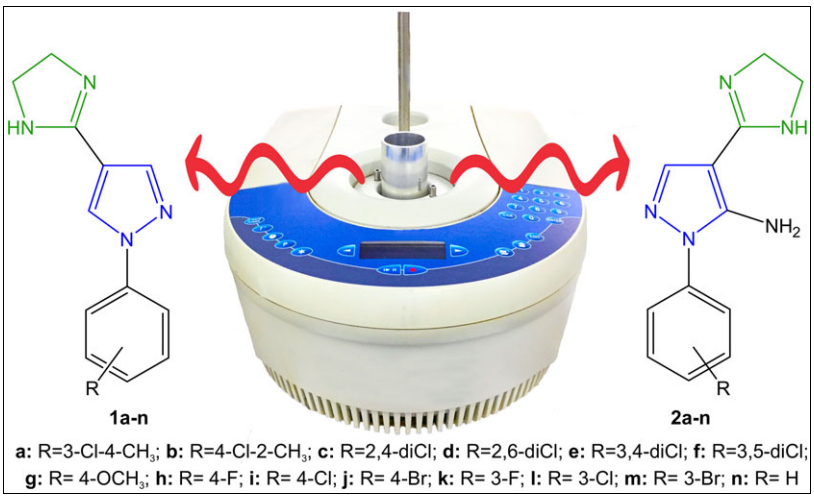
A Convenient Synthesis of Pyrazole-imidazoline Derivatives by Microwave Irradiation

Getúlio de S. Rosa, Bernardo A. Souto, Cynthia N. Pereira, Bruna C. Teixeira, and Maurício S. dos Santos*

Laboratório de Síntese Orgânica (LABSINTO), Instituto de Física e Química, Universidade Federal de Itajubá, 1303 BPS Avenue, Itajubá-, MG 37500-903, Brazil
*E-mail: mauriciosantos@unifei.edu.br

Received October 19, 2018
DOI 10.1002/jhet.3557
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



A series of 28 hybrids pyrazole-imidazolines **1a**–**n** and **2a**–**n** were synthesized by a new methodology using microwave irradiation, in short time (20–30 min), in low power (50–70 W), and in 34–92% yield. Among all methodologies evaluated, no side products were obtained. All derivatives were completely characterized by FT–IR, ^{1}H and ^{13}C NMR, GC–MS, and HRMS.

INTRODUCTION

Pyrazole is a five-membered heterocycle ring widely found in a large variety of compounds that possess important biological activities, such as antileishmanial, analgesic, anti-inflammatory, antibacterial, antifungal, antitumoral, and antiviral [1–6]. Because of the wide range of applications involving compounds containing pyrazole moiety, many publications concerning methodologies to obtain this heterocycle have been reported [7–9]. Most of them are based on two classical methods: Knorr's and Pechmann's syntheses [10,11].

On the other hand, 2-imidazoline ring, an azole derivative from imidazole, also named as cyclic amidine, is of considerable importance because the derivatives have been employed against several diseases, such as hyperglycemia, hypertension, and cancer [12–15]. The main synthetic route to 2-imidazoline formation is based on cyclization from nitriles and ethylenediamine (EDA) with different catalysts, solvents, and reaction conditions [16–19]. There are some reports showing carboxylic acids [20], amides [21], and esters [22] as raw materials instead of nitriles. Many of these protocols have some disadvantages, such as the use of strong Lewis acid, expensive reagents, toxic metals, long time reaction, and poor yields.

In the last 8 years, few papers related to new synthetic methodologies to obtain 2-imidazoline were published. Zhow *et al*. synthesized 14 2-imidazolines from olefins, amines, NBS, and acetonitrile as solvent, with reaction time from 4 to 16 h, in 45–99% yield [23]. Wróbel and colleagues obtained six new 2-imidazoline derivatives using N^{1}-(4-nitrophenyl)ethylenediamine, cyanogen bromide (Br—CN), isopropanol, and six substituted isocyanates. The global reaction time was approximately 3.5 h, and the yields were not cited on the paper [24]. A series of six novel hybrids benzofuran/2-imidazoline was reported by Giorgioni *et al*. from esters, EDA derivatives, NaH (in mineral oil), trimethylaluminum as catalyst and inert atmosphere. The reaction time was approximately 12 h, and the compounds were isolated in 40–58% yield [25].

