A Facile Access to Polysubstituted Bipyrazoles and Pyrazolylpyrimidines

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3-(Pyrazol-3-yl)-3-oxo-propanenitrile derivative reacts with several nitrogen nucleophiles to give bipyrazole, pyrazolyloxazole, and pyrazolylpyrimidine derivatives. The structures of the products were confirmed on the basis of their elemental and spectral analyses.

Keywords: Pyrazoles; Hydrazonoyl halides; Enaminonitriles; Bipyrazoles; Pyrazolyloxazoles; Pyrazolylpyrimidines.

INTRODUCTION

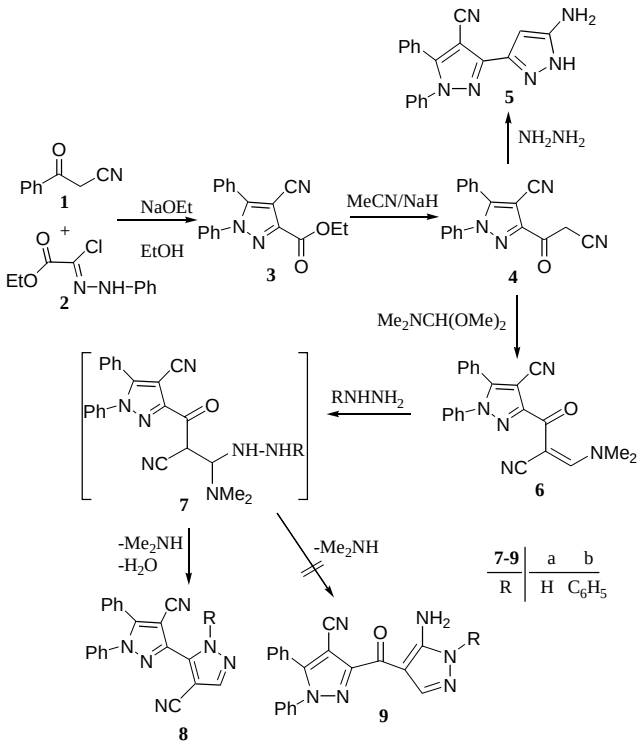
Bipyrazole derivatives are very interesting class of heterocyclic compounds that have remarkable pharmacological activity. They have proven to be useful as potential anti-inflammatory agents,[1,2] cytotoxic agents,[3] insecticides,[4] herbicides,[5] and fungicides.[6-8] In continuation of our recent work aiming at the synthesis of a wide variety of 3,3′-bipyrazole systems,[9,10] we report herein a facile route to various 3,3′- and 3,5′-bipyrazoles, pyrazolyloxazoles, and pyrazolylpyrimidines. In this manner, we have found that 3-(4-cyano-1,5-diphenyl-1H-pyrazol-3-y1)-3-oxo-propanenitrile (**4**) is an excellent building block for the synthesis of the entitled objectives.

RESULTS AND DISCUSSION

The starting compound **4** could be synthesized through treatment of 4-cyano-1,5-diphenyl-1H-pyrazole-3-carboxylic acid ethyl ester (**3**) with acetonitrile in the presence of sodium hydride, in refluxing benzene (Scheme I). The structure of compound **4** was established on the basis of its elemental analysis and spectral data. For example, its ^{1}HNMR spectrum displayed a singlet signal at δ 4.14 characteristic for active methylene protons, whereas its IR spectrum revealed two absorption bands at 2270 and 2230 cm^{-1} due to two nitrile groups and a strong absorption band at 1710 due to a carbonyl group.

Treatment of the cyanoacetylpyrazole derivative **4** with hydrazine hydrate, in refluxing ethanol afforded the corresponding 3,3′-bipyrazole derivative **5** (Scheme I). The structure of compound **5** was confirmed on the basis of its elemental analysis and spectral data. The IR spectrum of compound **5** revealed three bands in the region 3371-3248 cm^{-1} corresponding to NH and NH_2 groups and showed only one nitrile absorption band at 2230 cm^{-1}. Its ^{1}H NMR spectrum revealed two broad bands (D_2O-exchangeable) at δ 5.41 and 11.9 due to NH_2 and NH protons, respectively, in addition to a multi-

Scheme I



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plet at δ 7.37-7.47 due to aromatic protons.

