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Synthesis and characterization of novel 1-chloroacetyl derivatives of 2-pyrazolines

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Abstract

Five novel acetyl derivatives of 2-pyrazoline **6–10** were synthesized by the reaction of chalcones **1–5** with hydrazine hydrate and chloroacetic acid in ethanol. The products were purified by silica gel chromatography and characterized by ESI-MS, FT-IR, UV, ^{1}H NMR, ^{13}C NMR and microanalysis.

Keywords: chalcones; chloroacetic acid; chromatography; hydrazine hydrate; pyrazolines.

Introduction

Pyrazoline derivatives are antiangiogenic (Abadi et al., 2003), antifungal (Dawane et al., 2010), antidepressant (Rajendra et al., 2005), immunosuppressive (Lombardino and Otterness, 1981), anticonvulsant (Ozdemir et al., 2007), antitumor (Congiu et al., 2010), antiamoebic (Budakoti et al., 2006), antibacterial (Zitouni et al., 2005), antimycotic (Nauduri and Reddy, 1998), anti-inflammatory (Sharma et al., 2010), antiproliferative (Kostakis et al., 2002) and antiviral (Manfredini et al., 1992), agents. Pyrazolines have also been used extensively as useful synthons in organic synthesis (Azarifar and Ghasemnejad, 2003). The reaction of chalcones and related α,β-unsaturated ketones with hydrazine hydrate has been investigated under various conditions (Mishriky et al., 1996; Pant et al., 2011). Similar derivatives have also been synthesized by the reaction of chromones with hydrazines (Sammour, 1964). The reaction of exocyclic α,β-unsaturated ketones with diphenylmethane has provided spiro-1-pyrazolines as stable products (Toth et al., 1993; Neudeck, 1996; Levai et al., 2004). Carboxylic acid derivatives of 2-pyrazolines have been synthesized by Levai and Jeko (2007). The present paper deals with the synthesis of novel 2-pyrazolines (Scheme 1) by the reaction of chalcones with hydrazine hydrate in the presence of chloroacetic acid.

Results and discussion

Reaction of chalcones, hydrazine hydrate and chloroacetic acid afforded 2-pyrazolines **6–10** in moderate yields. The structures of the products were elucidated by UV, IR, ESI-MS, ^{1}H NMR, ^{13}C NMR and DEPT spectral methods. For example, the IR spectra of compounds **6–10** show a strong band at 1675–1660 cm^{-1} for a carbonyl group. The bands at 1590–1440 cm^{-1} for C=N and 1090–1056 cm^{-1} for C-N moieties are also present. The electronic spectra of 2-pyrazoline in the UV region in methanol show three absorption bands in the regions of 318–291, 285–255 and 242–232 nm assignable to the respective n-π*, π-π* and n-σ* transitions. The ^{1}H NMR and ^{13}C NMR spectra of compounds **6–10** are also highly informative. In summary, a series of 2-pyrazolines bearing chloroacetyl group at the N-1 atom were synthesized and characterized. Biological assays of these compounds are under study.

Experimental

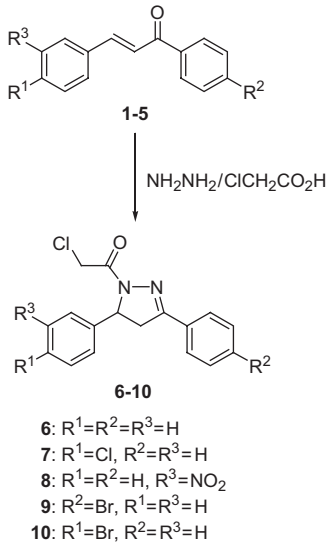
Melting points were determined in open capillary on a Metzer apparatus and are uncorrected. The IR spectra were recorded in KBr pellets on a Perkin Elmer FT-IR-RX-01 spectrophotometer. The UV spectra were recorded on a λ-25 Perkin Elmer UV-Visible spectrophotometer in chloroform. The ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively, on a Brucker DPX spectrometer using TMS as the reference. Chalcones **1–5** were prepared as reported previously (Rojas et al., 2002).

General method for the synthesis of 2-pyrazolines 6–10

A mixture of chalcone **1–5** (15 mmol) and chloroacetic acid (15 mmol) was treated dropwise with a solution of hydrazine hydrate (30 mmol) in ethanol (15 ml). The mixture was heated under reflux for 24 h with constant stirring. Then the resultant solution was cooled and poured onto crushed ice. The product **6–10** was separated by either column or radial chromatography on silica gel eluting with hexane/ethyl acetate (95:5). The fractions were visualized by TLC on Kieselgel 60 F_{254} layer using the same eluent.

