Note

N-Acyltriazinedione; a Novel Acylating Reagent Synthesized from a Triazinone-Type Condensing Reagent

Kohei Yamada,[†] Jeongsu Lee, Mika Kota, Yukiko Karuo, Masanori Kitamura,[‡] and Munetaka Kunishima*

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

Received November 26, 2020; accepted February 1, 2021

In this paper, we report the synthesis of *N*-acyltriazinedione via the unexpected *O*–*N* acyl rearrangement of acyloxytriazinone and its utility as an acylating reagent. *N*-Acyltriazinedione can be isolated by silica gel column chromatography and reacts with amines in the absence of any base to give the corresponding amides in good yields.

Key words acylating reagent; triazinedione; *O*–*N* acyl rearrangement

Introduction

The condensation of carboxylic acids and amines using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) involves two steps: the formation of an acyloxytriazine intermediate, which is the rate-determining step in the condensation, and aminolysis^{1–3} (Chart 1(A)). Recently, we reported that triazinone-based condensing reagent **1X** exhibits superior reactivity to DMT-MM because the electrophilicity of **1X** is enhanced compared to DMT-MM⁴ (Chart 1(B)). On the other hand, according to the calculation study of the sequential tautomerization of cyanuric acid to isocyanuric acid^{5,6} and the studies of triazine-, triazinedione-based benzylating reagents, 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT),⁷ and 6-(benzyloxy)-1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (DMBOT),⁸ the aminolysis of acyloxytriazinone, which is an intermediate derived from **1X**, is considered to be faster than that of the corresponding acyloxytriazine. To investigate the reactivity of acyloxytriazinone toward aminolysis, we attempted to isolate it using **1** and carboxylic acids **2** without an amine as a coupling partner (Chart 1(C)). Unexpectedly, *N*-acyltriazinedione **3**, which can be produced via *O*–*N* acyl rearrangement, was obtained and was found to show acylating ability (*vide infra*). The structure of *N*-acyltriazinedione was confirmed by X-ray crystallography using **3X-a** synthesized with *p*-bromobenzoic acid **2a**⁹ (Table 1, entry 9). It has been reported that when 2-benzyloxy-4,6-dimethoxy-1,3,5-triazine is reacted at 100 °C in toluene, benzoyl group and two methyl groups can be transferred to the nitrogen atoms of the triazine ring to produce *N*-benzoyl-*N'*,*N''*-dimethyltriazinedione.¹⁰ However, the acylating ability of the product was not referred. Dicyclohexylcarbodiimide (DCC) has been reported to proceed via a similar *O*–*N* acyl rearrangement from the *O*-acylisourea intermediate to form *N*-acylurea, which does not have an acylating ability.^{11,12} Several acylating reagents possessing an amide moiety such as *N*-

acylimidazoles,¹³ *N*-acylureas,¹⁴ *N*-acylsuccinimides,^{15,16} and *N*-acylbenzotriazoles¹⁷ have also been reported. However, it is necessary to activate a carboxylic acid by using a condensing reagent to introduce each leaving group. In the case of our new reagent, synthesis of the corresponding acylating reagent is easy because the condensing reagent itself is converted to the leaving group moiety of the amide-type acylating reagent. In this paper, we describe the synthesis and reaction of *N*-acyltriazinediones.

Results and Discussion

To investigate the stability and reactivity of *N*-acyltriazinedione, we attempted to synthesize *N*-acyltriazinedione **3** using condensing reagent **1X** in the presence of a catalytic amount of *N*-methylmorpholine (NMM). Moreover, the synthesis *via in situ* generation of the condensing reagents from chlorotriazinone **1X'** or its analogue **1Y'** possessing dimethylamino group instead of the isopropoxy group by the reaction with 1.2 equivalents (equiv.) of NMM was also investigated (Table 1). The reaction of 3-phenylpropionic acid **2b** with **1X**, **1X'**, and **1Y'** smoothly proceeded to produce **3X-b** and **3Y-b** in yields of 82, 95, and 77%, respectively (entries 1–3). The reaction of racemic naproxen **2c** as a secondary carboxylic acid and bulky adamantane-1-carboxylic acid **2d** as a tertiary carboxylic acid proceeded to give the corresponding *N*-acyltriazinediones **3X-c** and **3X-d**, respectively, in good yields (entries 4, 5). Aromatic carboxylic acid derivatives **3X-e**, **3X-f**, and **3X-a** were also prepared (entries 6–9).

