Reaction of 3-Amino-5,6-dimethyl-1,2,4-triazine with Electrophiles

Toshinobu Suzuki, Masahiko Okazaki and Keiryo Mitsuhashi*

Department of Industrial Chemistry, College of Technology, Seikei University,
Musashino-shi, Tokyo 180, Japan

Received July 8, 1985

The title compound was reacted with four types of electrophiles and the respective reaction sites were investigated. The reaction with aryl isocyanates in the conventional way yielded the corresponding ureas. In the presence of triethylamine, the 3-amino group was diacylated with acyl chlorides. On the other hand, in the cases with arylsulfonyl chlorides and *p*-nitrobenzaldehyde under similar conditions, the methyl group at 5-position was preferentially attacked to give arylsulfonylmethyl and *p*-nitrostyryl derivatives, respectively.

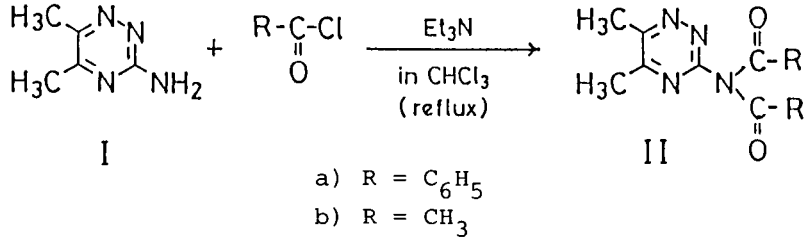
J. Heterocyclic Chem., **23**, 935 (1986).

The present paper deals with the reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (I), as a target substrate, with several electrophiles, where the reaction site of the triazine was found to depend on the class of electrophile.

In the reaction of the triazine I with an excess of benzoyl chloride in the presence of triethylamine in refluxing chloroform, the amino group was dibenzoylated to give 3-dibenzoylamino-5,6-dimethyl-1,2,4-triazine (IIa). Acetyl chloride also yielded the corresponding diacetyl derivative IIb. Such a facile diacylation seemed to proceed by our previously reported mechanism [1-3] (Scheme 1).

On the other hand, benzenesulfonyl chloride under similar conditions attacked unexpectedly not the 3-amino but either the 5- or 6-methyl group of the triazine I to yield a phenylsulfonylmethyl derivative, according to the following interpretations of the analytical and spectral data. Elemental analysis suggested the mono-sulfonylated product and the ir spectrum indicated the amino group remaining unreacted. This shows either a methyl group or a ring nitrogen atom would have been attacked to give one of those in Scheme 2. In the ^{1}H-nmr spectrum of the product, one of the original methyl signals at δ = 2.3 and δ =

