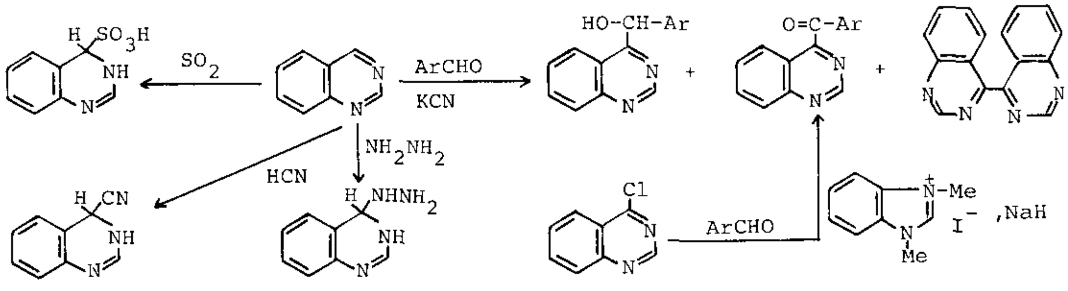
HETEROCYCLES, Vol. 24, No. 5, 1986

STUDIES ON as-TRIAZINE DERIVATIVES. VII.[1]
RESEMBLANCE BETWEEN as-TRIAZINES AND QUINAZOLINES IN NUCLEOPHILIC ADDITION-ELIMINATION REACTIONS

Shoetsu Konno, Setsuya Ohba, Mataichi Sagi, and
Hiroshi Yamanaka*
Pharmaceutical Institute, Tohoku University
Aobayama, Sendai 980, Japan

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-aroyl-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[2] as shown below.



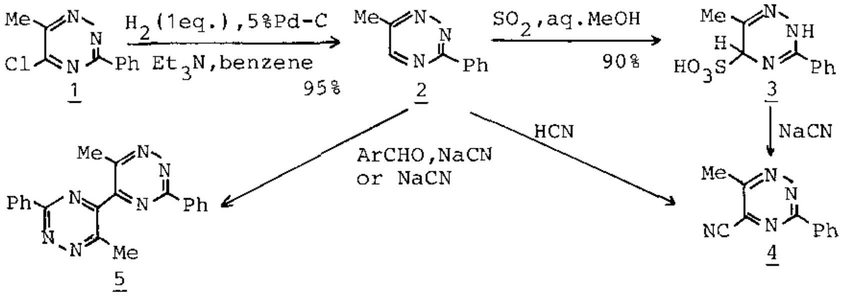
Scheme 1

The cross-benzoin condensation with benzaldehyde by catalytic action of potassium cyanide was reported to proceed distinctively,[3] and 4-benzhydryl- and 4-benzoylquinazoline were isolated togehter 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.[4]

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-aroyl-*as*-triazines accomplished by the above point of view.

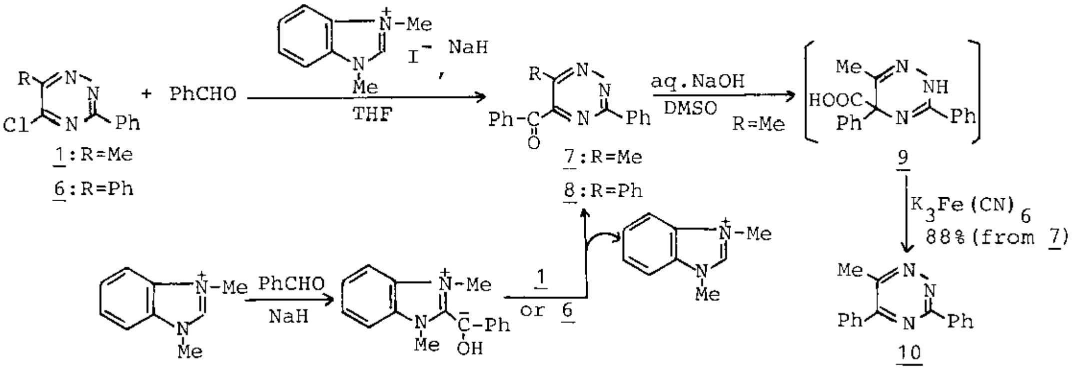
In order to test the conventional preparation of 5-aroyl-*as*-triazines by Grignard rection, 6-methyl-3-phenyl-*as*-triazine-5-carbonitrile (**4**) was synthesized according to the following manner. 5-Chloro-6-methyl-3-phenyl-*as*-triazine (**1**)[5] was submitted to catalytic reduction in the presence 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

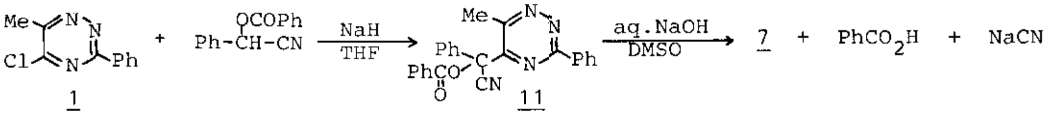
Accordingly it is no wonder that the reaction of 4 with phenylmagnesium bromide fails to give 5-benzoyl-6-methyl-3-phenyl-*as*-triazine (7).[6] Furthermore, the trial of cross-benzoin condensation of 2 with benzaldehyde in the presence of sodium cyanide did not give 7, and in this case, the 5,5'-bi-*as*-triazine (5) [mp 197-199°C; MS m/z: 340 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 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,[4] 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}; ^{1}H-NMR ($CDCl_3$) δ: 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 quinazolium derivatives,[4] 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)[7] to give 5-benzoyl-3,6-diphenyl-*as*-triazine (8) [mp 182-184°C; IR ($CHCl_3$): 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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).[8,9]
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 α-benzoyloxy-α-phenyl-*as*-triazine-5-acetonitrile (11) [mp 246-248°C (decomp.); IR (KBr): 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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 degradated to 7 (54 %) by alkaline hydrolysis in aqueous DMSO.



Scheme 4

ACKNOWLEDGEMENT

The authors wish to thank Prof. T. Higashino and Dr. A. Miyashita, Shizuoka College of Pharmacy, for their helpfull suggestions. This work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan, which is acknowledged.

REFERENCES AND NOTES

1. Part VI: S. Konno, M. Sagi, Y. Yūki, and H. Yamanaka, Heterocycles, 1985, 23, 2807.
2. T. Higashino, Yakugaku Zasshi, 1960, 80, 245.
3. T. Higashino, M. Goi, and E. Hayashi, Chem. Pharm. Bull., 1974, 22, 2493.
4. A. Miyashita and E. Hayashi, Abstracts of Papers, the 9th International Congress of Heterocyclic Chemistry (Tokyo, August 1983), p.303.
5. S. Konno, M. Sagi, M. Agata, Y. Aizawa, and H. Yamanaka, Heterocycles, 1984, 22, 2241.
6. Resinous material was obtained in this reaction.
7. R. Fusco and S. Rossi, Tetrahedron, 1958, 3, 209.
8. R. Metze, Chem. Ber., 1955, 88, 772.
9. The analogous result had been reported on the alkaline treatment of 4-benzoylquinazoline [T. Higashino, M. Takemoto, and E. Hayashi, Chem. Pharm. Bull., 1985, 33, 1351].
10. Satisfactory analytical data were obtained for all new compounds (2, 3, 4, 5, 7, 8, and 11).

Received, 27th January, 1986