Microwave irradiation is an important technique to access many functional groups, including heterocyclic systems [26]. Zhang *et al*. reported the synthesis of 2-imidazolines from the reaction of aromatic nitriles with EDA or *N*-(2-aminoethyl)ethanolamine, using cupric indole-3-acetate (Cu (II)-$(IAA)_2$) as catalyst under microwave irradiation, in good to excellent yields

(79–94%) and reaction time from 5 to 20 min. The power applied was very high: 1000 W [27]. De La Hoz and coworkers obtained seven compounds containing 2-imidazoline linked to pyrazole, imidazole, and benzene rings, under microwave irradiation. They used nitriles, EDA, and elemental sulfur under solvent-free conditions. The power was 30 W, during 3 to 30 min, in 18–98% yields [28].

Our research group have synthesized pyrazoles containing 2-imidazoline moiety using carbon disulfide (CS_2) and EDA, under reflux, with a long reaction time (14–15 h), in moderate to good yields (65–77%) [29]. In search for new methodologies to obtain 2-imidazolines, in better yields, shorter reaction time, and milder reaction conditions, we planned to synthesize 1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazoles **1a–n** and 5-amino-1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazoles **2a–n**, from key intermediates 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–n** and 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **4a–n**, respectively, by microwave irradiation. The compounds **1a–d**,**g–i** and **2a–d**,**g–i** are reported for the first time. The synthesis of the compounds is summarized in Scheme 1.

Results and Discussion. We have synthesized the key intermediates **4a–n** starting from commercially available arylhydrazine hydrochlorides **5a–n**. First of all, **5a–n** were converted to the unprotonated arylhydrazines by treatment with sodium acetate in ethanol, under reflux, for 20 min. After that, ethoxymethylenemalononitrile was added to give the corresponding **4a–n**, after 1 h, in good to excellent yields: 70–93%. The aprotic deamination of **4a–n** with *t*-butyl nitrite and tetrahydrofuran, under reflux for 2 h, afforded the desired compounds **3a–n** in good to excellent yields as well: 68–92%. Both methodologies have been reported by our research group previously [29,30].

Finally, the targets **1a–n** and **2a–n** were obtained from **4a–n** and **3a–n**, respectively, EDA, CS_2 under mild conditions employing microwave irradiation, in 44–92% and 34–84% yields, respectively, and they are shown in Table 1. The structures could be assigned on the basis of its Fourier transform infrared (FT–IR), ^{1}H and ^{13}C NMR spectra, and high-resolution mass spectrometry (HRMS) data.

We investigated the influence of CS_2 and EDA in the reaction. The optimal reaction conditions with regard to reagents quantities were 2.0 mL of EDA and 4 mmol of CS_2 for each mmol of **3a–n** and **4a–n**, raw materials to synthesize **1a–n** and **2a–n**, respectively. The power was also optimized. For the synthesis of **1a–n**, the best results were obtained when 50 W, a very low power, was employed. After 10 min, the thin layer chromatography (TLC) analysis showed that the reactions had not been completed yet. However, the corresponding raw material **3a–n** was not identified by TLC after 20 min. In an attempt to evaluate the influence of the power, a new procedure increasing the power to 70 W was made, but the reaction time did not reduce, and no side products were identified by TLC and gas chromatography coupled to mass spectrometry. To synthesize **2a–n**, first of all we used 50 W, but a long time reaction was required. So a little higher power, 70 W, was enough to complete the reaction in 30 min. Samples were collected to accompany the reaction by TLC as well as in the reaction to obtain **1a–n**.

A characteristic band in 1620 cm^{-1} approximately was revealed using FT–IR spectra, attributed to C=N stretching of imidazoline ring. It was not observed any absorption band in the 2200 cm^{-1} region related to nitrile group. The ^{1}H NMR spectra of **1a–n** showed two singlets at 7.98–8.16 ppm and 8.31–8.99 corresponding

Scheme 1. Synthetic route to obtain the compounds **1(a–n)** and **2(a–n)**. Reagents and conditions: (i) sodium acetate, ethanol, 20 min, reflux; (ii) ethoxymethylenemalononitrile, 1 h, reflux; (iii) *t*-butyl nitrite, THF, 2 h, reflux; (iv) ethylenediamine, CS_2, MW irradiation (50 W), 20 min; (v) ethylenediamine, CS_2, MW irradiation (70 W), 30 min.

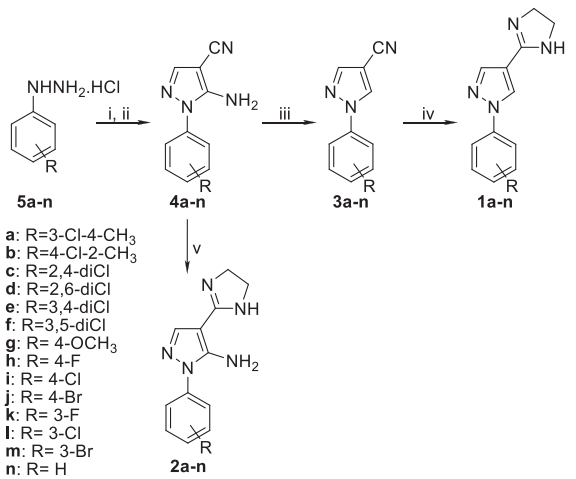


Table 1

Isolated yields of **1a–n** and **2a–n**.

