RADICAL NUCLEOPHILIC CARBAMOYLATION OF 1,2,3-TRIAZINE DERIVATIVES

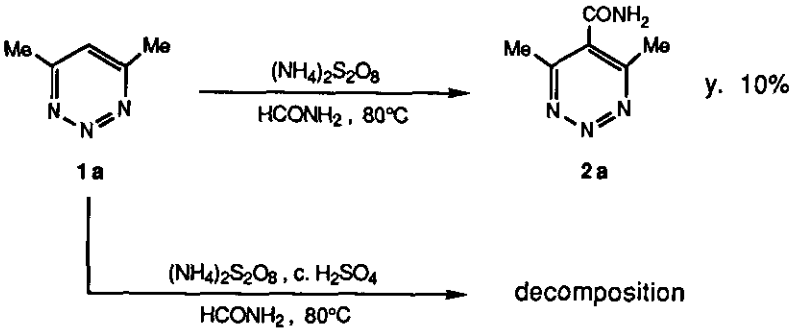
Kazuhiro Nagata, Takashi Itoh, Mamiko Okada, Hiroyuki Takahashi, and Akio Ohsawa*

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

Abstract - Radical nucleophilic carbamoylation was carried out to various 1,2,3-triazine derivatives. In the case of parent triazines as substrates, Minisci's system was not effective, and in the absence of acid, a small amount of radical adduct was obtained. Triazinium dicyanomethylides reacted with carbamoyl radical to give 5-carbamoyltriazines in good yields. Other 1,2,3-triazine derivatives were also investigated.

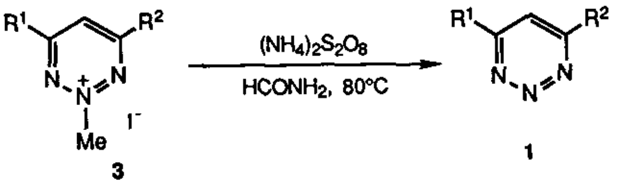
In recent years considerable development has been achieved by Minisci *et al.* in the field of the radical substitution of heteroaromatics.[1] Their method includes protonation of heteroaromatics followed by the attack of nucleophilic radicals.[2] We have been investigating the synthesis and reaction of monocyclic 1,2,3-triazines.[3] In this paper we describe the detailed results[4] of the attempted radical nucleophilic reaction to them.

At first, the application of Minisci's systems was carried out to the parent triazines (**1**) using carbamoyl radicals.[5] Minisci *et al.* used sulfuric acid for protonation of heteroaromatics, which made ring carbon more electron deficient and the attack of nucleophilic radical successful. However, in the case of **1a**, a small amount of 5-carbamoyl-4,6-dimethyl-1,2,3-triazine (**2a**) was obtained only in the absence of the acid (Scheme 1). This fact suggests that triazine was electron deficient enough to react with a nucleophilic radical by itself even though the yield was low.[6]



Scheme 1

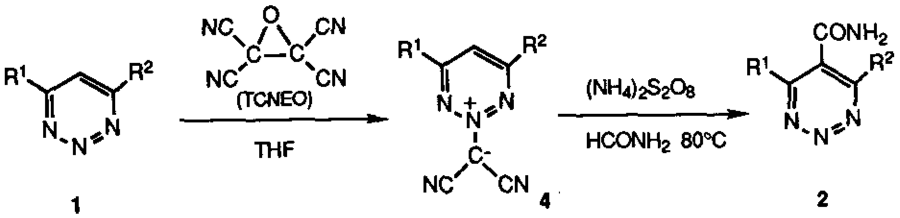
The reason for the decomposition in the presence of sulfuric acid was thought to be multiple attack of radical species to the parent nucleus,[7] because the proton, which activates the ring, existed in large excess, and was regenerated through the reaction. Therefore we tried to search activators which would be alternative to proton. The reaction of 2-methyltriazinium iodides (**3**)[8] with carbamoyl radical resulted in the demethylation to afford triazines (**1**) (Scheme 2). In the reaction, 2-methyl group was supposed to be reactive and the radical species abstracted hydrogen from the methyl group followed by the oxidation with molecular oxygen to bring about the demethylation.



a $R^1 = R^2 = Me$; 43 %
b $R^1 = Me$, $R^2 = Ph$; 88 %
c $R^1 = R^2 = Ph$; 78 %

Scheme 2

Next, 1,2,3-triazinium 2-dicyanomethylides (**4**) were allowed to react with carbamoyl radical in the absence of sulfuric acid to give 5-carbamoyltriazines in moderate to good yields (Scheme 3 and Table 1). The compounds (**4**) were readily prepared by the reaction of **1** with tetracyanoethylene oxide (TCNEO)[9] in THF.



