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4-Arylation of 3-alkoxypyrazoles

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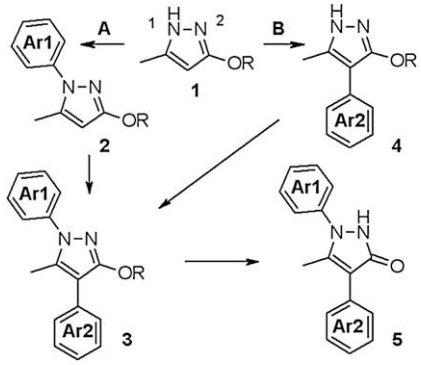
ABSTRACT

Following the study of the alkoxypyrazoles nitrogen's reactivity toward arylation or alkylation reactions, we report here our results on the introduction of various aryl groups on carbon 4 position of 3-alkoxy pyrazoles. This was achieved from the corresponding 4-halogeno derivatives via a Suzuki–Miyaura aryl–aryl coupling reaction. The unexpected difficulties (lack of reactivity or unwanted halogen reduction) encountered in the C-4 arylation of NH-free 4-halogenopyrazoles led us to design solutions to this recurrent problem. The cleavage of the 3-alkoxy group was also investigated using hydrogen bromide in acetic acid or boron tribromide in dichloromethane. This led, in one case, to the observation of a remarkable neighboring group-assisted electrophilic aryl boronylation. This second part of our work paves the way to the synthesis of many original chemical libraries featuring 3-alkoxy 1,4-diaryl pyrazoles as well as the corresponding 1,4-diaryl pyrazol-3-ones.

1. Introduction

Inexhaustible interest in the synthesis of arylated heterocyclic compounds is sustained by their value to medicinal chemistry. For instance, pyrazol-3-one is present in many organic compounds of biological interest. A data base survey points out that more than 76,790 derivatives featuring this nucleus were prepared, which led (from 1891 up to October 2008) to 15,593 patents. Interestingly, about half of these patents are less than 20 years old. These figures, better than anything, convey the fact that this heterocycle is a popular scaffold used in the design of many compounds of pharmaceutical or agricultural interest. The starting point of this work stems from our simple preparation of a vast array of 3-alkoxypyrazoles such as **1**.[1] From these compounds, the two general chemical pathways described in Scheme 1 were investigated. In the preceding paper,[2] we have described the 3-alkoxypyrazole nitrogens reactivity toward alkylation or arylation reactions leading to compound **2**. We report here the results of our investigation on the palladium-catalyzed arylation of the pyrazole ring to give 4-aryl derivatives such as **3** as well as the subsequent 3-alkoxy hydrolysis to provide an access to the 4-arylpyrazol-3-ones of the general formula **5**. Most of the *C*4-arylated pyrazol-3-ones have so far been usually prepared *per item* by condensation between hydrazines and various 1,3-dicarbonyl precursors.[3–10] As the introduction of the aryl moiety follows the construction of the pyrazole ring, our approach would provide a quicker method for the fine-tuning of any structure–activity relationship study undertaken in these series.



Scheme 1. General pathways investigated.

2. Results and discussion

The palladium-catalyzed coupling reaction of halogenated heterocycles featuring an NH component appears to be one of the few possibly limiting parameters of the Suzuki–Miyaura aryl–aryl cross-coupling reaction.[11–14] A short literature survey points out that this reaction has been found problematic in the case of 2-bromoindole,[15] some 4-iodopyrazoles,[16,17] or even worse from 4-bromopyrazole in comparison with *N*-benzyl-4-bromopyrazole.[18] The same phenomenon is actually seen when comparing the

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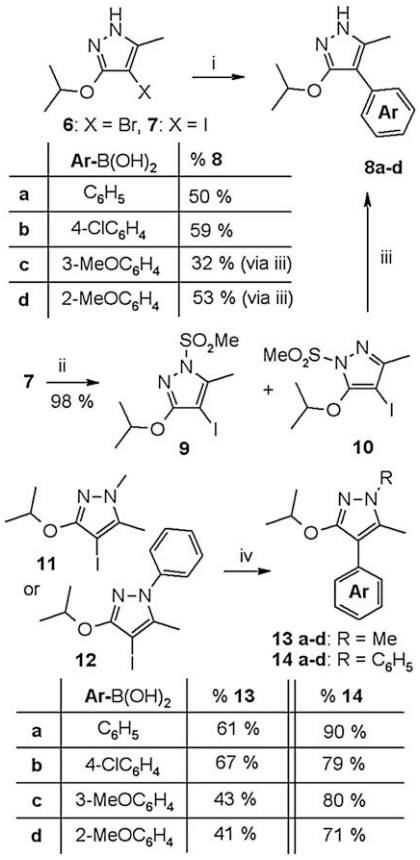
coupling reaction between 3-iodo-7-methyl-1,8-naphthyridin-4(1*H*)-one and its *N*-alkyl homologue.[19] We started scouting the routes for the Suzuki–Miyaura cross-coupling from 4-halogenated pyrazoles **6** and **7**,[2] and representative phenylboronic acids. A number of catalysts ($Pd[PPh_3]_4$, $PdCl_2(PPh)_3$, $PdCl_2$dppe, $PdCl_2$dppp, $PdCl_2$dppb, PEPPSI™-IPr catalyst, and several more) in the presence of various bases (K_3PO_4, K_2CO_3, Cs_2CO_3) in different aqueous solvents (THF, dioxane, propanol) appeared ineffective for the cross-coupling of **7** and phenylboronic acid. On the other hand, the reaction in the presence of [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium as a catalyst and cesium carbonate as a base in aqueous dioxane[20] provided the expected arylated product **8a**, albeit in moderate and fluctuating yields. Addition of lithium chloride has been reported to improve a few palladium-catalyzed aryl coupling reaction involving halogenated heterocycles with an NH component.[15,17,21,22] This turned out to be also true in our case, as the yields, in the presence of LiCl, became reproducible. Little or no improvements were observed when we switched from dioxane to propanol as a solvent for this reaction. We also noted that the 4-iodo-pyrazole **7** is more reactive in this reaction, as compared to its 4-bromo homologue **6**. Furthermore, the reaction time was shortened by the use of a microwave irradiation. Under these conditions, 4-chlorophenylpyrazole **8b** could also be synthesized. On the other hand, from **7** and the electron-rich 3-methoxyphenylboronic acid, a host of unidentified product(s) along with a very low yield of the coupling product **8c** were observed. Even worse, only traces of the coupling product **8d** were detected by LC/MS with the more sterically demanding 2-methoxyphenylboronic acid. These results led us to suggest that the problems encountered in this palladium-catalyzed aryl–pyrazole coupling reaction are due to the trapping of active catalytic species by NH-bearing pyrazole derivatives.

