

A ONE-STEP SYNTHESIS OF PURINE DERIVATIVES BY THE REACTION OF
PHENYLZOMALONAMIDAMIDINE WITH ARYL ALDEHYDES

Fumio YONEDA,* Ryosuke KOGA, and Masatsugu HIGUCHI

Faculty of Pharmaceutical Sciences, Kumamoto University

Oe-honmachi, Kumamoto 862

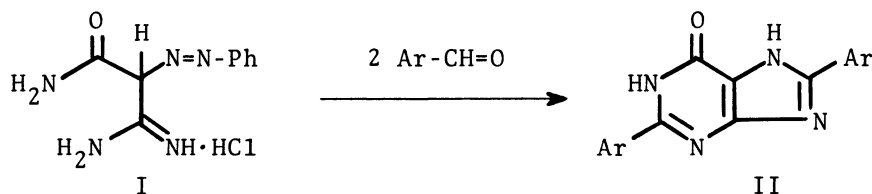
Treatment of phenylzomalonamidamide (I) with aryl aldehydes yielded the corresponding 2,8-diarylhyloxanthines (II) in a single step. The reaction under milder conditions formed the intermediary monoarylidene derivatives (III) of I, from which the corresponding 6-amino-2-aryl-5-phenylazopyrimidine-4(3H)-ones (IV) were obtained by the oxidative cyclization with diethyl azodicarboxylate. Treatment of IV with second aryl aldehydes gave the unsymmetrical 2,8-diarylated hyloxanthines.

The one-step synthesis of purine derivatives by the simultaneous ring closure of the pyrimidine and imidazole rings has been an important subject of purine chemistry.¹ It has been known that aminomalonamidamide² and aminomalondiamidamide can be cyclized into purine derivatives in one step by the reaction with one-carbon reagents such as ethyl orthoformate.³ In this report, we describe the first utilization of readily available phenylzomalonamidamide hydrochloride (I),² which is the precursor of aminomalonamidamide, as the starting material for the one-step synthesis of purine derivatives involving double ring closure.

For example, fusion of I (0.6 g, 0.0024 mole) with excess *p*-chlorobenzaldehyde (1.69 g, 0.012 mole) at 170 °C (oil bath temperature) for 1 hr, followed by dilution with methanol, afforded 2,8-di(*p*-chlorophenyl)-hyloxanthine (IIb) in quantitative yield. Similarly, fusion of I with other aryl aldehydes under the same conditions led to the formation of the corresponding 2,8-diarylhyloxanthines (II). As shown in Table I, the reaction using the aryl aldehydes possessing electron-withdrawing groups gave the products in excellent yields. The structures of II were confirmed by satisfactory elemental analyses and spectral data including mass spectrometry. Furthermore, compound IIa^{3,4,5} was identified with the authentic sample prepared by known procedures.^{4,5}

The synthesis of hyloxanthines can be rationalized in terms of the initial formation of the intermediary monoarylidene derivatives of I. Subsequent oxidative cyclization by ambient air would give the corresponding 6-amino-2-aryl-5-phenylazopyrimidine-4(3H)-ones, which further react with aryl aldehydes to cause the cycli-

zation followed by concomitant elimination of phenylnitrene giving the final products as depicted in Scheme 2. The latter cyclization involves the thermal cycloaddition of aza analogs of hexatriene and this type of reactions have been demonstrated in the preparation of several heterocycles.^{5,6}

