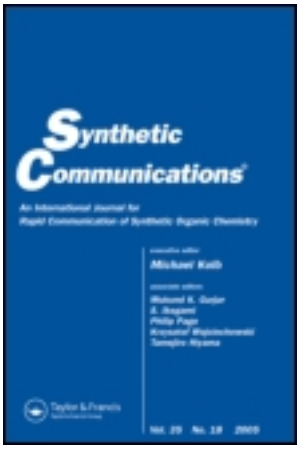

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Chemoselective and Regiospecific Formylation of 1-Phenyl-1H-pyrazoles Through the Duff Reaction

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CHEMOSELECTIVE AND REGIOSPECIFIC FORMYLATION OF 1-PHENYL-1*H*-PYRAZOLES THROUGH THE DUFF REACTION

C. H. A. de Oliveira,[1] L. M. Mairink,[1] F. Pazini,[1] L. M. Lião,[2] A. L. de Oliveira,[2] C. Viegas Jr.,[3] V. de Oliveira,[1] L. C. Cunha,[1] F. G. F. Oliveira,[1] J. L. Paz Jr.,[4] M. N. Eberlin,[4] and Ricardo Menegatti[1]

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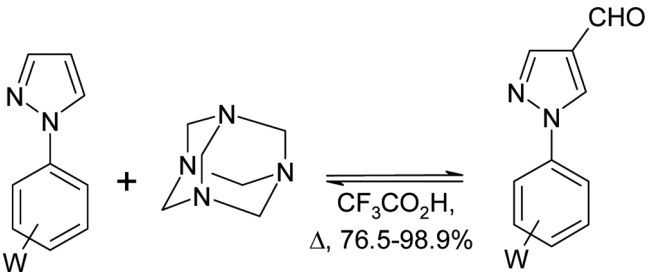
GRAPHICAL ABSTRACT



Abstract *The synthesis of formylated 1-phenyl-1*H*-pyrazole derivatives under the Duff reaction conditions is reported. Our results indicate that 1-phenyl-1*H*-pyrazole systems containing electron-withdrawing and electron-donating substituents at the phenyl moiety react under the Duff reaction conditions to furnish formylated derivatives in good yields.*

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Address correspondence to Ricardo Menegatti, Laboratório de Química Farmacêutica Medicinal (LQFM), Faculdade de Farmácia, Universidade Federal de Goiás, Goiânia 74 605 220, Brazil. E-mail: rm_rj@yahoo.com

INTRODUCTION

1-Phenyl-1*H*-pyrazoles are important compounds in many fields of chemistry, including the dye and pharmaceutical industries, supramolecular chemistry, and others. Formylation in position 4 of 1-phenyl-1*H*-pyrazole systems are often a key step in the synthesis of other compounds, such as (1*E*,4*E*)-1,5-bis(1-phenyl-1*H*-pyrazol-4-yl)-1,4-pentadien-3-one, tris-pyrazolyl-1,3,5-triazines, meso-tetrakis(1-arylpyrazol-4-yl)porphyrins, benzylic ethers of oximes derived from 1-phenylpyrazole compounds, and lead compounds for diabetes, in addition to derivatives with anti-inflammatory, analgesic, and antipyretic acivities.[1–6] The formylation of 1-phenyl-1*H*-pyrazoles is usually achieved under Vilsmeier–Haack conditions, in which phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) are used to generate the formyl moiety.[7] Reaction of the amide with phosphorus oxychloride generates an electrophilic iminium cation that reacts with activated arenes.[8] The 1-phenyl-1*H*-pyrazole-4-carbaldehydes have been produced under these conditions since 1957.[7]

