



Environmentally friendly sonocatalysis promoted preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles

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ABSTRACT

An efficient and green synthesis of thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles via the condensation of chalcones with thiosemicarbazide in ethanol and KOH under ultrasound irradiation is reported. The products were isolated in good yields after short reaction times.

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1. Introduction

Increasing evidence suggest that pyrazoles and derivatives possess a broad spectrum of important biological and pharmaceutical activities such as antimicrobial, antihypertensive, antitumor, anti-inflammatory, antidepressant and anticonvulsant activities [1–4]. It was recently reported that 1-thiocarbamoyl-2-pyrazolines are cholinesterase [5] and selective monoamine oxidase [5–7] inhibitors that may have promising features in the treatment of Parkinson's and Alzheimer's diseases. They are also useful intermediates for important pharmaceutical products, such as Rimonabant [8] and Celecoxib [9].

In recent years, we described the synthesis of many heterocycles by non-traditional conditions, such as microwaves [10,11] and sonocatalysis [12–15]. In particular, the beneficial effects of ultrasound irradiation are playing an increasing role in process chemistry, especially in cases where classical methods require drastic conditions or prolonged reaction times. When the process involves sensitive reagents or there is the possibility of product decomposition under prolonged reactions conditions, ultrasound also has an advantage [16]. The use of ultrasound irradiation to decrease reaction times and improve yields has been demonstrated [16–18]. We report here an efficient and clean procedure to prepare 1-thiocarbamoyl-3,5-

diaryl-4,5-dihydro-1H-pyrazoles by sonocatalysis with ethanol as solvent.

2. Method

2.1. Apparatus and analysis

NMR spectra were recorded on a Bruker DPX 300 spectrometer (300.13 MHz for ¹H and 75.48 MHz for ¹³C) at 300 K. Low resolution mass spectra were obtained on a Varian Saturn 2200 GC/MS spectrometer operating at 70 eV. IR spectra were recorded on a Bomem MB 100 FT-IR spectrometer as KBr pellets. Melting points were determined using open capillaries on a Tecnopon PFM II apparatus and are uncorrected. The reactions were carried out with a microtip probe connected to a 500 W Sonics Vibra-cell ultrasonic processor operating at 20 KHz at 25% of the maximum power output. The progress of reactions was monitored on a Thermo Trace GC Ultra chromatograph, Column I.D., 0.25 mm; Column length, 30 m; Column Head Pressure, 14 psi.

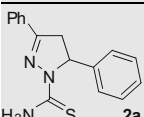
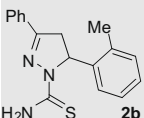
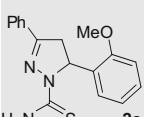
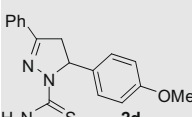
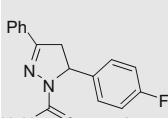
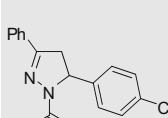
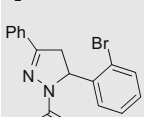
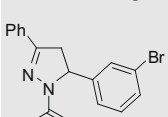
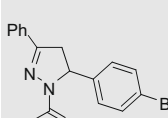
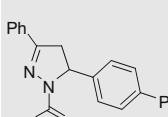
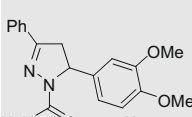
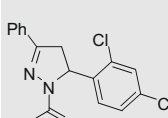
2.2. Preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles (2)

In a 25 ml beaker, the chalcone **1** (2.0 mmol) and thiosemicarbazide (4.0 mmol, 0.36 g) were mixed with EtOH (10 ml) and KOH (4.0 mmol, 0.22 g) was added. The reaction mixtures were then sonicated by an ultrasonic probe with a frequency of 20 KHz at room temperature (25 °C). The complete consumption

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Table 1
Preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1*H*-pyrazoles **2** via sonocatalysis.

