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Development of a triazinedione-based dehydrative condensing reagent containing 4-(dimethylamino) pyridine as an acyl transfer catalyst†

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A new triazinedione-based reagent, (*N*,*N*′-dialkyl)triazinedione–4-(dimethylamino)pyridine (ATD-DMAP) was developed for the operationally simple dehydrative condensation of carboxylic acids. This reagent comprises an ATD core and DMAP as the leaving group, which is liberated into the reaction system to accelerate acyl transfer reactions. Upon adding ATD-DMAP to a mixture of carboxylic acids and alcohols in the presence of an amine base, the corresponding esters were formed rapidly at room temperature. Moreover, dehydrative condensation between carboxylic acids and amines using ATD-DMAP proceeded in high yield.

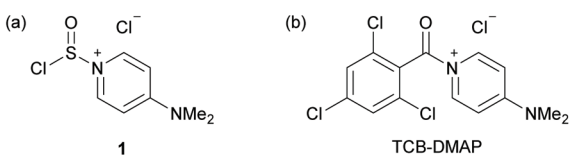
Introduction

Various esterification reactions have been developed, owing to the wide presence of esters in natural products, organic materials, and biologically active compounds such as drug molecules.[1–5] Dehydrative condensing reagents are commonly used for the esterification of carboxylic acids with near-equimolar amounts of alcohols under mild reaction conditions. Several dehydrative condensing reagents, such as carbodiimides[6,7] and carboxylic anhydrides,[8] enable direct esterification without a stepwise procedure that includes the pre-activation of carboxylic acids. Indeed, such esterification can be initiated by adding the dehydrative condensing reagent to a mixture comprising a carboxylic acid and an alcohol.

4-(Dimethylamino)pyridine (DMAP) is an inexpensive and effective nucleophilic catalyst for acyl transfer reactions.[9–14] This catalyst increases the esterification reaction rate because of the formation of a highly reactive *N*-acylpyridinium intermediate in the reaction mixture. Thus, in some cases, even tertiary alcohols can be converted to the corresponding esters. DMAP is therefore widely used in esterification reactions, combined with dehydrative condensing reagents.

If the DMAP-containing dehydrative condensing reagent releases this molecule during the reaction, the DMAP addition step can be omitted. Thus, the experimental procedure for the DMAP-mediated esterification is simplified. To date, two dehydrative condensing reagents containing DMAP have been reported. In 1982, Arrieta *et al.* isolated 4-(dimethylamino)pyridinium chlorosulfite chloride (**1**, Fig. 1a) as a solid reagent composed of DMAP and $SOCl_2$.[15,16] However, esterification using **1** required a stepwise procedure. Thus, after this reagent activated a carboxylic acid as an acyl chloride in the first step, an alcohol and one more equivalent of DMAP were added in the second step to afford the corresponding ester. In 2014, Okuno *et al.* reported the stable and storable dehydrative condensing reagent 2,4,6-trichlorobenzoyl chloride–4-(dimethylamino)pyridine (TCB-DMAP; Fig. 1b), which was synthesized from the reaction between TCB (Yamaguchi reagent) and DMAP.[17] In the general procedure, TCB-DMAP and alcohol were almost simultaneously added to a solution of a carboxylic acid and $^{i}Pr_2EtN$ in toluene. Although this simple procedure afforded esters in high yield, esterification using TCB-DMAP generally required 24 h at room temperature.

In this paper, we describe the development of a new DMAP-containing reagent for operationally simple dehydrative condensation, based on our previous work, for a series of triazine-



1 TCB-DMAP

Fig. 1 Previously reported dehydrative condensing reagents containing DMAP.

