Site-Selectivity in the reaction of hydrazine hydrate with 3,4'-Bis-(functionalized carbonyl)-4,3'-bis(pyrazolyl)ketones. Synthesis of 4-(pyrazol-3-yl)-2H-pyrazolo[3,4-d]-pyridazines

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Abstract

Reaction of hydrazine hydrate with 3,4-bis-(functionalized carbonyl)-4,3-bis(pyrazolyl)ketones proceeds regioselectively affording the corresponding 4-(pyrazol-3-yl)-2H-pyrazolo[3,4-d]pyridazine derivatives in high yields. The structures of the products were determined by spectroscopic and elemental analyses and supported by comparison with the possible isomers prepared by an independent route.

Keywords: Hydrazonoyl halides, enaminones, pyrazoles, pyrazolopyridazines

Introduction

We\(^1\) and others\(^2\) have reported that vicinal 3,4-di-(functionalized carbonyl)pyrazoles 1 react with hydrazines to give the respective pyrazolo[3,4-d]pyridazines 2 (Figure 1). Also, in conjunction with our continued studies on the chemistry of hydrazonoyl halides,\(^3\)-\(^13\) we reported the synthesis of several 3,4'-bis(functionalized-carbonyl)-4,3'-bis(pyrazolyl) ketones of type 3 (Figure 1).\(^14,15\)

We have now studied the site-selectivity of the condensation between hydrazine hydrate and functionalized tricarbonyl compounds 3 which theoretically can lead to 4-(pyrazol-3-yl)-2H-pyrazolo[3,4-d]pyridazines 4 and/or 7-(pyrazol-4-yl)-2H-pyrazolo[3,4-d]pyridazines 5 (Figure 1). These structures are of possible biological interest since they contain both the pyrazole motif present in pharmaceuticals such as Sildenafil (Viagra),\(^16\) Ionazlac\(^17\) and Difenamizole\(^18\) and since several pyrazolo[3,4-d]pyridazine derivatives exhibit antibacterial and antifungal activities.\(^19\)
Results and Discussion

The synthetic strategy adopted in this work for synthesis of the target compounds 9-14 is depicted in Scheme 1. The required enaminone precursors 7(8) were prepared as previously described from our laboratory.\textsuperscript{14,20} Reaction of the hydrazonoyl halides 6A-C with the enaminone 7 in benzene in the presence of triethylamine gave, in each case, one isolable product as evidenced by TLC analysis. Both mass spectra and elemental analysis data of the isolated products from these reactions were consistent with the structures 9-11 (Scheme 1). Similar reactions of the enaminone 8 with each of 6A-C under the same reaction conditions furnished the products 12-14, respectively (Scheme 1). The physical properties of the products 9 and 12-14 were consistent with those reported in literature.\textsuperscript{14,15} The structures of the new products 10 and 11 were established on the basis of their spectroscopic (IR, MS, \textsuperscript{1}H-NMR) and elemental analyses (see Experimental). For example, while the IR spectrum of the compound 10 exhibited three CO bands at $\nu$ 1726, 1670 and 1640 cm\textsuperscript{-1}, the spectrum of compound 11 revealed an NH band at $\nu$ 3430 and three CO bands at $\nu$ 1692, 1670 and 1640 cm\textsuperscript{-1}. Also, the \textsuperscript{1}H NMR spectrum of compound 10 revealed, in addition to the aromatic proton signals, a characteristic singlet signal at $\delta$ 9.23 assignable to the pyrazole-CH proton. The \textsuperscript{1}H NMR spectrum of compound 11 exhibited two characteristic signals at $\delta$ 9.28 and 10.6 assignable to the pyrazole-CH and amide NH protons, respectively.
Scheme 1

Reaction of compound 9 with hydrazine hydrate in refluxing EtOH yielded a product the spectroscopic (IR, MS, $^1$H NMR) and elemental analysis data (see Experimental) for which were consistent with structure 15. Thus, the mass spectrum showed a molecular ion peak at $m/z$ 500 and the IR spectrum displayed one carbonyl absorption band at $\nu$ 1712 cm$^{-1}$ attributed to the ester carbonyl group. The $^1$H NMR spectrum showed, in addition to the aromatic proton signals, signals at $\delta$ 1.06 (t), 4.16 (q) and 2.26 (s) revealing the presence of CH$_3$CH$_2$OCO and CH$_3$ groups. Based on these data, the other possible structure 16 was discarded (Scheme 2). This conclusion is further confirmed by our finding that compound 15 was different from a sample of 16 prepared by an independent route as depicted in Scheme 6.

