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NEW SIMPLE AND ONE-POT SYNTHETIC ROUTES TO POLYFUNCTIONALLY SUBSTITUTED IMIDAZO-[1,2-*a*]PYRIDINES, PYRIDO[1,2-*a*]PYRIMIDINES, PYRIDO-[1,2-*a*]-1,3-DIAZEPINES, AND IMIDAZO[1,2-*a*]PYRIMIDINES

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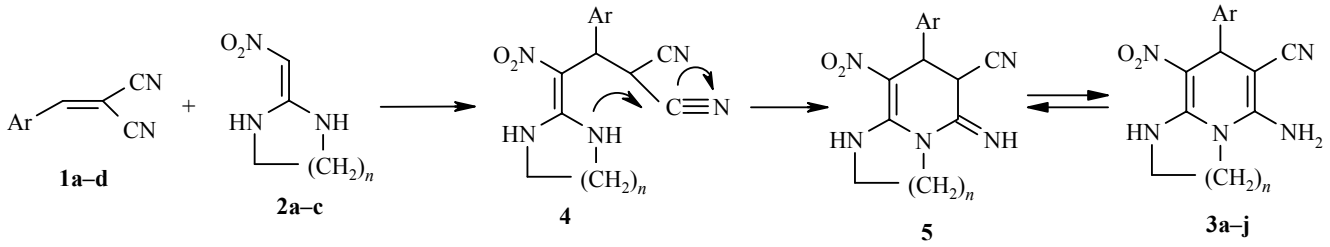
Reactions of arylidenemalononitriles with 2-nitromethylene-substituted imidazolidine, hexahydropyrimidine, and hexahydro-1,3-diazepine afforded the title derivatives. Reaction of 2-nitromethylenehexahydropyrimidine with benzylamine or n-butylamine and formalin in a molar ratio of 1:1:2 gave the hexahydro-1H-imidazo[1,2-c]pyrimidine derivatives. Treatment of 2-nitro-methyleneimidazolidine and hexahydropyrimidine with secondary aliphatic amines and formalin in a molar ratio of 1:1:1 afforded the corresponding methylene bis-compounds.

Keywords: arylidenemalononitriles, nitroenamines, Mannich reaction

In light of the reported biological activity of some imidazo[1,2-*a*]pyridines [1, 2], and pyrido[1,2-*a*]-pyrimidine [3] and in continuation of our program aiming to synthesize polyfunctionally substituted heterocycles of potential biological activity [4-8], it was interesting to study the reactions of arylidenemalono- nitriles **1a-d** with some nitroenamines **2a-c** as a new synthetic route to polyfunctionally substituted imidazo-[1,2-*a*]pyridines, pyrido[1,2-*a*]pyrimidines, and pyrido[1,2-*a*]-1,3-diazepines.

Scheme 1



2 a n = 1, **b** n = 2, **c** n = 3; **3 a** Ar = Ph, **b, e, h** Ar = C_6H_4Cl-*p*, **c, f, i** Ar = C_6H_4Br-*p*, **d**, **g, j** Ar = $C_6H_4NO_2$-*p*; **a-d** n = 1, **e-g** n = 2, **h-j** n = 3

Thus, the reaction with 2-(nitromethylene)imidazolidine (**2a**) [9], hexahydro-2-(nitromethylene)pyrimidine (**2b**) [10], and/or hexahydro-2-(nitromethylene)-1H-1,3-diazepine (**2c**) [11] in a molar ratio of 1:1:1 in refluxing ethanolic piperidine afforded imidazo[1,2-*a*]pyridines **3a-d**, hexahydro-

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pyrido[1,2-*a*]pyrimidines **3e-g,** and hexahydro-1H-pyrido[1,2-*a*]-1,3-diazepines **3h-j**, respectively. The structures of **3** were established for the reaction products, based on their analytical and spectral data (see Experimental).

