Tetrahedron 65 (2009) 2660–2668

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Nitrogen's reactivity of various 3-alkoxypyrazoles

Sandrine Guillou, Frédéric J. Bonhomme, Yves L. Janin *

Institut Pasteur, URA 2128 CNRS-Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris Cedex 15, France

ARTICLE INFO

Article history:
Received 21 November 2008
Received in revised form 23 January 2009
Accepted 28 January 2009
Available online 4 February 2009

Keywords:
3-Alkoxypyrazole
N-Arylation
N-Alkylation

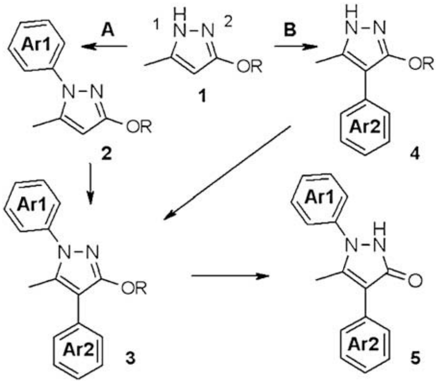
ABSTRACT

Our current interest in the design of original chemical libraries featuring a pyrazole nucleus led us to focus on the chemistry of the 3-alkoxy-5-methylpyrazoles we have recently made readily available. With in mind the preparation of an array of the less accessible 1-arylpyrazol-3-ones, the present report describes the respective nitrogen's reactivity of various 3-alkoxypyrazoles toward arylation reaction, using arylboronic acids, as well as alkylation reactions using methyl iodide or benzylbromide. The structure assignments of the isomers obtained were achieved using long distance ^{15}N–^{1}H NMR correlation measurements or by the recourse to unambiguous synthetic pathways.

1. Introduction

The starting point of this work stems from our simple preparation of a vast array of 3-alkoxylpyrazoles such as **1**.[1] With in mind the preparation of libraries of original chemical entities, we investigated the chemistry of these 3-alkoxypyrazoles as much of it has not been studied in the past. This aspect is likely due to the fact that the starting 3-alkoxypyrazoles are fairly invisible on TLC and were thus not readily available in the past. The inherent protection of the oxygen along with a possible decrease of the nucleophilic character of the neighboring nitrogen of the 3-alkoxypyrazole **1** led us to focus on the reactivity of its N1 centre. In fact, few reports describe the preparation of N1-aryl (or alkyl) pyrazol-3-ones isomers. The first work describes a condensation between acylhydrazines and acetoacetates in the presence of phosphorus trichloride.[2–5] More recently, the reaction of β-acylarylhydrazines with calcium hydride in refluxing dimethylformamide was shown to lead to 1-arylpyrazol-3-ones and 1,4-diarylpyrazol-3-ones devoid of a substituent on carbon 5.[6] Another type of preparation requires the oxidation[7–9] of pyrazolidin-3-ones, which would, for instance, result from the addition of arylhydrazines on acrylic esters. Such reaction was actually at the base of early photographic imaging processes.[10] The reaction between arylhydrazines and diketene also provides an access to this type of compounds.[11,12] Another approach requires reactions between either 2,3-dichloropropionic acid amide[13] or β-ethoxyacryloylchloride[14,15] and phenylhydrazines as well as α-acetylenic esters with either phenylhydrazine in the presence of alkoxides[16] or, in the last case, methylhydrazine without a base.[17] A more recent method takes place via a rearrangement of the reaction product between either biacetyldimer[18] or the intermediate furanone[19,20] and aryldiazonium salts. The latest reported approach requires the polylithiation of *N*′-phenylphenylacetohydrazides.[21]

Thus, from the many 3-alkoxylpyrazoles we could prepare in a one-step process,[1] we sought a simple and general access to N1-aryl or N1-alkyl pyrazol-3-ones as most of the alternative synthesis listed above may not lend themselves to easy generalization. Moreover, we also investigated its combination with C4 arylation reactions. The two general chemical pathways described in Scheme 1 sum up most of the investigations described in the present work and in a following paper.[22] Path A required the study of nitrogen 1



Scheme 1. General pathways investigated.

---

* Corresponding author. Tel.: +33 06 85 42 49 47; fax: +33 1 45 68 84 04.
E-mail address: yves.janin@pasteur.fr (Y.L. Janin).

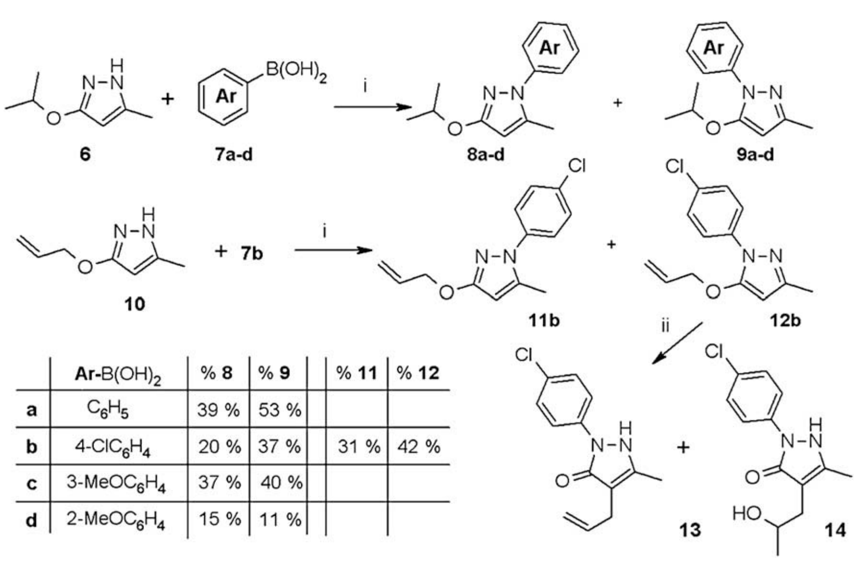
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.01.099

arylation to give compounds such as **2**. This choice took into account a previously reported work on the regioselective N-arylation of 3-alkoxypyrazoles featuring copper-chelating moieties.[23] Following this, we envisioned a halogenation/palladium-catalyzed arylation sequence of carbon 4 of the pyrazole ring to give **3**. Path B undertook to attempt first the halogenation/arylation sequence leading to **4** followed by the nitrogen arylation to provide compound **3**. The last step in this scheme implied a deprotection of the oxygen on carbon 3 to give pyrazol-3-ones with the general formula **5**.