Similar reaction of hydrazine hydrate with each of 10 (R=EtO) and 11 (R=PhNH) was found to give in both cases one and the same product that proved to be 17 (Scheme 3). The assigned structure 17 was consistent with its spectroscopic (IR, Mass and $^1$H NMR) and elemental analysis data (see Experimental). The other possible structures 18A (R=EtO) and 18B (R=PhNH) were thus discarded. This conclusion is also supported by our finding that the isolated compound 17 was different from compound 18A (R = EtO) which was prepared by an independent route as outlined in Scheme 6 (see Experimental).
Also, refluxing 12 with hydrazine hydrate in EtOH yielded a single product that was identified, on the basis of its spectroscopic data (IR, MS, and $^1$H NMR) and elemental analysis, as 4-[(1,5-diphenyl-4-benzoyl-pyrazol-3-yl)]-1-phenyl-7-methylpyrazolo[3,4-d]pyridazine 19 (Scheme 4).
Similar reaction of each of the compounds 13 (R = EtO) and 14 (PhNH) with hydrazine hydrate under the same conditions gave in both cases one and the same product that was identified as 21 (Scheme 5). For example, its $^1$H NMR spectrum revealed a broad singlet (D$_2$O-exchangeable) at $\delta$ 12.9 due to the pyridazine-NH proton. This NH group gave an absorption band at 3148 cm$^{-1}$ in the IR spectrum of 21. The other isomeric structure 22 was thus discarded.

To provide conclusive evidence for the assigned structures for the products isolated from reaction of the pyrazole derivatives 9-14 with hydrazine and in turn the site selectivity in the studied reactions, the two products 15 and 17, taken as examples of the series prepared, were compared with authentic samples of their isomers, 16 and 18A, respectively prepared by unambiguous routes as depicted in Scheme 6. Thus, reaction of hydrazine hydrate with the pyrazole derivative 23 in refluxing EtOH gave a product that was identified as 24 (Scheme 6) on the basis of its spectra (IR, $^1$H NMR and MS) and elemental analysis (see Experimental). Reaction of 24 with DMFDMA gave the enamine 25. Treatment of the latter with each of the hydrazonoyl chlorides 6A and 6B in refluxing dry dioxane in the presence of triethylamine yielded the two products 16 and 18A, respectively (Scheme 6), which were found to be different from their respective isomers 15 (Scheme 2) and 17 (Scheme 3).
Scheme 5

Scheme 6

6B = EtOOC-C(=N)NHPh
6A = MeCO(=N)NHPh
The foregoing results provide unambiguous evidence that the studied reactions are site selective. The observed site-selectivity in the studied reactions can be rationalized in terms of the difference in electrophilicity of the carbonyl groups involved. In general, in a given 3,4-disubstituted pyrazole derivative having two functionalized carbonyl groups at the 3- and 4-positions, the former group is expected to be more electron deficient than the latter. This is because the C=N moiety is more electron-withdrawing than the C=C moiety. On this basis, in the studied reactions, hydrazine is expected to condense preferentially with the two C=O groups at 3 and 3'-sites in the compounds 9-14 to give the products 15, 17, 19 and 21 as end products, respectively (Schemes 2 and 3).

Conclusions

Reaction of hydrazine hydrate with various functionalized tricarbonyl heterocycles proved to be site selective. The reaction provides a convenient method for synthesis of various 4-(pyrazol-3-yl)-2H-pyrazolo[3,4-d]pyridazine derivatives.