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based reagents.[18–27] 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM, Fig. 2) is a distinct dehydrative condensing reagent because amidation between a carboxylic acid and an amine using DMT-MM proceeds in high yield, even in protic solvents.[18,19] This is attributed to the mild reactivity of the triazinyl ester intermediates toward hydrolysis and alcoholysis. Therefore, esterification of carboxylic acids by DMT-MM typically requires an excess amount of alcohol to complete the alcoholysis of triazinyl esters.[20] We recently developed a new esterifying reagent, DMT-3,5-LUT, by modifying the *tert*-amine moiety in DMT-MM.[25] DMT-3,5-LUT contains 3,5-lutidine as a nucleophilic catalyst for acyl transfer instead of the *N*-methylmorpholine (NMM) in DMT-MM. In contrast to DMT-MM, DMT-3,5-LUT provided esters from near-equimolar amounts of carboxylic acids and alcohols, although moderate yields and long reaction times (>24 h) were observed for the relatively low-reactive carboxylic acids, such as benzoic acid. Since DMAP is a superior acyl transfer catalyst to 3,5-lutidine, we attempted to introduce DMAP into the triazine core at the early development stage of the various reagents. Unfortunately, esterification using DMT-DMAP (Fig. 2) proceeded only in low yield.[21] This was attributed to the decreased electrophilicity of the triazine moiety, which was stabilized by strong electron donation from the dimethylamino group in the DMAP moiety. Our recent alternative approach toward DMT-MM modification is the transformation of the triazine core. Studies on triazine-based acid-catalyzed alkylating reagents indicated that "isomerization" of the core structure, from a (dialkoxy)triazine to an (alkoxy)triazinone or triazinedione, increases the electron deficiency of the triazine moiety.[28–31] Thus, *N*-alkyl groups were introduced to fix the isomerized triazinone and triazinedione cores. In particular, the *N*-allyl group is preferred because of its synthetic accessibility. Triazinone-based dehydrative condensing reagent **2** exhibited higher reactivity than DMT-MM in amide-forming reactions.[26] On the other hand, synthesis of triazinedione-based reagent **3** was unsuccessful, despite its predicted potent reactivity.

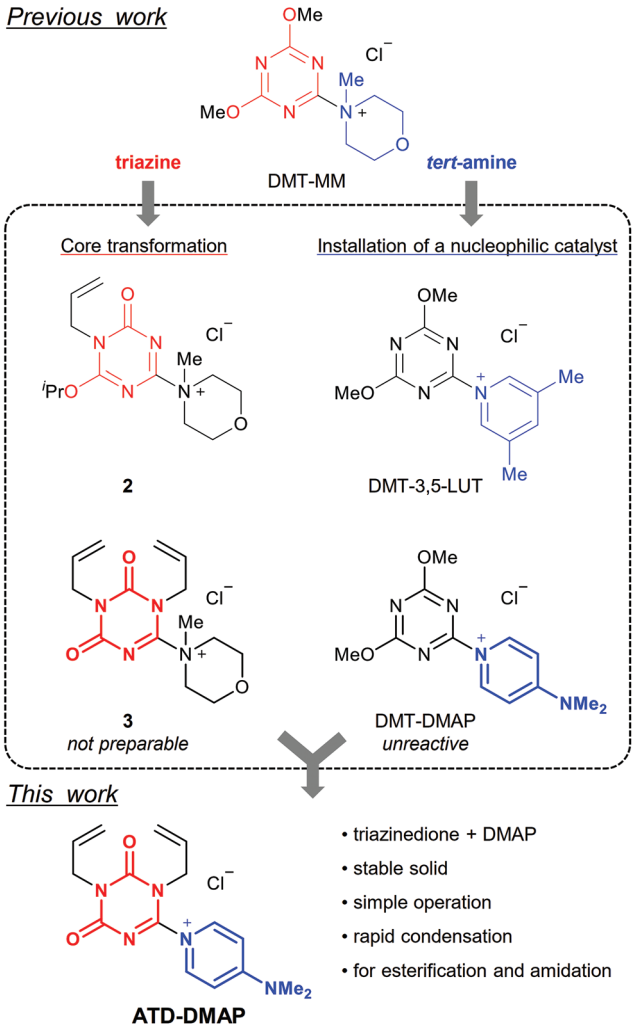
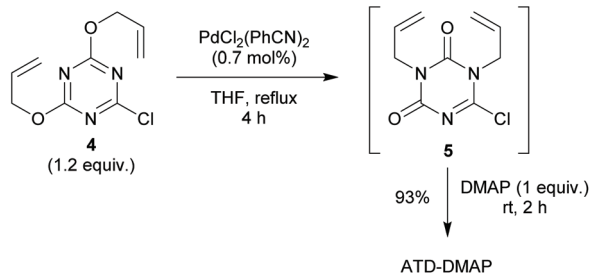
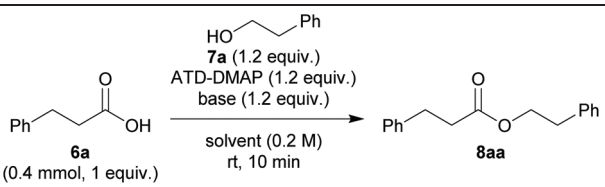