2. Results and discussion

We choose to study the room temperature N-arylation of the model compound **6** using arylboronic acids **7a–d** and copper salts.[23–30] This turned out to be reliably reproductive and free of the necessity of the long heating time usually used with other N-arylation methods involving halogenated aryl derivatives and copper catalysts.[31–42] Interestingly, only one report describes an N-arylation of pyrazoles using a palladium-based catalyst.[43]

We first used dichloromethane as solvent and as long as the reaction was left in open air, we obtained N-arylation reactions in usually 48 h. However, in order to either minimize the evaporation taking place in the course of the reaction or improve the solubility of the arylboronates used we also used acetonitrile. Few interesting results came out of this change and are further described below. The main point we found out is that water is detrimental to this reaction but air is needed. Thus, it is necessary to use reasonably dry solvents and add some molecular sieves if the copper salt added is hydrated. As we used stoichiometric amount of copper salts, this did not seem to be necessary on a small scale as we observed that some N-arylation reactions proceeded without molecular sieves. However, on a gram scale, the molecular sieves and air were essential in achieving a transformation in a high yield. Accordingly, the use of the hydrophobic dichloromethane allowed running the reaction without any particular precautions. On the other hand, the use of the hygroscopic acetonitrile required a calcium guard, which has the potential of lessening a proper oxygenation of the reaction media in reactions run at room temperature. In the course of this study, we did not try to lower the proportion of copper salts used although recent reports seem to point out that a catalytic version of this reaction is possible.[44–46] The two isomeric N-aryl products resulting from the arylation of compound such as **1** were usually obtained and were most often separated by chromatography. The structure assignment was quite often achieved using long distance $^{15}N–^{1}H$ NMR correlation techniques. In the case of N-arylated compounds, it is only for the N1-aryl-5-alkoxypyrazoles that the N1 and N2 signals were observed at a different value (around -100 ppm and -185 ppm in respect to nitromethane). This fact, along with the uncertainty of signal transmissions to achieve a ^{15}N resonance of both nitrogens especially in the case of N1-aryl-3-alkoxypyrazoles made a comparison of the $^{15}N–^{1}H$ NMR correlation spectrum of each isomer necessary. Moreover, this NMR experiment requires the presence of hydrogen atoms in the vicinity of the one of the two nitrogens to obtain a ^{15}N signal. Thus, as described below, we also resorted to unequivocal synthesis in some cases or postponed the structural assignment to a study of the product resulting from further transformation steps. As depicted in Scheme 2, the arylation of compound **6** or **10** led to the separable pairs of isomers **8a–d**/**9a–d** and **11b**/**12b**. The N1/N2 arylation ratio of the 3-alkoxypyrazoles **6** and **10**, pointed out a tendency in favor of the ‘N2-arylation products’ (more correctly, the 1-aryl-5-alkoxypyrazoles). Moreover, an improvement in the reaction yield was seen in the case of the preparation of compounds **8c** and **9c** when we switched from dichloromethane (30 and less than 10% yield) to boiling acetonitrile (37 and 47% yield, respectively). This effect was not seen in the case of the pair of compounds **8d** and **9d** although the very low UV absorption of compound **8d** (either on TLC or with a liquid chromatography UV detector) probably lessens its isolated yield. An even lower N-arylation yield has actually been reported in a previous case also using 2-methoxyphenylboronic acid.[23] We also undertook the N-arylation of compound **10**, which leads to the allyl-bearing compounds **11b** and **12b** in order to increase the array of protecting groups possible in our synthetic schemes. Interestingly, we observed that, contrary to the N1-arylation product **11b**, the N2-arylation compound **12b** was not stable upon storage. It turns out that the allylic side chain undergoes a decomposition process, which starts with a slow room temperature Claisen rearrangement. Refluxing compound **12b** in toluene overnight led to a mixture of at least four compounds from which we could isolate and fully characterize the allyl-bearing product **13** and the hydrated derivative **14** in, respectively, 30 and 12% yield. Related Claisen rearrangements have actually been reported to take place at 250 °C for 3-(allyloxy)-1-phenyl-1*H*-pyrazole[47]



	Ar-B(OH)$_2$	% **8**	% **9**	% **11**	% **12**
a	C_6H_5	39 %	53 %		
b	4-ClC_6H_4	20 %	37 %	31 %	42 %
c	3-MeOC_6H_4	37 %	40 %		
d	2-MeOC_6H_4	15 %	11 %		

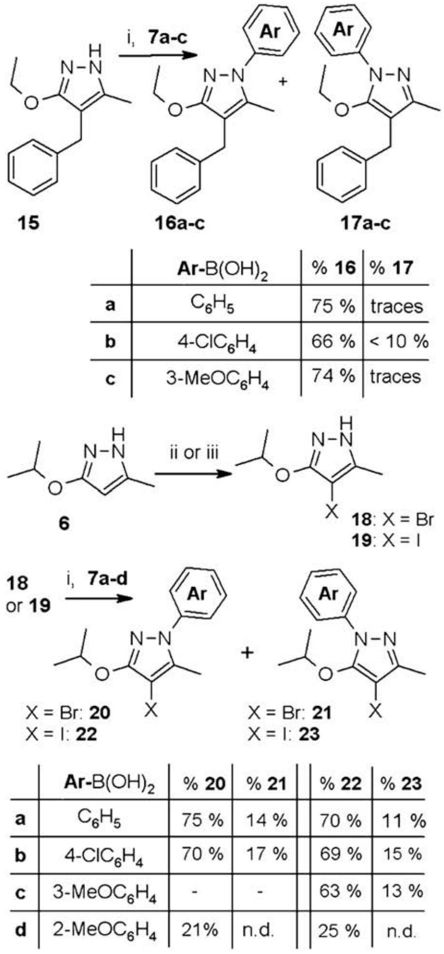
Scheme 2. (i) $Cu(OAc)_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2 or MeCN, air, 25 °C or reflux; (ii) toluene, reflux.

and at 40 °C for 5-(allyloxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde.[48]

As shown in Scheme 3, the arylation of the 4-benzyl derivative **15** in dichloromethane gave a far more important **16**/**17** ratio in favor of the N-1 arylation products **16a–c**. For instance compounds **16a** and **16c** were obtained in at least 74% yield along with only traces of compounds **17a** and **17c**. On a bigger scale, we could properly isolate less than 10% of the N-2 arylation isomer **17b**. These results first underlie the influence of a substituent on carbon 4 of the pyrazole in governing the ratio of N1 or N2 arylation of 3-alkoxypyrazoles along with a somewhat smaller effect of the arylboronate considered. The $^{1}H–^{15}N$ long distance correlation experiments on compound **16a** were of small help in its structural assignment (only one ^{15}N NMR signal is visible). Accordingly, as described in the experimental part, the corresponding minor isomer **17a** was prepared unambiguously in a 37% yield from ethyl 2-benzyl-3-oxobutanoate and phenylhydrazine hydrochloride, using our improved procedure.[1]

From compound **6**, good to excellent yields of the 4-bromo or the 4-iodo derivatives **18** and **19** were obtained using simple halogenation methods. The occurrence of so far unidentified side products in the course of the preparation of compound **18** forced us to purify it by chromatography over silica gel. On the other hand, the preparation of the iodinated derivative **19** only required a filtration and drying. The N-arylation of compounds **18** and **19**, turned out to lead to a large proportion of N-1 arylation products whatever the solvent used (dichloromethane or acetonitrile). Again, the yields from 2-methoxyphenylboronic acid were low and the N-2 arylation product corresponding to compound **23d** was often overlooked because of its lack of UV absorption properties. As an alternative path we also undertook the iodination of the N1-phenylated product **8a**. Thus, using stronger iodination conditions,[49] we could prepare the 4-iodo derivative **22a** from the *N*-phenyl compound **8a** in a 90% yield. This experiment, along with the hydrolysis of the isopropyl group of compounds **8a** and **8b**, described in the following paper,[22] fully confirmed our structural assignments including derivatives stemming from compound **22a**.