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 NMR spectra were recorded on a Varian Mercury VXR-300 MHz spectrometer and the chemical shifts $\delta$ downfield from tetramethylsilane (TMS) as an internal standard. 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 the hydrazonoyl chlorides 6A-C and the enaminones 7 and 8 were prepared as previously described. 14, 20

Preparation of 4-[1,5-diphenyl-4-substituted-1H-pyrazole-3-carbonyl]-1-aryl-3-substituted-1H-pyrazoles 9-14. General procedure

To a stirred solution of the appropriate hydrazonoyl halide 6 (5 mmol) and the enaminone 7 (1.94 mmol) in dry benzene (30 mL), was added triethylamine (0.5 ml) and the mixture was refluxed for 20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with MeOH. The solid product so formed was filtered off, washed with water, and dried. Recrystallization from EtOH afforded the corresponding 4-[1,5-diphenyl-4-ethoxycarbonyl-1H-pyrazole-3-carbonyl]-1-aryl-3-substituted-1H-pyrazoles 9-11.
When the above procedure was repeated using the enaminone in lieu of 7, the respective 4-[1,5-diphenyl-4-benzoyl-1H-pyrazole-3-carbonyl]-1-aryl-3-substituted-1H-pyrazoles 12-14 were obtained. The products 9-14 together with their physical properties are listed below.

**Ethyl 3-(3-acetyl-1-phenyl-1H-pyrazole-4-carbonyl)-1,5-diphenyl-pyrazole-4-carboxylate (9).** Yellow crystals, (1.89 g, 75% yield), mp 110-12 °C (Lit mp 110 °C).

**Ethyl 4-[1,5-Diphenyl-4-ethoxy carbonyl-1H-pyrazole-3-carbonyl]-1-phenyl-1H-pyrazole-3-carboxylate (10).** Yellow crystals, (2.13 g, 80% yield), mp 72-74 °C; IR (KBr) ν_m_ / cm^-1 1726, 1670, 1640 (C=O); ^1^H NMR (DMSO-d_6) δ 1.08 (t, J = 7 Hz, 6H, OCH_2CH_3), 4.15 (q, J = 7 Hz, 4H, 2 OCH_2CH_3), 7.24-7.95 (m, 15H, Ar-H), 9.23 (s, 1H, pyrazole); MS m/z (%) 534 (M^+, 1), 180 (23), 138 (24), 110 (32), 77 (100). Anal. Calcd. for C_{31}H_{26}N_{4}O_{5} (534.56): C, 69.65; H, 4.90; N, 12.12%. Found: C, 69.80; H, 4.99 ; N, 12.12%.

**4-[1,5-Diphenyl-4-benzoyl-1H-pyrazole-3-carbonyl]-1-phenyl-1H-pyrazole-3-carboxamidine (11).** Yellow solid, (1.74 g, 60% yield), mp 110 °C; IR (KBr) ν_m_ / cm^-1 3430 NH), 1692, 1670, 1640 (C=O); ^1^H NMR (DMSO-d_6) δ 1.02 (t, J = 7 Hz, 3H, OCH_2CH_3), 4.06 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.11-8.01 (m, 20H, Ar-H), 9.28 (s, 1H, pyrazole), 10.68 (s, 1H, CONH-); MS m/z (%) 579 (M^+, 1), 97 (17), 91 (48), 77 (100), 64 (61). Anal. Calcd. for C_{35}H_{27}N_{5}O_{4} (581.62): C, 72.28; H, 4.68; N, 12.04. Found: C, 72.39 ; H, 4.80 ; N, 12.12%.

**4-[1,5-Diphenyl-4-benzoyl-1H-pyrazole-3-carbonyl]-1-phenyl-3-acetyl-1H-pyrazole (12).** This compound was obtained as pale yellow crystals, (yield 2.01 g, 75%), m.p. 150 °C (Lit mp. 150-152 °C).

**Ethyl 4-[1,5-diphenyl-4-benzoyl-1H-pyrazole-3-carbonyl]-1-phenyl-1H-pyrazole-3-carboxylate (13).** This compound was obtained as pale orange crystals, (yield 2.12, 75%), mp 108 °C, (Lit mp. 105-107 °C).

**4-[1,5-diphenyl-4-benzoyl-1H-pyrazole-3-carbonyl]-1-phenyl-1H-pyrazole-3-carboxanilide (14).** This compound was obtained as yellow crystals, (2.29 g, yield 72%), mp. 122 °C (Lit mp. 120-122 °C).

**Reaction of hydrazine hydrate with the compounds 9-14. General method**

A mixture of the pyrazole derivative 9 (1.0 g, 2 mmol) and hydrazine hydrate (10 ml) in absolute EtOH was heated at reflux for 10 h and the reaction mixture was then cooled. The solid that precipitated was filtered off and crystallized from EtOH to give 15.

