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Efficient sonochemical synthesis of novel 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides

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ABSTRACT

An ultrasound-assisted preparation of a series of novel 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides that proceeds via the efficient reaction of chalcones with aminoguanidine hydrochloride under clean conditions is described.

1. Introduction

Pyrazole and derivatives are key substructures in a large variety of compounds with important biological activities and pharmacological properties [1–3]. On the other hand, the use of ultrasonic irradiation to activate organic reactions has recently taken on a new dimension. It has been used for a great variety of organic reactions, such as oxidations, reductions, cleavage of epoxides, imination of aldehydes, multicomponent reactions, preparation of acetylenes, synthesis of ionic liquids, etc. [4–7].

The phenomenon responsible for the beneficial effects of ultrasound on chemical reactions is cavitation. During the rarefaction cycle of the wave, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle [8]. These rapid and violent implosions generate short-lived regions with temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates above 10 billion °C per second [9]. Such localized hot spots can be thought as microreactors in which the energy of sound is transformed into a useful chemical form.

Recently, we have reported the synthesis of many heterocycles under mild conditions, such as microwaves, sonochemistry and aqueous media [9–14]. These observations and our interest in the clean production of organic compounds triggered our interest in examining the applicability of ultrasound to synthesize novel pyrazole derivatives. We sought methods for conversion of chalcones to pyrazoles via condensation with hydrazines in the presence of KOH and ethanol. For the preparation of pyrazole nucleus, an examination of previously reported methods revealed serious synthetic drawbacks, such as a mixture of products, long reaction times, high temperatures and use of catalysts [15]. The increasing environmental consciousness worldwide has triggered the search for new products and processes that are compatible with an eco-friendly environment.

2. Method

2.1. Apparatus and analysis

Starting chalcones **1** were prepared according to the literature and characterized by ^{1}H and ^{13}C NMR [16]. All solvents and reagents were obtained from Aldrich and used without further purification. High-resolution mass analyses were carried out on a time-of-flight instrument (Micro-TOF) equipped with an ESI source, operated in the positive ion mode. Samples dissolved in

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MeOH/H_2O 1:1 (≈0.5 mg/ml) were introduced into the source at 5 ml/min via an infusion pump (Cole-Parmer, Vernon Hills, IL, USA). Nitrogen gas was used for nebulising (2 bar) and drying (4 l/min, 160 °C). An accurate-mass calibration was obtained using a solution of sodium trifluoroacetate (10 mg/ml) as internal standard. NMR spectra were recorded on a Bruker DPX 300 spectrometer (300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C) at 300 K.

The reactions were carried out with a microtip probe connected to a 500 Watt Sonics Vibracell 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. Classical synthesis of 3,5-diaryl-4,5-dihydro-1H-pyrazole-1-carboximidamides (**2**)

A mixture of chalcone **1** (2.0 mmol), aminoguanidine hydrochloride (4.0 mmol, 0.44 g) and KOH (4.0 mmol, 0.22 g) in ethanol (10 ml) was stirred at reflux. After the time indicated (Table 1), the reaction was allowed to cool, the excess of aminoguanidine hydrochloride was removed by filtration in a Büchner funnel and the ethanol was evaporated under reduced pressure. The solid residue was dissolved in water (20 ml) and the product was extracted in ethyl acetate (3 × 20 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. The product **2** obtained was purified by recrystallization from hexane/EtOAc (1:1).

2.3. Ultrasound-promoted synthesis of 3,5-diaryl-4,5-dihydro-1H-pyrazole-1-carboximidamides (**2**)

A mixture of chalcone **1** (2.0 mmol), aminoguanidine hydrochloride (4.0 mmol, 0.44 g) and KOH (4.0 mmol, 0.22 g) in ethanol (10 ml) was irradiated in an ultrasound probe at 25–30 °C for the appropriate time (see Table 1). After filtration in a Büchner funnel, to remove the excess of the aminoguanidine hydrochloride, the ethanol was evaporated under reduced pressure. The solid residue was dissolved in water (20 ml) and the product was extracted in ethyl acetate (3 × 20 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. Finally, the 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides were obtained in excellent purity.

