An efficient synthesis of functionalized 3-(hetaryl)pyrazoles

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DOI: http://dx.doi.org/10.3998/ark.5550190.0011.903

Abstract

An efficient synthesis of novel 3-heteroaryl-pyrazoles, which have not been reported hitherto, is described *via* reactions of ethyl 3-[(*E*)-3-(*N*,*N*-dimethylamino)acryloyl]-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate with hydrazine hydrate, hydroxylamine, various heterocyclic amines, active methylene compounds and diazotized heterocyclic amines. The structures of the compounds prepared were determined by spectral and elemental analyses and alternative syntheses wherever possible.

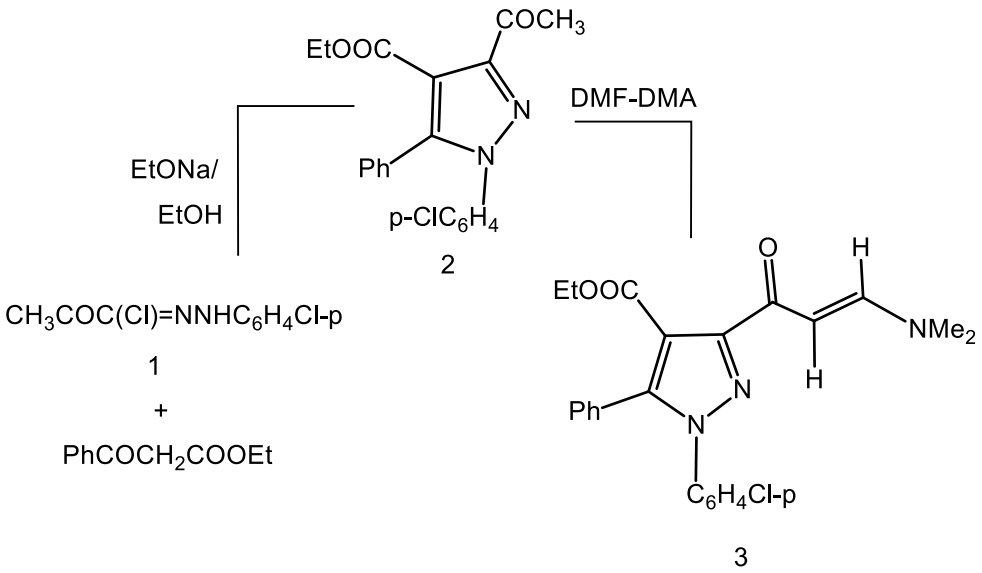
Keywords: Hydrazonoyl halides, heterocycles, enaminones, pyrazoles

Introduction

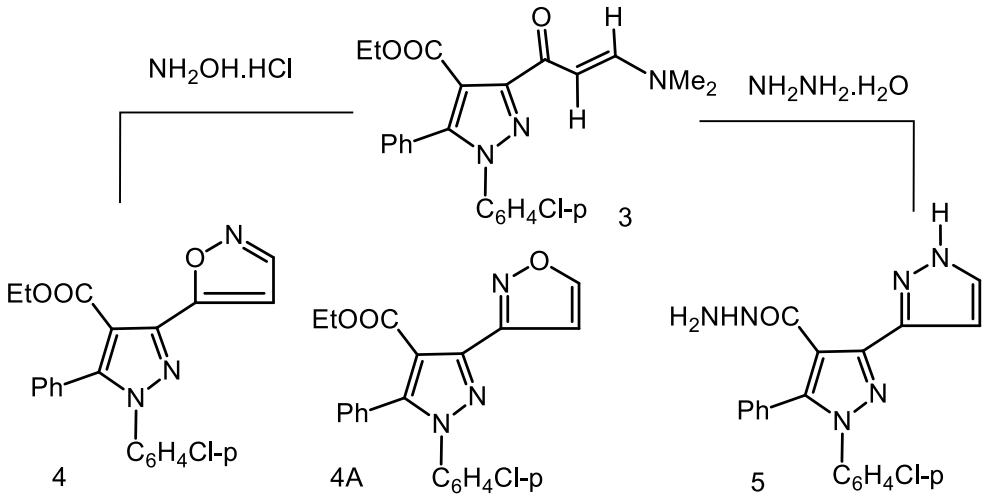
Pyrazoles are an important class of heterocyclic compounds. Literature reports reveal that many synthetic pyrazole derivatives are used in the pharmaceutical, agrochemical, photographic and other fields. Examples of such synthetic pyrazole derivatives are Sildenafil (Viagra),[1] Ionazlac[2] and Difenamizole.[3] In addition, hydrazonoyl halides (RC(X)=NNHR') proved useful precursors for synthesis of numerous biologically active pyrazoles and fused pyrazoles.[4] These findings oriented our attention to the synthesis of a new series of functionalized 3-(hetaryl)pyrazoles that might have bioactivity. In connection with our continued studies on such hydrazonoyl halides[4-14] and our recently reported synthesis of 3-[(*E*)-3-(*N*,*N*-dimethylamino)acryloyl]-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate **3**[15] from *N*-(4-chlorophenyl) 2-oxo-propanehydrazonoyl chloride **1** (Scheme 1), we report herein the results of our study of the reactions of **3** with several N- and C-nucleophiles as well as some N-electrophiles namely diazotized heterocyclic amines. The aim of the present paper is to present an efficient synthesis of novel 3-heteroaryl-pyrazoles, which have not been reported hitherto. The results of screening of their biological activity will be reported in due course.