When the above procedure was repeated using 10 or 11 each in place of 9, it yielded in both cases only one product namely 17.

Also, reaction of hydrazine with 12 yielded the product 19. Reaction with hydrazine of either 13 or 14 following the same procedure gave the product 21, respectively.

**Ethyl 3-(2-phenyl-7-methyl-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1,5-diphenyl-pyrazole-4-carboxylate (15).** White solid, 1.5 g (60% yield), mp. 296-298 °C (EtOH/dioxane); IR(KBr) ν_m_ / cm^-1 1684 (C=O); ^1^H NMR (DMSO-d_6): δ 1.04 (t, J = 7 Hz, 3H, CH_3-CH_2O), 2.88 (s, 3H, CH_3), 4.15 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.29-7.53 (m, 15H, ArH), 8.75 (s, 1H, pyrazole-H). MS m/z (%) 502 (M^+ +2, 4), 500 (M^+ , 0.58), 486 (19), 470 (27), 455 (19), 178 (18), 76 (83), 63 (24),
Ethyl 3-(2-phenyl-7-oxo-6H,7H-pyrazolo[3,4-d]pyridazin-4-yl)-1,5-diphenyl-pyrazole-4-carboxylate (17). Pale yellow solid, 1.5 g (60% yield), mp. 170-180 °C (EtOH); IR(KBr) ν max / cm⁻¹ 3426 (NH), 1689, 1650 (C=O); ¹H NMR (DMSO-d6): δ 7.46 (m, 10H, ArH), 7.81 (d, J = 13 Hz, 1H, pyrazole-H), 7.34-7.25 (m, 7H, ArH), 6.18 (s, 1H, pyrazole-H), 4.65 (q, J = 7 Hz, 2H, OCH₂), 2.24 (s, 3H, CH₃), 1.28 (t, J = 7 Hz, 3H, CH₃). MS m/z (%) 502 (M⁺, 35), 478 (100), 458 (11), 448 (19), 438 (29), 430 (30), 404 (14), 398 (22), 390 (15), 180 (20), 104 (27), 77 (100), 50 (17). Anal. Calcd. For C₃₃H₂₄N₆O₃ (532.58): C, 76.68; H, 4.54; N, 15.78. Found : C, 76.69; H, 4.65; N, 15.83.

4-(1,5-Diphenyl-4-benzoyl-pyrazol-3-yl)-2-phenyl-7-methyl-2H-pyrazolo-[3,4-d]pyridazine (19). Pale orange solid, 0.53 g (50% yield), mp. 148-150 °C (EtOH); IR(KBr) ν max / cm⁻¹ 3450 (NH), 1689, 1660 (C=O); ¹H NMR (DMSO-d6): δ 7.25-7.65 (m, 20H, ArH), 9.45 (s, 1H, pyrazole-H). MS m/z (%) 532 (M⁺, 10), 518 (33), 504 (17), 514 (16), 481 (19), 464 (17), 448 (13), 438 (30), 398 (22), 390 (15), 404 (14), 180 (20), 104 (15), 92 (12), 77 (100), 50 (24). Anal. Calcd. For C₃₃H₂₂N₆O (532.61): C, 76.68; H, 4.41; N, 15.72. Found : C, 76.40; H, 4.53; N, 15.79.

Synthesis of 7-methyl-2,3-diphenyl-4-oxo-2H,5H-pyrazolo[3,4-d]pyridazine (24). A mixture of compound 23 (1.67 g, 5 mmol) and hydrazine hydrate (5 ml) in absolute EtOH (30 ml) was heated at reflux for 10 h and the mixture was then cooled. The solid that precipitated was filtered off and crystallized from EtOH to compound 24 as white solid, 1.50 g (64% yield), mp. 260 °C (EtOH); IR(KBr) ν max / cm⁻¹ 3119 (NH), 1502 (C=O), 1502 (C=O); ¹H NMR (DMSO-d6): δ 7.43-7.64 (m, 10H, ArH), 6.94 (s, 1H, pyrazole-H), 4.05 (q, J = 7 Hz, 2H, OCH₂), 2.34 (s, 3H, CH₃), 1.28 (t, J = 7 Hz, 3H, CH₃). MS m/z (%) 301 (M⁺, 1.5), 506 (14), 139 (11), 77 (100). Anal. Calcd. For C₁₉H₁₄N₄O (302.34): C, 71.51; H, 4.67; N, 18.53. Found : C, 71.60; H, 4.70; N, 18.65.

