Synthesis and studies of pyrazolo[3,4-b]piperidin-4-one derivatives

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ABSTRACT
A series of isolated/fused of pyrazole, isoxazole, pyrimidine, pyrimidine thione, spiro thiazolidine and spiro β-lactam derivatives incorporating to 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline have been synthesized by different methods of chemical reactions. The structure assignments of these compounds, based on chemical and spectroscopic evidence were deduced from their IR, 1H NMR, elemental analysis and mass spectrometry.

1. Introduction

Mannich reaction is a versatile reaction and was studied used widely in the synthesis of biologically important molecules and natural products [1-5]. The reaction between benzaldehyde, aniline and cyclohexanone as a model reaction in water in the presence of various amounts of first generation dendrimer [6-14]. It was found that only 2 mol % of the catalyst was required to drive the reaction smoothly to completion. The scope of the dendrimer catalyzed Mannich reaction was extended to other aldehydes, ketones and anilines [15-25]. In a similar manner condensation between other substrates like 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (1) also a short period of time with excellent yield and high purity and non more purification was required. As literature search, it has found that Mannich bases had antimicrobial activities [26,27] besides various activities. The pyrazole nucleus is present in a wide variety of biologically interesting compounds, which exhibit antihypertensive, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative - hypnotic activity [28-31]. Pyrazoles and their derivatives are widely used as pharmaceutical [32,33] and agrochemical agents [34] and consequently a large number of synthetic routes to pyrazoles has been reported [35-38]. However, there is still great interest in finding milder and more efficient methods to these valuable compounds. Amino pyrazole derivative and imino pyrazole derivative undergo various reactions, and as such are excellent and general starting materials for the development of the organic synthesis.

2. Experimental

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 Spectrophotometer KBr disc; 1H NMR spectra were recorded on a Varian EM-390 90 MHz spectrophotometer using DMSO d6 as a solvent and TMS as an internal standard chemical shifts are expressed as ppm units. The microanalysis was performed by the microanalytical centers at Cairo University. Mass spectra were obtained on a Shimadzu GCMS QP 1000 EX mass spectrometer at 70 eV.

2.1. Synthesis of 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (1)

The compound (1) was carried out according to Mohanty et al., 1977 [39].

2.2. Synthesis of 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline (2)

The compound 1 (2 g, 0.004 mol) was dissolved in 20 mL acetic acid with 1 g zinc dust, reflux for 2-3 hr. The hot mixture was filtered to get off zinc dust residue. The filtrate was poured on ice/water with continuous stirring. The solid product was collected by filtration and crystallized from the diluted acetic acid (Scheme 1, Tables 1, 2).

2.3. Synthesis of 3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (3)

A solution of compound 2 (1.78 g, 0.008 mol) in dimethyl formamide was treated with paraformaldehyde (0.25 g, 0.008 mol) and piperidine (0.82 mL, 0.009 mol) and HCl (0.41 mL, 0.01 mol). The reaction mixture was heated under reflux for 3 hr, then left to cool and was poured into ice/water with the stirring. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.4. Synthesis of 5-benzylidene-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (4a), 5-(4-methoxybenzylidene)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (4b), 5-(4-hydroxybenzylidene)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (4c)
A solution of compound 3 (1.17 g, 0.005 mol) was treated with aromatic aldehyde compounds (4a: 0.54 mL, 0.005 mol; 4b: 0.68 mL, 0.005 mol; 4c: 0.61 g, 0.005 mol) in the presence of 3 drops piperidine as a catalyst. The reaction mixture was heated under reflux for 4 hr, then left to cool and was poured on ice/water with stirring. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.5. Synthesis of 1-(8-methyl-3,6-diphenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d]pyridin-2(8aH)-yl)ethanone (5a), 1-(3-(4-methoxyphenyl)-8-methyl-6-phenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d]pyridin-2(8aH)-yl)ethanone (5b), 1-(3-(4-hydroxyphenyl)-8-methyl-6-phenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d]pyridin-2(8aH)-yl)ethanone (5c)

