SHORT PAPER

J. Chem. Research (S), 2001, 346–348

Cyanoacetylurea in heterocyclic synthesis: A simple synthesis of heterocyclic condensed uracils†

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The condensation products of cyanoacetylurea with carbonyl compounds were utilized to prepare fused uracils through the intermediate formation of o-aminoureidocarbonyl heterocycles.

Keywords: cyanoacetylurea, fused pyrimidines

Cyanoacetylurea **1** has been used as starting material for the synthesis of a variety of heterocycles[1] being easily prepared from low cost materials. Also, uracils and their substitued derivatives have been prepared to investigate their biological behaviour.[2,3] In continuation of this work, **1** was used to synthesise uracils fused with different heterocyclic rings.

Thus, cyanoacetylurea[4] condensed readily with aromatic aldehydes, namely, benzaldehyde, 2-furaldehyde, 2-nitrobenzaldehyde and thiophene-2-carboxaldehyde, affording the corresponding arylmethylene derivatives **2a–d.** These compounds showed the ylidene H at $\delta \sim 8.1$ ppm[5] in addition to signals from the aryl group. Compound **2a** reacted with cyanoacetohydrazide **3** in ethanol in the presence of triethylamine to afford a new compound with a molecular ion peak at *m/z* 312. It showed in its ^{1}H NMR spectrum the ureido NH_2 and NH signals at δ 7.1, 7.8 and 9.7 ppm. It revealed in the IR a CN absorption at 2200 cm^{-1} already present in **2a** but it lacked the methine singlet. Accordingly, the aminopyridone structure **4a** was given to this product. Upon repeating the same reaction with the furyl derivative **2b**, compound **4b** was obtained in good yield. This structure assignment was supported by microanalytical, spectral data and previous reports.[6]

The chemical behaviour of **4a,b** was also in accordance with their structure. Thus, when each of compounds **4a,b** was refluxed in DMF, new products were formed with three ν CO absorptions, a CN and three (D_2O exchangeable) singlets beside the aryl radical, and absence of the characteristic ureido NH_2 and NH signals.[1] Their mass spectral data, exemplified by the reaction product from **4a**, showed a molecular ion peak corresponding to that of the parent compound minus a mole of ammonia which could be detected during the reaction course. Based on these data, the pyridopyrimidinetrione structure **5** was assigned to these compounds, plausibly formed via cyclization between the ureido residue and the adjacent amino group with loss of ammonia. These compounds, *i.e.* **5a,b** could be also obtained in a one step reaction by refluxing **2a,b** with two moles of cyanoacetohydrazide in DMF.

Following a parallel pathway, when compound **2c** was reduced with Zn dust in acetic acid, the quinolinopyrimidine derivative **6** was obtained in moderate yield. It showed the quinolinopyrimidine 5-H at δ = 9.0 ppm along with the other aromatics at their expected locations while in its mass spectral data the molecular ion peak appeared as the base peak at *m/z* 213. Compound **6** is assumed to be formed through the intermediacy of 2-amino-3-ureidocarbonylquinoline via transformation of the NO_2 group to NH_2 with subsequent cyclisation accompanied by loss of ammonia similar to the formation of **5**.

Then, the reaction of **2a,d** with 2-cyanomethylthiazol-4-one **7** was carried out in the presence of triethylamine. New compounds were formed showing ^{1}H NMR singlets at $\delta \sim 5.0$ and 8.3 ppm and the mass spectral data of the thienyl derivative gave a molecular ion peak at *m/z* 438. On these bases and the abovementioned results, the thiazolopyridouracil structure **8** was given to these products where the *o*-aminoureidocarbonylthiazolopyridines were formed first,[7] followed by self-cyclisation with loss of ammonia to give the uracil fragment as stated in the formation of structures **5** and **7.**

Following a similar synthetic pathway, when compound **2d** was heated with 6-amino-*N*,*N*-dimethyluracil[8] **9** in DMF at 100 °C, the pyrimidopyridouracil derivative **10** was obtained. The ^{1}H NMR spectrum of the latter showed two signals (D_2O exchangeable, 1H each) attributable to the NH groups and lacking the NH_2 ureido one. Also, the mass spectal data of **10** was in accordance with the given structure.

