A new entry to the synthesis of 5-substituted 1,2,3-triazines by reaction with silyl enol ethers and ceric ammonium nitrate

Takashi Itoh, Yûji Matsuya, Hiroshi Hasegawa,[1] Kazuhiro Nagata, Mamiko Okada and Akio Ohsawa *

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan

Monocyclic 1,2,3-triazines have been allowed to react with silyl enol ether or ketene silyl acetal in the presence of 1-chloroethyl chloroformate to give 2-(1-chloroethoxycarbonyl)-5-substituted-2,5-dihydrotriazines in good yields. These dihydro adducts are oxidized by ceric ammonium nitrate in CH_3CN–H_2O to afford 5-substituted 1,2,3-triazines.

Introduction

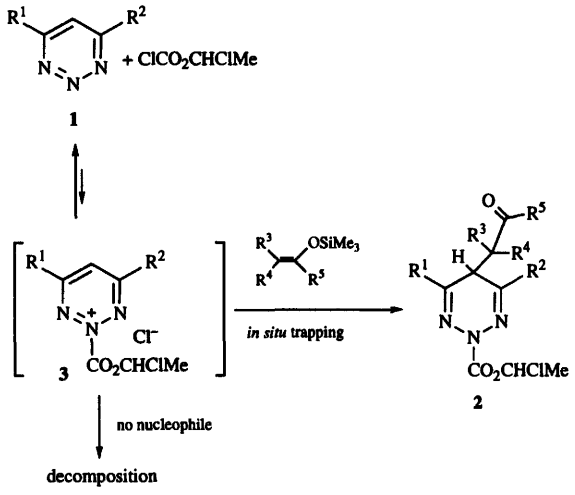
In the course of our study of monocyclic 1,2,3-triazines,[2] we found that they are highly reactive toward nucleophiles,[3] and that the reaction site is almost exclusively at the C-4 position even in the presence of a substituent at C-4[4] or a leaving group at C-5;[5] such reactions resulted in ring opening accompanied by N_2 elimination. The 1,2,3-triazine ring system was, therefore, shown to have insufficient stability for direct introduction of substituents.[6] Since most monocyclic 1,2,3-triazines have been synthesized by reaction of the corresponding *N*-aminopyrazoles with rather strong oxidants such as lead tetraacetate,[2] the substituents of *N*-aminopyrazoles are limited to those which can withstand oxidative conditions.[7] Although addition of nucleophiles was successful when 2-methyltriazinium salts were used as substrates, the 2,5-dihydro adducts thus obtained were poor intermediates for aromatized triazines.[8]

In view of these results, we focussed our interest on substituent introduction at C-5 of the triazine ring, an activating group at N-2 changing the reaction site from C-4 to C-5.[9] Although 1,2,3-triazinium 2-dicyanomethylides undergo both radical[10] and vicarious nucleophilic substitution,[11] this system was limited to these two reactions because of the instability of the dicyanomethylene group toward other nucleophiles. Thus, we have investigated alternative methods for ring activation, and found that ketene silyl acetals and silyl enol ethers reacted with 1,2,3-triazine in the presence of 1-chloroethyl chloroformate,[12] to give 2,5-dihydro adducts which upon aromatization with ceric ammonium nitrate (CAN) in CH_3CN–H_2O gave the corresponding 5-substituted triazines. This paper describes detailed results of these reactions.[13]

Results and discussion

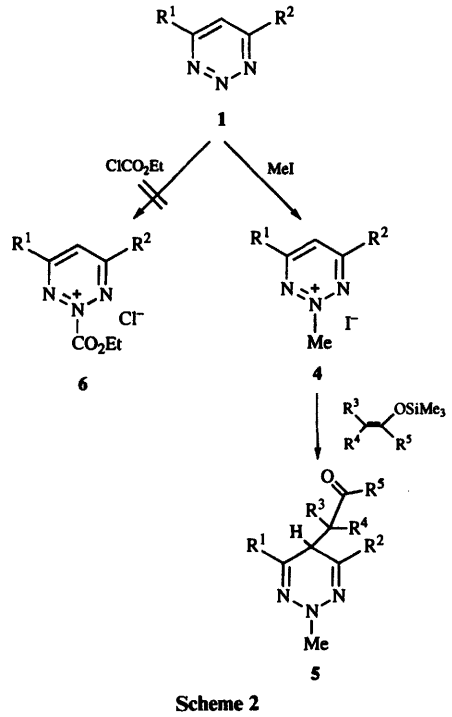
The 1,2,3-triazine **1** slowly decomposed when treated with 1-chloroethyl chloroformate in the absence of a nucleophile, giving no isolable products. Although this result indicated the instability of alkoxycarbonyl quaternary salts of triazine which may be formed *in situ*, addition of a ketene silyl acetal or a silyl enol ether to the mixture gave formation of 5-substituted 2-(1-chloroethoxycarbonyl)-2,5-dihydrotriazines **2** in good yields. The results indicate that 2-(1-chloroethoxycarbonyl)-1,2,3-triazinium salts **3** are formed in the solution in low concentration, and trapped by the silyl reagents *in situ* (Scheme 1). The yields are summarized in Table 1.

Some of the compounds **2** were obtained as rotational and/or diastereoisomeric isomers as evidenced by the NMR results. The use of ethyl chloroformate instead of 1-chloroethyl chloroformate resulted in a complete recovery of the starting material,



Scheme 1

whereas 2-methyltriazinium salts **4** were readily attacked by silyl reagents to form the corresponding 2,5-dihydro adducts **5** (Scheme 2).