Treatment of the 3-(pyrazol-3-yl)-3-oxo-propanenitrile derivative **4** with dimethylformamide-dimethylacetal (DMF/DMA) in dry xylene, at refluxing temperature, afforded a yellow crystalline product identified as 3-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2-(N,N-dimethylamino)methylene-3-oxo-propanenitrile (**6**) (Scheme I). Its IR spectrum revealed two absorption bands at 2230 and 2205 cm^{-1} due to two nitrile functions and a carbonyl band at 1693 cm^{-1}. ^1H NMR spectrum of **6** exhibited two characteristic singlet signals at δ 3.33 and at δ 8.42 due to the *N,N*-dimethylamino and methine protons, respectively.

The reactivity of the enaminonitrile **6** towards some nitrogen nucleophiles was investigated. Thus, treatment of compound **6** with hydrazine hydrate, in refluxing ethanol, afforded a colorless product for which the two possible structures **8a** and **9a** can be formulated (Scheme I). The spectral data of the isolated product was, however, in complete agreement with structure **8a** [see Experimental Part].

Similarly, compound **6** reacted with phenylhydrazine in ethanol, at refluxing temperature to afford a yellow colored product that was identified as 1,5,1′-triphenyl-1H,1′H-3,5′-bipyrazolyl-4,4′-dicarbonitrile (**8b**).

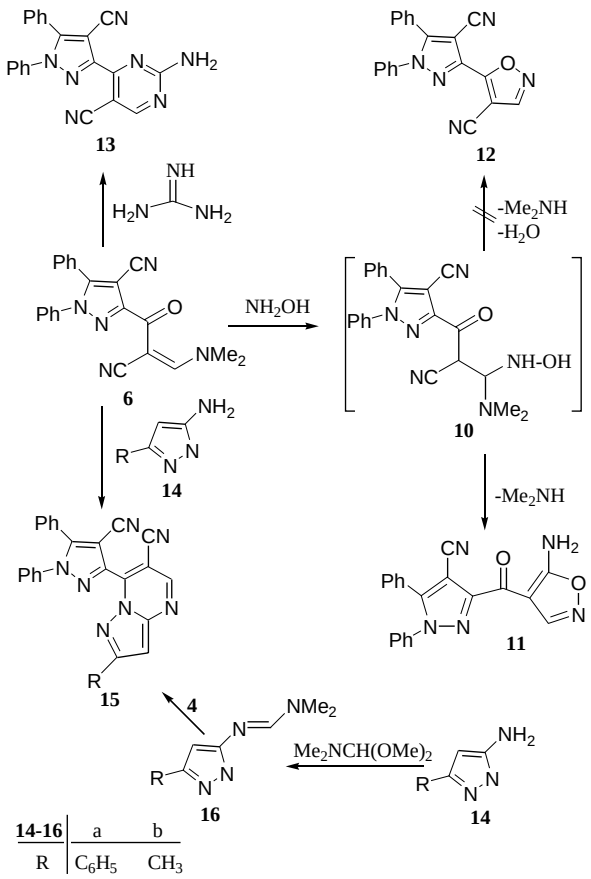
The formation of compounds **8a**,**b** is assumed to take place *via* a Michael-type addition of the amino group of hydrazines to the enamine double bond in **6** that undergoes intramolecular cyclization into the pyrazole derivatives **8a**,**b** *via* the loss of dimethylamine and water molecules (Scheme I).

In contrast to its behaviour towards hydrazine derivatives, compound **6** reacted with hydroxylamine in ethanol, and afforded one product for which the aminoisoxazole structure **11** was established on the basis of the elemental analysis and spectral data of the isolated product (Scheme II).

IR spectrum of **11** revealed a strong carbonyl absorption at 1659 cm^{-1} and one nitrile absorption band at 2230 cm^{-1} in addition to two bands at 3425 and 3333 cm^{-1} corresponding to an amino group. The isolated product is assumed to be formed *via* the addition of the NH_2 group of hydroxylamine to the activated double bond in compound **6** to form the non-isolable intermediate **10** which underwent intramolecular cyclization *via* loss of a dimethylamine molecule to afford the isoxazole derivative **11** (Scheme II).

The enaminonitrile **6** reacts also with guanidine in refluxing ethanol to give a high yield of a single product (as examined by TLC) that was identified as 2-amino-4-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)pyrimidine-5-carbonitrile (**13**) according to its elemental and spectral analyses.