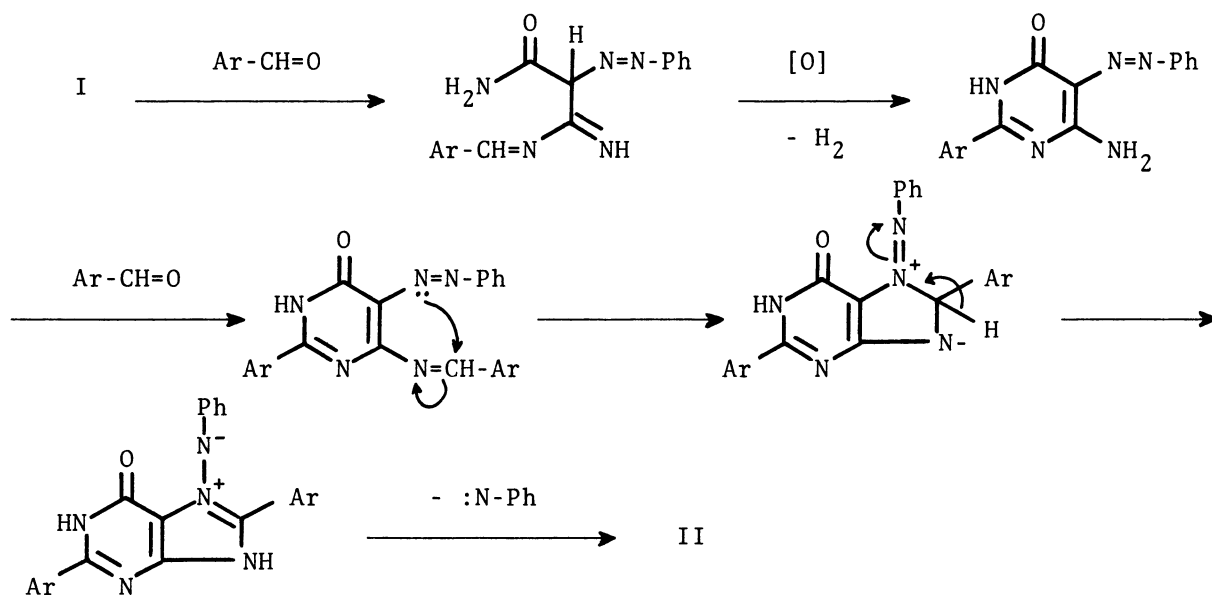


Scheme 1

Table 1. 2,8-Diarylhydropoxanthines (II)

Compound No.	Ar	Appearance	Mp (°C) ^{a)}	Yield (%)
IIa	C ₆ H ₅	colorless powder	>330	27
IIb	4-Cl-C ₆ H ₄	colorless needles	>330	100
IIc	3-Cl-C ₆ H ₄	colorless needles	>330	100
IId	3,4-Cl ₂ -C ₆ H ₃	colorless needles	>330	100
IIe	4-Br-C ₆ H ₄	colorless powder	>330	100
IIf	4-CH ₃ -C ₆ H ₄	colorless needles	>330	20
IIg	3-CH ₃ -C ₆ H ₄	colorless needles	>330	34

a) All compounds were recrystallized from dimethylformamide.



Scheme 2

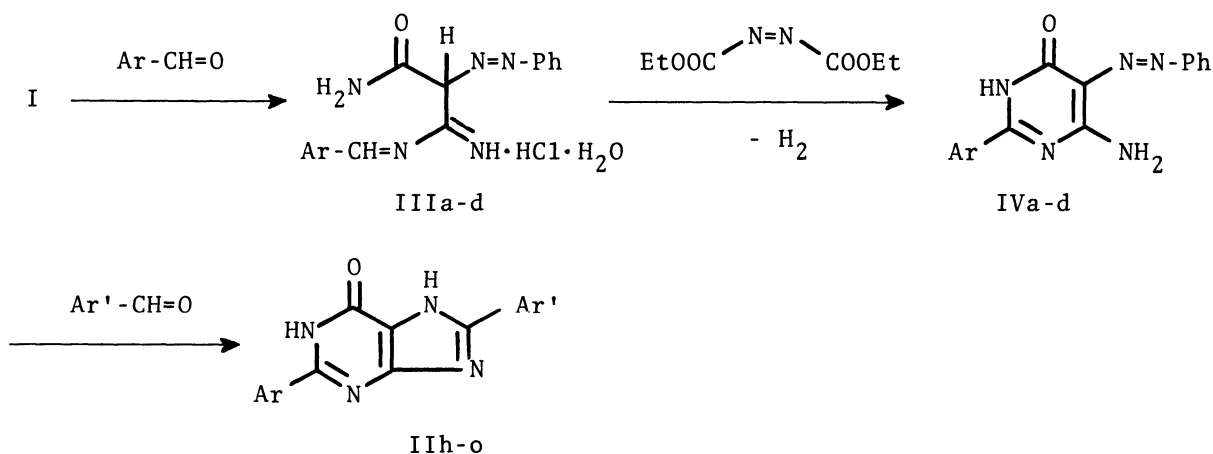
The above double cyclization has also served as a convenient synthesis of the hypoxanthines possessing different aryl substituents at positions 2 and 8 (unsymmetrical 2,8-diarylated hypoxanthines), by performing stepwise the reactions. Namely, the reaction of I (0.6 g, 0.0024 mole) with aryl aldehydes (0.0048 mole)

