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One Step Syntheses of Hypoxanthines from 2-Cyano-2-phenylazoacetamides

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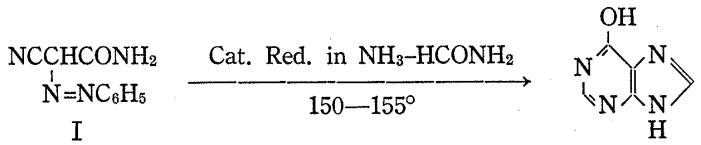
A facile one step synthesis of hypoxanthine and 1-alkylhypoxanthines from 2-cyano-2-phenylazoacetamide and its N-alkyl analogs has been achieved by means of catalytic reduction in ammonia–formamide system at elevated temperature. Mechanistic investigation has revealed a pathway involving pyrimidine ring-closure followed by imidazole ring-closure for this reaction.

In the one step purine synthesis outlined in the recent communication[2] hypoxanthine has been reported to be synthesized directly from 2-cyano-2-phenylazoacetamide (I) by catalytic reduction in an ammonia-formamide system. We now wish to disclose the detail of our investigation relating to this reaction.

The two step synthesis of hypoxanthine from I has been reported in a Japanese patent,[3] that is, the conversion of I into 4-amino-6-hydroxy-5-phenylazopyrimidine (II) by the interaction with formamidine acetate and the succeeding conversion of II into hypoxanthine by reduction with sodium dithionite in formamide. Our trial was successful in synthesizing hypoxanthine directly from I by means of high pressure hydrogenation at 150—155° over Raney nickel catalyst in dimethylformamide (DMF) in the presence of formamidine acetate. The yield attained was 65%, when calculated from the starting I. In this reaction use of formamide in place of formamidine–DMF resulted in only 14% of hypoxanthine, but the presence of ammonia was found to exert a remarkable effect in increasing the yield of hypoxanthine. Thus a facile one step synthesis of hypoxanthine from I in 60—70% yield was provided by high pressure hydrogenation in 7% ammonia–formamide at 150—155° over Raney nickel catalyst.



For this hypoxanthine formation reaction several extensions were made by the use of varying substrates and by some other reduction methods. Instead of the substrate I ethyl 2-cyano-2-phenylazoacetate and 2-cyano-2-nitrosoacetamide were also applicable to the above reaction, but under the same conditions the yields of hypoxanthine were lower, 50% and 22%, respectively. Examinations were also made to assess the adaptabilities of some other chemical reduction methods, using sodium dithionite, sodium and ammonium sulfite, zinc amalgam and aluminium amalgam, in modified ways. Among these trials sodium dithionite and sodium sulfite were somewhat efficient in affording hypoxanthine. Yields of 19% and 22% were obtained, respectively, by addition of these agents in small portions to solutions of I in formamide containing ammonium chloride at temperature of 110—120°, which was raised at 150—155° after the addition. From these results the original catalytic hydrogenation of I in the ammonia-formamide system appears best for the synthesis of hypoxanthine.

1) Location: *2–2–1, Oshika, Shizuoka-shi.*
2) M. Sekiya and J. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **20**, 209 (1972).
3) Y. Fujimoto and M. Teranishi, Japan Patent 20067 (1967) [*C.A.*, **69**, 10477 (1968)].

Furthermore, the catalytic hydrogenation method was successfully applied for syntheses of 1-alkylhypoxanthines by the use of N-alkyl-2-cyano-2-phenylazoacetamides as substrates. Four N-alkyl-2-cyano-2-phenylazoacetamides possessing alkyl substituents *i.e.*, methyl, benzyl, propyl and cyclohexyl, which have not been described in the literature, were synthesized by the phenylazo-coupling reaction of the relevant N-alkyl-2-cyanoacetamides. These were subjected to catalytic hydrogenation over Raney nickel catalyst in 7% ammonia-formamide at 150—155°, giving fair yields of the corresponding 1-alkylhypoxanthines. Since the known syntheses of 1-alkylhypoxanthines are rather laborious, this method appears to provide a new practical means for their syntheses.