2.4. Data spectra of products **2a-j**

3,5-Diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2a**): (0.40 g, 75%) $C_{16}H_{16}N_4$, 264.33, 167–169 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.05 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 5.6 Hz, H_A), 3.84 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.1 Hz, H_B), 5.53 (dd, 1H, J_{BX} = 12.0 Hz, J_{AX} = 5.5 Hz, H_X), 7.20–7.77 (m, 10H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.8 (C-4), 60.6 (C-5), 125.4, 126.1, 126.9, 128.4, 128.5, 129.2, 131.6, 143.1 (12C, Ar), 149.1 (C-3), 154.3 (C(NH)NH_2).

5-(2-Methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2b**): (0.42 g, 75%) $C_{17}H_{18}N_4$, 278.35, 188–190 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 2.38 (s, 3H, CH_3), 2.91 (dd, 1H, J_{AB} = 17.6 Hz, J_{AX} = 5.8 Hz, H_A), 3.87 (dd, 1H, J_{AB} = 17.6 Hz, J_{BX} = 12.2 Hz, H_B), 5.61 (dd, 1H, J_{BX} = 12.2 Hz, J_{AX} = 5.8 Hz, H_X), 6.95–7.75 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 18.9 (CH_3), 41.5 (C-4), 58.0 (C-5), 124.1, 125.9, 125.9, 126.6, 128.5, 129.1, 130.3, 131.8, 133.9, 141.2 (12C, Ar), 148.5 (C-3), 154.4 (C(NH)NH_2).

5-(2-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2c**): (0.58 g, 98%) $C_{17}H_{18}N_4O$, 294.35, 165–167 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 2.92 (dd, 1H, J_{AB} = 17.6 Hz, J_{AX} = 5.2 Hz, H_A), 3.79 (dd, 1H, J_{AB} = 17.6 Hz, J_{BX} = 12.0 Hz, H_B), 3.83 (s, 3H, OCH_3), 5.67 (dd, 1H, J_{BX} = 12.0 Hz, J_{AX} = 5.2 Hz, H_X), 6.84–7.74 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 41.5 (C-4), 55.4 (OCH_3), 55.9 (C-5), 111.1, 120.1, 125.3, 126.0, 128.1, 128.4, 129.1, 130.1, 131.7, 149.4 (12C, Ar), 154.2 (C-3), 155.6 (C(NH)NH_2).

5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2d**): (0.47 g, 80%) $C_{17}H_{18}N_4O$, 294.35, 147–149 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.06 (dd, 1H, J_{AB} = 17.6 Hz, J_{AX} = 5.8 Hz, H_A), 3.71 (s, 3H, OCH_3), 3.78 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.1 Hz, H_B), 5.43 (dd, 1H, J_{BX} = 12.0 Hz, J_{AX} = 5.8 Hz, H_X), 6.85–7.75 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.7 (C-4), 54.9 (OCH_3), 60.2 (C-5), 113.8, 125.9, 126.7, 128.4, 129.0, 131.8, 135.4, 148.2 (12C, Ar), 154.5 (C-3), 158.2 (C(NH)NH_2).

5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2e**): (0.58 g, 98%) $C_{16}H_{15}ClN_4$, 298.77, 163–165 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.04 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 5.9 Hz, H_A), 3.82 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.2 Hz, H_B), 5.50 (dd, 1H, J_{BX} = 12.1 Hz, J_{AX} = 5.8 Hz, H_X), 7.20–7.75 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.4 (C-4), 60.1 (C-5), 126.0, 127.5, 128.3, 128.5, 129.2, 131.3, 131.6, 142.4 (12C, Ar), 148.6 (C-3), 154.5 (C(NH)NH_2).