Product 2	Sonocatalysed reaction			Control experiments ^b		Literature		
	Time (min)	MP (°C)	Yield (%) ^a	Conversion (%)	Yield (%) ^a	Time (h) [ref.]	MP (°C) [ref.]	Yield (%) [ref.]
 2a	20	200–202	76	27	16	2 [22]	203–204 [22]	66 [22]
 2b	20	211–216	68	–	–	–	–	–
 2c	20	211–215	61	–	–	–	–	–
 2d	20	165–166	73	–	–	8 [23]	172[23]	87[23]
 2e	20	235–237	78	32	27	–	–	–
 2f	20	174–178	74	–	–	–	–	–
 2g	20	170–174	60	–	–	–	–	–
 2h	20	213–215	71	–	–	–	–	–
 2i	20	195–197	70	–	–	–	–	–
 2j	20	193–194	71	–	–	–	–	–
 2k	20	159–160	75	–	–	4 [6]	163 [6]	84 [6]
 2l	20	217–220	68	–	–	–	–	–

^a Isolated products.

^b Same reaction conditions as the sonocatalysed reactions, without ultrasonic irradiation.

100), 361 (M + 1, 32), 360 (M+, 92), 343 (8), 328 (38), 300 (25), 282 (>5), 182 (11), 91 (10), 77 (20).

1-Thiocarbamoyl-5-(4-biphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (**2j**): (71%, 0.51 g), C₂₂H₁₉N₃S, MW 357.47. IR (KBr): ν (cm⁻¹); ¹H NMR (300 MHz; DMSO-*d*₆): δ (ppm) 3.18 (dd, 1H, *J*_{AB} = 18.1 Hz, *J*_{AX} = 3.4 Hz, H_A), 3.92 (dd, 1H, *J*_{AB} = 18.1 Hz, *J*_{BX} = 11.5 Hz, H_B), 6.00 (dd, 1H, *J*_{BX} = 11.3 Hz, *J*_{AX} = 3.2 Hz, H_X), 7.22–7.91 (m, 14H, aromatic H), 7.96 and 8.10 (two br s, 2H, NH₂); ¹³C NMR (75 MHz; DMSO-*d*₆): δ (ppm) 42.2 (C-4), 62.6 (C-5), 125.8, 126.5, 126.8, 127.0, 127.2, 128.6, 128.8, 130.5, 130.8, 138.8, 139.8, 142.1 (18C, Ar), 154.9 (C-3), 176.1 (C(S)NH₂); MS (EI, 70 eV): *m/z* (%) 298 (100), 221 (<5), 91 (<5), 77 (<5).

1-Thiocarbamoyl-5-(3,4-dimethoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (**2k**): (75%, 0.51 g), C₁₈H₁₉N₃O₂S, MW 341.43. IR (KBr): ν (cm⁻¹) 3421–3262 (N–H), 1597 (C=N), 1505–1448 (C=C), 1373 (C=S); ¹H NMR (300 MHz; DMSO-*d*₆): δ (ppm) 3.16 (dd, 1H, *J*_{AB} = 18.0 Hz, *J*_{AX} = 3.3 Hz, H_A), 3.70 (OCH₃), 3.71 (OCH₃), 3.86 (dd, 1H, *J*_{AB} = 18.0 Hz, *J*_{BX} = 11.3 Hz, H_B), 5.88 (dd, 1H, *J*_{BX} = 11.2 Hz, *J*_{AX} = 3.2 Hz, H_X), 6.58–7.89 (m, 14H, aromatic H), 7.89 and 8.04 (two br s, 2H, NH₂); ¹³C NMR (75 MHz; DMSO-*d*₆): δ (ppm) 42.3 (C-4), 55.4 (OCH₃), 55.4 (OCH₃), 62.5 (C-5), 109.6, 111.8, 116.9, 127.0, 128.6, 130.4, 130.9, 135.3, 147.7 (12C, Ar), 154.9 (C-3), 176.1 (C(S)NH₂); MS (EI, 70 eV): *m/z* (%) 342 (M + 1, 46), 341 (M+, 37), 340 (M–1, 100), 325 (13), 308 (32), 281 (45), 237 (47), 223 (61), 207 (35), 164 (36), 91 (17), 77 (29).