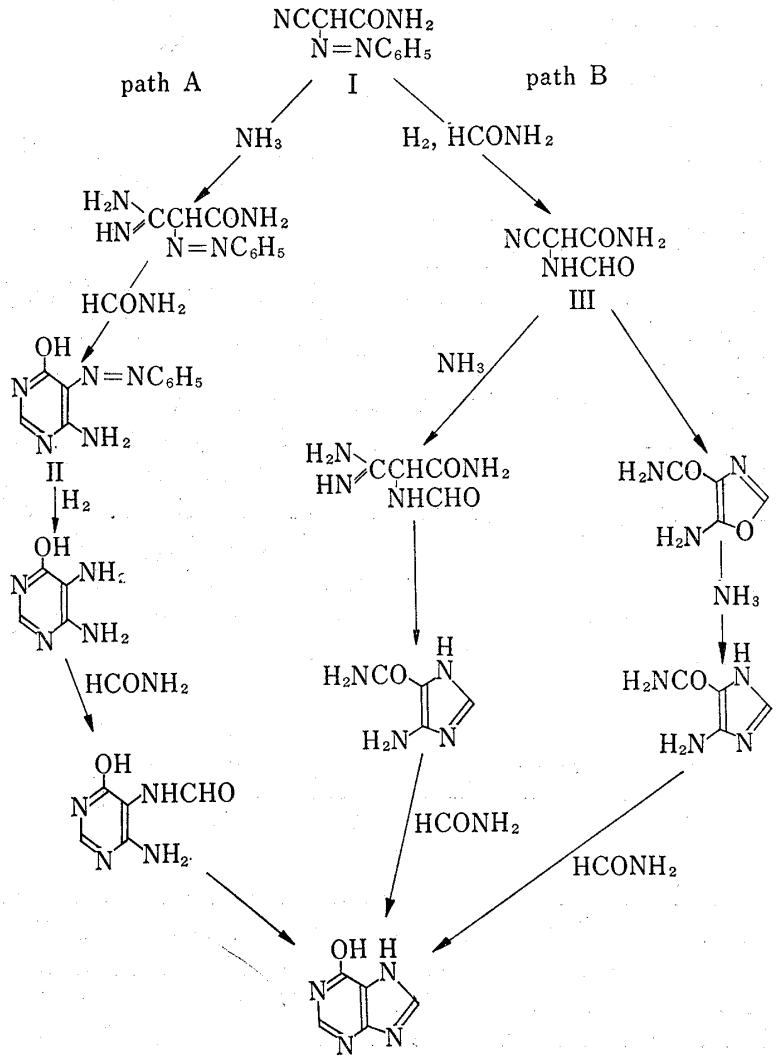


Chart 1

The hypoxanthine forming process is considered to involve several elementary reactions such as amidination, formylation, pyrimidine ring-closure, reduction and imidazole ring-closure. We were interested to know whether the reaction proceeds through either of the two paths (see Chart 1). One (path A) involves pyrimidine ring-closure and followed by imidazole ring-closure and the other (path B) involves the reverse of this. Possible intermediates in these paths were synthesized and allowed to react under the reaction conditions. The path B involves 5-aminoimidazole-4-carboxylamide as an intermediate. Its formation may be led by two routes, through the amidination of 2-cyano-2-formamidoacetamide (III) and through

oxazole ring-closure of the same, as shown in Chart 1. A Japanese patent[4] has described hypoxanthine formation by heating III in ammonia–formamide at 180°. Subjection of III and 5-aminooxazole-4-carboxyamide to heating in 7% ammonia–formamide at 150—155°, however, resulted in no formation of hypoxanthine. The involvement of path A was examined by subjection of II, which is conceived as an intermediate, to the catalytic hydrogenation operation similarly to the hypoxanthine forming reaction of I. In this case even in the absence of ammonia hypoxanthine was obtained in 83% yield. Furthermore, conversion of I into II was successfully performed by heating at 150—155° in the ammonia–formamide medium. In this reaction the presence of ammonia was necessary but its optimum concentration was 1—2%, over which the yield decreased considerably. In view of the above facts it seems that the hypoxanthine forming reaction of I proceeds through path A involving II as an intermediate.