R	Product	Yield (%)	Product	Yield (%)
3-Cl-4-CH_3	**1a**	92	**2a**	79
4-Cl-2-CH_3	**1b**	45	**2b**	76
2,4-diCl	**1c**	70	**2c**	53
2,6-diCl	**1d**	76	**2d**	34
3,4-diCl	**1e**	79	**2e**	71
3,5-diCl	**1f**	80	**2f**	83
4-OCH_3	**1g**	57	**2g**	50
4-F	**1h**	87	**2h**	66
4-Cl	**1i**	78	**2i**	42
4-Br	**1j**	65	**2j**	84
3-F	**1k**	55	**2k**	67
3-Cl	**1l**	47	**2l**	74
3-Br	**1m**	61	**2m**	47
H	**1n**	44	**2n**	55

to pyrazole protons, while only one singlet at 7.64–7.76 ppm was identified for **2a–n**. The phenyl protons were assigned according to standard coupling/integration expected. The presence of just one signal for two CH_2 groups at 3.55–3.58 and 3.49–3.65 ppm for **1a–n** and **2a–n**, respectively, indicates the prototropic tautomerism in the imidazoline ring. It is important to highlight that all NMR spectra for **1a–n** were recorded in DMSO-d_6, while for **2a–n**, either in DMSO-d_6 (**2a–f**,**k**) or MeOH-d_4 (**2g–j**,**l–n**), which explain the wide range of chemical shifts for methylene protons of **2a–n**. For **1a**, **1b**, **1g**, **2a**, **2b**, and **2g**, a singlet corresponding to methyl group was identified. The amine protons (NH_2) were assigned as broad at 6.29–6.85 ppm for compounds **2a–f**,**k**, only on spectra recorded in DMSO-d_6, an aprotic solvent; in methanol, a protic solvent, this signal was not observed. The ^{13}C NMR spectra of **1a–n** and **2a–n** showed a broad signal in 48.35–49.93 ppm corresponding for the two CH_2 groups in the imidazoline ring. The carbons of the aromatic rings were identified as expected. HRMS confirmed all structures **1a–n** and **2a–n**, after FT–IR, ^1H NMR, and ^{13}C NMR analyses.

CONCLUSION

In this work, we have reported an efficient and highly selective microwave irradiation method to obtain imidazoline linked to different 1-aryl-1*H*-pyrazoles. Twenty-eight compounds, **1a–n** and **2a–n**, were synthesized and characterized. The derivatives **1a–d**,**g–i** and **2a–d**,**g–i** have been reported for the first time. Most reactions have high yields, no side products were identified, and the reaction time was no longer than 30 min in low power: 50 and 70 W. This new methodology can be applied in the synthesis of imidazoline ring in future works.

EXPERIMENTAL

All commercial reagents were used as received unless otherwise noted. The reaction progress was monitored by TLC with precoated 60 F254 silica gel plates. The melting points were determined on a Fisatom 430 apparatus. FT–IR were recorded on a PerkinElmer Spectrum 100, ATR diamond-ZnSe apparatus, wave numbers expressed in cm^{-1}. NMR spectra were recorded on a Bruker Avance (500 MHz), at 298 K, in methanol-d_4 or DMSO-d_6. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Gas chromatography coupled to mass spectrometry was executed on an Agilent equipment, column HP-5 Agilent, 30 m, split ratio 20:1, operating at 70 eV (electron impact ionization). The HRMS was performed using Micromass/Waters ZQ-4000 Spectrometer, capillary 3.0 kV, cone 30.0 V, extrator 1 V, RF lens 1.0 V, source temperature 150°C, desolvation temperature 300°C (electrospray ionization [ESI]).

The key intermediates 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–n** and 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **4a–n** were synthesized by our research group according to the previously described [29,30].

General procedure for the synthesis of 1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazoles 1a–n. A mixture of 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–n** (0.001 mol), 2.0 mL of EDA (1,2-diaminoethane), and CS_2 (0.004 mol), in a 50 mL round-bottom flask adapted with a glass condenser, was irradiated with microwave (CEM–Discover apparatus), power 50 W, during 20 min. Then, the reaction mixture was poured into cold water; the precipitate was filtered out and washed with cold water. The reactions were accompanied by means of TLC and dichloromethane as eluent.

