New Simple and One-Pot Synthetic Routes to Polyfunctionally Substituted Pyridines; 1,4-Dihydropyridazines and 4H-1,2-Oxazine

M. M. Mashaly[a], M. Hammouda[b,*]

Chemistry Department, Faculty of Science at Damietta[a] and Mansoura[b], Mansoura University, Mansoura, A. R. Egypt

* Reprint requests to Prof. Dr. M. Hammonda

Z. Naturforsch. **54b,** 1205–1209 (1999); received February 15, 1999

Arylidenemalononitriles, 2-Cyano-1,1-diaminoethene, Arylhydrazones, *syn*-2-Pyridinealdoxime, Pyridines

Reactions of arylidenemalononitriles **1a-d** with 2-cyano-1,1-diaminoethene (**5**); arylhydrazones **14a,b** and *syn*-2-pyridinealdoxime **15** afforded the title derivatives **3a-d**; **16a,b** and **17**, respectively. Bipyridyl derivatives **11–13** were also synthesized. Unambiguous syntheses and/or spectral analyses confirmed the suggested structures of **3a-d**, **11–13, 16a,b** and **17**.

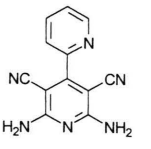
In the light of the reported important biological activity of some pyridines [1–7] and in continuation of our programme aiming to synthesize polyfunctionally substituted heterocycles of potential biological activity [8,9], it was interesting to us to study the behaviour of 2-cyano-1,1-diaminoethene towards arylidenemalononitriles as a new synthetic route to polyfunctionally substituted pyridines. Thus, the reaction of arylidenemalononitriles **1a-d** with ethyl cyanoiminoacetate (**2**) in a molar ratio of 1:1, in the presence of ammonium acetate in refluxing absolute ethanol, afforded 4-aryl-2,6-diamino-3,5-dicyanopyridine **3a-d** (Scheme 1). The structure of **3a-d** was established for the reaction product based on analytical and spectral data, while structure of **4** was excluded on the same bases (*cf.* Scheme 1 and Experimental).

The ^{1}H NMR spectrum of **3a** showed an accumulated broad singlet at δ 7.28 ppm for four protons of the two symmetrical NH_2 groups and a multiplet signal at δ 7.45–7.60 ppm for the five aromatic protons and its mass spectrum showed the molecular ion, M^+, as the base peak at *m/e* 235.

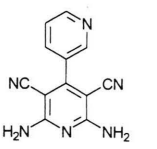
Formation of **3** can be explained *via* initial Michael addition of 2-cyano-1,1-diaminoethene (**5**) – which was generated from **2** and ammonium acetate [10] – to the ylidenic bond in **1**, leading to the formation of an acyclic intermediate **6** which cyclized into the intermediate **7** *via* a nucleophilic attack of an NH_2 group on a cyano carbon. The cyclic intermediate **7** underwent tautomerization into the dihydropyridine intermediate **8**, which aromatized into the final product **3** *via* dehydrogenation. Ready autoxidation of dihydropyridines into pyridines under comparable conditions has been reported [11,12].

Further confirmation of structure **3** was obtained unambiguously *via* direct condensation of the appropriate aromatic aldehyde **9** and **2** in a molar ratio of 1:2, under the same reaction conditions (Scheme 1). In this case, one molecule of the aldehyde condensed with two molecules of **5** at the highly nucleophilic site C_2, with the elimination of a water molecule to afford an acyclic intermediate **10**, which cyclized into **8** *via* intramolecular elimination of an ammonia molecule, then **8** aromatized to **3**.