Experimental[5]

Syntheses of Amides and Ester of Phenylazocyanoacetic Acid General Procedure——To an aqueous or ethanolic solution of 1 mole of each cyanoacetic acid derivative an aqueous solution of benzenediazonium chloride, which was prepared from 1.1 mole of aniline by the usual method, was added with stirring. This mixture was adjusted to pH 4 by addition of aqueous sodium acetate and allowed to stand overnight. The precipitate was collected by filtration, washed with water and ethanol, then dried and recrystallized from an appropriate solvent.

2-Cyano-2-phenylazoacetamide (I)——Yield, 96%. Yellow prisms (EtOH), mp 243—244° (decomp.) (lit.,[6] 245°). IR ν_{max}^{KBr} cm^{-1}: 3480, 3460 (NH), 2200 (CN), 1660 (CO). UV λ_{max}^{EtOH} nm (ε): 239 (11000), 355 (20300). *Anal.* Calcd. for $C_9H_8ON_4$: C, 57.44; H, 4.29; N, 29.27. Found: C, 57.67; H, 4.40; N, 29.54.

Ethyl 2-Cyano-2-phenylazoacetate——Yield, 75%. Yellow leaflets (EtOH), mp 80—81° (lit,[7] mp 128—129°). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1680 (CO). UV λ_{max}^{EtOH} nm (ε): 242 (7800), 358 (21800). *Anal.* Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.88; H, 5.11; N, 19.27.

N-Methyl-2-cyano-2-phenylazoacetamide——Yield, 87%. Brownish yellow prisms (EtOH), mp 155—156°. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 2210 (CN), 1638 (CO). UV λ_{max}^{EtOH} nm (ε): 241 (9300), 355 (24400). *Anal.* Calcd. for $C_{10}H_{10}ON_4$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.44; H, 5.04; N, 27.61.

N-Benzyl-2-cyano-2-phenylazoacetamide——Yield, 78%. Pale yellow leaflets ($CHCl_3$), mp 147—148°. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 2200 (CN), 1644 (CO). UV λ_{max}^{EtOH} nm (ε): 240 (10900), 357 (18900). *Anal.* Calcd. for $C_{16}H_{14}ON_4$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.05; H, 5.03; N, 20.12.

N-Propyl-2-cyano-2-phenylazoacetamide——Yield, 81%. Yellow leaflets (MeOH), mp 147—148°. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 2210 (CN), 1640 (CO). UV λ_{max}^{EtOH} nm (ε): 240 (11000), 356 (19600). *Anal.* Calcd. for $C_{12}H_{14}ON_4$: C, 62.59; H, 6.13; N, 24.37. Found: C, 62.70; H, 6.14; N, 24.37.

N-Cyclohexyl-2-cyano-2-phenylazoacetamide——Yield, 75%. Yellow prisms (EtOH), mp 146—147°. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 2200 (CN), 1633 (CO). UV λ_{max}^{EtOH} nm (ε): 241 (9700), 356 (25000). *Anal.* Calcd. for $C_{15}H_{18}ON_4$: C, 66.66; H, 6.71; N, 20.73. Found: C, 66.74; H, 6.66; N, 20.18.

Synthesis of Hypoxanthine——1) Catalytic Reduction in DMF in the Presence of Formamidine Acetate: In an autoclave 7.5 g (0.04 mole) of I, 12.5 g (0.12 mole) of formamidine acetate, 60 ml of DMF and Raney nickel catalyst freshly prepared by usual means from 1 g of 50% alloy were placed. Under 80 kg/cm^2 of an initial hydrogen pressure at room temperature the whole was heated at 150—155° and then constant shaking was started. Shaking and heating were continued for 3 hr, while uptake of hydrogen proceeded. After cooling the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue with 200 ml of added water was refluxed for 1 hr. After insoluble material was filtered off the filtrate was decolorized with charcoal and concentrated to dryness. The residual solid was recrystallized from water to give needles of hypoxanthine, mp>300°. Yield, 3.4 g (65%). IR ν_{max}^{KBr} cm^{-1}: 3250—2150 (OH & NH), 1660 (CO). UV $\lambda_{max}^{pH\ 1}$ nm (ε): 249 (10600), $\lambda_{max}^{pH\ 7}$: 250 (10600), $\lambda_{max}^{pH\ 11}$: 262 (11600). (lit,[8] UV $\lambda_{max}^{pH\ -0.75}$ nm: 248, $\lambda_{max}^{pH\ 5.18}$: 249, $\lambda_{max}^{pH\ 10.75}$: 258, $\lambda_{max}^{pH\ 13.0}$: 262). These spectral data were in good agreement with

