European Journal of Chemistry 4 (2) (2013) 176-179

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis of pyrazoline derivatives from the 1,3-dipolar cycloadditions using α,β-unsaturated cyclohexanone derivatives

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ARTICLE INFORMATION

Received: 21 February 2013
Received in revised form: 04 April 2013
Accepted: 05 April 2013
Online: 30 June 2013

KEYWORDS

Acetic acid
Pyrazolines
Spectroscopy
Hydrazine hydrate
1,3-Dipolar cycloadditions
α,β-Unsaturated cyclohexanone derivatives

ABSTRACT

A series of 2-pyrazolines (3a-d) were obtained by reaction 1,3-dipolar cycloadditions of α,β-unsaturated cyclohexanone derivatives (2a-c) with hydrazine hydrate and 4-nitrophenylhydrazine in the presence of acetic acid and ethanol as solvents. The structures of the synthesized compounds were confirmed by spectroscopic methods; IR, ^{1}H and ^{13}C NMR.

1. Introduction

Pyrazoline belongs to a class of five-membered ring compounds having two nitrogen atoms located adjacent to each other [1]. Several pyrazoline derivatives possess important biological activities such as anti-inflammatory [2-4], antidepressant [5-6], antipyretic [7], antibacterial [8-13], antifungal [8,11,14] and antitumoral [15]. Over the years, the structure of pyrazoline [1,16] has received considerable attention. Of particular interest is the use of pyrazolines as synthetic intermediates for preparing cyclopropane [17-19] and pyrazole [1,20-23] derivatives. Moreover pyrazolines have played a crucial role in the development of theory in heterocyclic chemistry and also are extensively useful synthons in organic chemistry [1].

1,3-Dipolar cycloadditions is a general methodology that has been applied both to the synthesis of five-membered heterocyclic compounds such as 2-pyrazolines using α,β-unsaturated ketones as starting materials [1].

The α,β-unsaturated ketones have been attracting much more attention, particularly the α,β-unsaturated derivatives of cyclohexanone, not only due to their intriguing biological activities such as antiangiogenic [24,25], cytotoxicity [26,27], cholesterol-lowering activity [28], use in agrochemicals, pharmaceuticals and perfumes [29], and as liquid crystalline polymer units [30], but also as important precursors for the synthesis of heterocyclic compounds such as pyrazolines. Generally, these compounds are prepared by Claisen-Schmidt condensation from aromatic aldehydes and ketons [31-39].

In this study, we have synthesized a series of pyrazoline derivatives **3a-d** using α,β-unsaturated cyclohexanone derivatives **2a-c** as starting materials (Scheme 1 and 2). The structures of the newly synthesized compounds **2c**, **3a** and **3d** were confirmed by IR and their spectroscopic analyses. Compounds **3b** and **3c**, were synthesized by Kok *et. al.* [40], using another method which was reported in the cited reference. We report also in this paper, reaction of the new α,β-unsaturated ketone **2c** with hydrazine hydrate in hot acetic acid, this reaction produced complex mixture of unidentified products. Bioactivities studies of all synthesized compounds will be the subject of future publication.

2. Experimental

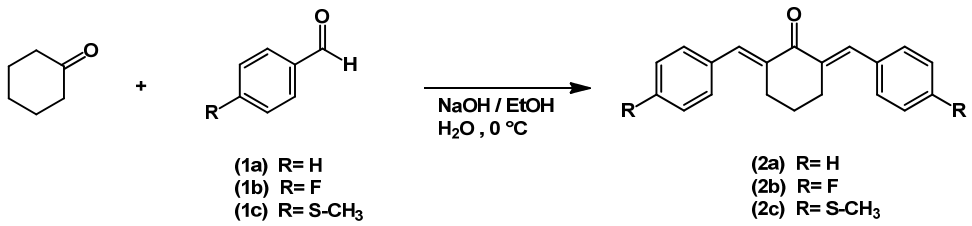
2.1. Instrumentation

Melting points were determined with a (Bransted/-Electrothermal) apparatus and are uncorrected. IR spectra were recorded in KBr pellets on (a Perkin-Elmer FT-IR-01 and a Shimadzu FT-IR-8400S) spectrophotometers. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Advance DRX 400 spectrometer (400.13 MHz for ^{1}H NMR and 100.62 MHz for ^{13}C NMR) and Bruker Advance 250 spectrometer (250.13 MHz for ^{1}H NMR and 62.89 MHz for ^{13}C NMR). Chemical shift values are reported in ppm relative to TMS as internal reference in $CDCl_3$.

