HETEROCYCLES, Vol. 4, No. 11, 1976

DEHYDROGENATIVE CYCLIZATION OF 6-AMINO-5-BENZYLIDENEAMINOPYRIMIDINES TO PURINES WITH DIETHYL AZODICARBOXYLATE

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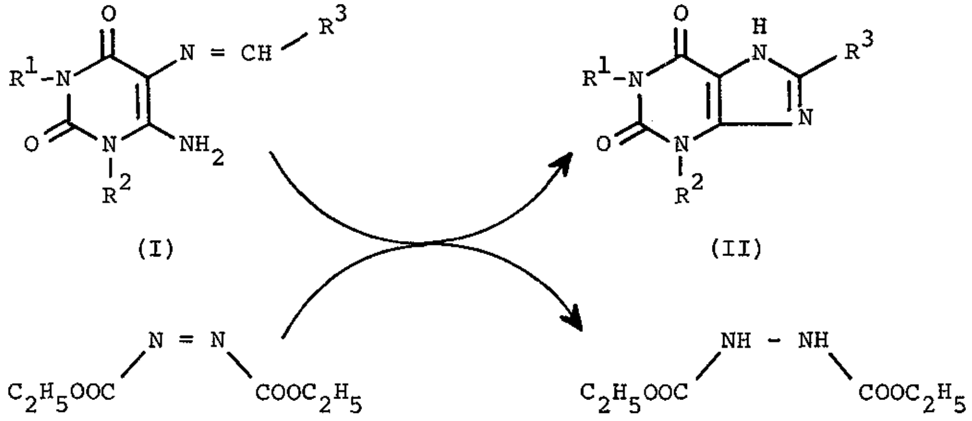
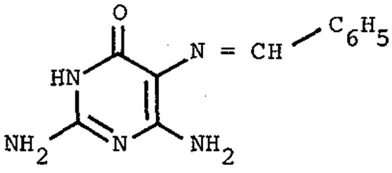
The treatment of 6-amino-5-benzylideneaminopyrimidines with diethyl azodicarboxylate (DAD) gave the corresponding purines in essentially quantitative yields.

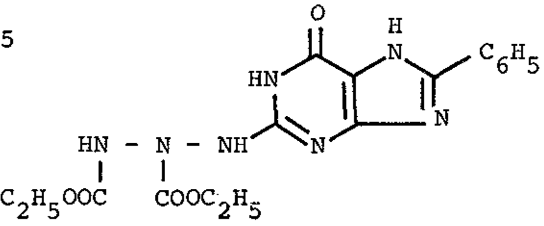
It is well known that diethyl azadicarboxylate (DAD) is a strong hydrogen acceptor.[1] For instance, DAD is capable of dehydrogenating alcohols,[1] mercaptans,[1,2] hydrazobenzenes,[1] hydroxylamines,[3,4] phenols,[5] secondary formamides,[6] and tertiary amines[7] and converting them into carbonyl compounds, disulfides, azobenzenes, nitroso compounds, biphenyls, isocyanates, and enamines. In this process DAD undergoes hydrogenation to diethyl hydrazodicarboxylate. DAD is also an effective reagent for the oxidation of several sulfur-containing amino acids[8] to sulfoxides. Recently the usefulness of this reagent as an oxidant has been extended to the syntheses of a variety of heterocycles. Namely, the dehydrogenation of 1,2-dihydropyrimido[5,4-e]-as-triazines,[9,10] 1,2,3,4-tetrahydroquinoxalines,[11] cyclic hydrazine derivatives,[12,13] 1,3-diphenylimidazolidine,[14] and the alkaloids mesembrine and mesembrenone[15] were successfully accomplished with DAD to yield pyrimido[5,4-e]-as-triazines, 1,2-dihydroquinoxalines, cyclic azo derivatives, 1,3-diphenylimidazolium salts, and the corresponding β-enamino-ketones, respectively. Furthermore, new syntheses of alloxazines,[16] purines,[17] flavins,[18] pyrimido[5,4-e]-as-triazine 4-oxides,[19] dithia[3.3]metacyclophanes[20] and 5-amino-3,4-diphenylisoxazole,[21] in which DAD as an oxidant played an important role, have been reported successively. In this communication we wish to describe the dehydrogenative cyclization of 6-amino-5-benzylideneaminopyrimidines to the corresponding purines with DAD.

