# Studies on Uracils. 10.[1] A Facile One-Pot Synthesis of Pyrido[2,3-*d*]- and Pyrazolo[3,4-*d*]pyrimidines

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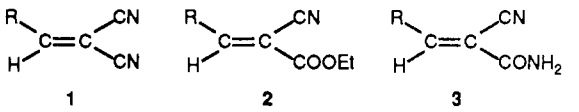
The reaction of functionalised uracils bearing amino and hydroxyamino groups at C-6 position (**4** and **5**) with strongly electrophilic cyano olefins (**1**, **2**, and **3**) gave rise to pyrido[2,3-*d*]pyrimidines **7–9** in excellent yields. Hydrazine-substituted uracil **6** gave access to an efficient one-step synthesis of pyrazolo[3,4-*d*]pyrimidines **10**. The capture of an eliminated hydrogen molecule by cyano olefins in the case of their reaction with **4** and **6** was confirmed by the isolation of dihydrocyano olefins. This fact further supported the plausible mechanism for the formation of compounds **7–10** via dihydropyrido[2,3-*d*]- and dihydropyrazolo[3,4-*d*]pyrimidine intermediates A and C.

The importance of uracil and its annelated substrates is well recognized by synthetic[2] as well as biological chemists.[3] With the development of clinically useful anticancer (5-fluorouracil[4]) and antiviral drugs (AZT,[5] BVDU[6]), there has recently been remarkable interest in the synthetic manipulations of uracils.[1,2,7] The synthetic exploitation of the nucleophilic double bond of uracil is an important undeveloped field in view of a great variety[8] of potential products. There have been reports for direct functionalization of uracil using the $C_5$–$C_6$ double bond via thermolytic[9] and photocycloaddition reactions.[10] The heteroannulation of uracils usually requires either forcing conditions[11] or relatively longer synthetic pathways.[12] The readily available cyano olefins are a class of important organic synthones having exciting chemistry.[13] In view of the considerable chemical reactivity of activated cyano olefins, we felt it would be valuable to investigate their reaction with strongly nucleophilic 6-amino-, 6-(hydroxyamino)-, and 6-hydrazinouracil (**4**, **5**, and **6**).

A previous synthesis for pyrazolo[3,4-*d*]pyrimidine reported by Yoneda et al.[11] involved the cycloaddition of azahexatriene obtained from the reaction of arylaldehyde and 6-uracil hydrazone. One disadvantage of this approach is the concomitant alkylation of the pyrazolo moiety. Another synthesis reported by Maki et al.[12] required the cycloaddition of arylhydrazone with 6-chloro-5-nitrouracil involving several steps. Broom et al.[14a] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracil in protic solvent but obtained uncyclized condensed acetylenic adduct[14b] when the reaction was carried in dimethylformamide.

Our synthetic strategy utilizing cyano olefins viz arylidenemalononitrile (**1**), arylidenecyanoacetate (**2**), and arylidenecyanoacetamide (**3**) with **4**, **5**, and **6** afforded an unprecedented one-pot synthesis of pyrido[2,3-*d*]pyrimidines (**7–9**) and pyrazolo[3,4-*d*]pyrimidine (**10**).




**1** **2** **3**

R = **a**, Ph; **b**, 2-furyl; **c**, 2-thienyl

The activated cyano olefins **1**, **2**, and **3** were prepared by the knoevenagel condensation of malononitrile, ethylcyanoacetate, and cyanoacetamide with aromatic aldehydes.[15] The reaction of **4a** with an excess of **1a** in refluxing 1-propanol afforded 2-amino-6,8-dimethyl-5,7-dioxo-4-phenylpyrido[2,3-*d*]pyrimidine-3-nitrile (**7a**) and benzylmalononitrile in excellent yields. The products were fully characterized through spectral and elemental analysis. The IR spectra of **7a** exhibited sharp bands at 3435 and 3300 $cm^{-1}$ ($NH_2$), 2195 (CN), and 1710 (C=O). The $^1H$ NMR spectrum showed singlets at $\delta$ 3.42 and 2.90 for *N*-methyl protons and a multiplet at $\delta$ 6.78–7.25 for aromatic protons. The mass spectrum gave a molecular ion peak at $m/z$ 307. The structure of benzylmalononitrile was confirmed through comparison of spectral data and mixture melting point with an authentic sample.[22] It was

(1) For part 9, see: Prajapati, D.; Bhuyan, P. J.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 607.