Fig. 2 Design of a new triazinedione-based dehydrative condensing reagent containing DMAP.



Scheme 1 Synthesis of ATD-DMAP.

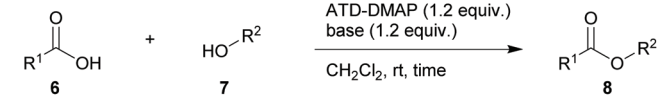
Table 1 Screening of bases and solvents for esterification using ATD-DMAP

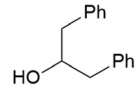
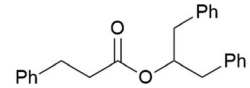
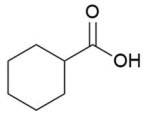
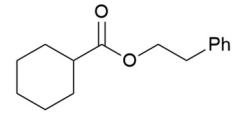
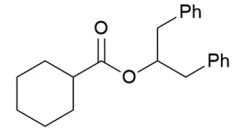
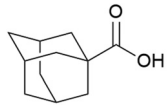
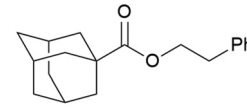
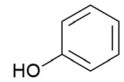
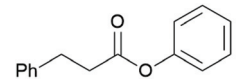
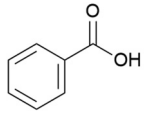
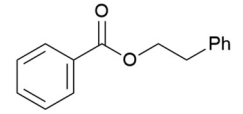
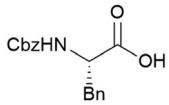
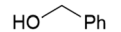
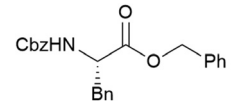
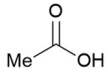
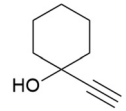
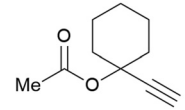


Entry	Base	Solvent	Yield[a] (%)
1	NMM	CH_2Cl_2	98
2	NMM[b]	CH_2Cl_2	82
3	None	CH_2Cl_2	5
4	DMAP	CH_2Cl_2	98
5	$^{i}Pr_2EtN$	CH_2Cl_2	97
6	DBU	CH_2Cl_2	93
7	$NaHCO_3$	CH_2Cl_2	44 (80)[c]
8	NMM	$CHCl_3$	99
9	NMM	MeCN	97
10	NMM	THF	97
11	NMM	EtOAc	96
12	NMM	DMF	95

[a] Calculated from ^{1}H NMR spectroscopic analysis using an internal standard. [b] NMM (0.6 equiv.) was used. [c] Reaction time of 30 min.

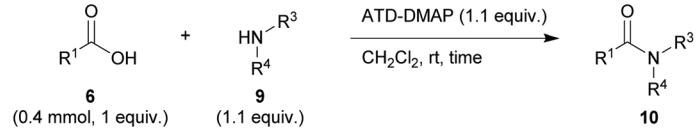
Table 2 Esterification between various carboxylic acids and alcohols using ATD-DMAP



Entry	Carboxylic acid	Alcohol	Base	Time	Product	Yield[a] (%)
1	**6a**	 **7b**	NMM	10 min	 **8ab**	89
2	 **6b**	**7a**	NMM	10 min	 **8ba**	94
3	**6b**	**7b**	NMM	10 min	 **8bb**	83
4	**6b**	**7b**	$^{i}Pr_2EtN$	10 min	**8bb**	93
5	 **6c**	**7a**	$^{i}Pr_2EtN$	24 h	 **8ca**	36
6[b]	**6c**	**7a**	NMM	20 min	**8ca**	83
7	**6a**	 **7c**	NMM	10 min	 **8ac**	86
8	 **6d**	**7a**	NMM	10 min	 **8da**	94
9	 **6e**	 **7d**	NMM	10 min	 **8ed**	Quant. >99%ee
10[c]	 **6f**	 **7e**	NMM (2 equiv.)	30 h	 **8fe**	64