4) M. Ochiai and K. Morita, Japan patent 10794 (1969) [*C.A.*, **71**, 112987 (1969)].
5) All melting points were uncorrected. Infrared (IR) and Ultraviolet (UV) spectra were recorded on a Hitachi EPI-G2 spectrophotometer and a Hitachi EPS-3T spectrophotometer, respectively. NMR spectra were taken at 60 MHz with a JEOL-JNM-C-60H spectrometer using tetramethylsilane as an internal standard. Abbreviation used: s=singlet, t=triplet, and m=multiplet.
6) Y. Fujimoto and M. Teranishi, Japan Patent 20930 (1966) [*C.A.*, **66**, 46231 (1967)].
7) M.I. Latosh, *Zh. Obshch. Kim.*, **37**, 649 (1967).
8) D.B. Brown and S.F. Mason, *J. Chem. Soc.*, **1957**, 682.

those of an authentic sample. *Anal.* Calcd. for $C_5H_4ON_4$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.11; H, 3.15; N, 41.12.

2) Catalytic Reduction in 7% Ammonia–Formamide: A mixture of 7.5 g (0.04 mole) of I, 75 g of 7% ammoniaformamide and Raney nickel catalyst freshly prepared by usual means from 1 g of 50% alloy placed in an autoclave was allowed to react under 80 kg/cm² of initial hydrogen pressure and worked up by the same procedure as described in 1). Yield of hypoxanthine was 68%. When the reaction was carried out in the absence of ammonia yield of hypoxanthine was 14%.

3) Catalytic Reduction of Ethyl 2-Cyano-2-phenylazoacetamide in 7% Ammonia–Formamide: By the use of ethyl 2-cyano-2-phenylazoacetamide (0.03 mole) in place of I the reaction was carried out by the same procedures as described in 2) to give 50% yield of hypoxanthine.

4) Catalytic Reduction of 2-Cyano-2-nitrosoacetamide in 7% Ammonia–Formamide: By the use of 2-cyano-2-nitrosoacetamide in place of I the reaction was carried out by the same procedures as described in 2) to give 22% yield of hypoxanthine.

5) Reduction with Sodium Dithionite in Formamide in the Presence of Ammonium Chloride: To a mixture of 7.5 g (0.04 mole) of I, 20 g of ammonium chloride and 100 g of formamide 20.9 g (0.12 mole) of sodium dithionite was gradually added with stirring at 110—120°. After the addition the reaction temperature was raised to 150—155° and then stirring was continued for further 3 hr. After cooling insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting residue was extracted with 300 ml of water by refluxing and the aqueous solution was evaporated under reduced pressure. The residual solid was recrystallized from water containing a small amount of acetic acid to give hypoxanthine in 19% yield.

6) Reduction with Sodium Sulfite in Formamide in the Presence of Ammonium Chloride: By the use of sodium sulfite in place of sodium dithionite the reaction was carried out by the same procedures as described in 5) to give 22% yield of hypoxanthine.

Syntheses of 1-Alkylhypoxanthines General Procedure——In an autoclave 0.04 mole of each N-alkyl-2-cyano-2-phenylazoacetamide (alkyl: methyl, propyl, benzyl and cyclohexyl), 10-fold amount of 7% ammonia–formamide and Raney nickel catalyst prepared from 1 g of alloy were placed and 80 kg/cm² of an initial hydrogen pressure was introduced. The whole was heated at 150—155° and shaken constantly for 4 hr. After cooling the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was solidified by washing with ethanol and recrystallized from appropriate solvent.

