Facile One-Pot Syntheses of New Polyfunctional Pyrazolyl Substituted and Pyrazolofused Pyridines

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Ethyl 2-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)acrylate (**1**) undergoes both conjugate addition of a number of methylene-active ethanenitriles and direct addition of other active methylene donors to the cyano carbon atom. These additions are the starting events of cascades of subsequent reactions eventually forming (i) novel polyfunctional pyrazolyl-substituted monocyclic pyridines (**4a**, **b** and **6**), (ii) 1,3-benzothiazole and benzimidazole-fused pyridines (**11**, **13**) and (iii) pyrazolo[5,4-*b*]pyridines (**19b**, **20**) in one-pot reactions in ethanolic solution containing catalytic amounts of piperidine.

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Introduction.

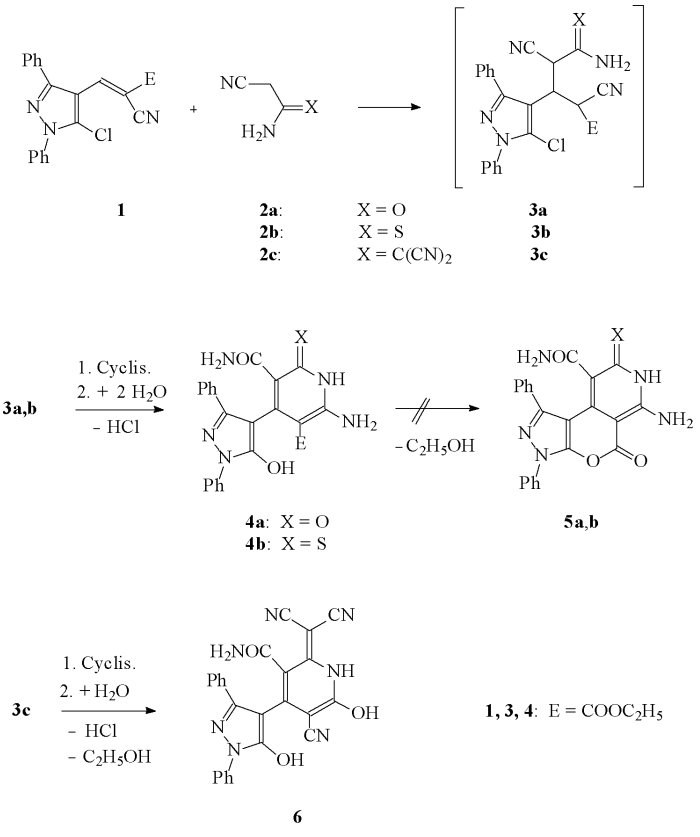
Pyrazole derivatives are pharmacologically important and have been demonstrated to possess antiinflammatory, antimicrobial [1], insecticidal [2], herbicidal [3], pesticidal [4, 5] and antischistosomal [6] properties. Recently we have described the synthesis of new heterocyclic compounds incorporating pyrazole and pyridine rings [7-11]. These results prompted us to continue our investigations on the utility of ethyl 2-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)acrylate (**1**) [8] as a readily available precursor for the synthesis of such new heterocyclic systems which might show pharmacological effects. Since **1** is prone to undergo *Michael*-additions readily, six methylene-active nitriles, namely cyanoacetamide (**2a**), cyanothioacetamide (**2b**), 2-aminopropene-1,1,3-tricarbonitrile (**2c**), 1,3-benzothiazol-2-ylethanenitrile (**7a**), benzimidazol-2-ylethanenitrile (**7b**), and 4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-ethanenitrile (**14**) as well as 3-methyl-4,5-dihydropyrazol-5-one (**17a**) and its 3-phenyl analogue (**17b**) have been selected as carbon nucleophiles.

Results and Discussion.

In all cases, the reactants were exposed to catalytic amounts of piperidine in moist ethanol solution at reflux temperature. Products were isolated by filtration of the precipitates formed, and after purification, the plausible structures indicated below were delinated from elemental composition, mass spectrometry and spectrocopic evidence (see experimental part). It became clear, that the primary products obtained from initial conjugate addition or attack on the nitrile group of **1** had undergone a variety of further individual reactions as intramolecular additions or condensations.Thus, **1** and **2a**,**b** highly likely reacted to give **3a**,**b** (not isolated), which subsequently underwent cyclization to form the pyridine ring by intramolecular attack of the nitrile group originating from starting material **1**. In addition, two functions underwent hydrolysis, namely the remaining cyano group being transformed to carbamoyl and the chlorine atom on the pyrazolyl moiety (Scheme 1). A further condensation involving the 5-ester group and the 5'-hydroxy group, which should have formed compounds **5a**,**b**, was not observed.