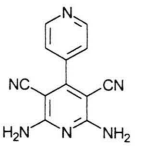
As certain bipyridyl derivatives were reported to have some pharmaceutical [5,6] or agrochemical [7] applications, it was worthy to apply the above given reaction as a new synthetic route to 4,2′-; 4,3′- and 4,4′-bipyridyl derivatives, *e.g.*, **11–13**. Thus, treatment of **2** with 2-, 3-, or 4-pyridinecarboxaldehyde in a molar ratio of 2:1, in the presence of ammonium acetate afforded, under the same reaction conditions, derivatives **11–13**, respectively (*cf.* Experimental). The mass spectrum of **13** gave its molecular ion, M^+, as the base peak at *m/e* 236. The ^{1}H NMR spectrum of



11



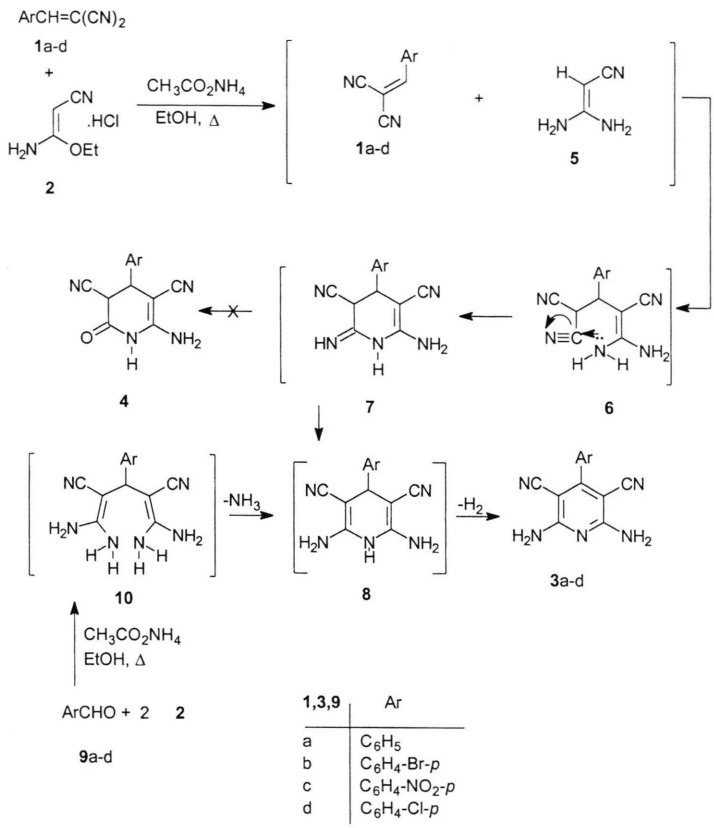
12



13

0932–0776/99/0900–1205 $06.00 © 1999 Verlag der Zeitschrift für Naturforschung, Tübingen · www.znaturforsch.com

Brought to you by | provisional account
Unauthenticated
Download Date | 6/11/15 8:08 AM



Scheme 1.

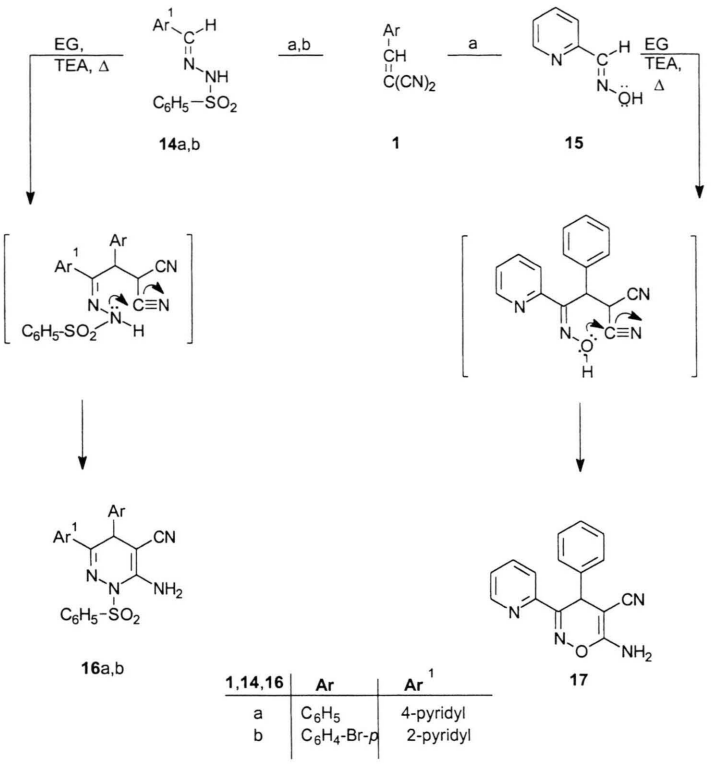
13 showed a doublet at δ 7.54 ppm for the two protons at C-3′ and C-5′ and a doublet at δ 8.81 ppm for the two protons at C-2′ and C-6′.

