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Facile sonochemical synthesis of novel pyrazolyne derivates at ambient conditions

Dency José Pacheco [a], Luis Prent [a], Jorge Trilleras [a,*], Jairo Quiroga [b]

[a] Grupo de Investigación en Compuestos Heterocíclicos, Programa de Química, Facultad de Ciencias Básicas, Universidad del Atlántico, Km 7 Antigua vía Puerto Colombia, Barranquilla-Atlántico, Colombia
[b] Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A. A 25360 Cali, Colombia

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ABSTRACT

Claisen–Schmidt condensation reaction of 4-acetamidoacetophenone with aromatic aldehydes under ultrasonic irradiation affords acetylaminochalcones (yields: 71–90%) which also under ultrasonic irradiation and in the presence of sodium acetate and acetic acid aqueous undergo facile and clean cyclocondensation with hydrazine to afford 3-(4-acetamidophenyl)-5-(aryl)-1-*H*-pyrazolines. The pyrazolines were obtained in good to excellent yields (81–89%), and were characterized by conventional spectral data. The work-up is simple and the results obtained indicate that, unlike classical heating, ultrasonic irradiation results in higher yields, shorter reaction times (1.5–2.3 h) and milder conditions.

1. Introduction

Chalcones are one of the major classes of natural product with wide spread distribution in nature and food, which have attracted great interest, in addition to their pharmacological activities [1]. They display a wide range of pharmacological properties, including cytotoxity towards cancer cell lines [2], antiviral [3], anti-inflammatory [4], antiulcerative [5], and hepatoprotective chalconas [6]. Chalcones are an-easy-to synthesize template five-, six- and seven-membered heterocyclic compounds [7]. It is therefore not surprising that many synthetic methods have been developed for the preparation of chalcones and heterocycles starting from chalcones precursors that have been tested for their potential applications.

Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds and have attracted interest because of their broad spectrum of biological activities [8] such as antimicrobial [9], antidepressant [10], insecticidal [11], anti-inflammatory [12], antitumor [13] and antinociceptive activities [14]. 2-Pyrazolines are the most frequently studied isomers, and various methods have been worked out for their synthesis. Among them are the reactions of α,β-unsaturated ketones with diazomethane [15] and cycloaddition reactions [16]. The cyclocondensation of chalcones with hydrazines has become one of the most popular methods [17].

On the other hand, recently ultrasound has been utilized to accelerate a wide number of synthetically useful organic reactions. Compared with traditional methods, the procedure is more convenient and can be carried out in higher yields, shorter reaction time or milder conditions [17]. Among the ultrasound-promoted reactions are heterocyclization of suitably functionalized substrates [18], in this sense, recently reported the synthesis assisted by ultrasound of pyrazolines [19] and chalcones, using KOH and KF-Al_2O_3 as catalysts [20]. With this in mind, we decided to direct our efforts towards the synthesis of various pyrazolinic derivatives using the ultrasound-assisted methodology. Our interest in these target heterocycles is stimulated by their close structural relationship to molecules of known biological activity [13,15].

2. Methods

2.1. Apparatus and analysis

Melting points were determined using a Thermo Scientific Fluke 51 II, model IA 9100 melting point apparatus and are reported uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at room temperature on a Bruker Ultra Shield 400 using TMS as internal standard and deuterated chloroform ($CDCl_3$) as solvent. EIMS were run on a Shimadzu GC–MS 2010 spectrometer, which was operating at 70 eV. IR spectra were recorded as KBr pellets on a Shimadzu FTIR-8400 instrument. The ultrasonic irradiation was performed by using a Branson ultrasonic cleaner bath, model 1510, 115v, 1.9 L with mechanical timer (60 min with continuous hold) and heater switch, 47 kHz. The aromatic aldehydes and solvents used, such as, ethanol, dichloromethane, glacial

* Corresponding author. Tel.: +57 5 3599484; fax: +57 5 3599481.
E-mail addresses: dencypacheco@mail.uniatlantico.edu.co (D.J. Pacheco), luisprent@gmail.com (L. Prent), jorgetrilleras@mail.uniatlantico.edu.co (J. Trilleras), jairo.quiroga@correounivalle.edu.co (J. Quiroga).

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acetic acid and ethyl acetate were obtained from Merck Chemical Company. 4-Acetylaminoacetophenone and hydrazine monohydrate were obtained from Aldrich.