(2) (a) Lunt, E. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1974; Vol. 4, p 493. (b) Brown, J. D. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 57. (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865 and references cited therein. (d) Bradshaw, T. K.; Hutchison, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.

(3) (a) Marumoto, R.; Furukawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2974. (b) Cheng, C. C.; Roth, B. *Prog. Med. Chem.* **1971**, *8*, 61. (c) Jones, A. S.; Swgers, J. R.; Walker, R. T.; Clercq, E. D. *J. Med. Chem.* **1988**, *31*, 268. (d) Griengl, H.; Wanck, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. *J. Med. Chem.* **1987**, *30*, 1199. (e) Clercq. E. D.; Bernaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.

(4) Heidelberger, C.; Arafield, F. J. *Cancer Res.* **1963**, *23*, 1226; *Chem. Abstr.* **1964**, *60*, 2197.

(5) (a) Baba, M.; Pauwels, R.; Herdwig, P.; Clercq, E. D.; Desmyster, J.; Vandepulfe, M. *Biochem. Biophys. Res. Commun.* **1987**, *142*, 128. (b) Clercq, E. D. *J. Med. Chem.* **1986**, *29*, 1561.

(6) (a) Clercq, E. D. *Anticancer Res.* **1986**, *6*, 549. (b) Jones, A. S.; Verhalst, G.; Walker, R. T. *Tetrahedron Lett.* **1974**, 4415.

(7) (a) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 846. (b) Su, T. L.; Huang, J. T.; Burchanal, J. H.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 709. (c) Prajapati, D.; Sandhu, J. S. *Synthesis* **1988**, 342.

(8) (a) Taylor, E. C.; Sowinski, F. *J. Org. Chem.* **1974**, *39*, 907. (b) Yoneda, F.; Kawamura, M.; Matsumoto, S.; Higuichi, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2285. (c) Wamhoff, H.; Winfried, S. *J. Org. Chem.* **1986**, *51*, 2787. (d) Hirota, K.; Banno, K.; Yumuda, Y.; Senda, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1137. (e) Sasaki, T.; Minamoto, T.; Suzuki, T.; Suguira, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248.

(9) Blank, H. V.; Fox, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 7175.

(10) (a) Wexlar, A.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 1602. (b) Hyatt, J. A.; Swenton, J. S. *J. Am. Chem. Soc.* **1972**, *94*, 7605.

(11) (a) Yoneda, F.; Higuichi, M.; Nagamatsu, T. *J. Am. Chem. Soc.* **1974**, *96*, 5607. (b) Yoneda, F.; Nagamatsu, T.; Senga, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 765.

(12) Maki, Y.; Tzuta, K.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1971**, 1442.

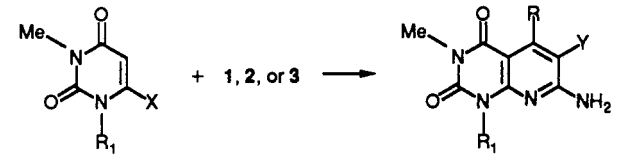
(13) For reviews and synthetic development, see: (a) Campaigne, E.; Schneller, S. W. *Synthesis* **1976**, 705. (b) Freeman, F. *Chem. Rev.* **1980**, *80*, 324. (c) Freeman, F. *Synthesis* **1981**, 925.

(14) (a) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095. (b) Shim, J. L.; Neiss, R.; Broom, A. D. *J. Org. Chem.* **1972**, *37*, 578.

(15) (a) Emerson, W. S.; Patric, T. M. *J. Org. Chem.* **1949**, *14*, 795. (b) Popp, F. D.; Catala, A. *J. Org. Chem.* **1961**, *26*, 2738.

(16) A part of this work was published as a preliminary communication: Gogoi, M.; Bhuyan, P. J.; Sandhu, J. S.; Baruah, J. N. *J. Chem. Soc., Chem. Commun.* **1984**, 1550.

0022-3263/90/1955-0568$02.50/0 

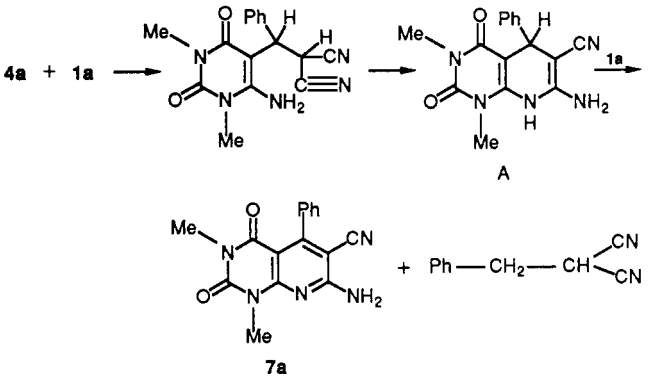


| | X | $R_1$ |
|---|---|---|
| 4a | $NH_2$ | Me |
| b | $NH_2$ | H |
| 5a | NHOH | Me |
| b | NHOH | H |