1-(3-Chloro-4-methylphenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1a). Yield: 92%; mp: 168–170°C; FT–IR ν (cm^{-1}): 3199, 3122, 2941, 2879, 1627, 1604, 1583, 1564. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.85 (s, 1H), 8.02 (s, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.74 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 3.55 (s, 4H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.58, 140.25, 138.27, 134.00, 133.79, 132.10, 127.64, 118.68, 117.06, 116.27, 49.26, 19.02. HRMS (ESI): *m/z* $[M + H]^+$: Calcd for $C_{13}H_{13}ClN_4$: 261.0907; found: 261.0927.

1-(4-Chloro-2-methylphenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1b). Yield: 37%; mp: 174–176°C; FT–IR ν (cm^{-1}): 3108, 2962, 2921, 2869, 1621, 1547. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.35 (s, 1H), 8.02 (s, 1H), 7.54 (s, 1H), 7.42 (s, 2H), 3.56 (s, 4H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.65, 139.50, 137.94, 135.08, 132.66, 131.21, 130.84, 127.31, 126.63, 114.75, 48.89, 17.56. HRMS (ESI): *m/z* $[M + H]^+$: Calcd for $C_{13}H_{13}ClN_4$: 261.0907; found: 26.0927.

1-(2,4-Dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1c). Yield: 70%; mp: 110–111°C; FT–IR ν (cm^{-1}): 3239, 3110, 2935, 2873, 1626, 1570, 1483. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.49 (s, 1H), 8.08 (s, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.8 Hz, 1H), 3.58 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.06, 140.67, 136.79, 134.36, 132.52, 130.56, 129.78, 129.55, 128.98, 115.29, 49.26. HRMS (ESI): *m/z* $[M + H]^+$: Calcd for $C_{12}H_{10}Cl_2N_4$: 281.0361; found: 281.0357.

1-(2,6-Dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1d). Yield: 76%; mp: 221–223°C; FT–IR ν (cm^{-1}): 3116, 3069, 2941, 2869, 2800, 1620, 1568, 1550. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.31 (s, 1H), 8.06 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.62 (t, *J* = 8.3 Hz, 1H), 3.55 (s, 4H). ^{13}C NMR (126 MHz,

DMSO-d_6): δ = 157.49, 140.04, 135.38, 133.17, 132.29, 132.00, 128.99, 115.17, 49.09. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{10}Cl_2N_4$: 281.0361; found: 281.0373.

1-(3,4-Dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1e). Yield: 79%; mp: 185–186°C (lit. 187–188°C [29]); FT–IR ν (cm^{-1}): 3200, 3120, 2952, 2862, 1628, 1596, 1581. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.94 (s, 1H), 8.16 (d, *J* = 2.5 Hz, 1H), 8.07 (s, 1H), 7.88 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 3.57 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.37, 140.67, 138.74, 132.05, 131.48, 128.75, 128.03, 120.08, 118.46, 116.47, 49.01. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{10}Cl_2N_4$: 281.0361; found: 281.0362.

1-(3,5-Dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1f). Yield: 80%; mp: 83–84°C (lit. 170–171°C [29]); FT–IR ν (cm^{-1}): 3174, 3140, 3098, 3079, 2944, 2870, 1629, 1579, 1552. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.99 (s, 1H), 8.08 (s, 1H), 7.97 (d, *J* = 1.5 Hz, 2H), 7.60 (s, 1H), 3.57 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.40, 140.97, 135.11, 128.40, 125.98, 117.26, 117.12, 116.71, 49.26. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{10}Cl_2N_4$: 281.0361; found: 281.0363.

4-(4,5-Dihydro-1H-imidazol-2-yl)-1-(4-methoxyphenyl)-1H-pyrazole (1g). Yield 57%; mp: 196–197°C; FT–IR (cm^{-1}): 3142, 3101, 2934, 2873, 2844, 1631, 1562, 1518. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.68 (s, 1H), 7.98 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 3.55 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.44, 158.27, 140.02, 133.38, 127.64, 120.64, 116.11, 115.16, 55.92, 49.68. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{13}H_{14}N_4O$: 243.1246; found: 243.1255.