It is assumed that **9** reacts with **2d** via initial Michael addition on the C-5 active methylene nucleophile of **9** then self-cyclisation on the CN group affording the uracil aminopyridine intermediate which further cyclised as explained above to form **10.**

Continuing our investigation, when compound **1** was fused with acetylacetone at 130°C, the known[9] 3-cyano-4,6-dimethylpyridin-2-one was obtained. However, when the reaction was repeated in acetic acid under reflux, a new compound was formed with a molecular formula $C_9H_{11}N_3O_3$ *m/z* 209, for which the iminoureidocarbonylpyran structure **11** was given. Its ^{1}H NMR showed the pyran 5-H at δ = 6.2 ppm with absence of the parent IR CN absorption.

The chemical behaviour of **11** also confirmed this structure. Thus, upon its treatment with hydrazine hydrate, the reaction afforded a new compound having a molecular ion peak as the base peak equivalent to the sum of both reactants minus a mole of H_2O and a mole of NH_3. It showed only three (D_2O exchangeable) signals at δ = 11.5, 11.1 (2H) and 11.9 (1H) ppm. So, the *N*-aminopyridouracil structure **12** was given to this product. The nucleophilic attack of hydrazine on the iminopyran caused its ring opening to form an intermediate which self-cyclised twice to form the pyridine nucleus (via loss of H_2O) and the uracil ring (via loss of NH_3). These assumptions could be explained in terms of structure **12** and its *N*-aminouracil analogue. However, the latter was excluded based on the mass spectral data which showed a fragment corresponding to the *N*-aminopyridine structure.

Experimental

Melting points were taken on an Electrothermal 9100 apparatus. IR spectra were recorded with a Carl Zeiss spectrophotometer model UR 10 in KBr pellets. ^{1}H NMR spectra were determined with a JEOL 270 MHz instrument (internal TMS). Mass spectra were recorded with a Finnigan SSQ 7000 mass spectrometer. Microanalyses were per-

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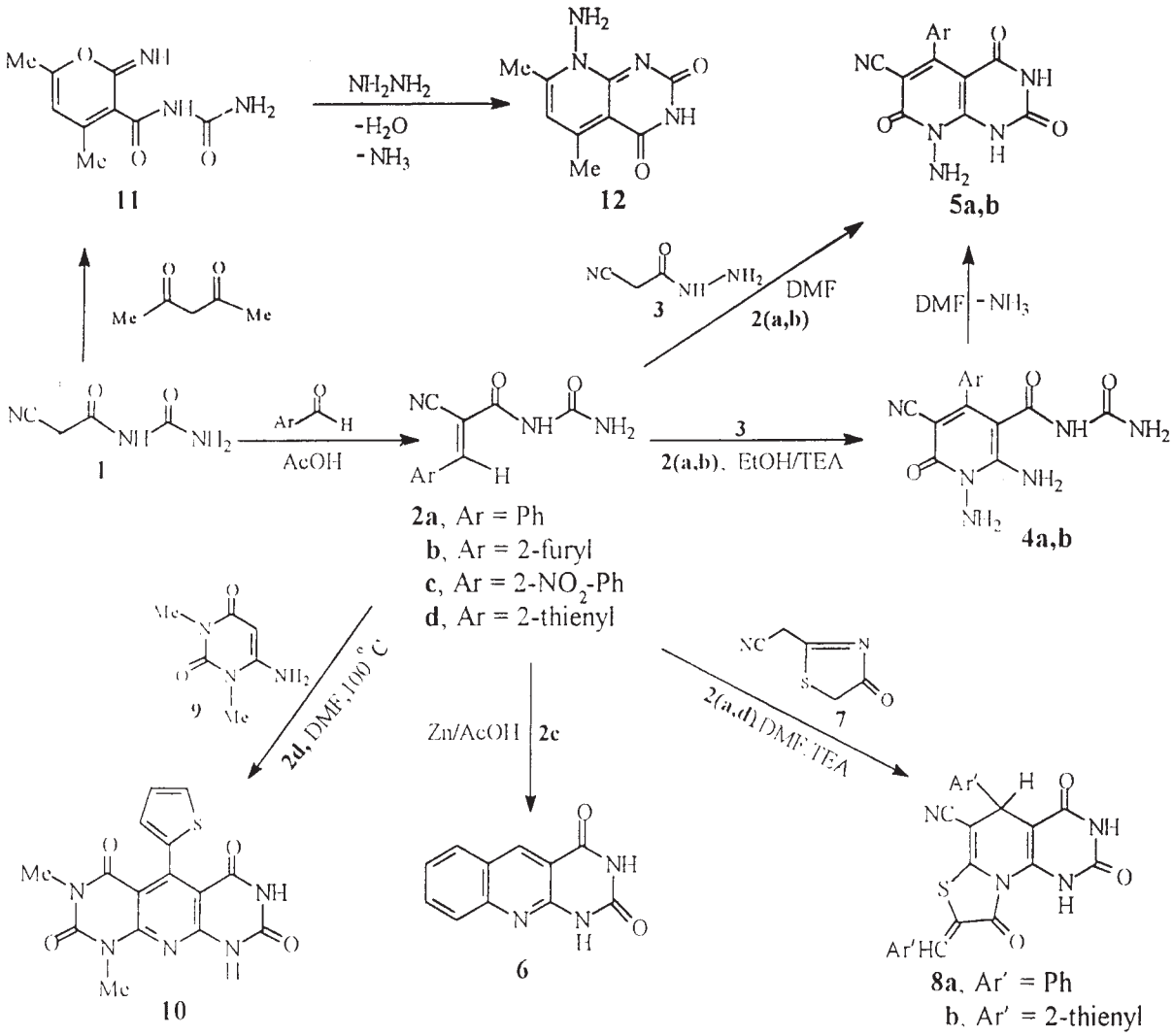
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