Results and Discussion

The starting 3-[(*E*)-3-(*N*,*N*-dimethylamino)acryloyl]-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate **3** was prepared as previously described from our laboratory[15] *via* condensation of the pyrazole derivative **2**[16] with dimethylformamide dimethyl acetal (DMF-DMA) (Scheme 1).
Treatment of **3** with hydroxylamine hydrochloride in refluxing ethanol in the presence of potassium carbonate afforded only one isolable product that was identified, on the basis of its spectra (MS, IR, ^{1}H NMR) and elemental analysis, as the isoxazole derivative **4** and not its regioisomer **4A** (Scheme 2). Similar treatment of **3** with hydrazine hydrate in ethanol under reflux yielded 3-(1*H*-pyrazol-3-yl)-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carbohydrazide **5** (Scheme 2). The structures of the products **4** and **5** were confirmed by their spectral (MS, IR, ^{1}H- and ^{13}C-NMR) and elemental analysis data (see Experimental). For example, their IR spectra revealed the absence of the carbonyl group present in the spectrum of the enaminone **3**. The ^{1}H NMR (DMSO-d_6) of **4** showed two characteristic signals at δ 6.79 (d, *J* = 8 *Hz*, 1H, isoxazole-H) and 7.13 (d, *J* = *8Hz*, 1H, isoxazole-H). Also, the IR spectrum of **5** revealed bands at ν_{max} 3414, 3295, 3219 (NH_2, NH), 1646 (C=O) cm^{-1} for the –$CONHNH_2$ group and its ^{1}H NMR exhibits the pyrazole ring protons and the –$CONHNH_2$ protons at δ 4.33 (s, 2H, NH_2), 7.42 (d, *J* = 8*Hz*, 1*H*, pyrazole-H), 7.53 (d, *J* = 8*Hz*, 1H, pyrazole-H), 10.24 (s, 1H, NH), 13.16 (s, 1H, NH).