2.2. Synthesis

2.2.1. Synthesis of α,β-unsaturated derivatives of cyclohexanone

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.4.2.176-179.757



Scheme 1

A mixture of the aromatic aldehyde (20 mmol, 2 eq.) and cyclohexanone (10 mmol, 1 eq.) were dissolved in 15 mL of ethanol in a simple necked round bottomed flask and stirred for several minutes at 0 °C (ice bath). Into this solution, 10 mL of a 40% NaOH solution in water was then added drop wise over several minutes. The mixture is then allowed to stir at room temperature for approximately 4 h. The yellow solid obtained was filtered and washed with cold water and dried. The product, so-obtained, was crystallized with ethanol to give the desired compounds in good yields (Scheme 1).

2,6-Dibenzylidenecyclohexanone (**2a**): Color: Yellow crystals. Yield: 90% yield. M.p.: 118-119 °C (117-118 °C [41]). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.66-1.83 (m, 2H, CH_2), 2.89-2.95 (m, 4H, 2 CH_2), 7.24-7.48 (m, 10H, Ar-H), 7.80 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 22.8 (CH_2), 28.3 (2 CH_2), 128.2 (4 CH of Ar-H), 128.4 (2 Ar-H), 130.2 (4 CH of Ar-H), 135.8 (2 CH), 135.9 (2 C-Ar), 136.7 (2 C=C), 190.0 (C=O).

2,6-Bis(4-fluorobenzylidene)cyclohexanone (**2b**): Color: Yellow crystals. Yield: 86%. M.p.: 155-156 °C (156-158 °C [37]). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 2.75-1.82 (m, 2H, CH_2), 2.86-2.89 (m, 4H, 2 CH_2), 7.05-7.11 (m, 4H, Ar-H), 7.42-7.46 (m, 4H, Ar-H), 7.74 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 22.9 (CH_2), 28.3 (2 CH_2), 115.5 (d, *J* = 22.1 Hz, 4 CH of Ar-H), 132.0 (d, *J* = 4.0 Hz, 2 Ar-C), 132.3 (d, *J* = 9.0 Hz, 4 CH of Ar-H), 135.7 (d, *J* = 2.0 Hz, 2 CH), 135.8 (2 C=C), 189.9 (C=O).

2,6-Bis(4-(methylthio)benzylidene)cyclohexanone (**2c**). Color: Yellow powder. Yield: 87%. M.p.: 184-185 °C. IR (KBr, ν, cm^{-1}): 2922 (C-H), 1658 (C=O), 1599 (C=C). ^{1}H NMR (400.13 MHz, CD_2Cl_2, δ, ppm): 1.77-1.83 (m, 2H, CH_2), 2.51 (s, 6H, 2 S-CH_3), 2.91-2.94 (m, 4H, 2 CH_2), 7.27 (d, *J* = 8.0 Hz, 4H, Ar H), 7.43 (d, *J* = 8.0 Hz, 4 H, Ar H), 7.69 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 14.6 (2 CH_3), 22.5 (CH_2), 28.1 (2 CH_2), 125.1 (4 CH of Ar H), 130.4 (4 CH of Ar-H), 132.1 (2 Ar-C), 135.3 (2 CH), 135.4 (2 C=C), 139.6 (2 Ar-C), 189.0 (C=O).