We thus resorted to the transient protection of the 3-alkoxy pyrazole nitrogens by a mesylation reaction. This gave a 1/4 proportion of the two possible mesyl-bearing isomers **9** and **10**. No attempt was made to separate them or to elucidate the regioselectivity of this reaction. This proportion seems actually quite variable upon the solvent used for the reaction. The palladium-catalyzed coupling of these isomers with 2 and 3-methoxy phenylboronic acids was then followed in situ by the basic hydrolysis of the mesylate group using potassium hydroxide. This allowed the preparation of compounds **8c** and **8d** in, respectively, 32% and 55% overall yield.

Somehow logically, from the *N*-methylated and *N*-arylated iodo derivatives **11** and **12**, much less problems were encountered. Indeed, without the recourse neither to lithium chloride nor, in early cases, to a microwave oven, consistent (and better) yields of the arylation products **13a**–**d** and **14a**–**d** were obtained from **11** and **12** and the corresponding arylboronates. We suggest that the difference in coupling efficiency seen between the *N*-methyl and the *N*-phenyl compounds **11** and **12** is due to their relative stability toward the reaction conditions (Scheme 2).

The N-arylation of compound **8a**, by the copper-mediated method previously used,[2] was also studied. From this compound, the N-1 arylation product **14a** could be isolated in 83% yield along with traces amount (4%) of the N-2 arylation product **15**. The 4-iodo-5-phenylpyrazole **17** was easily prepared by iodination of the readily available[1] pyrazole **16**. The 4-arylation reaction of this hindered 4-iodo-5-phenylpyrazole under the conditions described above led to the bis-arylated compound **18** although in only a 20% yield along with large amount (50%) of the reduced material **16**. Further work aiming at avoiding this was undertaken. The reported[23,24] use of 1-ethoxyethyl as a pyrazole protecting group prompted us to treat compound **17** with vinylethylether and an acid catalyst. This led to a mixture of the 1-ethoxyethyl-protected regioisomers **19**. These products were not further



	Ar-B(OH)$_2$	% 8
a	C_6H_5	50 %
b	4-ClC_6H_4	59 %
c	3-MeOC_6H_4	32 % (via iii)
d	2-MeOC_6H_4	53 % (via iii)

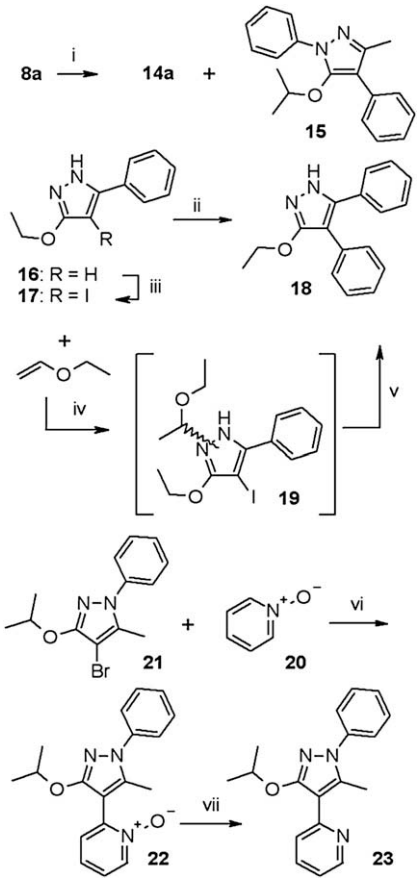
	Ar-B(OH)$_2$	% 13	% 14
a	C_6H_5	61 %	90 %
b	4-ClC_6H_4	67 %	79 %
c	3-MeOC_6H_4	43 %	80 %
d	2-MeOC_6H_4	41 %	71 %

Scheme 2. (i) ArB(OH)$_2$, $PdCl_2$dppf, Cs_2CO_3, LiCl, dioxane–H_2O, 130 °C, MW. (ii) MeSO$_2$Cl, NEt_3, AcOEt. (iii) ArB(OH)$_2$, $PdCl_2$dppf, Cs_2CO_3, LiCl, propanol–H_2O, 130 °C, MW then KOH, 90 °C. (iv) ArB(OH)$_2$, $PdCl_2$dppf, Cs_2CO_3, dioxane–H_2O, 90 °C.

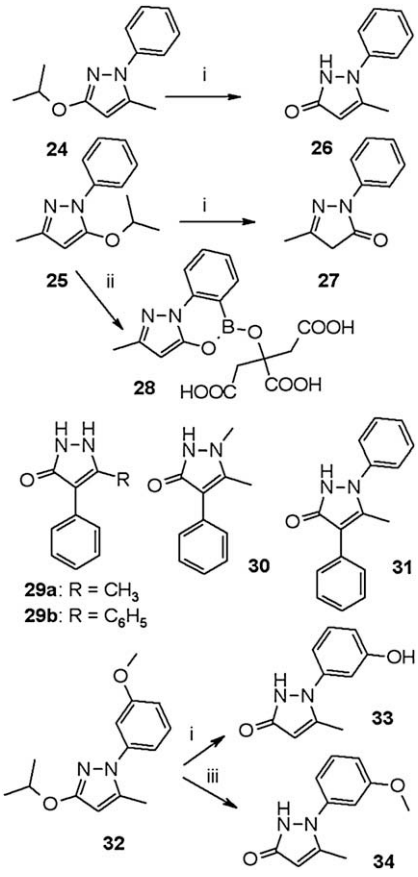
characterized and upon arylation reaction conditions followed by the treatment with hydrochloric acid, the bis-arylated compound **18** was then obtained in an unoptimized 59% yield. A trial with compound **7** also pointed out the efficiency of this approach in that case. This fruitful use of a 1-ethoxyethyl group is reminiscent of the pyran moiety reported recently as an efficient protecting group in pyrazole chemistry;[25–27] previous work has also reported the use of a trityl protecting group.[16] In our case, this 1-ethoxyethyl significantly improved the Suzuki–Miyaura aryl–pyrazole cross-coupling reaction. Further work in this domain is in progress.