2.2. General procedure for the synthesis of 4-acetylaminochalcones 3

A mixture of 4-acetamidoacetophenone (5 mmol), appropriate aromatic aldehyde (5 mmol), KOH (1 mmol) and ethanol (2 mL), was sonicated for 5–20 min in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by TLC using dichlorometane:ethyl acetate (9:1 v/v) as eluent. The reaction mixture was cooled in ice-water bath. The formed precipitate was filtered, washed with cool water and purified by recrystallization from ethanol to give the target compounds in high yields of 71–92%. The spectral data and melting point of compounds **3a**–**c** were consistent with literature values [21].

2.2.1. Compound *3a–c*

(2*E*)-1-(4-acetylaminophenyl)-3-(phenyl)prop-2-enone **3a**: Yield: 71% (lit: 80%); m.p. = 161–163 °C (lit: 161.7–162.2 °C).

(2*E*)-1-(4-acetylaminophenyl)-3-(4-chlorophenyl)prop-2-enone **3b**: Yield = 84% (lit: 79%); m.p. = 215–217 °C (lit: 215–215.7 °C).

(2*E*)-1-(4-acetylaminophenyl)-3-(4-methylphenyl)prop-2-enone **3c**: Yield = 75% (lit: 83%); m.p. = 198–199 °C (lit: 197.5–199 °C).

The authenticity of the products (**3d**–**e**) was established by their ^{1}H NMR, IR, MS data.

2.2.2. Compound *3d*

(2*E*)-1-(4-acetylaminophenyl)-3-(3,4-metilendioxyphenyl)prop-2 -enone **3d**: Yield = 92%; m.p. = 175 °C (dec); FT-IR (ν, cm^{-1}): 3287 (H–NCO, *st*), 1673 (NC═O, *st*), 1598 (–C═O, *st*), 1532 (–C═C, *st*); ^{1}H NMR: δ (ppm), 8.00 (d, J = 8.7 Hz, 2H, H*m*, 1-Aryl), 7.72 (d, J = 15.6 Hz, 1H, Hβ), 7.63 (d, J = 8.6 Hz, 2H, 1-Ar), 7.35 (d, J = 15.5 Hz, 1H, Hα), 7.15 (d, J = 1.5 Hz, 1H, H*o*, 3-Ar), 7.12 (dd, J = 8.03, 1.5 Hz, 1H, H*o*, 3-Ar), 6.84 (d, J = 8.03 Hz, 1H, H*m*, 3-Ar), 6.02 (d, J = 8.0 Hz, 1H, –CH_2), 2.21 (s, 3H, –CH_3). MS: *m*/*z* (%), 309 (100, M$^+$), 308 (18), 267 (20), 145 (25), 120 (30), 89 (20), 43 (50).

2.2.3. Compound *3e*

(2*E*)-1-(4-acetylaminophenyl)-3-(3,4,5-trimetoxyphenyl)prop-2-enone **3e**: Yield = 83%, m.p. = 150 °C (dec); FT-IR (ν, cm^{-1}): 3312 (H–NCO, *st*), 1661 (NC═O, *st*), 1599 (–C═O, *st*), 1535 (–C═C, *st*); ^{1}H NMR: δ (ppm), 7.99 (d, J = 8.5 Hz, 2H, H*m*, 1-Ar), 7.93 (s, 1H, N–H), 7.68 (m, 3H, H*o*, 1-Ar y Hα), 7.39 (d, J = 15.6 Hz, 1H, Hβ), 6.84 (s, 2H, H*o*, 3-Ar), 3.91 (s, 6H, *m* $(OCH_3)_2$), 3.89 (s, 3H, *p* OCH_3), 2.21 (s, 3H, –CH_3). MS: m/z (%), 355 (100, M$^+$), 340 (30), 334 (35), 120 (25), 43 (40).

2.3. General procedure for the synthesis of 3-(4-acetylaminophenyl)-5-(aryl)-1H-pyrazolines *4*

A mixture of respective acetylaminochalcone 3 (1 mmol), hydrazine hydrate (150 mg, 3 mmol) and sodium acetate (24.6 mg, 0.3 mmol) in 3 mL acid acetic–water (2:1), were sonicated for 1.5–2.3 h. The progress of the reaction was monitored by TLC using dichlorometane:ethyl acetate (9:1 v/v) as eluent. The reaction mixture was placed on ice-water. The obtained precipitate was filtered, washed with cool water and purified by recrystallization from ethanol to give the target compounds in high yield. The obtained yields are summarized in Table 1.