under milder conditions (120 °C, 15 min), followed by the treatment of the reaction mixture with ether, yielded the monoarylidene derivatives (III) of I in almost quantitative yields (Table 2).

Table 2. Arylidene Derivatives (III) of Phenylazomalonamide (I)

Compound No.	Ar	Appearance	Mp (°C) ^{a)}	Yield (%)
IIIa	C ₆ H ₅	yellow powder	177	100
IIIb	4-Cl-C ₆ H ₄	yellow powder	184	100
IIIc	4-Br-C ₆ H ₄	yellow powder	182	100
IIId	3,4-Cl ₂ -C ₆ H ₃	yellow powder	183	98

a) All compounds were recrystallized from ethanol and were obtained as their hydrochloride monohydrate.



Next, the treatment of IIIa (0.7 g, 0.002 mole) with excess diethyl azodicarboxylate (DAD)⁷ (0.7 g, 0.004 mole) at 160 °C for 15 min, followed by dilution with ethanol, precipitated 6-amino-2-phenyl-5-phenylazopyrimidine-4(3H)-one (IVa).⁵ In complete analogy with the above result, the reaction of other aryldene derivatives (IIIb-d) with DAD provided the corresponding 6-amino-2-aryl-5-phenylazopyrimidine-4(3H)-ones (IVb-d) (Table 3). This reaction would establish an interesting precedent for the preparation of pyrimidine derivatives by the oxidative cyclization with DAD.

Table 3. 6-Amino-2-aryl-5-phenylazopyrimidine-4(3H)-ones (IV)

Compound No.	Ar	Appearance	Mp (°C) ^{a)}	Yield (%)
IVa	C ₆ H ₅	orange powder	>300	58
IVb	4-Cl-C ₆ H ₄	orange powder	>300	79
IVc	4-Br-C ₆ H ₄	orange powder	>300	69
IVd	3,4-Cl ₂ -C ₆ H ₃	orange powder	>300	77

a) All compounds were recrystallized from ethanol.

Finally, fusion of IV (0.002 mole) with second aryl aldehydes (0.004 mole) at 200 °C for 1 hr, followed by dilution with methanol, caused the separation of the unsymmetrical 2,8-diarylated hypoxanthines (IIh-o) (Table 4).

The direct fusion of III with second aryl aldehydes in order to get the unsymmetrical 2,8-diarylated hypoxanthines was unsuccessful, because of the thermal exchange of the arylidene groups of III with second aryl aldehydes.

Table 4. Unsymmetrical 2,8-Diarylated Hypoxanthines (IIh-o)

Compound No.	Ar	Ar'	Appearance	Mp (°C) ^{a)}	Yield (%)
IIh	C ₆ H ₅	4-Cl-C ₆ H ₄	colorless powder	>330	46
IIi	C ₆ H ₅	4-Br-C ₆ H ₄	colorless powder	>330	67
IIj	4-Cl-C ₆ H ₄	C ₆ H ₅	colorless powder	>330	41
IIk	4-Cl-C ₆ H ₄	4-Br-C ₆ H ₄	colorless powder	>330	78
III	4-Br-C ₆ H ₄	C ₆ H ₅	colorless powder	>330	70
IIm	4-Br-C ₆ H ₄	4-Cl-C ₆ H ₄	colorless powder	>330	58
IIn	4-Br-C ₆ H ₄	3,4-Cl ₂ -C ₆ H ₃	colorless powder	>330	67
IIo	3,4-Cl ₂ -C ₆ H ₃	4-Cl-C ₆ H ₄	colorless powder	>330	36

a) All compounds were recrystallized from dimethylformamide.

The scope and limitation of this purine synthesis are currently under investigation.

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