Scheme 2

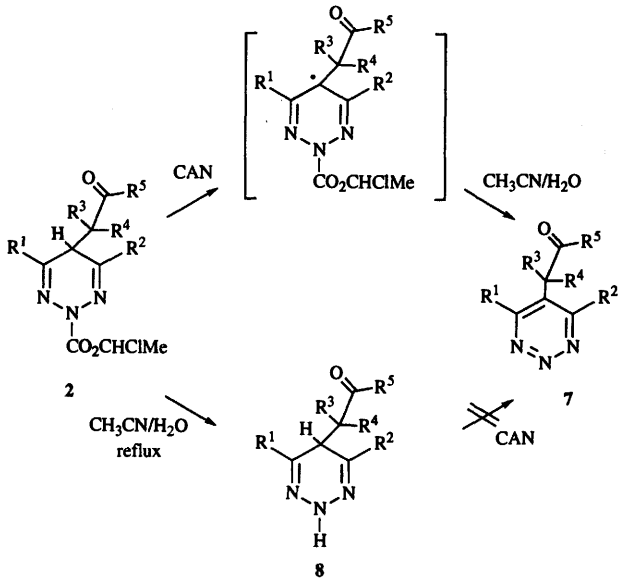
Table 1 Reaction of 1,2,3-triazines with silyl enol ethers in the presence of 1-chloroethyl chloroformate

Entry	R^1	R^2	R^3	R^4	R^5	Reaction time (h)	Product	Yield(%)
1	Me	Me	Me	Me	OMe	2.5	**2a**	88
2	Et	Et	Me	Me	OMe	3.0	**2b**	77
3	Me	Ph	Me	Me	OMe	4.0	**2c**	82
4	Ph	Ph	Me	Me	OMe	24	**2d**	75
5	Me	Me	H(Me)	Me(H)	OMe	1.5	**2e**	82
6	Et	Et	H(Me)	Me(H)	OMe	2.5	**2f**	76
7	Me	Ph	H(Me)	Me(H)	OMe	5.0	**2g**	91
8	Ph	Ph	H(Me)	Me(H)	OMe	48	**2h**	79
9	Me	Me	H	-CH=CH-O-		2.5	**2i**	87[a]
10	Et	Et	H	-CH=CH-O-		4.0	**2j**	69[a]
11	Me	Ph	H	-CH=CH-O-		23	**2k**	60[a]
12	Ph	Ph	H	-CH=CH-O-		42	**2l**	55[a]
13	Me	Me	H	H	Ph	3.5	**2m**	13[b]
14	Et	Et	H	H	Ph	48	**2n**	15[b]
15	Me	Ph	H	H	Ph	5.5	**2o**	77
16	Ph	Ph	H	H	Ph	48	**2p**	69

[a] In the cases where 2-trimethylsilyloxyfuran was used as a nucleophile, addition occurred at its 5-position to give 5-(2,5-dihydro-2-oxo-5-furyl)-2,5-dihydrotriazine derivatives. [b] In these cases, the nucleophilicity of the reagent was lower than that of the above examples, and the instability of the intermediary quaternary salts lowered the product yields.

These results indicate that the corresponding quaternary salts **6** do not exist in solution since their electrophilicity would be higher than that of **4**. In the case of 4,6-diphenyltriazine as a substrate, although the reaction proceeded slowly because of the steric hindrance arising from the two bulky substituents, the adducts were obtained in good yields (entries 4, 8, 12 and 16). These facts also suggest that the rate-limiting process in the reaction is the first quaternization step, because such an elongation of the reaction time would cause the decomposition of triazine if the second step were rate-limiting.

Compounds **2** thus obtained were treated with ceric ammonium nitrate (CAN) in CH_3CN–H_2O at room temperature to give the corresponding 5-substituted triazines **7**[14] (Scheme 3 and Table 2).



Scheme 3

Although other oxidants such as 2,3-dichloro-5,6-dicyanoquinone (DDQ), *o*- and *p*-chloranils, iodine, lead tetraacetate and sodium periodate could also be used, the product yields were much lower than those where CAN was used.

Since oxidation with CAN in the absence of water resulted in complete recovery of **2**, the reaction process must include the hydrolysis process. In fact, the 2,5-dihydro adduct **8** was obtained by the hydrolysis of **2** in CH_3CN–H_2O under reflux, but was not obtained at room temperature. In addition, the oxidation of **8** with CAN gave rise to the almost complete decomposition of the starting material.[15] These results suggest that the first oxidation followed by the hydrolysis occurred in the reaction without the intermediate **8** (Scheme 3).

In conclusion, we have developed a new synthesis of 5-substituted 1,2,3-triazines, which proceeds by trapping of unstable and unisolable *N*-(1-chloroethoxycarbonyl) quaternary salts[16] with a silyl reagent, which does not react with alkyl chloroformate. The 2-(1-chloroethoxycarbonyl)-2,5-dihydro adducts **2** thus obtained were then readily oxidized and hydrolysed to afford **7**. The 1-chloroethoxycarbonyl group was shown to act as both an effective activator and a good leaving group. Since it is well known that a variety of ketene silyl acetals and silyl enol ethers are available for nucleophilic reactions,[17] this reaction is thought to be of wide use. The application of this reaction system to the introduction of other substituents is under current investigation.[18]

Experimental

All melting points were taken on a Büchi 535 micro melting point apparatus and are uncorrected. The mass spectra were recorded on JEOL JMS-SX102A instruments. The NMR spectra were measured with JEOL GX400 spectrometers using tetramethylsilane as an internal standard. The abbreviations used are as follows: s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, qd = quartet doublet and m = multiplet.

Reaction of 1,2,3-triazines with silyl enol ethers (or ketene silyl acetals) in the presence of 1-chloroethyl chloroformate

1,2,3-Triazines **1** were synthesized by a reported method.[2b,c] In a typical procedure, 1-chloroethyl chloroformate (1.2 mmol) was added dropwise at room temperature to a CH_2Cl_2 solution (2 ml) of the triazine **1** (1 mmol) and the silyl enol ether (1.2 mmol). The mixture was stirred for several hours until the starting material was entirely consumed; the reaction times are shown in Table 1. After this the mixture was evaporated to leave a residue which was chromatographed on silica gel to give the product. The NMR data for the products **2** are summarized in Tables 3 and 4. Almost all the ^{13}C NMR data for **2** were obtained as those of mixtures of diastereoisomeric and/or rotational isomers. These phenomena were not observed in the ^1H NMR spectra probably because of their low resolutions when compared with ^{13}C NMR.