formed by the Central Service Laboratory at Cairo University and the Microanalytical Unit at the National Research Center.

1-Aryl-2-ureidocarbonylacrylonitriles **(2a–d)**: *General procedure*: A mixture of **1** (10 mmol) with an equimolecular amount of the appropriate aldehyde was refluxed in acetic acid (25 ml) for 1h. A precipitate was formed on hot, filtered off and crystallised. The phenyl derivative **2a** (yield 90 %) had m.p. 230–232 °C (from acetic acid); ν_{max} /cm^{-1} (KBr) 3320, 3180 (NH_2, NH), 2200 (CN), 1680, 1670 (2 CO); δH (DMSO) 7.2–7.6 (m, 7H, Ph and NH_2), 8.1 (s, 1H, ylidene H), 9.7 (brs, 1H, NH) (Found: C,61.2; H, 4.1; N, 19.2. $C_{11}H_9N_3O_2$ (215.20) requires: C, 61.4; H, 4.2; N, 19.5 %).

The furyl derivative **2b** (yield 80%) had m.p. 240-242 (from acetic acid); ν_{max}/ cm^{-1} (KBr) 3320, 3180 (NH_2, NH), 2200 (CN), 1680, 1670 (2 CO); δ_H (DMSO) 6.2 (m, 2H, furan 4-H and 3-H), 7.6–7.8 (m, 3H, furan 5-H and NH_2), 8.1 (s, 1H, ylidene H), 9.6 (brs, 1H, NH) (Found: C, 52.6; H, 3.2; N, 20.2. $C_9H_7N_3O_3$ (205.17) requires C, 52.7; H, 3.4; N, 20.5 %).

The 2-nitrophenyl derivative **2c:** (yield 90%) had m.p. 208–210 °C (from acetic acid) ; ν_{max}/ cm^{-1} (KBr) 3450, 3300 (NH_2, NH), 2220 (CN), 1690, 1680 (2 CO); δ_H (DMSO) 7.5, 7.6 (2s, 2H, NH_2), 7.8–8.0 (m, 3H, Ph 4-6-H), 8.2 (dd, *J* = 7Hz, 1H, Ph 3-H), 8.7 (s, 1H, ylidene H), 10.6 (s, 1H, NH) (Found: C, 50.5; H, 3.0; N, 21.2. $C_{11}H_8N_4O_4$ (260.20) requires C, 50.8; H, 3.1; N, 21.5 %).