5-(2-Bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2f**): (0.68 g, 99%) $C_{16}H_{15}BrN_4$, 343.22, 168–170 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 2.92 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 5.8 Hz, H_A), 3.91 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.3 Hz, H_B), 5.68 (dd, 1H, J_{BX} = 12.2 Hz, J_{AX} = 5.8 Hz, H_X), 7.06–7.74 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 41.3 (C-4), 60.5 (C-5), 120.8, 126.0, 126.4, 127.8, 128.4, 128.7, 129.1, 131.6, 132.6, 141.8 (12C, Ar), 148.4 (C-3), 154.3 (C(NH)NH_2).

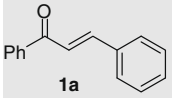
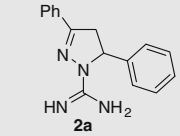
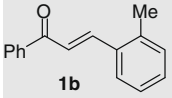
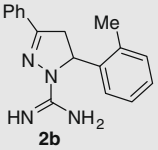
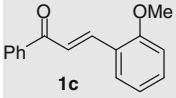
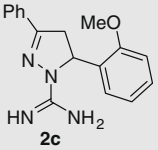
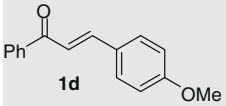
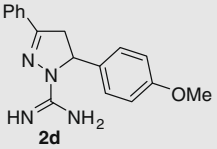
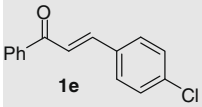
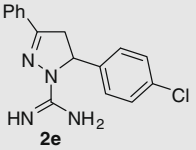
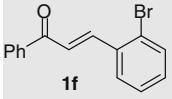
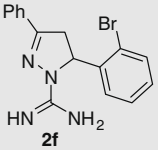
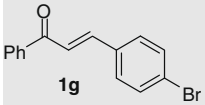
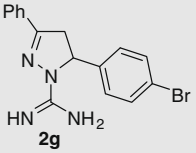
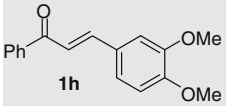
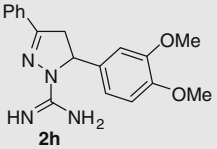
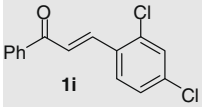
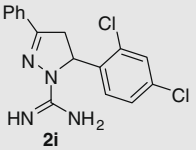
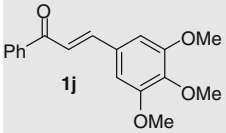
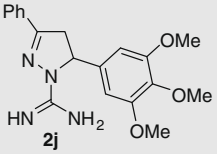
5-(4-Bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2g**): (0.55 g, 80%) $C_{16}H_{15}BrN_4$, 343.22, 136–138 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.08 (dd, 1H, J_{AB} = 17.8 Hz, J_{AX} = 5.5 Hz, H_A), 3.85 (dd, 1H, J_{AB} = 17.8 Hz, J_{BX} = 12.1 Hz, H_B), 5.52 (dd, 1H, J_{BX} = 12.0 Hz, J_{AX} = 5.5 Hz, H_X), 7.15–7.77 (m, 9H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.5 (C-4), 60.1 (C-5), 120.0, 126.2, 127.8, 128.5, 129.4, 131.3, 131.4, 142.3 (12C, Ar), 149.7 (C-3), 154.2 (C(NH)NH_2).

5-(3,4-Dimethoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2h**): (0.64 g, 99%) $C_{18}H_{20}N_4O_2$, 324.38, 146–148 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.08 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 5.8 Hz, H_A), 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.81 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.0 Hz, H_B), 5.44 (dd, 1H, J_{BX} = 11.9 Hz, J_{AX} = 5.8 Hz, H_X), 6.70–7.77 (m, 8H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.9 (C-4), 55.4 (OCH_3), 55.5 (OCH_3), 60.6 (C-5), 109.2, 111.9, 117.3, 126.1, 128.5, 129.3, 131.6, 135.4, 147.8, 149.4 (12C, Ar), 148.7 (C-3), 154.4 (C(NH)NH_2).