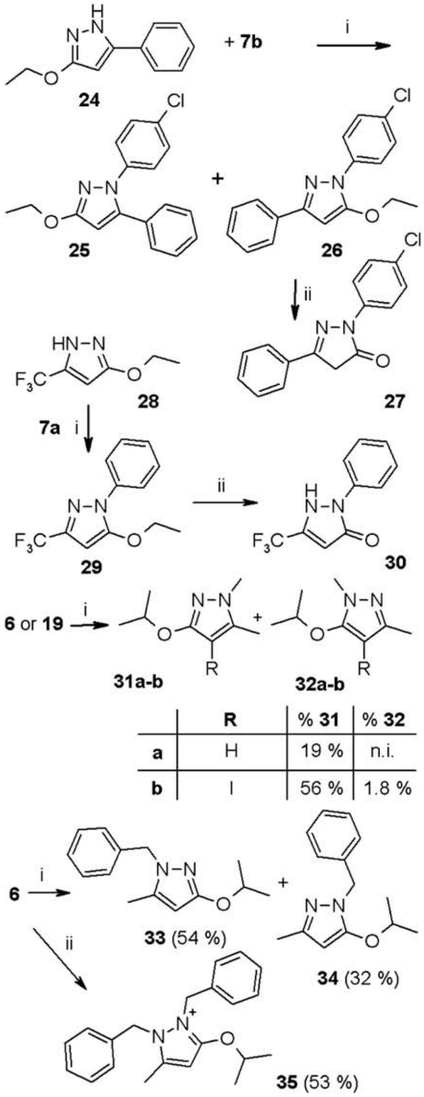
As depicted in Scheme 4, further insights on the reactivity of these 3-alkoxypyrazoles were obtained as the arylation of the 5-phenyl-bearing compound **24**[1] led to 2% of, for once, the least migrating N1-arylation product **25** along with 83% of the N2-arylation product **26**. In the present case, the structural assignment of **26** had to be made via the acid cleavage of its ethoxy moiety, which gave the corresponding diaryl-1*H*-pyrazol-5(4*H*)-one **27** featuring the unambiguous methylene ^{1}H and ^{13}C NMR signals. The arylation of the trifluoromethyl-bearing substrate **28** also led to the N2-arylation product **29** in a 94% yield. None of the alternative isomer was detected in the reaction mixture. Its structure assignment was



	Ar-B(OH)$_2$	% 16	% 17
a	C_6H_5	75 %	traces
b	4-ClC_6H_4	66 %	< 10 %
c	3-MeOC_6H_4	74 %	traces

	Ar-B(OH)$_2$	% 20	% 21	% 22	% 23
a	C_6H_5	75 %	14 %	70 %	11 %
b	4-ClC_6H_4	70 %	17 %	69 %	15 %
c	3-MeOC_6H_4	-	-	63 %	13 %
d	2-MeOC_6H_4	21%	n.d.	25 %	n.d.

Scheme 3. (i) Cu(OAc)$_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2, air, 25 °C; (ii) Br_2, $NaHCO_3$, EtOH, 25 °C; (iii) I_2, NaI, K_2CO_3, EtOH/H_2O, 25 °C.



	R	% 31	% 32
a	H	19 %	n.i.
b	I	56 %	1.8 %

Scheme 4. (i) Cu(OAc)$_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2, air, 25 °C; (ii) 33% HBr/AcOH, 110 °C; (iii) NaH, DMF, MeI or BnBr, 25 °C; (iv) BnBr, K_2CO_3, MeCN, MW, 140 °C, 7 min.

made by comparison with the previously reported data[50] as well as, after the acid-assisted cleavage of the ethoxy moiety, a comparison of the spectra of the resulting pyrazole-5-one **30** with unambiguous data.[50] Thus, for these two cases a preparation of the alternative isomers remains a challenge.

We also investigated the methylation of some of these 3-alkoxypyrazoles. The ^{1}H NMR monitoring of the methylation of compound **6** or its iodinated derivative **19** using sodium hydride in DMF and methyl iodide showed a 10:3 or 17:3 ratio in favor of the N1-methylation product of compound **6** or **19**, respectively. This ratio improvement actually follows what has been observed for the N-arylation reactions ratio of compound **6** and its 4-iodinated derivative **19** described above. The notable lack of UV-absorbance of the N2-methylation products **32a**,**b** made them fairly hard to isolate. Moreover the volatility of the methylation product **31a** probably explains the low isolated yield reported as an optimization of the workup procedure was not undertaken. The structure assignment of these methylation products could not be achieved with the ^{15}N–^{1}H correlation data as both nitrogens correlate with the methyl residues. On the other hand, ^{13}C–^{1}H long distance correlations allowed unequivocal structural assignments. The *N*-methyl residues of **31a** and **32a**,[1] respectively, correlate with the carbon bearing the methyl side chain or the one bearing the isopropyloxy side chain. The same observation was made for the pair of compounds **31b**–**32b**.

Benzylation of **6** also proceeded with a preference for the N1-benzylation product **33**, which was obtained in a 54% yield. As described in the experimental part, the structure assignment of compounds **33** and **34** were further established by the synthesis of **34** from isopropylacetoacetate and benzylhydrazine hydrochloride under our reaction conditions.[1] Moreover, we could also prepare substantial amount (53%) of the pyrazolium **35** when heating the reaction in a microwave-reactor.

3. Conclusions

The originality of the chemical libraries that can be generated from this work is due to the unique fact: the 3-alkoxypyrazoles were previously tedious to prepare and this somehow hampered the study of their chemistry. From the use of a stoichiometric reaction protocol between alkylacetoacetates and hydrazine hydrochloride, the corresponding alkoxypyrazoles previously considered as a side compound were quite often obtained in sizable 50% yield.[1] From this, further chemical transformations insured accesses to fully original chemical entities as the presence of an oxygen protecting group substantially altered the pyrazole reactivity.

In this work, depending on the substituents of the 3-alkoxypyrazole ring system, a preference for the otherwise not so easy to attain 1-aryl or 1-alkyl 3-alkoxypyrazoles was observed. This is of interest as a brute statistical survey of all the pyrazolone-bearing substances ever reported up to 2008 leads to the following facts. As much as 76,790 compounds featuring this ring system were actually reported. However, most of these compounds (66,103) are N1-substituted pyazol-5-ones and ‘only’ 4563 are N1-substituted pyrazol-3-ones. This bias is very much due to the regiochemistry of any Knorr reactions between the vast array of available arylhydrazines and acetoacetates.[51,52] Interestingly, small amount of the alternative aryl isomers have been reported in some Knorr reaction, as mentioned recently.[53] We hope that, amongst the many possibilities offered by our results, this work will help in the preparation and evaluation of 1-substituted pyrazol-3-ones featuring properly designed substituents in regards with the considered medicinal chemistry field. Moreover, a combination of these transformations with the C4 arylation chemistry described in the following report,[22] can lead to even more original chemical entities with potential biological interest.

4. Experimental section

4.1. General methods

A Biotage Initiator 2 microwave oven was used for reactions requiring microwaves irradiations. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometers 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 were performed either 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/min) 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.