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-4,6-dimethyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-1,2,3-triazine 2a. Colourless

Table 2 Oxidation of 5-substituted 2,5-dihydrotriazines **2** with ceric ammonium nitrate in CH_3CN–water

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Reaction time (h)	Product	Yield (%)
1	**2a**	Me	Me	Me	Me	OMe	2.0	**7a**	69
2	**2b**	Et	Et	Me	Me	OMe	2.0	**7b**	40
3	**2c**	Me	Ph	Me	Me	OMe	1.0	**7c**	51
4	**2d**	Ph	Ph	Me	Me	OMe	24	**7d**	0[a]
5	**2e**	Me	Me	H(Me)	Me(H)	OMe	0.5	**7e**	82
6	**2f**	Et	Et	H(Me)	Me(H)	OMe	0.5	**7f**	83
7	**2g**	Me	Ph	H(Me)	Me(H)	OMe	0.25	**7g**	79
8	**2h**	Ph	Ph	H(Me)	Me(H)	OMe	0.5	**7h**	100
9	**2m**	Me	Me	H	H	Ph	1.0	**7m**	53
10	**2n**	Et	Et	H	H	Ph	0.5	**7n**	53
11	**2o**	Me	Ph	H	H	Ph	1.0	**7o**	46
12	**2p**	Ph	Ph	H	H	Ph	0.5	**7p**	52

[a] In the case of **2d** as a substrate, it was almost totally recovered after 24 h of reaction probably because of steric hindrance at the C-5 position.

Table 3 ^{1}H NMR spectra for the products **2**

Product	^{1}H NMR ($CDCl_3$–TMS) δ(J/Hz)
2a	1.15 (6 H, s), 1.93 (3 H, d, *J* 5.9), 2.13 (6 H, s), 3.51 (1 H, s), 3.74 (3 H, s), 6.72 (1 H, q, *J* 5.9)
2b	1.12–1.16 (12 H, m), 1.93 (3 H, d, *J* 5.9), 2.22–2.27 (2 H, m), 2.57–2.63 (2 H, m), 3.62 (1 H, s), 3.73 (3 H, s), 6.72 (1 H, q, *J* 5.9)
2c	1.02 (3 H, s), 1.16 (3 H, s), 1.96 (3 H, d, *J* 5.9), 2.24 (3 H, s), 3.43 (3 H, s), 4.24 (1 H, s), 6.73 (1 H, q, *J* 5.9), 7.39–7.45 (3 H, m), 7.71–7.88 (2 H, m)
2d	1.06 (6 H, s), 2.00 (3 H, d, *J* 5.9), 3.10 (3 H, s), 4.99 (1 H, s), 6.77 (1 H, q, *J* 5.9), 7.41–7.47 (6 H, m), 7.92–7.98 (4 H, m)
2e	1.11 (3 H, d, *J* 7.3), 1.94 (3 H, d, *J* 5.9), 2.11 (3 H, s), 2.14 (3 H, s), 2.65 (1 H, qd, *J* 7.3, 6.4), 3.43 (1 H, d, *J* 6.4), 3.73 (3 H, s), 6.73 (1 H, q, *J* 5.9)
2f	1.09–1.18 (9 H, m), 1.94 (3 H, d, *J* 5.9), 2.25–2.36 (2 H, m), 2.51–2.62 (3 H, m), 3.51 (1 H, d, *J* 7.7), 3.71 (3 H, s), 6.73 (1 H, q, *J* 5.9)
2g[a]	For the major isomer: 1.06 (3 H, d, *J* 7.3), 1.97 (3 H, d, *J* 5.9), 2.18 (3 H, s), 2.59–2.75 (1 H, m), 3.59 (3 H, s), 4.17 (1 H, d, *J* 8.1), 6.77 (1 H, q, *J* 5.9), 7.44 (3 H, m), 7.89–7.90 (2 H, m); for the minor isomer: 1.10 (3 H, d, *J* 7.3), 1.99 (3 H, d, *J* 5.9), 2.24 (3 H, s), 2.59–2.75 (1 H, m), 3.61 (3 H, s), 4.20 (1 H, d, *J* 8.1), 6.77 (1 H, q, *J* 5.9), 7.44 (3 H, m), 7.89–7.90 (2 H, m)
2h	1.06 (3 H, d, *J* 7.0), 2.01 (3 H, d, *J* 5.9), 2.73 (1 H, qd, *J* 7.0, 7.0), 3.30 (3 H, s), 4.92 (1 H, d, *J* 7.0), 6.82 (1 H, q, *J* 5.9), 7.43–7.44 (6 H, m), 7.96–8.02 (4 H, m)
2i	1.94 (3 H, d, *J* 5.9), 2.17 (3 H, s), 2.28 (3 H, s), 3.53 (1 H, d, *J* 6.4), 5.00 (1 H, d, *J* 6.4), 6.22 (1 H, d, *J* 5.4), 6.71 (1 H, q, *J* 5.9), 7.23 (1 H, d, *J* 5.4)
2j	1.15 (3 H, t, *J* 7.3), 1.22 (3 H, t, *J* 7.3), 1.94 (3 H, d, *J* 5.9), 2.30–2.74 (4 H, m), 3.61 (1 H, d, *J* 6.6), 4.96 (1 H, ddd, *J* 6.6, 3.3, 1.1), 6.18 (1 H, dd, *J* 5.5, 1.1), 6.71 (1 H, q, *J* 5.9), 7.22 (1 H, dd, *J* 5.5, 3.3)
2k[b]	1.97–2.00 (3 H, m), 2.24 (2.38) (3 H, s), 4.03 (4.43) [1 H, d, *J* 8.1 (5.5)], 4.93 (5.16) [1 H, d, *J* 8.1 (5.5)], 6.14–6.16 (1 H, m), 6.74–6.77 (1 H, m), 7.11–7.15 (1 H, m), 7.43–7.51 (3 H, m), 7.84–7.86 (1 H, m), 7.94–7.96 (1 H, m)
2l	2.02 (3 H, d, *J* 5.9), 4.94 (1 H, dd, *J* 6.6, 1.8), 5.10 (1 H, d, *J* 6.6), 6.09 (1 H, dd, *J* 5.9, 1.8), 6.81 (1 H, q, *J* 5.9), 7.14 (1 H, d, *J* 5.9), 7.44–7.49 (6 H, m), 7.93–8.00 (4 H, m)
2m	2.19 (3 H, s), 2.19 (3 H, s), 3.03 (2 H, d, *J* 6.2), 3.70 (1 H, t, *J* 6.2), 6.75 (1 H, q, *J* 5.9), 7.45–7.49 (2 H, m), 7.58–7.62 (1 H, m), 7.87–7.89 (2 H, m)
2n	1.18 (3 H, t, *J* 7.3), 1.19 (3 H, t, *J* 7.3), 1.95 (3 H, d, *J* 5.9), 2.43–2.50 (2 H, m), 2.55–2.63 (2 H, m), 2.95 (2 H, d, *J* 6.2), 3.87 (1 H, t, *J* 6.2), 6.76 (1 H, q, *J* 5.9), 7.45–7.48 (2 H, m), 7.57–7.61 (1 H, m), 7.84–7.87 (2 H, m)
2o	1.99 (3 H, d, *J* 5.9), 2.28 (3 H, s), 2.93 (1 H, dd, *J* 18, 3.4), 3.26 (1 H, dd, *J* 18, 8.8), 4.52 (1 H, dd, *J* 8.8, 3.4), 6.80 (1 H, q, *J* 5.9), 7.41–7.59 (6 H, m), 7.84–7.94 (4 H, m)
2p	2.02 (3 H, d, *J* 5.9), 3.15 (2 H, d, *J* 5.5), 5.31 (1 H, t, *J* 5.5), 6.86 (1 H, q, *J* 5.9), 7.32–7.49 (9 H, m), 7.75–7.77 (2 H, m), 8.02–8.06 (4 H, m)

