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STUDIES ON as-TRIAZINE DERIVATIVES. IV.[1] SYNTHESIS OF UNSYMMETRICAL 5,6-DISUBSTITUTED 1,2,4-TRIAZINES

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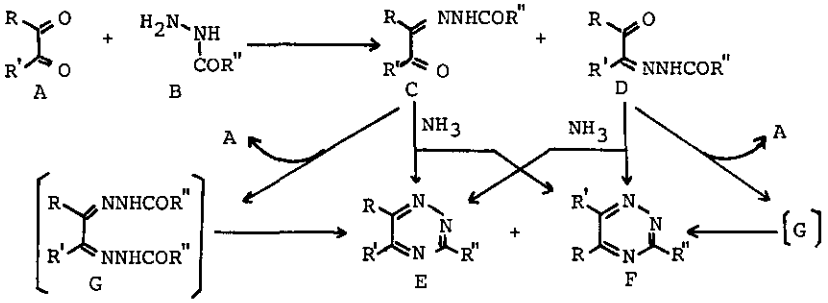
Abstracts ——— The reaction of 5-chloro-6-methyl-3-phenyl-1,2,4-triazine (4a) with ethylidenetriphenylphosphorane followed by the hydrolysis of the resulting as-triazinylphosphorane afforded 5-ethyl-6-methyl-3-phenyl-1,2,4-triazine (6a) in 88 % yield. The condensation of 5-chloro-6-ethyl-3-phenyl-1,2,4-triazine (4b) with dimethyloxosulfonium methylide and subsequent desulfurization of the resulting triazinylmethylide gave 6-ethyl-5-methyl-3-phenyl-1,2,4-triazine (6g) in 32 % overall yield. Using these triazines (6a, 6g) as standard specimens, the ratio of isomers (6a, 6g) formed from the condensation of 2,3-pentanedione with benzamidrazone, was determined to be 3:1.

The synthesis of 5,6-dialkyl-1,2,4-triazines (as-triazines) is accomplished by the condensation of α-diketones (A) with acylhydrazines (B) and subsequent treatment of the resulting acylhydrazones (C & D) with ammonia.[2] In the case of an unsymmetric α-diketone, however, the condensation is resulted in the formation of two positional isomers of the acylhydrazones (C & D), unless the character of the two carbonyl group is different. Furthermore, when a pure acylhydrazone (C or D) is treated with ammonia, the cyclization still proceeds non-regioselectively to give two isomers of 5,6-disubstituted as-triazines (E & F). This fact was reasonably explained by assuming the formation of diacylhydrazones (G) due to intermolecular re-composition of the acylhydrazone (C or D) during the triazine cyclization.[3]
Accordingly, the above route is concluded not to have wide applicability for the preparation of unsymmetrical 5,6-disubstituted as-triazines.[4] On the other hand, the reaction of α-keto acids (1) with amidrazones (2) has been reported[5] to give

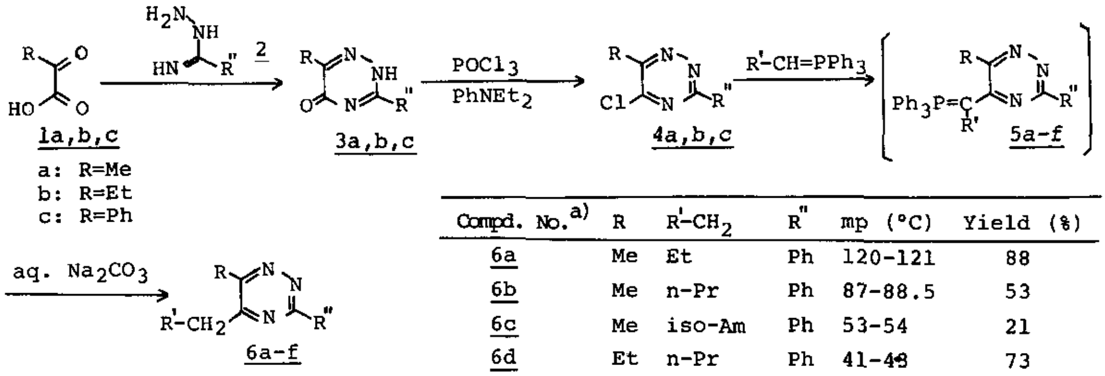
the corresponding 5-triazinones (3) exclusively. In the present paper, we describe the stepwise introduction of different alkyl groups at the 5- and 6-position of as-triazines using 3 as starting materials.