4.2. General procedure for the N-arylation of 3-alkoxypyrazoles

The corresponding alkoxypyrazole (1.45 mmol), arylboronic acid (1.60 mmol), pyridine (3 mmol, dried over 4 Å molecular sieves), 4 Å molecular sieves (0.6 g), and copper(II) acetate hydrate (2.2 mmol) were dispersed in dichloromethane (20 mL). The reaction was stirred in open air for 48 h. After concentration to dryness, the residue was absorbed on a small amount of silica gel and purified as described below. An alternative method was to run the reaction in boiling acetonitrile (20 mL, dried over 4 Å molecular sieves) for 12 h using the same reagents, as long as the reaction media was protected from moisture by a calcium chloride guard.

Isomers **8a** and **9a**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–ethyl acetate 9:1) led to 39% of compound **8a** followed by 53% of compound **9a**.

*4.2.1. 3-Isopropoxy-5-methyl-1-phenyl-1H-pyrazole **8a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.39 (d, 6H, J=6.1 Hz); 2.31 (s, 3H); 4.85 (sept, 1H, J=6.1 Hz); 5.65 (s, 1H); 7.28–7.46 (m, 5H). ^{13}C ($CDCl_3$): 13.2; 22.6; 71.7; 94.1; 124.8; 127.0; 129.3; 140.4 (two signals?); 163.0. ^{15}N ($CDCl_3$): -184 (CH_3, H-4, Ar). HRMS: Calcd for $C_{13}H_{16}N_2O+H$: 217.1341. Found: *m*/*z*, 217.1372.

*4.2.2. 5-Isopropoxy-3-methyl-1-phenyl-1H-pyrazole **9a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.40 (d, 6H, J=6.1 Hz); 2.31 (s, 3H); 4.45 (sept, 1H, J=6.1 Hz); 5.48 (s, 1H); 7.21–7.73 (m, 5H). ^{13}C ($CDCl_3$): 14.9; 22.3; 76.0; 87.4; 122.3; 126.0; 129.0; 139.4; 149.1; 154.4. ^{15}N ($CDCl_3$): -99 (CH_3); -185 (H-4, Ar). HRMS: Calcd for $C_{13}H_{16}N_2O+H$: 217.1341. Found: *m*/*z*, 217.1381.

Isomers **8b** and **9b**: A chromatography over silica gel (cyclohexane–ethyl acetate 98:2) led to 20% of compound **8b** followed by 37% of compound **9b**.

*4.2.3. 1-(4-Chlorophenyl)-3-isopropoxy-5-methyl-1H-pyrazole **8b***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.38 (d, 6H, J=6.1 Hz); 2.29 (s, 3H); 4.83 (sept, 1H, J=6.1 Hz); 5.65 (s, 1H); 7.35–7.40 (m, 4H). ^{13}C ($CDCl_3$): 12.9; 22.1; 71.4; 94.3; 125.3; 129.0; 132.1; 138.6; 140.0; 162.8. ^{15}N ($CDCl_3$): -185 (CH_3, H-4, Ar). HRMS: Calcd for $C_{13}H_{15}N_2O^{35}Cl+H$: 251.0951. Found: *m*/*z*, 251.0967.

4.2.4. *1-(4-Chlorophenyl)-5-isopropoxy-3-methyl-1H-pyrazole* ***9b***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.38 (d, 6H, J=6.1 Hz); 2.27 (s, 3H); 4.42 (sept, 1H, J=6.1 Hz); 5.45 (s, 1H); 7.28–7.37 (m, 2H); 7.67–7.71 (m, 2H). ^{13}C ($CDCl_3$): 14.3; 21.9; 75.9; 87.2; 123.0; 128.8; 131.2; 137.3; 149.1; 154.1. ^{15}N ($CDCl_3$): −100 (CH_3); −184 (H-4 and Ar). HRMS: Calcd for $C_{13}H_{15}N_2O^{35}Cl+H$: 251.0903. Found: *m*/*z*, 251.0951.

Isomers **8c** and **9c**: The reaction was run in boiling acetonitrile. A chromatography over silica gel (cyclohexane–ethyl acetate 4:1) led to 37% of compound **8c** and a fraction containing compound **9c** and unidentified material. This second fraction was further purified by a second chromatography (cyclohexane–ethyl acetate 4:1) to give 40% of compound **9c**.

4.2.5. *3-Isopropoxy-1-(3-methoxyphenyl)-5-methyl-1H-pyrazole* ***8c***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.39 (d, 6H, J=6.1 Hz); 2.31 (s, 3H); 3.85 (s, 3H); 4.85 (sept, 1H, J=6.1 Hz); 5.65 (s, 1H); 6.85–7.35 (m, 4H). ^{13}C ($CDCl_3$): 13.0; 22.2; 55.4; 71.4; 93.8; 110.2; 112.5; 116.5; 129.5; 140.0; 141.1; 160.1; 162.6. ^{15}N ($CDCl_3$): −182 (CH_3, H-4). HRMS: Calcd for $C_{14}H_{18}N_2O_2+H$: 247.1447. Found: *m*/*z*, 247.1468.

4.2.6. *5-Isopropoxy-1-(3-methoxyphenyl)-3-methyl-1H-pyrazole* ***9c***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.41 (d, 6H, J=6.1 Hz); 2.29 (s, 3H); 3.86 (s, 3H); 4.45 (sept, 1H, J=6.1 Hz); 5.48 (s, 1H); 6.80 (m, 1H); 7.32 (m, 3H). ^{13}C ($CDCl_3$): 14.5; 21.9; 55.3; 75.6; 87.1; 107.4; 111.8; 114.1; 129.3; 140.1; 148.7; 154.1; 159.9. ^{15}N ($CDCl_3$): −100 (CH_3); −182 (H-4, ArH). HRMS: Calcd for $C_{14}H_{18}N_2O_2+H$: 247.1447. Found: *m*/*z*, 247.1465.

Isomers **8d** and **9d**: The reaction was run in boiling acetonitrile. A chromatography over silica gel (cyclohexane–ethyl acetate 4:1) led to 15% of compound **8d** and a fraction containing compound **9d** and some starting material. This second fraction was further purified by a second chromatography (cyclohexane–ethyl acetate 4/1) to give 11% of compound **9d**.

4.2.7. *3-Isopropoxy-1-(2-methoxyphenyl)-5-methyl-1H-pyrazole* ***8d***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.36 (d, 6H, J=6.1 Hz); 2.07 (s, 3H); 3.80 (s, 3H); 4.84 (sept, 1H, J=6.1 Hz); 5.61 (s, 1H); 7.05 (m, 2H); 7.35 (m, 2H). ^{13}C ($CDCl_3$): 12.0; 22.6; 56.2; 71.4; 92.2; 112.6; 121.3; 129.2; 129.9; 130.0; 142.5; 155.3; 163.0. ^{15}N ($CDCl_3$): −192 (CH_3, H-4). HRMS: Calcd for $C_{14}H_{18}N_2O_2+H$: 247.1447. Found: *m*/*z*, 247.1459.