[a] Isolated yield. [b] Reaction was carried out at 130 °C (microwave). [c] Reaction was carried out using **6f** (2 equiv.), **7e** (1 equiv.), and ATD-DMAP (1.5 equiv.) in the presence of 4A molecular sieves.

Table 3 Amidation between various carboxylic acids and amines using ATD-DMAP



6 (0.4 mmol, 1 equiv.) + **9** (1.1 equiv.) → **10**

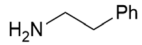
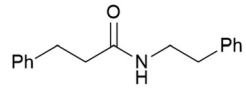
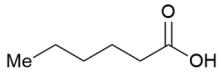
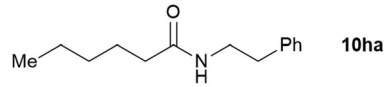
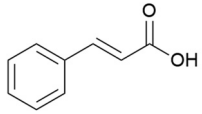
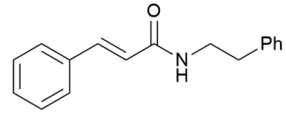
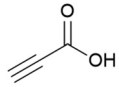
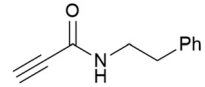
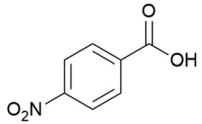
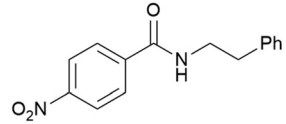
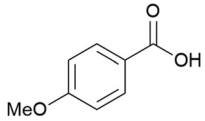
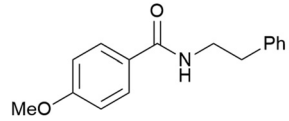
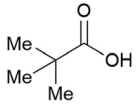
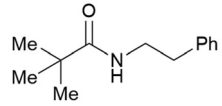
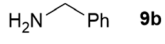
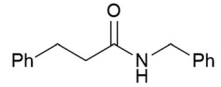
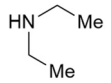
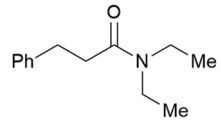
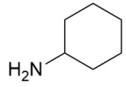
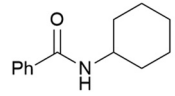
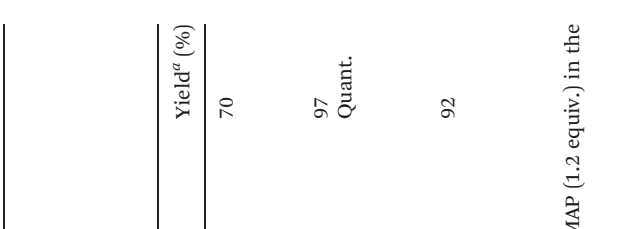
Entry	Carboxylic acid	Amine	Time	Product	Yield[a] (%)
1	**6a**	 **9a**	10 min	 **10aa**	93
2	 **6h**	**9a**	10 min	 **10ha**	98
3	 **6i**	**9a**	10 min	 **10ia**	93
4	 **6j**	**9a**	10 min	 **10ja**	81
5	 **6k**	**9a**	10 min	 **10ka**	91
6	 **6l**	**9a**	10 min	 **10la**	92
7	 **6m**	**9a**	10 min	 **10ma**	28
8	**6m**	**9a**	3 h	**10ma**	91
9	**6a**	 **9b**	10 min	 **10ab**	94
10	**6a**	 **9c**	10 min	 **10ac**	Quant.
11	**6d**	 **9d**	10 min	 **10dd**	Quant.