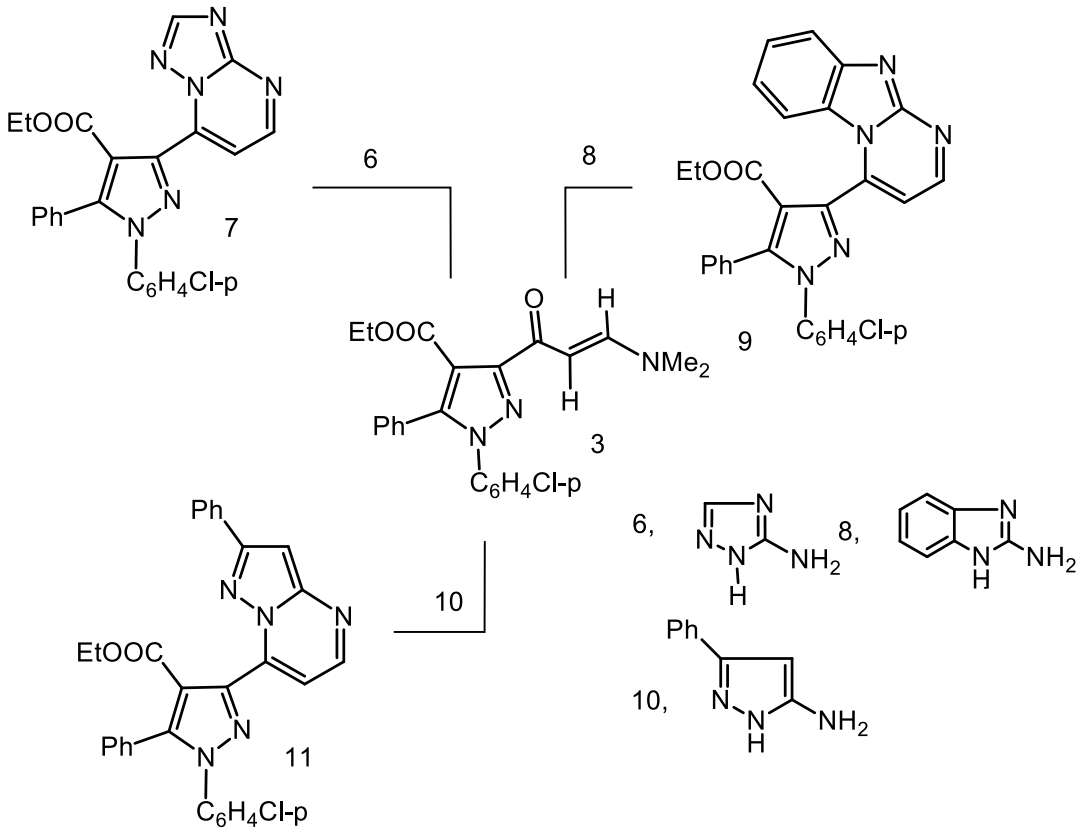


Scheme 1

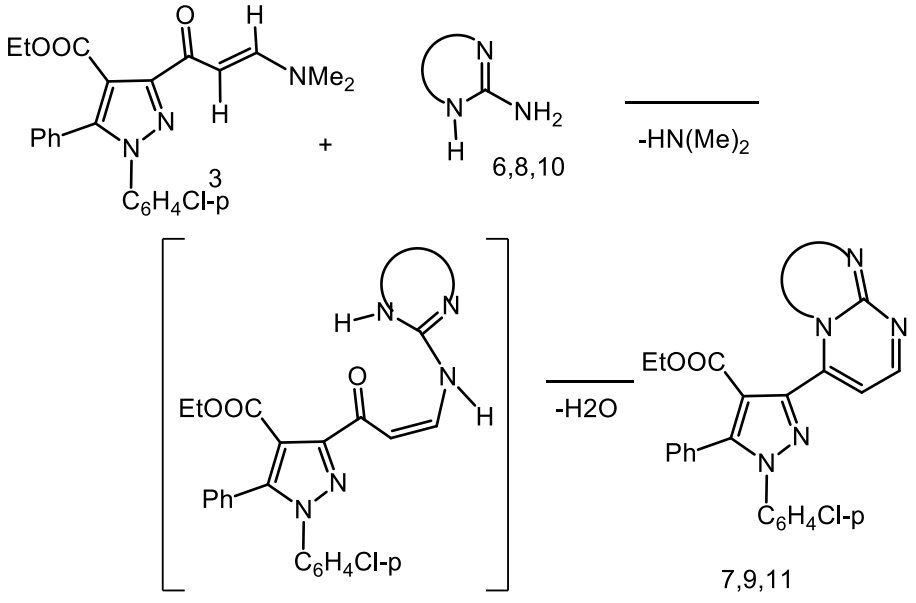


Scheme 2

The reactivity of the enaminone **3** towards some heterocyclic amines was also examined. Thus, reaction of **3** with 5-amino-1,2,4-triazole **6** in acetic acid under reflux yielded the respective 1,2,4-triazolo[1,5-*a*]pyrimidine derivative **7** (Scheme 3). Similar treatment of **3** with 2-aminobenzimidazole **8** and 5-amino-3-phenylpyrazole **10** under the same reaction conditions afforded the respective benzimidazo[1,2-*a*]pyrimidine and pyrazolo[1,5-*a*]pyrimidine derivatives **9** and **11**, respectively (Scheme 3). To account for the formation of the products **7**, **9** and **11**, it is suggested that the studied reactions started with Michael-type addition of the exocyclic amino group of each the amines used to the activated double bond of **3** followed by *in situ* tandem elimination of dimethylamine and dehydrative cyclization (Scheme 4). The ^{1}H NMR spectrum of each of the products **7**, **9** and **11** revealed two doublets signals in the regions δ 7.53-7.99 and 7.96-8.67 with J = 4.5 *Hz* assignable to the two vicinal protons of the pyrimidine ring residue.[17]

