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

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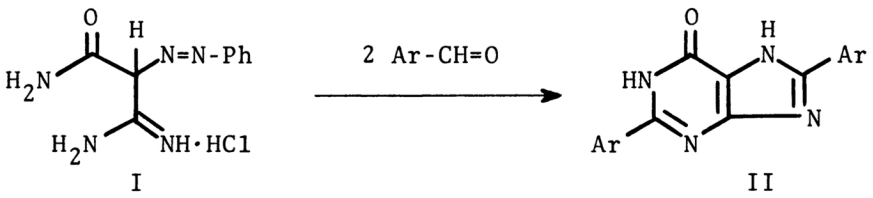
Treatment of phenylazomalonamidamidine (I) with aryl aldehydes yielded the corresponding 2,8-diarylhypoxanthines (II) in a single step. The reaction under milder conditions formed the intermediary monoarylidene derivatives (III) of I, from which the corresponding 6-amino-2-aryl-5-phenylazopyrimidine-4(3H)-ones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

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 aminomalonamidamidine[2] and aminomalondiamidine 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 phenylazomalonamidamidine hydrochloride (I),[2] which is the precursor of aminomalonamidamidine, 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)-hypoxanthine (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-diarylhypoxanthines (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 hypoxanthines 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]

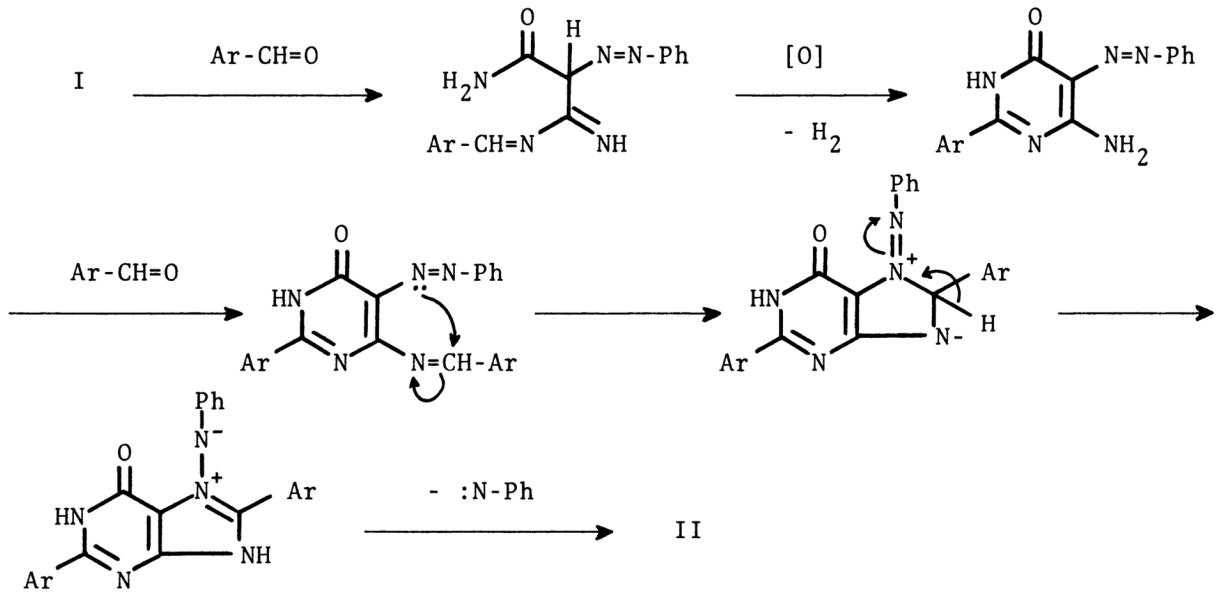


Scheme 1

Table 1. 2,8-Diarylhypoxanthines (II)

Compound No.	Ar	Appearance	Mp (°C)[a]	Yield (%)
IIa	C_6H_5	colorless powder	>330	27
IIb	4-Cl-C_6H_4	colorless needles	>330	100
IIc	3-Cl-C_6H_4	colorless needles	>330	100
IId	3,4-Cl_2-C_6H_3	colorless needles	>330	100
IIe	4-Br-C_6H_4	colorless powder	>330	100
IIf	4-CH_3-C_6H_4	colorless needles	>330	20
IIg	3-CH_3-C_6H_4	colorless needles	>330	34

a) All compounds were recrystallized from dimethylformamide.



