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Synthesis and characterization of 1-formyl-3-phenyl-5-aryl-2-pyrazolines

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ABSTRACT

Reaction of chalcone derivatives **1**-**4** with hydrazine hydrate in presence of formic acid yielded 2-pyrazolines **5**-**8**. Structures of these compounds have been elucidated by spectroscopic methods; IR, UV, ^{1}H NMR, ^{13}C NMR. Their purities were confirmed by elemental analyses.

1. Introduction

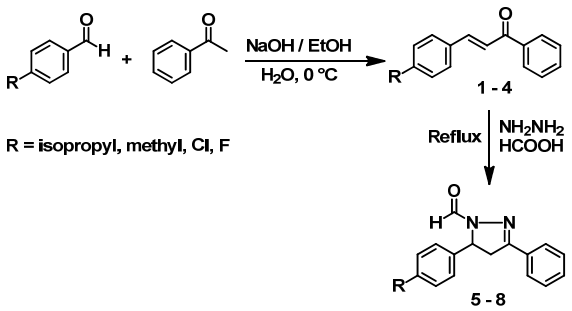
Numerous pyrazolines type compounds have been found to exhibit bioactivities. Pyrazolines derivatives with a phenyl group at the 5-position possess good film-forming properties, exhibit excellent characteristics of blue photoluminescence and electroluminescence [1]. Pyrazolines are also used as optical brighteners and whiteners. They display various biological activities such as antimicrobial [2], antifungal [3], antidepressant [4], immunosuppressive [5], anticonvulsant [6], anti-tumor [7], antiamoebic [8], antibacterial [9] and anti-inflammatory [10] activities. Synthesis of pyrazolines by reaction of *α,β*-unsaturated carbonyl compounds with diazoalkanes [11] or with hydrazine hydrate were reported in the literature [12,13]. *N*-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives having NS donor, their palladium π complexes [14] and hydroxylphenyl pyrazolines have also been synthesised [15]. The reaction of *E*-arylidenes with diazomethane affords *trans*-pyrazolines while *Z*-arylidenes gave *cis*-isomers [16]. 1,3-Dipolar cycloaddition of exocyclic *α,β*-unsaturated ketones with diazomethane has also been studied [17-22].

The present paper deals with the synthesis of four 2-pyrazolines derivatives **5**-**8** from the reaction of chalcone derivatives **1**-**4** and hydrazine hydrate in the presence of formic acid (Scheme 1). The structures of these compounds were established by spectroscopic techniques.

2. Experimental

2.1. Instrumentation

Melting points were determined with a (Bransted/-Electrothermal) apparatus and are uncorrected. UV spectra were recorded on a Perkin-Elmer double beam UV-visible spectrophotometer (λ-25) in ethanol. IR spectra were recorded in KBr pellets on a Perkin-Elmer FT-IR-01 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on an Avance 400 Bruker spectrometer (400.13 MHz in ^{1}H) using TMS as internal standard.



Scheme 1

2.2. Synthesis

2.2.1. Synthesis of chalcones

In a round-bottomed flask, substituted benzaldehydes (50 mmol) and acetophenone (50 mmol) were dissolved in ethanol. The reaction mixture was cooled in an ice bath and a solution of 10 % sodium hydroxide was added dropwise. The mixture was stirred for 4 hours. The yellow precipitate obtained was filtered and washed by HCl (0.1 N) then crystallised from ethanol or ethyl acetate to afford chalcone derivatives **2**,**3**,**4** except for the chalcone **1** that is obtained as yellow oil. The chalcones **1**-**4**

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were afforded with excellent yields (85-91 %). Their melting points are 111, 102 and 113 °C, respectively.

2.2.2. Synthesis of pyrazolines

A mixture of chalcone (10.0 mmol), hydrazine hydrate (50.0 mmol) and formic acid (40 mL) were refluxed for 24 h. The resulting mixture was poured into water (100 mL) and allowed to stand. The precipitate that has formed was separated by filtration, washed with cold water and then crystallized from a mixture of ethanol:toluene (1:1) to yield 2-pyrazolines (Scheme 1).

