

STUDIES ON as-TRIAZINE DERIVATIVES. VII.<sup>1</sup>RESEMBLANCE BETWEEN as-TRIAZINES AND QUINAZOLINES  
IN NUCLEOPHILIC ADDITION-ELIMINATION REACTIONS

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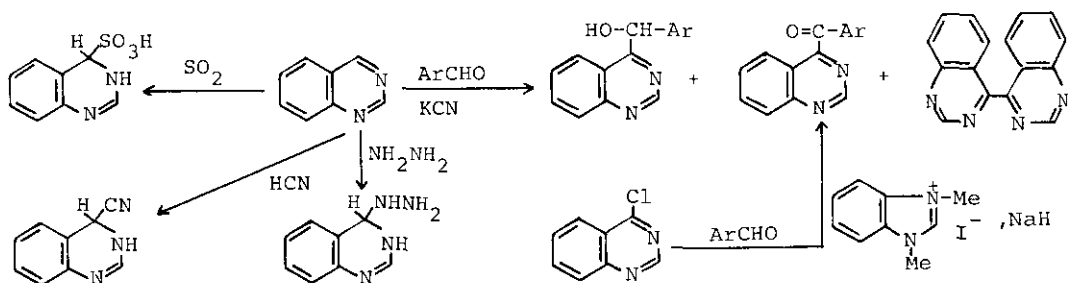
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**Abstracts** — Alike 4-chloroquinazoline, 5-chloro-1,2,4-triazines (as-triazines) reacted with aromatic aldehydes in the presence of 1,3-dimethylbenzimidazolium iodide under basic conditions to give 5-aroaryl-as-triazines. The Grignard reaction of 5-cyano-as-triazine with arylmagnesium bromides failed to give any significant product. Some analogy of as-triazines with quinazolines, in their chemical properties, was additionally investigated.

It is well known that quinazoline derivatives sometimes exhibit peculiar behavior for the nucleophilic addition-elimination reactions at their 4-positions. For example, unsubstituted quinazoline smoothly reacts with sulfur dioxide, hydrogen cyanide, and hydrazine to give the corresponding adducts<sup>2</sup> as shown below.



Scheme 1

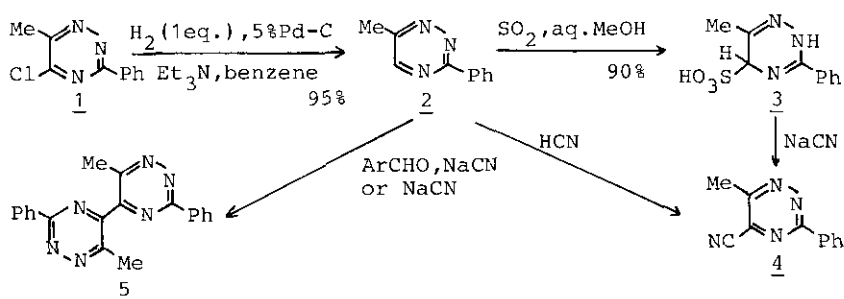
The cross-benzoin condensation with benzaldehyde by catalytic action of potassium

cyanide was reported to proceed distinctively,<sup>3</sup> and 4-benzhydryl- and 4-benzoylquinazoline were isolated together with 4,4'-biquinazoline. 4-Benzoylquinazoline was alternatively obtained by the condensation of 4-chloroquinazoline with benzaldehyde in the presence of 1,3-dimethylbenzimidazolium iodide under basic conditions.<sup>4</sup>

During the investigation on the synthesis of 1,2,4-triazine (as-triazine) derivatives, we recognized 5-chloro-as-triazines to be extremely reactive toward nucleophilic substitutions. Thus, our interest was focussed on comparison of quinazoline derivatives and the corresponding as-triazine derivatives in their chemical properties. In the present paper, we wish to report the synthesis of 5-aroyle-as-triazines accomplished by the above point of view.

In order to test the conventional preparation of 5-aroyle-as-triazines by Grignard reaction, 6-methyl-3-phenyl-as-triazine-5-carbonitrile (4) was synthesized according to the following manner. 5-Chloro-6-methyl-3-phenyl-as-triazine (1)<sup>5</sup> was submitted to catalytic reduction in the presence of triethylamine, to give 6-methyl-3-phenyl-as-triazine (2), mp 68-69°C, in 95 % yield.