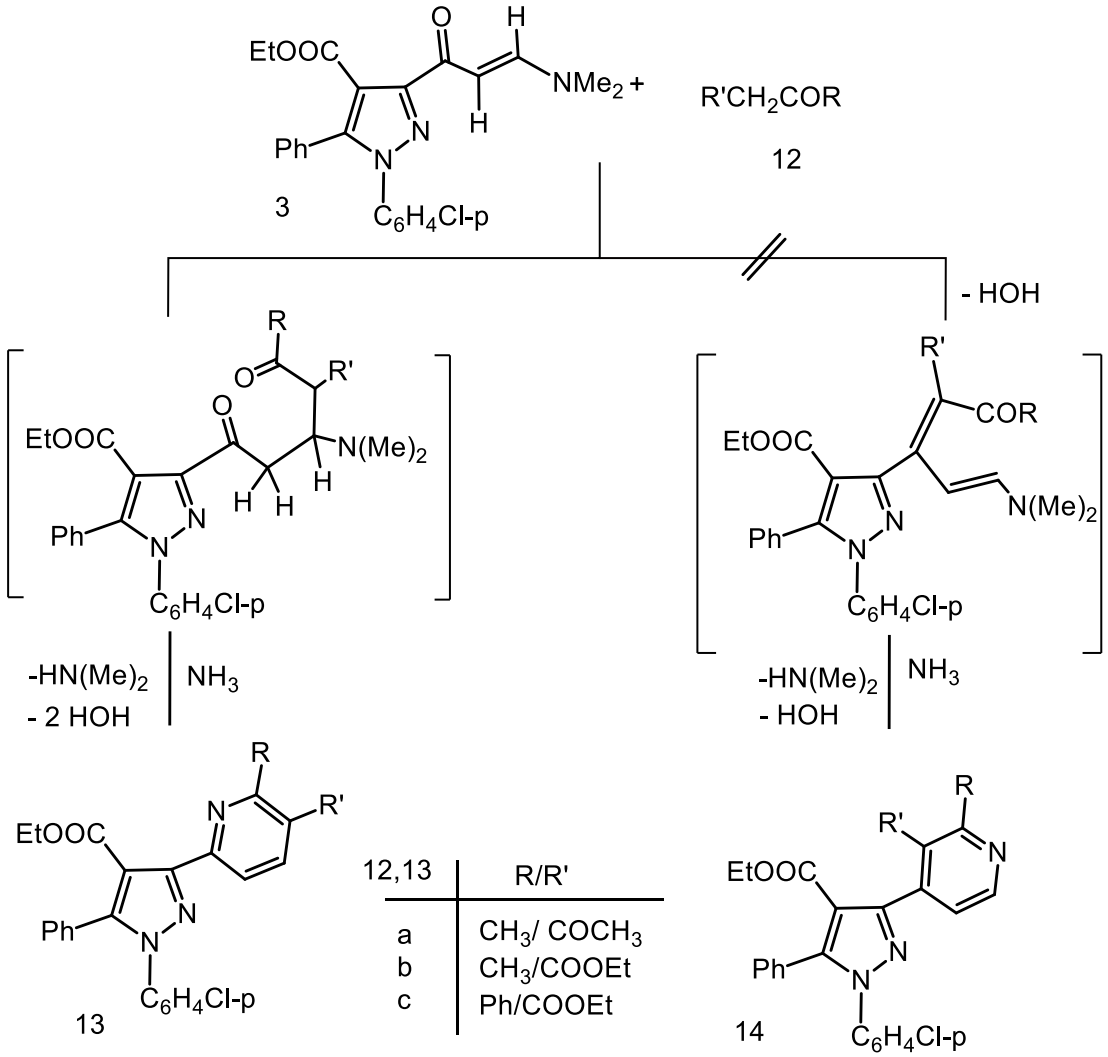


Scheme 3



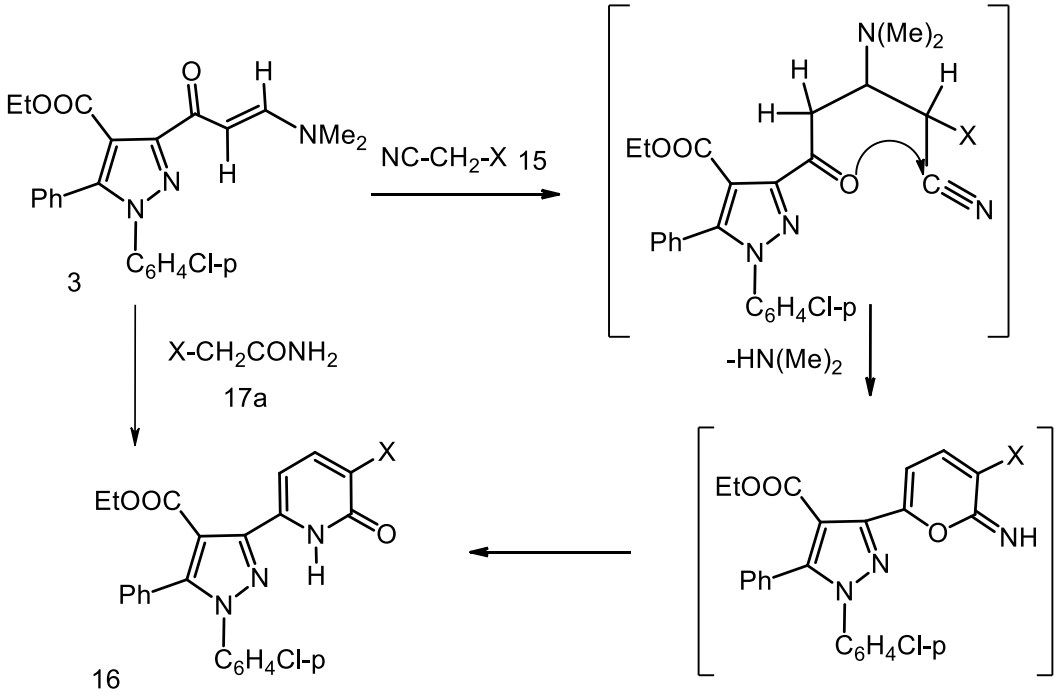
Scheme 4

Next, reactions of the enaminone **3** with some active methylene compounds were examined. Thus, reaction of **3** with acetylacetone **12a**, ethyl acetoacetate **12b** and ethyl benzoylacetate **12c** in acetic acid in the presence of ammonium acetate under reflux yielded products that were identified as 2-(pyrazol-3-yl)pyridine derivatives **13a-c**, respectively (Scheme 5). As depicted in the latter Scheme 5, the formation of **13** seems to start with Michael addition of the active methylene compound **12** to the activated double bond of **3** followed by tandem elimination of dimethylamine and condensation with ammonia. The other possible isomeric structure **14** was discarded on the basis of spectral data. For example, each of the products **13a-c** exhibits in its ^{1}H NMR spectrum two doublet signals in the regions δ 7.86-8.07 and 8.28-8.34 due to pyridine H-3 and H-4, respectively with J = 9 *Hz*. The latter coupling constant value is characteristic for pyridine H-3 and H-4 and much higher than that for H-2 and H-3 (J = 4-6 *Hz*).[18]



Scheme 5

Reactions of **3** with malononitrile **15a** and ethyl cyanoacetate **15b** in refluxing ethanol in the presence of sodium ethoxide afforded products that were identified as **16a** and **16b**, respectively. The assignment of the structures of the latter products was based on their spectral (IR, ^{1}H NMR and MS) and elemental analyses data (see Experimental). Furthermore, the structure of the product **16a** was confirmed by its alternative synthesis by reaction of **3** with cyanoacetamide **17a** under the same reaction conditions (Scheme 6). Here also, it is suggested that the formation of **16** seems to start with Michael addition of the active methylene compound **15** to the activated double bond of **3** followed by tandem cyclization, elimination of dimethylamine and Dimroth type rearrangement of the formed pyran intermediate to give **16** as end product.