Scheme 1



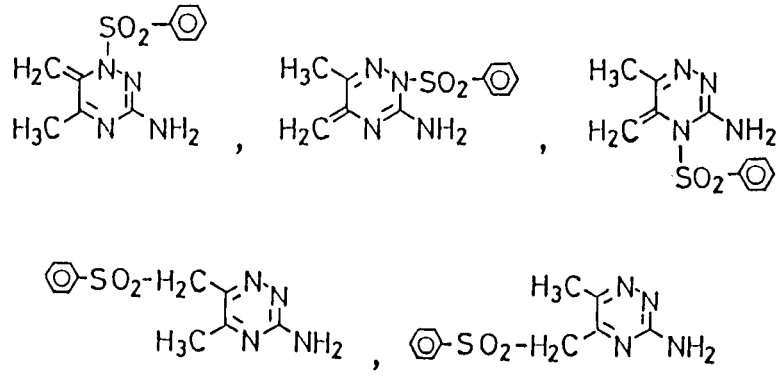
I

II

a) R = C_6H_5

b) R = CH_3

Scheme 2



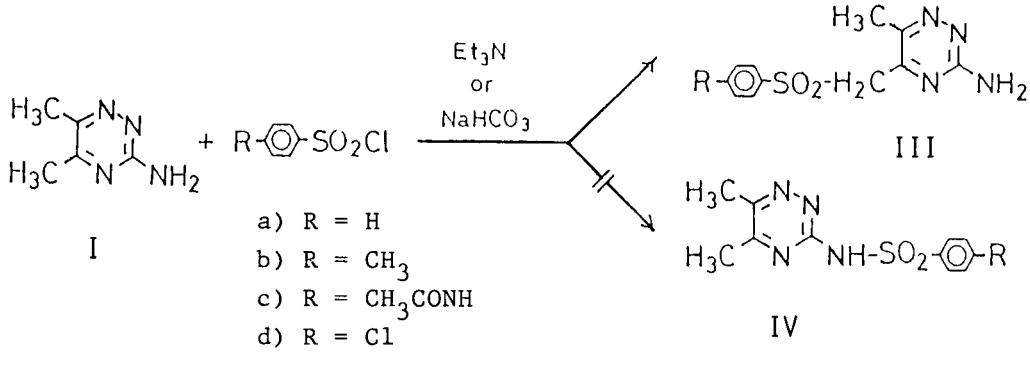
2.4 ppm disappeared, and in its place a new methylene peak appeared at δ = 4.5 ppm. The ^{13}C-nmr spectrum showed a triplet signal of methylenic sp^3-carbon at δ = 60.3 ppm attributable to the sulfonylmethyl group and a quartet signal of methyl carbon at δ = 17.6 ppm, olefinic sp^2-carbon signal being undetected. Therefore, the product must be either 5- or 6-phenylsulfonylmethyl derivative.

Saikawa *et al.* reported [4] the cyclization of 1-amino-3-tosylguanidine with diacetyl to give 3-tosylamino-5,6-dimethyl-1,2,4-triazine (IVb), mp 174-176°, whereas our product from the triazine I with tosyl chloride melted at 227-228°. Such an apparent difference in melting points also supports our contention that sulfonyl chloride attacked the methyl group rather than the amino group. On the other hand, Kono *et al.* described [5] the direct sulfonylation of the triazine I with *N*-acetylsulfanilyl chloride in the presence of sodium bicarbonate in refluxing acetone and claimed the product, mp 210-215°, to be 3-(*N*-acetylsulfanilamido)-5,6-dimethyl-1,2,4-triazine (IVc). The reaction of I with *N*-acetylsulfanilyl chloride under both Kono's and our reaction conditions yielded the same product, mp 211-213°, in either case, which was identified as the acetylsulfanilylmethyl derivative IIIc on the basis of spectral analyses.

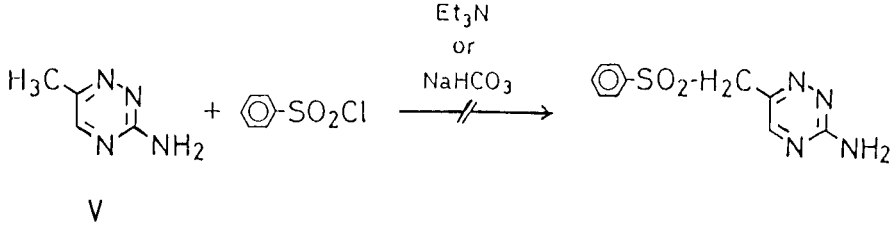
Then, 3-amino-6-methyl-1,2,4-triazine (V), prepared from pyruvaldehyde with aminoguanidine by Saikawa's method [6], was treated with benzenesulfonyl chloride in a similar procedure, resulting in only recovery of the substrate. In contrast, 3-amino-5-methyl-1,2,4-triazine (VI), another isomeric product of Saikawa's reaction [6], was converted to the 5-phenylsulfonylmethyl derivative VII. And Saikawa *et al.* also clarified [7] that the methyl group at 5-position of 1,2,4-triazine was more reactive than that of 6-position. Finally, our sulfonylation products of the triazine I were determined to be 3-amino-6-methyl-5-arylsulfonylmethyl-1,2,4-triazines III. Here it should be emphasized that such a sulfonylation did not occur at all in the absence of triethylamine (Scheme 3).