| | Y | R | $R_1$ |
|---|---|---|---|
| 7a | CN | Ph | Me |
| b | CN | 2-furyl | Me |
| c | CN | 2-thienyl | Me |
| d | CN | Ph | H |
| e | CN | 2-furyl | H |
| f | CN | 2-thienyl | H |
| 8a | COOEt | Ph | Me |
| b | COOEt | 2-furyl | Me |
| c | COOEt | 2-thienyl | Me |
| d | COOEt | Ph | H |
| e | COOEt | 2-furyl | H |
| f | COOEt | 2-thienyl | H |
| 9a | $CONH_2$ | Ph | Me |
| b | $CONH_2$ | 2-furyl | Me |
| c | $CONH_2$ | 2-thienyl | Me |
| d | $CONH_2$ | Ph | H |
| e | $CONH_2$ | 2-furyl | H |
| f | $CONH_2$ | 2-thienyl | H |

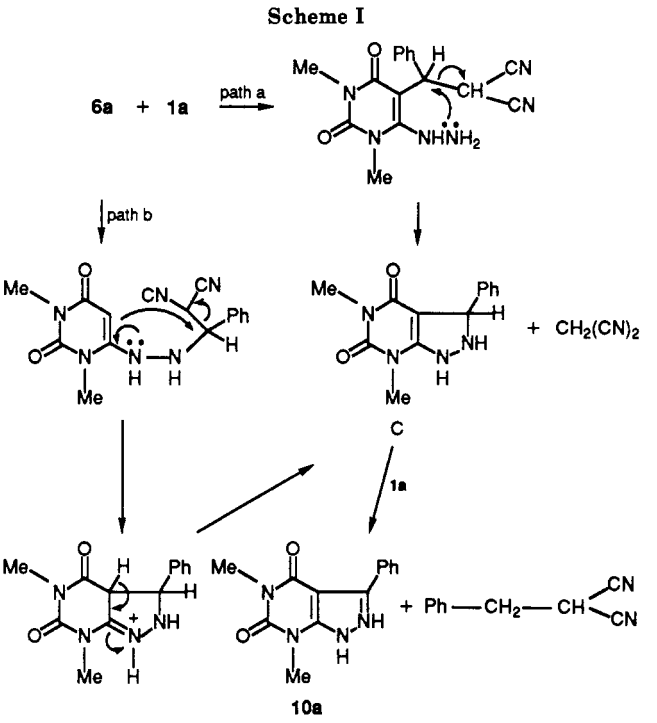
observed that the yield of **7a** was decreased considerably when equimolar amounts of **1a** and **4a** were allowed to react under identical conditions. Similarly reaction of **4** with an excess of **2** and **3** afforded **8** and **9** in high yields (Table I and II).

The formation of byproduct benzylmalononitrile in case of reaction of **4a** with **1a** indicated the participation of cyano olefin both as reactant as well as oxidizing agent. A reasonable mechanism[16] for the formation of **7a** could be explained via initial michael addition of **4a** to **1a** followed by cyclization to dihydropyrido[2,3-*d*]pyrimidine intermediate A,[17] which subsequently underwent oxidation in presence of **1a** to fully aromatized **7a**.

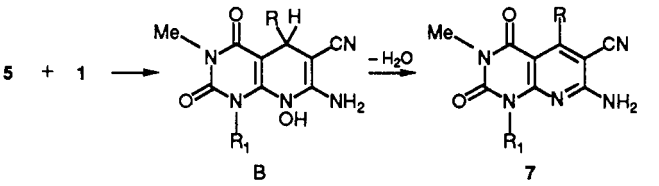


The reaction of **5** with equimolar quantities of **1–3** gave identical substituted pyrido[2,3-*d*]pyrimidines (**7–9**) in excellent yields. In this series of reactions, it was interesting to note that neither was there any formation of reduced products of cyano olefins nor was the use of excess

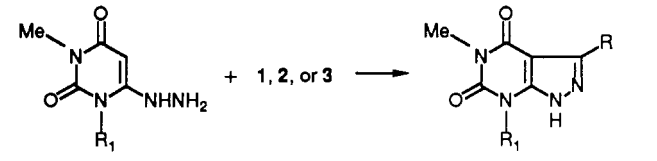
Scheme I



of **1–3** affecting the yield of **7–9**. Evidently in this reaction sequence there was no loss of hydrogen molecule; rather, the final products (**7–9**) were formed due to aromatization by elimination of a water molecule from the plausible intermediate B.



