SHORT PAPER

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Reaction of N^1, N^2-diarylamidines with 2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene) propanedinitrile†

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2-Arylamino-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)ethanenitriles (**6a–c**) together with the corresponding formanilides (**7a–c**) are formed in the reaction of N^1,N^2-diarylformamidines (**1a–c**) with 2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene)propanedinitrile **(2)**. The analogous N^1,N^2-diarylacetamidines (**8b–d**) with **2** gave 5-oxospiro[(1,5-dihydro-4*H*-pyrazole)-4,4′-(1′,2′,3′,4′-tetrahydropyridine)]-5′-carbonitriles (**17b–d**) and in two cases 2-arylamino-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene) ethanenitriles (**6b,c**) together with the acetanilides (**12b,c**), which were obtained as minor products.

Keywords: spiro compounds, pyrazoles, amidines, fused tetrahydropyridines

2-(1,5-Dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene)propanedinitrile **2** reacts with aliphatic, aromatic and heterocyclic amines by HCN exchange reaction to yield 2-arylamino-2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene)ethanenitriles.[1,2] *o*-Substituted arylamines react with **2** to afford similar products which readily cyclise to give 4-azolylidene pyrazolones, while secondary and tertiary amines and activated phenols react (at a *p*-carbon atom) with **2** *via* replacement of a cyano group by a phenyl ring.[2] The active methylene compounds react with **2** by a Michael addition to afford 4-spirocyclobutenes *via* a 1,2-addition pathway or spiropyran-2-pyrazolin-5-ones *via* a 1,4 addition pathway.[3] Similarly, α-amino acids and their esters react with **2** by a Michael addition/elimination sequence with replacement of one cyano group by the amino function.[4] Junek and co-workers have synthesised some chromoionophores by reaction of **2** with the corresponding aminophenyl crown ethers.[5,6] Recently we have reported that **2** reacts with cyclic 1,3-dicarbonyl compounds such as indane-1,3-dione, 4-hydroxy-2*H*-chromen-2-one and 5,5-dimethylcyclohexane-1,3-dione to give new spiro compounds: 2-amino-3′-methyl-5,5′-dioxo-1′-phenylspiro [indeno[1,2-*b*]pyran-4(5*H*),4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**A**), 2-amino-3′-methyl—5,5′-dioxo-1′-phenylspiro-[4*H*,5*H*-pyrano[3,2-*c*][1]chromene-4,4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**B**), and 2-amino-3′,7,7-trimethyl-5,5′-dioxo-1′-phenyl-5,6,7,8-tetrahydrospiro[4*H*-chromene-4,4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**C**)**,** respectively (Fig. 1).[7]

Results and discussion

In the light of the above-mentioned findings we undertook an investigation of the reactions of open-chain amidines with **2**. N^1,N^2-Diarylformamidines (**1a–c**) reacted with **2** in ethyl acetate at room temperature to give 2-arylamino-2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene) ethanenitriles (**6a-c**) together with the formanilides **7a-c**. The nitriles **6a–c**[1,2] and the formanilides **7a–c**[8-10] were identified by comparision of their melting points with those reported for authentic samples.

These results indicate that formamidines **1a–c** with **2** ultimately form the same products as the corresponding primary amines, that is by a Michael-addition elimination-type sequence similar to the one well documented[1-7] through a nucleophilic attack of N^2 on the exo-methylene carbon atom of **2** to form intermediates **3a–c** and **4a–c**, which *via* elimination of HCN give **5a–c**. The latter in turn, undergo hydrolysis[11] (by taking up a molecule of water from the atmosphere or the solvent), probably due to the presence of liberated HCN to form **6a–c** and **7a–c**.

In this work we report another access to spirocyclic systems *via* the reaction of N^1,N^2-diarylacetamidines with **2**. Thus, N^1,N^2-diarylacetamidines **8b–d** reacted with **2** in ethyl acetate at room temperature (**8b,c**) or at reflux (**8d**) to form the novel 5-oxospiro[4,5-dihydro-1*H*-pyrazole)-4,4′-(1′,2′,3′,4′-tetrahydropyridine)]-5′-carbonitriles **17b-d** in (34–47% yield). In two cases **(8b,c)**, the ethanenitriles **6b,c** were also