In order to increase the chemical diversity attainable from these pyrazoles, we also applied the reported coupling of pyridine *N*-oxide[28] (**20**) to our halogenated pyrazoles **11** and **12**. From the 4-iodo derivative **12**, under microwave irradiation, none of the expected arylation product was obtained. A slow reduction of the 4-iodopyrazole to the parent compound was the sole transformation we could monitor by LC/MS. On the other hand, from the 4-bromopyrazole **21**,[2] the coupling reaction proceeded in a 61% yield to give compound **22**. Unfortunately, much less *C*4-arylated product could be obtained from the *N*-methyl analogue of **21** and none from the NH-bearing compounds **6** and **7** (with or without lithium chloride added). Compound **22** was further catalytically reduced to the corresponding 2-pyridyl derivative **23** using ammonium formate as a source of hydrogen in boiling ethanol (Scheme 3).

In order to complete this synthetic exploration, we undertook the cleavage of the ethyl or isopropyl ether protecting the oxygen moiety of these compounds. This cleavage was best achieved using hydrogen bromide acetic acid in a sealed tube at high temperature and under argon atmosphere to prevent oxidative bromination of



Scheme 3. (i) $Cu(OAc)_2$, $PheB(OH)_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2, air, 25 °C. (ii) I_2, NaI, K_2CO_3, EtOH, H_2O, 25 °C. (iii) $PheB(OH)_2$, $PdCl_2dppf$, Cs_2CO_3, LiCl, PrOH–H_2O, 120 °C, MW. (iv) APTS, dichloromethane. (v) $PheB(OH)_2$, $PdCl_2dppf$, Cs_2CO_3, PrOH–H_2O, 120 °C, MW then HCl, 12 N. (vi) PBu_2Me–HBF_4, $Pd(OAc)_2$, K_2CO_3, toluene, 170 °C, MW. (vii) 10% Pd–C, NH_3–HCO_2H, ethanol reflux.



Scheme 4. (i) HBr–AcOH, 140 °C. (ii) BBr_3, CH_2Cl_2, reflux. (iii) HCl, 37% reflux.

some of the substrates. As mentioned in the proceeding report,[2] stronger structural assignment was obtained by the deprotection of the isomers[2] **24** and **25** into the corresponding pyrazol-3-ones **26** and **27** in 74 and 76% yield, respectively. As only the isomer **27** can display methylenic ^1H and ^{13}C signals, this lifted any doubt on structures of compounds **24** and **25**. A more thorough NMR study of the behavior of compound **27** has actually been reported recently.[29] The use of boron tribromide in boiling dichloromethane to deprotect compound **24** also led to compound **26** although in a lower yield. On the other hand, a remarkable process took place when trying to deprotect compound **25** with this reagent. Indeed, the sole product we could isolate from this trial was the boronic ester resulting from a boronylation of the proximate phenyl moiety. This reaction product was actually characterized as the citric acid ether derivative **28**, which precipitates from the reaction mixture upon addition of citric acid. Further work on this original electrophilic boronylation reaction is in progress. By using hydrogen bromide in acetic acid at 140 °C, many other pyrazol-3-ones were obtained such as compounds **29a** and **29b** from compounds **8a** and **18** in 45% and 73% yield, respectively, or compound **30** from **13a** and compound **31** from **14a** in 76% and 92% yield, respectively. Under these conditions, the 3-methoxyphenyl derivative **32**[2] underwent full cleavage of the ether residues to give compound **33** in a 64% yield. A selective deprotection of 3-alkoxypyrazole moiety of **32** to 3-methoxyphenyl pyrazole-3-one **34** could be achieved in boiling hydrochloric acid in 43% yield. All these deprotected compounds are depicted in their 'oxo' tautomeric form. However, depending on their substituent these compounds often exist in their 'hydroxy' tautomeric form in solution (Scheme 4).[30]

In summary, the introduction of a halogen atom at C-4 position of 3-alkoxypyrazole ring system followed by the Suzuki–Miyaura cross-coupling reaction with arylboronic acids allowed preparation of arylpyrazoles in satisfactory yields. This work encountered the recurrent problem of achieving a Suzuki–Miyaura coupling reaction with a halogenated substrate bearing exchangeable hydrogen. The addition of lithium chloride[15,17,21,22] to the reaction mixture answered this problem only partially. Accordingly, we developed the use of the mesyl and 1-ethoxyethyl as transient protecting groups for this heterocycle, which allowed a greater scope for the Suzuki–Miyaura reaction. The use of [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium as a precatalyst afforded the cross-coupling products in reasonable yields and in short reaction time, which can be further reduced by the microwave irradiation. The cleavage of ethyl or isopropyl ether group protecting the oxygen of the 3-alkoxypyrazoles moiety can be achieved by treatment with HBr/AcOH at elevated temperature. Alternatively, the cleavage of some of these ethers is also possible with boron tribromide in boiling dichloromethane. On the new chemical entities aspect, we hope that the present work will provide an easier access to 4-arylated-3-alkoxypyrazoles and related pyrazol-3-ones of potential biological interest that have been overlooked in the past. Efforts aiming at further refinement of the reaction sequence leading to these challenging molecules are in progress. These results, as well as the biological evaluation of the corresponding chemical libraries, will be communicated in due course.

3. Experimental part

3.1. General

A Biotage Initiator 2 microwave oven was used for reactions requiring microwave irradiations. The ^1H NMR and ^{13}C NMR spectra

were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Unless otherwise noted, $CDCl_3$ was the solvent used. Shifts (δ) are given in parts per million with respect to the TMS signal and coupling constants (J) are given in hertz. Column chromatography was performed either with Merck silica gel 60 (0.035–0.070 mm) or neutral alumina containing a suitable proportion of water, using a solvent pump operating at pressure between 2 and 7 bar (25–50 mL/mn) and an automated collecting system driven by a UV detector set to 254 nm unless stated otherwise (i.e., if ethyl acetate was used then it would be set to 280 nm). Sample deposition was always carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high resolution mass spectroscopy spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source.