The ir spectra of **4a**,**b** revealed the presence of OH, NH_2, NH and ester C=O groups while a CN absorption is com-

Scheme 1

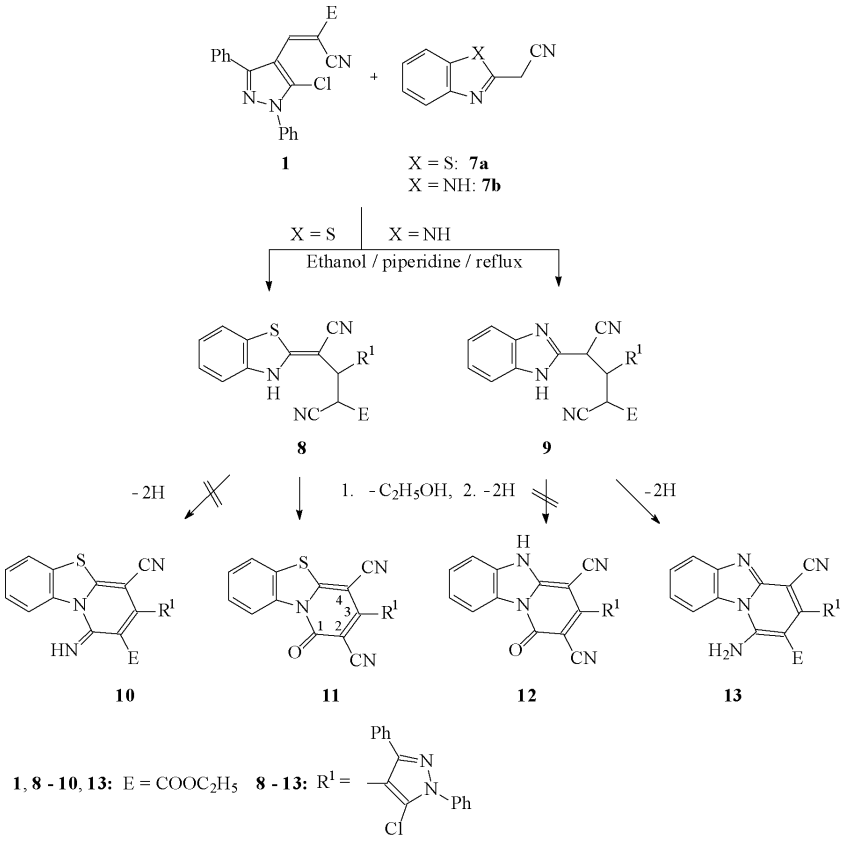


pletely absent. On the other hand, under analogous conditions, the plausible adduct **3c** from **1** and **2c** obviously preferred to undergo cyclization by a condensation of the amino group with the ester function leaving the cyanoacetate CN group intact. The two consecutive hydrolyses of the remaining CN and the chlorine atom must have occurred in the same way as in the case of **4a**,**b**. Thus, the ^{1}H nmr of product **6** revealed the absence of an ester group, while the ir showed absorptions for CN at 2225, 2215 and 2200 cm^{-1} and CO at 1680 and 1665 cm^{-1} (amide). A pyrido[2,1-*b*]benzothiazole derivative **11** is formed by the addition of **7a** to **1** first generating **8** (not isolated) which in turn undergoes a condensative cyclization followed by dehydrogenation to generate **11**. The option of adding the NH group to the cyanoacetate nitrile carbon atom (which would form **10** eventually after dehydrogenation) is not executed. In contrast, addition of **7b** to **1** does form **13** *via* **9** and subsequent dehydrogenation, while the product from condensative cyclization, namely **12**, is not formed (Scheme 2). There seems to be a delicate balance between the two options available in either case. The dehydrogenations are certainly due to the instability of the cyclized intermediates to air exposure under reflux.

Whereas in the aforementioned cases the methylene-active reagents were added to the ß-carbon atoms of **1**, (4-oxo-4,5-dihydro-1,3-thiazol-2-yl)ethanenitrile (**14**) prefers to add to the cyano carbon atom of cyanoacrylate **1** to give the proposed intermediate **15** which is cyclized with loss of one molecule of hydrogen chloride to form the pyrazolo[5,4-*b*]pyridine **16** (Scheme 3). On the basis of the HSAB-principle [12] one might envisage the cyanomethylene carbon of **14** as "hard" attacking preferentially the "hard" cyanocarbon of **1**.