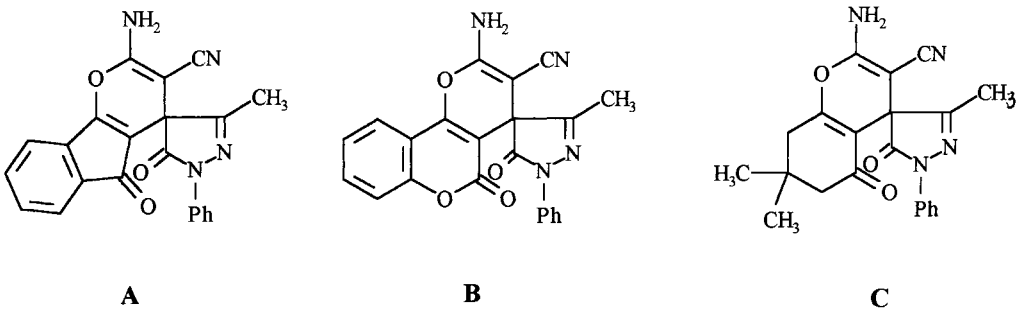

Fig. 1

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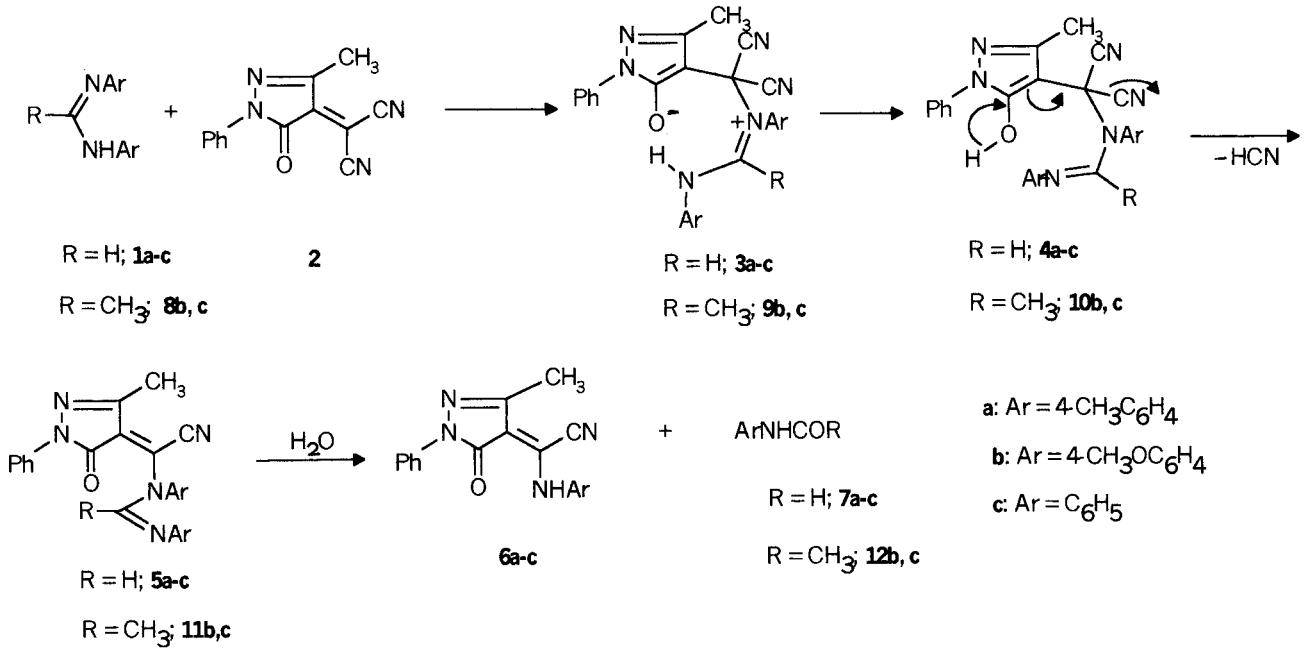


Scheme 1

formed in minor amounts together with the corresponding acetanilides **12b,c**. Acetanilides **12b,c**[12] were identified by comparison of their melting points with those reported for authentic samples.

The IR spectra of **17b–d** showed strong absorptions between 3450 and 3320 cm^{-1} (NH_2), 2190 (CN) and 1690 cm^{-1} (C=O). ^{1}H-NMR AB patterns with δ_A = 3.16 ppm and δ_B = 2.97 ppm and $|^2J|$ = 15.6 Hz are assigned to the C-3′ methylene group adjacent to the chiral carbon atom, in addition to signals at 6.59 ppm for NH_2 protons. The ^{13}C DEPT spectrum showed a negative signal at δ = 26.25 ppm, confirming the presence of a CH_2 group. The broad-band ^{1}H-decoupled ^{13}C-NMR spectra showed one signal at 51.41 ppm for the spiro carbon atom C-4 and one at 118.43 ppm for the cyano group. It is interesting to mention that the position of the signals of the olefinic C-atoms bearing the cyano group, *i.e.* C-5′ in **17b–d**, show up at relatively higher field at δ = 52.01-52.13. The upfield shift in the range 52–57 ppm for the sp^2 carbon attached to the nitrile group has been previously reported.[13,14]