4-(4,5-Dihydro-1H-imidazol-2-yl)-1-(4-fluorophenyl)-1H-pyrazole (1h). Yield: 87%; mp: 210–212°C; FT–IR ν (cm^{-1}): 3142, 3105, 2934, 2882, 2848, 1632, 1563, 1516. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.78 (s, 1H), 8.02 (s, 1H), 7.87 (dd, *J* = 9.0, 4.7 Hz, 2H), 7.37 (t, *J* = 9.0 Hz, 2H), 3.55 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.51 (d, ^1J = 243.6 Hz), 157.64, 140.07, 135.86 (d, ^4J = 2.6 Hz), 127.57, 120.64 (d, ^3J = 8.6 Hz), 116.39 (d, ^2J = 23.1 Hz), 116.19, 49.93. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}FN_4$: 231.1046; found: 231.1040.

1-(4-Chlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1i). Yield: 78%; mp: 214–216°C; FT–IR ν (cm^{-1}): 3151, 3111, 3071, 2934, 2878, 1629, 1567, 1504. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.83 (s, 1H), 8.04 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 3.56 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.55, 140.35, 138.07, 130.86, 129.58, 127.58, 120.18, 116.38, 49.14. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}ClN_4$: 247.0750; found: 247.0749.

1-(4-Bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1j). Yield: 65%; mp: 228–230°C (lit. 222–223°C [29]); FT–IR ν (cm^{-1}): 3144, 3110, 2931, 2863, 1632, 1589, 1565. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.83 (s, 1H), 8.04 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 3.56 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.54, 140.38, 138.47, 132.49, 127.53, 120.48, 119.09, 116.43, 49.15. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}BrN_4$: 291.0245; found: 291.0256.

4-(4,5-Dihydro-1H-imidazol-2-yl)-1-(3-fluorophenyl)-1H-pyrazole (1k). Yield: 55%; mp: 164–167°C (lit. 155–156°C [29]); FT–IR ν (cm^{-1}): 3170, 3111, 3075, 2934, 2880, 2852, 1631, 1600, 1564. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.88 (s, 1H), 8.05 (s, 1H), 7.72–7.75 (m, 2H), 7.54–7.59 (m, 1H), 7.18–7.21 (m, 1H), 3.56 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.58 (d, ^1J = 244.0 Hz), 157.53, 140.65 (d, ^3J = 10.6 Hz), 140.44, 131.55 (d, ^3J = 9.4 Hz), 127.81, 116.46, 114.34 (d, ^4J = 2.6 Hz), 113.34 (d, ^2J = 21.1 Hz), 105.89 (d, ^2J = 26.7 Hz), 49.30. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}FN_4$: 231.1046; found: 231.1048.

1-(3-Chlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1l). Yield: 47%; mp: 120–124°C (lit. 175–177°C [29]); FT–IR ν (cm^{-1}): 3198, 3113, 2941, 2873, 1633, 1589, 1566. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91 (s, 1H), 8.06 (s, 1H), 7.95 (t, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.57 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 158.01, 141.00, 140.79, 134.54, 131.88, 128.37, 126.97, 118.78, 117.50, 116.83, 49.64. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}ClN_4$: 247.0750; found: 247.0752.

1-(3-Bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (1m). Yield: 61%; mp: 116–120°C (lit. 180–181°C [29]); FT–IR ν (cm^{-1}): 3178, 3139, 3099, 2936, 2867, 1627, 1590, 1551. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.91 (s, 1H), 8.07 (t, *J* = 1.8 Hz, 1H), 8.06 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 3.58 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.56, 140.56, 140.38, 131.65, 129.45, 127.99, 122.38, 121.13, 117.44, 116.15, 49.04. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}BrN_4$: 291.0245; found: 291.0253.

4-(4,5-Dihydro-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole (1n). Yield: 44%; mp: 149–150°C (lit. 185–186°C [29]); FT–IR ν (cm^{-1}): 3142, 3105, 3075, 2934, 2848, 1630, 1597, 1562. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.80 (s, 1H), 8.03 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 3.56 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.16, 140.53, 139.73, 130.13, 127.79, 127.22, 119.01, 116.62, 49.56. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}N_4$: 213.1140; found: 213.1151.

General procedure for synthesis of 5-amino-1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazoles 2a–n. A mixture of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **4a–n** (0.001 mol), 2.0 mL of EDA (1,2-diaminoethane), and CS_2 (0.004 mol), in a 50 mL round-bottom flask adapted with a glass condenser, was irradiated with microwave (CEM–Discover apparatus), power 70 W, during 30 min. Then, the reaction mixture was poured into cold water; the precipitate was filtered out and washed with cold water. The reactions were accompanied by means of TLC and dichloromethane as eluent.