Although enamines are already established as synthetic intermediates, particularly in heterocyclic chemistry [10, 13–20], the utility of arylhydrazones and aldoximes, which have structures closely related to them, have been little studied [21–23]. There is no available report on a reaction of an arylhydrazone, as a binucleophile, with an arylidenemalononitrile for constructing a pyridazine nucleus. Based on these findings and the reported biological activity of some pyridazines [24–26], it was interesting to us to introduce a new one-pot synthetic route to polyfunctionally substituted 1,4-dihydropyridazines, *e.g.*, **16a,b** (Scheme 2).

Thus, condensation of **14a** with **1a** and **14b** with **1b** in a molar ratio of 1:1, in presence of triethylamine (TEA) in refluxing ethylene glycol (EG), afforded the new 1,4-dihydropyridazine derivatives **16a,b** respectively (Scheme 2). The structure of **16** was established for the reaction product based on analytical and spectral data (*cf.* Experimental). The mass spectra of **16a,b** showed the moelcular ion, M^+, at *m/e* values of 415 and 493, respectively. Compounds **16a,b** underwent rearrangement involving the participation of the pyridazine H-4 proton, followed by elimination of tropylium ($C_7H_7^+$, *m/e* = 91, 100%) and bromotropylium ($C_7H_6Br^+$, *m/e* = 169, 100%) ions as base peaks, respectively. In parallel to what was suggested for **3**, formation of **16** could be explained *via* initial Michael addition of compound **14** to the ylidenic bond in **1**, forming an acyclic intermediate which was cyclized by the nucleophilic attack of the NH group on a cyano carbon, followed by tautomerization to the final product **16**. Trials to obtain these pyridazines in either absolute ethanol or n-propanol were unsuccessful. Their synthesis could be achieved on using the higher boiling point solvent ethylene glycol (EG).

Similarly, it was convenient to investigate the first reaction between *syn*-2-pyridinealdoxime (**15**) and **1a** as a representative example for a new syn-

Brought to you by | provisional account
Unauthenticated
Download Date | 6/11/15 8:08 AM



1,14,16	Ar	Ar[1]
a	C_6H_5	4-pyridyl
b	C_6H_4-Br-*p*	2-pyridyl

Scheme 2.

thetic route to polyfunctionally substituted 4H-1,2-oxazines, *e.g.*, **17** (Scheme 2). Condensation of **15** and **1a** in a molar ratio of 1:1, in the presence of TEA in refluxing EG, afforded 6-amino-5-cyano-4-phenyl-3-(pyrid-2′-yl)-4H-1,2-oxazine (**17**). In analogy to **16a,b**, the mass spectrum of **17** (*cf.* Experimental) suggested the participation of the oxazine H-4 in a rearrangement followed by elimination of a tropylium ion (59.85%).

Experimental

Melting points were determined on Griffin Melting Point Apparatus and were uncorrected. The IR spectra were recorded on an SP-2000 Pye-Unicam Spectrophotometer as KBr discs (ν in cm^{-1}). ^1H NMR spectra were obtained on a Varian-Gemini 200 MHz, using TMS as an internal standard and DMSO-d_6 as solvent. Chemical shifts were expressed as δ ppm. Electron impact mass spectra were recorded on a GC-MS QP1000 EX Schimadzu, or HP Model: MS-5988 Mass Spectrometer, at 70 eV. Elemental analysis were performed at the Microanalytical Data Unit at Mansoura and Cairo Universities. The new compounds gave satisfactory elemental analysis.