Acylation of several amines **4** (1.0 equiv.) using *N*-acyltriazinedione **3** (1.1 equiv.) was conducted without any base in tetrahydrofuran (THF) or MeOH (Table 2). Reaction of **3X-b** with 2-phenylethylamine **4a** afforded the corresponding amide **5ba** in good yield (in THF: 3 h, 84%, in MeOH: 1.5 h, 97%, entries 1, 2). *N*-Acyltriazinedione with dimethylamino group **3Y-b** also gave the product (entry 3). Polar amine **4b** and secondary amine **4c** afforded the corresponding amides (entries 4 and 5, respectively), whereas aromatic amine **4d** did not yield the amide owing to its low nucleophilicity (entry 6). The reaction of *N*-adamantanoyltriazinedione **3X-d** with **4a** required a prolonged reaction time (entries 9, 10), whereas

[†]Present address: Faculty of Pharmaceutical Sciences, Nagasaki International University; Nagasaki 859–3298, Japan.

[‡]Present address: Faculty of Pharmaceutical Sciences, Matsuyama University; Matsuyama, Ehime 790–8578, Japan.

*To whom correspondence should be addressed. e-mail: kunishima@p.kanazawa-u.ac.jp

Chart 1. Triazine-Type and Triazinone-Type Condensing Reagents

Table 1. Synthesis of *N*-Acyltriazenedione **3**

Method A: 1X (1.1 equiv.), NMM (0.2 equiv.) Method B: 1X' or 1Y' (1.1 equiv.), NMM (1.2 equiv.)					
Entry	1	2	Time	3	Yield
1	1X	2b 	2 h	3X-b	82%
2	1X'	2b	30 min	3X-b	95%
3	1Y'	2b	2 h	3Y-b	77%
4	1X'	2c 	2 h	3X-c	92%
5	1X	2d 	30 min	3X-d	quant.
6	1X	2e 	1 h	3X-e	91%
7	1X	2f 	1.5 h	3X-f	92%
8	1X'	2f	4.5 h	3X-f	81%
9 ^{a)}	1X'	2a 	30 min	3X-a	68%

^{a)} The yield was not optimized.

Table 2. Scope and Limitation of the Substrate for Acylation with *N*-Acyltriazinedione **3**

Entry	3	4	Solvent, time	5	Yield
1	3X-b	4a	THF, 3 h	5ba 	84%
2	3X-b	4a	MeOH, 1.5 h	5ba	97%
3	3Y-b	4a	MeOH, 20 min	5ba	84%
4	3X-b	4b	MeOH, 30 min	5bb 	Quant.
5	3X-b	4c	MeOH, 30 min	5bc 	93%
6	3X-b	4d	MeOH, 2 h	5bd 	0%
7	3X-c	4a	MeOH, 10 min	5ca 	91%
8	3X-c	4c	MeOH, 1.5 h	5cc 	82%
9	3X-d	4a	THF, 93 h	5da 	78%
10	3X-d	4a	MeOH, 40 h	5da	84%
11	3X-e	4a	THF, 5 h	5ea 	91%
12	3X-e	4a	MeOH, 1.5 h	5ea	96%
13	3X-e	4c	MeOH, 24 h	5ec 	81%
14	3X-f	4a	THF, 1.5 h	5fa 	71%
15	3X-f	4a	MeOH, 30 min	5fa	Quant.
16 ^{a)}	3X-c	BnOH	THF, 48 h	6 	71%

^{a)} The reaction was conducted in the presence of DMAP (10 mol%) and *N,N*-diisopropylethylamine (DIPEA) (1.1 equiv.) at 0 °C.

