STUDIES ON as-TRIAZINE DERIVATIVES. V.[1] SYNTHESIS AND HYDRATION OF ALKYNYL-1,2,4-TRIAZINES

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Abstracts ——— Palladium catalyzed cross-coupling reaction of 3- and 5-iodo-as-triazines with monosubstituted acetylenes gave the corresponding alkynyl-as-triazines in good yields. The hydration of 3- and 5-trimethylsilylethynyl-as-triazines thus obtained in the presence of mercuric sulfate afforded 3- and 5-acetyl-as-triazines, whereas the reaction of the other alkynyl-as-triazines with piperidine followed by the hydrolysis of the resulting enamines gave the acylmethyl-as-triazines, as expected.

It is well known that the palladium catalyzed cross-coupling reaction of aryl halides with monosubstituted acetylenes, which was reported by Sonogashira, et al.,[2] is conveniently applied to the synthesis of diazine derivatives from the corresponding heteroaromatic halides.[3,4] As an extensive work of the above reaction, we describe the reaction of several halo-1,2,4-triazines (as-triazines), together with the hydration of the resulting alkynyl-as-triazines.

Firstly, the reaction of 5-chloro-6-methyl-3-phenyl-as-triazine (1a) was compared with that of 5-iodo-6-methyl-3-phenyl-as-triazine (2a). As shown in Table I, the iodide (2a) was concluded to be better starting material than the chloride (1a), though 2a, mp 99-100°C, was prepared by the chlorine-iodine exchange on 1a. Furthermore, the reaction of 1a at 50°C brought about the slight decrease of the yield.

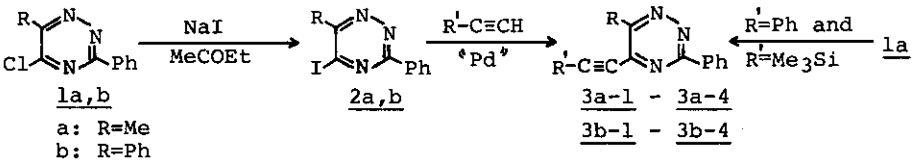
On the basis of these results, 2a and 5-iodo-3,6-diphenyl-as-triazine (2b), mp 136.5-138°C, were treated with various monosubstituted acetylenes in triethylamine in the presence of palladium dichloride-triphenylphosphine and cupric iodide as catalysts for 12 h at room temperature. As listed in Table II, the yields of the desired alkynyl-as-triazines (3a-1 - 3a-4, 3b-1 - 3b-4) were satisfactory.

Table I. The Reaction of 5-Chloro- (1a) and 5-Iodo-6-methyl-3-phenyl-as-triazine (2a) with Phenylacetylene and Trimethylsilylacetylene.

Run	as-Triazine	Leaving Group	Monosubstituted Acetylene[a)]	Catalyst	Solvent	Temperature	Reaction Time (h)	Yield of Product
1	1a	Cl	PhC≡CH	$Pd(PPh_3)_2Cl_2$ CuI 0.001mol eq. (each)	Et_3N[b)]	room temp.	12	64%(3a-1)
2	2a	I	PhC≡CH			room temp.	12	92%(3a-1)
3	1a	Cl	$Me_3SiC≡CH$			room temp.	12	37%(3a-3)
4	2a	I	$Me_3SiC≡CH$			room temp.	12	70%(3a-3)
5	1a	Cl	PhC≡CH			50°C	12	56%(3a-1)

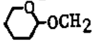
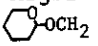
a) In all the cases, 1.0 mole of as-triazines and 1.2 mole eq. of acetylenes were used.

b) as-Triazines were dissolved in triethylamine at 10% weight/weight.



Scheme 1

Table II. Physical Properties and Yields of Alkynyl-as-triazines (3a-1 - 3b-4).

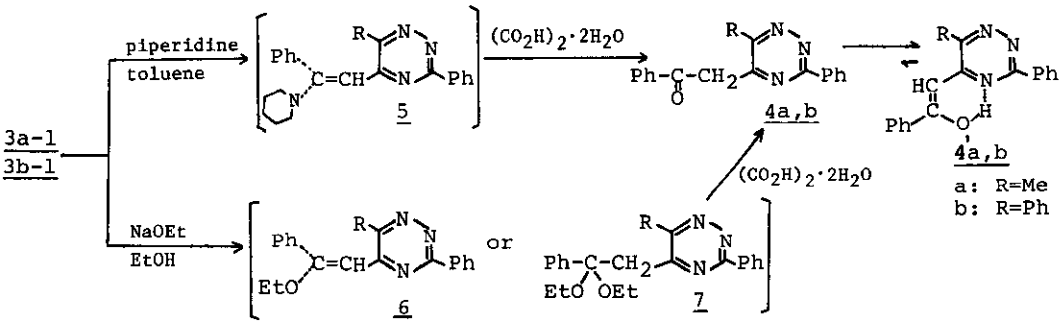
Compd. No.[a)]	R	R'	Yield (%)[b)]	mp (°C)	Appearance (recryst. solv.)
3a-1	Me	Ph	92	115-117	yellow prisms(AcOEt-hexane)
3a-2	Me	n-Bu	83	50-51	yellow prisms(pentane)
3a-3	Me	Me_3Si	70	68-70	yellow prisms(pentane)
3a-4	Me		64	65-66.5	yellow prisms(Et_2O-hexane)
3b-1	Ph	Ph	83	175-177	yellow prisms(AcOEt)
3b-2	Ph	n-Bu	79	76.5-78	yellow prisms(hexane)
3b-3	Ph	Me_3Si	72	105-107	yellow prisms(hexane)
3b-4	Ph		64	91-93	yellow prisms(AcOEt-hexane)

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

b) The yields observed on the reaction under the conditions of run 1 are listed.