5-Amino-1-(3-chloro-4-methylphenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2a). Yield: 79%; mp: 188–190°C; FT–IR ν (cm^{-1}): 3384, 3261, 3115, 2924, 2853, 1603, 1581, 1566. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.69 (s, 1H), 7.62 (s, 1H), 7.49 (s, 2H), 6.64 (br, 2H), 3.50 (s, 4H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.93, 147.60, 138.58, 137.48, 133.77, 133.42, 131.59, 122.54, 121.06, 94.58, 43.95, 19.03. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{13}H_{14}ClN_5$: 276.1016; found: 276.1022.

5-Amino-1-(4-chloro-2-methylphenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2b). Yield: 76%; mp: 144–146°C; FT–IR ν (cm^{-1}): 3411, 3262, 3205, 3127, 2925, 2851, 1596, 1570, 1524. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.64 (s, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.29 (br, 2H), 3.49 (s, 4H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.65, 148.91, 139.13, 138.75, 138.10, 136.20, 133.75, 129.98, 127.09, 93.41, 49.39, 18.04. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{13}H_{14}ClN_5$: 276.1016; found: 276.1032.

5-Amino-1-(2,4-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2c). Yield: 53%; mp: 167–169°C; FT–IR ν (cm^{-1}): 3437, 3240, 3098, 2929, 2862, 1598, 1572, 1524. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.87 (d, *J* = 2.2 Hz, 1H), 7.65 (s, 1H), 7.59 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 6.44 (br, 2H), 3.49 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.09, 148.95, 139.26, 138.20, 134.51, 132.95, 130.63, 130.48, 129.03, 92.73. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}Cl_2N_5$: 296.0470; found: 296.0499.

5-Amino-1-(2,6-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2d). Yield: 34%; mp: 126–128°C; FT–IR ν (cm^{-1}): 3275, 3170, 3129, 2940, 2866, 1604, 1566, 1531. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.68 (s, 2H), 7.67 (s, 1H), 7.58 (t, *J* = 8.2 Hz, 1H), 6.48 (br, 2H), 3.50 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.09, 149.02, 139.19, 134.78, 133.10, 132.01, 129.05, 92.34, 44.04. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}Cl_2N_5$: 296.0470; found: 296.0499.

5-Amino-1-(3,4-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2e). Yield: 71%; mp: 197–199°C (lit. 190–192°C [29]); FT–IR ν (cm^{-1}): 3418, 3298, 3074, 2935, 2873, 1611, 1560, 1522. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85 (d, *J* = 2.5 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.73 (s, 1H), 7.63 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.77 (br, 2H), 3.51 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.89, 147.98, 139.22, 138.37, 131.63, 131.17, 128.88, 124.01, 122.56, 94.89. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}Cl_2N_5$: 296.0470; found: 296.0472.

5-Amino-1-(3,5-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2f). Yield: 83%; mp: 96–98°C (lit. 109–111°C [29]); FT–IR ν (cm^{-1}): 3420, 3282, 3083, 2946, 2873, 1619, 1583, 1568. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.76 (s, 1H), 7.67 (d, *J* = 1.8 Hz, 2H), 7.62 (t, *J* = 1.8 Hz, 1H), 6.85 (br, 2H), 3.53 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.12, 148.60, 140.88, 140.20, 135.09, 126.73, 121.63, 94.65, 48.35. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{11}Cl_2N_5$: 296.0470; found: 296.0474.

5-Amino-4-(4,5-dihydro-1H-imidazol-2-yl)-1-(4-methoxyphenyl)-1H-pyrazole (2g). Yield: 50%; mp: 171–173°C; FT–IR ν (cm^{-1}): 3263, 2940, 2857, 2837, 1602, 1561, 1510. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.65 (s, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.64 (s, 4H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 162.80, 161.19, 148.85, 139.60, 131.88, 127.47, 115.85, 95.34, 56.10, 49.76. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{13}H_{15}N_5O$: 258.1355; found: 258.1366.

5-Amino-4-(4,5-dihydro-1H-imidazol-2-yl)-1-(4-fluorophenyl)-1H-pyrazole (2h). Yield: 66%; mp: 164–166°C; FT–IR ν (cm^{-1}): 3280, 3075, 2943, 2872, 1611, 1598, 1567. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.68 (s, 1H), 7.55 (dd, *J* = 9.0, 4.8 Hz, 2H), 7.28 (t, *J* = 9.0 Hz, 2H), 3.65 (s, 4H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 163.61 (d, ^1J = 244.2.3 Hz), 162.56, 149.02, 140.10, 135.50 (d, ^4J = 2.9 Hz), 127.90 (d, ^3J = 8.9 Hz), 117.47 (d, ^2J = 23.3 Hz), 95.61, 49.77. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}FN_5$: 246.1155; found: 246.1062.