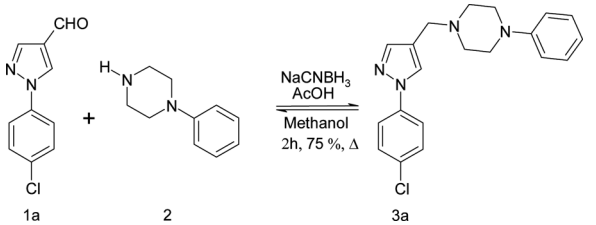
Although the Vilsmeier–Haack reaction is an important tool for the formation of C-C bonds in synthetic organic chemistry, it requires the use of dangerous reagents, such as phosphorus oxychloride. This reagent is also commercially restricted in many countries. Phosphorus oxychloride is corrosive and very toxic when inhaled. It is controlled by the Army in Brazil and restricted because of its environmental impact.[9] The Duff reaction presents a viable alternative because it can be used under milder, cheaper, and safer conditions than the Vilsmeier–Haack reaction.[10,11]

In the course of a research program aimed at developing drugs for the treatment of neurological disorders, we recently described the synthesis and pharmacological evaluation of new *N*-phenylpiperazine derivatives such as **3**, which were originally designed to be selective dopaminergic D_2 or D_4 receptor ligands (Scheme 1).[12,13] In this context, we are also interested in the development of a process that will allow us to attain intermediates such as **1a**. Thus, the aim of this work is to propose an alternative methodology for the formylation of 1-phenyl-1*H*-pyrazole derivatives.

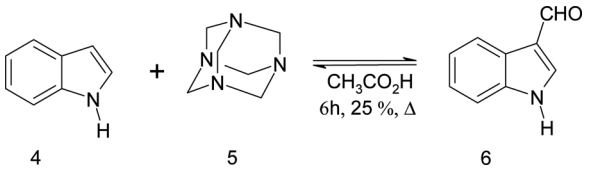
RESULTS AND DISCUSSION

The Duff reaction has been used mainly for the formylation of indole derivatives (e.g., **4**), which produces **6** in a modest 25% yield (Scheme 2).[14]

According to Scheme 2 and other experimental data available in the literature, we adapted the experimental conditions by changing the solvent from acetic acid to trifluorocetic acid. We kept the stoichiometry of 1 eq. of 1-phenyl-1*H*-pyrazoles 7**a–q**



Scheme 1. Synthesis of new *N*-phenylpiperazine derivatives that are selective D2 or D4 receptor lignads.



Scheme 2. Indol formylation through the use of Duff reactions.

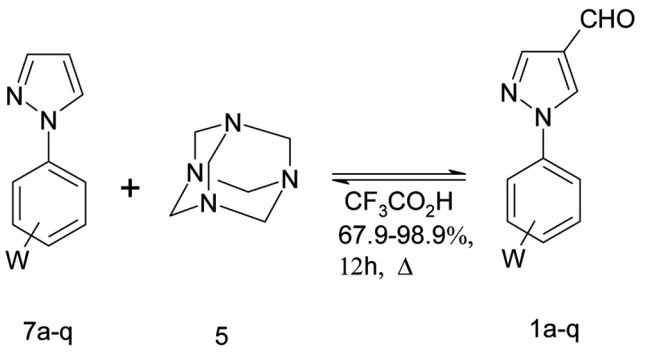
and 1.5 eq. of hexamethylenetetramine **5** under reflux temperature for 12 h (Scheme 3).[14–17]

All 1-phenyl-1*H*-pyrazoles **7a–q** used as substrates were synthesized as described by Finar and Godfey.[1] Under these conditions, a variety of substituted 1-phenyl-1*H*-pyrazoles **7a–q** with diverse electron-withdrawing and electron donating-subunits were chemoselectively formylated to generate compounds **1a–p** in 76.5–98.9% yields (Table 1).

Our results indicated that the presence of substituents at the *ortho*-position on the phenyl ring, as in **7h, 7n, 7k**, and **7p**, or at C-3 and C-5 on the pyrazole ring, as in **7o**, does not interfere with the chemoselectivity, regiospecificity, or yield of the reaction. However, when we submitted a 1-phenyl-1*H*-pyrazole with a strong electron-donor substituent, 1-(4-methoxyphenyl)-1*H*-pyrazole **7q**, to react with 1 eq. of **5**, we observed the formation of compounds **1q a** and **1q b** in 67.9% yields at a ratio of 94.2:5.5 respectively (entry 17).