Table 3 *(Contd.)*



Entry	Carboxylic acid	Amine	Time	Product	Yield[a] (%)
12[b]	**6a**	**9e**	10 min	**10ae**	70
13[b]	**6a**	**9e**	3 h	**10ae**	97
14[c]	**6n**	**9f**	10 min	**10nf**	Quant.
15[d]	**6e**	**9g**	15 min	**10eg**	92

[a] Isolated yield. [b] Reaction was carried out using **9e** (1 equiv.). [c] Reaction was carried out using **6n** (1.1 equiv.) and **9f** (1 equiv.). [d] Reaction was carried out using ATD-DMAP (1.2 equiv.) in the presence of Et_3N (1.1 equiv.).

Results and discussion

A new dehydrative condensing reagent was designed by merging the two concepts for DMT-MM modification described in Fig. 2, whereby installation of DMAP to the ATD core led to ATD-DMAP. ATD-DMAP was synthesized by adding DMAP (1 equiv.) to a THF solution of chlorotriazinedione **5** (Scheme 1), which was prepared in a flask *via* the Pd-catalyzed *O*-to-*N* allylic rearrangement of bis(allyloxy)triazine **4** (1.2 equiv.) according to our previously described procedure.[31] The precipitate was collected to afford ATD-DMAP as a stable white solid in 93% yield. The product can be stored for more than six months in a refrigerator and handled in open air at room temperature.

Following the general esterification procedure using DMT-3,5-LUT,[25] ATD-DMAP (1.2 equiv.) was added to a solution of 3-phenylpropionic acid (**6a**, 1 equiv.), 2-phenylethanol (**7a**, 1.2 equiv.), and NMM (1.2 equiv.) in CH_2Cl_2 at room temperature. The reaction was completed within 10 min to afford the corresponding ester **8aa** in 98% yield (entry 1, Table 1). When the amount of NMM was decreased (0.6 equiv.), the product was obtained in 82% yield after 10 min (entry 2). The reaction proceeded very sluggishly in the absence of NMM (5%, entry 3), indicating that as a base NMM plays an important role in promoting esterification. Other organic bases such as DMAP, $^{i}Pr_2EtN$, and DBU afforded ester **8aa** in 93–98% yield (entries 4–6). The yield of **8aa** decreased to 44% when using $NaHCO_3$ as a heterogeneous inorganic base; however, a longer reaction time (30 min instead of 10 min) improved the yield to 80% (entry 7). The reactions using NMM (1.2 equiv.) also proceeded in other common organic solvents, such as $CHCl_3$, MeCN, THF, EtOAc, and DMF, without any significant loss in the product yield (entries 8–12, respectively).

We next carried out esterification reactions between various carboxylic acids and alcohols using ATD-DMAP (Table 2). Esterification of **6a** with secondary alcohol **7b** (entry 1), cyclohexanecarboxylic acid (**6b**) with **7a** (entry 2), and **6b** with **7b** (entry 3) under the standard reaction conditions (NMM, rt, 10 min) afforded the corresponding esters in 89, 94, and 83% yield, respectively. Notably, the yield of **8bb** improved to 93% when $^{i}Pr_2EtN$ was used as the base (entry 4). The reaction of sterically hindered 1-adamantanecarboxylic acid (**6c**) with **7a** afforded **8ca** in 36% yield, even after 24 h in the presence of $^{i}Pr_2EtN$ (entry 5). A higher yield (83%) was obtained under microwave irradiation conditions (130 °C, 20 min) using NMM as the base (entry 6). Both the esterification reactions of **6a** with phenol (**7c**, entry 7) and benzoic acid (**6d**) with **7a** (entry 8) proceeded in 86–94% yield under the standard reaction conditions. α-Chiral carboxylic acid **6e** (entry 9) was converted to the corresponding benzyl ester **8ed** in quantitative yield without loss in enantiomeric purity. Acetylation of the tertiary alcohol **7e** (1 equiv.) proceeded in 64% yield when using excess ATD-DMAP (1.5 equiv.) and NMM (2 equiv.) in the presence of 4A molecular sieves to remove any residual moisture in the reaction mixture (entry 10).