Scheme 1

When 6-methyl-3-phenyl-as-triazin-5(2H)-one (3a)[6] prepared by the condensation of pyruvic acid (1a) and benzamidrazone (2) was treated with phosphoryl chloride in the presence of diethylaniline at room temperature for 30 min, 5-chloro-6-methyl-3-phenyl-as-triazine (4a), mp 87-88°C, was obtained in 83 % yield. The condensation of 4a with ethylidenetriphenylphosphorane[7] followed by alkaline hydrolysis of the resulting as-triazinylphosphorane (5a) gave 5-ethyl-6-methyl-3-phenyl-as-triazine (6a), mp 119-121°C (lit.[2] mp 122°C) in 88 % yield as expected. The ^{1}H-NMR ($CDCl_3$) spectrum of 6a showed the signals due to a methyl group (2.70 ppm, 3H, s) and an ethyl group (1.38 ppm, 3H, t, 2.87 ppm, 2H, q, J=7.0 Hz each). According to this manner, several kinds of 5,6-disubstituted 3-phenyl-as-triazine (6b-f) were synthesized from the corresponding α-keto acids and benzamidrazone. The yields and melting points are listed in the additional Table in Scheme 2.

Since the alkaline hydrolysis of α-(6-ethyl-3-phenyl-5-as-triazinyl)methylenetriphenylphosphorane prepared from 5-chloro-6-ethyl-3-phenyl-as-triazine (4b), mp 97-98°C, and methylenetriphenylphosphorane by the above method did not proceed, the alternative synthesis of 6-ethyl-5-methyl-3-phenyl-as-triazine (6g) was devised as follows. The condensation of 4b with dimethyloxosulfonium methylide[8] in tetrahydrofuran proceeded smoothly to give the dimethyloxosulfonium 6-ethyl-3-phenyl-5-as-triazinylmethylide (7a). The desulfurization of crude 7a with deactivated Raney nickel[9] afforded 6g, mp 106-107°C, in 32 % overall yield from 4b. The ^{1}H-NMR ($CDCl_3$) spectrum of 6g is evidently different from that of 6a, showing the signals at 1.40 ppm (3H, t, J=7.0 Hz), 2.57 ppm (3H, s), and 3.00 ppm (2H, q, J=7.0 Hz). Similarly, 5-methyl-3,6-diphenyl-as-triazine (6h), mp 125-126°C, was obtained from 5-chloro-3,6-diphenyl-as-triazine (4c)[10] via 7b in 53 % yield.

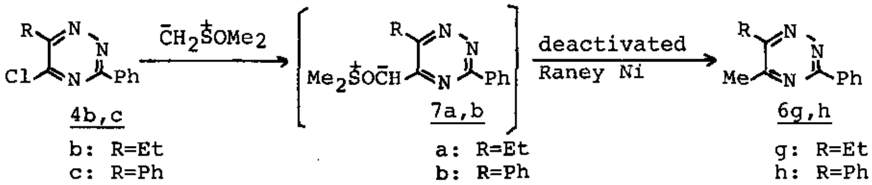


Scheme 2

Compd. No.[a)]	R	R'-CH_2	R''	mp (°C)	Yield (%)
6a	Me	Et	Ph	120-121	88
6b	Me	n-Pr	Ph	87-88.5	53
6c	Me	iso-Am	Ph	53-54	21
6d	Et	n-Pr	Ph	41-43	73
6e	Ph	Et	Ph	64-65	48
6f	Ph	n-Pr	Ph	69-71	76
6g	Et	Me	Ph	106-107	32 [b)]
6h	Ph	Me	Ph	125-126	53 [b)]

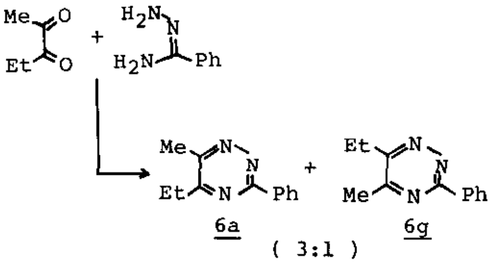
a) Satisfactory analytical and spectral (IR, ^{1}H-NMR) data were obtained for all new compounds.

b) Yields based on 5-chloro-as-triazines.



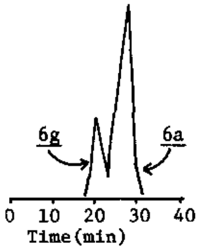
Scheme 3

Finally, the reaction of pentane-2,3-dione with benzamidrazone[11] was tested for the preparation of dialkyl-as-triazines. The reaction was smoothly proceeded under basic conditions, but the product (76 % total yield) was a mixture of 6a and 6g, the ratio of which was determined to be 3:1 by high-performance liquid chromatography using authentic specimens synthesized above.



Scheme 4

Figure 1. High-Performance Liquid Chromatogram



COLUMN: Hitachi gel 3040 4mmID×25cm
SOLVENT: $CHCl_3$/hexane(50/50,v/v)
FLOW RATE: 0.5ml/min
DETECTOR: UV: 290nm

Thus, our present investigation provides a method for the preparation of _as_-triazine derivatives having different alkyl groups at the 5- and 6-position.

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