1-Thiocarbamoyl-5-(2,4-dichlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (**2l**): (68%, 0.48 g), C₁₆H₁₃Cl₂N₃S, MW 350.27. IR (KBr): ν (cm⁻¹) 3424–3274 (N–H), 1592 (C=N), 1503–1430 (C=C), 1371 (C=S); ¹H NMR (300 MHz; DMSO-*d*₆): δ (ppm) 3.11 (dd, 1H, *J*_{AB} = 18.1 Hz, *J*_{AX} = 4.1 Hz, H_A), 3.99 (dd, 1H, *J*_{AB} = 18.1 Hz, *J*_{BX} = 11.7 Hz, H_B), 6.11 (dd, 1H, *J*_{BX} = 11.7 Hz, *J*_{AX} = 4.0 Hz, H_X), 6.94–7.88 (m, 8H, aromatic H), 8.02 and 8.21 (two br s, 2H, NH₂); ¹³C NMR (75 MHz; DMSO-*d*₆): δ (ppm) 40.7 (C-4), 60.3 (C-5), 127.0, 127.5, 128.5, 128.9, 130.5, 131.3, 132.1, 138.9 (12C, Ar), 154.9 (C-3), 175.9 (C(S)NH₂); MS (EI, 70 eV): *m/z* (%) 351 (M + 2, 41), 350 (M+, 51), 333 (<5), 316 (100), 315 (98), 289 (<5), 91 (<5), 77 (6).

3. Results and discussion

A variety of synthetic routes to pyrazoles have been developed [19]. However, these syntheses typically demand long reaction times, products are isolated in low yields and the usual product purification procedures such as recrystallization or column chromatography require large volumes of organic solvent. Due to environmental concerns, there is currently emphasis on the use of green solvents and more efficient reaction conditions for synthesis. These observations and our interest in clean production of heterocyclic compounds prompted us to explore a new methodology for the preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles based on sonocatalysis in ethanol, a bio-renewable solvent [20].

The starting compounds (**1a–l**) (chalcone derivatives) were obtained from acetophenone (0.02 mol) and the appropriate aldehydes (0.02 mol) by known methods [21]. The best condition for preparing the 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles (**2a–l**) was achieved when two equivalents of both KOH and thiosemicarbazide and 1 equivalent of the chalcone were sonicated for 20 min, affording the desired pure product in good yield (Scheme 1). The reaction time was determined by monitoring the consumption of chalcone by GC. The scope and generality of this process are illustrated by the preparation of a series of 12 compounds. The catalytic role of ultrasound in our sonocatalysed syntheses was confirmed by control experiments in which the chalcone (**1a** or **1e**) was allowed to react under the same condi-

tions (two equivalents of thiosemicarbazide and KOH, room temperature for 20 min), but in the absence of ultrasonic irradiation (Table 1). Table 1 also compares our results with those reported in the literature [6,22,23] employing conventional synthetic protocols.

We have developed a mild, convenient and improved protocol for the preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles via sonocatalysis. Significant advantages of the method include the fact that: (i) the reaction is simple to execute; (ii) the products are isolated in good yields (60–78%); (iii) the work-up is very simple; (iv) the reaction time is short (20 min); and (v) the products are obtained in excellent purity (>99%). Extension of this reaction to other substrates and organic species is currently in progress and will be reported in due course.

4. Conclusion

In summary, we have developed a new methodology and synthesized several 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles by ultrasound irradiation. Our method has many advantages over existing methods, including high yields, simple work-up, short reaction times, no side reactions and no column chromatography. This procedure represents a convenient, economic and environmentally friendly process for the synthesis of pyrazole derivatives.

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