A similar reactivity is shown by the methylene-active pyrazolinones **17a,b**: Formation of the fused pyrazolo[5,4-*b*]pyridines **19a,b** is best explained by the attack of C-4 of **17** on the cyano carbon of **1** generating the proposed intermediates **18a,b** which undergo a cyclisation with loss of hydrogen chloride generating **19a,b**, as supported by the absence of chlorine and cyano groups in the latter products. One of these, namely **19a** (but not **19b**) undergoes a facile

Scheme 2



Spectroscopically, the absence of signals for the ethoxy group in the ^{1}H nmr of **11** in contrast to the presence of such signals in the nmr of **13** is most significant. Also, in the ir spectrum of **13**, the presence of characteristic amino group absorptions at 3325 and 3225 cm^{-1} supports the structure assignment.

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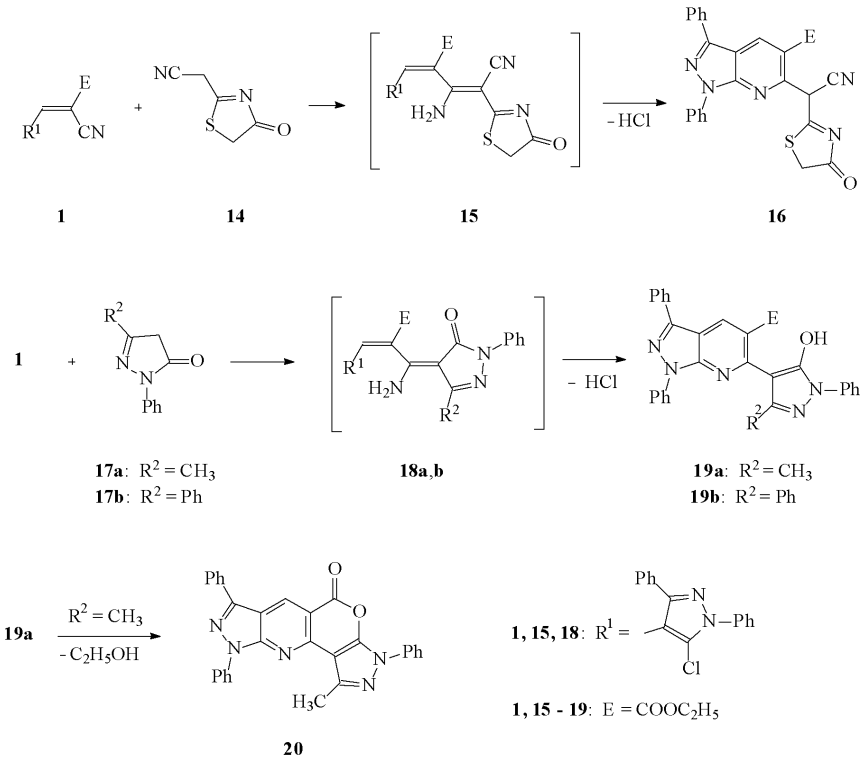
Scheme 3



Conclusion.

In the cases investigated in this study, the 2-cyanoacrylate **1**, shows acceptor reactivity at both the ß-carbon atom and the cyano group towards typical Michael-donors. Various optional sequential additions and/or condensations allow the preparation of various pyrazolyl substituted or pyrazolo-fused pyridines in one-pot reactions.

EXPERIMENTAL

Melting points have been determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra (ν in cm^{-1}) were recorded on a Pye-Unicam SP-1100 spectrophotometer. The ^1H nmr spectra (δ in ppm) were run on a Varian EM 390 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Varian MAT 311 A instrument, and the elemental analyses were determined at the Microanalytical Center of Cairo University.

Ethyl 2-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)acrylate (**1**) was prepared according to a published procedure [8]. Cyanoacetamide (**2a**), cyanothioacetamide (**2b**) and 2-aminopropene-1,1,3-tricarbonitrile (**2c**), 3-methyl-1-phenyl- (**17a**), 1,3-diphenyl-4,5-dihydropyrazol-5-one (**17b**) and benzimidazol-2-ylacetonitrile (**7b**) were purchased from Aldrich Chemical Co. Benzothiazol-2-ylacetonitrile (**7a**) and (4-oxo-4,5-dihydro-1,3-thiazol-2-yl)acetonitrile (**14**) were prepared according to ref. [13,14].