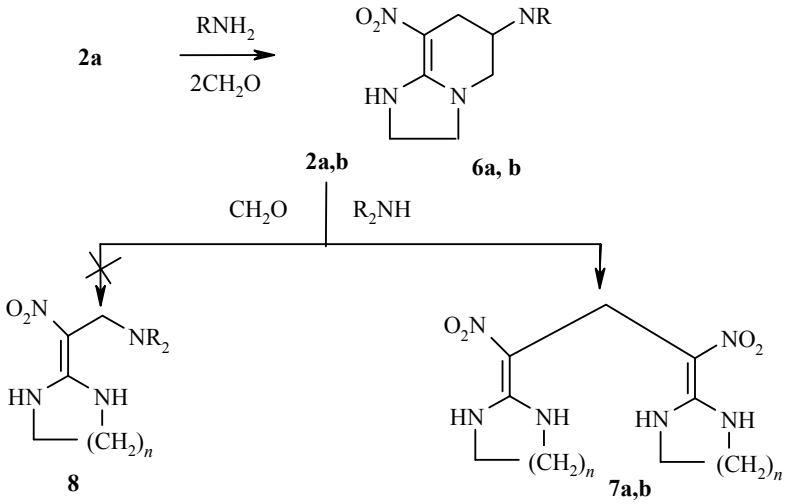
Formation of **3** can be explained *via* the initial Michael addition of **2a-c** to the ylidenic bond in **1**, leading to the formation of an acyclic intermediate **4** which cyclized into the intermediate **5** *via* nucleophilic attack of an NH group on a cyano carbon, followed by tautomerization to the final product **3**.

Compounds **3a-j** were also synthesized by another route involving one-pot condensation of the appropriate aromatic aldehyde, ArCHO, malononitrile, and compounds **2a-c** in a molar ratio of 1:1:1 in ethanolic piperidine.

In this case, formation of **3** is interpreted in terms of the initial condensation of aldehyde with malononitrile affording the activated cyano olefin **1**, followed by addition of **2** to **1** as above.

It has been reported that acyclic N-monosubstituted nitroenamines react with primary amines and 2 mol of formaldehyde to yield tetrahydropyrimidines [12]. It appeared of interest to study the behavior of **2a,b** towards a double Mannich reaction as a route to condensed pyrimidine systems.

Thus, when **2a** was subjected to reaction with benzylamine or *n*-butylamine and formalin in a molar ratio of 1:1:2 it afforded hexahydro-1H-imidazo[1,2-*a*]- pyrimidine derivatives **6a,b**. The products **6a,b** were characterized by elemental analyses and spectral data (cf. Experimental).



6 a R = CH_2Ph, **b** R = *n*-Bu; **7 a** *n* = 1, **b** *n* = 2

Attempts to synthesize pyrimido[1,2-*c*]pyrimidine from **2b** (*n* = 2) under the same reaction conditions have been unsuccessful. On the other hand, treatment of **2a,b** with formalin and secondary aliphatic amines in a molar ratio of 1:1:1 under Mannich reaction conditions afforded methylene bis-compounds **7a,b** instead of the expected products **8**. The formation of **7** could be rationalized through a mechanism which involves the formation of **8** as intermediate followed by attack on nitroenamines **2a,b**.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed in the Microanalytical Unit, Mansoura and Cairo University. IR spectra were recorded in pellets of KBr on a Pye-Unicam spectrophotometer. ^{1}H NMR spectra are obtained on Bruker 250 at 200 MHz using TMS as an internal standard. Mass spectra were obtained using GC-MS QP 1000 EX Schimadzu, or HP model: MS-5988 mass spectrometer at 70 eV.

5-Amino-7-aryl-6-cyano-8-nitroimidazo[1,2-*a*]pyridines (3a-d), 6-Amino-8-aryl-7-cyano-9-nitro-1,2,3,4,5,8-hexahydropyrido[1,2-*a*]pyrimidines (3e-g) and 7-Amino-9-aryl-8-cyano-10-nitro-2,3,4,5,6,9-hexahydro-1H-pyrido[1,2-*a*]-1,3-diazepines (3h-j) (General Procedure). A. A mixture of **2a-c** (0.003 mol) and the appropriate arylidenemalononitriles **1a-d** (0.003 mol) in absolute ethanol (25 ml) and piperidine (0.1 ml) was refluxed for 4 h. The solid products deposited or obtained after concentration and cooling were filtered off and crystallized from the proper solvent to give compounds **3a-j**.

B. A mixture of **2a-c** (0.003 mol), the appropriate aldehyde (0.003 mol), and malononitrile (0.003 mol) in absolute ethanol (25 ml) and piperidine (0.1 ml) was refluxed for 4 h, then processed as in the general procedure A to give compounds **3a-j** (analytical and spectral data).

3a. Obtained as yellow crystals (ethanol), yield 81%; mp 178-179°C. IR spectrum, ν, cm^{-1}: 3433, 3213 (NH_2), 3345 (NH-imidazoline), 2178 (CN) and 1647 (C=C–NO_2). Found, %: C 59.63; H 4.85; N 24.85. $C_{14}H_{13}N_5O_2$. Calculated, %: C 59.36; H 4.62; N 24.72.

