Synthesis of some new 2,6-bis pyridines functionalized with tetra-substituted pyrazole heterocycles

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.775

Abstract
Several new tetra-substituted pyrazoles attached to pyridine nucleus at positions 2 and 6 were synthesized from the reactions of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) with different series of hydrazonoyl chlorides including; C-acetyl-N-aryl-hydrazonoyl chlorides (3a-c) and (C-ethoxycarbonyl)-N-aryl-hydrazonoyl chlorides (12a-c). The structures of the synthesized products were established on the basis of their elemental analysis and spectral data in addition to, the chemical behavior of the reaction products with hydrazine hydrate to afford the corresponding pyrazolo[4,3-d]pyridazine derivative.

Keywords: β-Keto esters, 2,6-bis pyridine- pyrazole, pyrazolo[4,3-d]pyridazine

Introduction

Several compounds containing heterocycles incorporating pyridine nucleus were found to possess interesting pharmaceutical applications.1-4 For example, several 2-pyridone derivatives such milirinone are cardiotonic agent and has potential HIV-1 specific transcriptase inhibitor.5,6 Other applications of pyridines used as agrochemicals: insecticides, herbicides and fungicides.7 On the other hand, various pyrazole derivatives were found to possess interesting pharmacological activities that include antirheumatic, anti-inflammatory, antipyretic and analgesic properties.8-10 In view of these observations and in continuation of our interest in the synthesis of 2,6-disubstituted pyridines for different applications,11-15 we considered it attractive to synthesize some poly substituted pyrazoles incorporated into the 2,6-pyridine moiety using 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) as starting material.
Results and Discussion

Firstly, We have prepared 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) by Claisen condensation of dimethyl pyridine-2,6-dicarboxylate ester (1) with the ethyl acetate using our procedure to synthesize pyridine-2,6-bis-(3-oxopropanenitrile)\textsuperscript{11} with excellent yields (91\%) that are more than the reported methods\textsuperscript{16} (Scheme 1).

![Scheme 1](image)

We have investigated the reactivity of compound 2 towards a variety of hydrazonoyl chlorides. Thus, Treatment of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) with C-acetyl-N-aryl-hydrazonoyl chlorides (3a-c) in absolute ethanol containing sodium ethoxide, yielded, in each case, only one isolable product. The identities of the isolated products were assigned as 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1H-pyrazol-5-yl)pyridine (5a-c) on the basis of their elemental analysis and spectral data (Scheme 2). For example; The IR spectra of compounds 5a-c showed, in each case, the presence of tow carbonyl stretching bands near 1730 and 1690 cm\textsuperscript{-1} corresponding to ester and acetyl carbonyl groups, respectively. The \textsuperscript{1}H NMR spectrum of 5a taken as an example of the series synthesized, displayed triplet signals at \( \delta \) 1.15 , quartet signals at \( \delta \) 4.21 (\( J \) 7.2 Hz) corresponding to CH\(_3\) and CH\(_2\) of the ester group, respectively and a singlet signal at \( \delta \) 2.26 due to CH\(_3\) of acetyl groups. Additionally there are multiplets at \( \delta \) 7.15-7.43 and \( \delta \) 7.57-8.13 due to aromatic and pyridine protons, respectively. The presence of the ester group in the IR and NMR spectra of the isolated products supported the formation of structure 5.