2.2.2. Synthesis of pyrazolines

Compound **2a** (3 mmol) was treated with 4-nitrophenylhydrazine (3 mmol) in ethanol (15 mL). The mixture was refluxed for 12 h. A precipitation of a yellow powder **3a** was separated by filtration, and crystallized from ethanol. Compounds **3b** and **3d** were prepared from compound **2b** and **2c** (1.5 mmol), respectively, and hydrazine hydrate (1.5 mmol) in ethanol (12 mL) using the same procedure given for compound **3a**. The products **3b** and **3d** were obtained as yellow and white crystals respectively. Pyrazoline **3c**, a white powder, was prepared from compound **2b** (3 mmol) and hydrazine hydrate (3 mmol) using the same procedure given for compound **3a** but with acid acetic as solvent (Scheme 2).

7-Benzylidene-2-(4-nitrophenyl)-3-phenyl-3,3a,4,5,6,7-hexa hydro-2H-indazole (**3a**): Color: Yellow crystals. Yield: 92%. M.p.: 182 °C. IR (KBr, ν, cm^{-1}): 2949 (C-H), 1595 (C=N), 1500 (C=C), 1560 (N-O), 1382 (N-O), 1045 (C-N). ^{1}H NMR (250.13 MHz, $CDCl_3$, δ, ppm): 1.45-1.55 (m, 1H, C-H), 1.72-1.77 (m, 1H, C-H), 1.95-2.00 (m, 1H, C-H), 2.25 (m, 1H, C-H), 2.45 (m, 1H, C-H), 3.05-3.10 (m, 2H,CH), 4.75 (d, *J* = 10.5 Hz, 1H, N-CH), 7.01 (d, *J* = 9.25 Hz, 2H, ArH), 7.30-7.41 (m, 11H, Ar + =CH). 8.02 (d, *J* = 9.25 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ, ppm): 24.2 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 57.9 (CH), 72.2 (CH), 113.1 (2 CH of Ar-H), 125.4 (2 CH of Ar-H), 125.6 (2 CH of Ar-H), 127.4 (CH of Ar-H), 127.9 (CH of Ar-H), 128.0 (CH=C), 128.3 (2 CH of Ar-H), 129.5 (2 CH of Ar-H), 129.6 (2 CH of Ar-H), 130.1 (Ar-C), 136.2 (C=C), 139.5 (Ar-C), 140.8 (Ar-C), 150.3 (Ar-C), 156.6 (C=N).