5-Amino-1-(4-chlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2i). Yield: 42%; mp: 179–181°C; FT–IR ν (cm^{-1}): 3397, 3265, 3122, 2932, 2852, 1606, 1568, 1523. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.69 (s, 1H), 7.54 (s, 4H), 3.65 (s, 4H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 162.65, 148.99, 140.39, 138.09, 134.77, 130.81, 126.85, 95.81, 49.77. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}ClN_5$: 262.0859; found: 262.0861.

5-Amino-1-(4-bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2j). Yield: 84%; mp: 184–188°C (lit. 189–191°C [29]); FT–IR ν (cm^{-1}): 3387, 3260, 3119, 2926, 2852, 1605, 1566, 1523. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.68–7.70 (m, 3H), 7.49 (d, *J* = 8.9 Hz, 2H), 3.65 (s, 4H). ^{13}C NMR (101 MHz, MeOH-d_4): δ = 161.16, 147.51, 138.99, 137.10, 132.40, 125.61, 121.11, 94.29. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}BrN_5$: 306.0354; found: 306.0365.

5-Amino-4-(4,5-dihydro-1H-imidazol-2-yl)-1-(3-fluorophenyl)-1H-pyrazole (2k). Yield: 67%; mp: 164–166°C (lit. 169–171°C [29]); FT–IR ν (cm^{-1}): 3388, 3269, 3206, 3162, 2936, 2877, 1603, 1575, 1521. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (s, 1H), 7.55–7.56 (m, 1H), 7.46–7.49 (m, 2H), 7.19–7.22 (m, 1H), 6.73 (br, 2H), 3.51 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.10 (d, ^1J = 244.0 Hz), 159.91, 147.68, 139.98 (d, ^3J = 10.3 Hz), 138.78, 130.96 (d, ^3J = 9.2 Hz), 118.16 (d, ^4J = 2.7 Hz), 113.24 (d, ^2J = 21.0 Hz), 109.42 (d, ^2J = 25.3 Hz), 94.69. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}FN_5$: 246.1155; found: 246.1163.

5-Amino-1-(3-chlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2l). Yield: 74%; mp: 160–162°C (lit. 127–128°C [29]); FT–IR ν (cm^{-1}): 3376, 3280, 3222, 3171, 2948, 2922, 2876, 1632, 1609, 1594, 1569. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.70 (s, 1H), 7.61–7.62 (m, 1H), 7.52–7.53 (m, 2H), 7.42–7.44 (m, 1H), 3.65 (s, 4H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 162.74, 149.16, 140.76, 140.67, 136.29, 132.12, 129.18, 125.40, 123.48, 96.09. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}ClN_5$: 262.0859; found: 262.0877.

5-Amino-1-(3-bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole (2m). Yield: 47%; mp: 88–92°C (lit. 143–145°C [29]); FT–IR ν (cm^{-1}): 3442, 3321, 3249, 3088, 3063, 2941, 2869, 1614, 1592, 1527. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.76 (t, *J* = 1.9 Hz, 1H), 7.70 (s, 1H), 7.56–7.60 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 3.65 (s, 4H). ^{13}C NMR (101 MHz, MeOH-d_4): δ = 161.14, 147.61, 139.25, 139.13, 130.77, 130.63, 126.79, 122.39, 122.37, 94.42. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{12}BrN_5$: 306.0354; found: 306.0357.

5-Amino-4-(4,5-dihydro-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole (2n). Yield: 55%; mp: 138–140°C (lit. 135–136°C [29]); FT–IR ν (cm^{-1}): 3351, 3264, 3149, 3074, 934, 2885, 2864, 1595, 1567. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.69 (s, 1H), 7.53–7.54 (m, 4H), 7.42–7.45 (m, 1H), 3.65 (s, 4H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 162.83, 148.92, 140.18, 139.40, 130.87, 129.43, 125.60, 95.68, 49.82. HRMS (ESI): *m/z* [M + H]$^+$: Calcd for $C_{12}H_{13}N_5$: 228.1249; found: 228.1261.

Acknowledgments. This work is a collaboration research project of the members of the Rede Mineira de Química (RQ-MG) supported by FAPEMIG (Project: CEX – RED-00010-14). The authors thank CAPES, CNPq, and the Program for Technological Development in Tools for Health-RPT-FIOCRUZ for allowing the use of their facilities.

REFERENCES AND NOTES

[1] Faria, J. V.; Vergi, P. F.; Miguita, A. G. C.; Santos, M. S.; Boechat, N.; Bernardino, A. M. R. Bioorg Med Chem 2017, 25, 5891.

[2] El-Sehemi, A. G.; Bondock S; Ammar, Y. A. Med Chem Res 2013, 827.