3.2. Palladium-catalyzed C-arylation of compound 7; preparation of 8a and 8b

In a Biotage 10 mL tube a mixture of the considered pyrazole (1 mmol), the relevant boronic acid (1.3 mmol), cesium carbonate (2.5 mmol), lithium chloride (2.1 mmol) in dioxane (4 mL), and water (4 mL) was degassed with a slow stream of argon for 10 min. Following this, [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.05 mmol) was added, the tube was sealed and heated at 120 °C for 30 min in the microwave oven. After cooling to room temperature, the reaction mixture was diluted in water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel as described below.

3.2.1. 3-Isopropoxy-5-methyl-4-phenyl-1H-pyrazole **8a**

Obtained as an oil that slowly solidified in a 50% yield after a chromatography over silica gel (cyclohexane–dichloromethane 2/8). Mp=86 °C. ^1H ($CDCl_3$): 1.47 (d, 6H, J=6.1 Hz), 2.38 (s, 3H), 5.00 (sept, 1H, J=6.1 Hz), 7.30 (m, 1H), 7.44 (m, 2H), 7.57 (m, 2H), 10.5 (br s, 1H). ^{13}C ($CDCl_3$): 11.9, 22.8, 72.2, 105.4, 126.0, 128.6, 128.7, 133.1, 138.1, 160.5. HRMS: Calcd for $C_{13}H_{16}N_2O$+H: 217.1341. Found: m/z, 217.1348.

3.2.2. 4-(4-Chlorophenyl)-3-isopropoxy-5-methyl-1H-pyrazole **8b**

Obtained as a solid in a 59% yield after a chromatography over silica gel (dichloromethane–ethanol 99/1). Mp=145 °C. ^1H ($CDCl_3$): 1.27 (d, 6H, J=6.1 Hz), 2.20 (s, 3H), 4.79 (sept, 1H, J=6.1 Hz), 7.23 (m, 2H), 7.29 (m, 2H), 9.00 (br s, 1H). ^{13}C ($CDCl_3$): 11.7, 22.4, 71.9, 104.1, 128.5, 129.3, 131.1, 131.3, 137.6, 160.1. HRMS: Calcd for $C_{13}H_{15}^{35}ClN_2O$+H: 251.0951. Found: m/z, 251.0978.

3.3. Preparation of the mixture of 4-iodo-5-isopropoxy-3-methyl-1-(methylsulfonyl)-1*H*-pyrazole and 4-iodo-3-isopropoxy-5-methyl-1-(methylsulfonyl)-1*H*-pyrazole 9 and 10

Compound **7** (2.31 g, 8.68 mmol) was dissolved in ethyl acetate (90 mL), triethylamine (1.9 mL, 13.8 mmol, dried over 4 Å molecular sieves) was added followed by mesyl chloride (1 mL, 13.0 mmol). The solution was protected from moisture by a calcium chloride guard and stirred for 2 h at room temperature. This was washed with 2 N potassium carbonate, 0.5 N hydrochloric acid and brine, dried over sodium sulfate, and concentrated to dryness to yield the 1/4 mixture of compounds **9** and **10** as a dark oil (2.84 g, 95%). ^1H ($CDCl_3$): 1.40 (d, 4/5 of 6H, J=6.1 Hz), 1.42 (d, 1/5 of 6H, J=6.1 Hz), 2.28 (s, 1/5 of 3H), 2.54 (s, 4/5 of 3H), 3.23 (s, 4/5 of 3H), 3.24 (s, 1/5 of 3H), 5.02 (m, 1H).

3.4. Palladium-catalyzed C-arylation of the mixture of compounds 9 and 10, preparation of 8c and 8d

In a Biotage 10 mL tube a mixture of the considered pyrazole (1.1 mmol); the relevant boronic acid (1.45 mmol), cesium carbonate (2.8 mmol), lithium chloride (2.24 mmol) in propanol (5 mL), and water (5 mL) were degassed with a slow stream of argon for ten minutes. Following this, [1,1′-bis(diphenylphosphino)-ferrocene] dichloropalladium complexed with dichloromethane (0.044 mmol) was added, the tube was sealed and heated at 120 °C for 60 min in the microwave oven. After cooling to room temperature, potassium hydroxide (5 mmol) was added and the tube heated in an oil bath at 90 °C for 2 h. This was diluted in water, extracted with ethyl acetate, the organic layer was washed with brine and dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel as described below.

3.4.1. 3-Isopropoxy-4-(3-methoxyphenyl)-5-methyl-1H-pyrazole **8c**

Obtained as an oil in a 32% yield after a chromatography over neutral alumina containing 1.5% of water (cyclohexane–ethyl acetate 7/3). ^1H ($CDCl_3$): 1.39 (d, 6H, J=6.1 Hz), 2.37 (s, 3H), 3.85 (s, 3H), 4.93 (sept, 1H, J=6.1 Hz), 6.80 (m, 1H), 7.08 (m, 1H), 7.12 (m, 1H), 7.30 (m, 1H), 9.10 (br s, 1H). ^{13}C ($CDCl_3$): 11.7, 22.2, 55.1, 71.6, 105.0, 111.2, 113.7, 120.5, 129.2, 133.9, 137.5, 159.5, 160.2. HRMS: Calcd for $C_{14}H_{18}N_2O_2$+H: 247.1447. Found: m/z, 247.1387.

3.4.2. 3-Isopropoxy-4-(2-methoxyphenyl)-5-methyl-1H-pyrazole **8d**

Obtained as an oil in a 53% yield after a chromatography over neutral alumina containing 1.5% of water (cyclohexane–ethyl acetate 7/3) followed by a second chromatography over silica gel (dichloromethane–ethanol 98.5/1.5). ^1H ($CDCl_3$): 1.35 (d, 6H, J=6.1 Hz), 2.20 (s, 3H), 3.83 (s, 3H), 4.86 (sept, 1H, J=6.1 Hz), 7.01 (m, 2H), 7.28 (m, 2H), 7.40 (br s, 1H). ^{13}C ($CDCl_3$): 11.5, 22.2, 55.3, 102.2, 110.0, 120.4, 120.8, 128.2, 132.0, 139.2, 156.9, 160.5. HRMS: Calcd for $C_{14}H_{18}N_2O_2$+H: 247.1447. Found: m/z, 247.1398.