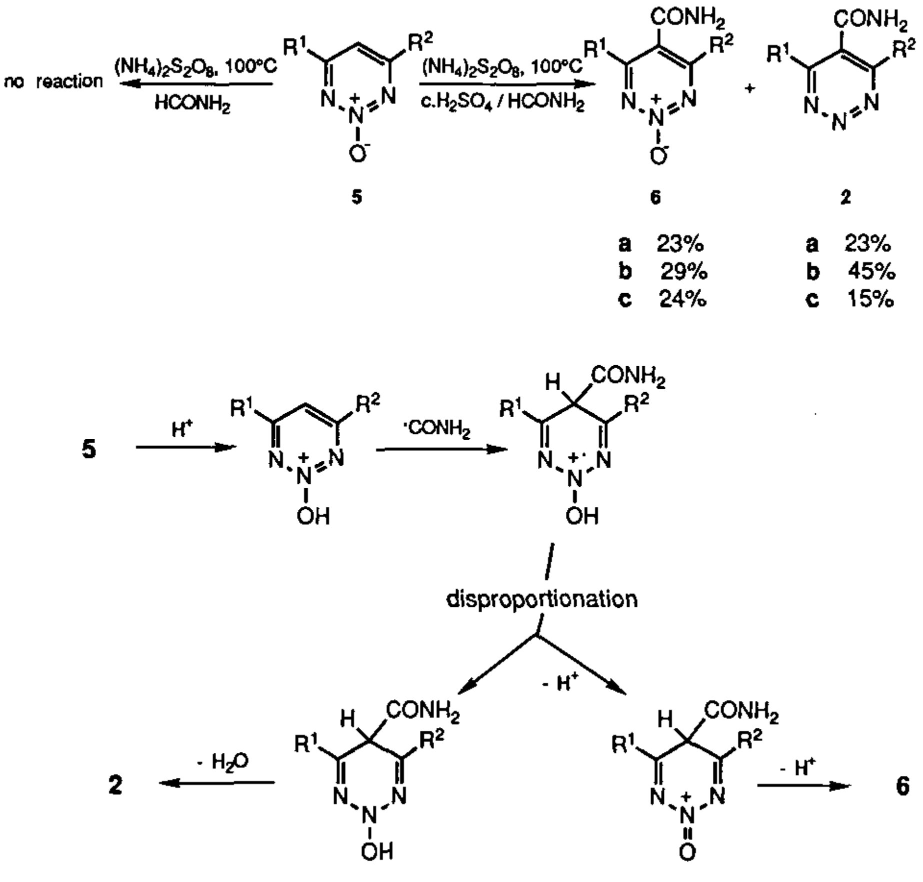
Scheme 3

Table 1. Isolated Yields of 4 and Corresponding Carbamoyltriazines (2)

	R^1	R^2	Yield of **4** (mp)	Yield of **2** (mp)
1a	Me	Me	86 % (194 °C)	69 % (210 °C)
1b	Me	Ph	80 % (201 °C)	71 % (192 °C)
1c	Ph	Ph	82 % (296 °C)	68 % (230 °C)
1d	Et	Et	97 % (142 °C)	61 % (174 °C)
1e	Me	Et	82 % (138 °C)	46 % (167 °C)

Dicyanomethylene group was thought to act as an electron-withdrawing group to make *p*-position of 1,2,3-triazine ring more π-deficient and as a good leaving group after the addition of carbamoyl radical to eliminate irreversibly.

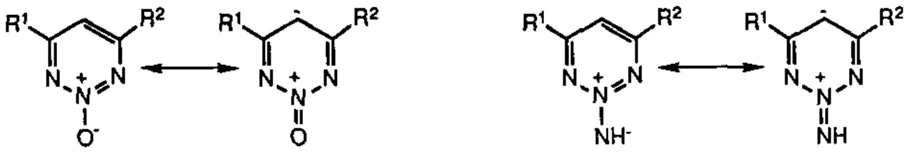
Similar activation effect was expected for triazine 2-oxides (**5**), whose structures are analogous to betain (**4**). However, compounds (**5**) did not react with nucleophilic radicals in the absence of protic acid, and the additional sulfuric acid promoted the reaction to give corresponding carbamoyl triazine 2-oxides (**6**) and deoxygenated products (**2**). Formation mechanism of **2** remained unclarified, but fairly identical yields of **6** and **2** might suggest that the disproportionation occurred in the reaction (Scheme 4). After protonation and succeeding radical attack, cation radical thus obtained was supposed to be disproportionated to its reduced and oxidized forms, which led to **2** and **6**, respectively.