2.3.1. Compound *4a*

3-(4-Acetylaminophenyl)-5-(phenyl)-1*H*-pyrazoline **4a**: Yield = 82%, m.p. = (220–223) °C; FT-IR (ν, cm^{-1}): 3309–3062 (H–N amide, N–H pyrazoline, *st*), 1671 (NC═O, *st*), 1598 (C═N, *st*), 1497 (C═C, *st*); ^{1}H NMR: δ (ppm), 7.61 (d, J = 8.3 Hz, 2H, H*m*, 3-Ar), 7.47 (s, 1H, N–H acetylamino),7.45 (s, 1H, N–H pyrazoline), 7.21 (d, 2H, H*o*, phenyl), 7.11 (d, 2H, H*m*, phenyl), 7.01 (d, J = 8.03 Hz, 2H, H*o*, 3-aryl), 6.72 (t, 1H, H*p*, phenyl), 5.18 (dd, J = 12.2, 7.4 Hz, 1H, –CH), 3.75 (dd, J = 16.9, 12.3 Hz, 1H, –CH), 3.05 (dd, J = 17.0, 7.3 Hz, 1H, –CH), 2.11 (s, 3H, –CH_3). MS: *m*/*z* (%), 279 (100, M$^+$), 278 (23), 91 (50), 77 (20), 43 (33).

2.3.2. Compound *4b*

3-(4-Acetylaminophenyl)-5-(4-clorophenyl)-1*H*-pyrazoline **4b**: Yield = 89%, m.p. = 222–223 °C; FT-IR (ν, cm^{-1}): 3297–3039 (H–N amide, N–H pirazoline, st), 1667 (NC═O, *st*), 1596 (C═N, *st*), 1498 (C═C, *st*); ^{1}H NMR: δ (ppm), 8.01 (d, J = 8.78 Hz, 2H, H*m*, 3-Ar), 7.57 (s, 1H, N–H acetylamino), 7.55 (s, 1H, N–H pyrazoline), 7.17–7.39 (m, 4H, 5-Ar), 7.03 (d, J = 8.78 Hz, H*o*, 3-Ar), 5.22 (dd, J = 12.2, 7.2 Hz, 1H, –CH), 3.80 (dd, J = 17.0, 12.3 Hz, 1H, –CH), 3.07 (dd, J = 17.0, 7.2 Hz, 1H, –CH), 2,18 (s, 3H, CH_3). MS: *m*/*z* (%), 313 (100, M$^+$), 278 (20), 91 (60), 77 (20), 43 (95).

2.3.3. Compound *4c*

3-(4-Acetylaminophenyl)-5-(4-methylphenyl)-1*H*-pyrazoline **4c**: Yield = 85%, m.p. = 223.3–225.5 °C; FT-IR (ν, cm^{-1}): 3299–3040 (H–N amide, N–H pyrazoline, *st*), 1667 (NC═O, *st*), 1596 (C═N, *st*), 1498 (C═C, *st*); ^{1}H NMR: δ (ppm), 7.66 (d, J = 8.5 Hz, 2H, H*m*, 3-Ar), 7.52 (s, 1H, N–H acetylamino), 7.50 (s, 1H, N–H pyrazoline), 7.20–7.13 (m, 4H, 5-Ar), 7.07 (d, J = 7.8 Hz, 2H, H*o*, 3-Ar), 5.18 (dd, J = 12.2, 7.4 Hz, 1H, –CH), 3.75 (dd, J = 16.9, 12.3 Hz, 1H, –CH), 3.05 (dd, J = 17.0, 7.3 Hz, 1H, –CH), 2.32 (s, 3H, -CH_3, 5-Ar), 2,17 (s, 3H, –CH_3, acetylamino). MS: *m*/*z* (%), 293 (100, M$^+$), 278 (20), 91 (35), 77 (15), 43 (25).

2.3.4. Compound *4d*

3-(4-Acetylaminophenyl)-5-(3,4-metilendioxyphenyl)-1*H*-pyrazoline *4d*: Yield = 82%, m.p. = 219–221 °C; FT-IR (ν, cm^{-1}): 3306–3058 (H–N amide, N–H pyrazoline, st), 1667 (NC═O, *st*), 1596 (C═N, *st*), 1499 (C═C, *st*); ^{1}H-NMR: δ (ppm), 7.66 (d, J = 8.7 Hz, 2H, H*m*, 3-Ar), 7.52 (s, 1H, N–H acetylamino), 750 (s, 1H, N–H pyrazoline), 7.18 (dd, J = 8.7, 7.3 Hz, 2H, H*o*, 5-Ar), 7.08 (d, J = 8.7 Hz, 2H, H*o* 3-Ar), 6.67 (m, 5H, H*m*, 5-Ar), 5.91 (s, 2H, –CH_2, 5-Ar), 5.15 (dd, J = 12.2, 7.2 Hz, 1H, –CH), 3.75 (dd, J = 17.0, 12.2 Hz, 1H, CH), 3.07 (dd, J = 17.0, 7.2 Hz, 1H, CH), 2.17 (s, 3H, CH_3). MS: *m*/*z* (%), 323 (100, M$^+$), 278 (15), 91 (45), 77 (12), 43 (32).