[a] The spectrum was obtained as that of a mixture of two isomers whose intensity ratio was 3 : 1. [b] The spectrum obtained was that of a 1 : 1 mixture of two isomers.

oil (88%) [Found (HRMS): *m/z* 216.0547 ($M^+ - C_5H_9O_2$). Calc. for $C_8H_{11}ClN_3O_2$: 216.0540].

2-(1-Chloroethoxycarbonyl)-4,6-diethyl-2,5-dihydro-5-[1-methyl-1-(methoxycarbonyl)ethyl]-1,2,3-triazine 2b. Colourless needles from hexane (77%); mp 127–128 °C (Found: C, 52.14; H, 7.14; Cl, 9.99; N, 12.08. $C_{15}H_{24}ClN_3O_4$ requires C, 52.10; H, 6.99; Cl, 10.25; N, 12.15%).

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-4-methyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-6-phenyl-1,2,3-triazine 2c. Colourless oil (82%) [Found (HRMS): *m/z* 278.0692 ($M^+ - C_5H_9O_2$). Calc. for $C_{13}H_{13}ClN_3O_2$: 278.0697].

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-5-[1-methyl-1-(methoxycarbonyl)ethyl]-4,6-diphenyl-1,2,3-triazine 2d. Colourless prisms from hexane–CH_2Cl_2 (75%); mp 155–156 °C (Found: C, 62.38; H, 5.42; Cl, 7.75; N, 9.47. $C_{23}H_{24}ClN_3O_4$ requires C, 62.51; H, 5.47; Cl, 8.02; N, 9.51%).

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-5-[1-(methoxycarbonyl)ethyl]-4,6-dimethyl-1,2,3-triazine 2e. Colourless oil (82%) [Found (HRMS): *m/z* 303.1001 (M^+). Calc. for $C_{12}H_{18}ClN_3O_4$: 303.0986. Found (HRMS): *m/z* 216.0555 ($M^+ - C_4H_7O_2$). Calc. for $C_8H_{11}ClN_3O_2$: 216.0540].

2-(1-Chloroethoxycarbonyl)-4,6-diethyl-2,5-dihydro-5-[1-(methoxycarbonyl)ethyl]-1,2,3-triazine 2f. Colourless needles from hexane (76%); mp 90–92 °C (Found: C, 50.89; H, 6.80; Cl, 10.37; N, 12.67. $C_{14}H_{22}ClN_3O_4$ requires C, 50.68; H, 6.68; Cl, 10.69; N, 12.66%).

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-5-[1-(methoxycarbonyl)ethyl]-4-methyl-6-phenyl-1,2,3-triazine 2g. Colourless oil (91%); [Found (HRMS): *m/z* 365.1115 (M^+). Calc. for $C_{17}H_{20}ClN_3O_4$: 365.1142. Found (HRMS): *m/z* 278.0696 ($M^+ - C_4H_7O_2$). Calc. for $C_{13}H_{13}ClN_3O_2$: 278.0696].

2-(1-Chloroethoxycarbonyl)-2,5-dihydro-5-[1-(methoxycarbonyl)ethyl]-4,6-diphenyl-1,2,3-triazine 2h. Colourless needles from hexane (79%); mp 123–125 °C (Found: C, 61.83; H, 5.17; Cl, 8.55; N, 9.79. $C_{22}H_{22}ClN_3O_4$ requires C, 61.76; H, 5.18; Cl, 8.29; N, 9.82%).