Chart 2. Synthesis and Reaction of Amino Acid Type *N*-Acyltriazinedione Chart 3. Amidation of Benzoic Acid **2e** and Phenethylamine **4a** Using **1X** with/without Waiting Time of 30 min

the triazinedione composed of a secondary acyl group **3X-c** smoothly underwent the reaction with **4a** (entries 7, 8). The aromatic amides were obtained when *N*-acyltriazinediones derived from aromatic carboxylic acids were used (entries 11–15). Methanolysis of *N*-acyltriazinedione **3X-b** was not observed even in the reaction with low-nucleophilic aniline in methanol (entry 6). However, in the presence of *N,N*-dimethyl-4-aminopyridine (DMAP) and Hünig's base, *O*-acylation of benzyl alcohol with *N*-acyltriazinedione was accomplished in a 71% yield (entry 16).

Storable *N*-protected amino acid based acylating reagents are desired because the automated peptide synthesis operation can be simplified.¹⁷⁾ Therefore, we attempted to synthesize *N*-acyltriazinedione using benzyloxycarbonyl (Cbz)-phenylalanine **2g**. When **2g** was reacted with **1X'** and NMM in CH_2Cl_2 at -40°C , the desired **3X-g** was obtained in a 70% yield with 98%*ee* (Chart 2(A)). Further investigation of the reaction conditions failed to improve the optical purity (Supplementary Material Table S1). Next, acylation was conducted using **3X-g** with 90%*ee* and alanine methyl ester hydrochloride **4e** in the

presence of NMM as a proton scavenger (Chart 2(B)). When MeOH was used, the desired dipeptide (**5ge**) was obtained without loss of the optical purity. Other solvents, such as THF, CH_3CN , CH_2Cl_2 , and *N,N*-dimethylformamide (DMF) resulted in partial racemization, although the yields improved (Supplementary Material Table S2).¹⁸⁾ For use as a practical peptide synthesis reagent, further study is needed to improve the yield and optical purity by modification of the substituents on the triazinedione core.

Acylation of **4a** using *N*-benzoyltriazinedione **3X-e** requires a longer reaction time (in THF: 5 h, in MeOH: 1.5 h, Table 2, entries 11, 12, respectively) compared with the condensation of benzoic acid **2e** and **4a** using triazinone-type condensing reagent **1X** (in THF with triethylamine: 10 min, in MeOH with NMM: 10 min).⁴⁾ To investigate if either acyloxytriazinone or *N*-acyltriazinedione is the true active intermediate in the condensation using **1X**, time-course analyses were performed. The reaction was initiated by the addition of **1X** to a THF solution of **2e**, **4a**, and triethylamine (Chart 3(A)). Aliquots of the reaction mixture were withdrawn at appropriate intervals

and analyzed by ^1H -NMR spectroscopy using coumarin as the internal standard. As a result, 10 min after the initiation of the reaction, product **5ea** was observed in a yield of 95%, and reaction was completed at 30 min (triangles). Next, the reaction, which was designed to proceed through *N*-acyltriazinedione, was also conducted (Chart 3(B)). After the reaction of **2e** and **1X** for 30 min, at this point, a significant amount of acyloxytriazinone is thought to have been converted to **3X-e** by the *O*-*N* acyl rearrangement, **4a** was added. In contrast to the former reaction, the yield of the latter reaction was obviously lower. Then, 10 min after addition of **4a**, product **5ea** was observed in a yield of 66%, and it required 3 h to reach 93% yield (dots). These results indicate that when the condensation was carried out using **1X** in the presence of a carboxylic acid and an amine, the reaction would proceed *via* the more reactive initial intermediate acyloxytriazinone.

Conclusion

We found that the initial intermediate, acyloxytriazinone, which was synthesized from triazinone-type condensing reagent **1** and a carboxylic acid, was immediately converted to *N*-acyltriazinedione **3** *via* a *O*-*N* acyl rearrangement. *N*-Acyltriazinedione **3** was stable enough to isolate by silica gel column chromatography and can be used as an acylating reagent in protic and aprotic solvents.