A solution of compounds 4a-c (4a: 0.31 g, 0.001 mol; 4b: 0.34 g, 0.001 mol; 4c: 0.33 g, 0.001 mol) in dimethyl formamide was treated with hydrazine monohydrate (0.05 mL, 0.001 mol) in the presence of 4 drops of acetic acid. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).
2.6. Synthesis of 8-methyl-2,3,6-triphenyl-2,3a,4,5,5a,6,8a-octahydropyrazolo[3,4-b:3',4'-d]pyridine (6a), 3-(4-methoxyphenyl)-8-methyl-2,6-diphenyl-2,3a,4,5,5a,6,8a-octahydropyrazolo[3,4-b:3',4'-d] pyridine (6b), 3-(4-hydroxyphenyl)-8-methyl-2,6-diphenyl-2,3a,4,5,5a,6,8a-octahydropyrazolo[3,4-b:3',4'-d] pyridine (6c)

A solution of compounds 4a-c (4a: 0.31 g, 0.001 mol; 4b: 0.34 g, 0.001 mol; 4c: 0.33 g, 0.001 mol) in dimethyl formamide was treated with phenyl hydrazine (0.1 mL, 0.001 mol) in the presence of piperidine as catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.7. Synthesis of 8-methyl-3,6-diphenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine (7a), 3-(4-methoxyphenyl)-8-methyl-6-phenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine (7b), 3-(4-hydroxyphenyl)-8-methyl-6-phenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine (7c)

A solution of compounds 4a-c (4a: 0.31 g, 0.001 mol; 4b: 0.34 g, 0.001 mol; 4c: 0.33 g, 0.001 mol) in dimethyl formamide was treated with hydroxyl amine hydrochloride (0.1 g, 0.001 mol) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

A solution of compounds 4a-c (4a: 0.31 g, 0.001 mol; 4b: 0.34 g, 0.001 mol; 4c: 0.33 g, 0.001 mol) in dimethyl formamide was treated with urea (0.06 g, 0.001 mol) in the presence of sodium hydride as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.9. Synthesis of 9-methyl-4,7-diphenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3';5,6]pyrido[4,3-d]pyrimidine-2-thione (9a), 4-(4-methoxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3';5,6]pyrido[4,3-d]pyrimidine-2-thione (9b), 4-(4-hydroxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3';5,6]pyrido[4,3-d]pyrimidine-2-thione (9c).

A solution of compounds 4a-c (4a: 0.31 g, 0.001 mol; 4b: 0.34 g, 0.001 mol; 4c: 0.33 g, 0.001 mol) in dimethyl formamide was treated with thiourea (0.076 g, 0.001 mol) in the presence of sodium hydride as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.10. Synthesis of 5-((4-(dimethylamino)phenyl)imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3H)-one (10a). 5-((4-hydroxyphenyl)imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3H)-one (10b). 5-((2-hydroxynaphthalen-1-yl)imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3H)-one (10c).

A solution of compound 10a (0.5 g, 0.002 mol) in dimethyl formamide was treated with nitroso compounds (10a: 0.32 mL, 0.002 mol; 10b: 0.24 g, 0.002 mol; 10c: 0.34 mL, 0.002 mol) in presence of 2 drops of piperidine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 2, Tables 1, 2).

2.11. Synthesis of 3′-(4-(dimethylamino)phenyl)-3-methyl-1-phenyl-1,6,7,7a-tetrahydrospiro[pyrazolo[3,4-b]pyridine-5,2′-thiazolidine]-4′(3′H)-dione (11b), 3′-(4-hydroxyphenyl)-3-methyl-1-phenyl-1,6,7,7a-tetrahydrospiro[pyrazolo[3,4-b]pyridin-5,2′-thiazolidine]-4′(3′H)-dione (11c).

