THE SYNTHESIS OF 5-SUBSTITUTED 1,2,3-TRIAZINES WITH KETENE SILYL ACETALS AND CERIC AMMONIUM NITRATE

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Monocyclic 1,2,3-triazines were reacted with ketene silyl acetal or silyl enol ether in the presence of 1-chloroethyl chloroformate to give 5-substituted 2-(1-chloroethoxycarbonyl)-2,5-dihydrotriazines. These dihydro-adducts were readily oxidized and hydrolyzed with ceric ammonium nitrate in CH_3CN/H_2O to afford 5-substituted triazines.

KEY WORDS 1,2,3-triazine; ketene silyl acetal; 1-chloroethyl chloroformate; ceric ammonium nitrate

In recent years, we have been investigating the synthesis, reactivity and physical properties of 1,2,3-triazines.[2] These studies revealed that 1,2,3-triazines were highly reactive toward nucleophiles,[3] and that the reaction site was almost at their C-4 position even in the presence of a substituent at C-4[4] or a leaving group at C-5,[5] and these reactions resulted in the ring opening accompanied by N_2 elimination. Therefore, triazines were revealed not to be suitable compounds for the direct introduction of substituents.[6] Moreover, 1,2,3-triazines were synthesized by the oxidation of *N*-aminopyrazoles; [2] hence the preliminarily introduced substrates were limited to those which resist the oxidative conditions.[7]

Upon seeing the results, we focused our interest on the substituent introduction at C-5 of triazine ring which has an activating group at N-2,[8] and it was revealed that 1,2,3-triazinium 2-dicyanomethylides were available for radical[9] and vicarious[10] nucleophilic substitutions. However, this system was limited to these two reactions, and they did not react with any organometallic reagents. Thus we investigated another reaction and found that ketene silyl acetals or silyl enol ethers reacted with triazine in the presence of 1-chloroethyl chloroformate, and that the 2,5-dihydro-adducts thus obtained were aromatized with ceric ammonium nitrate (CAN) to give corresponding 5-substituted triazines. This paper describes these results.

When 1,2,3-triazines **1** were treated with 1-chloroethyl chloroformate without nucleophile, they were decomposed and gave no isolable products. Although the results indicated the instability of alkoxycarbonyl quaternary salts of triazines, addition of a ketene silyl acetal or a silyl enol ether changed the reaction process to the formation of 5-substituted 2-(1-chloroethoxycarbonyl)-2,5-dihydrotriazines **2** in good yields as shown in Chart 1 and Table 1. In the typical procedure, 1-chloroethyl chloroformate (1.2 mmol) was added dropwise at room temperature to the CH_2Cl_2 solution (2 ml) of triazine **1** (1 mmol) and a ketene silyl acetal (1.2 mmol), and the mixture was allowed to stir for several hours until the starting material was entirely consumed. Then the solvent was evaporated off to leave a residue, which was chromatographed on silica gel to give the product. Some of the compounds **2** were obtained as conformational and/or diastereometrical isomers, which were confirmed by ^{1}H-NMR spectroscopy.[11] The use of ethyl chloroformate resulted in complete recovery of the starting material, which suggests that its electrophilicity was not enough to form the corresponding quaternary salt. In the cases of 4,6-diphenyltriazine as a substrate, the reaction proceeded slowly due to the steric hindrance, but the adducts were obtained in satisfactory yields (entries 4, 8, 12, and 16). The reaction was specific for silyl reagents, since the other nucleophiles react with chloroformate before the formation of alkoxycarbonyl quaternary salts. Although organotin reagents were also expected to be suitable because they are inert to carbonyl groups in the absence of a Lewis acid, their use afforded low yields of the products, probably because of the redox reaction between organotin and the quaternary salts.

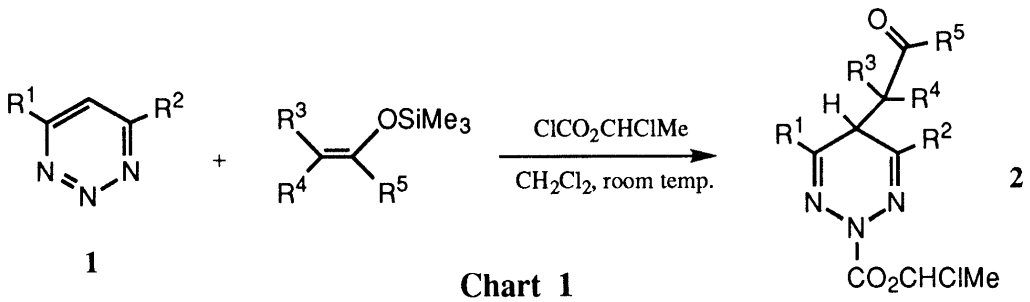

Chart 1

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Table 1. The Reaction of 1,2,3-Triazines with Organosilanes in the Presence of 1-Chloroethyl Chloroformate

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

a) In these cases, nucleophilicity of the reagent was lower than those of the above examples, and the instabilities of intermediary quaternary salts were supposed to make the yields low.