Since the substrate I, 3-amino-5,6-dimethyl-1,2,4-triazine, has multiple reaction sites depending on a class of electrophile, the reaction with aldehyde was next investigated. The triazine I was treated with *p*-nitrobenzaldehyde in the presence of triethylamine in refluxing ethanol, giving 3-amino-6-methyl-5-(*p*-nitrostyryl)-1,2,4-triazine (VIII) without any detectable amount of an alternative Schiff's base. The structure was determined by

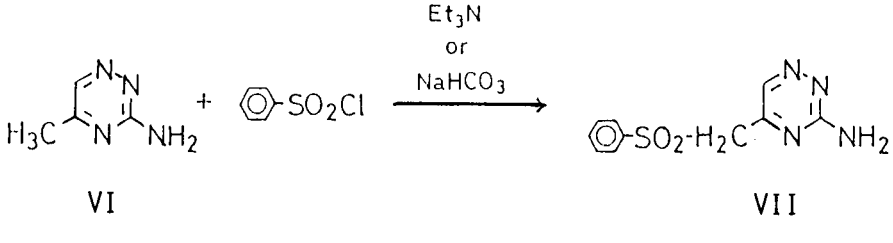
Scheme 3



I III IV

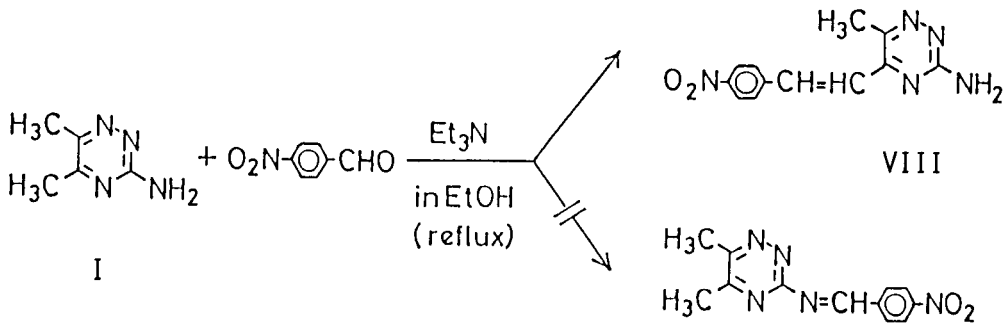


V

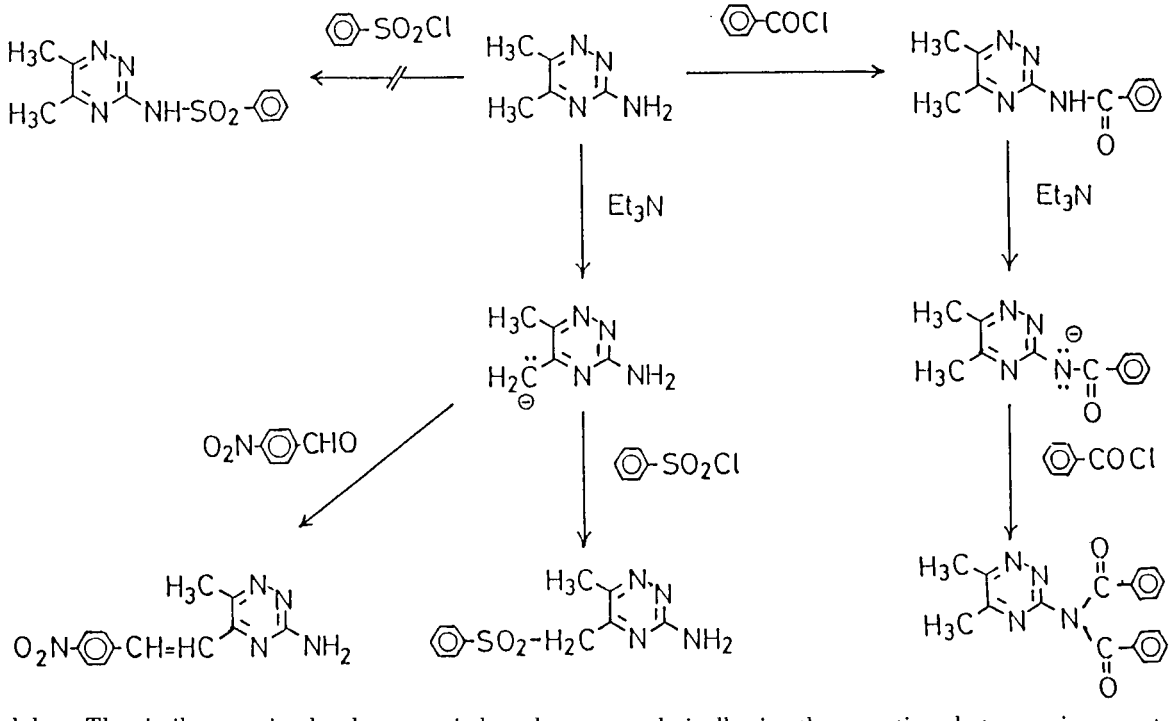


VI VII

Scheme 4



Scheme 5



spectral data. The similar reaction has been carried out by Saikawa *et al.* [7] in acidic media such as acetic acid, yielding the same product as ours. Here again it should be noted that the present reaction did not occur in the absence of triethylamine, the role of which will be discussed later (Scheme 4).