The thienyl derivative **2d:** (yield 80%) had m.p. 210 °C (from DMF/ H_2O); ν_{max}/ cm^{-1} (KBr) 3320, 3180 (NH_2,NH), 2200 (CN), 1680, 1670 (2 CO); δH (DMSO) 7.0 (dd, 1H, thiophene 4-H), 7.4, 7.6 (2s, 2H, NH_2),7.8 (dd, 1H, thiophene 3-H), 8.1, (dd, 1H, thiophene 5-H), 8.2 (s, 1H, ylidene H), 10.4 (s, 1H, NH) (Found: C,48.8; H, 3.0; N, 18.7; S, 14.2. $C_9H_7N_3O_2S$ (221.32) requires C, 48.9; H, 3.2 ; N, 19.0; S, 14.5 %).

4-Aryl-5-cyano-3-ureidocarbonyl-1,2-diaminopyridin-6-one **(4a,b):** *General procedure*: Each of compounds **2a,b** (20 mmol) was refluxed with **3** (10 mmol) in ethanol (30 ml) in presence of triethylamine (3 drops) for 1h. The solid formed was collected by filtration then crystallised.

The phenyl derivatve **4a** (yield 70%) had m.p. 235–237 °C (from ethanol); ν_{max}/ cm^{-1} (KBr) 3280, 3200 (NH_2, NH), 2200 (CN), 1690, 1680, 1660 (3CO); δH (DMSO) 5.7 (2s, 2H, NH_2), 7.1–7.5 (m, 7H, Ph and NH_2), 7.8 (s, 2H, NH_2), 9.7 (s, 1H, NH) (Found: C, 53.6; H, 3.7; N, 26.6. $C_{14}H_{12}N_6O_3$ (312.29) requires C, 53.8; H, 3.9; N, 26.9%). MS: *m/z* 312 [M$^+$].

The furyl derivative **4b** (yield 60%) had m.p. 248–250 °C (from ethanol); ν_{max}/ cm^{-1} (KBr) 3300, 3200 (NH_2, NH), 2200 (CN), 1700, 1680, 1660, (3CO); δH (DMSO) 5.7(s, 2H, NH_2), 6.8 (s, 1H, furan 4-H), 7.5, 7.6 (2s, 1H, NH_2), 8.2 (m, 4H, furan 3-H, 5-H and NH_2),10.4 (s,1H, NH) (Found: C, 47.5; H, 3.2; N, 27.5. $C_{12}H_{10}N_6O_4$ (302.25) requires C, 47.7; H, 3.3 ; N, 27.8 %).

8-Amino-5-aryl-6-cyanopyrido[2,3-d]pyrimidine-2,4,7 (1H,3H,8H)-trione **(5a,b)**: *General procedure*: (a) From **2**. A mixture of each of **2a,b** (20 mmol) with **3** (10 mmol) was refluxed in DMF (20ml) in presence of triethylamine (20 mmol) for 2–3 h. After cooling , water was added to the solution until precipitation commenced; the solid formed was filtered off and crystallised. (b) From **4**. The procedure was the same as in (a) except that **4a,b** (10 mmol) was used in place of the mixture (**2** with **3**).

The phenyl derivative **5a** (Yield 45% by method a and 60% by method b) had m.p. 270 °C (from acetic acid). ν_{max}/ cm^{-1} (KBr) 3310, 3200 (NH_2, NH), 2200 (CN), 1680, 1660, 1650 (3 CO); δ_H (DMSO) 5.7(s, 2H, NH_2), 7.0–7.5 (m, 5H, Ph), 10.6 (s,1H, NH), 11.1 (s, 1H, NH) (Found: C, 56.8; H, 3.0; N, 23.5. $C_{14}H_9N_5O_3$ (295.25) requires C, 57.0; H, 3.1 ; N, 23.7 %). MS: *m/z* 295 [M$^+$].