4.2.8. *5-Isopropoxy-1-(2-methoxyphenyl)-5-methyl-1H-pyrazole* ***9d***

Obtained as a solid. ^{1}H ($CDCl_3$): 1.28 (d, 6H, J=6.1 Hz); 2.28 (s, 3H); 3.78 (s, 3H); 4.37 (sept, 1H, J=6.1 Hz); 5.44 (s, 1H); 6.99 (m, 2H); 7.32 (m, 2H). ^{13}C ($CDCl_3$): 14.7; 21.9; 55.6; 75.0; 85.6; 111.9; 120.4; 127.2; 128.9; 129.5; 148.7; 154.8; 154.9. ^{15}N ($CDCl_3$): −95 (CH_3); −191 (H-4, ArH). HRMS: Calcd for $C_{14}H_{18}N_2O_2+H$: 247.1447. Found: *m*/*z*, 247.1469.

Isomers **11b** and **12b**: A chromatography over silica gel (cyclohexane–ethyl acetate 99:1) led to 31% of compound **11b** followed by 42% of compound **12b** when the reaction was run in acetonitrile and to 39% of compound **11b** followed by 28% of compound **12b** when it was run in dichloromethane.

4.2.9. *3-(Allyloxy)-1-(4-chlorophenyl)-5-methyl-1H-pyrazole* ***11b***

Obtained as an oil. ^{1}H ($CDCl_3$): 2.30 (s, 3H); 4.73 (m, 2H); 5.27 (d, 1H, J=9.0 Hz); 5.41 (d, 1H, J=15.0 Hz); 5.70 (s, 1H); 6.09 (m, 1H); 7.36–7.42 (m, 4H). ^{13}C ($CDCl_3$): 12.9; 69.4; 93.7; 117.6; 125.4; 129.1; 132.3; 133.4; 138.5; 140.4; 163.2. ^{15}N ($CDCl_3$): −180 (CH_3 and H-4). HRMS: Calcd for $C_{13}H_{13}N_2O^{35}Cl+H$: 249.0795. Found: *m*/*z*, 249.0815.

4.2.10. *5-(Allyloxy)-1-(4-chlorophenyl)-3-methyl-1H-pyrazole* ***12b***

Obtained as an oil. ^{1}H ($CDCl_3$): 2.29 (s, 3H); 4.65 (m, 2H); 5.33–5.48 (m, 2H); 5.51 (s, 1H); 6.04 (m, 1H); 7.28 (m, 2H); 7.68 (m, 2H). ^{13}C ($CDCl_3$): 14.5; 69.4; 87.1; 118.6; 122.7; 128.8; 131.0; 131.7; 137.4; 149.0; 154.5. ^{15}N ($CDCl_3$): −100 (CH_3); −185 (H-4 and ArCl). HRMS: Calcd for $C_{13}H_{13}N_2O^{35}Cl+H$: 249.0795. Found: *m*/*z*, 249.0821.

Isomers **16a** and **17a**: The reaction was run in dichloromethane and a chromatography over silica gel (cyclohexane–dichloromethane 85:15) led to 75% of compound **16a** followed by only traces of compound **17a**.

4.2.11. *4-Benzyl-3-ethoxy-1-phenyl-5-methyl-1H-pyrazole* ***16a***

Obtained as a white solid. ^{1}H ($CDCl_3$): 1.22 (t, 3H, J=7.0 Hz); 2.17 (s, 3H); 3.81 (s, 2H); 3.86 (q, 2H, J=7.0 Hz); 7.21–7.74 (m, 10H). ^{13}C ($CDCl_3$): 13.5; 15.6; 28.8; 70.9; 105.0; 122.3; 126.4; 125.5; 128.5; 128.8; 129.3; 151.7. ^{15}N ($CDCl_3$): −185 (CH_3). HRMS: Calcd for $C_{19}H_{20}N_2O+H$: 293.1654. Found: *m*/*z*, 293.1684.

4.2.12. *4-Benzyl-5-ethoxy-1-phenyl-3-methyl-1H-pyrazole* ***17a***

As this compound was not be isolated in sizable quantity in the course of the arylation of compound **15**, it was prepared in 37% yield by using our reported method.[1] Thus, ethyl-2-benzylacetoacetate (1 g, 4.54 mmol) and phenylhydrazine hydrochloride (0.65 g, 4.54 mmol) were refluxed in ethanol (50 mL) for 4 h. This was then concentrated to dryness and the residue dispersed in water made basic with solid sodium hydrogenocarbonate, and extracted with dichloromethane. The organic phase was washed with 1 N sodium hydrogenocarbonate, dried over sodium sulfate and concentrated to dryness. The resulting residue was further purified by a chromatography over silica gel (cyclohexane–ethyl acetate 4:1) to yield compound **17a** as a white solid (0.5 g; 37%). ^{1}H ($CDCl_3$): 1.22 (t, 3H, J=7.0 Hz); 2.20 (s, 3H); 3.84 (s, 2H); 3.88 (q, 2H, J=7.0 Hz); 7.23–7.28 (m, 6H); 7.30–7.47 (m, 2H); 7.76–7.78 (d, 2H). ^{13}C ($CDCl_3$): 13.5; 15.6; 28.9; 70.9; 105.0; 122.3; 126.4; 128.7; 128.8; 129.3; 139.5; 140.8; 148.8; 151.7. ^{15}N ($CDCl_3$): −96 (CH_3); −169 (Ar). HRMS: Calcd for $C_{19}H_{20}N_2O+H$: 293.1654. Found: *m*/*z*, 293.1684.

Isomers **16b** and **17b**: The reaction was run in dichloromethane and a chromatography over silica gel (cyclohexane–ethyl acetate 98:2) led to 66% of compound **16b** followed by less than 10% of compound **17b** as it still contained traces of unidentified compounds and had to be purified again by another chromatography over silica gel.

4.2.13. *4-Benzyl-1-(4-chlorophenyl)-3-ethoxy-5-methyl-1H-pyrazole* ***16b***

Obtained as a wax. ^{1}H ($CDCl_3$): 1.42 (t, 3H, J=7.0 Hz); 2.21 (s, 3H); 3.76 (s, 2H); 4.34 (q, 2H, J=7.0 Hz); 7.21–7.42 (m, 9H). ^{13}C ($CDCl_3$): 11.4; 14.9; 28.1; 64.3; 105.2; 125.4; 125.8; 128.2; 128.3; 129.0; 131.9; 137.4; 138.8; 141.0; 162.2. ^{15}N ($CDCl_3$): −187 (CH_3 and ArCl). HRMS: Calcd for $C_{19}H_{19}^{35}ClN_2O+H$: 327.1264. Found: *m*/*z*, 327.1244.

4.2.14. *4-Benzyl-1-(4-chlorophenyl)-5-ethoxy-3-methyl-1H-pyrazole* ***17b***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.21 (t, 3H, J=7.0 Hz); 2.15 (s, 3H); 3.81 (s, 2H); 3.87 (q, 2H, J=7.0 Hz); 7.15–7.71 (m, 9H). ^{13}C ($CDCl_3$): 13.1; 15.2; 28.5; 70.6; 104.8; 122.9; 126.1; 128.1; 128.4; 129.0; 131.4; 137.6; 140.2; 148.9; 151.4. ^{15}N ($CDCl_3$): −100 (CH_3); −180 (ArCl). HRMS: Calcd for $C_{19}H_{19}^{35}ClN_2O+H$: 327.1264. Found: *m*/*z*, 327.1258.

Isomers **16c** and **17c**: The reaction was run in dichloromethane and a chromatography over silica gel (cyclohexane–ethyl acetate 98:2) led to 75% of compound **16c** followed by only traces of compound **17c**.