ATD-DMAP can also be used for amide-forming coupling reactions between carboxylic acids and amines (Table 3). The dehydrative condensation of **6a** (1 equiv.) and 2-phenylethylamine (**9a**, 1.1 equiv.) using ATD-DMAP (1.1 equiv.) in CH_2Cl_2 at room temperature afforded the corresponding amide **10aa** in 93% yield after 10 min (entry 1). Under the same reaction conditions, aliphatic (**6h**), α,β-unsaturated (**6i,j**), and aromatic (**6k,l**) carboxylic acids provided the desired amides in 81–98% yield (entries 2–6, respectively). Although the reaction of pivalic acid (**6m**) proceeded slowly (28% after 10 min, entry 7), the yield reached 91% after 3 h (entry 8). Amidation of **6a** with benzylamine (**9b**, entry 9) and diethylamine (**9c**, entry 10) afforded the product in 94–100% yield. Similarly, amide **10dd** was obtained from **6d** and cyclohexylamine (**9d**) in quantitative yield (entry 11). The reaction of aniline (**9e**, 1 equiv.) was completed after 3 h (70% after 10 min, entry 12; 97% after 3 h, entry 13). *N*-Acetylation of L-phenylalanine methyl ester hydrochloride (**9f**, 1 equiv.) was carried out using sodium acetate (**6n**, 1.1 equiv.) to afford **10nf** in quantitative yield (entry 14). Amidation between Cbz-L-Phe-OH (**6e**) and L-Ala-OMe hydrochloride (**9g**) in the presence of Et_3N afforded dipeptide **10eg** in 92% yield (entry 15), under slightly modified conditions [(ATD-DMAP (1.2 equiv.), 15 min)]. Racemization of the phenylalanine moiety in **10eg** was not detected in ^1H NMR spectrum of the crude mixture (Fig. S1 and S2†).

To compare the effect of the reagent core structure, we next prepared triazinone-based reagent **12** containing DMAP from chlorotriazinone **11**[26] (Fig. 3a). Treatment of a mixture of **6a** and **9a** with **12** provided the corresponding amide **10aa** in 5% yield based on **6a**, along with aminotriazinone **13** in 75% yield based on **12** after 3 h (Fig. 3b). This result suggests that the triazinone core of **12** reacts with amines faster than with carboxylates, whereas the more reactive triazinedione core of ATD-DMAP reacts selectively with carboxylates in the presence of amines (Table 3, entry 1). The reason for this selectivity difference is unclear at present.

Tables 2 and 3 reveal that esterification and amidation using ATD-DMAP were completed rapidly (within 10 min in most cases), attributed to the formation of a highly reactive *N*-acylpyridinium intermediate in the reaction mixture. Fig. 4 illustrates the plausible reaction mechanism of ATD-DMAP: the triazinedione electrophilic carbon in ATD-DMAP is attacked by carboxylate **14**, which is formed by deprotonation of carboxylic acid **6** with NMM (esterification) or amine **9** (amidation), to afford activated ester **15**. The DMAP liberated from ATD-DMAP then reacts with **15** to form *N*-acylpyridinium intermediate **16** paired with the cyanurate anion. Alcoholysis or aminolysis of this intermediate with alcohol **7** or amine **9** affords the corresponding ester **8** or amide **10**, respectively, along with *N*,*N*′-diallylcyanuric acid (**17**) and DMAP. NMM or amine **9** is regenerated from the corresponding conjugated acid under acid–base equilibria with DMAP.

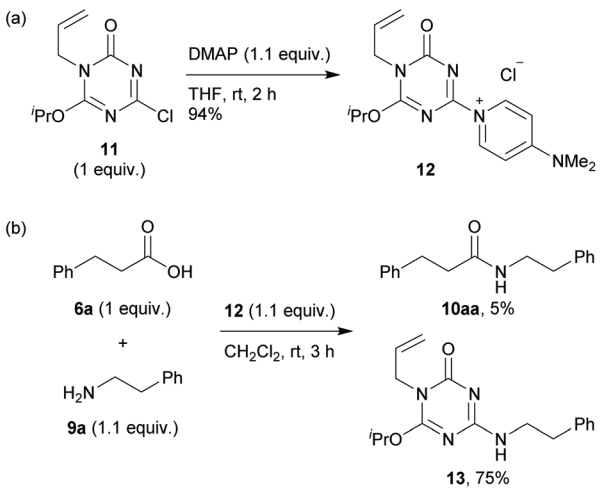


Fig. 3 (a) Preparation of triazinone-based reagent **12** containing DMAP and (b) attempted amidation using **12**.

