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STUDIES ON AS-TRIAZINE DERIVATIVES. XVII[1]
CHLORINATION OF 5,6-DIMETHYL-3-PHENYL-as-TRIAZINE

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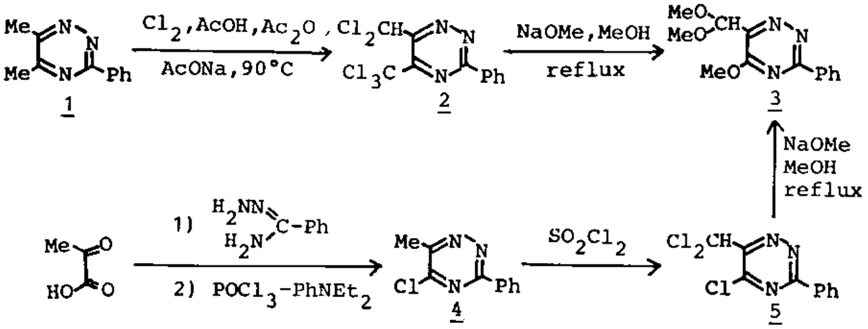
Abstract——Homolytic chlorination of 5,6-dimethyl-as-triazine(**1**) with Cl_2 gave 6-dichloromethyl-5-trichloromethyl-as-triazine(**2**) selectively. Structural determination of **2** by chemical method and synthesis of 5-amino-6-formyl-as-triazine derivatives are described.

It is well known that the methyl groups attached to the 3-, 5-, and 6-positions of 1,2,4-triazine(as-triazine) ring are highly active towards homolytic chlorination, and monomethyl-as-triazines are, in principle, converted into the corresponding trichloromethyl compounds.[2] In the present paper, we report an exhaustive chlorination of 5,6-dimethyl-3-phenyl-as-triazine(**1**), the structural determination of the resulting pentachloro compound(**2**), and the synthesis of 6-formyl-as-triazine derivatives from **2**.

When chlorine gas was bubbled slowly into a solution of **1** in acetic acid and acetic anhydride in the presence of sodium acetate at 90°C, the pentachloride, mp 156-158°C, 77%, of **1** was obtained as a single product. The product(**2**) smoothly reacted with sodium methoxide(5 eq. mol) to give 5-methoxy-6-dimethoxymethyl-3-phenyl-as-triazine(**3**), mp 124-126°C, 43%, which was identical with an authentic specimen prepared by the following procedure.

5-Chloro-6-methyl-as-triazine(**4**) site-selectively synthesized by the condensation of pyruvic acid with benzamidrazone[3] and subsequent dehydroxy-chlorination of the resulted 5-triazinone with phosphoryl chloride was easily chlorinated with sulfuryl chloride to give 5-chloro-6-dichloromethyl-3-phenyl-*as*-triazine(**5**), mp 129-131°C, in 74% yield from **4** . On heating with sodium methoxide(3 eq. mol) in methanol, **5** was readily changed to **3** in almost quantitative yield.