2-(1-Chloroethoxycarbonyl)-5-(2,5-dihydro-2-oxo-5-furyl)-2,5-dihydro-4,6-dimethyl-1,2,3-triazine 2i. Colourless oil (87%) [Found (HRMS): *m/z* 299.0668 (M^+). Calc. for $C_{12}H_{14}ClN_3O_4$: 299.0670].

2-(1-Chloroethoxycarbonyl)-4,6-diethyl-5-(2,5-dihydro-2-oxo-5-furyl)-2,5-dihydro-1,2,3-triazine 2j. Colourless oil (69%)

Table 4 ^{13}C NMR spectra for the products **2**

Product	^{13}C NMR ($CDCl_3$–TMS) δ
2a[a]	22.71 (22.72), 23.02 (23.06), 25.07, 46.22, 47.68, 52.33, 83.53, 146.62, 149.88, 175.68
2b[a]	10.93 (10.99), 22.73, 25.16, 29.42 (29.44), 42.86, 47.99, 52.33, 83.53, 150.20, 151.04 (151.13), 175.88
2c[b]	22.50, 23.14 (23.17), 23.27, 25.11, 41.48 (41.54), 48.17 (48.18), 52.01, 83.63, 126.03 (126.07), 128.31 (128.34), 129.93 (129.95), 134.95, 144.21, 147.94 (148.04), 149.91 (149.95), 175.38
2d[a]	23.07, 25.20, 37.27, 48.77, 51.71, 83.84, 126.23 (126.26), 128.47 (128.49), 130.22, 134.87, 145.52 (145.61), 150.03, 175.12
2e[b]	13.58 (13.60), 21.10 (21.13), 22.51 (22.53), 25.10, 38.88 (38.90), 41.08, 52.14, 83.57, 146.97 (146.98), 147.99 (148.02), 150.25, 173.72 (173.74)
2f[b]	10.39 (10.45), 10.56 (10.62), 14.27 (14.28), 25.20, 27.80 (27.83), 29.28 (29.30), 38.61 (38.64), 38.86, 52.13, 83.62, 150.82, 151.45 (151.54), 152.55 (152.59), 174.08 (174.10)
2g[c]	12.66 (12.68, 15.34), 21.76 (21.79, 22.91, 22.93), 25.32 (25.34), 36.78 (37.69, 37.72), 38.96 (38.98, 40.25), 52.18, (52.24), 83.86 (83.88), 126.23 (126.26, 126.55, 126.60), 128.64 (128.65, 128.72), 130.57, 134.12, 144.33 (144.36, 144.41), 148.00 (148.06, 149.78, 149.83), 150.83 (150.85), 173.77 (173.80, 174.18, 174.20)
2h[b]	14.06, 25.32, 33.60, 40.01, 51.83, 83.96 (83.97), 126.52 (126.54), 126.61 (126.64), 128.65, 130.65, 132.89, 134.12, 145.21 (145.25), 145.98 (146.03), 150.65, 173.63
2i[d]	21.84 (21.85), 22.49, 25.16 (25.19, 25.22), 42.75 (42.77), 79.48, 83.90, 123.51 (123.53), 144.20, 144.82 (144.90), 150.25, 151.66, 170.97
2j[b]	10.11 (10.16), 10.18 (10.25), 25.02 (25.06), 28.39, 28.87 (28.89), 40.46, 79.47 (79.49), 83.72, 123.00 (123.02), 148.36 (148.39), 148.98 (149.09), 150.37 (150.38), 151.94, 171.01
2k[c]	22.27 (22.31, 22.96), 25.16 (25.22, 25.23), 38.26 (38.29, 39.49, 39.55), 78.86 (78.91, 80.53), 84.01, 122.73 (123.47, 123.51), 126.34 (126.37, 126.63), 128.91 (129.00), 131.15 (131.20), 132.43 (132.45), 140.66 (140.96), 145.58 (145.65, 146.89, 146.99), 150.09 (151.38), 152.78, 171.00 (171.09)
2l[d]	25.18 (25.20), 35.47 (35.51), 79.69, 84.12, 122.89, 126.86 (126.89, 126.92), 128.75 (128.81), 131.09 (132.63), 141.74 (141.76), 142.59 (142.64), 150.22, 152.20, 170.89
2m[a]	21.15 (21.19), 25.19, 33.81, 36.88, 83.66, 127.83, 128.65, 133.69, 135.60, 150.03 (150.09), 150.75, 196.20
2n[a]	10.63 (10.72), 25.36, 28.11 (28.13), 31.24, 37.31, 83.80, 128.02, 128.79, 133.83, 135.80, 151.34, 154.56 (154.71), 196.56
2o	22.22, 25.38, 29.67, 38.57, 83.91, 126.48, 128.06, 128.78, 128.84, 130.82, 132.50, 133.88, 135.69, 146.22, 150.95, 151.89, 196.28
2p[a]	25.45, 26.01, 39.77, 84.07, 127.02, 127.05, 128.14, 128.68 (128.75), 130.86, 132.78, 133.75, 135.92, 148.10 (148.21), 151.06, 196.03

[a] The spectrum obtained was that of a mixture of two rotational isomers. [b] The spectrum obtained was that of a mixture of two diastereoisomeric isomers. [c] The spectrum obtained was that of a mixture of four diastereoisomeric isomers. [d] The spectrum obtained was that of three diastereoisomeric and/or rotational isomers.

[Found (HRMS): m/z 327.0994 (M^+). Calc. for $C_{14}H_{18}ClN_3O_4$: 327.0986].