1) Synthesis of 4-aryl-2,6-diamino-3,5-dicyanopyridines (**3a-d**)

General procedure A:

A solution of **2** (1 g, 0.0067 mol), the arylidenemalononitrile **1a-d** (0.0067 mol) and ammonium acetate (3.2 g) in absolute ethanol (25 ml) was refluxed for 3 h. The solid product deposited, or obtained after concentration and cooling, was filtered off, washed with water (6 x 15 ml) to get rid of ammonium chloride, dried in air and crystallized from absolute ethanol to afford **3a-d**.

General procedure B:

A solution of **2** (1 g, 0.0067 mol), the appropriate aldehyde **9a-d** (0.0034 mol) and ammonium acetate (3.2 g), in absolute ethanol (25 ml) was refluxed for 3 h, then proceeded as in the general procedure A to give compounds **3a-d** (analytical and spectral data).

3a: white, yield 75%, m.p. > 300 °C.

Brought to you by | provisional account
Unauthenticated
Download Date | 6/11/15 8:08 AM

^{1}H NMR: δ 7.28 (s, br., 4H, $2NH_2$) and 7.45–7.60 (m, 5H, C_6H_5); MS: M^+ at *m/e* = 235 (100%) and (M^+–HCN) at *m/e* = 208 (15.58%); IR (cm^{-1}): 3476, 3422, 3362 (NH_2), 2207 (CN) and 761 and 702 (monosubstituted benzene).

$C_{13}H_9N_5$ (235.24)
Calcd C 66.38 H 3.86%,
Found C 66.25 H 3.80%.

3b: yellow, yield 71%, m.p. > 300 °C.
^{1}H NMR: δ 7.30 (s, br., 4H, $2NH_2$), 7.46 (d, 2H, 3′-H, 5′-H) and 7.77 (d, 2H, 2′-H, 6′-H); MS(Br = 79): $(M + 2)^+$ at *m/e* = 315 (100%), M^+ at *m/e* = 313 (66.31%), (M^+–HCN) at *m/e* = 286 (5.82%) and (M^+–Br) at *m/e* = 234 (7.72%); IR(cm^{-1}): 3480, 3424, 3365 (NH_2), 2205 (CN) and 826 (*p*-disubstituted benzene).

$C_{13}H_8$79.9BrN_5 (314.13)
Calcd C 49.71 H 2.57%,
Found C 49.70 H 2.53%.

3c: greenish, yield 73%, m.p. > 300 °C.
^{1}H NMR: δ7.40 (s, br., 4H, $2NH_2$), 7.81 (d, 2H, 3′-H, 5′-H) and 8.39 (d, 2H, 2′-H, 6′-H); MS: M^+ at *m/e* = 280 (100%) and (M^+–NO_2) at *m/e* = 234 (13.08%); IR(cm^{-1}): 3455, 3383, 3347, 3237 (NH_2), 2213 (CN), 1515, 1352 (NO_2) and 855 (*p*-disubstituted benzene).

$C_{13}H_8N_6O_2$ (280.24)
Calcd C 55.72 H 2.88%,
Found C 55.69 H 2.92%.

3d: yellowish, yield 70% m.p. > 300 °C.
IR(cm^{-1}): 3480, 3427, 3369, 3294 (NH_2), 2218 (CN) and 835 (*p*-disubstituted benzene).

$C_{13}H_8ClN_5$ (269.68)
Calcd C 57.90 H 2.99%,
Found C 57.80 H 2.96%.

2) Synthesis of 2,6-diamino-3,5-dicyano-4-(pyrid-2′-; 3′- and 4′-yl)pyridines **11–13**, *respectively*

General procedure:

A solution of **2** (1 g, 0.0067 mol), 2-; 3-; or 4-pyridinecarbox-aldehyde (0.0034 mol) and ammonium acetate (3.2 g), in absolute ethanol (25 ml) was refluxed for 3 h, then proceeded as in the general procedure 1A to afford compounds **11–13**, respectively.