The most plausible origin of the methylene group is the acetyl methyl group in the acetamidines **8b–d**, and the formation of spiro[1*H*-pyrazole-4,4′-pyridines] **17b–d** can be rationalized as follows: initial nucleophilic attack by N^2 of **8b–d** on one nitrile carbon of **2** forms **14b-d** being in equilibrium with **15b-d**. The nucleophilic methylene carbon of the latter obviously prefers attacking C-4 instead of C-5 of the pyrazolinone moiety in **15** forming **16b–d** which is ultimately isolated as **17b–d**. Lack of attack at C-5 is plausibly due to its amide carbonyl nature and therefore reduced electrophilic character. A minor fraction of **8b,c** undergoes the Michael-addition elimination sequence giving **6b,c** together with **12b,c** after hydrolysis.

Conclusion

N^1,N^2-Diarylformamidines **1a–c** react with **2** like amines by a Michael-addition elimination-type sequence, while the analogous N^1,N^2-diarylacetamidines **8b–d**, due to their ambident nature, react with **2** as enamines in a Michael type addition reaction.

Experimental

Melting points were determined on a Griffin & George apparatus. Elemental analyses were carried out by the Microanalysis Center at Cairo University. IR spectra (KBr) were recorded on a Shimadzu 470 spectrophotometer. 400MHz ^{1}H NMR and 100MHz ^{13}C NMR spectra were obtained using a Bruker AM 400 spectrometer. The MS (70 eV, electron impact mode) were recorded on a Jeol JMS600 instrument. Preparative layer chromatography (PLC) used air dried 1.0 mm thick layers of slurry-applied silica gel PF_{254} Merck on 48 cm wide and 20 cm high glass plates and toluene-ethyl acetate (2:1) as developing solvent. Zones were detected by the color or by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone.

Starting materials: N^1,N^2-diarylformamidines (**1a–c**),[15] *2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4H-pyrazol-4-ylidene)propanedinitrile* (**2**),[1] *and N^1,N^2-diarylacetamidines* (**8b–d**)[16] were prepared according to the literature procedures quoted.

Reaction of N^1,N^2-diarylformamidines **1a–c** *with* **2***: General procedure*: A solution of **2** (236 mg, 1.0 mmol) in ethyl acetate (20 cm^3) was added dropwise to a solution of formamidine **1a-c** (1.0 mmol) in ethyl acetate (10 cm^3) at room temperature, whereupon the solution assumed a reddish-brown colour. The reaction mixture was left standing at room tempertaure for 1 h, concentrated, and subjected to PLC using toluene–ethyl acetate (10:1) as developing solvent to give two zones. The faster-moving contained **6a, 6b,** or **6c**, respectively, while the second contained the corresponding formanilide **7a, 7b**, or **7c**,. The zones were crystallised and identified as follows:

2-(4-Methylphenylamino)-2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4H-pyrazol-4-ylidene)ethanenitrile (**6a**): 80 mg (26 %) reddish brown crystals m.p. 145 °C (from ethyl acetate) (lit.,[1] 144 °C).

2-(4-Methoxyphenylamino)-2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4H-pyrazol-4-ylidene)ethanenitrile (**6b**)**:** 90 mg (25 %) reddish brown crystals m.p. 108–111°C (from ethyl acetate) (lit.,[1] 110°C).