The furyl derivative **5b:** (yield 30% by method a and 40% by method b) had m.p. 246–248 °C (from acetic acid). ν_{max}/ cm^{-1} (KBr) 3300, 3150 (NH_2, NH), 2200 (CN), 1680, 1660, 1650 (3CO); δ_H (DMSO) 5.7(s, 2H, NH_2), 6.7 (m, 1H, furan 4-H), 7.0 (m, 1H, furan 3-H), 7.7 (m, 1H, furan 5-H),7.8 (s, 1H, NH), 10.0 (s, 1H, NH) (Found: C, 50.2; H, 2.3; N, 24.3. $C_{12}H_7N_5O_4$ (285.22) requires C, 50.5; H, 2.5; N, 24.6 %).

Pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(6)**: To a boiling solution of **2c:** (10mmol) in acetic acid (20 ml), Zn dust (2g) was added portionwise over 10 minutes; reflux was continued for 2 h and the precipitate formed was collected, washed with water then crystallised to give **6** (yield 40 %) had m.p. > 350 °C (from acetic acid); ν_{max}/ cm^{-1} (KBr) 3050 (NH), 1710, 1700 (2 CO); δ_H (DMSO) 7.5 (m, 1H, pyrimidoquinoline 9-H), 7.8 (m, 2H, pyrimidoquinoline 7-H, 8-H), 8.1 (dd, 1H, pyrimidoquinoline 6-H), 9.0 (s, 1H, pyrimidoquinoline 5-H), 11.4 (s, 1H, NH), 11.7 (brs, 1H, NH) (Found: C,61.7; H, 3.1; N, 19.4. $C_{11}H_7N_3O_2$ (213.19) requires C, 62.0; H, 3.3; N, 19.7 %). MS: *m/z* 213 [M$^+$].

8-Arylmethylene-5-aryl-6-cyanothiazolo[3,2:1,6]pyrido [2,3-d]pyrimidine-2,4,9(1H,3H,5H)-triones **(8a,b)**: *General procedure*: A mixture of each of **2a,d** (10mmol) was refluxed in DMF (20 ml) in presence of triethylamine (3 drops) for 4-5 h. After partial concentration and cooling, a precipitate was formed, filtered off and crystallised.

The phenyl derivative **8a**: (yield 60 %) had m.p. > 350 °C (from DMF); ν_{max}/ cm^{-1} (KBr) 3250, 3200 (2 NH), 1710, 1700 (uracil CO), 1650 (ureido CO); δH (DMF) 5.0 (s, 1H, pyridine 4-H), 7.2, 7.5 (2m, 10H, 2Ph), 8.3 (s, 1H, ylidene H), 10.7 (s,1H, NH), 11.6 (s, 1H, NH) (Found: C,64.6; H, 3.2; N, 12.9; S, 7.2. $C_{23}H_{14}N_4O_3S$ (426.43) requires: C, 64.8; H, 3.3; N, 13.1; S, 7.5 %).

The thienyl derivative **8b** (yield 50 %) had m.p. > 350 ºC (from DMF);. ν_{max}/ cm^{-1} (KBr) 3250, 3200 (2NH), 1710, 1700 (uracil CO), 1660 (ureido CO); δH (DMSO) 5.1 (s, 1H, pyridine 4-H), 7.1, 7.2 (2dd, 2H, 2 thiophene 4-H), 7.4, 7.5, (2dd, 2H, 2 thiophene 3-H), 7.8, 8.1 (2dd, 2H, 2 thiophene 5-H), 8.3 (s, 1H, ylidene H), 10.8 (brs,1H, NH), 11.6 (s, 1H, NH) (Found : C, 51.8; H, 2.2; N, 12.5; S, 21.6. $C_{19}H_{10}N_4O_3S_3$ (438.48) requires : C, 52.0; H, 2.3; N, 12.8; S, 21.9 %). MS : *m/z* 438 [M$^+$].