1-Formyl-3-phenyl-5-(4-isopropylphenyl)-2-pyrazoline (**5**): Pale crystals. Yield: 76%. M.p.: 144-145 °C. UV/VIS (λ_{max}, nm): 407, 337, 325. IR (KBr, cm^{-1}): 1662 (C=O), 1636 (C=N), 1224 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$): 8.96 (d, 1H, *J* = 1.0 Hz, C*H*O), 7.78-7.69 (m, 2H of Ar *H*), 7.48-7.38 (m, 3H of Ar *H*), 7.22-7.14 (m, 4H, symmetrical system, AA'BB' system of the *p*-substituted aromatic), 5.52 (ddd, 1H, *J* = 11.7, 4.8, 1.0 Hz, C*H*), 3.78 (dd, 1H, *J* = 17.7, 11.7 Hz, CH_2), 3.22 (dd, 1H, *J* = 17.7, 4.8 Hz, CH_2), 2.87 (septet, 1H, *J*= 6.9 Hz, C$H(CH_3)_2$), 1.21 (d, 6H, *J* = 6.9 Hz, CH(CH_3)$_2$. ^{13}C NMR (100 MHz, $CDCl_3$): 160.10 (*C*H), 155.85 (*C*), 148.59 (Ar-*C*), 137.94 (Ar-*C*), 130.97 (Ar-*C*), 130.62 (*C*H *para* of Ar H), 128.81 (2 *C*H of Ar-H), 127.08 (2 *C*H of *p*-C_6H_4-*i*-Pr), 126.69 (2 *C*H of Ar H), 125.62 (2 *C*H of *p*-C_6H_4-*i*-Pr), 58.80 (*C*H),42.60 (*C*H_2), 33.77 (*C*H$(CH_3)_2$), 23.92 (CH(*C*H_3)$_2$), 23.90 (CH(*C*H_3)$_2$). Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05, H, 6.89, N, 9.42; found: C, 78.05, H, 6.84, N, 9.42%.

1-Formyl-3-phenyl-5-(4-methylphenyl)-2-pyrazoline (**6**). Yellow crystals. Yield: 80%. M.p.: 148-149 °C. UV/VIS (λ_{max}, nm): 409, 335, 322. IR (KBr, cm^{-1}): 1658 (C=O), 1630 (C=N), 1225 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (d, 1H, *J* = 1.0 Hz, C*H*O), 7.77-7.68 (m, 2H of Ar *H*), 7.47-7.37 (m, 3H of Ar *H*), 7.20-7.12 (s, 4H of the *p*-substituted aromatic), 5.50 (ddd, 1H, *J* = 11.7, 4.8, 1.0 Hz, C*H*), 3.75 (dd, 1H, *J* = 17.7, 11.7 Hz, CH_2), 3.20 (dd, 1H, *J* = 17.7, 4.8 Hz, CH_2), 1.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 160.30 (*C*H), 155.55 (*C*), 148.32 (Ar-*C*), 137.35 (Ar-*C*), 130.85 (Ar-*C*), 130.60 (*C*H *para* of Ar H), 128.73 (2 *C*H of Ar H), 126.90 (2 *C*H of *p*-Ar-Me), 126.69 (2 *C*H of Ar H), 125.62 (*C*H of *p*-Ar-Me), 58.79 (*C*H), 42.58 (*C*H_2), 23.86 (*C*H_3). Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25, H, 4.60, N, 9.83; found: C, 76.98, H, 6.10, N, 10.72%.

1-Formyl-3-phenyl-5-(4-chlorophenyl)-2-pyrazoline (**7**). Pale Yellow crystals. Yield: 87% M.p: 140-141 °C. UV/VIS (λ_{max}, nm): 405, 334, 322. IR (KBr, cm^{-1}): 1660 (C=O), 1632 (C=N), 1135 (C-N), 754 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$): 8.94 (d, 1H, *J* = 1.0 Hz, C*H*O), 7.45-7.42 (m, 2H of Ar *H*), 7.28-7.30 (m, 3H of Ar *H*), 7.18-7.20 (m, 4H of the *p*-C_6H_4-Cl), 5.53 (ddd, 1H, *J* = 11.8, 4.8, 1.0 Hz, C*H*), 3.82 (dd, 1H, *J*= 18.3, 11.8 Hz, CH_2), 3.21 (dd, 1H, *J* = 18.3, 4.8 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 160.15 (*C*H), 155.83 (*C*), 148.48 (Ar-*C*), 137.86 (Ar-*C*), 130.95 (Ar-*C*), 130.59 (*C*H *para* of Ar H), 128.80 (2 *C*H of Ar H), 127.02 (2 *C*H of *p*-C_6H_4-Cl), 126.59 (2 *C*H of Ar H), 125.60 (2 *C*H of *p*-C_6H_4-Cl), 57.70 (*C*H), 42.40 (*C*H_2). Anal. Calcd. for $C_{16}H_{13}N_2OCl$: C, 67.49, H, 4.60, N, 9.84; found: C, 67.27, H, 4.52, N, 9.83%.