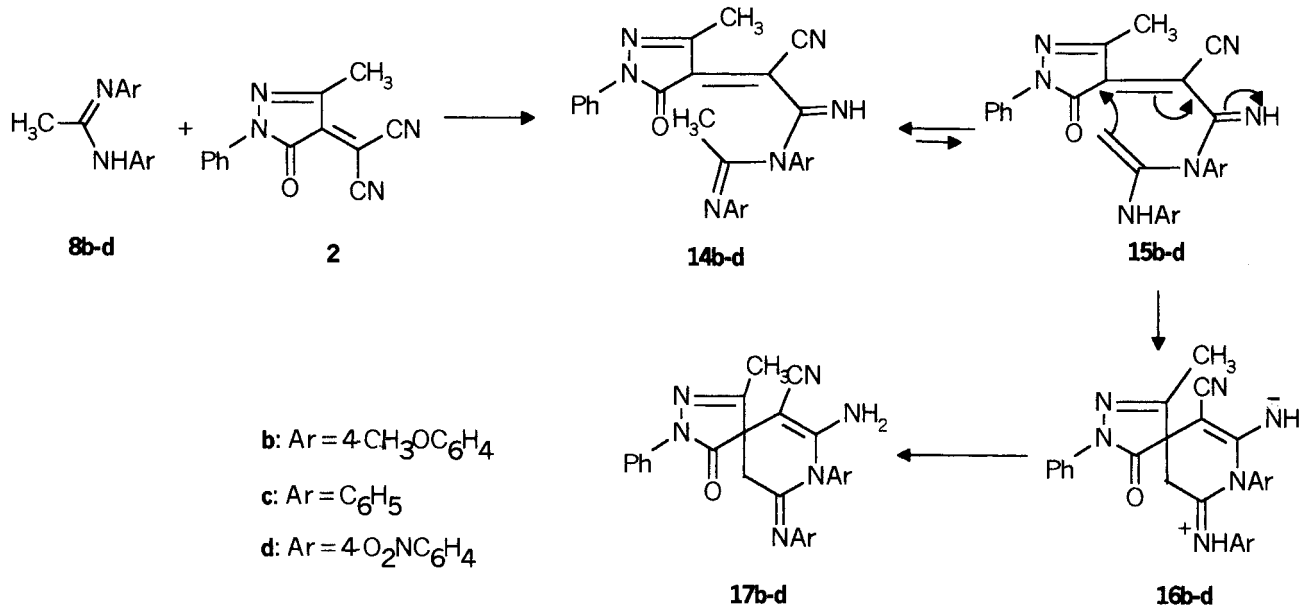
2-Phenylamino-2-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4H-pyrazol-4-ylidene)ethanenitrile (**6c**)**:** 50 mg (17 %) orange crystals m.p. 150 °C (from ethyl acetate) (lit.,[1] 151 °C).

4′-Methylformanilide (**7a**): 60 mg (74 %) colourless crystals, m.p. 53 °C (from light petroleum, b.p. 40–60°C) (lit.,[8] 52°C).

4′-Methoxyformanilide (**7b**): 90 mg (60 %) colourless crystals, m.p .81°C (from light petroleum, b.p. 40–60°C) (lit.,[9] 84–85 °C).

Formanilide (**7c**), 80 mg (67 %) colourless crystals, m.p. 48–50°C (from light petroleum, b.p. 40–60°C) (lit.,[10] 50°C).

Reaction of N^1,N^2-diarylacetamidines **8a–d** *with* **2**: *General procedure*: To a stirred solution of each of the acetamidines **8b–d** in ethyl acetate (5 cm^3) a solution of **2** (236 mg, 1.0 mmol) in ethyl acetate



Scheme 2

(20 cm^3) was added dropwise at room temperature. The reaction mixture was either left standing overnight (**8b,c**) or refluxed for 6 h (**8d**), concentrated and subjected to PLC using toluene-ethyl acetate (2:1) as developing solvent to give two or three zones. The faster moving contained **6b** or **6c** respectively, while the second contained the corresponding acetanilides **12b** or **12c**. The more slowly moving zones contained **17b, 17c**, or **17d**, respectively. Additional minor zones were discarded. Compounds **6b,** and **6c** were collected and identified as before.

4′-Methoxyacetanilide (**12b**): 24 mg (15 %) colourless crystals m.p. 130–131 °C (from light petroleum) (lit.[12] 130 °C).

Acetanilide (**12c**): 18 mg (13 %) colourless crystals m.p. 113–114 °C (from light petroleum) (lit.[12] 114 °C).