The reaction of **6a** with excess of **1a** under refluxing 1-propanol within 2 h gave 1*H*-4,6-dioxo-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine (**10a**) in quantitative yield. The compound **10a** was identified by spectral and elemental analysis (Table III). In this reaction also malononitrile and benzylmalononitrile could be isolated as byproducts from the mother liquor.



**6a**, $R_1$ = Me
**b**, $R_1$ = H

| | R | $R_1$ |
|---|---|---|
| 10a | Ph | Me |
| b | 2-furyl | Me |
| c | 2-thienyl | Me |
| d | Ph | H |
| e | 2-furyl | H |
| f | 2-thienyl | H |

The formation of **10a** could be explained in parallel by initial Michael addition of **6a** to cyano olefin **1a** either via path a or b followed by cyclization to intermediate C (see Scheme I). The oxidation of dihydropyrazolo[3,4-*d*]pyrimidine C to stable **10a** is corroborated by reduction of the carbon–carbon double bond of **1a** to benzylmalononitrile.

In contrast to the earlier reported reaction of DMAD with **4a** wherein the product formation was reported to be dependent on the nature of solvent,[14b] we did not observe

(17) Dihydropyrimidines are well known as reducing agent for olefins and organic halides; for example, see: (a) Nakamura, K.; Fujii, M.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1984**, *25*, 3185. (b) Nakamura, K.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1983**, *24*, 3335. (c) Yasui, S.; Nakamura, K.; Fujii, M.; Ohno, A. *J. Org. Chem.* **1985**, *50*, 3283.

(18) Itoh, T.; Tmin, T.; Ogura, H.; Kawahara, N.; Nakajima, T.; Watanabe, K. A. *Heterocycles* **1983**, *20*, 2177 and references cited therein.

(19) Petvie, C. R.; Cottam, H. B.; Mckernaa, P. A.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1985**, *28*, 1010 and references cited therein.

(20) Blicke, F. F.; Godl, H. C. *J. Am. Chem. Soc.* **1954**, *76*, 2798.

(21) Pfleiderer, W.; Ferch, H. *Ann.* **1958**, *52*, 615.

(22) (a) Russell, P. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1952**, *74*, 3443. (b) Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Kazuyoshi, I. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 937.