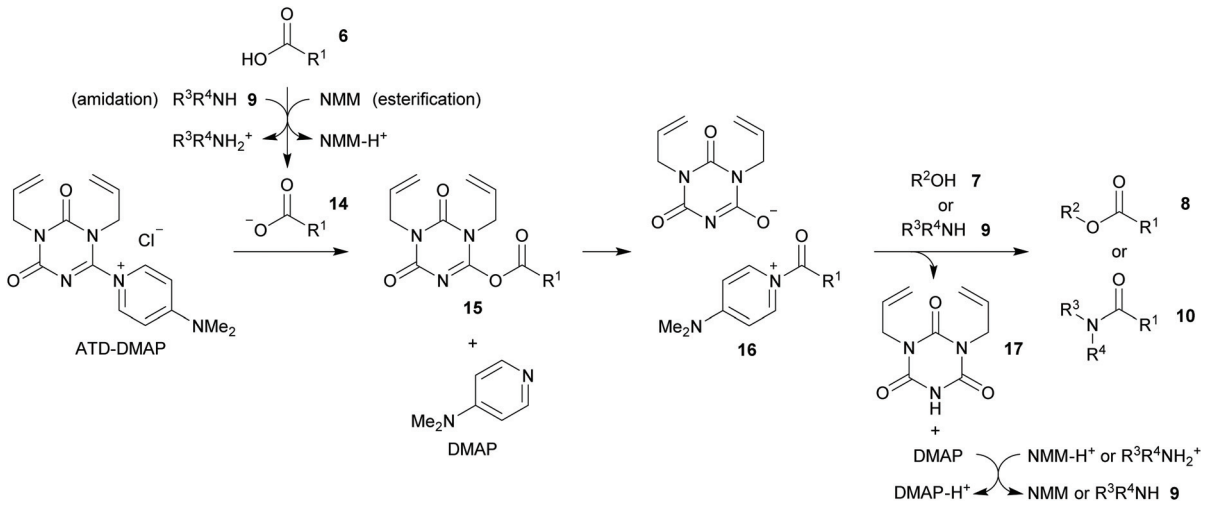


Fig. 4 Plausible reaction mechanism for esterification and amidation using ATD-DMAP.

DMAP did not efficiently catalyze the transfer reaction of bulky acyl groups such as the pivaloyl group.[32] This is consistent with the fact that the esterification of **6c** (Table 2, entry 5) and amidation of **6m** (Table 3, entries 7 and 8) using ATD-DMAP proceeded slowly under the standard conditions. In both these cases, we supposed that the products formed directly from the reaction between activated ester **15** and the corresponding nucleophiles.

Conclusions

We developed a new triazinedione-based dehydrative condensing reagent, ATD-DMAP. The advantages of this reagent include its easy handling, simple experimental operation, and short reaction time. The DMAP contained in this reagent is designed to work as both an *in situ*-formed nucleophilic catalyst and a leaving group on the triazinedione core. ATD-DMAP exhibited powerful reactivity both in the esterification and amidation of carboxylic acids and a variety of esters and amides were obtained in high yield using this dehydrative condensing reagent.