Scheme II

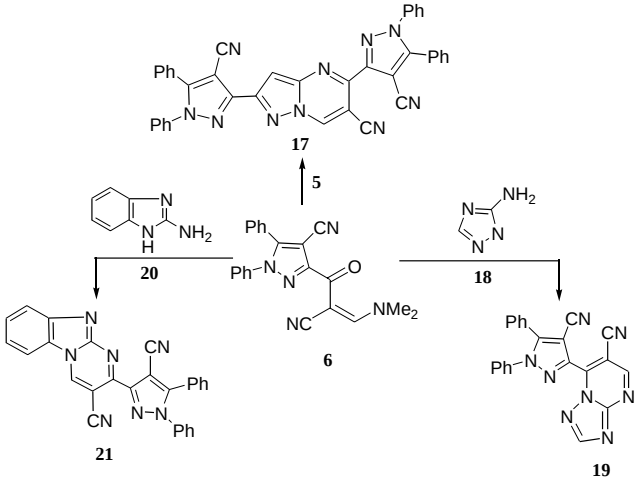


The reactivity of enaminonitrile **6** towards some heterocyclic amines was also investigated. Thus, when compound **6** was treated with 5-amino-3-aryl-(1H)-pyrazoles **14a**,**b**, in refluxing ethanol and in the presence of a catalytic amount of piperidine, it furnished in each case, a single product. The structures of the isolated products were identified as the pyrazolo[1,5-a]pyrimidine derivatives **15a**,**b**, on the basis of their elemental analyses and spectral data. Further evidence for the proposed structure **15** was obtained by an independent synthesis of compound **15a** *via* the reaction of 5-*N*-(*N,N*-dimethylaminomethylene)imino-3-phenyl-1H-pyrazole (**16**) with the cyanoacetylpyrazole **4**, in refluxing ethanol and in the presence of a catalytic amount of piperidine that afforded a product identical in all respects (m.p., TLC and spectra) with that obtained from the reaction of the enaminonitrile **6** and 5-amino-3-phenyl-1H-pyrazole **14a** (Scheme II).

Similarly, the aminopyrazole derivative **5** reacted with the enaminonitrile **6** under similar reaction conditions to afford the pyrazolo[1,5-a]pyrimidine derivative **17** according to its elemental analysis and spectral data [see Experimental Part].

In a similar manner, compound **6** reacted with 3-amino-1,2,4-triazole (**18**) to afford the 1,2,4-triazolo[1,5-a]pyrimidine derivative **19** (Scheme III). The mass spectrum of the product revealed a peak at *m/z* 388 corresponding to its molecular ion. Its IR spectrum revealed the appearance of two nitrile absorption bands at 2237 and 2210 cm^{-1} and showed the lack of a band characteristic for a carbonyl group.

Scheme III



At the end, the enaminonitrile **6** reacted also with 2-aminobenzimidazole (**20**) to give 2-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-benzo[4,5]imidazo[1,2-a]-pyrimidine-3-carbonitrile (**21**) (Scheme III). The structure of the isolated product was confirmed on the basis of its elemental analysis and spectral data [see Experimental Part].

EXPERIMENTAL

Benzoylacetonitrile (**1**),[11] and hydrazonoyl chlorides **2**,[12] pyrazole derivatives **3**,[13] **14**[14] and **16**[15] were prepared according to literature procedures.

3-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-3-oxopropanenitrile (4)

To a mixture of 4-cyano-1,5-diphenyl-1H-pyrazole-3-carboxylic acid ethyl ester (**3**) (15.85 g, 50 mmol), acetonitrile (2.7 mL, 50 mmol) and dimethylformamide (10 mL), in dry benzene (200 mL) was added sodium hydride (1.2 g, 85%). The reaction mixture was refluxed for 4 h, then allowed to cool. The solid that precipitated was collected by filtration, washed with petroleum ether (60-80 °C) and dried. The crude product was dissolved in water (50 mL) and the resulting alkaline solution was treated with concentrated hydrochloric acid until it became neutral (pH = 7). The precipitated solid product was filtered off, washed with water, dried and finally recrystallized from ethanol to afford 11.7 g (75% yield) of **4**, mp. 195-6 °C (EtOH); IR (KBr) ν/cm^{-1} 2270, 2230 (2C≡N), 1710 (C=O), 1593 (C=N); ^{1}H NMR ($CDCl_3$) δ 4.14 (s, 2H, CH_2), 7.23-7.40 (m, 10H, ArH's); MS, *m/z* 312 (M^+), 273, 141, 77. Anal. Calcd for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.87; N, 17.94. Found: C, 73.1; H, 3.9; N, 18.0%.