Experimental

General Methods NMR (^1H -NMR (400, 500 or 600 MHz), ^{13}C -NMR (100 or 150 MHz)) spectra were determined on a JEOL JNM-ECS400 spectrometer, a JEOL JNM-ECZ500R spectrometer, and JEOL JNM-ECS600 spectrometer. Chemical shifts for ^1H -NMR are reported as δ values relative to tetramethylsilane as the internal standard for CDCl_3 , and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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 CDCl_3 . MS were measured on JMS-T100TD (electrospray ionization-time-of-flight (ESI-TOF)) and JMS-SX102A (FAB). Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F₂₅₄. Flash chromatography separations were performed on KANTO CHEMICAL (Tokyo, Japan) Silica Gel 60N (spherical, neutral, 40–100 mesh) unless otherwise noted. Reagents were commercial grades and were used without any purification unless otherwise noted. All re-

actions sensitive to oxygen or moisture were conducted under a N_2 atmosphere.

Acknowledgments This work was partially supported by JSPS KAKENHI Grant No. 19K06995, 17H03970.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

References and Notes

- 1) Kunishima M., Kawachi C., Iwasaki F., Terao K., Tani S., *Tetrahedron Lett.*, **40**, 5327–5330 (1999).
- 2) Kunishima M., Kawachi C., Morita J., Terao K., Iwasaki F., Tani S., *Tetrahedron*, **55**, 13159–13170 (1999).
- 3) Kunishima M., Kawachi C., Hioki K., Terao K., Tani S., *Tetrahedron*, **57**, 1551–1558 (2001).
- 4) Yamada K., Kota M., Takahashi K., Fujita H., Kitamura M., Kunishima M., *J. Org. Chem.*, **84**, 15042–15051 (2019).
- 5) Liang X., Zheng W., Wong N.-B., Li J., Tian A., *J. Mol. Struct. THEOCHEM.*, **672**, 151–159 (2004).
- 6) Liang X., Pu X., Zhou H., Wong N.-B., Tian A., *J. Mol. Struct. THEOCHEM.*, **816**, 125–136 (2007).
- 7) Yamada K., Fujita H., Kunishima M., *Org. Lett.*, **14**, 5026–5029 (2012).
- 8) Fujita H., Kakuyama S., Kunishima M., *Eur. J. Org. Chem.*, **2017**, 833–839 (2017).
- 9) CCDC 2046282 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.
- 10) Kamiński Z. J., Głowska M. L., Olczak A., Martynowski D., *Pol. J. Chem.*, **70**, 1316–1323 (1996).
- 11) Kurzer F., Douraghi-Zadeh K., *Chem. Rev.*, **67**, 107–152 (1967).
- 12) Hegarty A. F., McCormack M. T., Ferguson G., Roberts P. J., *J. Am. Chem. Soc.*, **99**, 2015–2016 (1977).
- 13) Fujishima S., Yasui R., Miki T., Ojida A., Hamachi I., *J. Am. Chem. Soc.*, **134**, 3961–3964 (2012).
- 14) Sola R., Sagner P., David M.-L., Pascal R., *J. Chem. Soc. Chem. Commun.*, **1993**, 1786–1788 (1993).
- 15) Boyd H., Calder I. C., Leach S. J., Milligan B., *Int. J. Pept. Protein Res.*, **4**, 109–115 (1972).
- 16) Goodman C. A., Eagles J. B., Rudahindwa L., Hamaker C. G., Hitchcock S. R., *Synth. Commun.*, **43**, 2155–2164 (2013).
- 17) Katritzky A. R., Angrish P., Todadze E., *Synlett*, **15**, 2392–2411 (2009).
- 18) Kunishima M., Kitao A., Kawachi C., Watanabe Y., Iguchi S., Hioki K., Tani S., *Chem. Pharm. Bull.*, **50**, 549–550 (2002).