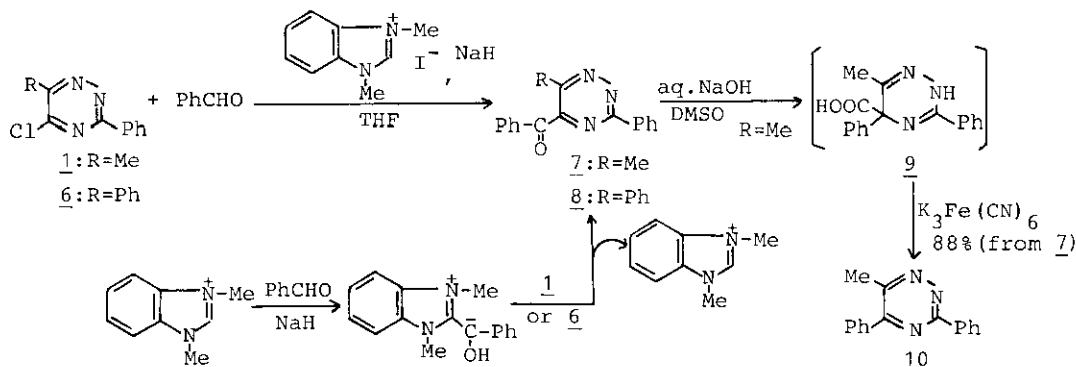
An aqueous methanolic solution of 5-unsubstituted compound (2) easily absorbed sulfur dioxide and the corresponding adduct, 6-methyl-3-phenyl-2,5-dihydro-as-triazine-5-sulfonic acid (3) was isolated as a stable, colorless solid, mp 198°C (decomp.), in 90 % yield. On treatment with sodium cyanide in DMF, 3 was transformed into the desired carbonitrile (4) (83 %), although the reason of the concomitant oxidation is obscure. When hydrogen cyanide was bubbled into a DMF solution of 2, the same carbonitrile (4) was obtained directly, in 71% yield. The synthesis of 4, described above, seems to show the similarity between the reactivity of quinazolines and that of as-triazines.



Scheme 2

Accordingly it is no wonder that the reaction of 4 with phenylmagnesium bromide fails to give 5-benzoyl-6-methyl-3-phenyl-as-triazine (7).<sup>6</sup> Furthermore, the trial of cross-benzoin condensation of 2 with benzaldehyde in the presence of sodium cyanide did not give 7, and in this case, the 5,5'-bi-as-triazine (5) [mp 197-199°C; MS  $m/z$ : 340 ( $M^+$ );  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.94 (s), 7.45-7.71 (m), 8.45-8.71 (m), the integrated ratio is 3:3:2] was obtained as a sole product (63-70 %).

According to the manner reported on the 4-chloroquinazoline,<sup>4</sup> 1 was treated with benzaldehyde and 1,3-dimethylbenzimidazolium iodide in THF under basic conditions, and 5-benzoyl-6-methyl-3-phenyl-as-triazine (7) [mp 127-128°C; IR ( $CHCl_3$ ): 1680  $cm^{-1}$ ;  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.79 (3H, s), 7.36-7.77 (6H, m), 7.88-8.13 (2H, m), 8.42-8.68 (2H, m)] was isolated in 62 % yield as expected. As shown in Scheme 3, an adduct of benzaldehyde with the benzimidazolium, similar to the case of quinazolinium derivatives,<sup>4</sup> probably acts as the main reagent for the formation of 7 from 1. The same type of reaction proceeded on 5-chloro-3,6-diphenyl-as-triazine (6)<sup>7</sup> to give 5-benzoyl-3,6-diphenyl-as-triazine (8) [mp 182-184°C; IR ( $CHCl_3$ ): 1680  $cm^{-1}$ ;  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 7.32-8.07 (13H, m), 8.49-8.83 (2H, m)].

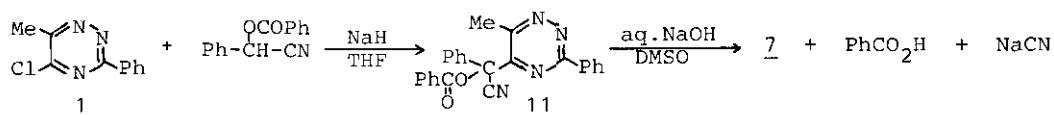


Scheme 3

When 7 was treated with sodium hydroxide in aqueous DMSO, a benzilic acid rearrangement type reaction occurred to give 6-methyl-3,5-diphenyl-2,5-dihydro-as-triazine-5-carboxylic acid (9) as an amorphous powder. The oxidation of crude 9 with potassium ferricyanide afforded 6-methyl-3,5-diphenyl-as-triazine (10).<sup>8,9</sup>

In addition to the above investigation, it should be mentioned that the reaction of 1 with O-benzoylmandelonitrile in the presence of sodium hydride yielded  $\alpha$ -benzoyloxy- $\alpha$ -phenyl-as-triazine-5-acetonitrile (11) [mp 246-248°C (decomp.); IR (KBr): 1740  $cm^{-1}$ ;  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.65 (3H, s), 7.47-7.84 (11H, m), 8.15-8.33

(2H, m), 8.47-8.71 (2H, m)] in 43 % yield, which was degraded to 7 (54 %) by alkaline hydrolysis in aqueous DMSO.



Scheme 4

#### ACKNOWLEDGEMENT

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10. Satisfactory analytical data were obtained for all new compounds (2, 3, 4, 5, 7, 8, and 11).

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