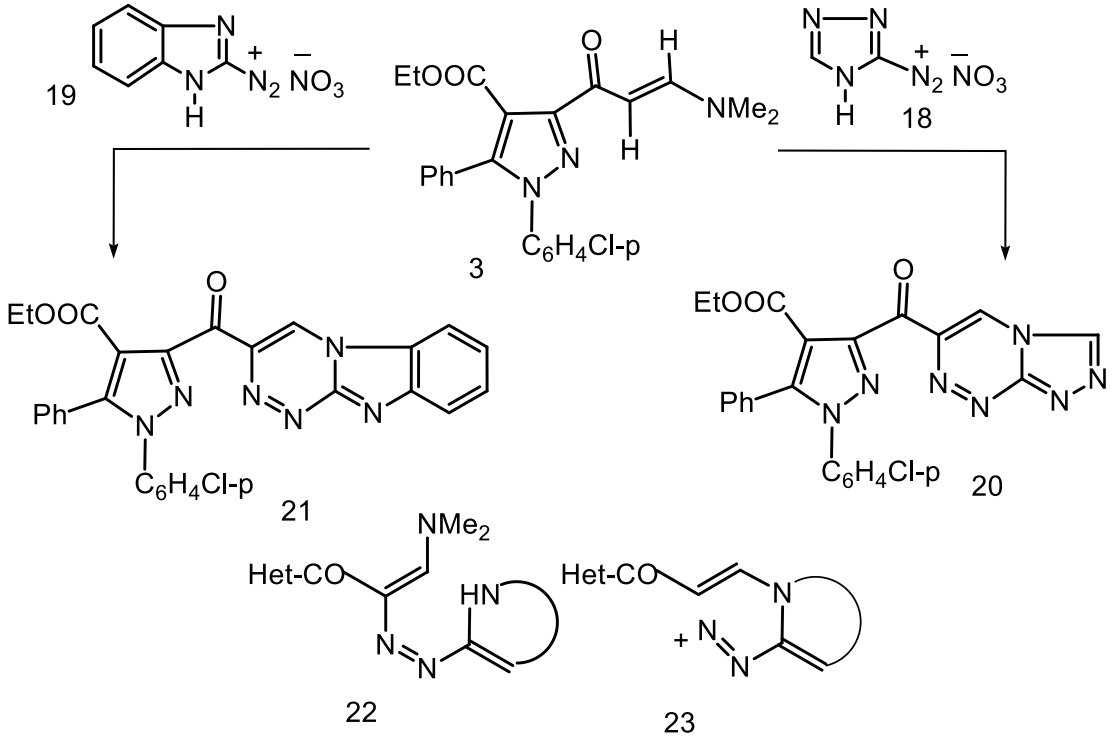


15, 16, 17 : X: a, CN; b, EtOCO

Scheme 6

Finally, reactions of the enaminone **3** with diazotized heterocyclic amines were examined. Thus, reaction of **3** with diazotized 3-amino-1,2,4-triazole **18** and 2-aminobenzimidazole **19** in pyridine at 0-5^{o}C yielded the 3-[(3-ethoxycarbonyl-5-phenyl-1-4-chlorophenyl)pyrazol-3-yl] derivatives of 1,2,4-triazolo[3,4-*c*][1,2,4]triazine and benzoimidazo[2,1-*c*][1,2,4]triazine derivatives **20** and **21**, respectively (Scheme 7). The formation of such products seems to result *via* initial substitution of the α-hydrogen in the enaminone **3** to form the respective azo coupling intermediate **22** which then undergoes intramolecular Michael addition followed by elimination of dimethylamine. Although the reverse sequence of these steps is also possible and will lead to the same products *via* the intermediate **23**, it seems that the former sequence is more plausible as

it involves the formation of the intermediate **22** which is more stable than the intermediate **23**. The structures of both products **20** and **21** were consistent with their elemental and spectral (MS, IR and ^{1}H NMR) analyses (see Experimental).



Scheme 7

Conclusions

The results of the present study indicate that the hydrazonoyl halides and enaminones are useful precursors for the synthesis of different functionalized 3-hetarylpyrazoles. In addition, they indicate that reactions of the studied enaminone are regiospecific as they yielded, in each case, one product in good yield. The compounds prepared are expected to be of pharmacological interest.

Experimental Section

General. All melting points were determined on an electrothermal Gallenkamp apparatus. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H

and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Mercury VXR spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts δ downfield from tetramethylsilane (TMS) as an internal standerd. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Both compounds **2**[16] and **3**[15] were prepared as previously described.

5-[4-Ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-pyrazol-3-yl)]-isoxazole 4. To a solution of **3** (2.11 g, 0.005 mole) in absolute ethanol were added hydroxylamine hydrochloride (0.35 g, 0.005 mole) and anhydrous potassium carbonate (0.5 g, 5 mmole). The reaction mixture was refluxed for 5 h. The solid product was filtered off and crystallized from ethanol to give compound **4** as yellow crystals, yield 1.57g (80 %), mp 150 - 152 ºC, ir: (KBr) ν_{max}/cm^{-1}1709 (C=O). ^{1}H nmr: δ 1.18 (t, *J* = 7 *Hz*, 3H, CH_3), 4.22 (q, *J* = 7 *Hz*, 2H, CH_2), 6.79 (d, *J* = 8 *Hz*, 1H, isoxazol-H), 7.13 (d, *J* = *8Hz*, 1H, isoxazole-H), 7.27 – 7.80 (m, 9H, ArH); ms: m/z (%) 395 (M^++2, 19), 394 (M^++1, 17), 393 (M^+, 42), 379 (51), 348 (100), 339 (21), 214 (54), 111 (78), 77 (30). *Anal*. Calcd. For $C_{21}H_{16}ClN_3O_3$ (393.83) C, 64.05; H, 4.10; N, 10.67. Found C, 64.02; H, 4.17; N, 10.78%.