Scheme 2

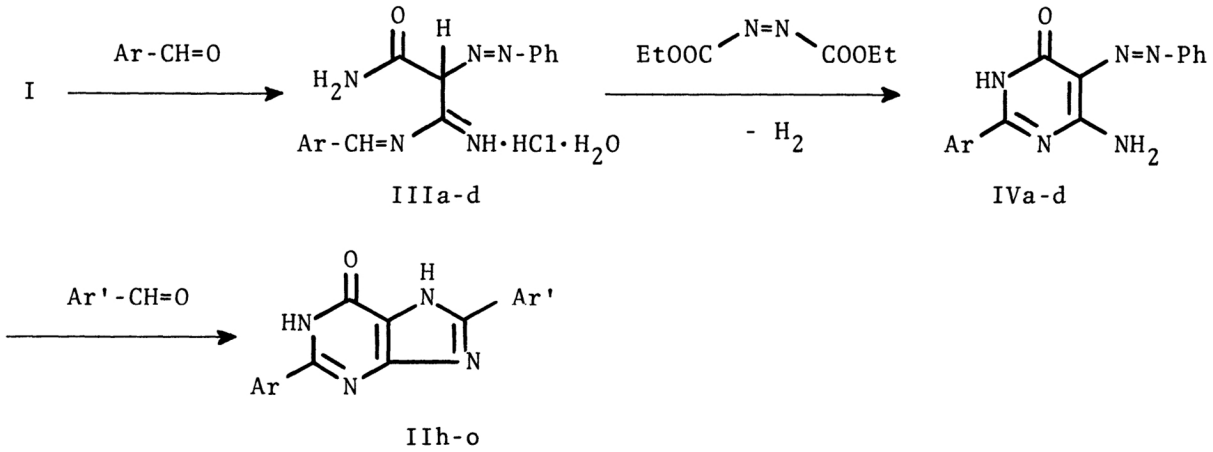
The above double cyclization has also served as a convenient synthesis of the hypoxanthines possessing different aryl substituents at positions 2 and 8 (unsymmetrical 2,8-diarylated hypoxanthines), by performing stepwise the reactions. Namely, the reaction of I (0.6 g, 0.0024 mole) with aryl aldehydes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

Compound No.	Ar	Appearance	Mp (°C)[a]	Yield (%)
IIIa	C_6H_5	yellow powder	177	100
IIIb	4-Cl-C_6H_4	yellow powder	184	100
IIIc	4-Br-C_6H_4	yellow powder	182	100
IIId	3,4-Cl_2-C_6H_3	yellow powder	183	98

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



Scheme 3

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 arylidene 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_6H_5	orange powder	>300	58
IVb	4-Cl-C_6H_4	orange powder	>300	79
IVc	4-Br-C_6H_4	orange powder	>300	69
IVd	3,4-Cl_2-C_6H_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_6H_5	4-Cl-C_6H_4	colorless powder	>330	46
IIi	C_6H_5	4-Br-C_6H_4	colorless powder	>330	67
IIj	4-Cl-C_6H_4	C_6H_5	colorless powder	>330	41
IIk	4-Cl-C_6H_4	4-Br-C_6H_4	colorless powder	>330	78
III	4-Br-C_6H_4	C_6H_5	colorless powder	>330	70
IIm	4-Br-C_6H_4	4-Cl-C_6H_4	colorless powder	>330	58
IIn	4-Br-C_6H_4	3,4-Cl_2-C_6H_3	colorless powder	>330	67
IIn	3,4-Cl_2-C_6H_3	4-Cl-C_6H_4	colorless powder	>330	36

a) All compounds were recrystallized from dimethylformamide.

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

References

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