1-Formyl-3-phenyl-5-(fluorophenyl)-2-pyrazoline (**8**). Pale crystals. Yield: 76%. M.p.: 142-143 °C. UV/VIS (λ_{max}, nm): 404, 337, 322. IR (KBr, cm^{-1}): 1659 (C=O), 1635 (C=N), 1136 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$): 8.93 (d, 1H, *J* = 1.0 Hz, C*H*O), 7.44-7.41 (m, 2H of Ar-*H*), 7.29-7.27 (m, 3H of Ar-*H*), 7.18-7.14 (m, 4H, of *p*-C_6H_4-F), 5.51 (ddd, 1H, *J* = 11.9, 4.8, 1.0 Hz, C*H*), 3.81 (dd, 1H, *J* = 18.4, 11.9 Hz, CH_2), 3.22 (dd, 1H, *J* = 18.4, 4.8 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 159.30 (*C*H), 154.75 (*C*), 147.69 (Ar-*C*), 138.94 (Ar-*C*), 130.97 (C), 130.62 (*C*H *para* of Ar-H), 128.81 (2 *C*H of *p*-C_6H_4-F), 127.05 (2 *C*H of *p*-C_6H_4-F), 126.65 (2 *C*H of Ar-H), 125.61 (2 *C*H of *p*-C_6H_4-F), 58.79 (*C*H), 41.95 (*C*H_2). Anal. Calcd. for C_{16} $H_{13}N_2OF$: C, 58.90, H, 4.54, N, 9.14, found: C, 60.42, H, 4.56, N, 9.24.

3. Results and discussion

Formation of 2-pyrazolines by the reaction of *α,β*-unsaturated ketones and hydrazine hydrate takes place under various reaction conditions using ethanol [23], acetic acid [24], formic acid [25] or pyridine [26] as solvent. After some preliminary experiments, formic acid was found to be a convenient solvent in our case. Chalcone derivatives **1**-**4** was allowed to react with hydrazine hydrate in hot formic acid to afford 1-formyl-3-phenyl-5-aryl-2-pyrazolines (**5**-**8**) with excellent yields due to the stability of 2-pyrazolines. Structures of compounds **5**-**8** have been elucidated by UV, IR, ^{1}H NMR and ^{13}C NMR (2D, J-mod, HSQC) measurements. Their spectra showed a strong band for the carbonyl group at (1662-1658 cm^{-1}) and a band at (1636-1630 cm^{-1}) for C=N. In the ^{1}H NMR spectra of 2-pyrazolines, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system and a doublet signal at around 8.94 ppm, which refers to the presence of *N*-formyl group. Measured chemical shift and coupling constant values prove the 2-pyrazoline structure. In the ^{13}C NMR spectra of new 1-formyl-3-phenyl-5-aryl-2-pyrazolines, the chemical shift values of carbon atoms C-3 (154-156 ppm), C-4 (41-40 ppm) and C-5 (56-58 ppm) corroborate the 2-pyrazoline structures determined by ^{1}H NMR spectroscopic measurements. ^{13}C NMR chemical shifts of the *N*-formyl group have been assigned at (159-160 ppm). The electronic spectra of the pyrazolines derivatives (studied in the UV region) in ethanol showed three absorption bands at (321-325 nm), (334-337 nm), (404-409 nm) assignable to n-π^*, π-π^* and n-σ^* transitions. Substituted pyrazolines have strong fluorescence in different solvents. They also give excellent fluorescence properties in solid state because the conjugation system contains two nitrogen atoms and one carbon atom while the other carbon atoms are sp^3 hybridized.

4. Conclusion

We have synthesized substituted 3-phenyl-5-aryl-2-pyrazolines by the reaction of hydrazine hydrate and chalcones bearing a *para*-substituted group in their benzaldehyde rings. These new substances allow the investigation of the possible linkage of the 2-pyrazolines to various sites in living organisms in the course of the investigation of their bioactivities. The new 1-formyl-3-phenyl-5-aryl-2-pyrazolines described in this paper are very stable compounds, a property which may render them especially useful substances in drug research.

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