2.3.5. Compound *4e*

3-(4-Acetylaminophenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazoline **4e**: Yield = 81%, m.p. = 248–249 °C; FT-IR (ν, cm^{-1}): 3344–3042 (H–N amide, N–H pyrazoline, *st*), 1689 (NC═O, *st*), 1596 (C═N, *st*), 1500 (C═C, *st*); ^{1}H NMR: δ (ppm), 7.68 (d, J = 8.42, 2H, H*m*, 3-Ar), 7.53 (s, 1H, N–H acetylamino), 7.51 (s, 1H, N–H pyrazoline), 7.09 (d, 2H, H*o*, 3-Ar), 6.54 (s, 2H, H*o*, 5-Ar), 5.12 (dd, J = 12.2, 7.8 Hz, 1H, –CH), 3.82 (m, 9H, C*m* –OCH_3, 1H, CH_2) 3.12 (dd, J = 17.0, 7.8 Hz, 1H, –CH), 2.18 (s, 3H, CH_3). MS: *m*/*z* (%), 369 (100, M$^+$), 278 (25), 91 (35), 77 (8), 43 (20).

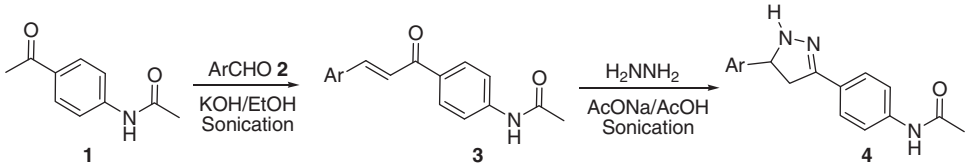
3. Results and discussion

The aim of present study was to synthesize novel 2-pyrazolines with an acetylamino type side-chain, which were synthetized in two steps (Scheme 1). In the first step, the acetylaminochalcones 3 were obtained by Claisen–Schmidt condensation reaction between 4-acetylaminoacetophenone 1 and aromatic aldehydes 2 in ethanol with basic catalysis and under ultrasonic irradiation at room temperature during 5–20 min. Although the yields are similar those reported in the literature for conventional method [21,22], the reaction times were significantly shorter.

Table 1
Synthesized chalcones and pyrazolines: advantage of sonochemical method over conventional method.

	Ar	Compound 3				Compound 4							
		Conventional method		Ultrasonic method		Conventional method		Ultrasonic method					
		Time (h)	% Yield	Time (min)	% Yield	Time (h)	% Yield	1:1 mol ratio		1:2 mol ratio		1:3 mol ratio	
								Time (h)	% Yield	Time (h)	% Yield	Time (h)	% Yield
a	C_6H_5	Overnight[a]	80[a]	20	71	3	70	1.5	70	1.5	75	1.5	82
b	4-ClC_6H_4	Overnight[a]	79[a]	8	84	3	75	2	80	2	83	2	89
c	4-$CH_3C_6H_4$	Overnight[a]	83[a]	17	75	3	75	2	78	2	81	2	85
d	3,4-$(OCH_2O)C_6H_3$	–	–	6	90	3.5	75	2.2	73	2.2	75	2.2	82
e	3,4,5-*tri*-$CH_3OC_6H_2$	–	–	5	83	3.5	75	2.3	75	2.3	78	2.3	81

[a] Time and % yield reaction reported in the literature [21].



Scheme 1. Synthesis of 3-(4-acetylaminophenyl)-5-(aryl)-1*H*-pyrazolines **4** by ultrasonic-assisted.