2-(1-Chloroethoxycarbonyl)-5-(2,5-dihydro-2-oxo-5-furyl)-2,5-dihydro-4-methyl-6-phenyl-1,2,3-triazine 2k. Colourless oil (60%) [Found (HRMS): m/z 361.0819 (M^+). Calc. for $C_{17}H_{16}ClN_3O_4$: 361.0827].

2-(1-Chloroethoxycarbonyl)-5-(2,5-dihydro-2-oxo-5-furyl)-2,5-dihydro-4,6-diphenyl-1,2,3-triazine 2l. Colourless oil (55%) [Found (HRMS): m/z 423.0993 (M^+). Calc. for $C_{22}H_{18}ClN_3O_4$: 423.0987].

5-Benzoylmethyl-2-(1-chloroethoxycarbonyl)-2,5-dihydro-4,6-dimethyl-1,2,3-triazine 2m. Colourless oil (13%) [Found (HRMS): m/z 335.1036 (M^+). Calc. for $C_{16}H_{18}ClN_3O_3$: 335.1036].

5-Benzoylmethyl-2-(1-chloroethoxycarbonyl)-4,6-diethyl-2,5-dihydro-1,2,3-triazine 2n. Colourless oil (15%) [Found (HRMS): m/z 363.1338 (M^+). Calc. for $C_{18}H_{22}ClN_3O_3$: 363.1348].

5-Benzoylmethyl-2-(1-chloroethoxycarbonyl)-2,5-dihydro-4-methyl-6-phenyl-1,2,3-triazine 2o. Colourless needles from hexane–ethyl acetate (77%); mp 194–195 °C (Found: C, 63.14; H, 4.90; Cl, 8.66; N, 10.50. $C_{21}H_{20}ClN_3O_3$ requires C, 63.40; H, 5.07; Cl, 8.91; N, 10.56%).

5-Benzoylmethyl-2-(1-chloroethoxycarbonyl)-2,5-dihydro-4,6-diphenyl-1,2,3-triazine 2p. Colourless needles from hexane–diisopropyl ether (69%); mp 142–144 °C (Found: C, 67.75; H, 4.78; Cl, 7.50; N, 9.08. $C_{26}H_{22}ClN_3O_3$ requires C, 67.90; H, 4.82; Cl, 7.71; N, 9.14%).

Reaction of the 2-methyltriazinium salt 4 with a ketene silyl acetal

2,4,6-Trimethyl-1,2,3-triazinium iodide **4** was synthesized by a reported method.[19] Compound **4** (1 mmol) was suspended in CH_2Cl_2 (2 ml), and methyl trimethylsilyl dimethylketene acetal (1 mmol) was added to the suspension. After being allowed to stand for 18 h at room temperature, the mixture was evaporated to leave a residue, which was chromatographed on silica gel to give the product (45%).

2,5-Dihydro-2,4,6-trimethyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-1,2,3-triazine 5. Colourless oil; δ_H(400 MHz; $CDCl_3$) 1.13 (6 H, s), 2.01 (6 H, s), 3.30 (3 H, s), 3.40 (1 H, s) and 3.71 (3 H, s); δ_C(100 MHz; $CDCl_3$) 22.96, 23.46, 46.26, 46.80, 48.02, 52.28, 137.69 and 176.69 [Found (HRMS): m/z 124.0869 ($M^+ - C_5H_9O_2$). Calc. for $C_6H_{10}N_3$: 124.0874].

General procedure for the oxidation of the 2,5-dihydrotriazines 2 with ceric ammonium nitrate.

Ceric ammonium nitrate (3 mmol) was added to a CH_3CN (3 ml)–H_2O (3 ml) solution of the dihydro adduct **2** (1 mmol), and the mixture was stirred at room temperature. After completion of the reaction, the mixture was diluted with water, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated to leave a residue, which was chromatographed on silica gel to afford the aromatized product **7**, the NMR data for which are shown in Table 5.

4,6-Dimethyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-1,2,3-triazine 7a. Colourless needles from hexane (69%); mp 70–71 °C (Found: C, 57.57; H, 7.47; N, 20.10. $C_{10}H_{15}N_3O_2$ requires C, 57.40; H, 7.23; N, 20.08%).

4,6-Diethyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-1,2,3-triazine 7b. Yellow oil (40%) [Found (HRMS): m/z 237.1444 (M^+). Calc. for $C_{12}H_{19}N_3O_2$: 237.1477].

4-Methyl-5-[1-methyl-1-(methoxycarbonyl)ethyl]-6-phenyl-1,2,3-triazine 7c. Colourless flakes from hexane–diisopropyl ether (51%); mp 116–118 °C (Found: C, 66.36; H, 6.35; N, 15.51. $C_{15}H_{17}N_3O_2$ requires C, 66.40; H, 6.32; N, 15.49%).

5-[1-(Methoxycarbonyl)ethyl]-4,6-dimethyl-1,2,3-triazine 7e. Colourless prisms from hexane (82%); mp 55–56 °C (Found: C, 55.22; H, 6.90; N, 21.84. $C_9H_{13}N_3O_2$ requires C, 55.37; H, 6.71; N, 21.52%).

4,6-Diethyl-5-[1-(methoxycarbonyl)ethyl]-1,2,3-triazine 7f. Colourless needles from hexane (83%); mp 70–71 °C (Found: C, 59.20; H, 7.89; N, 18.89. $C_{11}H_{17}N_3O_2$ requires C, 59.17; H, 7.67; N, 18.82%).