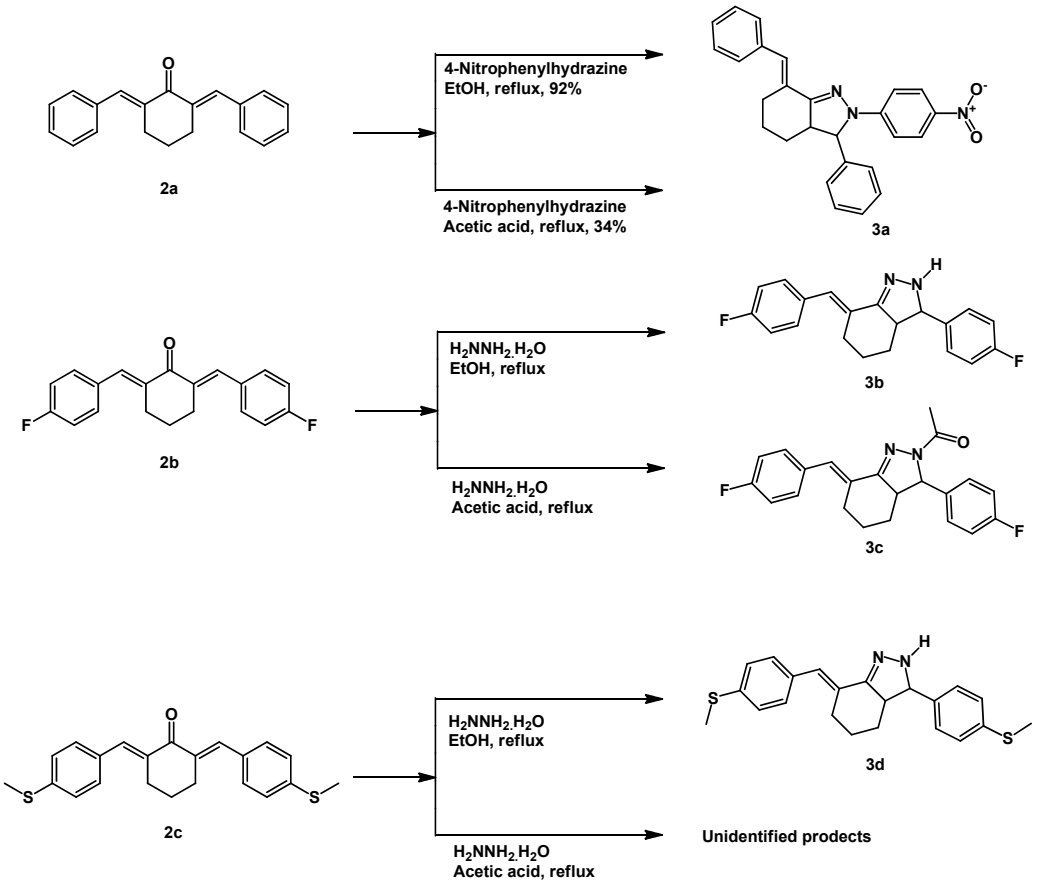
7-(4-Fluorobenzylidene)-3-(4-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H- indazole [40] (**3b**): Color: Pale yellow powder. Yield: 70%. M.p.: 179-181 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.36-1.58 (m, 2H, CH), 1.91-2.06 (m, 2H, CH), 2.40-2.33 (m, 1H, CH), 2.70-2.98 (m, 2H, CH), 4.48 (d, *J*= 12.0 Hz, CH), 7.01-7.47 (m, 10H, 8 Ar-H+ CH=C + N-H).

1-(7-(4-fluorobenzylidene)-3-(4-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-indazol-2-yl) ethanone [40] (**3c**): Color: White powder. Yield: 91%. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.48-1.51 (m, 1H, CH), 1.68-1.72 (m, 1H, CH), 1.94-2.20 (m, 2H, CH), 2.38 (s, 3H, CH_3), 2.38-2.43 (m, 1H, CH), 2.95-3.04 (m, 2H, 2 CH), 4.92 (d, *J*= 8.0 Hz, 1H, CH), 7.03-7.36 (m, 9H, 8 Ar-H + CH=C).

7-(4-(Methylthio)benzylidene)-3-(4-(methylthio)phenyl)-3, 3a,4,5,6,7-hexahydro-2H-indazole (**3d**): Color: White crystals. Yield: 85%. M.p.: 150 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.47-1.54 (m, 2H, C-H), 1.93-2.06 (m, 2H, C-H), 2.43 (m, 1H, C-H), 2.52 (s, 6H, 2 S-CH_3), 2.79 (m, 1H, C-H), 3.02 (m, 1H, C-H), 4.48 (d, *J* = 8.0 Hz, 1H, N-CH), 5.95 (s, 1H, CH=C), 7.18 (s, 1H, N-H) 7.24 -7.44 (m, 8H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 15.6 (S-CH_3), 15.9 (S-CH_3), 24.4 (CH_2), 28.4 (CH_2), 28.6 (CH_2), 53.7 (CH), 72.8 (CH), 126.0 (2 CH of Ar-H), 126.8 (2 CH of Ar-H), 127.6 (2 CH of Ar-H), 127.7 (Ar-C),130.1 (2 CH of Ar-H), 130.6 (CH=C), 133.5 (C=C), 137.2 (Ar-C), 137.5 (Ar-C), 137.8 (Ar-C), 156.7 (C=N).