The reaction of the triazine I with various aromatic isocyanates occurred *via* the conventional addition on the amino group to give the corresponding 3-arylureido derivatives IX as summarized in Table 1. Contrary to our expectation, the presence of triethylamine decreased the ureido yields, though triethylamine is known to behave catalytically in the reaction between isocyanates and amines.

The dependence of the reaction site of the triazine I upon the class of electrophile and upon triethylamine is shown in Scheme 5.

The triazine ring itself seems to have a strong electron-withdrawing effect to cause the deactivation of the 3-amino group toward electrophilic attack and, at the same time cause the enhancement of the acidity of 5-methyl group. Benzoyl chloride must be an electrophile strong enough to attack such an electron-deficient amino group to form the mono-benzoylated intermediate, whose

Table 1

3-(*N*-Arylureido)-5,6-dimethyl-1,2,4-triazines IX

I IX

Compound IX	R	Mp °C	Recrystallization solvent	Yield %	Formula	Analysis % Calcd. C	H	N	Found C	H	N
a	H	192-194	CH_3OH	91	$C_{12}H_{13}N_5O$	59.26	5.35	28.81	59.47	5.32	28.71
b	2-Cl	173-174	CH_3OH	36	$C_{12}H_{12}ClN_5O$	51.89	4.32	25.23	51.92	4.25	25.21
c	3-Cl	181-182	C_6H_6-C_6H_{14}	36	$C_{12}H_{12}ClN_5O$	51.89	4.32	25.23	51.73	4.27	25.10
d	4-Cl	194-195	C_6H_6	32	$C_{12}H_{12}ClN_5O$	51.89	4.32	25.23	51.63	4.30	25.35
e	2,3-Cl_2	189-190	C_6H_6-C_6H_{14}	32	$C_{12}H_{11}Cl_2N_5O$	46.15	3.53	22.44	46.40	3.59	22.39
f	2,5-Cl_2	234-235	C_2H_5OH	40	$C_{12}H_{11}Cl_2N_5O$	46.15	3.53	22.44	45.87	3.34	22.55
g	3,4-Cl_2	214-215	C_2H_5OH	64	$C_{12}H_{11}Cl_2N_5O$	46.15	3.53	22.44	46.32	3.47	22.40
h	3,5-Cl_2	197-198	C_6H_6	48	$C_{12}H_{11}Cl_2N_5O$	46.15	3.53	22.44	46.39	3.61	22.27
i	2-CH_3	200-202	C_6H_6	84	$C_{13}H_{15}N_5O$	60.70	5,84	27.24	60.80	5.83	27.19
j	4-CH_3	198-200	CH_3OH	43	$C_{13}H_{15}N_5O$	60.70	5.84	27.24	60.61	5.93	27.41
k	3-CF_3	170-171	C_6H_6-C_6H_{14}	13	$C_{13}H_{12}F_3N_5O$	50.16	3.86	22.51	49.84	3.91	22.65
l	4-CF_3	219-221	C_2H_5OH	99	$C_{13}H_{12}F_3N_5O$	50.16	3.86	22.51	50.21	3.80	22.52
m	4-Cl-2-CH_3	225-227	C_6H_6	79	$C_{13}H_{14}ClN_5O$	53.52	4.80	24.01	53.59	4.59	23.74
n	3-Cl-4-CH_3	219-221	C_2H_5OH	56	$C_{13}H_{14}ClN_5O$	53.52	4.80	24.01	53.40	4.85	23.81

amido proton, owing to its enhanced acidity, is then abstracted with triethylamine, as reported in our previous investigations [1-3] on the different ring systems. The resulting anion is further benzoylated readily to yield the dibenzoylated product IIa. In contrast, benzenesulfonyl chloride, a weaker electrophile, cannot attack the electron-deficient amino group. It can however react with the comparably electron-rich 5-methyl carbanion generated by abstraction of the acidic proton with triethylamine. Thus the 5-phenylsulfonylmethyl derivative IIIa can be obtained, without accompanying successive sulfonylation because of steric hindrance. The reaction with *p*-nitrobenzaldehyde can be accounted for in a similar manner to the sulfonylation, and that with phenyl isocyanate on the basis of the conventional addition.