11: dark brown, yield 76%, m.p. > 300 °C.
^{1}H NMR: δ 7.62 (dd, 1H, 4′-H), 8.08 (d, 1H, 3′-H) and 8.83 (d, 1H, 6′-H).

IR(cm^{-1}): 3421, 3391, 3336, 3265 (NH_2) and 2209 (CN).

$C_{12}H_8N_6$ (236.23)
Calcd C 61.01 H 3.41%,
Found C 60.90 H 3.31%.

12: dark brown, yield 75%, m.p. > 300 °C.
IR(cm^{-1}): 3414, 3204 (NH_2) and 2208 (CN).

$C_{12}H_8N_6$ (236.23)
Calcd C 61.01 H 3.41%,
Found C 60.83 H 3.20%.

13: dark brown, yield 72%, m.p. > 300 °C.
^{1}H NMR: δ 7.54 (d, 2H, 3′-H, 5′-H), 7.94 (s, br., 4H, $2NH_2$) and 8.81 (d, 2H, 2′-H, 6′-H); MS: M^+ at *m/e* = 236 (100%) and (M^+–HCN) at *m/e* = 209 (17.85%); IR(cm^{-1}): 3479, 3330, 3221 (NH_2) and 2217 (CN).

$C_{12}H_8N_6$ (236.23)
Calcd C 61.01 H 3.41%,
Found C 60.97 H 3.38%.

3) Synthesis of 6-amino-4-aryl-1-benzenesulphonyl-5-cyano-[3-pyrid-4′- (and -2′-)yl]-1,4-dihydropyridazines (**16a,b**)

A solution of **14a,b** (0.0021 mol) and the appropriate arylidenemalononitrile **1a,b** (0.0021 mol) in ethylene glycol, EG, (20 ml) and triethylamine, TEA, (0.2 ml) was refluxed for 4 h, cooled and poured onto cold water (200 ml). The deposited solid product was filtered off, dried in air and crystallized from ethanol to afford **16a,b**, respectively.

16a: brown, yield 65%, m.p. > 300 °C.
MS: M^+ at *m/e* = 415 (9.02%), $C_7H_7^+$ at *m/e* = 91 (100%), $C_6H_5^+$ at *m/e* = 77 (64.95%), $C_5H_4N^+$ at *m/e* = 78 (21.08%) and $(C_5H_4N.CN)^+$ at *m/e* = 104 (34.33%); IR(cm^{-1}): 3445, 3354, 3224 (NH_2), 2194 (CN) and 1418, 1309 (SO_2-N).

$C_{22}H_{17}N_5O_2S$ (415.47)
Calcd C 63.60 H 4.12%,
Found C 63.20 H 4.35%.

16b: brown, yield 60%, m.p. > 300 °C.
MS: M^+ at *m/e* = 493 (49.35%), $(M+2)^+$ at *m/e* = 495 (24.74%), $C_7H_6Br^+$ at *m/e* = 169 (100%), $(C_7H_6Br + 2)^+$ at *m/e* = 171 (80.13%), ($M-C_6H_4Br$)$^+$ at *m/e* = 338 (26.60%) and $C_6H_4Br^+$ at *m/e* = 155 (18.26%); IR(cm^{-1}): 3444, 3356, 3220 (NH_2), 2198 (CN) and 1418, 1334 (SO_2-N).

Brought to you by | provisional account
Unauthenticated
Download Date | 6/11/15 8:08 AM

$C_{22}H_{16}BrN_5O_2S$ (494.37)
Calcd C 53.45 H 3.26%,
Found C 53.00 H 3.20%.

4) Synthesis of 6-amino-5-cyano-4-phenyl-3-(pyrid-2'-yl)-4H-1,2-oxazine (**17**)

A solution of **15** (0.5 g, 0.0041 mol) and benzylidenemalononitrile **1a** (0.63 g, 0.0041 mol) in ethylene glycol (20 ml) and triethylamine (0.2 ml) was refluxed for 4 h, then proceeded as for **16a,b**, to afford **17**.