Compounds 5a-c is assumed to be formed via the carbanion attacks the hydrazonoyl chlorides to give the open chain intermediate hydrazones (4a-c) followed by intramolecular cyclization through loss of water molecules (route A) (Scheme 3). Although no attempt was made to isolate or identify the reaction intermediate, the possibilities of formation of nitrilimine intermediate (8a-c) from dehydrochlorination of the hydrazonoyl chlorides (3a-c) by the carbanion are excluded (route B), because if nitrilimine (8) was formed, it might dimerize to afford tetrazine (9) as presented in scheme 3. On the other hand, we have excludeed the reaction of hydrazonoyl halide with sodium ethoxide firstly, because we have applied the reaction sequence as follow: firstly we added compound 2 to equal amount of NaOEt and left for 1/2 h that led to the formation of sodium salt of compound 2 followed by the addition of the hydrazonoyl chloride.
The possibility of formation of 6a-c is excluded on the basis of the spectral data and the chemical behavior of the reaction product 5a as example with hydrazine hydrate. The corresponding pyrazolo[4,3-d]pyridazine derivative 10 was obtained by the reaction of 5a with an excess of hydrazine upon refluxing in ethanol for 5h (Scheme 4). Treatment of 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-phenyl-1H-pyrazol-5-yl) (5a) with phenyl hydrazine in refluxing EtOH afforded a single product identified as 2,6-bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1H-pyrazol-5-yl)pyridine (11). The formation of compound 11 is assumed to proceed via condensation of the un-substituted nitrogen atom of phenyl hydrazine with the carbonyl function of the acetyl group and the reaction has stopped at this stage and didn’t undergoes intramolecular cyclization may be due to the steric hindrance effect of the two terminals phenyl groups of the phenyl hydrazine (Scheme 4).
Scheme 3

Scheme 4
Also we have extended our strategy to study the reactivity of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) towards (C-ethoxycarbonyl)-N-arylhydrazonoyl chlorides (12a-c). Treatment of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) with C-ethoxycarbonyl)-N-arylhydrazonoyl chlorides (12a-c) in absolute ethanol containing sodium ethoxide, yielded, in each case, only one isolable product. The identities of the isolated products were assigned as 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1H-pyrazol-5-yl)pyridine (13a-c) on the basis of their elemental analysis and spectral data (Scheme 5). The IR spectra of compounds 13a-c showed, in each case, the presence of tow carbonyl stretching bands near 1730 cm⁻¹ corresponding to two ester groups [see Exp. Part]. The ¹H NMR spectrum of 13a taken as example, displayed triplet signals at δ 1.13 and 1.40 in addition to, quartet signals at δ 4.13 (J 7.2 Hz) and 4.43 (J 7.2 Hz) corresponding to CH₃ and CH₂ of the ester group, respectively. Additionally there are multiplets at δ 7.07-7.30 and δ 7.35-8.10 due to aromatic and pyridine protons, respectively. The mass spectrum of compound 13a revealed a peak at m/z 651 corresponding to its molecular ion peak.

Finally, 2,6-bis(3,4-(diethoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl)pyridine (13a) condensed with hydrazine hydrate, in refluxing EtOH and afforded the pyrazolo[4,3-d]pyridazine derivative 14 the structure of the later product was established on the basis of its elemental analysis and spectral data (Scheme 5).

![Scheme 5]

**Experimental Section**

**General.** All melting points were measured on a Gallenkamp melting point apparatus (Weiss Gallenkamp, London, UK). The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam
The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). $^1$H spectra were run at 300 MHz and $^{13}$C spectra were run at 75.46 MHz in deuterated chloroform (CDCl$_3$) or dimethyl sulfoxide (DMSO-$d_6$). Chemical shifts are given in parts per million and were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu) at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt and recorded on Elementar-Vario EL (Germany) automatic analyzer.

Preparation of starting materials
We have prepared 2,6-bis(ethoxycarbonyl-acetyl)pyridine (2) by Claisen condensation of diethyl pyridine-2,6-dicarboxylate ester (1) with ethyl acetate in dry toluene, using NaH as a base at room temperature, and the experimental data of the product were as reported.16 2-oxo-$N$-arylp propanehydrazonoyl chlorides (3a-c) and ethyl 2-(2-aryldihydrazono)-2-chloroacetate derivatives (12a-c) were prepared following the procedures reported in the literature.17,18