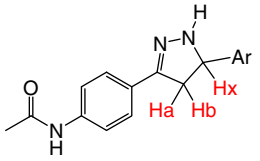


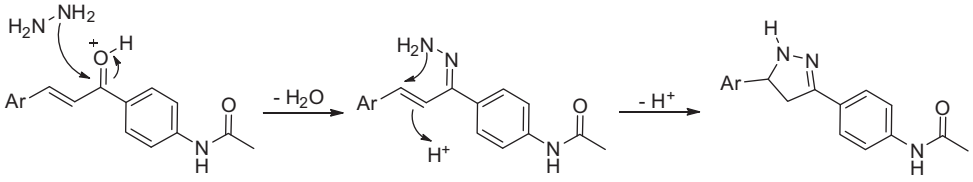
Fig. 1. Structures of 3-(4-acetylaminophenyl)-5-(aryl)-1*H*-pyrazolines **4**.

The reaction time for the conventionally synthesized chalcones was overnight while reaction times used for sonochemically synthesized chalcones were 5–20 min. In the next step, the substituted chalcones were cyclized to 2-pyrazolines using hydrazine monohydrate under ultrasound irradiation. The effect of the reaction conditions on the reaction of chalcones with hydrazine monohydrate under ultrasound irradiation was summarized in (Table 1).

When the molar ratio of chalcones/hydrazine monohydrate was 1:1, the yield of 2-pyrazoline obtained was around 70%. The use of a 1:2, and 1:3 M ratios led to an increase of reaction yield 75% and 82%, respectively (Table 1). The results showed that the optimum molar ratio of chalcones/hydrazine monohydrate was found to be 1:3. In order to verify the effect of ultrasound irradiation, we have performed the reaction of chalcone with hydrazine monohydrate by conventional heating in ethanol for 3.5 h. The yield of 2-pyrazolines was lesser as compared to ultrasonic induced synthesis (Table 1). Unlike literature reports [13b,23], when the same reaction was carried out starting with chalcones in the presence of formic or acetic acid by microwave assisted heating, formation of *N*-formyl or *N*-acetyl derivatives was observed. Our sonochemical methodology is presented as an efficient method to obtain *N*-unsubstituted pyrazolines.

The structures of pyrazolinic derivates were elucidated on the basis of its ^{1}H NMR, IR and mass spectra. The ring closure is demonstrated by the IR spectra of **4a–e** compounds, which showed the characteristic band for NH at 3344–3297 cm^{-1} and a band at 1596 cm^{-1} corresponding to C=N stretching. The ^{1}H NMR spectra showed an ABX spin system caused by the coupling of three hydrogen atoms attached to the C-4 and C-5 of the heterocyclic ring (Fig. 1). Methylene protons of heterocyclic ring appeared as two double doublets, one at δ = 3.75–3.82 ppm (H4a, J = 17, 12.3 Hz) and the other at δ = 3.05–3.12 ppm (H4b, J = 17, 7.2 Hz). The existence of these double doublets clearly indicates the magnetic non-equivalence of these two protons for being adjacent to a chiral center, whose hydrogen have chemical shift at 5.2 ppm (Hx, J = 12.2, 7.2 Hz). The NH's protons of compounds 4 were observed. These spectral data unequivocally prove the 2-pyrazoline structure.

As depicted from Table 1, the yields of compound 4 were excellent. It is worth noting that the electronic nature of the substituents affects only to a lesser extent the yields of the products and the reaction proceeds quite well with both electron-withdrawing and electron-releasing substituents on acetylaminochalcones. In contrast, the presence of various electron-releasing substituents on the aryl decreases the rate, because of the lower electrophilicity caused by these groups on α,β-unsaturated system. In addition to test the usefulness of the sonication, the appropriate reaction conditions allow obtain NH-pyrazolines stable at ambient conditions and exhibiting a high fluorescence in both solution and solid state. The reaction may tentatively be visualized to occur via a tandem sequence of reactions depicted in reaction mechanism (Scheme 2) involving (i) attack of nitrogen on carbonyl carbon to yield an imine derivative, (ii) attack of nitrogen on carbon–carbon double leading to a five membered ring in either a sequential or a concerted manner, and (iii) proton transfer and removal of water molecule resulting to 2-pyrazolines [13b,15].



Scheme 2. Plausible formation of 3-(4-acetylaminophenyl)-5-(aryl)-1*H*-pyrazolines **4** ultrasonic-assisted.

4. Conclusion

In the present paper, we report the preparation in two steps of pyrazolinic derivates under ultrasonic irradiation. This mild, convenient and improved protocol for the ultrasound-promoted preparation of pyrazolinic derivates indicate that, unlike classical heating, ultrasonic irradiation results in higher yields, shorter reaction times and milder conditions. Due to the broad spectrum of biological activities of pyrazolines, evaluation of the biological activity and fluorescence properties of the new compounds is in progress.

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