3. Results and discussion

The α,β-unsaturated cyclohexanone derivatives, **2a-c**, (Scheme 1) were obtained by condensation of cyclohexanone with substituted benzaldehydes, **1a-c**, with excellent yields due to the stability of α,β-unsaturated cyclohexanone derivatives [41]. Compounds **2a** [42] and **2b** [37] were identified by comparing their ^{1}H and^{13}C NMR spectral data with those reported in the cited references. But the new compound **2c** was elucidated by IR, ^{1}H NMR and ^{13}C NMR. In the IR spectrum, a strong band around 1658 cm^{-1} indicates the presence of conjugated carbonyl and a band at 1599 cm^{-1} for (C=C) group. In the ^{1}H NMR spectra, the olefinic protons gave a singlet signal at (7.69 ppm). ^{13}C NMR chemical shifts of the C=O group have been assigned at (189.0 ppm). Pyrazoline **3a** was synthesized by reaction of compound **2a** with 4-nitrophenylhydrazine in the presence of glacial acetic acid in low yield (34%). When the reaction was repeated using ethanol as solvent rather glacial acetic acid, compound **3a** was obtained in high yield (92%) (Scheme 2). Pyrazolines **3b** and **3d** were obtained by reaction of compounds **2b** and **2c** respectively with hydrazine hydrate in ethanol using the same procedure given for compound **3a** [43].



Scheme 2

Compound **2b** was allowed to react with hydrazine hydrate in hot acetic acid to afford pyrazoline derivative **3c** with good yields. Analogous synthesis using compound **2c** with hydrazine hydrate in the presence of glacial acetic acid could not be achieved, formation of a complex mixture of unidentified products was observed. Pyrazolines **3b** and **3c** were synthesized by Kok *et al*. [40], using another method which was reported in the cited reference. For the synthesis of compound 7-(4-fluorobenzylidene)-3-(4-fluorophenyl)-3,3a,4,5,6,7-hexa hydro-2*H*-indazole (**3b**), we have used Claisen-Schmidt condensation [31-39] (Yield: 70%), without catalyst. But Kok et al. have used few drops of acetic acid as catalyst (Yield: 72%). For the synthesis of compound 1-(7-(4-fluorobenzylidene)-3-(4-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-indazol-2-yl) ethanone (**3c**), Kok *et al*. was used a method [40] which contains two steps: Step 1, preparation of 7-(4-fluoro benzylidene)-3-(4-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (**3b**); Step 2, Alkylation of compound **3b**, using pyridine as a solvent, and benzoyl chloride as reagent. As against we have synthesized compound (**3c**) in a single step by the classical 1,3-dipolar cycloadditions [1] using the compound, 6-*bis*(4-fluoro benzylidene)cyclohexanone (**2b**) as substrate, and ethanol as solvent. Compounds **3a** and **3d** were two new pyrazolines characterized by melting points, IR, ^{1}H and ^{13}C NMR spectra. The IR spectra showed a strong band for the (C=N) group at 1595 cm^{-1} and a band at 1500 cm^{-1} for C=C group. In the spectra ^{1}H NMR, the olefinic protons gave a singlet signal at (5.95-7.41 ppm). ^{13}C NMR chemical shifts of the (C=N) group have been assigned at (156.6-156.7 ppm).

4. Conclusion

In conclusion, we have synthesized a series of 2-pyrazolines **3a**-**d** by 1,3-dipolar cycloadditions using α,β-unsaturated cyclohexanone derivatives as starting materials. Pyrazolines **3a** and **3c** are very stable compounds, a property which may render them especially useful substances in drug research. Compounds **3b** and **3d** would be useful as synthetic precursors for preparing various pyrazoline derivatives due to the presence of reactive group (N-H). Bioactivities studies of all synthesized compounds will be reported elsewhere in near future.

Acknowledgements

We gratefully acknowledge Professor Mustafa Bouhenguel director of the Laboratory of Applied Chemistry and Materials Technology of the University of Oum El Bouaghi for his support of this work. We also thank Professor Paul Mosset for bibliographical search.

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