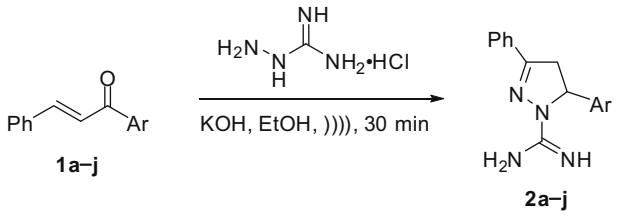
5-(2,4-Dichlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2i**): (0.58 g, 87%) $C_{16}H_{14}Cl_2N_4$, 333.22, 94–96 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 2.99 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 6.1 Hz, H_A), 3.91 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.3 Hz, H_B), 5.69 (dd, 1H, J_{BX} = 12.3 Hz, J_{AX} = 6.0 Hz, H_X), 7.08–7.75 (m, 8H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 40.9 (C-4), 58.1 (C-5), 126.1, 127.4, 127.9, 128.5, 128.8, 129.3, 131.4, 131.6, 139.4 (12C, Ar), 149.0 (C-3), 154.3 (C(NH)NH_2).

3-Phenyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2j**): (0.64 g, 90%) $C_{19}H_{22}N_4O_3$, 354.40, 179–181 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ (ppm) 3.09 (dd, 1H, J_{AB} = 17.7 Hz, J_{AX} = 6.5 Hz, H_A), 3.63 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3), 3.81 (dd, 1H, J_{AB} = 17.7 Hz, J_{BX} = 12.2 Hz, H_B), 5.41 (dd, 1H, J_{BX} = 12.0 Hz, J_{AX} = 6.5 Hz, H_X), 6.53–7.76 (m, 7H, aromatic H); ^{13}C NMR (75 MHz; DMSO-d_6): δ (ppm) 42.8 (C-4), 55.7 (2 OCH_3), 59.8 (OCH_3), 61.1 (C-5), 102.6, 126.1, 128.5, 129.2, 131.7, 136.3, 139.0, 152.9 (12C, Ar), 149.0 (C-3), 154.8 (C(NH)NH_2).

Table 1
Preparation of 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides **2**.

Chalcone (**1**)	Product (**2**)[a]	MP (°C)	Sonochemical method		Classical method	
			Time (min)	Yield[b] (%)	Time (h)	Yield[b] (%)
 **1a**	 **2a**	167–169	30	75	3	57
 **1b**	 **2b**	188–190	30	75	6	64
 **1c**	 **2c**	165–167	30	98	6	60
 **1d**	 **2d**	147–149	30	80	6	69
 **1e**	 **2e**	163–165	30	98	6	66
 **1f**	 **2f**	168–170	30	99	6	65
 **1g**	 **2g**	136–138	30	80	6	60
 **1h**	 **2h**	146–148	30	99	6	66
 **1i**	 **2i**	94–96	30	87	6	61
 **1j**	 **2j**	179–181	30	90	3	63

[a] Novel compounds.
[b] Yields of isolated products.



Scheme 1. Synthesis of 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides **2**.

3. Results and discussion

Strict legislative restrictions on pollution exposure have enforced the application of biorenewable solvents in practice [17]. In this endeavor, we report here the synthesis of novel 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides by the reaction of chalcones with aminoguanidine hydrochloride in KOH. The starting compounds **1** (chalcone derivatives) were obtained from acetophenone (0.02 mol) and the appropriate aldehydes (0.02 mol) by known methods [16].

The mixture of reagents was sonicated by use of an ultrasound probe for 30 minutes. In our studies, we found that ethanol was the solvent most appropriate for these reactions, giving the best results. The scope and generality of this process are illustrated by the preparation of the series of ten pyrazoles shown in the Table 1 (Scheme 1). We have developed a mild and eco-friendly protocol for the preparation of novel heterocycles, 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides under ultrasonic irradiation.