EXPERIMENTAL

Melting points were determined in a capillary and are uncorrected. The ir spectra were measured on a JASCO IRA-1 spectrometer in a potassium bromide wafer. The ^{1}H-nmr and ^{13}C-nmr spectra were obtained on JEOL JNM-PMX 60 and JEOL JNM-FX 60 spectrometers, respectively. Chemical shifts are reported in ppm from tetramethylsilane and are given in δ units. Mass spectra were obtained on a Finnigan 3300E GC-MS instrument by chemical ionization method with methane reagent gas. The substrate, 3-amino-5,6-dimethyl-1,2,4-triazine (I) was prepared from diacetyl with aminoguanidine bicarbonate by Erickson's method [8]. 3-Amino-5-methyl-1,2,4-triazine (VI) and 3-amino-6-methyl-1,2,4-triazine (V) were separated from each other from the reaction mixture of pyruvaldehyde aqueous solution with aminoguanidine bicarbonate according to Saikawa's method [6], and identified. A typical procedure of the reaction with each class of electrophile is shown as an example.

Reaction with Acyl Chlorides.

3-Dibenzoylamino-5,6-dimethyl-1,2,4-triazine (IIa).

The substrate I (1.24 g, 10 mmoles) was dissolved in chloroform (150 ml) containing triethylamine (4.04 g, 40 mmoles) by gentle warming. Into the resulting solution was added dropwise a solution of benzoyl chloride (2.81 g, 20 mmoles) in chloroform (10 ml). After refluxing for 5 hours, the mixture was evaporated to dryness under reduced pressure, and the residue was washed with cold hexane and extracted with benzene. The extract was evaporated again to give a solid, which was recrystallized repeatedly from ethanol, giving 0.67 g (20%) of IIa as white needles, mp 170-171°; ir: 1680, 1380, 1350, 1270, 1240, 1120 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.4 (s, CH_3, 3H), 2.6 (s, CH_3, 3H), 7.1-7.8 (m, phenyl CH, 10H); ms: (m/e) 332 M$^+$.

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.67; H, 4.82; N, 16.87. Found: C, 68.92; H, 4.83; N, 16.83.

3-Diacetylamino-5,6-dimethyl-1,2,4-triazine (IIb).

White needles of IIb were obtained by recrystallization from hexane in a yield of 0.85 g (41%) from the reaction of I (1.24 g) with acetyl chloride (3.41 g) in the presence of triethylamine (10.1 g); mp 82-84°; ir: 1740, 1720, 1370, 1240 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.3 (s, CH_3, 6H), 2.6 (s, CH_3, 3H), 2.8 (s, CH_3, 3H).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.77; N, 26.92. Found: C, 51.91; H, 5.81; N, 27.07.

Reaction with Arylsulfonyl Chlorides.

3-Amino-6-methyl-5-phenylsulfonylmethyl-1,2,4-triazine (IIIa).

Method A (Using Triethylamine as a Base).

Into a solution of the substrate I (1.24 g, 10 mmoles) in chloroform (150 ml) containing triethylamine (1.01 g, 10 mmoles), benzenesulfonyl chloride (1.77 g, 10 mmoles) in chloroform (20 ml) was added dropwise. The mixture was then heated with stirring under reflux for 20 hours. The resulting pale yellow precipitate was collected on a filter. The filtrate was evaporated to dryness *in vacuo* to give a solid, which was washed with hexane and then with water. The solids were combined and recrystallized

repeatedly from ethanol to yield 1.35 g (51%) of IIIa as pale yellow needles; mp 208-210°; ir: 3320, 3120, 1640, 1490, 1300, 1140, 1070 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.45 (s, 6-CH_3, 3H), 4.5 (s, -CH_2-, 2H), 6.5 (broad, NH_2, 2H), 7.3-8.1 (m, phenyl CH, 5H); ^{13}C-nmr (DMSO-d_6): 17.6 (q, 6-CH_3), 60.3 (t, -CH_2-), 127.7, 129.1, 134.0, 141.7 (phenyl C), 147.8 (s, C-6), 149.4 (s, C-5), 161.8 (s, C-3).