Synthesis of 5′-amino-1,5-diphenyl-3,3′-bipyrazolyl-4-carbonitrile (5)

A mixture of cyanoacetylpyrazole **4** (6.24 g, 20 mmol) and hydrazine hydrate (1 mL, 80%) in absolute ethanol (20 mL) was refluxed for 4 h. The reaction mixture was allowed to cool and then diluted with water. The precipitated solid was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded 5′-amino-1,5-diphenyl-3,3′-bipyrazolyl-4-carbonitrile (**5**). Yield 73%; mp. 250-2°; IR (KBr) ν cm^{-1} 3371, 3248 (NH, NH_2), 2230 (C≡N); ^{1}H NMR (DMSO-d_6) δ 5.14 (br, s, 2H, NH_2, D_2O-exchangable), 5.81 (s, 1H, CH), 7.37-7.47 (m, 10H, ArH's), 11.9 (br, s, 1H, NH, D_2O-exchangable) ppm. Anal. Calcd for $C_{19}H_{14}N_6$: C, 69.93; H, 4.32; N, 25.75. Found: C, 70.0; H, 4.2; N, 25.8%.

3-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2-(N,N-dimethylamino)-methylene-3-oxopropanenitrile (6)

A mixture of cyanoacetylpyrazole **4** (6.24 g, 20 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (2.66 mL, 20 mmol) in dry xylene (30 mL) was refluxed for 3 h, then allowed to cool. The orange yellow precipitate was filtered off, washed with petroleum ether (60/80 °C) and dried. Recrystallization from ethanol/DMF gave 6.76 g of compound **6** (92% yield); mp. 223-5°; IR (KBr) ν cm^{-1} 2230, 2205 (2C≡N), 1693 (C=O). ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 6H, $2CH_3$), 7.39-7.49 (m, 10H, ArH's), 8.42 (s, 1H, CH); MS, *m/z* 367 (M^+), 273, 180, 123, 77. Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.92; H, 4.66; N, 19.06. Found: C, 71.8; H, 4.7; N, 19.2%.

Reactions of enaminonitrile 6 with hydrazines

To a solution of the enaminonitrile **6** (0.73 g, 2 mmol) in ethanol (20 mL), hydrazine hydrate (80%, 0.2 mL) or phenyl hydrazine (0.2 mL, 2 mmol) was added and the reaction mixture was refluxed for 4 h, then left to cool. The solid product that formed was filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide/ethanol afforded yellow crystals of 3,3′-bipyrazolyl-4,4′-dicarbonitrile (**8a**) and 3,5′-bipyrazolyl-4,4′-dicarbonitrile (**8b**), respectively.

1,5-Diphenyl-1H,1′H-3,3′-bipyrazolyl-4,4′-dicarbonitrile (8a)

Yield 73%; mp. >300°; IR (KBr) ν cm^{-1} 3263 (NH), 2230 (2C≡N); ^{1}H NMR (DMSO-d_6) δ 3.35 (s, br, 1H, NH), 7.33-7.59 (m, 10H, ArH's), 8.81 (s, 1H, CH). MS, *m/z* 336 (M^+), 310, 284, 244, 92, 77. Anal. Calcd for $C_{20}H_{12}N_6$: C, 71.42; H, 3.60; N, 24.99. Found: C, 71.5; H, 3.4; N, 25.1%.

1,5,1′-Triphenyl-1H,1′H-3,5′-bipyrazolyl-4,4′-dicarbonitrile (8b)

Yield 76%; mp. 262-4°; IR (KBr) ν cm^{-1} 2230, 2210 (2C≡N). Anal. Calcd for $C_{26}H_{16}N_6$: C, 75.71; H, 3.91; N, 20.38. Found: C, 75.5; H, 4.0; N, 20.5%.