General procedure for the reactions of pyridine-2,6-bis(1-ethoxycarbonyl-propane-1,3-dione) (2) with the hydrazonoyl halide derivatives (3a-c) and (12a-c). 2,6-Bis(ethoxycarbonyl-acetyl)pyridine (2) (0.73 g, 2 mmol) was added to a stirred solution of sodium ethoxide [prepared from Na metal (0.11 g) and absolute ethanol (20 mL)]. After 30 min, the appropriate hydrazonoyl halide 3a-c and 12a-c, (4 mmol) was added and the reaction mixture was stirred at room temperature for additional 7-13 h. The formed solid products were collected by filtration, washed with EtOH, dried and finally recrystallized from the appropriate solvent, to afford the corresponding 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1H-pyrazol-5-yl) pyridine (5a-c) and 2,6-bis(4-(diethoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl)pyridine (13a-c) derivatives, respectively.

2,6-Bis(4-(ethoxycarbonyl)-3-acetyl-1-phenyl-1H-pyrazol-5-yl)pyridine (5a). Yield (82 %); pale yellow crystals (EtOH); IR (KBr): $\nu$ 1732, 1694 (2C=O) cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 1.15 (t, 6H, 2CH$_3$, $J$ 7.2 Hz), 2.62 (s, 6H, 2CH$_3$), 4.21 (q, 4H, 2CH$_2$, $J$ 7.2 Hz), 7.15-7.43 (m, 10H, Ar-H), 7.57-8.02 (t, 1H, pyridine-H), 8.13 (d, 2H, pyridine-H). $^{13}$C NMR (CDCl$_3$): $\delta$ 13.7, 23.21, 63.2, 117.3, 120.0, 121.3, 122.31, 126.14, 129.2, 139.1, 141.4, 145.2, 156.5, 168.11, 185.2. MS m/z (%): 591 [M$^+$] (37), 544 (100), 499 (22), 431 (17), 388 (23), 252 (26), 77 (79). Analysis Calcd for C$_{33}$H$_{29}$N$_5$O$_6$ (591.61): C, 67.00; H, 4.94; N, 11.84. Found: C, 66.97; H, 4.97; N, 11.84. Analysis Calcd for C$_{33}$H$_{29}$N$_5$O$_6$ (591.61): C, 67.00; H, 4.94; N, 11.84. Found: C, 66.97; H, 4.97; N, 11.84.
2,6-Bis(4-(ethoxycarbonyl)-3-acetyl-(4-chlorophenyl)-1H-pyrazol-5-yl)pyridine (5c). Yield (86%); pale yellow crystals (EtOH/dioxane); mp: 198-199 °C. IR (KBr): ν 1731, 1698 (2C=O) cm⁻¹. 1H NMR (CDCl₃): δ 1.10 (t, 6H, 2CH₃), 2.71 (s, 6H, 2CH₃), 4.11 (q, 4H, 2CH₂), δ 7.17-7.39 (m, 8H, Ar-H), 7.61-8.01 (t, 1H, pyridine-H), 8.15 (d, 2H, pyridine-H). 13C NMR (CDCl₃): δ 14.2, 25.23, 61.22, 116.13, 120.11, 121.23, 125.31, 126.44, 130.2, 137.1, 142.40, 146.12, 155.15, 168.11, 188.21. MS m/z (%): 660 [M+] (5), 644 (23), 586 (31), 324 (15), 291 (32), 263 (5), 152 (100), 111 (75), 77 (40). Analysis Calcd for C₃₃H₂₇Cl₂N₅O₆ (660.5): C, 60.01; H, 4.12; N, 10.60. Found: C, 60.21; H, 4.29; N, 10.75.