Anal. Calcd. for $C_{11}H_{12}N_4O_2S$: C, 50.00; H, 4.55; N, 21.21. Found: C, 50.10; H, 4.49; N, 21.27.

Method B (Using Sodium Bicarbonate as a Base).

A solution of benzenesulfonyl chloride (1.77 g, 10 mmoles) in acetone (20 ml) was added dropwise to a suspension of I (1.24 g, 10 mmoles) and sodium bicarbonate (0.8 g, 10 mmoles) in acetone (50 ml). The mixture was refluxed for 20 hours, and then cooled on an ice bath, and the resulting precipitate was collected on a filter and washed with water. The pale yellow solid was recrystallized from ethanol to give 1.58 g (60%) of IIIa as pale yellow needles.

3-Amino-6-methyl-5-tosylmethyl-1,2,4-triazine (IIIb).

Pale yellow needles of IIIb were obtained by recrystallization from ethanol in a yield of 1.06 g (38%) from 1.24 g of I, according to the method A; mp 227-228°; ir: 3560, 3240, 1640, 1550, 1480, 1290, 1120, 1050 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.42 (s, CH_3, 3H), 2.47 (s, CH_3, 3H), 4.6 (s, -CH_2-, 2H), 6.8 (broad, NH_2, 2H), 7.3-7.8 (m, phenyl CH, 4H); ^{13}C-nmr (DMSO-d_6): 17.6 (q, 6-CH_3), 20.9 (q, tosyl CH_3), 60.4 (t, -CH_2-), 127.8, 129.6, 136.0, 144.7 (phenyl C), 147.8 (s, C-6), 149.5 (s, C-5), 161.8 (s, C-3).

Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.80; H, 5.04; N, 20.14. Found: C, 51.61; H, 5.07; N, 19.94.

5-(*N*-Acetylsulfanilylmethyl)-3-amino-6-methyl-1,2,4-triazine (IIIc).

Pale yellow leaflets of IIIc were obtained by recrystallization from ethanol-water in a yield of 1.73 g (54%) and 1.16 g (36%) from 1.24 g of I, according to the method A and method B, respectively, mp 211-213°; ir: 3380, 1700, 1620, 1580, 1530, 1320, 1120 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.10 (s, CH_3, 3H), 2.39 (s, CH_3, 3H), 4.55 (s, -CH_2-, 2H), 6.8 (broad, NH_2, 2H), 7.5-7.9 (q, phenyl CH, 4H), 10.3 (s, -NH-, 1H); ms: (m/e) 322 MH^+.

Anal. Calcd. for $C_{13}H_{15}N_5O_3S$: C, 48.60; H, 4.67; N, 21.81. Found: C, 48.84; H, 4.66; N, 21.63.

3-Amino-5-(*p*-chlorophenylsulfonylmethyl)-6-methyl-1,2,4-triazine (IIId).

Pale yellow leaflets of IIId were obtained by recrystallization from ethanol in a yield of 0.30 g (20%) and 1.25 g (84%) from 0.62 g of I, according to the method A and method B, respectively, mp 228-230°; ir: 3370, 3200, 1660, 1550, 1490, 1470, 1300, 1120, 1060 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.47 (s, CH_3, 3H), 4.6 (s, -CH_2-, 2H), 6.8 (broad, NH_2, 2H), 7.3-8.0 (m, phenyl CH, 4H).

Anal. Calcd. for $C_{11}H_{11}ClN_4O_2S$: C, 44.22; H, 3.69; N, 18.76. Found: C, 44.37; H, 3.65; N, 19.00.

3-Amino-5-phenylsulfonylmethyl-1,2,4-triazine (VII).