The progress of the reactions was monitored by gas chromatography and the pyrazole derivatives were isolated after simple filtration in a Büchner funnel to exclude the excess of the aminoguanidine hydrochloride, followed by dissolution in water and extraction with ethyl acetate (twice). Significant advantages of the ultrasound-assisted method include the fact that:

(i) the reaction is simple to execute;
(ii) the products are isolated in good yields;
(iii) the work-up is very simple;
(iv) the reaction time is short (30 min);
(v) recrystallization or column chromatography are not necessary to purification;
(vi) the products are obtained in excellent purity (>99%).

All compounds **2** were characterized by ^{1}H NMR and ^{13}C NMR. The structures **2** were confirmed by mass analyses with errors for all compounds of less than 5 ppm. More investigations are currently in progress to explore the reaction.

4. Conclusion

In summary, we report a very simple, fast and environmentally benign synthesis of novel 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides by simple mixing of the reactants in ethanol under ultrasonic irradiation.

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References

[1] J. Elguero, P. Goya, N. Jagerovic, A.M.S. Silva, Targets in Heterocyclic System, Italian Society of Chemistry, Roma, 2002.
[2] S.R. Donohue, C. Halldin, V.W. Pike, Tetrahedron Lett. 49 (2008) 2789.
[3] G. Szabó, J. Fischer, Á. Kis-Varga, K. Gyires, J. Med. Chem. 51 (2008) 142.
[4] T.J. Manson, Chem. Soc. Rev. 26 (1997) 447.
[5] H.A. Stefani, R. Cella, F.A. Dörr, C.M.P. Pereira, F. Gomes, G. Zeni, Tetrahedron Lett. 46 (2005) 2001.
[6] H.A. Stefani, C.B. Oliveira, R.B. Almeida, C.M.P. Pereira, R.C. Braga, R. Cella, V.C. Borges, L. Savegnago, C.W. Nogueira, Eur. J. Med. Chem. 41 (2006) 513.
[7] G. Cravotto, P. Cintas, Chem. Soc. Rev. 35 (2006) 180.
[8] T.J. Mason, J.P. Lorimer, Applied Sonochemistry: The Uses of Power Ultrasound in Chemistry and Processing, Wiley-VCH GmbH and Co. KGaA, Weinheim, 2002.
[9] M.A.P. Martins, C.M.P. Pereira, W. Cunico, S. Moura, F. Rosa, R.L. Peres, P. Machado, N. Zanatta, H.G. Bonacorso, Ultrason. Sonochem. 13 (2006) 364.
[10] M.A.P. Martins, C.M.P. Pereira, P. Beck, P. Machado, S. Moura, M.V. Teixeira, H.G. Bonacorso, N. Zanatta, Tetrahedron Lett. 44 (2003) 6669.
[11] M.A.P. Martins, C.M.P. Pereira, S. Moura, C.P. Frizzo, P. Beck, H.G. Bonacorso, N. Zanatta, A.F.C. Flores, J. Heterocycl. Chem. 44 (2007) 1195.
[12] C.M.P. Pereira, H.A. Stefani, K.P. Guzen, A.T.G. Órfão, Lett. Org. Chem. 4 (2007) 43.
[13] C.M.P. Pereira, F.H. Quina, F.A.N. Silva, D.J. Emmerich, A. Machulek, Mini-Rev. Org. Chem. 5 (2008) 331.
[14] L. Pizzuti, L.A. Piovesan, A.F.C. Flores, F.H. Quina, C.M.P. Pereira, Ultrason. Sonochem. 16 (2009) 728.
[15] T. Eicher, S. Hauptmann, The Chemistry of Heterocycles, Wiley-VCH GmbH and Co. KGaA, Weinheim, 2003.
[16] V.N. Pathak, R. Gupta, R. Tiwari, R. Gupta, V. Sareen, B. Varshney, Synth. Commun. 37 (2007) 977.
[17] R.A. Sheldon, Green Chem. 9 (2007) 1273.