3.5. Palladium-catalyzed C-arylation of compounds 11 and 12

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, a mixture of the considered pyrazole (1.14 mmol), the relevant boronic acid (2.27 mmol), cesium carbonate (2.27 mmol) in dioxane (4 mL), and water (1 mL) was degassed with a slow stream of argon for 10 min. Following this, [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.057 mmol) was added, the tube was closed tightly and heated at 90 °C overnight. After cooling to room temperature, the reaction mixture was diluted in water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel as described below.

3.5.1. 3-Isopropoxy-1,5-dimethyl-4-phenyl-1H-pyrazole **13a**

This compound was obtained as an oil in a 61% yield from **11** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 1/4). ^1H ($CDCl_3$): 1.36 (d, 6H, J=6.1 Hz), 2.31 (s, 3H), 3.71 (s, 3H), 4.88 (sept, 1H, J=6.1 Hz), 7.23 (m, 1H), 7.41 (m, 4H). ^{13}C ($CDCl_3$): 10.7, 22.3, 35.7, 71.4, 105.8, 125.5, 128.2, 128.6, 133.0, 136.6, 158.6. HRMS: Calcd for $C_{14}H_{18}N_2O$+H: 231.1497. Found: m/z, 231.1528.

3.5.2. 4-(4-Chlorophenyl)-3-isopropoxy-1,5-dimethyl-1H-pyrazole ***13b***

This compound was obtained as a yellow solid in a 67% yield from **11** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 1/9). Mp=86 °C. ^{1}H ($CDCl_3$): 1.35 (d, 6H, *J*=6.1 Hz), 2.29 (s, 3H), 3.70 (s, 3H), 4.88 (sept, 1H, *J*=6.1 Hz), 7.34 (m, 4H). ^{13}C ($CDCl_3$): 10.7, 22.2, 35.7, 71.4, 104.7, 128.3, 129.7, 131.1, 131.5, 136.6, 158.4. HRMS: Calcd for $C_{14}H_{17}^{35}ClN_2O$+H: 265.1108. Found: *m*/*z*, 265.1037.

3.5.3. 3-Isopropoxy-4-(3-methoxyphenyl)-1,5-dimethyl-1H-pyrazole ***13c***

This compound was obtained as an oil in a 43% yield from **11** after a chromatography over silica gel (cyclohexane–ethyl acetate 97/3). ^{1}H ($CDCl_3$): 1.38 (d, 6H, *J*=6.1 Hz), 2.31 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.91 (sept, 1H, *J*=6.1 Hz), 6.80 (m, 1H), 7.05 (m, 2H), 7.30 (m, 1H). ^{13}C ($CDCl_3$): 10.8, 22.2, 35.6, 55.1, 71.4, 105.6, 111.1, 114.2, 129.4, 134.3, 136.8, 158.6, 159.5. HRMS: Calcd for $C_{15}H_{20}N_2O_2$+H: 261.1603. Found: *m*/*z*, 261.1553.

3.5.4. 3-Isopropoxy-4-(2-methoxyphenyl)-1,5-dimethyl-1H-pyrazole ***13d***

This compound was obtained as an oil in a 41% yield from **11** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 1/9). ^{1}H ($CDCl_3$): 1.34 (d, 6H, *J*=6.1 Hz), 2.13 (s, 3H), 3.71 (s, 3H), 3.83 (s, 3H), 4.85 (sept, 1H, *J*=6.1 Hz), 6.98 (m, 2H), 7.28 (m, 2H). ^{13}C ($CDCl_3$): 10.9, 22.3, 35.7, 55.3, 71.1, 102.1, 110.9, 120.4, 121.4, 127.8, 132.1, 138.1, 156.9, 158.7. HRMS: Calcd for $C_{15}H_{20}N_2O_2$+H: 261.1603. Found: *m*/*z*, 261.1531.

3.5.5. 3-Isopropoxy-5-methyl-1,4-diphenyl-1H-pyrazole ***14a***

This compound was obtained as an oil in a 90% yield from **12** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 1/4). ^{1}H ($CDCl_3$): 1.42 (d, 6H, *J*=6.1 Hz), 2.39 (s, 3H), 5.06 (sept, 1H, *J*=6.1 Hz), 7.27 (m, 1H), 7.34 (m, 1H), 7.47 (m, 8H). ^{13}C ($CDCl_3$): 13.0, 22.7, 71.8, 108.5, 125.2, 126.2, 127.2, 128.6, 129.1, 129.4, 132.9, 137.2, 140.4, 160.6. HRMS: Calcd for $C_{19}H_{20}N_2O$+H: 293.1654. Found: *m*/*z*, 293.1672.

3.5.6. 4-(4-Chlorophenyl)-3-isopropoxy-5-methyl-1-phenyl-1H-pyrazole ***14b***

This compound was obtained as a white solid in a 79% yield from **12** after a chromatography over silica gel (dichloromethane–cyclohexane 2/8). Mp=92 °C. ^{1}H ($CDCl_3$): 1.43 (d, 6H, *J*=6.1 Hz), 2.38 (s, 3H), 5.08 (sept, 1H, *J*=6.1 Hz), 7.38 (m, 3H), 7.50 (m, 6H). ^{13}C ($CDCl_3$): 12.6, 22.3, 71.5, 107.0, 124.8, 126.9, 128.4, 129.0, 129.9, 131.0, 131.6, 136.7, 139.9, 160.0. HRMS: Calcd for $C_{19}H_{19}N_2^{35}ClO$+H: 293.1654. Found: *m*/*z*, 293.1672.