	6	2
a	23%	23%
b	29%	45%
c	24%	15%

Scheme 4

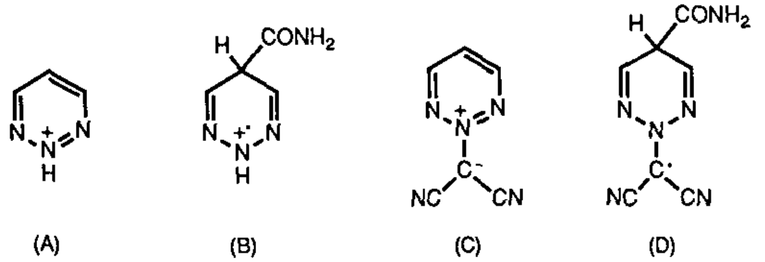
Triazine 2-imines (**7**) and their *N*-acyl derivatives[10] were also allowed to react with nucleophilic radicals to result in the recovery of starting materials, thus **4** was revealed to be the only useful substrate for radical substitution. The ineffectiveness of **5** and **7** was supposed to be due to the back-donation effect. The X-ray crystallographic analyses[11] showed the N(1)-N(2)(and N(2)-N(3)) bond elongation of **5** or **7** compared to those of parent (**1**), which points to an effect of back-donation by the oxygen or nitrogen system as observed in pyridine *N*-oxide.[12] Thus, **8** and **9** are suggested to be important canonical structures for **5** and **7** respectively, and the contribution of the structures (**8**) and (**9**) would cause the elongation of N1-N2 (N2-N3) bond (Scheme 5). On the contrary, molecular orbital calculation of **4**[13] using semiempirical AM1 method[14] suggested that the elongation of N1-N2 (N2-N3) bond was not observed in the optimized structure of **4**, which indicated the lack of back donation effect.



5 **8** **7** **9**

Scheme 5

Accordingly, dicyanomethylene group is supposed to act only as an electron-withdrawing one to activate the triazine ring. Thus nucleophilic carbamoyl radical easily reacted with **4** to generate an intermediates (**10**) (Scheme 6). Moreover, the intermediates (**10**) were suggested to be stabilized because of the existence of two cyano group adjacent to the radical center. Stability of intermediates was compared using MO calculations. Figure 1 shows the results of the AM1 calculations of parent systems and the radical adducts. These data suggest that dicyanomethylene group has more stabilizing effect than the proton at 13.69 kcal/mol ([H_f(D)-H_f(C)]-[H_f(B)-H_f(A)]).

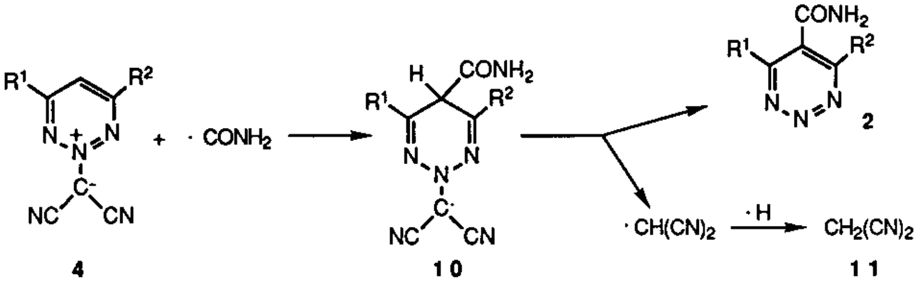


Heat of Formation (H_f)

(A)	263.72 kcal/mol	H_f (A) - H_f (B) = 32.26 kcal/mol
(B)	231.46 kcal/mol	
(C)	183.27 kcal/mol	H_f (C) - H_f (D) = 45.95 kcal/mol
(D)	137.32 kcal/mol	

Figure 1

After the addition, dicyanomethyl radical was eliminated to form carbamoyltriazines (**2**). Dicyanomethyl radical thus released was thought to abstract hydrogen from solvent to afford malononitrile (**11**), which means that the activator was consumed irreversibly. Our reaction system is superior to Minisci's one that would possibly undergo the second attack. The presence of **11** in the reaction mixture was confirmed by comparison of retention time and mass fragmentation with those of the authentic sample on gcms.



Scheme 6

In this paper, we reported the application of modified radical substitution to 1,2,3-triazine ring system. In order to make triazine ring more electronegative, we introduced dicyanomethylene group, which was eliminated after the addition, and transformed into inert species. Thus the reaction was controlled to mono-substitution, which is difficult to perform under usual radical conditions.[16]

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. The ir spectra recorded on a JASCO A-102 spectrophotometer. The ms and gcms were measured with a JEOL JMS-D300 instrument. The ^{1}H-nmr and ^{13}C-nmr spectra were taken on JEOL JNM-FX100 and GX400 spectrometers using tetramethylsilane as an internal standard.