3-(1*H*-Pyrazol-3-yl)-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carbohydrazide 5. To a solution of **3** (2.11 g, 0.005 mole) in absolute ethanol (20 mL) was added hydrazine monohydrate (5 mL, 0.1 mole). The mixture was refluxed for 5 hours. The precipitate formed upon cooling filtered off and crystallized from ethanol as white solid yield 1.51 g (80 %) mp 262 -264 ºC, ir: (KBr) ν_{max}/cm^{-1} 3414, 3295, 3219 (NH_2, NH), 1646 (C=O). ^{1}H nmr: δ 4.33 (s, 2H, NH_2), 6.67 – 7.37 (m, 9H, ArH), 7.42 (d, *J* = 8*Hz*, 1H, pyrazole-H), 7.53 (d, *J* = 8*Hz*, 1H, pyrazole-H), 10.24 (s, 1H, NH), 13.16 (s, 1H, NH). ^{13}C nmr: δ 109.09, 111.98, 120.58, 126.35, 128.34, 128.72, 129.40, 132.54, 132.69, 134.90, 135.23, 138.74, 139.00, 159.55, 164.24. Ms: m/z (%) 380 (M^++2, 3), 379 (M^++1, 2), 378 (M^+, 31), 347(100), 111 (26), 75 (36), 51 (17). *Anal*. Calcd. For $C_{19}H_{15}ClN_6O$ (378.82) C, 60.24; H, 3.99; N, 22.18. Found C, 60.49; H, 3.87; N, 22.01 %.

Reaction of enaminone 3 with heterocyclic amines. To a solution of **3** (2.11 g, 0.005 mole) in acetic acid (20 ml) was added the appropriate heterocyclic amine (**6**, **8** or **10**) (0.005 mole). The mixture was refluxed for 6 h then cooled. The solid that deposited after cooling was filtered off and crystallized from ethanol-dioxane mixture. The physical constants together with the spectral data of the products **7**, **9** and **11** prepared are depicted below.

5-[1-(4-Chlorophenyl)-5-phenyl-4-ethoxycarbonyl-1*H*-pyrazol-3-yl]-[1,2,4]triazolo[1,5-*a*]pyrimidine 7. Yellow solid, yield 1.67 g (75 %); mp. 95-97 ºC. ir: (KBr) ν_{max}/cm^{-1} 1719 (C=O). ^{1}H nmr: δ 1.05 (t, *J* = 7*Hz*, 3H, CH_3), 4.09(q, J = 7*Hz*, 2H, CH_2), 7.29-7.48 (m, 9H, Ar-H), 7.56 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H), 7.96 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H), 9.22 (s, 1H, triazole H). ms: m/z (%) 446 (M^++2, 11), 445 (M^++1, 10), 444 (M^+, 32), 399 (100), 372 (25), 111 (40), 75 (25). *Anal*. Calcd. For $C_{23}H_{17}ClN_6O_2$ (444.88) C, 62.10; H, 3.85; N, 18.89. Found C, 62.31; H, 3.62; N, 18.97%.

4-[1-(4-Chlorophenyl)-5-phenyl-4-ethoxycarbonyl-1*H*-pyrazol-3-yl]-benzo[4,5]imidazo[1,2-*a*]pyrimidine 9. White solid, yield 2.10 g (85 %); mp. 159-160 ^{o}C. ir: (KBr) ν_{max}/cm^{-1} 1722(C=O). ^{1}H nmr: δ 1.09 (t, *J* = 7*Hz*, 3H, CH_3) 4.14 (q, J = 7*Hz*, 2H, CH_2), 7.31-7.44 (m, 13H, Ar-H), 7.59 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H), 8.26 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H). ms: m/z (%) 495 (M^++2, 9), 494 (M^++1, 9), 493 (M^+, 41), 418 (11), 399 (11), 372 (22), 356 (100), 345 (17), 231 (15), 211 (100), 154 (69), 111 (26), 77 (40), 51 (50). *Anal*. Calcd. For $C_{28}H_{20}ClN_5O_2$ (493.96) C,68.09; H, 4.08; N, 14.18. Found C, 68.00; H, 4.24; N, 14.35%.

5-[1-(4-Chlorophenyl)-5-phenyl-4-ethoxycarbonyl-1*H*-pyrazol-3-yl]-2-phenyl-pyrazolo[1,5-*a*]pyrimidine 11. Pale yellow solid, yield 2.21 g (85 %); mp. 234 -236 ^{o}C. ir: (KBr) ν_{max}/cm^{-1} 1714 (C=O). ^{1}H nmr: δ 1.51 (t, *J* = 7*Hz*, 3H, CH_3) 4.25 (q, J = 7*Hz*, 2H, CH_2), 7.38-7.54 (m, 14H, Ar-H), 7.53 (s, 1H, pyrazole-H), 7.99 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H), 8.67 (d, *J* = 4.5 *Hz*, 1H, pyrimidine-H). ^{13}C nmr: δ 12.81, 60.04, 93.39, 108.07, 115.25, 126.11, 127.22, 127.48, 128.22, 128.29, 128.76, 129.58, 130.41, 130.48, 132.12, 133.30, 137.18, 138.72, 142.83, 145.52, 149.54, 149.87, 154.53, 161.87. ms: m/z (%) 522 (M^++2, 3), 521 (M^++1, 30), 520 (M^+, 54), 447 (100), 111 (8), 77 (29). *Anal*. Calcd. For $C_{30}H_{22}ClN_5O_2$ (520.0) C, 69.30; H, 4.26; N, 13.47. Found C, 69.04; H, 4.61; N, 13.74%.

Preparation of compounds 13a-c

To a solution of **3** (2.11 g, 5 mmole) in glacial acetic acid (20 mL) was added the appropriate active methylene compound (acetylacetone **12a** or ethyl acetoacetate **12b** or ethyl benzoylacetate **12c**) (0.005 mole) and ammonium acetate (0.5 g, 6 mmole). The reaction mixture was heated under reflux for 20-30 hours. The reaction was followed by TLC. The reaction mixture poured into cold water, the solid product that precipitated was filtered off and crystallized from ethanol to give the respective product **13**. The compounds **13a-c** prepared together with their physical constant are given bellow.