6′-Amino-1′-(4-methoxyphenyl)-2′-(4-methoxyphenylimino)-3-methyl-5-oxo-1-phenylspiro[(4,5-dihydro-1H-pyrazole)-4,4′-(1′,2′,3′,4′-tetrahydropyridine)]-5′-carbonitrile (**17b**): This compound was obtained as colourless crystals (220 mg, 43 %), m.p. 230–232 °C (from cyclohexane/ethyl acetate) (Found: C, 68.54; H, 5.06; N, 16.80. $C_{29}H_{26}N_6O_3$ requires C, 68.76; H, 5.17; N, 16.59); ν_{max} (KBr)/cm^{-1} 3400 (NH_2), 2190 (CN), 1700 (CO); δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s, CH_3), 3.25 (1H, d) and 2.98 (1H, d, $|^2J|$ 15.6, CH_2), 3.72 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.28 (2H, s, NH_2), 6.84, 7.01, 7.33, 7.46, 7.58, 7.60 and 7.94 (all *m*, aryl-CH); δ_C (100 MHz, $CDCl_3$) 13.56 (CH_3), 26.20 (C-3'), 51.51 (C-4 = C-4'), 52.11 (C-5'), 54.59 and 54.89 (OCH_3) 119.13, 120.59, 121.33, 128.39 and 130.90 (all aryl-CH), 118.22 (CN), 137.50, 147.15 and 152.66 (aromatic C-N), 154.20 (C-2'), 154.48 and 154.98 (aryl-C-OCH_3), 155.81 (C-3), 160.63 (C-6'), 172.89 (C-5); *m/z* 506 (M^+, 80%), 479 (41), 464 (8), 410 (11), 383 (12), 272 (10), 236 (62), 211 (11), 174 (47), 123 (12), 105 (20), 77 (100), 51 (35).

6′-Amino-1,1′-diphenyl-3-methyl-5-oxo-2′-phenylimino-spiro[(4,5-dihydro-1H-pyrazole)-4,4′-(1′,2′,3′,4′-tetrahydropyridine)]-5′-carbonitrile (**17c**): This compound was obtained as colourless crystals (150 mg, 34 %), m.p. 183–185 °C (from cyclohexane/ethyl acetate). (Found: C, 72.41; H, 4.86; N, 18.75. $C_{27}H_{22}N_6O$ requires C, 72.63; H, 4.97; N, 18.83); ν_{max} (KBr)/cm^{-1} 3410 (NH_2), 2190 (CN), 1700 (CO); δ_H (400 MHz, $CDCl_3$) 2.11 (3H, s, CH_3), 2.92 (1H, d) and 2.74 (1H, d, $|^2J|$ 15.2, CH_2), 4.65 (2H, s, NH_2), 6.58, 7.32, 7.44, 7.59, 7.88 and 7.93 (all *m*, aryl-CH); δ_C (100 MHz, $CDCl_3$) 13.60 (CH_3), 26.22 ((C-3'), 51.55 (C-4 = C-4'), 52.13 (C-5'), 117.12, 120.29, 123.35, 125.72, 127.67, 128.59 and 129.98 (all aryl-CH), 118.32 (CN), 137.44, 147.65 and 151.86 (aromatic C–N), 154.15 (C-2'), 155.81 (C-3), 160.78 (C-6'), 172.29 (C-5); *m/z* 446 (M^+, 11%),, 419 (6), 383 (38), 358 (12), 320 (71), 302 (15), 236 (32), 210 (40), 174 (65), 149 (10), 118 (87), 77 (100), 51 (19).

6′-Amino-3-methyl-1′-(4-nitrophenyl)-2′-(4-nitrophenylimino)-5-oxo-1-phenyl-spiro[(4,5-dihydro-1H-pyrazole)-4,4′-(1′,2′,3′,4′-tetrahydropyridine)]-5′-carbonitrile (**17d**): This compound (250 mg, 47 %) was obtained as pale yellow crystals, m.p. 279–281 °C (from ethyl acetate) (Found: C, 60.44; H, 3.76; N, 20.89. $C_{27}H_{20}N_8O_5$ requires C, 60.54; H, 3.73; N, 20.98); ν_{max} (KBr)/cm^{-1} 3400 (NH_2), 2190 (CN), 1700 (CO); δ_H (400 MHz, DMSO-d_6) 2.19 (3H, s, CH_3), 3.16 (1H, d) and 2.97 (1H, d, $|^2J|$ 15.6, CH_2), 6.59 (2H, s, NH_2), 6.83, 7.21, 7.44, 7.72, 7.80, 8.10 and 8.39 (all *m*, aryl-CH); δ_C (100 MHz, DMSO-d_6) 13.66 (CH_3), 26.25 (C-3'), 51.41 (C-4 = C-4'), 52.01 (C–5'), 118.20, 121.29, 124.85, 128.89 and 131.40 (all aryl-CH), 118.43 (CN), 137.44, 147.35 and 152.86 (aromatic C–N), 142.86 and 142.98 (aryl-C-NO_2), 154.07 (C-2'), 155.92 (C-3), 160.86 (C-6'), 172.97 (C-5); *m/z* 536 (M^+, 80%), 509 (41), 494 (8), 468 (11), 383 (38), 371 (30), 358 (80), 341 (38), 322 (28), 300 (16), 236 (21), 211 (12), 163 (100), 118 (44), 77 (35), 51 (9).

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