Heating of a suspension of 6-amino-5-benzylideneamino-1,3-dimethyluracil (Ia)[22] (0.001 mole) in an excess of DAD (0.002-0.003 mole) at 90° for 5 min, followed by dilution with ethanol, caused the separation of 8-phenyltheophylline (IIa)[23] in a high state of purity. Concentration of the filtrate gave diethyl hydrazodicarboxylate. Similarly, other anils (Ib-o), which were readily available by the condensation of 5,6-diaminouracils with aryl aldehydes, gave the corresponding 8-arylxanthines (IIb-o) under the conditions described in Table. The structures of compounds II were established by satisfactory analytical and spectral data and by comparison with authentic samples.[24,25]

When 5-benzylideneamino-2,6-diamino-4-hydroxypyrimidine (III)




(III)


(IV)

(mp >340°), prepared by the condensation of 4-hydroxy-2,5,6-triaminopyrimidine with benzaldehyde, was heated with an excess of DAD (3 equiv.) at 90° for 1 hr, 2-(1,2-bisethoxycarbonylhydrazino)amino-6-hydroxy-8-phenylpurine (IV) (mp > 340°) was formed in a good yield. Syntheses of other several kinds of purines by this method are currently under investigation.

We consider this purine synthesis as possessing considerable synthetic utility because of the essentially quantitative yields of products, the high purity of products, the simplicity of procedure, and the mild and neutral conditions employed.

TABLE 8-Substituted Xanthine Derivatives

Starting material (mp, °C)	R^1	R^2	R^3	Reaction condition	Product[a]	Yield (%)
Ia (225, dec)	CH_3	CH_3	C_6H_5	90°, 5 min	IIa	96
Ib (220)	CH_3	CH_3	$4\text{-}Cl\text{-}C_6H_4$	90°, 5 min	IIb	100
Ic (249)	CH_3	CH_3	$3,4\text{-}Cl_2\text{-}C_6H_3$	90°, 5 min	IIc	99
Id (233)	CH_3	CH_3	$4\text{-}CH_3\text{-}C_6H_4$	90°, 5 min	IId	100
Ie (206)	CH_3	CH_3	$4\text{-}CH_3O\text{-}C_6H_4$	90°, 5 min	IIe	98
If (248)	CH_3	CH_3	$4\text{-}(CH_3)_2N\text{-}C_6H_4$	90°, 5 min	IIf	90
Ig (>340)	H	CH_3	C_6H_5	90°, 30 min	IIg	92
Ih (>340)	H	CH_3	$4\text{-}Cl\text{-}C_6H_4$	90°, 30 min	IIh	98
Ii (>340)	H	CH_3	$3,4\text{-}Cl_2\text{-}C_6H_3$	90°, 30 min	IIi	96
Ij (>340)	H	CH_3	$4\text{-}CH_3O\text{-}C_6H_4$	90°, 30 min	IIj	96
Ik (>340)	H	CH_3	$3,4\text{-}CH_2O_2\text{-}C_6H_3$	90°, 30 min	IIk	100
Il (>340)	H	H	C_6H_5	120°, 100 min	IIl	91
Im (335)	H	H	$4\text{-}Cl\text{-}C_6H_4$	120°, 100 min	IIm	95
In (340)	H	H	$3,4\text{-}Cl_2\text{-}C_6H_3$	120°, 100 min	IIn	93
Io (311)	H	H	$4\text{-}CH_3O\text{-}C_6H_4$	120°, 100 min	IIo	92

a) These compounds were recrystallized from DMF and did not melt below 350°.

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Received, 8th September, 1976