General Procedure for the Reaction of 2-Methyltriazinium Iodides (3) with Carbamoyl Radical

To the suspension of **3** (1.0 mmol) in formamide (3 ml), ammonium persulfate (1.2 mmol) was added and the mixture was heated at 80°C for 1 h. Then the solvent was evaporated *in vacuo* and the residue was chromatographed on alumina to give **1**.

General Procedure for the synthesis of 1,2,3-Triazinium 2-Dicyanomethylides (4)

Tetracyanoethylene oxide (TCNEO) was prepared by the reaction of tetracyanoethylene with 30% aq. H_2O_2 in acetonitrile according to the literature.[9] To the solution of **1** (0.6 mmol) in THF (5 ml) at 0°C, THF (3 ml) solution of TCNEO (1.2 mmol) was added dropwise under stirring. The reaction was continued for 1 to 2 days until the consumption of **1** was confirmed by tlc. Thereafter, the solvent was evaporated and the residue was chromatographed on alumina (benzene:CH_2Cl_2=1:1) to give **5** as yellow solid.

4,6-Dimethyl-1,2,3-triazinium 2-Dicyanomethylide 4a

Yield 86%. Yellow needles from benzene; mp 194°C. *Anal.* Calcd for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.31; H, 3.83; N, 40.38. ^{1}H-Nmr ($CDCl_3$)δ: 2.48 (6H, s), 6.43 (1H, s).

4-Methyl-6-phenyl-1,2,3-triazinium 2-Dicyanomethylide 4b

Yield 80%. Yellow needles from benzene; mp 201°C. *Anal.* Calcd for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.25; H, 3.73; N, 29.54. ^{1}H-Nmr ($CDCl_3$)δ: 2.54 (3H, s), 6.86 (1H, s), 7.41-7.66 (3H, m), 7.94-8.06 (2H, m).

4,6-Diphenyl-1,2,3-triazinium 2-Dicyanomethylide 4c

Yield 82%. Yellow needles from benzene; mp 296°C. *Anal.* Calcd for $C_{18}H_{11}N_5$: C, 72.71; H, 3.73; N, 23.56. Found: C, 72.76; H, 3.48; N, 23.60. ^{13}C-Nmr ($CDCl_3$)δ: 99.65, 112.65, 127.43, 129.58, 131.10, 133.53, 162.71.

4,6-Diethyl-1,2,3-triazinium 2-Dicyanomethylide 4d

Yield 97%. Yellow needles from benzene; mp 142°C. *Anal.* Calcd for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81. Found: C, 59.83; H, 5.35; N, 34.79. ^{1}H-Nmr($CDCl_3$)δ: 1.32 (6H, t, *J*=7 Hz), 2.75 (4H, q, *J*=7 Hz), 6.36 (1H,s).

4-Ethyl-6-methyl-1,2,3-triazinium 2-Dicyanomethylide 4e

Yield 82%. Yellow needles from benzene; mp 138°C. *Anal.* Calcd for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.88; H, 4.66; N, 37.40. ^{1}H-Nmr ($CDCl_3$)δ: 1.29 (3H, t, *J*=7 Hz), 2.22 (3H, s), 2.70 (2H, q, *J*=7 Hz), 6.28 (1H,s).

General Procedure for the Reaction of 4 with Carbamoyl Radical: Synthesis of 5-Carbamoyl-1,2,3-triazines

To the solution of $HCONH_2$ (15 ml) containing 1.0 mmol of **4**, ammonium persulfate(3.0 mmol) was added and the mixture was heated at 80°C for 2 h. Then the solvent was evaporated off *in vacuo* and the residue was chromatographed on alumina (CH_2Cl_2:Et_2O=1:1) to give carbamoyltriazines (**2**).

5-Carbamoyl-4,6-dimethyl-1,2,3-triazine 2a

Yield 69%. Colorless needles from MeOH; mp 210°C. *Anal.* Calcd for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.60; H, 5.34; N, 36.62. ^{1}H-Nmr (CD_3OD)δ: 2.72 (6H, s), 6.60 (2H, br s). ^{13}C-Nmr (CD_3OD)δ: 17.48, 126.46, 154.77, 166.14.