Author contributions

J. Liu, H. Fujita and M. Kitamura: writing–original draft. J. Liu and H. Fujita: data curation. J. Liu and D. Shimada: investigation. H. Fujita and M. Kunishima: writing–review and editing. M. Kitamura: methodology. M. Kunishima: conceptualization, supervision, funding acquisition.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 J. Otera and J. Nishikido, *Esterification*, Wiley-VCH, Weinheim, 2009.
2 A. Parenty, X. Moreau, G. Niel and J.-M. Campagne, *Chem. Rev.*, 2013, **113**, PR1–PR40.
3 P. Siengalewicz, J. Mulzer and U. Rinner, in *Comprehensive Organic Synthesis II (Second Edition)*, ed. P. Knochel and G. A. Molander, Elsevier, Amsterdam, 2nd edn, 2014, vol. 6, pp. 355–410. 6.09 Synthesis of Esters and Lactones.
4 M. Tsakos, E. S. Schaffert, L. L. Clement, N. L. Villadsen and T. B. Poulsen, *Nat. Prod. Rep.*, 2015, **32**, 605–632.
5 K. Matsumoto, R. Yanagi and Y. Oe, in *Carboxylic Acid - Key Role in Life Sciences*, ed. G.-I. Badea and G. L. Radu, IntechOpen, Rijeka, 2018, ch. 2.
6 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522–524.
7 A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, **19**, 4475–4478.
8 I. Shiina, R. Ibuka and M. Kubota, *Chem. Lett.*, 2002, **31**, 286–287.
9 G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem.*, 1978, **90**, 602–615.
10 G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569–583.
11 E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129–161.
12 A. C. Spivey and S. Arseniyadis, *Angew. Chem., Int. Ed.*, 2004, **43**, 5436–5441.
13 E. Larionov and H. Zipse, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2011, **1**, 601–619.
14 N. De Rycke, F. Couty and O. R. P. David, *Chem. – Eur. J.*, 2011, **17**, 12852–12871.
15 A. Arrieta, T. García and C. Palomo, *Synth. Commun.*, 1982, **12**, 1139–1146.
16 T. Gallagher, in *Encyclopedia of Reagents for Organic Synthesis*, ed. A. B. Charette, John Wiley & Sons, Chichester, 2001, 4-(Dimethylamino)pyridinium Chlorosulfite Chloride. DOI: 10.1002/047084289X.rd312.
17 Y. Okuno, S. Isomura, A. Nishibayashi, A. Hosoi, K. Fukuyama, M. Ohba and K. Takeda, *Synth. Commun.*, 2014, **44**, 2854–2860.
18 M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao and S. Tani, *Tetrahedron Lett.*, 1999, **40**, 5327–5330.
19 M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, 1999, **55**, 13159–13170.
20 M. Kunishima, J. Morita, C. Kawachi, F. Iwasaki, K. Terao and S. Tani, *Synlett*, 1999, 1255–1256.
21 M. Kunishima, T. Ujigawa, Y. Nagaoka, C. Kawachi, K. Hioki and M. Shiro, *Chem. – Eur. J.*, 2012, **18**, 15856–15867.
22 M. Kunishima, M. Kitamura, H. Tanaka, I. Nakakura, T. Moriya and K. Hioki, *Chem. Pharm. Bull.*, 2013, **61**, 882–886.
23 M. Kunishima, D. Kato, N. Kimura, M. Kitamura, K. Yamada and K. Hioki, *Beilstein J. Org. Chem.*, 2016, **12**, 1897–1903.
24 M. Kitamura, S. Sasaki, R. Nishikawa, K. Yamada and M. Kunishima, *RSC Adv.*, 2018, **8**, 22482–22489.
25 K. Yamada, J. Liu and M. Kunishima, *Org. Biomol. Chem.*, 2018, **16**, 6569–6575.
26 K. Yamada, M. Kota, K. Takahashi, H. Fujita, M. Kitamura and M. Kunishima, *J. Org. Chem.*, 2019, **84**, 15042–15051.
27 M. Kitamura, S. Komine, K. Yamada and M. Kunishima, *Tetrahedron*, 2020, **76**, 130900.
28 H. Fujita, N. Hayakawa and M. Kunishima, *J. Org. Chem.*, 2015, **80**, 11200–11205.

29 M. Kunishima, R. Asao, K. Yamada, M. Kitamura and H. Fujita, *J. Fluor. Chem.*, 2016, **190**, 68–74.
30 H. Fujita, S. Kakuyama and M. Kunishima, *Eur. J. Org. Chem.*, 2017, 833–839.
31 H. Fujita, R. Yamashita, T. Fujii, K. Yamada, M. Kitamura and M. Kunishima, *Eur. J. Org. Chem.*, 2019, 4436–4446.
32 C. B. Fischer, S. Xu and H. Zipse, *Chem. – Eur. J.*, 2006, **12**, 5779–5784.