STUDIES ON as-TRIAZINE DERIVATIVES. VIII.[1] SYNTHESIS OF 5-SUBSTITUTED 1,2,4-TRIAZINES

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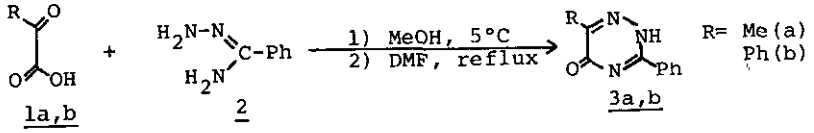
Abstract ——— Dehydroxy-chlorination of 6-methyl-3-phenyl- (3a), and 3,6-diphenyl-5-oxo-2,5-dihydro-1,2,4-triazine (3b) afforded the corresponding 5-chloro-1,2,4-triazines (4a,b). The chloro-1,2,4-triazines (4a,b) treated with sodium alkoxides or amines to give the 5-alkoxy- (5a,b), or 5-amino (6a,b) derivatives. Furthermore, 4 readily reacted not only with active methylene compounds but also with acetophenone and nitromethane under basic conditions.

The regio-selective formation of *3,6-disubstituted 5-oxo-2,5-dihydro-1,2,4-triazines* (as-triazines) (3) by the reaction of α-keto acids (1) with benzamidrazone (2)[2] prompted us to utilize this reaction for the synthesis of as-triazine derivatives with functional groups at the 5-position. Here we report the high-yield dehydroxy-chlorination of 3 to the corresponding 5-chloro-as-triazines (4) together with the synthesis of hitherto unknown as-triazine derivatives from 4.

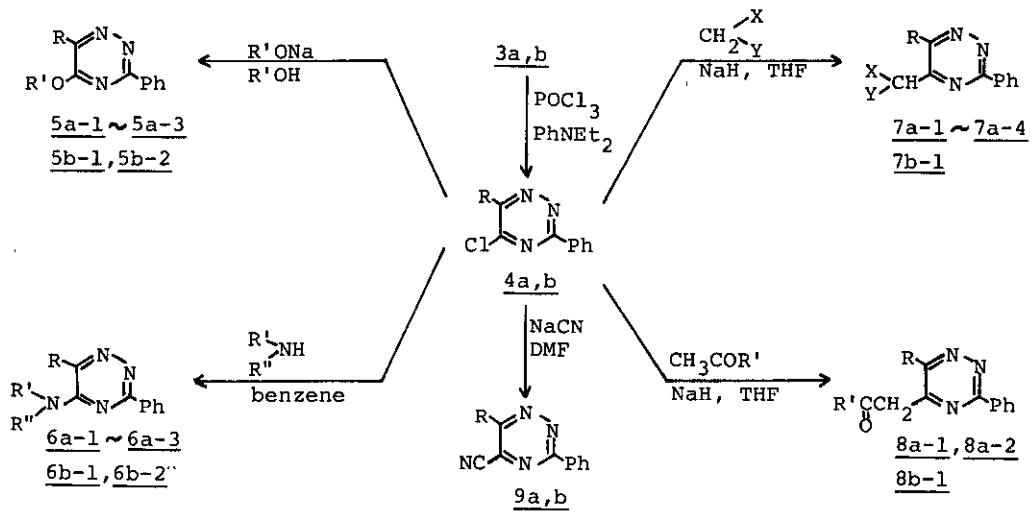


Scheme 1

The reaction of 3 with phosphoryl chloride under conventional conditions failed to give 4, but the additon of N,N-diethylaniline to the reaction mixture

facilitated the dehydroxy-chlorination to proceed at room temperature.[3] Under these conditions, 5-chloro-6-methyl-3-phenyl-as-triazine (4a) and 5-chloro-3,6-diphenyl-as-triazine (4b) were obtained in high yields. Additionally, facile synthesis of 4b was accomplished by use of thionyl chloride alone, as in the case of 9-acridinone,[4] whereas the reaction of 3a with thionyl chloride resulted in the resinification of 3a. These results suggest that the dehydroxy-chlorination of 2,5-dihydro-5-oxo-as-triazines is strongly affected by the structure of the substrate and by the reaction conditions.

Like many other active N-heteroaryl halides, 4a,b readily reacted with sodium alkoxides or amines to give the 5-alkoxy (5a,b) or 5-N-substituted-amino (6a,b) derivatives, as expected. Unlike many 4-chloropyrimidine derivatives,[5] the replacement of the chloro-substituent of 4a,b to a cyano group was successful on stirring with sodium cyanide at room temparature in dimethylformamide and the as-triazine-5-carbonitriles (9a,b) were obtained.



Scheme 2

Moreover, the condensation of 4a,b, with various active methylene compounds, methyl ketones, and nitromethane in the presence of sodium hydride in tetrahydrofuran gave the as-triazine derivatives (7a,b, 8a,b) containing the corresponding carbon side chains.

Generally, the use of much potent leaving groups, such as methanesulfonyl and benzenesulfonyl groups, is recommended to the condensation with active methylene

compounds in the case of π-deficient N-heteroaromatics.[6] At 5-position of as-triazine, however, it became clear that the conversion of a chloro-substituent into either methanesulfonyl group or benzenesulfonyl group in advance to the condensation is unnecessary.

