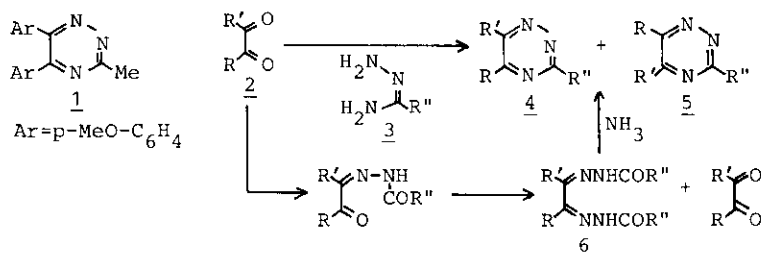


STUDIES ON as-TRIAZINE DERIVATIVES. VI.¹ INTRODUCTION OF
 ARYL GROUPS TO THE 5-POSITION OF 1,2,4-TRIAZINES

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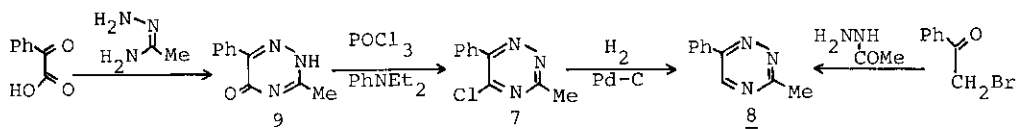
Abstract — 1,2,4-Triazine derivatives possessing different aryl groups at the 5- and 6-positions were synthesized by the addition of arylmagnesium bromides (Ar'MgBr) to 6-aryl(Ar)-3-methyl-1,2,4-triazines with the free 5-position, and subsequent oxidation of the resulting 2,5-dihydro intermediates. The synthesis of 6-aryl-3-methyl-1,2,4-triazines is also described.

Prior to our present investigation, the synthesis of 1,2,4-triazine (as-triazine) derivatives having two different aryl groups at the 5- and 6-positions was unexplored, although 5,6-bis(p-methoxyphenyl)-3-methyl-as-triazine (1) has been known to have a potent anti-inflammatory activity.² Namely, as shown in Scheme 1, the condensation of asymmetric α -diketone (2) with acid amidrazones (3) usually resulted in the formation of two positional isomers (4 and 5).³ The ring-closure reaction of a pure acylhydrazone of the α -diketone in the presence of ammonia affords unexpectedly a mixture of the same isomers (4, 5), whose formation is reasonably explained by assuming the formation of the corresponding dihydrazone (6) as an intermediate.⁴



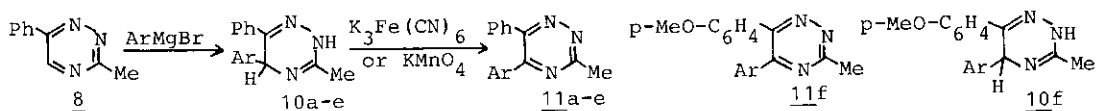
Scheme 1

In the present paper, we report an unequivocal and site-selective synthesis of 4 or 5, which is carried out in order to investigate the structure-activity relationships of 5,6-diaryl-as-triazines as for their anti-inflammatory action. Hydrogenolysis of 5-chloro-3-methyl-6-phenyl-as-triazine (7) over palladium catalyst⁵ in the presence of triethylamine in benzene gave 3-methyl-6-phenyl-as-triazine (8), mp 106-107°C (lit.⁶ mp 106-108°C) in 93 % yield. The alternative synthesis of 8 through the condensation of phenacyl bromide with acetylhydrazine has been reported by Saraswathi et al.,⁷ but 7 was site-selectively obtained by the reaction of phenylglyoxylic acid with acetamidrazone followed by dehydroxy-chlorination of resulting 3-methyl-6-phenyl-as-triazin-5-one (9), in good yield. Accordingly, these two methods are both effective for the preparation of 3-alkyl-6-aryl-as-triazines.



Scheme 2

When 8 was treated with *p*-methoxyphenylmagnesium bromide in ether, 5-(*p*-methoxyphenyl)-3-methyl-6-phenyl-2,5-dihydro-as-triazine (10a), mp 142-144°C, was obtained. The dihydro compound (10a), was easily oxidized with potassium permanganate in acetone or with potassium ferric cyanide under alkaline condition to give 5-(*p*-methoxyphenyl)-3-methyl-6-phenyl-as-triazine (11a), mp 85-87°C, as expected. Similarly, 6-(*p*-methoxyphenyl)-3-methyl-5-phenyl-as-triazine (11f), mp 99-100°C, a positional isomer of 11a, was prepared by the addition of phenylmagnesium bromide to 6-(*p*-methoxyphenyl)-3-methyl-as-triazine and subsequent aromatization of the resulting intermediate (10f). Based on the results described above, several asymmetric 5,6-diaryl-as-triazines were synthesized effectively, whose yields and melting points are listed in the table 1.