3.5.7. 3-Isopropoxy-4-(3-methoxyphenyl)-5-methyl-1-phenyl-1H-pyrazole ***14c***

This compound was obtained as an oil in a 80% yield from **12** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 1/9). ^{1}H ($CDCl_3$): 1.45 (d, 6H, *J*=6.1 Hz), 2.43 (s, 3H), 3.89 (s, 3H), 5.11 (sept, 1H, *J*=6.1 Hz), 6.88 (m, 1H), 7.16 (m, 2H), 7.36 (m, 2H), 7.50 (m, 4H). ^{13}C ($CDCl_3$): 12.7, 22.3, 55.1, 71.3, 107.9, 111.6, 114.4, 121.1, 125.0, 126.8, 128.7, 128.9, 133.8, 136.9, 140.0, 159.6, 160.2. HRMS: Calcd for $C_{19}H_{19}N_2^{35}ClO$+H: 293.1654. Found: *m*/*z*, 293.1672.

3.5.8. 3-Isopropoxy-4-(2-methoxyphenyl)-5-methyl-1-phenyl-1H-pyrazole ***14d***

This compound was obtained as an oil in a 71% yield from **12** after a chromatography over neutral alumina containing 1.5% of water (dichloromethane–cyclohexane 2/8). ^{1}H ($CDCl_3$): 1.47 (d, 6H, *J*=6.1 Hz), 2.29 (s, 3H), 3.90 (s, 3H), 5.12 (sept, 1H, *J*=6.1 Hz), 7.08 (m, 2H), 7.35 (m, 2H), 7.47 (m, 3H), 7.61 (m, 2H). ^{13}C ($CDCl_3$): 12.7, 22.3, 55.4, 71.2, 104.9, 111.2, 120.5, 121.1, 121.4, 124.4, 126.5, 128.2, 128.7, 132.3, 138.2, 140.1, 157.1, 160.5. HRMS: Calcd for $C_{19}H_{19}N_2^{35}ClO$+H: 293.1654. Found: *m*/*z*, 293.1672.

3.6. Preparation of 14a and 15 by the copper-catalyzed N-arylation of 8a

Compound **8a** (0.16 g, 0.74 mmol), phenylboronic acid (0.1 g, 0.81 mmol), pyridine (0.12 mL, 1.48 mmol, dried over 4 Å molecular sieves), copper(II) acetate hydrate (0.22 g, 1.11 mmol), and 4 Å molecular sieves (0.3 g) were stirred in open air for 48 h in dichloromethane (50 mL). The resulting suspension was absorbed on a small amount of silica gel and purified by a chromatography over silica gel (dichloromethane–cyclohexane 5/5 to 7/3) to yield compound **14a** (0.18 g, 83% as described above) and then compound **15** (0.01 g, 4%).

3.6.1. 5-Isopropoxy-3-methyl-1,4-diphenyl-1H-pyrazole ***15***

Obtained as an oil ^{1}H ($CDCl_3$): 1.03 (d, 6H, *J*=6.1 Hz), 2.39 (s, 3H), 4.06 (sept, 1H, *J*=6.1 Hz), 7.30 (m, 2H), 7.45 (m, 4H), 7.51 (m, 2H), 7.78 (m, 2H). ^{13}C ($CDCl_3$): 14.3, 22.6, 77.8, 108.6, 123.1, 127.0, 128.6, 128.8, 129.1, 129.3, 133.1, 139.3, 147.4, 149.9. HRMS: Calcd for $C_{19}H_{20}N_2O$+H: 293.1654. Found: *m*/*z*, 293.1665.

3.6.2. 3-Ethoxy-4-iodo-5-phenyl-1H-pyrazole ***17***

Compound **16**[1] (1.6 g, 8.51 mmol), potassium carbonate (3.52 g, 25.53 mmol), sodium iodide (1.27 g, 8.51 mmol) were dissolved in 80 mL of a water ethanol mixture 4–6. To this was added iodine (3.2 g, 12.76 mmol). The solution was stirred for 1 h dispersed in water (300 mL) and the resulting precipitate was filtered, washed with water, and dried under high vacuum to yield compound **17** as a slightly yellow powder (2.02 g, 75%). Mp=128 °C. ^{1}H ($CDCl_3$): 1.38 (t, 3H, *J*=7.0 Hz), 4.21 (q, 2H, *J*=7.0 Hz), 7.48 (m, 3H), 7.66 (m, 2H), 10.53 (s(br), H). ^{13}C ($CDCl_3$): 14.8, 45.1, 65.2, 126.6 (two signals), 128.8, 129.3, 144.5, 163.8. HRMS: Calcd for $C_{11}H_{11}IN_2O$+H: 314.9994. Found: *m*/*z*, 315.0020.

3.6.3. 3-Ethoxy-4,5-diphenyl-1H-pyrazole ***18***

In a 10 mL Biotage glass tube compound **17** (0.29 g, 9.2 mmol), phenylboronic acid (0.14 g, 1.20 mmol), cesium carbonate (0.75 g, 2.30 mmol), lithium chloride (0.078 g, 1.84 mmol) in propanol (2.5 mL), and water (2.5 mL) was degassed with a slow stream of argon for 10 min. Following this, [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.038 g, 0.046 mmol) was added, the tube was sealed and heated at 120 °C for 30 min in the microwave oven. After cooling to room temperature, the reaction mixture was diluted in water and extracted with dichloromethane. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified first by chromatography over silica gel (dichloromethane–ethanol 98/2) and the fractions containing compounds **17** and **18** were further purified by a second chromatography over alumina containing 1.5% water (dichloromethane and then dichloromethane–ethanol 99/1) to yield, in this order, compound **18** (0.05 g, 20%) and then the reduced compound **17** (0.09 g, 52%). Mp=151 °C (lit.[31]=157–158 °C). ^{1}H ($CDCl_3$): 1.42 (t, 3H, *J*=7.0 Hz), 4.34 (q, 2H, *J*=7.0 Hz), 7.20 (m, 1H), 7.32 (m, 2H), 7.37 (m, 7H), 9.67 (s(l), 1H). ^{13}C ($CDCl_3$): 15.0, 64.1, 104.6, 126.1, 127.8, 128.2, 128.7, 128.9, 129.1, 130.3, 131.6, 141.2, 161.6. HRMS: Calcd for $C_{17}H_{16}N_2O$+H: 265.1341. Found: *m*/*z*, 265.1292.