Synthesis of 7-(β-dimethylaminovinyl)-2,3-diphenyl-4-oxo-2H,5H-pyrazolo[3,4-d]pyridazine enamine (25). A mixture of compound 24 (0.66 g, 2.1 mmol) and dimethylformamide dimethyl acetal (2 g) was heated at reflux for 50 h, then left to cool then MeOH was added to the cold mixture. The resulting solid was collected by filtration, washed with MeOH, dried and finally crystallized from EtOH to give the enamine 25 as yellow solid, 1.50 g (80% yield), mp. 158 °C (EtOH); IR(KBr) ν max / cm⁻¹ 3450 (NH), 1660 (C=O); ¹H NMR (DMSO-d6): δ 3.21 (s, 6H, N(CH₃)₂), 5.66 (d, J = 13 Hz, 1H COCH=CH), 7.34-7.74 (m, 10H, ArH), 7.8 (d, J = 13 Hz, -CH=CHN), 11.95 (s, 1H, NH). MS m/z (%) 357 (M⁺, 0.05), 315 (100), 288 (11), 180 (16), 139 (16), 114 (12), 76 (45). Anal. Calcd. For C₂₁H₁₉N₅O (357.41): C, 70.57; H, 5.36; N, 19.59. Found : C, 70.45; H, 5.42; N, 19.68.
Synthesis of 16 and 18A. General method
To a stirred solution of the enamine 25 (0.36 g, 1 mmol) and the hydrazonoyl chloride 6A (0.196 g, 1 mol) in dry 1,4-dioxane (20 ml), triethylamine (0.2 ml) was added and the mixture was heated at reflux for 20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure and the residue was triturated with MeOH. The solid product, so formed, was collected by filtration and crystallized from EtOH to give compound 16.

When the above procedure was repeated using ethyl N-phenylhydrazonochloro-acetate 6B in place of the hydrazonoyl chloride 6A, the product 18A was produced. The physical constants of both products 16 and 18A are given below.

7-(1-Phenyl-3-acetyl-pyrazol-4-yl)-2,3-diphenyl-4-oxo-2H,5H-pyrazolo[3,4-d]pyridazine (16). Pale yellow solid, 0.27 g (78% yield), mp. 244-246 °C (EtOH); IR(KBr) ν_max / cm⁻¹: 1674, 1663 (C=O); ¹H NMR (DMSO-d₆): δ 2.73 (s, 3H, CH₃), 7.31-7.51 (m, 15H, ArH), 8.04 (s, 1H, pyrazole-H), 11.99 (s, 1H, NH). MS m/z (%): 472 (M⁺, 0.11), 506 (14), 301 (20), 139 (19), 114 (15), 102 (16), 90 (10), 77 (100), 64 (14); Anal. Calcd. For C₂₈H₂₀N₆O₂ (472.51): C, 71.18; H, 4.27; N, 17.79. Found : C, 71.30; H, 4.40; N, 17.86.

7-(1-Phenyl-3-ethoxycarbonyl-pyrazol-4-yl)-2,3-diphenyl-4-oxo-2H,5H-pyrazolo[3,4-d]pyridazine (18A). Pale yellow solid, 1.50 g (60% yield), mp. 212-214 °C (EtOH); IR(KBr) ν_max / cm⁻¹: 3426 (NH), 1710, 1660 (C=O); ¹H NMR (DMSO-d₆): δ 1.41 (t, J = 7 Hz, 3H, CH₂CH₂O), 4.15 (q, J = 7 Hz, 2H, OCH₂CH₃), 7.26-7.46 (m, 15H, ArH), 9.19 (s, 1H, pyrazole-H), 12.05 (s, 1H, NH). MS m/z (%): 502 (M⁺, 0.66), 301 (29), 458 (11), 179 (23), 139 (17), 118 (30), 140 (66), 91 (33), 76 (75), 56 (100), 45 (57); Anal. Calcd. For C₂₉H₂₂N₆O₃ (502.54): C, 69.31; H, 4.41; N, 16.72. Found : C, 69.40; H, 4.50; N, 16.76.

References