4.2.15. *4-Benzyl-3-ethoxy-1-(3-methoxyphenyl)-5-methyl-1H-pyrazole* ***16c***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.44 (t, 3H, J=7.0 Hz); 2.23 (s, 3H); 3.79 (s, 2H); 3.86 (s, 3H); 4.38 (q, 2H, J=7.0 Hz); 6.86–7.37 (m, 9H).

^{13}C ($CDCl_3$): 11.5; 15.0; 28.1; 55.4; 64.2; 104.7; 110.3; 112.3; 116.7; 125.8; 128.2; 128.3; 129.5; 137.5; 141.2; 141.3; 160.1; 162.0. ^{15}N ($CDCl_3$): −186 (CH_3). HRMS: Calcd for $C_{20}H_{22}N_2O_2$+H: 323.1760. Found: *m*/*z*, 323.1751.

Isomers **20a** and **21a**: The reaction was run either in dichloromethane or in acetonitrile; a chromatography over silica gel (cyclohexane–dichloromethane 4:6) led to 75% of compound **20a** followed by 14% of compound **21a** in both cases.

*4.2.16. 4-Bromo-3-isopropoxy-5-methyl-1-phenyl-1H-pyrazole **20a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.42 (d, 6H, *J*=6.2 Hz); 2.31 (s, 3H); 5.00 (sept, 1H, *J*=6.2 Hz); 7.35–7.48 (m, 5H). ^{13}C ($CDCl_3$): 12.4; 22.6; 72.7; 83.3; 124.8; 127.6; 129.2; 138.7; 140.3; 159.7. ^{15}N ($CDCl_3$): −182 (CH_3, Ar). HRMS: Calcd for $C_{13}H_{15}^{79}BrN_2O$+H: 295.0446. Found: *m*/*z*, 295.0471.

*4.2.17. 4-Bromo-5-isopropoxy-3-methyl-1-phenyl-1H-pyrazole **21a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.24 (d, 6H, *J*=6.1 Hz); 2.29 (s, 3H); 4.62 (sept, 1H, *J*=6.1 Hz); 7.28 (m, 1H); 7.41 (m, 2H); 7.66 (m, 1H). ^{13}C ($CDCl_3$): 13.1; 22.3; 78.1; 82.8; 122.6; 126.7; 128.8; 138.7; 147.4; 149.5. ^{15}N ($CDCl_3$): −95 (CH_3); −175 (Ar). HRMS: Calcd for $C_{13}H_{15}^{79}BrN_2O$+H: 295.0446. Found: *m*/*z*, 295.0472.

Isomers **20b** and **21b**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 7:3) led to 70% of compound **20b** followed by 17% of compound **21b** still containing 5% of **20b**, which could be removed by a second chromatography.

*4.2.18. 4-Bromo-1-(4-chlorophenyl)-3-isopropoxy-5-methyl-1H-pyrazole **20b***

Obtained as a white solid. Mp=75 °C. ^{1}H ($CDCl_3$): 1.41 (d, 6H, *J*=6.1 Hz); 2.31 (s, 3H); 4.97 (sept, 1H, *J*=6.1 Hz); 7.37 (m, 2H); 7.42 (m, 2H). ^{13}C ($CDCl_3$): 12.4; 22.5; 72.8; 83.9; 125.7; 129.6; 133.1; 138.7; 138.8; 159.9. ^{15}N ($CDCl_3$): −185 (CH_3 and Ar). HRMS: Calcd for $C_{13}H_{14}^{35}Cl^{79}BrN_2O$+H: 329.0056. Found: *m*/*z*, 329.0083.

*4.2.19. 4-Bromo-1-(4-chlorophenyl)-5-isopropoxy-3-methyl-1H-pyrazole **21b***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J*=6.1 Hz); 2.26 (s, 3H); 4.68 (sept, 1H, *J*=6.1 Hz); 7.41 (m, 1H); 7.63 (m, 2H); 7.66 (m, 1H). ^{13}C ($CDCl_3$): 13.6; 22.8; 72.8; 78.5; 123.8; 129.4; 132.5; 137.7; 148.2; 149.9. ^{15}N ($CDCl_3$): −96 (CH_3); −178 (Ar). HRMS: Calcd for $C_{13}H_{14}^{35}Cl^{79}BrN_2O$+H: 329.0056. Found: *m*/*z*, 329.0079.

Isomers **20d** and **21d**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 1:1) led to 21% of compound **20d** and no compound **21a** could be isolated.

*4.2.20. 4-Bromo-1-(2-methoxyphenyl)-3-isopropoxy-5-methyl-1H-pyrazole **20d***

Obtained as a white solid. Mp=80 °C. ^{1}H ($CDCl_3$): 1.39 (d, 6H, *J*=6.1 Hz); 2.08 (s, 3H); 3.97 (s, 3H); 4.95 (sept, 1H, *J*=6.1 Hz); 7.05 (m, 2H); 7.39 (m, 2H). ^{13}C ($CDCl_3$): 10.9; 22.2; 55.8; 72.1; 81.1; 112.2; 121.0; 128.7; 129.2; 130.0; 140.4; 154.7; 159.2. ^{15}N ($CDCl_3$): −192 (CH_3-5). HRMS: Calcd for $C_{14}H_{17}^{79}BrN_2O_2$+H: 325.0552. Found: *m*/*z*, 325.0564.

Isomers **22a** and **23a**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 3:7) led to 70% of compound **22a** followed by 11% of compound **23a** still containing traces (7%) of **22a**.

*4.2.21. 4-Iodo-3-isopropoxy-5-methyl-1-phenyl-1H-pyrazole **22a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.41 (d, 6H, *J*=6.1 Hz); 2.34 (s, 3H); 4.97 (sept, 1H, *J*=6.1 Hz); 7.39 (m, 5H). ^{13}C ($CDCl_3$): 13.5; 22.2; 50.8; 72.4; 126.6; 127.2; 129.1; 140.1; 141.3; 162.2. ^{15}N ($CDCl_3$): −182 (CH_3). HRMS: Calcd for $C_{13}H_{15}IN_2O$+H: 343.0307. Found: *m*/*z*, 343.0323.

*4.2.22. 4-Iodo-5-isopropoxy-3-methyl-1-phenyl-1H-pyrazole **23a***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.21 (d, 6H, *J*=6.2 Hz); 2.29 (s, 3H); 4.53 (sept, 1H, *J*=6.2 Hz); 7.31 (m, 1H); 7.43 (m, 2H); 7.65 (m, 2H). ^{13}C ($CDCl_3$): 14.9; 22.3; 50.7; 78.6; 122.7; 126.8; 128.9; 138.7; 150.4; 152.6. ^{15}N ($CDCl_3$): −90 (CH3); −170 (Ar). HRMS: Calcd for $C_{13}H_{15}IN_2O$+H: 343.0307. Found: *m*/*z*, 343.0321.

Isomers **22b** and **23b**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 7:3) led to 69% of compound **22b** followed by 15% of compound **23b**.