Synthesis of 5-aminoisoxazole 11 and 2-aminopyrimidine 13

General procedure

To a mixture of the enaminonitrile **6** (0.73 g, 2 mmol) and hydroxylamine hydrochloride or guanidine nitrate (2.3 mmol) in ethanol (30 mL), anhydrous potassium carbonate (0.552 g, 4 mmol) was added. The resulting mixture was refluxed for 6 h and allowed to cool to room temperature then diluted with water (20 mL). The solid products that formed were collected by filtration, washed with water and dried. Recrystallization from DMF afforded the 5-aminoisoxazole **11** and 2-aminopyrimidine **12**, respectively.

(**11**): Yield 81%; mp. 215-6°; IR (KBr) ν cm^{-1} 3425, 3333 (NH_2), 2230 (C≡N), 1659 (C=O); ^{1}H NMR (DMSO-d_6) δ 3.58 (s, br, 2H, NH_2, D_2O-exchangable), 7.35-7.52 (m, 10H, ArH's), 7.53 (s, 1H, CH) ppm. Anal. Calcd for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.69; N, 19.71. Found: C, 67.5; H, 3.8; N, 19.7%.

(**13**): Yield 83%; mp. 293-5°; IR (KBr) ν cm^{-1} 3337, 3219 (2NH), 2230, 2218 (2C≡N); ^{1}H NMR (DMSO-d_6) δ 7.37-7.80 (m, 10H, ArH's), 7.98 (br, s, 1H, NH), 7.99 (s, br, 1H, NH) D_2O-exchangeable, 8.81 (s, 1H, CH); MS, *m/z* 363 (M^+), 244, 119, 77. Anal. Calcd for $C_{21}H_{13}N_7$: C, 69.41; H, 3.61; N, 26.98. Found: C, 69.2; H, 3.5; N, 27.0%.

Reaction of enaminonitrile 6 with heterocyclic amines 5, 14, 18 and 20

General procedure

To a mixture of the enaminonitrile **6** (0.73 g, 2 mmol) and the appropriate heterocyclic amine **5**, **14**, **18** or **20** (2.2 mmol) in ethanol (30 mL), was added a few drops of piperidine. The reaction mixture was refluxed for 4 h, then left to cool at room temperature. The precipitated product was filtered off, washed with ethanol, dried and finally recrystallized from DMF to afford the corresponding products **17**, **15a**,**b**, **19** and **21**, respectively.

(**15a**): Yield 76%; mp. 257-9°; IR (KBr) ν cm^{-1} 2230, 2219 (2C≡N); ^{1}H NMR (DMSO-d_6) δ 7.44-7.56 (m, 16H, ArH's), 7.69 (s, 1H, CH). MS, *m/z* 463 (M^+), 387, 361, 244, 219, 143, 77. Anal. Calcd for $C_{29}H_{17}N_7$: C, 75.15; H, 3.70; N, 21.15. Found: C, 75.3; H, 3.6; N, 21.3%.

(**15b**): Yield 73%; mp. 274-6°; IR (KBr) ν cm^{-1} 2239, 2224 (2C≡N). Anal. Calcd for $C_{24}H_{15}N_7$: C, 71.81; H, 3.77; N, 24.42. Found: C, 71.9; H, 3.8; N, 24.5%.

(**17**): Yield 76%; mp. >300 °C; IR (KBr) ν cm^{-1} 2230, 2199 (3C≡N); MS, *m/z* 630 (M^+), 315, 244, 180, 142, 77. Anal. Calcd for $C_{39}H_{22}N_{10}$: C, 74.27; H, 3.52; N, 22.21. Found: C, 74.3; H, 3.4; N, 22.0%.

(**19**): Yield 70%; mp. 260-2°; IR (KBr) ν cm^{-1} 2237, 2210 (2C≡N); MS, *m/z* 338 (M^+), 362, 244, 168, 144, 77. Anal. Calcd for $C_{22}H_{12}N_8$: C, 68.03; H, 3.11; N, 28.85. Found: C, 68.3; H, 3.3; N, 28.6%.

(**21**): Yield 69%; mp. 285-7°; IR (KBr) ν cm^{-1} 2220, 2206 (2C≡N); MS, *m/z* 437 (M^+), 273, 244, 192, 189, 133, 77. Anal. Calcd for $C_{27}H_{15}N_7$: C, 74.13; H, 3.46; N, 22.41. Found: C, 74.0; H, 3.5; N, 22.3%.

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