1-Chloroacetyl-3,5-diphenyl-2-pyrazoline (6) Pale yellow crystals from ethyl acetate; yield 62%; mp 125–130°C; UV/VIS: λ_{max} 305, 275, 238 nm; IR: ν 1660, 1443, 1142, 750 cm^{-1}. ^{1}H NMR: δ 3.21 (dd, 1H), 3.78 (dd, 1H), 4.64 (s, 2H), 5.56 (dd, 1H), 7.81-7.21 (m, 10H); ^{13}C NMR: δ 164.1, 155.6, 148.7, 131.0-125.8, 60.6, 42.4; ESI-MS: m/z 299 $(M+H)^+$, 321 $(M+Na)^+$, 337 $(M+K)^+$. Anal. Calcd. for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.02; N, 9.38. Found: C, 68.31; H, 5.00; N, 9.35.

1-Chloroacetyl-5-(4-chlorophenyl)-3-phenyl-2-pyrazoline (7) Pale yellow crystals from ethyl acetate; yield 52%; mp 191–193°C; UV/VIS: λ_{max} 291, 255, 235 nm; IR: ν 1668, 1486, 1169, 552, 3315 cm^{-1}; ^{1}H NMR: δ 3.28 (dd, 1H), 3.81 (dd, 1H), 4.68 (s, 2H), 5.58 (dd, 1H), 7.82-7.21 (m, 9H); ^{13}C NMR: δ 160.1, 155.6, 148.6, 130.9-123.9, 60.5, 42.3; ESI-MS: m/z 333 $(M+H)^+$, 355 $(M+Na)^+$, 371 $(M+K)^+$. Anal. Calcd. for $C_{17}H_{14}N_2OCl_2$: C, 61.26; H, 4.20; N, 8.40. Found: C, 61.24; H, 4.17; N, 8.38.



Scheme 1 Synthesis of compounds **6**–**10.**

1-Chloroacetyl-5-(3-nitrophenyl)-3-phenyl-2-pyrazoline (8) Yellow crystals from ethyl acetate; yield 58%; mp 198–199°C. UV/VIS: λ_{max} 296, 268, 240 nm; IR: ν cm^{-1} 1672, 1478, 1180, 754 cm^{-1}; ^1H NMR: δ 3.24 (dd, 1H), 3.80 (dd, 1H), 4.66 (s, 2H), 5.61 (dd, 1H), 7.82-7.23 (m, 9H); ^{13}C NMR: δ 160.1, 155.5, 148.6, 131.8-125.6, 60.6, 42.4; ESI-MS: m/z 344 $(M+H)^+$, 366 $(M+Na)^+$, 382 $(M+K)^+$. Anal. Calcd. for $C_{17}H_{14}N_3O_3Cl$: C, 59.38; H, 4.07; N, 12.22. Found: C, 58.35; H, 4.03; N, 12.20.

1-Chloroacetyl-3-(4-bromophenyl)-5-phenyl-2-pyrazoline (9) Brown crystals from ethyl acetate; yield 62%; mp 211–213°C; UV/VIS: λ_{max} 311, 258, 236 nm; IR: ν 1674, 1490, 1098, 758, 548 cm^{-1}; ^1H NMR: δ 3.26 (dd, 1H), 3.81 (dd, 1H), 4.68 (s, 2H), 5.58 (dd, 1H), 7.82-7.22 (m, 9H); ^{13}C NMR: δ 160.1, 155.4, 148.3, 131.9-123.7, 60.5, 42.3 ($-CH_2$); ESI-MS: m/z 377 $(M+H)^+$, 399 $(M+Na)^+$, 415 $(M+K)^+$. Anal. Calcd. for $C_{17}H_{14}N_2OClBr$: C, 54.18; H, 3.71; N, 7.43. Found: C, 54.15; H, 3.68; N, 7.40.

1-Chloroacetyl-5-(4-bromophenyl)-3-phenyl-2-pyrazoline (10) Brown crystals from ethyl acetate; yield 62%; mp 205–207°C; UV/VIS: λ_{max} 307, 255, 232 nm; IR: ν 1664, 1482, 1091, 765, 546 cm^{-1}; ^1H NMR: δ 3.24 (dd, 1H), 3.79 (dd, 1H), 4.66 (s, 2H), 5.58 (dd, 1H), 7.81-7.22 (m, 9H); ^{13}C NMR: δ 160.1, 155.4, 148.3, 131.9-123.7, 60.5, 42.3; ESI-MS: m/z 377 $(M+H)^+$, 399 $(M+Na)^+$, 415 $(M+K)^+$. Anal. Calcd. for $C_{17}H_{14}N_2OClBr$: C, 54.18; H, 3.71; N, 7.43. Found: C, 54.12; H, 3.68; N, 7.40.

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