Preparation of Compounds **4a,b**.

A solution of **1** (0.50 g, 1.3 mmole), **2a** (0.11 g, 1.3 mmole), and 0.1 mL of piperidine in 20 mL of dry ethanol was warmed to reflux for seven hours and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 mL conc. HCl, 20 mL of water) was collected, washed well with 100 mL of cold water and crystallized from ethanol to give **4a**. Analogously **1** was reacted with **2b** (0.13 g, 1.3 mmole) to give **4b**.

Ethyl 2-Amino-5-carbamoyl-1,6-dihydro-4-(5-hydroxy-1,3-diphenylpyrazol-4-yl)-6-oxopyridine 3-carboxylate (**4a**).

This compound was isolated (43 mg, 70%) as colourless crystals, mp. 150-152°; ^1H nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_3); 4.25 (q, 2H, CH_2O), 7.12 – 8.16 (m, 16H, aryl-H, OH, NH, NH_2, $CONH_2$); ms (70 eV) m/z (%) 459 (55) [M^+]; ir (KBr) ν 3530 cm^{-1} (OH) 3450 and 3340 (NH_2), 3220 (NH), 1675 and 1655 (CO).

Anal. Calcd. for $C_{24}H_{21}N_5O_5$ (459.46): C, 62.74; H, 4.60; N, 15.24. Found: C, 62.59; H, 4.52; N, 15.15.

Ethyl 2-Amino-3-carbamoyl-1,6-dihydro-4-(5-hydroxy-1,3-diphenylpyrazol-4-yl)-6-thioxopyridine-3-carboxylate (**4b**).

This compound was isolated (46 mg, 73%) as yellow crystals, mp 160-162°, ^1H nmr (DMSO-d_6): δ 1.21 (t, 3H, CH_3), 4.22 (q, 2H, CH_2O), 7.11 – 8.15 (m, 16H, aryl-H, OH, NH_2, NH, and $CONH_2$); ms (70 eV) m/z (%) 475 (60) [M^+], ir (KBr) ν 3525 (OH), 3445, 3340 (NH_2), 3215 (NH) and 1670 cm^{-1} (CO).

Anal. Calcd for $C_{24}H_{21}N_5O_4S$ (475.52): C, 60.62; H 4.45; N, 14.72. Found: C, 60.50; H, 4.32; N, 14.61.

5-Cyano-2-dicyanomethylene-6-hydroxy-4-(5-hydroxy-1,3-diphenylpyrazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**6**).

An ethanolic solution (30 mL) containing 0.50 g (1.3 mmole) of **1**, 2-aminopropene-1,1,3-tricarbonitrile (**2c**, 0.17 g, 1.3 mmole) and 0.1 mL of piperidine was warmed to reflux for six hours and concentrated under vacuum. The residue was triturated with 5 mL of methanol and the yellow product collected by filtration and crystallized from methanol to give 0.39 g (65%), mp 235-238°. ^{1}H nmr ($CDCl_3$): δ 5.76 (s, 1H, NH), 7.14 – 8.15 (m, 14H, aryl-H, OH, $CONH_2$); ms (70 eV): m/z (%) 462 (13) [M+1]; ir (KBr) ν 3525, 3350, 3225 cm^{-1} (OH, NH_2), 2225, 2215, 2200 (CN) and 1680, 1665 (CO) cm^{-1}.

Anal. Calcd. for $C_{25}H_{15}N_7O_3$ (461.44): C, 65.07; H, 3.27; N 21.25. Found: C, 65.17; H, 3.15; N, 21.13.

Preparation of Compounds **11** and **13**.

Ethanolic solutions (30 mL) of **1** (0.50 g, 1,3 mmole), 0.1 mL of piperidine and (a) (benzthiazol-2-yl)ethanenitrile (**7a**, 0.50 g, 2.9 mmole) or (b) (benzimidazol-2-yl)ethanenitrile (**7b**, 0.23 g, 1.4 mmole) were kept at reflux for six hours.

3-(5-Chloro-1,3-diphenylpyrazol-4-yl)-1(1*H*)-oxopyrido-[2,1-*b*]benzothiazole-2,4-carbonitrile (**11**).