**Table I. Some Pertinent Data of Pyrido[2,3-*d*]pyrimidines 7–9**

| compd | yield,[a] % | mp, °C | IR: $\nu_{max}$, cm$^{-1}$ | $^1$H NMR:[b] $\delta$ | mass spectra,[c] *m/z* |
|---|---|---|---|---|---|
| **7a** | 92 | 308–312 | 3435, 3300, 2195, 1710 | 6.78–7.25 (5 H, m), 3.42 (3 H, s), 2.90 (3 H, s) | 307 |
| **7b** | 84 | 152–153 | 3430, 3310, 2200, 1695 | 7.20 (1 H, d), 6.45–6.65 (2 H, m), 3.30 (3 H, s), 3.20 (3 H, s) | 297 |
| **7c** | 89 | 157–158 | 3435, 3300, 2190, 1705 | 7.10 (1 H, d), 6.40–6.55 (2 H, m), 3.35 (3 H, s), 3.25 (3 H, s) | 313 |
| **7d** | 87 | 320–321 | 3440, 3350, 3100, 2210, 1710 | 7.10–7.30 (5 H, m), 3.20 (3 H, s) | 293 |
| **7e** | 79 | 171–172 | 3445, 3340, 3110, 2200, 1700 | 7.15 (1 H, d), 6.40–6.60 (2 H, m), 3.30 (3 H, s) | 283 |
| **7f** | 78 | 179–180 | 3440, 3300, 2200, 1705 | 7.00 (1 H, d), 6.45–6.55 (2 H, m), 3.30 (3 H, s) | 299 |
| **8a** | 85 | 149–151 | 3445, 3350, 1730, 1695 | 6.90–7.25 (5 H, m), 4.20–4.45 (2 H, q), 3.45 (3 H, s), 3.25 (3 H, s), 1.25–1.45 (3 H, t) | 354 |
| **8b** | 87 | 167–168 | 3435, 3350, 1730, 1700 | 7.25 (1 H, d), 6.20–6.35 (2 H, m), 4.35–4.45 (2 H, q), 3.40 (3 H, s), 3.35 (3 H, s), 1.15–1.45 (3 H, t) | 344 |
| **8c** | 92 | 173–175 | 3430, 3350, 1730, 1705 | 7.20 (1 H, d), 6.25–6.45 (2 H, m), 4.25–4.40 (2 H, q), 3.35 (3 H, s), 3.30 (3 H, s), 1.25–1.45 (3 H, t) | 360 |
| **8d** | 84 | 215–218 | 3425, 3275, 1730, 1705 | 6.90–7.20 (5 H, m), 4.20–4.50 (2 H, q), 3.40 (3 H, s), 1.20–1.45 (3 H, t) | 340 |
| **8e** | 90 | 170–175 | 3440, 3300, 1735, 1710 | 7.25 (1 H, d), 6.30–6.45 (2 H, m), 4.10–4.45 (2 H, q), 3.20 (3 H, s), 1.10–1.40 (3 H, t) | 330 |
| **8f** | 88 | 178–179 | 3425, 3320, 1740, 1695 | 7.30 (1 H, d), 4.45–6.60 (2 H, m), 4.05–4.30 (2 H, q), 3.25 (3 H, s), 1.15–1.40 (3 H, t) | 346 |
| **9a** | 81 | 212–214 | 3440, 3350, 3100, 1700 | 7.00–7.10 (5 H, m), 3.35 (3 H, s), 3.25 (3 H, s) | 325 |
| **9b** | 85 | 191–193 | 3430, 3300, 3125, 1705 | 7.15 (1 H, d), 6.40–6.60 (2 H, m), 3.30 (3 H, s), 3.15 (3 H, s) | 315 |
| **9c** | 83 | 198–199 | 3430, 3310, 3110, 1700 | 7.15 (1 H, d), 6.35–6.55 (2 H, m), 3.35 (3 H, s), 3.20 (3 H, s) | 331 |
| **9d** | 92 | 245–247 | 3440, 3325, 3110, 1710 | 7.00–7.20 (5 H, m), 3.25 (3 H, s) | 311 |
| **9e** | 91 | 208–209 | 3435, 3320, 3100, 1700 | 7.20 (1 H, d), 6.30–6.60 (2 H, m), 3.15 (3 H, s) | 301 |
| **9f** | 85 | 201–202 | 3430, 3315, 3100, 1700 | 7.15 (1 H, d), 6.25–6.50 (2 H, m), 3.10 (3 H, s) | 317 |

[a] Yield of the isolated products. [b] $^1$H NMR of compounds **7a–c** and **8a–f** were measured in $CDCl_3$; **7d–f** and **9a–f** were measured in TFA. [c] Molecular ion peak.