3b. Obtained as yellow crystals (ethanol), yield 83%; mp 205-206°C. IR spectrum, ν, cm^{-1}: 3418, 3237 (NH_2), 3341 (NH-imidazoline), 2174 (CN) and 1641 (C=C–NO_2). ^{1}H NMR spectrum, δ, ppm: 3.85 (4H, m, 2CH_2 imidazoline); 4.59 (1H, s, H-7); 6.48 (2H, br. s, NH_2); 7.12-7.38 (4H, m, aromatic); 9.38 (1H, br. s, NH imidazoline). Found, %: C 53.12; H 3.93; N 22.21. $C_{14}H_{12}ClN_5O_2$. Calculated, %: C 52.92; H 3.81; N 22.05.

3c. Obtained as yellow crystals (ethanol), yield 78%; mp 245-246 (dec.). IR spectrum, ν, cm^{-1}: 3445, 3225 (NH_2), 3333 (NH-imidazoline), 2182 (CN), 1629 (C=C–NO_2). Mass spectrum, *m/z* (*I,* %): 362 [M–C_6H_4Br]$^+$ (62.3); 206 [M–(C_6H_4Br + NO_2)]$^+$ (100); 156 [C_6H_4Br]$^+$ (7). Found, %: C 46.63; H 3.52; N 19.47. $C_{14}H_{12}BrN_5O_2$. Calculated, %: C 46.42; H 3.34; N 19.34.

3d. Obtained as yellow crystals (acetone), yield 76%; mp 235-236 dec. IR spectrum, ν, cm^{-1}: 3415, 3235 (NH_2), 3334 (NH-imidazoline), 2182 (CN), 1628 (C=C–NO_2). Found, %: C 50.94; H 3.52; N 25.47. $C_{14}H_{12}N_6O_4$. Calculated, %: C 51.22; H 3.69; N 25.60.

3e. Obtained as yellow crystals (acetone), yield 79%; mp 245-246 dec. IR spectrum, ν, cm^{-1}: 3385, 3325 (NH_2), 3300 (NH-pyrimidine), 2185 (CN), 1628 (C=C–NO_2). Mass spectrum, *m/z* (*I*, %): 331 (12), 285 [M–NO_2]$^+$ (34), 262 [M–C_6H_4Cl]$^+$ (100), 174 [M–(C_6H_4Cl + NO_2)]$^+$ (10). Found, %: C 54.13; H 4.12; N 21.03. $C_{15}H_{14}ClN_5O_2$. Calculated, %: C 54.29; H 4.25; N 21.11.

3f. Obtained as yellow crystals (acetone), yield 77%; mp 249-250 dec. IR spectrum, ν, cm^{-1}: 3386, 3226 (NH_2), 3300 (NH-pyrimidine), 2186 (CN), 1629 (C=C–NO_2). ^{1}H NMR spectrum, δ, ppm: 2.49-2.53 (2H, m, 3-CH_2); 3.73-3.80 (4H, m, 2-CH_2 and 4-CH_2); 4.68 (1H, s, H-8); 6.48 (2H, s, NH_2); 7.11-7.49 (4H, m, aromatic); 11.55 (1H, br. s, NH). Found, %: C 48.11; H 3.92; N 18.84. $C_{15}H_{14}BrN_5O_2$. Calculated, %: C 47.89; H 3.75; N 18.62.

3g. Obtained as yellow crystals (acetone), yield 76%; mp 225-226°C dec. IR spectrum, ν, cm^{-1}: 3391, 3228 (NH_2), 3300 (NH-pyrimidine), 2184 (CN), 1625 (C=C–NO_2). Found, %: C 52.41; H 3.92; N 24.73. $C_{15}H_{14}N_6O_4$. Calculated, %: C 52.63; H 4.12; N 24.55.

3h. Obtained as golden yellow crystals (acetone), yield 69%; mp 244-245°C dec. IR spectrum, ν, cm^{-1}: 3418, 3223 (NH_2), 3293 (NH-diazepine), 2190 (CN), 1624 (C=C–NO_2). Mass spectrum, *m/z* (*I,* %): 345 [M–NO_2]$^+$ (6.85); 299 [M–C_6H_4Cl]$^+$ (90.8), 234 [M–(NO_2 + C_6H_4Cl)]$^+$ (45.7), 188 (11.3), 55 (100). Found, %: C 55.42; H 4.37; N 20.08. $C_{16}H_{16}ClN_5O_2$. Calculated, %: 55.57; H 4.66; N 20.25.