*4.2.23. 4-Iodo-1-(4-chlorophenyl)-3-isopropoxy-5-methyl-1H-pyrazole **22b***

Obtained as a solid. Mp=96 °C. ^{1}H ($CDCl_3$): 1.41 (d, 6H, *J*=6.2 Hz); 2.33 (s, 3H); 4.95 (sept, 1H, *J*=6.2 Hz); 7.36 (m, 2H); 7.43 (m, 2H). ^{13}C ($CDCl_3$): 13.6; 22.1; 51.4; 72.5; 125.5; 129.2; 132.8; 138.7; 141.4; 162.3. ^{15}N ($CDCl_3$): −184 (CH_3 and Ar). HRMS: Calcd for $C_{13}H_{14}N_2OI^{35}Cl$+H: 376.9918. Found: *m*/*z*, 376.9940.

*4.2.24. 4-Iodo-1-(4-chlorophenyl)-5-isopropoxy-3-methyl-1H-pyrazole **23b***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.22 (d, 6H, *J*=6.2 Hz); 2.28 (s, 3H); 4.59 (sept, 1H, *J*=6.2 Hz); 7.41 (m, 2H); 7.63 (m, 2H). ^{13}C ($CDCl_3$): 14.9; 22.4; 50.7; 78.8; 123.9; 129.3; 132.2; 137.2; 150.8; 152.6. ^{15}N ($CDCl_3$): −92 (CH_3); −174 (Ar). HRMS: Calcd for $C_{13}H_{14}N_2OI^{35}Cl$+H: 376.9918. Found: *m*/*z*, 376.9928.

Isomers **22c** and **23c**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 1:1) led to 63% of compound **22c** and 13% of compound **23c**.

*4.2.25. 4-Iodo-1-(3-methoxyphenyl)-3-isopropoxy-5-methyl-1H-pyrazole **22c***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.42 (d, 6H, *J*=6.1 Hz); 2.35 (s, 3H); 3.84 (s, 3H); 4.99 (sept, 1H, *J*=6.1 Hz); 6.88 (m, 1H); 6.98 (m, 2H); 7.34 (m, 1H). ^{13}C ($CDCl_3$): 14.1; 22.6; 51.3; 55.9; 72.7; 109.4; 113.3; 117.1; 129.3; 141.5; 141.8; 160.5; 162.4. ^{15}N ($CDCl_3$): −190 (CH_3-5, Ar). HRMS: Calcd for $C_{14}H_{17}IN_2O_2$+H: 373.0413. Found: *m*/*z*, 373.0437.

*4.2.26. 4-Iodo-1-(3-methoxyphenyl)-5-isopropoxy-3-methyl-1H-pyrazole **23c***

Obtained as an oil. ^{1}H ($CDCl_3$): 1.22 (d, 6H, *J*=6.1 Hz); 2.29 (s, 3H); 3.85 (s, 3H); 4.54 (sept, 1H, *J*=6.1 Hz); 6.86 (m, 1H); 7.26 (m, 3H). ^{13}C ($CDCl_3$): 15.3; 22.7; 51.4; 55.8; 78.9; 108.4; 113.4; 115.2; 130.0; 140.1; 150.8; 153.0; 160.3. ^{15}N ($CDCl_3$): −95 (CH_3-5); −168 (Ar). HRMS: Calcd for $C_{14}H_{17}IN_2O_2$+H: 373.0413. Found: *m*/*z*, 373.0432.

Isomers **22d** and **23d**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 1:1) led to 25% of compound **22d** and no isomeric compound **23d** could be isolated.

*4.2.27. 4-Iodo-1-(2-methoxyphenyl)-3-isopropoxy-5-methyl-1H-pyrazole **22d***

Obtained as a solid. Mp=95 °C. ^{1}H ($CDCl_3$): 1.39 (d, 6H, *J*=6.2 Hz); 2.11 (s, 3H); 3.82 (s, 3H); 4.94 (sept, 1H, *J*=6.2 Hz); 7.04 (m, 2H); 7.30 (m, 1H); 7.39 (m, 1H). ^{13}C ($CDCl_3$): 12.4; 22.2; 48.5; 55.8; 72.1; 112.2; 120.9; 128.9; 129.2; 130.0; 143.5; 154.7; 162.1. ^{15}N ($CDCl_3$): −190 (CH_3-5). HRMS: Calcd for $C_{14}H_{17}IN_2O_2$+H: 373.0413. Found: *m*/*z*, 373.0434.

Isomers **25** and **26**: The reaction was run in dichloromethane; a chromatography over silica gel (cyclohexane–dichloromethane 4:1) led to 83% of compound **26** followed by 2% of compound **25**.

4.2.28. 1-(4-Chlorophenyl)-3-ethoxy-5-phenyl-1H-pyrazole ***25***

Obtained as a colorless solid in a 2% yield. Mp=72 °C. ^{1}H (CDCl$_3$): 1.46 (t, 3H, J=7.1 Hz); 4.32 (q, 2H, J=7.1 Hz); 5.97 (s, 1H); 7.24 (m, 5H); 7.35 (m, 3H). ^{13}C (CDCl$_3$): 14.9; 64.7; 94.3; 125.8; 128.6 (two signals); 128.7; 128.9; 130.5; 132.1; 138.7; 144.2; 163.7. ^{15}N (CDCl$_3$): −188 (H-4 and Ar). HRMS: Calcd for $C_{17}H_{15}{}^{35}ClN_2O+H$: 299.0951. Found: *m*/*z*, 299.0969.

4.2.29. 1-(4-Chlorophenyl)-5-ethoxy-3-phenyl-1H-pyrazole ***26***

Obtained as a white solid in an 83% yield. Mp=90 °C. ^{1}H (CDCl$_3$): 1.51 (t, 3H, J=7.1 Hz); 4.26 (q, 2H, J=7.1 Hz); 6.01 (s, 1H); 7.37 (m, 1H); 7.42 (m, 4H); 7.83 (m, 4H). ^{13}C (CDCl$_3$): 14.6; 68.2; 83.9; 122.9; 125.5; 128.2; 128.5; 128.9; 131.4; 133.3; 137.6; 150.8; 155.4. ^{15}N (CDCl$_3$): −184 (H-4 and Ar). HRMS: Calcd for $C_{17}H_{15}{}^{35}ClN_2O+H$: 299.0951. Found: *m*/*z*, 299.0974.

4.2.30. 1-(4-Chlorophenyl)-3-phenyl-1H-pyrazol-5(4H)-one ***27***

Structural characterization of compound ***26*** *by its hydrolysis*: Compound **26** (0.032 g, 0.1 mmol) and 33% hydrogen bromide in acetic acid (1 mL) were heated in a sealed flask at 110 °C for 36 h. The solution was dispersed in water and the precipitate extracted with dichloromethane. The organic phase was washed with water, dried over sodium sulfate, and concentrated to dryness to yield compound **27** (0.025 g, 86%) as a solid. Mp=163 °C. ^{1}H (CDCl$_3$): 3.86 (s, 2H); 7.40 (m, 2H); 7.48 (m, 2H); 7.78 (m, 2H); 7.99 (m, 2H). ^{13}C (CDCl$_3$): 39.6; 120.0; 126.0; 128.9; 129.0; 130.4; 130.7; 130.9; 154.9; 170.1. HRMS: Calcd for $C_{15}H_{11}{}^{35}ClN_2O+H$: 271.0638. Found: *m*/*z*, 271.0657.