3-Acetyl-6-[4-ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-pyrazol-3-yl)]-2-methyl-pyridine 13a. White solid, yield 1.95 g (85%); mp 288-290 ^{o}C; ir: (KBr) ν_{max}/cm^{-1} 1710, 1690 (2C=O). ^{1}H nmr: δ 1.37 (t, *J* = 7 *Hz*, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.75 (s, 3H, $COCH_3$), 4.36 (q, *J* = 7 *Hz*, 2H, CH_2), 7.40-7.89 (m, 9H, Ar-H), 7.90 (d, *J* = 9 *Hz*, 1H, pyridine-H), 8.34 (d, *J* = 9 *Hz*, 1H, pyridine-H); ms: m/z (%) 460 (M^++1, 28), 459 (M^+, 18), 445 (71), 414 (79), 389 (36), 372 (57), 167 (25), 111 (96), 77 (93), 75 (100). *Anal.* Calcd. For $C_{26}H_{22}ClN_3O_3$ (459.94) C, 67.90; H, 4.82; N, 9.14. Found. C, 67.67; H, 4.71; N, 9.40%.

3-Ethoxycarbonyl-6-[4-ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-pyrazol-3-yl)]-2-methyl-pyridine 13b.White solid, yield 1.96 g (80 %); mp. 125-126 ^{o}C IR: (KBr) ν_{max}/cm^{-1} 1725, 1720 (2C=O). ^{1}H nmr: δ 1.02 (t, *J* = 7*Hz*, 3H, CH_3), 1.35 (t, *J* = 7*Hz*, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.06 (q, J = 7*Hz*, 2H, CH_2), 4.34 (q, J = 7*Hz*, 2H, CH_2), 7.31-7.51 (m, 9H, Ar-H), 7.86 (d, *J* = 9 *Hz*, 1H, pyridine-H), 8.28 (d, *J* = 9 *Hz*, 1H, pyridine-H). ^{13}C nmr: δ 13.63, 13.99, 24.30, 60.36, 61.0, 114.55, 118.85, 124.35, 127.29, 127.75, 128.37, 129.01, 129.35, 129.77, 132.90, 137.45, 138.80, 144.08, 149.26, 152.29, 158.01, 163.51, 165.71. ms: m/z (%) 491 (M^++1, 9), 490 (M^+, 28), 489 (36), 444 (39), 488 (41), 370 (12), 215 (22), 190 (24), 151 (19), 129 (37), 111 (61),

77 (98), 51 (100). *Anal*. Calcd. For $C_{27}H_{24}ClN_3O_4$ (489.96) C,66.19; H, 4.94; N, 8.58. Found C, 66.32; H, 5.10; N, 8.47%.

3-Ethoxycarbonyl-6-[4-ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-pyrazol-3-yl)]-2-phenyl-pyridine 13c. White solid, yield 2.35g (85 %); mp. 80-81 ^oC. IR: (KBr) ν_{max}/cm^{-1} 1728, 1718 (2C=O). ^1H nmr: δ 1.21 (t, *J* = 7 *Hz*, 3H, CH_3), 1.32 (t, *J* = 7 *Hz*, 3H, CH_3), 4.25 (q, *J* = 7 *Hz*, 4H, $2CH_2$), 4.36 (q, *J* = 7 *Hz*, 4H, $2CH_2$), 7.40-7.52 (m, 14H, Ar-H), 8.07 (d, *J* = 9 *Hz*, 1H, pyridine-H), 8.30 (d, *J* = 9 *Hz*, 1H, pyridine-H). ms: m/z (%) 554 (M^++2, 2), 553 (M^++1, 7), 552 (M^+, 18), 476 (100), 407 (45), 239 (35), 179 (28), 111 (69), 75 (26), 63 (100). *Anal*. Calcd. For $C_{32}H_{26}ClN_3O_4$ (552.03) C, 69.63; H, 4.75; N, 7.61. Found C, 69.57; H, 4.81; N, 7.38%.

Preparation of compounds 16a,b

To compound **3** (2.11 g, 0.005 mole) in solution of sodium ethoxide in ethanol (0.12 g of sodium metal in 20 mL absolute ethanol) was added malononitrile **15a** or ethyl cyanoacetate **15b** (0.005 mole). The reaction mixture was refluxed for 5 h., then poured into ice-cold water. The solution was acidified with HCl (1 M) and the solid that deposited was filtered and crystallized from ethanol to give the respective compounds **16a, b**.

3-Cyano-6-[4-ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)]-pyridin-2(1*H*)-one 16a. Yellow solid, yield 1.89 g (85%); mp 278-280 ^oC. ir: (KBr) ν_{max}/cm^{-1} 3416 (NH), 2223 (CN), 1716, 1643 (2C=O). ^1H nmr: δ 0.93 (t, *J* = 7 *Hz*, 3H, CH_3), 4.11 (q, *J* = 7 *Hz*, 2H, CH_2), 6.91-7.45 (m, 9H, Ar-H), 8.04 (d, *J* = 9 *Hz*, 1H, pyridine-H), 8.60 (d, *J* = 9 *Hz*, 1H, pyridine-H), 12.52 (s, 1H, NH); ^{13}C nmr: δ 13.40, 60.25, 109.75, 117.67, 120.65, 121.52, 124.0, 126.58, 127.71, 128.77, 129.86, 131.00, 131.42, 136.27, 138.28, 139.52, 142.80, 153.91, 162.24, 165.65. ms: m/z (%) 445 (M^++1, 4), 444 (M^+, 9), 356 (100), 312 (11), 270 (12), 77 (32), 51 (26). *Anal*. Calcd. For $C_{24}H_{17}ClN_4O_3$ (444.88) C, 64.80; H, 3.85; N, 12.59. Found. C, 64.50; H, 4.06; N, 12.71%.

