

(14) Dev, D.; Palakurthy, N. B.; Thalluri, K.; Chandra, J.; Mandal, B. Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A Recyclable Coupling Reagent for Racemization-Free Synthesis of Peptide, Amide, Hydroxamate, and Ester. *J. Org. Chem.* **2014**, *79*, 5420−5431.

(15) Khattab, S. N. Sulfonate Esters of 1-Hydroxypyridin-2(1*H*)-one and Ethyl 2-Cyano-2-(hydroxyimino)acetate (Oxyma) as Effective Peptide Coupling Reagents to Replace 1-Hydroxybenzotriazole and 1-Hydroxy-7-azabenzotriazole. *Chem. Pharm. Bull.* **2010**, *58*, 501−506.

(16) Kuwano, S.; Harada, S.; Oriez, R.; Yamada, K. Chemoselective conversion of α-unbranched aldehydes to amides, esters, and carboxylic acids by NHC-catalysis. *Chem. Commun.* **2012**, *48*, 145−147.

(17) Yin, Z.; Wang, Z.; Wu, X.-F. Palladium-Catalyzed Carbonylative Synthesis of Amides from Aryltriazenes under Additive-Free Conditions. *Eur. J. Org. Chem.* **2017**, *2017*, 3992−3995.

(18) Smedley, C. J.; Barrow, A. S.; Spiteri, C.; Giel, M.-C.; Sharma, P.; Moses, J. E. Sulfur−Fluoride Exchange (SuFEx)-Mediated Synthesis of Sterically Hindered and Electron-Deficient Secondary and Tertiary Amides via Acyl Fluoride Intermediates. *Chem. - Eur. J.* **2017**, *23*, 9990−9995.

DOI: 10.1021/acs.joc.9b01261
J. Org. Chem. XXXX, XXX, XXX−XXX