**Table II. Synthesis of Pyrido[2,3-*d*]pyrimidines 7–9**

| entry | compd | R | $R_1$ | Y | reactn time, h | molecular formula | analytical data: calcd/found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **7a** | Ph | $CH_3$ | CN | 4 | $C_{16}H_{13}N_5O_2$ | 62.53/62.45 | 4.26/4.22 | 22.79/22.66 |
| 2 | **7b** | 2-furyl | $CH_3$ | CN | 3 | $C_{14}H_{11}N_5O_3$ | 56.57/56.40 | 3.73/3.62 | 23.56/23.42 |
| 3 | **7c** | 2-thienyl | $CH_3$ | CN | 4 | $C_{14}H_{11}N_5O_2S$ | 53.67/53.60 | 3.54/3.40 | 22.35/22.19 |
| 4 | **7d** | Ph | H | CN | 5 | $C_{15}H_{11}N_5O_2$ | 61.43/61.51 | 3.78/3.72 | 23.88/23.63 |
| 5 | **7e** | 2-furyl | H | CN | 4 | $C_{13}H_9N_5O_3$ | 55.13/55.25 | 3.20/3.05 | 24.73/24.59 |
| 6 | **7f** | 2-thienyl | H | CN | 3 | $C_{13}H_9N_5O_2S$ | 52.17/52.21 | 3.03/3.10 | 23.40/23.28 |
| 7 | **8a** | Ph | $CH_3$ | COOEt | 3 | $C_{18}H_{18}N_4O_4$ | 61.00/60.91 | 5.12/5.22 | 15.81/15.75 |
| 8 | **8b** | 2-furyl | $CH_3$ | COOEt | 4 | $C_{16}H_{16}N_4O_5$ | 55.81/55.63 | 4.68/4.59 | 16.27/16.11 |
| 9 | **8c** | 2-thienyl | $CH_3$ | COOEt | 4 | $C_{16}H_{16}N_4O_4S$ | 53.32/53.18 | 4.48/4.41 | 15.55/15.45 |
| 10 | **8d** | Ph | H | COOEt | 3 | $C_{17}H_{16}N_4O_4$ | 60.00/60.12 | 4.74/4.65 | 16.46/16.41 |
| 11 | **8e** | 2-furyl | H | COOEt | 3 | $C_{15}H_{14}N_4O_5$ | 54.55/54.51 | 4.27/4.30 | 16.96/16.88 |
| 12 | **8f** | 2-thienyl | H | COOEt | 4 | $C_{15}H_{14}N_4O_4S$ | 52.02/52.09 | 4.07/4.01 | 16.18/16.08 |
| 13 | **9a** | Ph | $CH_3$ | $CONH_2$ | 3 | $C_{16}H_{15}N_5O_3$ | 59.07/59.20 | 4.65/4.52 | 21.53/21.49 |
| 14 | **9b** | 2-furyl | $CH_3$ | $CONH_2$ | 2 | $C_{14}H_{13}N_5O_4$ | 53.33/53.17 | 4.16/4.30 | 22.21/22.17 |
| 15 | **9c** | 2-thienyl | $CH_3$ | $CONH_2$ | 2 | $C_{14}H_{13}N_5O_3S$ | 50.78/50.68 | 3.96/3.81 | 21.15/21.09 |
| 16 | **9d** | Ph | H | $CONH_2$ | 2 | $C_{15}H_{13}N_5O_3$ | 57.87/57.75 | 4.21/4.35 | 22.50/22.44 |
| 17 | **9e** | 2-furyl | H | $CONH_2$ | 3 | $C_{13}H_{11}N_5O_4$ | 51.82/51.95 | 3.68/3.72 | 23.25/23.14 |
| 18 | **9f** | 2-thienyl | H | $CONH_2$ | 3 | $C_{13}H_{11}N_5O_3S$ | 49.21/49.11 | 3.49/3.58 | 22.07/22.01 |

**Table III. Synthesis of Pyrazolo[3,4-*d*]pyrimidines 10**

| entry | compd | R | $R_1$ | reactn time, h | molecular formula | analytical data: calcd/found C | H | N |
|---|---|---|---|---|---|---|---|---|
| 19 | **10a** | Ph | $CH_3$ | 2 | $C_{13}H_{12}N_4O_2$ | 60.93/60.85 | 4.72/4.65 | 21.86/21.55 |
| 20 | **10b** | 2-furyl | $CH_3$ | 2 | $C_{11}H_{10}N_4O_3$ | 53.66/53.80 | 4.09/4.05 | 22.75/22.63 |
| 21 | **10c** | 2-thienyl | $CH_3$ | 2 | $C_{11}H_{10}N_4O_2S$ | 50.37/50.45 | 3.84/3.83 | 21.36/21.29 |
| 22 | **10d** | Ph | H | 3 | $C_{12}H_{10}N_4O_2$ | 59.50/59.41 | 4.16/4.22 | 23.13/23.02 |
| 23 | **10e** | 2-furyl | H | 3 | $C_{10}H_8N_4O_3$ | 51.73/51.79 | 3.47/3.39 | 24.13/24.08 |
| 24 | **10f** | 2-thienyl | H | 4 | $C_{10}H_8N_4O_2S$ | 48.38/48.32 | 3.25/3.18 | 22.57/22.49 |

any such influence of protic or aprotic solvent on reaction of **1a** with **4a**. In each case by performing reactions in 1-propanol or dimethylformamide we obtained the same product **7a** in high yields.

In conclusion our results delinated above demonstrate that it is possible to synthesize a variety of aromatic and heterocyclic substituted analogues of biologically important[18,19] pyrido[2,3-*d*] and pyrazolo[3,4-*d*]pyrimidines by using suitably substituted cyano olefins. Further study in these observed redox processes, i.e. conversion of intermediates A–C to aromatised products **7–10** on the line of NADH model, is in progress.