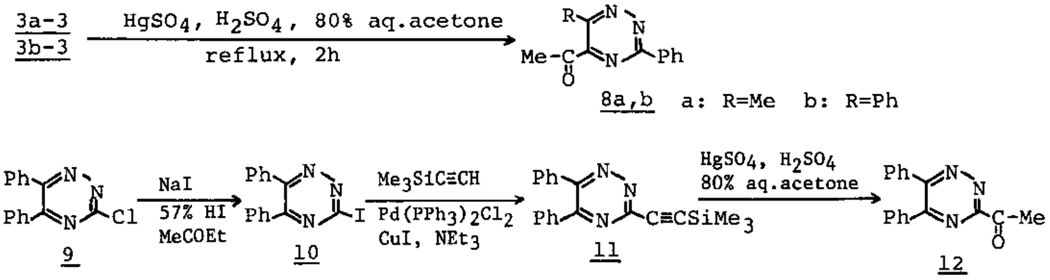
Secondary, in order to prepare as-triazine derivatives having a carbonyl side chain at the 5-position, the hydration of the alkynyl-as-triazines obtained above was investigated. When 3a-1 was heated with piperidine in toluene, a viscous oil was obtained. On the treatment with oxalic acid, the oil was converted into 6-methyl-

5-phenacyl-3-phenyl-as-triazine (4a), mp 135-136°C, in 76 % overall yield from 3a-1. Accordingly, a piperidine enamine (5), as shown in Scheme 2, is considered to be a likely intermediate.[5] Similarly, 5-phenacyl-3,6-diphenyl-as-triazine (4b), mp 194-196°C, was derived from 3b-1 in 86 % yield. The phenacyl compounds (4a,b) were alternatively obtained by the treatment of 3a-1, 3b-1, with excess sodium ethoxide in boiling ethanol and subsequent hydrolysis of the crude intermediate (6 or 7). Judging from the ^{1}H-NMR spectra of 4a,b, an enol form (4'a,b) seems to be predominant in the tautomerism in a CDCl$_3$ solution.[6]



Scheme 2

On the other hand, when the trimethylsilylethynyl derivatives (3a-3, 3b-3) were heated in aq. sulfuric acid in the presence of mercuric sulfate, 5-acetyl-6-methyl-3-phenyl-as-triazine (8a), mp 96-98°C, and 5-acetyl-3,6-diphenyl-as-triazine (8b), mp 108-110°C, were obtained in 47 and 69 % yields, respectively. In addition, this method is applicable to the synthesis of 3-acetyl-as-triazines. Namely, the cross-coupling reaction of trimethylsilylacetylene with 3-iodo-5,6-diphenyl-as-triazine (10), mp 147-149°C, which was easily obtained by the reaction of the corresponding chloride (9) with sodium iodide in the presence of 57 % hydriodic acid, proceeded smoothly to give 3-trimethylsilylethynyl-5,6-diphenyl-as-triazine (11), mp 126-127°C, in 78 % yield. The compound (11), like the positional isomer (3b-3), was hydrolyzed to give 3-acetyl-5,6-diphenyl-as-triazine (12), mp 159.5-161.5°C, as expected.[7] The synthesis of acyl derivatives of as-triazine has not yet been reported prior to the present work. Accordingly, the hydration of the trimethylsilylethynyl-as-triazines provides a method for the preparation of such compounds, though the products are limited in structures.



Scheme 3

In conclusion, the cross-coupling reaction with terminal acetylenes and the conversion of the resulting products are applicable to the synthesis of as-triazine derivatives as well as that of pyrimidine derivatives.

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6. The ^{1}H-NMR (60 MHz, in $CDCl_3$) data of 4a,b: 4a, δ 2.62 (3H, s), 6.18 (1H, s), 7.33-7.72 (6H, m), 7.77-8.08 (2H, m), 8.10-8.43 (2H, m), 15.72 (1H, bs, exchangeable with D_2O); 4b, δ 6.30 (1H, s), 7.30-8.05 (13H, m), 8.30-8.60 (2H, m), 15.85 (1H, bs, exchangeable with D_2O)
7. The hydration of trimethylsilylethynyl groups on heteroaromatics other than as-triazines was investigated by us; T. Sakamoto, Y. Kondo, M. Shiraiwa, and H. Yamanaka, Synthesis, 1984, 245.

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