EXPERIMENTAL

Melting points were obtained in open cappillary tubes and are uncorrected. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. All of the compounds gave correct microanalyses.

5-Chloro-6-methyl-3-phenyl-as-triazine (4a)

N,N-Diethylaniline (4.5 g, 0.03 mol) was added to a suspension of 6-methyl-5-oxo-3-phenyl-2,5-dihydro-as-triazine (3a)[2] (5.61 g, 0.03 mol) in $POCl_3$ (20 ml) and the mixture was stirred at room temperature for 30 min, then diluted with benzene. The benzene solution was washed successively with H_2O, 10% NH_4OH and sat. aq. NaCl, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by colomn chromatography on active alumina (Sumitomo, KCG-30) using benzene as an eluent. Recrystallization from hexane-AcOEt gave 5.2 g (84 %) of 4a, mp 87-88°C, as pale yellow prisms. ^{1}H-Nmr (in CCl_4): 2.42 (s, 3H), 7.3-7.7 (m, 3H), 8.3-8.7 (m, 2H).

5-Chloro-3,6-diphenyl-as-triazine (4b)

A suspension of 5-oxo-3,6-diphenyl-2,5-dihydro-as-triazine (3b)[7] (10 g, 0.04 mol) in $SOCl_2$ (50 ml) was refluxed for 90 min while stirring. The reaction mixture was concentrated to dryness under reduced pressure and a small amount of H_2O was added to the residue. The mixture was extracted with $CHCl_3$ and the organic extract was washed successively with H_2O, 10% NH_4OH, and sat. aq. NaCl solution, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from AcOEt to give 9.63 g (90%) of 4b, mp 131-132°C (lit.[7] mp 132-134°C), as pale yellow prisms. ^{1}H-Nmr (in $CDCl_3$): 7.4-7.8 (m), 7.8-8.1 (m), 8.4-8.8 (m), the integrated ratio is 1:1:3.

General Procedures for the Preparation of 5-Alkoxy-as-triazines (5)

A soltuion of 4 (0.002 mol) in the corresponding alcohol (10 ml) was added to a solution of sodium alkoxide [prepared from metallic sodium (0.05 g, 0.002 g atom) and corresponding alcohol], and the mixture was stirred at room temperature for

30 min. After removal of the solvent, a small amount of H_2O was added to the residue and extracted with $CHCl_3$. The product, obtained from the $CHCl_3$ extract, was purified by recrystallization. Melting points, yields, and ^{1}H-nmr data are listed in Table 1.

Table 1. 5-Alkoxy-as-triazines 5a and 5b prepared

Product No.	R	R'	Yield [%]	mp [°C]	^{1}H-Nmr(CCl_4) δ [ppm]
5a-1	CH_3	OCH_3	92	117-118[a]	2.54(s,3H);4.17(s,3H);7.3-7.5(m,3H);8.2-8.6(m,2H)
5a-2	CH_3	OC_2H_5	72	109-111	1.47(t,3H,J=7Hz);2.54(s,3H);4.57(q,2H,J=7Hz);7.3-7.5(m,3H); 8.3-8.6(m,2H)
5a-3	CH_3	OC_6H_5	61	92-94	2.82(s,3H);7.0-7.7(m,8H);8.1-8.4(m,2H)
5b-1	C_6H_5	OCH_3	78	117-118[b]	4.16(s,3H);7.3-7.7(m,6H);8.0-8.3(m,3H);8.4-8.7(m,2H)
5b-2	C_6H_5	OC_2H_5	72	101-103	1.53(t,3H,J=7Hz);4.65(q,2H,J=7Hz);7.1-7.7(m,6H);7.9-8.3 (m,2H);8.3-8.7(m,2H)

[a] lit.[8] mp 115-116°C

[b] lit.[8] mp 114-115°C

General Procedure for the Preparation of 5-(N-Substituted-amino)-as-triazines (6)

A solution of 4 (0.002 mol) and amine (0.004 mol) in dry benzene (15 ml) was stirred at room temperature for 4 -12 h. A small amount of H_2O was added to the reaction mixture. The organic layer was separated, and then dried over K_2CO_3. After removal of the solvent, the residue was purified by recrystallization. In the case of the reaction with $NH_2NH_2 \cdot H_2O$, no solvent was used. Melting points, yields, and ^{1}H-nmr data are listed in Table 2.