## Experimental Section

$^1$H NMR spectra were recorded in Varian T-60 and JEOL JNM-FX90Q spectrometers with tetramethylsilane as internal standard. IR spectra were obtained by using a Perkin-Elmer 237 and 580B infrared spectrometers in KBr disks. Mass spectra were recorded on a AEIMS-30 spectrometer. Melting points were determined by using a Büchi melting point apparatus and are uncorrected. 6-Aminouracils (**4a,b**) were prepared from condensation of ethyl cyanoacetate with dimethyl- or mono-

methylurea.[20] 6-(Hydroxyamino)uracil (5) and 6-hydrazinouracil (6) were prepared[21] from condensation of 6-chlorobarbituric acid with hydroxylamine hydrochloride or hydrazine hydrate.

**General Procedures for the Synthesis of Pyrido[2,3-*d*]pyrimidines 7–9 from the Reaction of Cyano Olefins 1–3 and 6-Aminouracil 4 or 6-(Hydroxyamino)uracil 5.** A solution of 1.55 g (10 mmol) of **4a** and 4.62 g (30 mmol) of cyano olefin (**1a**) in 50 mL of 1-propanol was refluxed for 4 h. The reaction mixture was concentrated to half of its volume, cooled, and filtered. Recrystallization from ethanol gave light brown crystals of **7a** (2.82 g, 92%): mp 308–312 °C; $^1$H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 3.42 (s, 3 H), 6.78–7.25 (m, 5 H); IR 3435, 3300, 2195, 1710 cm$^{-1}$; MS 307 ($M^+$).

Evaporation of the filtrate from **7a** followed by column chromatography on silica gel column (benzene) gave benzylmalononitrile (1.48 g, 95%): mp 90–92 °C (lit.[22] mp 91–92 °C); $^1$H NMR ($CDCl_3$) δ 3.15 (d, 2 H), 3.70 (t, 1 H), 7.18 (m, 5 H); IR 2250 cm$^{-1}$; MS 153 ($M^+$).

**General Procedure for the Synthesis of Pyrazolo[3,4-*d*]pyrimidine 10 from the Reaction of Cyano Olefins 1–3 and 6-Hydrazinouracil 6.** A solution of 1.70 g (10 mmol) of **6a** and 4.62 g (30 mmol) of cyano olefin **1a** in 50 mL of 1-propanol was refluxed for 3 h. The reaction mixture was concentrated, cooled, and filtered. Recrystallization from ethanol gave **10a** (2.30 g, 90%): mp 258–259 °C; $^1$H NMR (TFA) δ 2.95 (s, 3 H), 3.40 (s, 3 H), 6.75–7.20 (m, 5 H); IR 3220, 1700 cm$^{-1}$; MS 256 ($M^+$). Evaporation of the solvent from the filtrate of **7a** in vacuo and column chromatography on a silica gel column (benzene–petroleum ether) gave malononitrile (0.60 g, 90%) [mp 32–34 °C; bp 220 °C] and benzylmalononitrile (1.51 g, 97%): mp 90–92 °C; $^1$H NMR ($CDCl_3$) δ 3.15 (d, 2 H), 3.70 (t, 1 H), 7.18 (m, 5 H); IR 2250 cm$^{-1}$; MS 156 ($M^+$).

**10b**: yield 92%; mp 235–236 °C; $^1$H NMR (TFA) δ 3.00 (s, 3 H), 3.45 (s, 3 H), 6.35–6.65 (m, 2 H), 7.25 (d, 1 H); IR 3225, 1705 cm$^{-1}$; MS 246 ($M^+$).

**10c**: yield 92%; mp 243–244 °C; $^1$H NMR (TFA) δ 3.10 (s, 3 H), 3.50 (s, 3 H), 6.25–6.45 (m, 2 H), 7.15 (d, 1 H); IR 3220, 1705 cm$^{-1}$; MS 262 ($M^+$).

**10d**: yield 82%; mp 256–257 °C; $^1$H NMR (TFA) δ 2.95 (s, 3 H), 6.80–7.25 (m, 5 H); IR 3250, 3125, 1700 cm$^{-1}$; MS 242 ($M^+$).

**10e**: yield 84%; mp 242–243 °C; $^1$H NMR (TFA) δ 3.00 (s, 3 H), 6.30–6.45 (m, 2 H), 7.10 (d, 1 H); IR 3245, 3120, 1695 cm$^{-1}$; MS 232 ($M^+$).

**10f**: yield 87%; mp 257–258 °C; $^1$H NMR (TFA) δ 3.05 (s, 3 H), 6.35–6.50 (m, 2 H), 7.15 (d, 1 H); IR 3245, 3115, 1700 cm$^{-1}$; MS 248 ($M^+$).