3-Ethoxycarbonyl-6-[4-ethoxycarbonyl-1-(4-chlolorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)]-pyridin-2(1*H*)-one 16b. Yellow solid, yield 1.84 g (75 %); mp. 106-107 ^oC. ir: (KBr) ν_{max}/cm^{-1} 3061 (NH), 1723, 1700, 1655(3 C=O). ^1H nmr: δ 1.10 (t, *J* = 7*Hz*, 3H, CH_3), 1.36 (t, *J* = 7*Hz*, 3H, CH_3), 4.08 (q, J = 7*Hz*, 2H, CH_2), 4.20 (q, *J* = 7*Hz*, 2H, CH_2), 7.22-7.65 (m, 9H, Ar-H), 8.19 (d, *J* = 9 *Hz*, 1H, pyridine-H), 8.60 (d, *J* = 9 *Hz*, 1H, pyridine-H), 9.32 (s, 1H, NH). Ms: m/z (%) 493 (M^++1, 6), 492 (M^+, 8), 418 (11), 399 (11), 372 (22), 345 (17), 231 (15), 211 (100), 154 (69), 77 (40), 51 (50). *Anal*. Calcd. For $C_{26}H_{22}ClN_3O_5$ (491.94) C,63.48; H, 4.51; N, 8.54. Found C, 63.28; H, 4.24; N, 8.35%.

Alternative synthesis of compound 16a. To a solution of **3** (2.11 g, 5 mmole) in ethanolic sodium ethoxide solution (0.12 g. 5 mmole of sodium metal in 20 ml absolute ethanol) was added cyanoacetamide **17a** (0.42 g, 5 mmole). The reaction mixture was refluxed for 20 h., and the solid that precipitated was filtered off and washed with water then crystallized from ethanol to give compound **16a** which was found identical in all respects with that compound produced from reaction of compound **3** with malononitrile.

Coupling of enaminone 3 with diazonium salts of heteroamines

A solution of enaminone **3** (2.11 g, 0.005 mole) in pyridine (20 mL) was cooled in an ice bath at 0-5°C while being stirred. To the resulting cold solution was added portionwise a cold solution (0-5°C) of the appropriate diazonium salt of 3-amino-1,2,4-triazole **18** or 2-amino-benzoimidazole **19** prepared as usual by diazotizing the corresponding heterocyclic amine (5 mmole) in nitric acid (6M, 3ml) with sodium nitrite (0.35g, 5mmole) in water (5ml). After all the diazonium salt solution was added, the mixture was stirred for further 30 min. while cooling in an ice-bath. The reaction mixture was then left in a refrigerator for three days. The solid that precipitated was filtered off, washed with water, dried and finally crystallized from ethanol to give product **20** or **21** respectively.

6-[1-(4-Chlorophenyl)-5-Phenyl-4-ethoxycarbonyl-1*H*-pyrazol-3-carbonyl]-[1,2,4]triazolo [3,4-*c*][1,2,4]triazine 20. Yellow solid, yield 2.01 g (85%), mp. 75-76°C; ir: (KBr) ν_{max}/cm^{-1}1719, 1629 (2 C=O). ^{1}H nmr: δ 1.20 (t, *J* = 7*Hz*, 3H, CH_3), 4.22 (q, J = 7*Hz*, 2H, CH_2), 6.80-7.72 (m, 9H, Ar-H), 8.04 (s, 1H, pyrimidine-H), 8.77 (s, 1H, triazole-H); ^{13}C nmr: δ 12.79, 60.06, 110.36, 112.19, 120.74, 126.46, 128.75, 129.44, 130.91, 135.69, 136.64, 139.28, 142.82, 144.57, 150.09, 150.33, 156.75, 162.30, 188.91. ms: m/z (%) 475 (M^++2, 5), 474(M^++1, 4), 473 (M^+, 12), 444 (3), 214 (100), 111 (27), 77 (13). *Anal.* calcd. for $C_{23}H_{16}ClN_7O_3$ (473.88) C, 58.30; H, 3.40; N, 20.69. Found: C, 58.35; H, 3.03; N, 20.72%.

3-[1-(4-Chlorophenyl)-5-Phenyl-4-ethoxycarbonyl-1*H*-pyrazol-3-carbonyl]-benzo[4,5]imidazo[2,1-*c*][1,2,4]triazine 21. White solid, yield 2.09g (80%), mp. 190-192°C; ir: (KBr) ν_{max}/cm^{-1} 1722 (C=O). ^{1}H nmr: δ 1.19 (t, *J* = 7*Hz*, 3H, CH_3), 4.02 (q, *J* = 7*Hz*, 2H, CH_2), 7.24-7.92 (m, 13H, Ar-H), 8.62 (s, 1H, triazine-H); ms: m/z (%) 522 (M^+, 1), 423 (11), 406 (21), 360 (47), 214 (27), 111 (27), 98 (100), 77 (14). *Anal*. calcd. for $C_{28}H_{19}ClN_6O_3$ (522.96) C,64.31; H, 3.66; N, 16.07. Found: C,64.05; H, 3.38; N, 16.28%.

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