7,9-Dimethyl-5-(2-thienyl)pyrimido[4,5:6,5]pyrido[3,2-d]pyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone **(10)**: Compound **2d** (10 mmol) was heated with **9** (10 mmol) in DMF(25ml) at 100 °C for 6 h. A precipitate, formed after cooling, was filtered off and crystallized to give **10** (yield 40 %), m.p. > 350 ºC (from DMF); ν_{max}/ cm^{-1} (KBr) 1700, 1690, 1650, 1640 (4 CO); δH (DMSO) 3.2 ,3.3 (2s, 6 H, 2 CH_3), 7.1 (dd, 1H, thiophene 4-H), 7.5 (dd, 1H, thiophene 3-H), 7.9 (s, 1H, NH), 8.1 (dd, 1H, thiophene 5-H), 8.5 (s, 1H, NH) (Found : C, 50.3; H, 3.0; N, 19.4; S, 8.7. $C_{15}H_{11}N_5O_4S$ (357.34) requires : C, 50.4; H, 3.1; N, 19.6; S, 9.0 %). MS : *m/z* 357 [M$^+$].

4,6-Dimethyl-3-ureidocarbonyl-2-iminopyran **(11)**: Compound **1** (10 mmol) was refluxed with acetylacetone (10 mmol) in glacial acetic acid (20 ml) for 2 h . After cooling, water was added dropwise until precipitation occurred. The solid product formed was then filtered off and crystallised to give **11** (yield 60 %), m.p. 267 ºC (from acetic acid); ν_{max}/ cm^{-1} (KBr) 3400, 3200 (NH_2, NH), 1672, 1650 (2 CO); δ_H (DMSO) 2.3, 2.4 (2s, 6H, 2CH_3), 6.2 (s, 1H, pyran 5 H)), 7.3, 7.8 (2s, 2H, NH_2), 11.9 (s, 1H, NH), 12.4 (s, 1H, NH) (Found: C,51.7; H, 5.2; N, 19.8. $C_9H_{11}N_3O_3$ (209.21) requires C, 51.7; H, 5.3; N, 20.1 %). MS: *m/z* 209 [M$^+$].

8-Amino-5,7-dimethylpyrido[2,3-d]pyrimidine-2,4(3H,8H)-dione **(12)**: To a hot solution of **11** (10 mmol) in DMF (20 ml), hydrazine hydrate (20 mmol) was added and heating was continued at 90–100 °C for 1/2 h. After cooling, a precipitate was formed, collected and crystallized to give **12**: (yield 40 %) had m.p. > 350 °C (from acetic acid); ν_{max}/ cm^{-1} (KBr) 3350, 3200 (NH_2, NH), 1660, 1650 (2 CO); δH (DMSO) 2.2, 2.3 (2s, 6, 2CH_3), 6.0 (s, 1H, pyridopyrimidine 3-H)), 11.1, 11.5 (2s, 2H, NH_2), 11.9 (s, 1H, NH) (Found: C, 52.2; H, 4.7; N, 26.9. $C_9H_{10}N_4O_2$ (206.21) requires: C, 52.4; H, 4.9; N, 27.2 %). MS: *m/z* 206 [M$^+$].

Received 31 January 2000; accepted 26 March 2001
Paper 01/731

References

1 Y. A. Allam, L.M. Chabaka and G. A. M. Nawwar, *Heteroatom Chemistry*, 2000, **11**, 209.
2 C.I. Hong, A. Nechaev, A.J. Kirisits, R. Vig, C.R. West, K.K. Manouilov and C.K. Chu, *J. Med. Chem.*, 1996, **39**, 1771.
3 N. Borg, X.X. Zhou, N.G. Johansson, B. Oberg and L. Stahle, *Antiviral Chem., Chemother.*, 1997, **8**, 47.
4. B. Bobranski and Z. Synwiedski, *J. Am. Pharm. Assoc., Sci. Ed.* 1948, **37**, 62.
5 G.A.M. Nawwar and N.A. Shafik, *Collect. Czech. Chem. Commun*. 1995, **60**, 2200.
6 J.L. Soto, C. Seoane, P. Zamorano and F. J. Guadrado, *Synthesis*, 1981, **7**, 529.
7 S.A.M. Osman, G. Eldin-H. Elgemeie, G.A.M. Nawwar and M.H. Elnagdi, *Monatsh. Chem.* 1986, **117**, 105.
8 E.I. Abramora, A.V. Kuteliya and V. F. Feklistova, *Khim.-Farm. Zh*. 1979, **12**, 96.
9 V.S. Hawalder and S.V. Sunthankar, *Ind. J. Chem.* 1980, **19B**, 151.