5-[1-(Methoxycarbonyl)ethyl]-4-methyl-6-phenyl-1,2,3-tri-

Table 5 ^1H and ^{13}C NMR spectra for the products 7

Product	^1H and ^{13}C NMR ($CDCl_3$–TMS)
7a	δ_H 1.70 (6 H, s), 2.67 (6 H, s), 3.74 (3 H, s); δ_C 22.28, 25.85, 45.89, 52.83, 133.08, 156.78, 176.32
7b	δ_H 1.40 (6 H, t, *J* 7.3), 1.74 (6 H, s), 2.92 (4 H, q, *J* 7.3), 3.73 (3 H, s); δ_C 12.85, 26.52, 27.25, 45.72, 52.75, 131.64, 160.78, 176.64
7c	δ_H 1.42 (6 H, s), 2.68 (3 H, s), 3.61 (3 H, s), 7.45–7.50 (5 H, m); δ_C 21.22, 26.77, 45.74, 52.61, 128.02, 128.87, 129.38, 132.12, 137.49, 158.06, 158.78, 175.82
7e	δ_H 1.53 (3 H, d, *J* 7.3), 2.65 (6 H, s), 3.74 (3 H, s), 4.06 (1 H, q, *J* 7.3); δ_C 14.01, 19.45, 37.82, 52.39, 129.44, 157.24, 171.66
7f	δ_H 1.41 (6 H, t, *J* 7.3), 1.57 (3 H, d, *J* 7.3), 2.87–2.98 (4 H, m), 3.75 (3 H, s), 4.13 (1 H, q, *J* 7.3); δ_C 12.36, 15.49, 25.72, 37.08, 52.34, 128.27, 161.40, 172.10
7g	δ_H 1.46 (3 H, d, *J* 7.3), 2.67 (3 H, s), 3.71 (3 H, s), 4.15 (1 H, q, *J* 7.3), 7.54–7.58 (5 H, m); δ_C 14.96, 19.82, 38.49, 52.48, 128.47, 128.59, 128.66, 129.71, 134.16, 158.82, 158.85, 171.72
7h	δ_H 1.15 (3 H, d, *J* 7.3), 3.57 (3 H, s), 4.08 (1 H, q, *J* 7.3), 7.51–7.58 (10 H, m); δ_C 16.25, 39.39, 52.36, 128.51, 128.56, 128.91, 129.99, 134.87, 160.41, 172.03
7m	δ_H 2.59 (6 H, s), 4.44 (2 H, s), 7.55–7.59 (2 H, m), 7.68–7.72 (1 H, m), 8.06–8.08 (2 H, m); δ_C 19.58, 37.23, 124.87 128.20, 129.07, 134.31, 135.70, 158.83, 193.14
7n	δ_H 1.35 (6 H, t, *J* 7.3), 2.85 (4 H, q, *J* 7.3), 4.46 (2 H, s), 7.56–7.60 (2 H, m), 7.68–7.70 (1 H, m), 8.06–8.08 (2 H, m); δ_C 12.27, 26.01, 36.22, 123.43, 128.18, 129.06, 134.27, 135.65, 162.59, 193.78
7o	δ_H 2.62 (3 H, s), 4.47 (2 H, s), 7.40–7.52 (7 H, m), 7.62–7.64 (1 H, m), 7.97–7.99 (2 H, m); δ_C 19.80, 38.73, 123.97, 128.09, 128.62, 128.71, 128.84, 129.97, 134.12, 134.16, 135.29, 159.43, 160.67, 194.67
7p	δ_H 4.37 (2 H, s), 7.38–7.45 (8 H, m), 7.54–7.60 (5 H, m), 7.72–7.74 (2 H, m); δ_C 39.67, 123.43, 127.93, 128.70, 128.72, 128.84, 130.08, 133.86, 134.67, 135.60, 161.22, 196.16

azine 7g. Colourless oil (79%) [Found (HRMS): *m/z* 257.1159 (M^+). Calc. for $C_{14}H_{15}N_3O_2$: 257.1165].

5-[1-(Methoxycarbonyl)ethyl]-4,6-diphenyl-1,2,3-triazine 7h. Colourless needles from hexane–CH_2Cl_2 (100%); mp 115–117 °C (Found: C, 71.37; H, 5.36; N, 13.01. $C_{19}H_{17}N_3O_2$ requires C, 71.46; H, 5.37; N, 13.16%).

5-Benzoylmethyl-4,6-dimethyl-1,2,3-triazine 7m. Colourless needles from hexane (53%); mp 130–131 °C (Found: C, 68.64; H, 5.71; N, 18.24. $C_{13}H_{13}N_3O$ requires C, 68.71; H, 5.77; N, 18.49%).

5-Benzoylmethyl-4,6-diethyl-1,2,3-triazine 7n. Colourless needles from hexane–CH_2Cl_2 (53%); mp 110–112 °C (Found: C, 70.84; H, 6.78; N, 16.35. $C_{15}H_{17}N_3O$ requires C, 70.56; H, 6.71; N, 16.46%).

5-Benzoylmethyl-4-methyl-6-phenyl-1,2,3-triazine 7o. Colourless oil (46%) [Found (HRMS): *m/z* 289.1190 (M^+). Calc. for $C_{18}H_{15}N_3O$: 289.1216].

5-Benzoylmethyl-4,6-diphenyl-1,2,3-triazine 7p. Colourless needles from hexane–CH_2Cl_2 (52%); mp 184–186 °C (Found: C, 78.52; H, 4.85; N, 12.08. $C_{23}H_{17}N_3O$ requires C, 78.61; H, 4.88; N, 11.96%).

Hydrolysis of 2a

Hydrolysis of the dihydro adduct **2a** (1 mmol) at 60 °C in CH_3CN (5 ml)–water (5 ml), gave the 2,5-dihydro adduct **8** (90%) as a colourless solid (mp 91–93 °C); δ_H(400 MHz; $CDCl_3$) 1.16 (6 H, s), 2.00 (6 H, s), 3.45 (1 H, s), 3.73 (3 H, s) and 8.32 (1 H, br s); δ_C(100 MHz; $CDCl_3$) 22.92, 23.40, 46.50, 48.27, 52.32, 137.93 and 176.95 [Found (HRMS): *m/z* 211.1320 (M^+). Calc. for $C_{10}H_{17}N_3O_2$: 211.1320].