3.7. Alternative preparation of 18 via 19

Compound **17** (0.5 g, 1.59 mmol) was dissolved in dichloromethane (20 mL); ethylvinylether (0.9 mL, 9.5 mmol) and *p*-toluenesulfonic acid (0.015 g, 0.08 mmol) were added and the solution was stirred for 45 min at room temperature. Solid potassium carbonate (0.022 g) was added to the resulting dark solution, which was concentrated to dryness to yield a dark oil containing the mixture of product **19**. Without further purification, the residue was dispersed in propanol (5 mL) and transferred in a 10 mL Biotage tube. To this was added water (5 mL), potassium carbonate (0.55 g, 3.98 mmol), and phenylboronic acid (0.21 g, 1.75 mmol). The suspension was degassed by argon bubbling for 10 mn and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.064, 0.079 mmol) was added. The tube was sealed and heated at 120 °C for 30 min in the microwave oven. The resulting cooled mixture was treated with 12 N hydrochloric acid (0.70 mL), stirred for 45 min and then diluted in ethyl acetate. The organic phase was washed with brine three times, dried over sodium sulfate, and concentrated to dryness. The residue was then purified as described above to yield compound **18** (0.25 g, 59%).

3.7.1. 2-(3-Isopropoxy-5-methyl-1-phenyl-1H-pyrazol-4-yl)-pyridine 1-oxide **22**

In a 5 mL Biotage vial, 4-bromo-3-isopropoxy-5-methyl-1-phenyl-1*H*-pyrazole **21**[2] (0.28 g, 0.95 mmol), pyridine *N*-oxide (**20**) (0.35 g, 3.75 mmol), di-*tert*-butylmethyl phosphonium tetrafluoroborate (0.035 g, 0.14 mmol), potassium carbonate (0.26 g, 1.87 mmol), and palladium acetate (10.5 mg, 0.047 mmol) were dispersed in toluene (5 mL). This was degassed by a slow stream of argon for 10 min, sealed and heated in the microwave oven for 40 min at 170 °C. The resulting mixture was adsorbed over a small amount of silica and purified by a chromatography over silica gel (dichloromethane–ethanol 98/2) to yield compound **22** (0.18 g, 61%) as a solid. Mp=152 °C. ^{1}H ($CDCl_3$): 1.34 (d, 6H, *J*=6.1 Hz), 2.36 (s, 3H), 5.01 (sept, 1H, *J*=6.1 Hz), 7.11–7.34 (m, 3H), 7.42–7.53 (m, 5H), 8.30 (m, 1H). ^{13}C ($CDCl_3$): 14.2, 22.2, 71.8, 99.8, 123.4, 124.8, 125.0, 127.3, 128.8, 128.9, 139.5, 139.9, 141.3, 142.9, 159.9. HRMS: Calcd for $C_{18}H_{19}N_3O$+H: 310.1555. Found: *m*/*z*, 310.1570.

3.7.2. 2-(3-Isopropoxy-5-methyl-1-phenyl-1H-pyrazol-4-yl)-pyridine **23**

Compound **22** (0.15 g, 0.48 mmol), ammonium formate (0.3 g, 4.85 mmol), and 10% palladium over charcoal (5 mg, 0.05 mmol) were heated to reflux in methanol (10 mL) for 20 h. The crude residue obtained after concentration to dryness was purified by a chromatography over silica gel (dichloromethane) to yield compound **23** (0.1 g, 71%) as a solid. Mp=71 °C. ^{1}H ($CDCl_3$): 1.45 (d, 6H, *J*=6.1 Hz), 2.65 (s, 3H), 5.13 (sept, 1H, *J*=6.1 Hz), 7.07 (m, 1H), 7.36 (m, 1H), 7.49 (m, 4H), 7.66 (m, 1H), 7.90 (m, 1H), 8.62 (m, 1H). ^{13}C ($CDCl_3$): 13.2, 22.4, 71.6, 106.7, 119.9, 122.7, 125.3, 127.2, 129.0, 135.8, 139.7, 139.9, 148.8, 153.2, 160.5. HRMS: Calcd for $C_{18}H_{19}N_3$+H: 294.1606. Found: *m*/*z*, 294.1624.

3.7.3. 2-(2-Methyl-5H-benzo[c]pyrazolo[1,5-e][1,5,2]oxazaborinin-5-yloxy)propane-1,2,3-tricarboxylic acid **28**

The *N*-phenyl derivative **25** (0.2 g, 0.925 mmol) was dissolved in dichloromethane (20 mL). To this was added 1 M boron tribromide in dichloromethane (1.85 mL, 1.85 mmol) and the mixture was heated to reflux overnight. This was cautiously quenched with ice and an excess of citric acid was added. The precipitate was dispersed in water and dichloromethane, filtered, and dried in open air to yield compound **28** as a white powder (0.1 g, 28%). Mp >260 °C. ^{1}H (DMSO-d_6): 2.29 (s, 3H), 2.62 (d, 1H, *J*=14.1 Hz), 2.70 (d, 1H, *J*=14.1 Hz), 2.83 (d, 1H, *J*=15.5 Hz), 2.95 (d, 1H, *J*=15.5 Hz), 5.63 (s(l), 1H), 7.13 (m, 1H), 7.37 (m, 1H), 7.48 (d, 1H, *J*=8.0 Hz), 7.59 (d, 1H, *J*=7.4 Hz). ^{13}C (DMSO-d_6): 12.1, 41.0, 43.6, 76.3, 91.4, 111.2, 119 (very weak signal), 125.6, 128.5, 133.6, 136.2, 148.1, 155.0, 170.9, 171.3, 178.1. HRMS: Calcd for $C_{10}H_9BN_2O_2$−H: 199.0681. Found: *m*/*z*, 199.0639 and (much weaker signal), Calcd for $C_{16}H_{15}BN_2O_8$−H: 373.0846. Found: *m*/*z*, 373.0785.

3.8. General method for the deprotection of 3-alkoxypyrazoles using hydrogen bromide in acetic acid

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, a mixture of the considered 3-alkoxypyrazole (1 mmol) was degassed with argon. Following this, 33% hydrogen bromide in acetic acid (1.5 mL) was added; the tube was tightly closed and was heated at 140 °C for 2 h. The resulting solution was cooled, diluted in water extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified as described below.