Scheme 3

As well as arylmagnesium bromide, aryllithiums reacted with 8 to give the corresponding 2,5-dihydro-as-triazines. Thus the 5-furyl and 5-pyrrolyl derivatives (11g,h) were prepared by this method followed by the aromatization.

Table 1 Melting Points and Yields for 10 and 11.

	Ar	<u>10</u> ^{a)}		<u>11</u> ^{a)}	
		mp(°C)	Yield(%)	mp(°C)	Yield(%)
a	p-MeO-C ₆ H ₄	142-144	72	85-87	81
b	2-Thienyl	194-196	55	115-116	85
c	p-Me-C ₆ H ₄	219-220	70	71-72	73
d	p-PhO-C ₆ H ₄	171-173	64 ^{b)}	95-97	64
e	α-naphthyl	197-198	69 ^{b)}	126-127	66
g	2-furyl	176-177	49	106-107	75
h	1-methyl 2-pyrrolyl	115-116	29	128-129	65

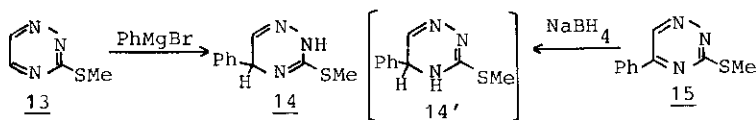
a) Satisfactory analytical and spectral (IR, ¹H-NMR) data were obtained for all new compounds.

b) KMnO₄ was used as oxidizing agent.

Typical experiments are as follows: 5-(p-Methoxyphenyl)-3-methyl-6-phenyl-2,5-dihydro-as-triazine (10a) ——— The Grignard reagent was prepared by the usual method from Mg (0.24 g, 0.01 mol) and p-bromoanisole (1.87 g, 0.01 mol) in dry THF (10 ml). This solution was added dropwise with shaking to a solution of 3-methyl-6-phenyl-as-triazine (8) (0.86 g, 0.005 mol) in dry Et₂O (40 ml). After the reaction mixture was stirred at room temperature for 6 h under nitrogen, a saturated NH₄Cl solution (10 ml) was added to hydrolyze the resulting magnesium complex. The ethereal layer was separated, and the aqueous layer was extracted with ether. The combined ether extract was dried over anhydrous K₂CO₃ and the solvent was evaporated. The residual oil was chromatographed on a silica gel column by elution with ether. Recrystallization from AcOEt-hexane gave 1.01 g (72 %) of colorless prisms, mp 142-144°C. Anal. Calcd for C₁₇H₁₇N₃O: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.61; H, 6.24; N, 14.86. ¹H-NMR (CDCl₃, TMS) ppm: 2.00 (3H, s), 3.73 (3H, s), 5.67 (1H, s), 6.73-6.96 (2H, d, J=10 Hz), 7.17-7.50 (5H, m), 7.93-8.00 (3H, m). 5-(p-Methoxyphenyl)-3-methyl-6-phenyl-as-triazine (11a) ——— A solution of K₃Fe(CN)₆ (8 g, 0.28 mol) and NaOH (1.5 g, 0.038 mol) in H₂O (50 ml) was added to a solution of 10a (2.0 g, 0.072 mol) in CH₂Cl₂ (40 ml) with stirring. After the reaction mixture was stirred at room temperature for 19 h, the CH₂Cl₂ layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined CH₂Cl₂ extract was dried over anhydrous Na₂SO₄. After removal of solvent, the residue was purified by passing it through a silica gel column with Et₂O-n-hexane (1:1) as the eluent. Recrystallization from AcOEt-n-hexane gave 1.12 g (81 %) of yellow prisms, mp 85-87°C. Anal. Calcd for C₁₇H₁₅N₃O: C, 73.63; H, 5.45 ; N,

15.15. Found: C, 73.83; H, 5.57; N, 15.43. $^1\text{H-NMR}$ (CCl_4 , TMS) ppm: 2.87 (3H, s), 3.80 (3H, s) 6.83 (1H, s), 7.23-7.67 (8H, m).

In connection with the above discussion, Daunis⁸ has reported that the addition of phenylmagnesium bromide to 3-methylthio-*as*-triazine (13) yields 3-methylthio-5-phenyl-4,5-dihydro-*as*-triazine (14').



Scheme 4

On the other hand, Sasaki et al.⁹ synthesized 14 by the sodium borohydride reduction of 3-methylthio-5-phenyl-*as*-triazine (15) and determined the structure of the product not to be the 4,5-dihydro compound, but the 2,5-dihydro one by the chemical conversions and X-ray crystallography. However, the dihydro compound¹⁰ thus prepared by our method was identical with the compound reported by Sasaki. Accordingly Grignard type reaction of *as*-triazine derivatives are considered to give 2,5-dihydro compound, generally.

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