This compound was collected from the hot solution by filtration, washed and crystallized from ethanol to give 53 mg (80%) of brown crystals, mp 205-207°; ^{1}H nmr (DMSO-d_6): δ 7.16 – 7.91 (m, 14 H, aryl-H); ms (70 eV) m/z 503/505 (10/3) [M$^+$]; ir (KBr) ν 2218 (CN) and 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{28}H_{14}ClN_5OS$ (503.96): C, 66.73; H, 2.80; N, 13.90. Found: C, 66.56; H, 2.65; N, 13.77.

Ethyl 1-Amino-4-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)pyrido[1,2-*a*]benzimidazole-2-carboxylate (**13**).

This compound was isolated upon cooling and acidification of the solution with dilute hydrochloric acid and crystallization from methanol to give 53 mg (75%) of colourless crystals, mp 160-162°; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_3), 4.21 (q, 2H, CH_2O), 7.12 – 7.82 (m, 14H, aryl-H), 7.95 (s, 2H, NH_2); ms (70 eV) m/z (%) 532/534 (4/1) [M$^+$]; ir (KBr) ν 3345, 3325 (NH_2), 2215 (CN) and 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{30}H_{21}ClN_6O_2$ (532.99): C, 67.71; H, 3.97; N, 15.77. Found: C, 67.50; H, 3.86; N 15.64.

Ethyl 1,3-Diphenyl-6-[cyano-(4,5-dihydro-4-oxothiazol-2-yl)methyl]pyrido[2,3-*c*]-pyrazole-5-carboxylate (**16**).

A mixture of **1** (0.50 g, 1.3 mmole), (4-oxo-4,5-dihydro-1,3-thiazol-2-yl)ethanenitrile (**14**, 0.18 g, 1.3 mmole) and 0.1 mL of piperidine in 40 mL of ethanol was refluxed for five hours. The solid formed was crystallized from dimethylformamide to give 38 mg (60%) of brown crystals, mp 195-197°; ^{1}H nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_3), 2.86 (s, 1H, 6-H), 2.91 (s, 2H, CH_2), 4.21 (q, 2H, CH_2O), 7.12 – 7.92 (m, 11H, phenyl-H and 4-H); ms (70 eV) m/z (%) 481 (100) [M$^+$]; ir (KBr) ν 2210 (CN), 1680, 1665 (C=O) cm^{-1}.

Anal. Calcd. for $C_{26}H_{19}N_5O_3S$ (481.53): C, 64.86; H, 3.98; N, 14.54. Found: C, 64.71; H, 3.82; N 14.35.

Preparation of Compounds **19b** and **20**.

Ethanol solutions (30 mL each) of **1** (0.5 g, 1.3 mmole) containing 0.1 mL of piperidine and (a) 3-methyl-1-phenyl 4.5-dihydro(1*H*)pyrazol-5-one (**17a**, 0.23 g, 1.3 mmole) or (b) 0.30 g (1.3 mmole) of 1,3-diphenyl-4,5-dihydropyrazol-5-one (**17b**) were kept at reflux temperature for five hours. The colourless precipitates were dried by suction, washed with ethanol and crystallized from dimethylformamide.

Ethyl 5,7-Diphenyl-2-(1,3-diphenyl-5-hydroxypyrazol-4-yl)-pyrazolo[3,4-*b*]pyridine-3-carboxlate (**19b**).

This compound was obtained as colourless crystals (56 mg, 72%), mp 240-242°; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_3), 4.21 (q, 2H, CH_2O), 7.13 – 7.82 (m, 22H, aryl-H); ms (70eV): m/z = 578 (17) [M+1]$^+$, 577 (13)[M$^+$], ir (KBr): ν 3455 (OH), 1710 (CO) cm^{-1}.

Anal. Calcd. for $C_{36}H_{27}N_5O_3$ (577.64): C, 74.86; H, 4.71; N, 12,12. Found: C, 74.69; H, 4.57; N, 12.01.

1-Methyl-3,7,9-triphenylpyrazolo[3,4-*b*]pyrido[5,6-*c*]pyrano-[2,3-*c*]pyrazol-5(5*H*)-one (**20**).

This compound was obtained (40 mg, 65%) as colourless crystals, mp 180-182°; ^{1}H nmr (DMSO-d_6): δ 1.50 (s, 3H, CH_3), 7.12 – 7.91 (m, 16H, aryl-H); ms (70 eV): m/z (%) 469 (15) [M$^+$]; ir (KBr) ν 1685 (CO) cm^{-1}.

Anal. Calcd. for $C_{29}H_{19}N_5O_2$ (469.50); C, 74.19; H, 4.08; N, 14.92. Found: C, 74.03; H, 4.22; N, 14.75.

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