3i. Obtained as golden yellow crystals (ethanol), yield 67 %; mp 240-242°C. IR spectrum, ν, cm^{-1}: 3400-3217 (NH_2), 3287 (NH-diazepine), 2191 (CN), 1622 (C=C–NO_2). ^{1}H NMR spectrum, δ, ppm: 2.53-2.55

(4H, m, 3-CH_2, 4-H_2); 3.73-3.82 (4H, m, 2-CH_2, 5-CH_2); 4.73 (1H, s, H-9); 6.52 (2H, s, NH_2); 7.16-7.51 (4H, m, aromatic); 11.25 (1H, br. s, NH). Found, %: C 49.48; H 4.27; N 18.11. $C_{16}H_{16}BrN_5O_2$. Calculated, %: C 49.25; H 4.13; N 17.95.

3j. Obtained as yellow crystals (ethanol), yield 71%; mp 235-236°C dec. IR spectrum, ν, cm^{-1}: 3385, 3216 (NH_2), 3290 (NH-diazepine), 2191 (CN), 1624 (C=C–NO_2). Found, %: C 54.19; H 4.35; N 23.30. $C_{16}H_{16}N_6O_4$. Calculated, %: C 53.93; H 4.53; N 23.59.

6-(Benzyl or butyl)-2,3,4,5,6,7-hexahydronitro-1H-imidazo[1,2-*c*]pyrimidines 6a,b. A mixture of **2a** (0.003 mol), benzylamine or *n*-butylamine (0.003 mol), and formalin (0.006 mol) in ethanol (30 ml) was refluxed for 3 h. The solid products obtained after concentration and cooling were filtered off and crystallized from ethanol to give compounds **6a,b.**

6a. Obtained as colorless crystals, yield 64%; mp 179-180°C. ^{P1}H NMR spectrum, δ, pmm: 3.45, 3.75 (8H, m, 4 × CH_2 heterocyclic); 4.04 (2H, s, CH_2 benzylic); 7.33 (5H, m, aromatic); 8.77 (1H, s, NH-imidazoline). Found, %: C 60.17; H 6.23; N 21.79. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.98; H 6.20; N 21.53.

6b. Obtained as pale yellow crystals, yield 56%; mp 118-120°C. IR spectrum, ν, cm^{-1}: 3259 (NH-imidazoline), 1594 (C=C–NO_2). Found, %: C 53.24; H 8.29; N 24.93. $C_{16}H_{18}N_4O_2$. Calculated, %: C 53.07; H 8.02; N 24.76.

2,2'-Methylenebis[2-(nitromethylene)imidazoline] and 2,2'-Methylenebis[hexahydro-2-(nitro-methylene)pyrimidine] (7a,b). A mixture of **2a** or **2b** (0.003 mol), the appropriate aliphatic secondary amine (0.003 mol), and formalin (0.003 mol) in ethanol (30 ml) was refluxed for 3 h. The solid products obtained after concentration and cooling were filtered off and crystallized from ethanol to give colorless crystals of **7a,b**.

7a. Yield 77%; mp 245-246°C (dec). IR spectrum, ν, cm^{-1}: 3357 (NH-imidazoline), 1601 (C=C–NO_2). ^{1}H NMR spectrum, δ, pmm: 3.81-3.87 (8H, complex pattern, 4CH_2-imidazolines) , 4.10 (2H, s, CH_2 side chain), 9.23-9.29 (4H, br. s, NH-imidazolines). Found, %: C 39.82; H 5.11; N 30.92. $C_9H_{14}N_6O_4$. Calculated, %: C 39.99; H 5.22; N 31.10.

7b. Yield 73%; mp 255-256°C, dec. IR spectrum, ν, cm^{-1}: 3256 (NH-pyrimidine), 1613 (C=C–NO_2). Mass spectrum, *m*/*z* (*I*, %): 206 $[M–2NO_2]^+$ (5), 156 $[C_6H_{10}N_3O_2]$ (16), 110 $[156–NO_2]^+$ (12) and 56 $[C_3H_6N]$ (100). Found, %: C 44.47; H 6.23; N 28.37. $C_{11}H_{18}N_6O_4$. Calculated, %: C 44.29; H 6.08; N 28.18.

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