Table 2. 5-(N-Substituted-amino)-as-triazines 6a and 6b prepared

Product No.	R	R'	R''	Yield [%]	mp [°C]	^{1}H-Nmr($CDCl_3$) δ [ppm]
6a-1	CH_3	H	NH_2	85	216 (decomp.)	2.27(s,3H);7.0-7.6(m,3H);7.6-8.1(m,2H)[a]
6a-2	CH_3	H	n-C_4H_9	74	152-154	0.97(t,3H,J=6Hz);1.2-2.0(m,4H);2.48(s,3H);3.65(q,2H, J=6Hz);4.9-5.4(br,1H);7.4-7.6(m,3H);8.4-8.5(m,2H)
6a-3	CH_3	-$(CH_2)_5$-		87	97-99	1.5-2.0(m,6H);2.64(s,3H);3.5-3.9(m,4H);7.4-7.6 (m,3H);8.4-8.6(m,2H)
6b-1	C_6H_5	H	NH_2	92	215-217 (decomp.)[b]	7.0-7.5(m);7.8-8.1(m);the integrated ratio is 4:1[a]
6b-2	C_6H_5	H	n-C_4H_9	88	90-92	0.95(t,3H,J=6Hz);1.1-2.1(m,4H);3.58(q,2H,J=6Hz); 5.4-5.8(br,1H);7.2-7.9(m,8H);8.3-8.7(m,2H)

[a] Measured in CF_3COOH

[b] lit.[7] mp 217-218°C (decomp.)

General Procedure for the Preparation of 5-Carbon-substituted as-Triazines (7 and 8)

A mixture of active methylene compound (0.0033 mol) and NaH, 50% in oil (0.16 g, 0.0033 mol) in dry THF (10 ml) was refluxed for 30 min, and thereto a solution of 4 (0.003 mol) in dry THF (20 ml) was added. The reaction mixture was stirred at room temperature for 12 -24 h, and concentrated under reduced pressure. To the residue, dil. HCl was added and then the aqueous solution was extracted with $CHCl_3$. The organic extract was dried over Na_2SO_4 and the solvent was evaporated. The product was purified by silica gel chromatography or recrystallization. Same procedure was applied in the case of methyl ketones and nitromethane. Melting points, yields, and ^{1}H-nmr data are listed in Table 3,4.

Table 3. 5-Carbon-substituted as-triazines 7a and 7b prepared

Product No.	R	X	Y	Yield [%]	mp [°C]	^{1}H-Nmr ($CDCl_3$) δ [ppm]
7a-1	CH_3	CN	$CO_2C_2H_5$	56	193-194	1.41(t,3H,J=7Hz);2.97(s,3H);4.41(q,2H,J=7Hz);7.3-7.6(m,3H);7.9-8.2(m,2H);14.4-14.9(br,1H)
7a-2	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	65	104-105	1.31(t,6H,J=7Hz);2.69(s,3H);4.34(q,4H,J=7Hz);4.96(s,1H);7.4-7.6(m,3H);8.4-8.6(m,2H)
7a-3	CH_3	$COCH_3$	$CO_2C_2H_5$	59	106-107	1.18(t,3H,J=7Hz);1.97(s,3H);2.65(s,3H);4.25(q,2H,J=7Hz);7.4-7.7(m,3H);8.3-8.7(m,2H);13.3-13.7(br,1H)
7a-4	CH_3	H	NO_2	67	150-152	2.82(s,3H);5.72(s,2H);7.4-7.7(m,3H);8.4-8.6(m,2H)
7b-1	C_6H_5	CN	$CO_2C_2H_5$	80	181-183	1.37(t,3H,J=7Hz);4.35(q,2H,J=7Hz);7.3-7.9(m,8H);14.7-15.0(br,1H)

Table 4. 5-Carbon-substituted as-triazines 8a and 8b prepared

Product No.	R	R'	Yield [%]	mp [°C]	^{1}H-Nmr ($CDCl_3$) δ [ppm]
8a-1	CH_3	CH_3	47	120-122	2.34(s,3H);2.49(s,3H);5.48(s,1H);7.5-7.9(m,3H);8.1-8.5(m,2H);15.0-15.5(br,1H)
8a-2	CH_3	C_6H_5	58	134-135	2.62(s,3H);6.16(s,1H);7.4-7.7(m,6H);7.9-8.1(m,2H);8.1-8.4(m,2H);15.6-16.0(br,1H)
8b-1	C_6H_5	C_6H_5	71	192-194	6.39(s,2H);7.2-8.0(m,13H);8.3-8.6(m,2H);15.8-16.0(br,1H)

6-Metyl-3-phenyl-as-triazine-5-carbonitrile (9a)

A solution of 4a (0.82 g, 0.004 mol) in DMF (5 ml) was added to a solution of NaCN (0.22 g, 0.0045 mol) in DMF (5 ml) with cooling in an ice bath. The reaction mixture was stirred for 1 h, and then poured onto an excess of ice-water mixture. The aqueous solution was extracted with benzene, and the organic

extract was washed with H_2O, dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography using benzene as an eluent. Recrystallization from cyclohexane gave 0.68 g (87 %) of 9a, mp 134-135°C, as yellow prisms. ^{1}H-Nmr (in $CDCl_3$): 3.01 (s, 3H), 7.5-7.7 (m, 3H), 8.4-8.7 (m, 2H).

3,6-Diphenyl-as-triazine-5-carbonitrile (9b)

Following the procedure for the preparation of 9a, treatment of 4b (1.07 g, 0.004 mol) in DMF (15 ml) with NaCN (0.22 g, 0.0045 mol) resulted in the formation of a crude product which was recrystallized from AcOEt to give 0.72 g (70 %) of 9b, mp 167-169°C, as yellow prisms.

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