2,6-Bis(4,5-dihydro-7-methyl-4-oxo-2-phenyl-2H-pyrazolo[4,3-d]pyridazin-3-yl) pyridine (10). Hydrazine hydrate 80% (3 mL) was added to a solution of compound 5a (0.6 g, 1 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 9 h, concentrated in vacuum, and cooled. The precipitate obtained was filtered, washed with EtOH, dried and finally recrystallized from ethanol to afford pale yellow crystals of compound 2,6-bis(4,5-dihydro-7-methyl-4-oxo-2-phenyl-2H-pyrazolo[4,3-d]pyridazin-3-yl) pyridine (10). Yield (80%); colorless crystals (EtOH/dioxane); mp: 298-300 °C. IR (KBr): ν 3191 (NH), 1664 (C=O) cm⁻¹. 1H NMR (CDCl₃): δ 1.24 (s, 6H, 2CH₃), 7.10-7.25 (m, 10H, Ar-H), 7.74-8.00 (t, 1H, pyridine-H), 8.15 (d, 2H, pyridine-H), 9.31 (s, 2H, 2NH). 13C NMR (CDCl₃): δ 20.13, 95.21, 115.21, 120.21, 122.32, 123.21, 125.11, 128.11, 138.11, 139.71, 144.61, 155.21. MS m/z (%): 527 [M+] (79), 469 (17), 264 (15), 77 (100). Analysis Calcd for C₂₉H₂₁N₉O₂ (527.54): C, 66.03; H, 4.01; N, 23.90. Found: C, 66.10; H, 3.97; N, 23.94.

2,6-Bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1H-pyrazol-5-yl)pyridine (11). A mixture of compound 5a (0.6 g, 1 mmol) and phenyl hydrazine (0.22 g, 2 mmol), in EtOH (10 mL), was refluxed for 10 h. The formed solid after cooling was filtered off, washed with EtOH, dried and finally recrystallized from EtOH to afford white powder of 2,6-bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1H-pyrazol-5-yl)pyridine (11). Yield (86%); colorless crystals (EtOH); mp: 230-232 °C. IR (KBr): ν 3298 (NH), 1710 (C=O) cm⁻¹. 1H NMR (CDCl₃): δ 1.04 (t, 6H, 2CH₃), 2.36 (s, 6H, 2CH₃), 4.13 (q, 4H, 2CH₂, J 7.1 Hz), 4.43 (q, 4H, 2CH₂, J 7.3 Hz), 6.84-7.32 (m, 20H, Ar-H), 7.46 (s, 2H, 2NH, D₂O exchangeable), 7.55-7.68 (t, 1H, pyridine-H), 8.01 (d, 2H, pyridine-H). 13C NMR (CDCl₃): δ 12.11, 13.17, 60.11, 63.21, 116.13, 119.2, 120.32, 122.11, 125.41, 126.11, 128.34, 129.11, 130.14, 130.13, 139.56, 144.11, 146.21, 155.11, 163.54. MS m/z (%): 772 (10), 771[M⁺] (3), 724 (10), 679 (63), 663 (31), 599 (100). Analysis Calcd for C₄₅H₄₁N₉O₄ (771.86): C, 70.02; H, 5.35; N, 16.33. Found: C, 70.12; H, 5.45; N, 16.39.

2,6-Bis(3,4-(diethoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl)pyridine (13a). Yield (86%); yellow crystals (EtOH); mp: 118-119 °C. IR (KBr): ν 118-119 (C=O) cm⁻¹. 1H NMR (CDCl₃): δ 1.13 (t, 6H, 2CH₃, J 7.1 Hz), 1.40 (t, 6H, 2CH₃, J 7.3 Hz), 4.13 (q, 4H, 2CH₂, J 7.1 Hz), 4.43 (q, 4H, 2CH₂, J 7.3Hz), 7.07-7.30 (m, 10H, Ar-H), 7.35-7.77 (t, 1H, pyridine-H), 8.10 (d, 2H, pyridine-H). 13C NMR (CDCl₃): δ 12.21, 13.17, 60.11, 63.21, 116.13, 121.0, 122.11,
122.31, 125.44, 128.12, 131.1, 139.61, 144.14, 145.22, 157.15, 166.11, 166.81. MS m/z (%): 651 [M⁺] (25), 77 (100). Analysis Calcd for C₃₅H₃₃N₅O₈ (651.67): C, 64.51; H, 5.10; N, 10.75. Found: C, 64.61; H, 5.17; N, 10.70.