3.8.1. 5-Methyl-1-phenyl-1H-pyrazol-3(2H)-one **26**

This compound was obtained in a 74% yield from compound **24**[2] as a white powder after a chromatography over silica gel (dichloromethane–ethanol 98/2). Mp=165 °C (lit.[32]=164 °C). ^{1}H ($CDCl_3$): 2.27 (s, 3H), 5.61 (s, 1H), 7.40 (m, 3H), 7.48 (m, 2H). ^{13}C ($CDCl_3$): 13.0, 93.8, 125.1, 127.3, 129.6, 139.2, 141.1, 163.2. HRMS: Calcd for $C_{10}H_{10}N_2O$+H: 175.0871. Found: *m*/*z*, 175.0894.

3.8.2. 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one **27**

This compound was obtained in a 76% yield from **25** as a white powder after a chromatography over silica gel (dichloromethane–ethanol 98/2). Its analytical data are identical with a commercially available sample. Note: a spectrum in deuterated chloroform displays a unique methylene signal whereas a spectrum in deuterated dimethylsulfoxide features a mixture of the two possible bonds distribution in the pyrazole ring. This observation and more have actually been reported recently.[29]

3.8.3. 5-Methyl-4-phenyl-1H-pyrazol-3(2H)-one **29a**

Obtained as a white solid in a 43% yield from **8a** after the extraction. Mp=140 °C (dec), (lit.[4]=211 °C). ^{1}H (DMSO-d_6): 2.27 (s, 3H, CH_3), 7.13 (m, 1H), 7.33 (m, 2H), 7.46 (m, 2H), 10.50 (br s, 2H). ^{13}C (DMSO-d_6): 11.5, 102.3, 124.7, 127.3, 128.1, 133.5, 136.5, 158.8. HRMS: Calcd for $C_{10}H_{10}N_2O_2$+H: 191.0821. Found: *m*/*z*, 191.0841.

3.8.4. 4,5-Diphenyl-1H-pyrazol-3(2H)-one **29b**

Obtained as a white solid in a 73% yield from **18** after a chromatography over silica gel (dichloromethane–ethanol 98/2). Mp=175 °C (dec), (lit.=111,[33] 232[34] or 194[35] °C). ^{1}H (DMSO-d_6): 7.15 (m, 1H), 7.34 (m, 9H), 10.00 (br s, 1H), 11.95 (br s, 1H). ^{13}C (DMSO-d_6): 102.6, 125.5, 127.4, 128.0 (two signals?), 128.6, 128.8, 130.6, 132.7, 139.6, 159.0. HRMS: Calcd for $C_{15}H_{12}N_2O$+H: 191.0821. Found: *m*/*z*, 191.0841.

3.8.5. 1,5-Dimethyl-4-phenyl-1H-pyrazol-3(2H)-one **30**

Obtained as white solid in a 76% yield from **13a** after the extraction of the aqueous phase, which had been saturated with sodium chloride. Mp >260 °C (lit.[36]=250–252 °C). ^{1}H (DMSO-d_6): 2.25 (s, 3H, CH_3), 3.58 (s, 3H), 7.17 (m, 1H), 7.34 (m, 4H), 9.71 (br s, 1H). ^{13}C (DMSO-d_6): 11.0, 35.8, 103.9, 125.4, 128.3, 128.6, 133.8, 136.5, 157.6. HRMS: Calcd for $C_{11}H_{12}N_2O$+H: 189.1028. Found: *m*/*z*, 189.1054.

3.8.6. 5-Methyl-1,4-diphenyl-1H-pyrazol-3(2H)-one **31**

Obtained as a white solid in a 92% yield from **14a** after precipitation of the reaction mixture with an excess of water followed by a filtration. Mp=237 °C. ^{1}H (DMSO-d_6): 2.35 (s, 3H, CH_3), 7.25 (m, 1H), 7.36

(m, 2H), 7.42 (m, 2H), 7.48 (m, 5H), 10.32 (br s, 1H). ^{13}C (DMSO-d_6): 13.0, 107.0, 124.4, 126.1, 127.0, 128.7, 128.8, 129.5, 132.9, 136.7, 139.9, 159.8. HRMS: Calcd for $C_{16}H_{14}N_2O$+H: 251.1184. Found: *m*/*z*, 251.1199.

3.8.7. 1-(3-Hydroxyphenyl)-5-methyl-1H-pyrazol-3(2H)-one ***33***

This compound was obtained in a 64% yield from **32**[2] as a white powder after a chromatography over silica gel (dichloromethane–ethanol 98/2 to 95/5). Mp=203 °C. ^{1}H (DMSO-d_6): 2.25 (s, 3H, CH_3), 5.55 (s, 1H), 6.70 (m, 1H), 6.86 (m, 2H), 7.22 (m, 1H), 9.68 (br s, 1H), 9.84 (br s, 1H). ^{13}C (DMSO-d_6): 12.8, 93.7, 110.4, 113.1, 113.7, 129.6, 139.4, 140.7, 157.7, 161.1. HRMS: Calcd for $C_{10}H_{10}N_2O_2$+H: 191.0821. Found: *m*/*z*, 191.0841.

3.8.8. 1-(3-Methoxyphenyl)-5-methyl-1H-pyrazol-3(2H)-one ***34***

Compound **32**[2] (0.080 g, 0.4 mmol) was refluxed for 4 h in 37% hydrochloric acid (10 mL). This was concentrated to dryness and the residue was purified by a chromatography over silica gel (cyclohexane–ethyl acetate 9/1) to yield compound **34** as a colorless solid (0.035 g, 43%). Mp=163 °C. ^{1}H ($CDCl_3$): 2.30 (s, 3H, CH_3), 3.88 (s, 3H), 5.61 (s, 1H), 6.90 (dd, 1H, *J*=2.4 and 0.8 Hz), 6.98 (m, 2H), 7.36 (t, 1H, *J*=8.3 Hz). ^{13}C ($CDCl_3$): 13.1, 55.9, 93.9, 110.6, 113.7, 117.0, 130.1, 140.3, 141.2, 160.5, 163.2. HRMS: Calcd for $C_{11}H_{12}N_2O_2$+H: 205.0977. Found: *m*/*z*, 205.0999.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.109.

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