Pale brown needles of VII were obtained by recrystallization repeatedly from methanol in a yield of 0.14 g (19%) from 0.33 g of VI, according to the method B, mp 228-229° dec; ir: 3300, 3100, 1630, 1530, 1480, 1300, 1140, 1070 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 4.7 (s, -CH_2-, 2H), 7.3 (broad, NH_2, 2H), 7.5-8.0 (m, phenyl CH, 5H), 8.5 (s, 6-triazinyl CH, 1H); ^{13}C-nmr (DMSO-d_6): 60.3 (t, -CH_2-), 127.9, 129.4, 134.3, 138.3 (phenyl C), 141.0 (d, C-6), 150.7 (s, C-5), 162.8 (s, C-3).

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 48.00; H, 4.00; N, 22.40. Found: C, 48.01; H, 3.97; N, 22.02.

Reaction with *p*-Nitrobenzaldehyde.

3-Amino-6-methyl-5-(*p*-nitrostyryl)-1,2,4-triazine (VIII).

A solution of I (1.24 g, 10 mmoles), *p*-nitrobenzaldehyde (3.02 g, 20 mmoles) and triethylamine (2.02 g, 20 mmoles) in ethanol (90 ml) was heated with stirring under reflux for 15 hours. After the mixture was evaporated to dryness *in vacuo*, the residue was washed with benzene and then water. The resulting yellow solid was recrystallized from ethanol to afford yellow powder, which was further purified by recrystallization from methyl cellosolve and ethanol mixture to give 1.43 g (56%) of VIII as reddish orange needles, mp 237-240° dec; lit [7] mp 241-242° dec; ir: 3160, 1600, 1520, 1480, 1340, 1080 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.63 (s, CH_3, 3H), 6.8 (broad, NH_2, 2H), 7.44 (d, J = 16 Hz, *trans* -CH=CH-, 1H), 8.05 (d, J = 16 Hz, *trans* -CH=CH-, 1H), 7.8-8.4 (m, phenyl CH, 4H).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.28; N, 27.24. Found: C, 56.16; H, 4.31; N, 26.96.

Reaction with Aryl Isocyanates.

3-(*N*-Phenylureido)-5,6-dimethyl-1,2,4-triazine (IXa).

The substrate I (1.24 g, 10 mmoles) was dissolved in chloroform (150 ml) without triethylamine by gentle warming. To the resulting solution was added dropwise a solution of phenyl isocyanate (1.19 g, 10 mmoles) in chloroform (10 ml). The mixture was heated with stirring under reflux for 6 hours, and then evaporated to dryness *in vacuo*. The residue was washed with cold hexane and recrystallized repeatedly from ethanol to yield 2.20 g (91%) of IXa as pale yellow needles; mp 192-194°; ir: 3200, 3020, 1700, 1600, 1540, 1480, 1440, 1410, 1290, 1230 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.51 (s, CH_3, 3H), 2.58 (s, CH_3, 3H), 7.0-7.7 (m, phenyl CH, 5H), 10.1 (broad, NH, 1H), 11.2 (broad, NH, 1H); ^{13}C-nmr (DMSO-d_6): 18.1 (q, CH_3), 21.2 (q, CH_3), 119.1, 122.7, 128.5, 138.1 (phenyl C), 150.7 (s, C=O), 151.8 (s, 6-C), 156.8 (s, 5-C), 160.5 (s, 3-C).

Anal. Calcd. for $C_{12}H_{13}N_5O$: C, 59.26, H, 5.35; N, 28.81. Found: C, 59.47; H, 5.32; N, 28.71.

Other arylureido derivatives were prepared by a similar procedure and the results are summarized in Table 1.

REFERENCES AND NOTES

[1] T. Suzuki and K. Mitsuhashi, *Nippon Kagaku Kaishi*, 631 (1979).

[2] T. Suzuki and K. Mitsuhashi, *ibid.*, 667 (1980).

[3] T. Suzuki and K. Mitsuhashi, *ibid.*, 1926 (1980).

[4] I. Saikawa and T. Maeda, Japanese Patent 70 26,106 (1970); *Chem. Abstr.*, **73**, 131039z (1970).

[5] S. Kono, S. Zoga and T. Komaki, Japanese Patent 67 20,313 (1967); *Chem. Abstr.*, **69**, 36183a (1968).

[6] I. Saikawa and T. Maeda, *Yakugaku Zasshi*, **87**, 1501 (1967).

[7] I. Saikawa, A. Takai and Y. Kodama, *ibid.*, **84**, 109 (1964).

[8] J. G. Erickson, *J. Am. Chem. Soc.*, **74**, 4706 (1952).