A solution of compounds 10a-c (10a: 0.73 g, 0.002 mol; 10b: 0.66 g, 0.002 mol; 10c: 0.77 g, 0.002 mol) in dimethyl formamide was treated with thiglycidic acid (0.18 mL, 0.002 mol) in presence of 2 drops of piperidine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 2, Tables 1, 2).
2.12. Synthesis of 3-chloro-1-(4-(dimethylamino)phenyl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro[azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione (12a), 3-chloro-1-(4-hydroxyphenyl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro[azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione (12b), 3-chloro-1-(2-hydroxynaphthalen-1-yl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro[azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione (12c)

A solution of compounds 10a-c (10a: 0.73 g, 0.002 mol; 10b: 0.66 g, 0.002 mol; 10c: 0.77 g, 0.002 mol) in dimethyl formamide was treated with chloroacetylchloride (0.23 mL, 0.002 mol) in presence of 2 drops of triethylamine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF Scheme 2, (Tables 1, 2).

3. Results and discussion

By using 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (1) [39], we could synthesize the new compound 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline (2). Scheme 1 which has been considered as starting material for the synthesis of all newly compounds involved in this our research project. The structure of compound 2 was confirmed by IR spectra which revealed the presence of peaks at 3550 cm⁻¹ (NH), at 1670 cm⁻¹ (C=O), at 1600 cm⁻¹ (C=N), also ¹H NMR spectra of compound 2 revealed the presence of signals peaks at 1.4 (s, 3H, CH₃), 2.25 (s, 3H, CH₃CO), 2.65 (s, 1H, CHN), 2.85 (s, 1H, CHCO), 4.20 (br, 2NH, NH₂), and 7.00-8.00 (m, 5H, Ar-H⁺) ppm, the mass spectrum showed the molecular ion peak at m/z = 229.28.

The structure of compound 3 was confirmed by IR spectra which revealed the presence of peaks at 3063 (NH), 1706 (C=O), 1596 (C=N) cm⁻¹, also ¹H NMR spectra of compound 3 revealed the presence of signals peaks at 0.86 (s, 3H, CH₃), 1.24 (d, J = 7.00 Hz, 1H, CHN), 2.16 (t, J = 7.30 Hz, 2H, CH₂O), 2.35 (d, J = 7.00 Hz, H, CHCO), 2.73 (t, J = 7.30 Hz, 2H, CH₂N), 3.37 (s,
1H, NH), and 7.24-7.97 (m, 5H, Ar-H') ppm and the mass spectra showed the molecular ion peak at m/z 228.

The active methylene group in compound 3 condensed with different aromatic aldehydes (benzaldehyde, anisaldehyde and p-hydroxybenzaldehyde) in dimethylformamide under piperidinamide as catalyst to yield the corresponding 5-arylidino-4-piperidinone derivatives (4a-c), respectively (Scheme 1). The structure of compounds 4a-c was confirmed by IR spectrum, 1H NMR spectrum and mass spectra (Tables 1, 2). The activity of oxocyclic C=C conjugated with the α-carbonyl group in compounds 4a-c was determined by the reaction with hydrazines, hydroxylamine hydrochloride, urea and thiourea, to yield the compounds 5-9a-c. (Scheme 1). The isoazoxo piperidinone derivatives (7a and 7b), the piperidine derivatives (8b, c) and the pyrimidine thione derivatives (9a, 9c) were confirmed by micro-analytical and spectroscopic data.

The compounds (10a-c) were prepared by the condensation of 3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-c]pyridin-4(3H)-one (3) with nitroso compounds such as (a) p-nitroso N,N-dimethyl aniline, (b) p-nitroso phenyl and (c) α-nitroso-β-naphthol in the presence of dimethylformamide as solvent under piperidine as catalyst (Scheme 2). When Schiff’s base compounds (10a-c) reacted with thiglycolic acid in dimethylformamide under piperidine as catalyst yielded the corresponding N-thiazole derivatives (11a-c). (Scheme 2). By the reaction of Schiff’s base compounds (10a-c) with chloroacetyl chloride in dimethylformamide under triethylamine as catalyst yielded the corresponding N-β-lactam derivatives (12a-c) (Scheme 2).

4. Conclusion

The present study deals with the development of some synthetic applications of 3-methyl-1-phenyl-5-pyrazolone and is based on the generation of building blocks containing fused isolated and spiro heterocyclic compounds.

References