1-Methylhypoxanthine——Yield, 63%. Needles (H_2O), mp>300°. IR ν_{max}^{KBr} cm^{-1}: 1690 (CO). UV $\lambda_{max}^{pH\,1}$ nm (ε): 250 (8700), $\lambda_{max}^{pH\,7}$: 251 (8400), $\lambda_{max}^{pH\,11}$: 261 (8900) (lit.,[9] UV $\lambda_{max}^{pH\,1}$ nm: 246, $\lambda_{max}^{pH\,5.12}$: 251, $\lambda_{max}^{pH\,11}$: 260). NMR (in CF_3CO_2H) τ: 6.30 (3H, s, NCH_3), 1.19 (1H, s, >CH), 0.70 (1H, s, >CH). *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.14; H, 4.29; N, 37.36.

1-Propylhypoxanthine——Yield, 58%. Prisms (THF), mp 179—180°. IR ν_{max}^{KBr} cm^{-1}: 1678 (CO). UV $\lambda_{max}^{pH\,1}$ nm (ε): 250 (9500), $\lambda_{max}^{pH\,7}$: 252 (8100), $\lambda_{max}^{pH\,11}$: 261 (9400). NMR (in CF_3CO_2H) τ: 8.90 (3H, t, J= 7.5 Hz, CH_3), 8.00 (2H, sextet, $CH_3\underline{CH}_2$), 5.63 (2H, t, J=8.0 Hz, $CH_3CH_2\underline{CH}_2$), 1.25 (1H, s, >CH), 0.74 (1H, s, >CH). *Anal.* Calcd. for $C_8H_{10}ON_4$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.86; H, 5.50; N, 31.55.

1-Benzylhypoxanthine——Yield, 62%. Leaflets (95% EtOH), mp 268—269° (lit.,[10] mp 268—270°). IR ν_{max}^{KBr} cm^{-1}: 1687 (CO). UV $\lambda_{max}^{pH\,1}$ nm (ε): 251 (10300), $\lambda_{max}^{pH\,7}$: 252 (9500), $\lambda_{max}^{pH\,11}$: 262 (10200) (lit.,[11] UV $\lambda_{max}^{neutral\ molecular}$ nm: 251, λ_{max}^{anion}: 261). NMR (in CF_3CO_2H) τ: 4.47 (2H, s, CH_2), 2.57 (5H, s, C_6H_5), 1.15 (1H, s, >CH), 0.72 (1H, s, >CH) [lit.,[11] NMR (in DMSO-d_6) τ: 4.73 (CH_2), 2.69 (C_6H_5), 1.61 and 1.49 (purine ring)]. *Anal.* Calcd. for $C_{12}H_{10}ON_4$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.54; H, 4.47; N, 24.88.

1-Cyclohexylhypoxanthine——Yield, 24%. Needles (EtOH), mp 279—280°. IR ν_{max}^{KBr} cm^{-1}: 1680 (CO). UV $\lambda_{max}^{pH\,1}$ nm (ε): 251 (9200), $\lambda_{max}^{pH\,7}$: 252 (9000), $\lambda_{max}^{pH\,11}$: 261 (9500). NMR (in CF_3CO_2H) τ: 8.85—7.55 (10H, m, $(CH_2)_5$), 5.30—4.58 (1H, m, N–CH<), 1.14 (1H, s, >CH), 0.72 (1H, s, >CH). *Anal.* Calcd. for $C_{11}H_{14}ON_4$: C, 60.53; H, 6.47; N, 25.57. Found: C, 60.81; H, 6.53; N, 25.73.

Acknowledgement The authors are indebted to the members of the Analysis Center of this college for microanalyses and spectral measurements.

9) G.B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).
10) E. Shaw, *J. Am. Chem. Soc.*, **80**, 3899 (1958).
11) J.A. Montgomery and H.J. Thomas, *J. Org. Chem.*, **31**, 1411 (1966).