5-Carbamoyl-4-methyl-6-phenyl-1,2,3-triazine 2b

Yield 71%. Colorless needles from MeOH; mp 192°C. *Anal.* Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.43; H, 4.84; N, 26.21. ^{1}H-Nmr($CDCl_3$)δ: 2.72 (3H, s), 7.42-7.60 (3H, m), 7.81-7.95 (2H, m). ^{13}C-Nmr($CDCl_3$)δ: 19.65, 126.56, 129.85, 130.25, 132.20, 134.92, 155.26, 158.12, 168.46.

5-Carbamoyl-4,6-diphenyl-1,2,3-triazine 2c

Yield 68%. Colorless needles from MeOH; mp 230°C. *Anal.* Calcd for $C_{16}H_{12}N_4O$: C, 69.55; 4.38; N, 20.28. Found: C, 69.56; H, 4.24; N, 20.32. ^{1}H-Nmr (CD_3OD)δ: 7.43-7.56 (3H, m), 7.80-7.93 (2H, m). ^{13}C-Nmr (CD_3OD)δ: 123.35, 127.72, 128.33, 130.04, 133.10, 155.03, 166.32.

5-Carbamoyl-4,6-diethyl-1,2,3-triazine 2d

Yield 61%. Colorless needles from MeOH; mp 174°C. Elemental analysis was unsuccessful because of the oily nature of the crystals. Exact ms *m/z* (M^+-N_2)[17] Calcd for $C_8H_{12}N_2O$: 152.095. Found: 152.093. ^{1}H-Nmr (CD_3OD)δ: 1.38 (6H, t, *J*=7 Hz), 2.97 (4H, q, *J*=7 Hz), 6.20 (2H, br s). ^{13}C-Nmr (CD_3OD)δ: 13.26, 27.45, 127.44, 160.82, 168.06.

5-Carbamoyl-4-ethyl-6-methyl-1,2,3-triazine 2e

Yield 46%. Colorless needles from MeOH; mp 167°C. Elemental analysis was unsuccessful because of the oily nature of the crystals. Exact ms *m/z* (M^+) Calcd for $C_7H_{10}N_4O$: 166.086. Found: 166.087. ^{1}H-Nmr (CD_3OD)δ: 1.38 (3H, t, *J*=7 Hz), 2.66 (3H, s), 2.97 (2H, q, *J*=7 Hz), 6.44 (2H, br s). ^{13}C-Nmr (CD_3OD)δ: 13.26, 19.40, 27.42, 127.92, 156.81, 160.70, 168.06.

General Procedure for the Reaction of Triazine 2-Oxides (5) with Carbamoyl Radical

Triazine 2-oxide (0.3 mmol) and ammonium persulfate (0.6 mmol) were dissolved in c.H_2SO_4/$HCONH_2$ (0.2 ml/2 ml) and heated at 80°C for 3 h. Then water (5 ml) was added and the mixture was made slightly basic with sat.Na_2CO_3 soln, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated off. The residue was chromatographed on alumina (CH_2Cl_2:Et_2O:MeOH=10:10:1) to give **6** and **2**.

5-Carbamoyl-4,6-dimethyl-1,2,3-triazine 2-Oxide 6a

Yield 23%. Colorless granules from MeOH; mp 280°C. *Anal.* Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.94; H, 4.79; N, 33.59. ^{1}H-Nmr (CD_3OD)δ: 2.53 (6H, s), 5.32 (2H, br s). ^{13}C-Nmr (CD_3OD)δ: 19.38, 132.05, 166.08, 168.22.

5-Carbamoyl-4-methyl-6-phenyl-1,2,3-triazine 2-Oxide 6b

Yield 29%. Colorless needles from MeOH; mp 265°C. *Anal.* Calcd for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.44; H, 4.22; N, 24.60. ^{1}H-Nmr (CD_3OD)δ: 2.59 (3H, s), 4.57 (2H, br s), 7.40-7.80 (5H, m). ^{13}C-Nmr (CD_3OD)δ: 19.58, 129.94, 130.30, 131.90, 132.86, 133.72, 164.49, 167.70, 168.80.

5-Carbamoyl-4,6-diphenyl-1,2,3-triazine 2-Oxide 6c

Yield 24%. Colorless granules from MeOH; mp 236°C. *Anal.* Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 66.04; H, 4.13; N, 18.91. ^{1}H-Nmr (CD_3OD)δ: 7.40-7.64 (3H, m), 7.75-7.96 (2H, m). ^{13}C-Nmr (CD_3OD)δ: 129.64, 129.75, 131.98, 132.54, 133.58, 166.14, 168.41.

The Molecular Orbital Calculations

The calculations were carried out using the AM1 procedure with the standard parameters, as implemented in the MOPAC program on a PANAFACOM A70 computer.

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