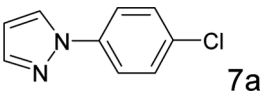
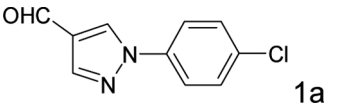
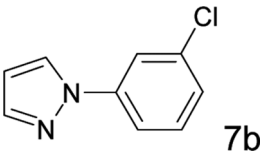
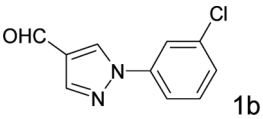
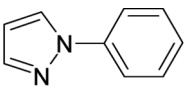
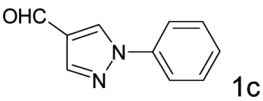
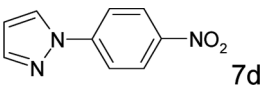
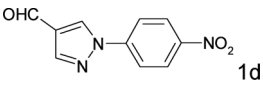
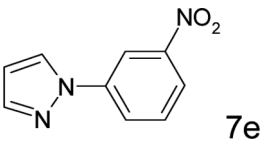
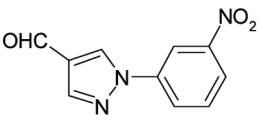
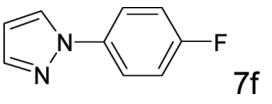
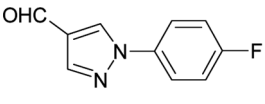
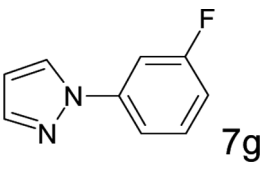
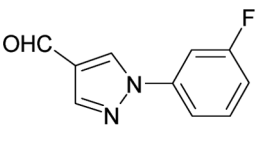
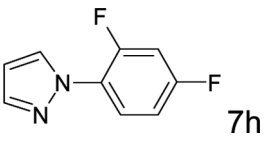
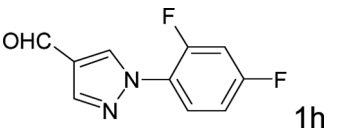
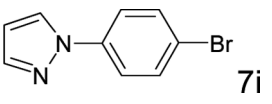
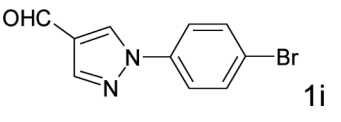
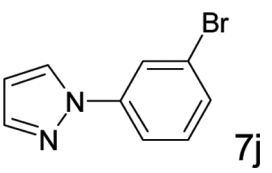
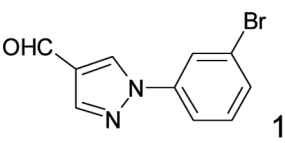
EXPERIMENTAL

All the melting points were determined with a Marte 284594 apparatus. NMR data were recorded using a Bruker Avance III spectrometer, operating at 500.13 MHz to proton frequency. The samples for NMR measurements were prepared in $CDCl_3$ containing 1% tetramethylsilane (TMS) as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; dddd, double double double doublet; td, triple doublet; t, triplet; tt, triple tiplet. The infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum



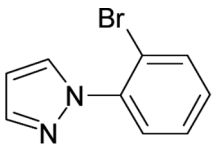
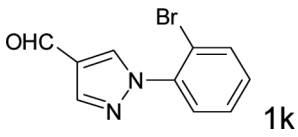
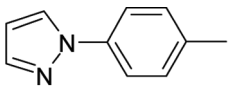
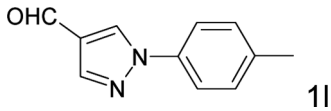
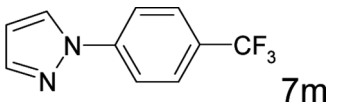
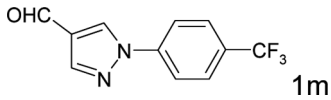
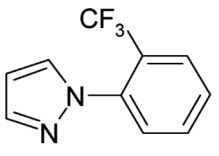
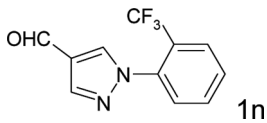
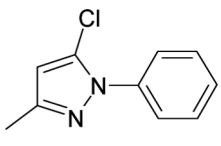
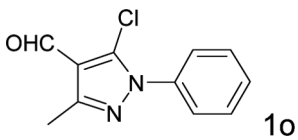
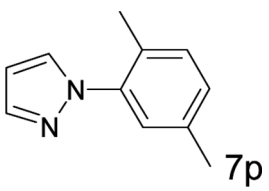
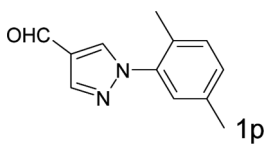
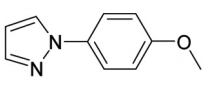
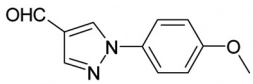
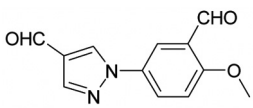
Scheme 3. 1-Phenyl-1*H*-pyrazole formylation of **7a–q** through the use of Duff reactions.

Table 1. Experimental data of the reactions of substituted-1-phenyl-1H-pyrazoles under the Duff reaction conditions

Entry	7a–q	T (h)	Compound	Yield (%)
1	 7a	12	 1a	77.9
2	 7b	12	 1b	98.5
3	 7c	12	 1c	98.0
4	 7d	12	 1d	76.5
5	 7e	12	 1e	89.2
6	 7f	12	 1f	98.9
7	 7g	12	 1g	95.4
8	 7h	12	 1h	88.8
9	 7i	12	 1i	79.3
10	 7j	12	 1j	98.6

(*Continued*)

Table 1. Continued

Entry	7a–q	T (h)	Compound	Yield (%)
11	 7k	12	 1k	97.9
12	 7l	12	 1l	97.6
13	 7m	12	 1m	93.9
14	 7n	12	 1n	95.0
15	 7o	6	 1o	98.0
16	 7p	12	 1p	88.9
17[a]	 7q	12	 1q a (94.2%)  1q b (5.5%)	67.9

[a]Determined by NMR and GC-MS.

400N Fourier transform (FT)-IR instrument in KBr plates. Microanalytical data were obtained with a Perkin-Elmer Spectrum BXII FT-IR system, using a digital analytical scale (Gehaka). Mass spectra (MS) were obtained with a Waters Micromass GCT Premier (Milford, MA, USA) orthogonal time-of-flight mass spectrometer. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on 2.0×6.0 cm aluminium sheets precoated with silica gel 60 (Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light (254–265 nm) and treated with iodine vapor. For column chromatography, we used Merck silica gel (70–230 mesh). Reagents and solvents were purchased from commercial suppliers and distilled prior the use.

Typical procedure was follows: 4.00 mmol of 1-phenyl-1*H*-pyrazoles **7a–p**, 6.00 mmol of hexamethylenetetramine **5**, and 5 mL of trifluoracetic acid were added to a 100 mL round-bottom flask. The reaction was heated under reflux with stirring for 12 h. At the end of the reaction, the resulting solution was neutralized with a 10% $NaHCO_3$ solution in an ice bath and the precipitate was filtered off under vacuum. When necessary, the crude products were purified by column chromatography.

CONCLUSION

In conclusion, 17 1-phenyl-1*H*-pyrazoles **7a–q** with different electron-withdrawing and electron-donating substituents at the phenyl moiety were chemoselectively and regiospecifically formylated with hexamethylenetetramine in trifluoroacetic acid under reflux in good yields. Thus, this methodology could be an efficient alternative method for the preparation of formylated 1-phenyl-1*H*-pyrazole derivatives under mild and safe conditions.

Full experimental details are available online in the Supplementary Information.

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