2,6-Bis(3,4-(diethoxycarbonyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl)pyridine (13b). Yield (76%), yellow crystals (EtOH); mp: 214-216 °C; IR (KBr): ν 1725 (2C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.12 (t, 6H, 2CH₃ J=7.4 Hz), 1.51 (t, 6H, 2CH₃ J=7.2 Hz), 2.43 (q, 4H, 2CH₂ J=7.2 Hz), 4.41(q, 4H, 2CH₂, J 7.2 Hz), 6.95-7.29 (m, 8H, Ar-H), 7.87-8.01 (t, 1H, pyridine-H), 8.18 (d, 2H, pyridine-H). MS m/z (%): 679 [M⁺] (5). Analysis Calcd for C₃₇H₃₇N₅O₈ (679.72): C, 65.38; H, 5.49; N, 10.30. Found: C, 65.44; H, 5.37; N, 10.36.

2,6-Bis(3,4-(diethoxycarbonyl)-1-(4-chlorophenyl)-1H-pyrazol-5-yl)pyridine (13c). Yield (86%); pale yellow crystals (EtOH); mp: 141-142 °C. IR (KBr): ν 1727, 1710 (2C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.11 (t, 6H, 2CH₃ J=7.2 Hz), 1.51 (t, 6H, 2CH₃ J=7.3 Hz), 4.23 (q, 4H, 2CH₂ J=7.2 Hz), 4.41 (q, 4H, 2CH₂, J=7.3 Hz), 7.01-7.39 (m, 8H, Ar-H), 7.87-7.98 (t, 1H, pyridine-H), 8.08 (d, 2H, pyridine-H). ¹³C NMR (CDCl₃): δ 12.23, 13.7, 58.22, 63.21, 116.3, 120.0, 121.21, 122.31, 125.14, 129.12, 139.61, 142.14, 145.32, 158.5, 165.11, 166.2. MS m/z (%): 720 [M⁺] (30), 719 (41), 718 (45), 671 (100), 597 (32), 527 (22), 456 (19), 286 (19), 216 (16), 111 (85), 75 (31) Analysis Calcd for C₃₅H₂₁Cl₂N₅O₈ (720.56): C, 58.34; H, 4.34; N, 9.72. Found: C, 58.44; H, 4.37; N, 9.81.

2,6-Bis(4,5,6,7-tetrahydro-4,7-dioxo-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-3-yl)pyridine (14)

This was prepared using the same procedure as that used for compound 10. Yield (69%); Colorless crystals (EtOH); mp: 141-142 °C. IR (KBr): ν 3320, 3172 (2NH), 1640, 1635 (2C=O) cm⁻¹. ¹H NMR (DMSO-d₆): δ 6.88-7.39 (m, 10H, Ar-H), 7.73-7.95 (t, 1H, pyridine-H), 8.12 (d, 2H, pyridine-H), 9.5, 11.3(s, 4H, 4NH, D₂O exchangeable). MS m/z (%): 531 [M⁺] (3). Analysis Calcd for C₂₇H₁₇N₉O₄ (531.48): C, 61.02; H, 3.22; N, 23.72. Found: C, 61.13; H, 3.29; N, 23.51.

Acknowledgements

Financial support for this work was provided by the program of the Science and Technology Development Fund (STDF) - Egypt (project No.170). The program is financed through the Ministry of State for Scientific Research and is administered by Higher Council for Science & Technology. Also, Support part of this work was provided by the EquipME Program. The program is financed through the Egyptian Ministry of State for Scientific Research. Also

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