References

1 On leave from the Central Research Laboratories, SS Pharmaceutical Co., Ltd., Narita (Japan).

2 (*a*) H. Neunhoeffer in *Comprehensive Heterocyclic Chemistry*, series eds. A. R. Katritzky and C. W. Rees, Vol. eds. A. J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984, vol. 3, pp. 369–384; (*b*) A. Ohsawa, H. Arai, H. Ohnishi, T. Itoh, T. Kaihoh, M. Okada and H. Igeta, *J. Org. Chem.*, 1985, **50**, 5520; (*c*) H. Neunhoeffer, M. Clausen, H.-D. Vötter, H. Ohl, C. Krüger and K. Angermund, *Liebigs Ann. Chem.*, 1985, 1732.

3 (*a*) A. Ohsawa, T. Kaihoh and H. Igeta, *J. Chem. Soc., Chem. Commun.*, 1985, 1370; (*b*) T. Itoh, M. Okada, K. Nagata and A. Ohsawa, *Heterocycles*, 1992, **34**, 1183.

4 T. Itoh, K. Nagata, T. Kaihoh, M. Okada, C. Kawabata, H. Arai, H. Ohnishi, K. Yamaguchi, H. Igeta, A. Ohsawa and Y. Iitaka, *Heterocycles*, 1992, **33**, 631.

5 For example, a 5-halogenotriazine reacted with hydroxide ion at the C-4 position, and a 5-hydroxy derivative was obtained only by the reaction with superoxide anion. See, (*a*) T. Itoh, K. Nagata, M. Okada and A. Ohsawa, *Tetrahedron Lett.*, 1990, **31**, 2429; (*b*) T. Itoh, K. Nagata, M. Okada, H. Takahashi and A. Ohsawa, *Tetrahedron*, 1991, **47**, 4317.

6 O. N. Chupakhin, V. N. Charushin and H. C. van der Plas, *Tetrahedron*, 1988, **44**, 1.

7 H. Neunhoeffer, R. Bopp and W. Diehl, *Liebigs Ann. Chem.*, 1993, 367.

8 T. Itoh, K. Nagata, M. Okada and A. Ohsawa, *Chem. Pharm. Bull.*, 1993, **40**, 2283.

9 When **1** was treated with various electrophiles, the reaction occurred exclusively at the N-2 position. A. Ohsawa, T. Itoh, K. Yamaguchi and C. Kawabata, *Chem. Pharm. Bull.*, 1991, **39**, 2117.

10 (*a*) K. Nagata, T. Itoh, M. Okada, H. Takahashi and A. Ohsawa, *Heterocycles*, 1991, **32**, 855; (*b*) K. Nagata, T. Itoh, M. Okada, H. Takahashi and A. Ohsawa, *Heterocycles*, 1991, **32**, 2015.

11 (*a*) T. Itoh, K. Nagata, M. Okada and A. Ohsawa, *Heterocycles*, 1993, **35**, 581; (*b*) K. Nagata, T. Itoh, M. Okada and A. Ohsawa, *Chem. Pharm. Bull.*, 1993, **41**, 1644; (*c*) T. Itoh, Y. Matsuya, K. Nagata, M. Okada and A. Ohsawa, *J. Chem. Soc., Chem. Commun.*, 1995, 2067.

12 Akiba *et al.* reported that silyl enol ethers reacted with *N*-alkoxycarbonylpyridinium salts to give 1,4-dihydro adducts. See, (*a*) K. Akiba, Y. Nishihara and M. Wada, *Tetrahedron Lett.*, 1983, **24**, 5269; (*b*) M. Wada, Y. Nishihara and K. Akiba, *Tetrahedron Lett.*, 1985, **26**, 3267. The application of this reaction system to five-membered azaaromatics was recently performed by our group; (*c*) T. Itoh, M. Miyazaki, H. Hasegawa, K. Nagata and A. Ohsawa, *Chem. Commun.*, 1996, 1217.

13 Preliminary communication; T. Itoh, Y. Matsuya, H. Hasegawa, K. Nagata, M. Okada and A. Ohsawa, *Chem. Pharm. Bull.*, 1995, **43**, 881.

14 In the cases of the 5-oxofuryl derivatives (Table 1, entries 9–12), the lactone ring was labile under the reaction conditions, and decomposed without formation of the aromatized compound **4**.

15 Only 3% of the product **7a** and 7% of the 5-desubstituted triazine **1a** were isolated from the reaction mixture.

16 The use of unstable quaternary salts of azaaromatics other than 1,2,3-triazines was reported by us using allyl(tributyl)tin and bis(tributylstannyl)acetylene as nucleophiles. See, (*a*) T. Itoh, H. Hasegawa, K. Nagata and A. Ohsawa, *J. Org. Chem.*, 1994, **59**, 1319; (*b*) T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, M. Okada and A. Ohsawa, *Chem. Pharm. Bull.*, 1994, **42**, 1768; (*c*) T. Itoh, H. Hasegawa, K. Nagata, M. Okada and A. Ohsawa, *Tetrahedron*, 1994, **50**, 13089.

17 T. H. Chan in *Comprehensive Organic Synthesis*, ed. C. H. Heathcock, Pergamon Press, Oxford, 1991, vol. 2, p. 595, and references cited therein.

18 Allyltributyltin was shown to react with 1,2,3-triazines in the presence of 1-chloroethyl chloroformate to give 2,5-dihydro adducts in a similar manner. The results will be published later.

19 A. Ohsawa, H. Arai, H. Ohnishi, T. Kaihoh, T. Itoh, K. Yamaguchi, H. Igeta and Y. Iitaka, *Yakugaku Zasshi*, 1985, **105**, 1122.

Paper 6/02477G
Received 10*th April* 1996
Accepted 21*st June* 1996