Compound **2** thus obtained was treated with ceric ammonium nitrate (CAN) in CH_3CN/H_2O at room temperature to give corresponding 5-substituted triazines **4**.[12] In the reaction, CAN (3 mmol) was added to the CH_3CN(3 ml)/H_2O(3 ml) solution of dihydro-adduct **2** (1 mmol), and the mixture was reacted at room temperature. After the reaction was completed, the mixture was diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated off to leave a residue, which was chromatographed on silica gel to afford the aromatized product (Chart 2 and Table 2).

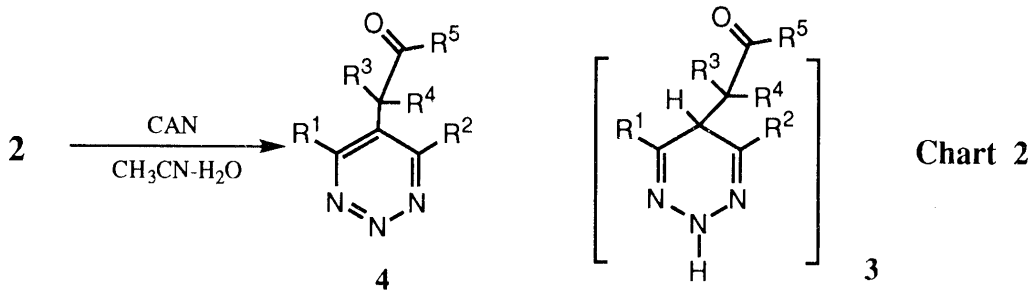

Chart 2

The absence of H_2O resulted in the complete recovery of **2**, therefore the reaction process must include the hydrolysis process. In fact, 2,5-dihydro-adduct **3** was isolated by the hydrolysis of **2** in CH_3CN/H_2O under reflux,[13] but the reaction did not proceed at room temperature. These results indicated that the first oxidation followed by hydrolysis occurred in the reaction without intermediary **3**.

In conclusion, we have developed a new synthetic method for rare 5-substituted 1,2,3-triazines. The reaction proceeded *via* the trapping of unstable and unisolable *N*-(1-chloroethoxylcarbonyl) quaternary salts[14] with the silyl reagent, which does not react with alkyl chloroformate. Then the 2-(1-chloroethoxycarbonyl)-2,5-dihydro-adducts **2** thus obtained were shown to be readily oxidized and hydrolyzed to afford **4**, revealing that the 1-chloroethoxycarbonyl group acted as both an effective activator and a good leaving group. The application of this reaction system to the introduction of other substituents is now under investigation.

Table 2. The Oxidation of 5-Substituted 2,5-dihydrotriazines **2** with Ceric Ammonium Nitrate in CH_3CN/H_2O

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

a) In the case of **2d**, it was almost recovered even after 24 hs' reaction probably due to steric hindrance of C-5 position.

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5) For example, 5-halotriazine was reacted with hydroxide ion at C-4 position, and 5-hydroxy derivative was obtained only by the reaction with superoxide anion. See, a) Itoh T., Nagata K., Okada M., Ohsawa A. *Tetrahedron Lett.*, **31**, 2429 (1990). b) Itoh T., Nagata K., Okada M., Takahashi H., Ohsawa A. *Tetrahedron*, **47**, 4317 (1991).
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11) Compounds **2a-2f**, **2h**, and **2m-2p** gave the ^{1}H-NMR spectra of sole products. Compounds **2i**,**2j**, and **2l** gave the spectra whose lactone moiety signals were splitting, which suggested the presence of conformational isomers. In the cases of **2g** and **2k**, the presences of two isomers were clearly observed in the ratio of 3:1 and 1:1, respectively. These were supposed to be mixtures of two diastereomers.
12) In the cases of compounds **2i-2l** (Table I, entries 9-12), the lactone ring was labile under the reaction conditions, and decomposed without the formation of aromatized compound **4**.
13) When a dihydro-adduct (Table I, entry 10) was hydrolyzed at 60°C in CH_3CN/H_2O, the corresponding 2*H*-2,5-dihydro-adduct was obtained in 90% yield.
14) The use of unstable quaternary salts of azaaromatics other than 1,2,3-triazines were reported by us using allyltributyltin and bis(tributylstannyl)acetylene as nucleophiles. See, a) Itoh T., Hasegawa H., Nagata K., Ohsawa A. *J. Org. Chem.*, **59**, 1319 (1994). b) Itoh T., Hasegawa H., Nagata K., Matsuya Y., Okada M., Ohsawa A. *Chem. Pharm. Bull.*, **42**, 1768 (1994). c) Itoh T., Hasegawa H., Nagata K., Okada M, Ohsawa A. *Tetrahedron*, **50**, 13089 (1994).

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