**Synthesis of Pyrazolo[3,4-*d*]pyrimidine 10 from Reaction of 6 and 1 in Aprotic Solvent.** A solution of 1.70 g (10 mmol) of **6a** and 3.08 g (20 mmol) of **1a** in 50 mL of dry DMF was heated at 125–130 °C for 2 h. The solvent was removed from the reaction mixture in vacuo, treated with water (75 mL), and filtered. Recrystallization of the crude compound from ethanol gave **10a** (2.18 g, 85%): mp 258–259 °C. Column chromatography of the residue obtained from the evaporation of the filtrate gave malononitrile (0.58 g, 88%), mp 32–34 °C, and benzylmalononitrile (1.48 g, 95%), mp 90–92 °C.

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**Registry No.** **1a**, 2700-22-3; **1b**, 3237-22-7; **1c**, 28162-32-5; **2a**, 2025-40-3; **2b**, 23973-22-0; **2c**, 31330-51-5; **3a**, 709-79-5; **3b**, 3695-90-7; **3c**, 54688-95-8; **4a**, 6642-31-5; **4b**, 21236-97-5; **5a**, 42963-41-7; **5b**, 123506-39-8; **6a**, 123506-40-1; **6b**, 123506-41-2; **7a**, 95548-64-4; **7b**, 123506-42-3; **7c**, 123506-43-4; **7d**, 95548-68-8; **7e**, 123506-44-5; **7f**, 123506-45-6; **8a**, 123506-46-7; **8b**, 123506-47-8; **8c**, 123506-48-9; **8d**, 123506-49-0; **8e**, 123506-50-3; **8f**, 123506-51-4; **9a**, 123506-52-5; **9b**, 123506-53-6; **9c**, 123506-54-7; **9d**, 123506-55-8; **9e**, 123506-56-9; **9f**, 123506-57-0; **10a**, 35221-08-0; **10b**, 123506-58-1; **10c**, 123506-59-2; **10d**, 42748-33-4; **10e**, 123506-60-5; **10f**, 123506-61-6; $PhCH_2CH(CN)_2$, 1867-37-4.

# Synthesis of 6*H*-Pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-Pyrrolo[1,2-*d*]tetrazoles: Alkylation and Acylation of the Monoanions

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Thermal cyclization of 1-azido-2-penten-4-ynes and 4-azido-2-butenenitriles led to 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-pyrrolo[1,2-*d*]tetrazoles, respectively, in good yields. Upon treatment with methyllithium these heterocyclic compounds gave the corresponding aromatic anions which can be alkylated with methyl iodide or acylated with ethyl chloroformate.

Unlike pentalene itself,[1] the corresponding pentalene dianion resulting from the addition of two electrons to the π-system is a stable material belonging to the class of aromatic compounds.[2] Ten general types of neutral heterocyclic systems have been recognized which are isoelectronic with the 10 π-electron system of the pentalenyl dianion.[3] Six of these can be represented by a covalent formulation, whereas only mesomeric betaine structures can be written for the four others. Several azapentalene anions have been prepared in solution as their lithium salts by deprotonation of the appropriate neutral compounds. The NMR spectra of these anions suggest that the negative charge is delocalized in a 10 π-electron system.[3,4] However little work has been devoted to the reactivity of these monoanions.[4,5]

In preliminary communications,[6] we reported that 1-azido-2-penten-4-ynes (**2**) can be thermally cyclized to a

(1) Block, R.; Marty, R. A.; de Mayo, P. *J. Am. Chem. Soc.* **1971**, *93*, 3071.

(2) (a) Katz, T. J.; Rosenberger, M.; O'Hara, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 249. (b) Willner, I.; Becker, J. Y.; Rabinovitz, M. *J. Am. Chem. Soc.* **1979**, *101*, 395.

(3) For reviews, see: (a) Ramsden, C. A. *Tetrahedron* **1977**, *33*, 3203. (b) Ramsden, C. A. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; p 1027. (c) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.

(4) For a review, see: Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heterocycl. Chem.* **1978**, *22*, 183.

(5) (a) Albini, A.; Bettinetti, G. F.; Minoli, G. *J. Org. Chem.* **1983**, *48*, 1080. (b) Albini, A.; Bettinetti, G. F.; Minoli, G.; Fulle Soldi, T. *Chem. Lett.* **1984**, 1197.

(6) (a) Dulcere, J. P.; Santelli, M.; Bertrand, M. *C. R. Hebd. Séances Acad. Sci. Série C* **1970**, *271*, 585. (b) Bertrand, M.; Dulcere, J. P.; Santelli, M. *Tetrahedron Lett.* **1977**, 1784.

0022-3263/90/1955-0571$02.50/0 