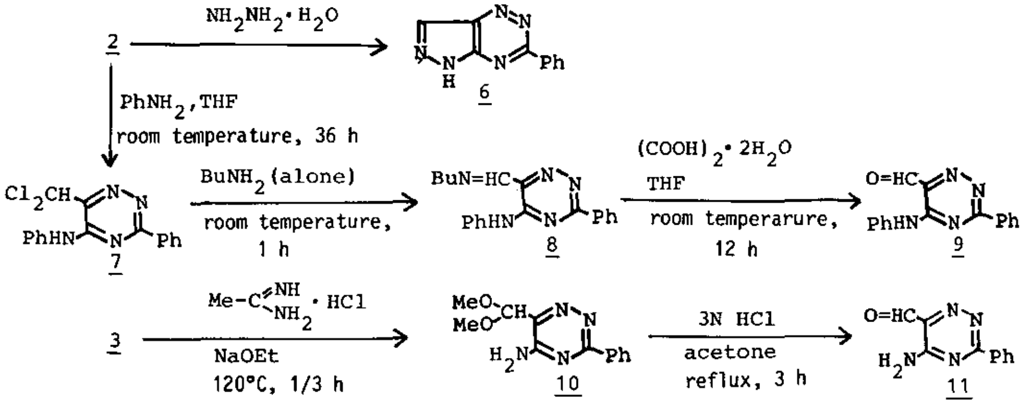
Scheme 1

These findings clearly demonstrated the structure of the pentachloride to be 6-dichloromethyl-5-trichloromethyl-3-phenyl-*as*-triazine(**2**). In connection with the conversion of **2** into **3**, it has been known that a trichloromethyl group on *as*-triazine rings acts as an efficient leaving group towards nucleophilic substitution.[4] Furthermore, no formation of 5,6-bis(trichloromethyl)-3-phenyl-*as*-triazine was observed on the exhaustive chlorination of **1**. Probably, the 5-trichloromethyl group predominantly formed retards the trichlorination of the less reactive 6-methyl group by its steric hindrance.[5]

When **2** was heated with hydrazine hydrate under reflux, the 6-dichloromethyl group and 5-trichloromethyl group acted as a masked formyl group and a leaving group respectively, and as a result, 3-phenyl-5*H*-pyrazolo[3,4-e]-1,2,4-triazine(**6**), mp 268-270°C, was isolated in 75% yield.

Based on the result described above, the synthesis of 6-formyl-*as*-triazine derivatives from the 6-dichloromethyl compounds was examined as follows. The reaction of **2** with aniline(2 eq. mol) in THF at room temperature gave 5-anilino-6-dichloromethyl-3-phenyl-*as*-triazine(**7**), mp 121-123°C, in 76% yield. Compound **7** reacted with butylamine alone to give the Schiff base(**8**), mp 109-111°C, which was easily hydrolyzed with oxalic acid dihydrate to the desired aldehyde(**9**), mp 147-148°C, in 80% overall yield from **7**.

On the other hand, the reaction of **2** with ammonia in methanol failed to give 5-amino-6-formyl-3-phenyl-*as*-triazine(**11**). In this case, the reaction mixture turned to dark brown immediately, and no formation of **11** or the corresponding aldimine was detected in the reaction mixture. Thus, in place of **2**, the acetal(**3**) was heated with acetamidine(free base) at 120°C to afford 5-amino-6-dimethoxymethyl-3-phenyl-as-triazine(**10**), on treatment of which with 3N hydrochloric acid in acetone, 5-amino-6-formyl-3-phenyl-as-triazine(**11**), mp 212-215°C(decomp.)[^{1}H-nmr(DMSO-d_6): 7.4-7.8 (3H, m), 7.8-8.3 (1H, br), 8.3-9.0 (3H, m), 10.23 (1H, s)] was obtained in 44% yield from **3**.



Scheme 2

These reactions are the first synthesis of as-triazine derivatives with bifunctional character corresponding to o-aminobenzaldehyde, although further investigations on reaction procedure are still remain. The synthesis of compounds containing bicyclic as-triazine nucleous from **11** is now under investigation, which will be reported in the near future.

REFERENCES AND NOTES

1. Part XVI: S. Ohba, S. Konno, and H. Yamanaka, Chem. Pharm. Bull., in press.
2. S. Konno, M. Sagi, E. Takaharu, S. Fujimura, K. Hayashi, and H. Yamanaka, Chem. Pharm. Bull., 1988, **36**, 1721.
3. V. Uchytilova, P. Fiedler, M. Prystas, and J. Gut, Coll. Czech. Chem. Commun., 1971, **36**, 1955.
4. S. Konno, M. Yokoyama, and H. Yamanaka, Heterocycles, 1982, **19**, 1865.
5. It is known that o-xylene is chlorinated with excess chlorine to give 1-dichloromethyl-2-trichloromethylbenzene in 70% yield since the size of the chlorine atoms prevents the introduction of six chlorine atoms into the side chains of o-xylene[J. Fernandez-Bolanos, W. G. Overend, A. Sykes, J. C. Tatlow, and E. H. Wiseman, J. Chem. Soc., **1960**, 4003].

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