[3] Küçükgüzel, S. G.; Senkardes, S. Eur J Med Chem 2015, 97, 786.

[4] Zhang, J.; Tan, D.; Wang, T.; Jing, S.; Kang, Y.; Zhang, Z. J Mol Struct 2017, 1149, 235.

[5] Sankappa, R. U.; Isloor, A. M.; Shetty, P.; Pai, K. S. R.; Fun, H. K. Arab J Chem 2015, 8, 317.

[6] Khan, M. F.; Alam, M. M.; Vera, G.; Akhtar, W.; Akhter, M.; Shaquiquzzaman, M. Eur J Med Chem 2016, 120, 170.

[7] Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. Chem Rev 2011, 111, 6984.

[8] Li, M.; Zhao, B. Eur J Med Chem 2014, 85, 311.

[9] Fustero, S.; Simon-Fuentes, A.; Sanz-Cervera, J. F. Org Prep Proced Int 2011, 41, 253.

[10] Knorr, L. Ber Dtsch Chem Ges 1884, 17, 1635.

[11] Pechmann, H. V. Ber Dtsch Chem Ges 1894, 27, 1888.

[12] Krasavin, M. Eur J Med Chem 2015, 97, 525.

[13] Bihan, G.; Rondu, F.; Pele-Tounian, A.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J Med Chem 1999, 42, 1587.

[14] Yu, A.; Frishman, W. H. J Clin Pharmacol 1996, 36, 98.

[15] Sun, M.; Wu, X.; Chen, J.; Cai, J.; Cao, M.; Ji, M. Eur J Med Chem 2010, 45, 2299.

[16] Ferm, R. J.; Riebsomer, J. L. Chem Rev 1954, 54, 593.

[17] Korshin, E. E.; Sabirova, L. I.; Akhmadullin, A. G.; Levin, Y. A. Russian Chem Bull 1994, 43, 431.

[18] Rousselet, G.; Capdeviell, P.; Maumy, M. Tetrahedron Lett 1993, 34, 6395.

[19] Spychala, J. Tetrahedron Lett 1999, 40, 2841.

[20] Vorbriiggen, H.; Krolikiewicz, K. Tetrahedron Lett 1981, 22, 4471.

[21] Welsch, S. J.; Umkehrer, M.; Kalinski, C.; Ross, G.; Burdack, C.; Kolb, J.; Wild, M.; Ehrlich, A.; Wessjohann, L. A. Tetrahedron Lett 2015, 56, 1025.

[22] Neef, G.; Eder, U.; Sauer, G. J Org Chem 1981, 46, 2826.

[23] Zhou, L.; Zhou, J.; Tan, C. K.; Chen, J.; Yeung, Y. Org Lett 2011, 13, 2448.

[24] Wrobel, T. M.; Kosikowska, U.; Kaczor, A. A.; Andrzejczuk, S.; Karczmarzyk, Z.; Wysocki, W.; Urbanczyk-Lipkowska, Z.; Morawiak, M.; Matosiuk, D. Molecules 2015, 20, 14761.

[25] Giorgioni, G.; Ambrosini, D.; Vesprini, C.; Hudson, A.; Nasuti, C.; Stefano, A.; Sozio, P.; Ciampi, O.; Costa, B.; Martini, C.; Carrieri, A.; Carbonara, G.; Enzensperger, C.; Pigini, M. Bioorg Med Chem 2010, 18, 7085.

[26] Romanova, N. N.; Kudan, P. V.; Gravis, A. G.; Bundel, Y. G. Chem Heterocyc Compd 2000, 36, 1130.

[27] Zhang, J.; Wang, X.; Yang, M.; Wan, K.; Yin, B.; Wang, Y.; Li, J.; Shi, Z. Tetrahedron Lett 2011, 52, 1578.

[28] De La Hoz, A.; Díaz-Ortiz, A.; Carmen, M. M.; Moral, M.; Moreno, A.; Elguero, J.; Foces-Foces, C.; Rodriguez, M. L.; Sánches-Migállon, A. Tetrahedron 2006, 62, 5868.

[29] Santos, M. S.; Oliveira, M. L. V.; Bernardino, A. M. R.; Léo, R. M.; Amaral, V. R.; Carvalho, F. T.; Leon, L. L.; Canto-Cavalheiro, M. M. Bioorg Med Chem 2011, 21, 7451.

[30] Santos, M. S.; Bernardino, A. M. R.; Pinheiro, L. C. S.; Canto-Cavalheiro, M. M.; Leon, L. L. J Heterocyclic Chem 2012, 49, 1425.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.