17: dark brown, yield 50%, m.p. > 300 °C.

MS: $HCNO^+$ at *m/e* = 43 (100%), $HCONH_2^+$ at *m/e* = 45 (99.08), $C_7H_7^+$ at *m/e* = 91 (59.85%) and $(C_5H_4N.CN)^+$ at *m/e* = 104 (26.38%); IR(cm^{-1}): 3404, 3327, 3211 (NH_2) and 2207 (CN).

$C_{16}H_{12}N_4O$ (276.30)
Calcd C 69.55 H 4.38%,
Found C 69.00 H 4.20%.

[1] The Merck Index of Chemicals and Drugs, 12th ed., item No. 8153–8168, pp. 1370–1373, Merck and Co., Inc., Whitehous Station, N. J., U. S. A. (1996).
[2] Principles of Medicinal Chemistry, 4th ed., W. O. Foye, T. L. Lemke, D. A. Williams, A Lea and Febiger Book, Williams and Wilkins, London (1995).
[3] Essentials of Medicinal Chemistry, 2nd ed., A Korlkovas, A Willey-Interscience Publication, New York (1988).
[4] Comprehensive Heterocyclic Chemistry, Vol. 2, Part 2A, pp. 511–524, A. R. Katritzky and C. W. Peer, ed. A. John Boulton and Alexander McKillop, Pergamon Press, Oxford (1984).
[5] Ref. No. [1], item No. 6284, p. 1060.
[6] Ref. No. [1], item No. 634, p. 100.
[7] Ref. No. [1], item No. 7165, p. 1208.
[8] M. Hammouda, M. M. Mashaly, A. A. Fadda, Arch. Pharm. Res. **18**(3), 213 (1995).
[9] M. Hammouda, M. M. Mashaly, E. M. Afsah, Pharmazie **49** (H5), 365 (1994).
[10] F. Coda, J. L. Di Martino, P. Jacquault, J. P. Bazureau, J. Hamelin, Bull. Soc. Chim. Fr. **133**, 587 (1996).
[11] H. Z. Shams, Y. M. Elkholy, N. S. Ibrahim, M. H. Elnagdi, J. Prakt. Chem. **330**(5), 817 (1988).
[12] J. L. Soto, C. Seoane, P. Zammorano, F. Javier, Synthesis **529** (1981).
[13] R. Troschütz, A. Lückel, Arch. Pharm. (Weinheim) **326**, 199 (1993).
[14] R. Troschütz, A. Lückel, Arch. Pharm. (Weinheim) **325**, 785 (1992).
[15] R. Troschütz, A. Lückel, Arch. Pharm. (Weinheim) **324**, 73 (1991).
[16] R. Troschütz, Arch. Pharm. (Weinheim) **332**, 285 (1989).
[17] T. Tokumitsu, Bull. Chem. Soc. Jpn. **59**, 3871 (1986).
[18] T. Tokumitsu, T. Hayashi, J. Org. Chem. **50**, 1547 (1985).
[19] P. W. Hickmott, Tetrahedron, Vol. **38**, No. 23, 3363 (1982).
[20] P. W. Hickmott, Tetrahedron, Vol. **38**, No. 14, 1975 (1982).
[21] E. M. Afsah, M. Hammouda, H. Zoorob, M. M. Khalifa, M. T. Zimaity, Z. Naturforsch. **45**b, 80 (1990).
[22] V. Boehnisch, G. Burzer, H. Neunhoeffer, Justus Liebigs Ann. Chem. **10**, 1713 (1977). C. A. Vol. **88**, 136572n (1978).
[23] W. E. Hahn, H. Zawadzka, Roczniki Chem. **38**(4), 557 (1964). C. A. Vol. **61**, 10685d (1964).
[24] Ref. No. [1], item No. 412, p. 69.
[25] Ref. No. [1], item No. 6287, p. 1060.
[26] Ref. No. [1], item No. 6794, p. 1150.

Brought to you by | provisional account
Unauthenticated
Download Date | 6/11/15 8:08 AM