4.2.31. 5-Ethoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole ***29***

Obtained as an oil in a 94% yield after a chromatography over silica gel (cyclohexane–dichloromethane 7:3). ^{1}H (CDCl$_3$): 1.48 (t, 3H, J=7.1 Hz); 4.23 (q, 2H, J=7.1 Hz); 5.94 (s, 1H); 7.37 (m, 1H); 7.45 (m, 2H); 7.73 (m, 2H). ^{13}C (CDCl$_3$): 14.6; 68.7; 84.7; 121.0 (q, J=260 Hz); 122.9; 127.5; 129.2; 138.0; 141.9 (q, J=36 Hz); 154.9. HRMS: Calcd for $C_{12}H_{11}F_3N_2O+H$: 257.0902. Found: *m*/*z*, 257.0928.

4.2.32. 1-Phenyl-3-(trifluoromethyl)-1H-pyrazol-5(2H)-one ***30***

Compound **29** (0.5 g, 1.95 mmol) and 48% hydrogen bromide in water (1 mL) were heated in a sealed flask at 140 °C for 4 h. The solution was dispersed in water and the precipitate extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was further purified by a chromatography over silica gel (cyclohexane–dichloromethane 1:1) to yield compound **30** (0.38 g, 85%) as a solid. Mp=190 °C (sublime). ^{1}H (DMSO-d_6): 5.93 (s, 1H); 7.38 (m, 1H); 7.51 (m, 2H); 7.71 (m, 2H). ^{13}C (DMSO-d_6): 86.1; 121.0 (q, J=260 Hz); 122.7; 127.7; 129.6; 138.2; 140.9 (q, J=37 Hz); 154.1. Spectra identical with the reported one.[50] HRMS: Calcd for $C_{10}H_7F_3N_2O+H$: 229.0589. Found: *m*/*z*, 229.0606.

4.2.33. 4-Bromo-3-isopropoxy-5-methyl-1H-pyrazole ***18***

Compound **6** (3.94 g, 28.1 mmol), sodium hydrogenocarbonate (2.80 g, 35.2 mmol), and bromine (1.73 mL, 33.7 mmol) were mixed in 100 mL of ethanol. The solution was stirred at room temperature for 1 h. After concentration to dryness, the residue was washed with sodium hydrogenocarbonate 1 N and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography on silica gel (dichloromethane–ethanol 99:1) to provide compound **18** (3.97 g, 64%) as a colorless solid. Mp <50 °C. ^{1}H (CDCl$_3$): 1.38 (d, 6H, J=6.1 Hz); 2.24 (s, 3H); 4.85 (sept, 1H, J=6.1 Hz); 8.10 (s(l), 1H). ^{13}C (CDCl$_3$): 11.1; 22.5; 73.2; 81.2; 139.6; 159.8. HRMS: Calcd for $C_7H_{11}{}^{79}BrN_2O+H$: 219.0133. Found: *m*/*z*, 219.0169.

4.2.34. 4-Iodo-3-isopropoxy-5-methyl-1H-pyrazole ***19***

Compound **1** (6.52 g, 0.046 mol), sodium iodide (7.68 g, 0.051 mol), and potassium carbonate (16 g, 0.116 mol) were dissolved in water (250 mL) and ethanol (60 mL). To this was added iodine (15.3 g, 0.06 mol). The resulting suspension was stirred for 90 min, decolorized (if necessary) with sodium bisulfite, and diluted with brine (1 L). The resulting precipitate was filtered, washed with water, and dried under vacuum while heating at 80 °C in a large Petri dish in order to sublimate the iodoform also occurring in this reaction to yield compound **19** as an yellow solid (10.2 g, 82%). Mp=98–100 °C. ^{1}H (CDCl$_3$): 1.38 (d, 6H, J=6.3 Hz); 2.25 (s, 3H); 4.84 (sept, 1H, J=6.3 Hz). ^{13}C (CDCl$_3$): 12.6; 22.5; 48.3; 73.8; 142.9; 162.9. HRMS: Calcd for $C_7H_{11}IN_2O+H$: 266.9994. Found: *m*/*z*, 267.0023.

Claisen rearrangement of ***12b****, isolation of compounds* ***13*** *and* ***14***: Compound **12b** (0.16 g, 0.64 mmol) was heated to reflux in toluene (30 ml) overnight. The resulting solution was concentrated to dryness and purified by a chromatography over silica gel (cyclohexane–ethyl acetate 95:5) to yield, in this order, compound **13** and compound **14** as described below.

4.2.35. 4-Allyl-2-(4-chlorophenyl)-5-methyl-1H-pyrazol-3(2H)-one ***13***

Obtained (0.05 g, 31%) as an oil. ^{1}H (CDCl$_3$): 1.79 (s, 3H); 2.77 (q, 1H, J=6.5 and 13.8 Hz); 3.50 (q, 1H, J=7.5 and 13.8 Hz); 4.98 (q, 1H, J=2.1 and 9.5 Hz); 5.18 (m, 2H); 7.29 (m, 2H); 7.75 (m, 2H). ^{13}C (CDCl$_3$): 14.9; 31.7; 59.1; 120.1; 121.4; 129.1; 129.3; 130.9; 135.6; 159.8; 171.8. HRMS: Calcd for $C_{13}H_{13}{}^{35}ClN_2O+H$: 249.0795. Found: *m*/*z*, 249.0812.

4.2.36. 2-(4-Chlorophenyl)-4-(2-hydroxypropyl)-5-methyl-1H-pyrazol-3(2H)-one ***14***

Obtained (0.02 g, 12%) as an oil. ^{1}H (CDCl$_3$): 1.50 (d, 6H, J=6.1 Hz); 1.68 (q, 1H, J=4.4 and 8.5 Hz); 1.90 (q, 1H, J=4.5 and 8.5 Hz); 1.95 (s, 3H); 2.13 (m, 1H); 7.36 (m, 2H); 7.94 (m, 2H). ^{13}C (CDCl$_3$): 10.8; 12.4; 25.9; 28.3; 37.7; 119.7; 129.8; 129.6; 137.5; 159.9; 171.7. HRMS: Calcd for $C_{13}H_{13}{}^{35}ClN_2O+H$: 249.0795. Found: *m*/*z*, 249.0790 (MH−H$_2$O; respective polarities of compound **13** and **14** preclude a bicyclic structure for **14**).

Methylation of compound ***6*** *and* ***19***: compound **6** and **19** (4.2 mmol) were dissolved in dimethylformamide (10 mL, dried over 4 Å molecular sieves). To this solution was added sodium hydride (60% in mineral oil, 4.6 mmol) and at the end of the hydrogen evolution methyl iodide (4.6 mmol) was added. The solution was stirred overnight at room temperature in a flask protected from moisture by a calcium chloride guard. It was then concentrated to dryness, the residue was absorbed on a small amount of silica gel and purified as described below.

4.2.37. 1,5-Dimethyl-3-isopropoxy-1H-pyrazole ***31a***

Obtained in a 19% yield after two consecutive chromatography over silica gel (dichloromethane and then dichloromethane–cyclohexane 7:3) as a volatile oil. *Note*: this compound is detected by the UV monitor but not by TLC, its isomer was not seen by the UV monitor although it was visible on as a minor component on ^{1}H NMR spectra of the crude mixture. ^{1}H (CDCl$_3$): 1.33 (d, 6H, J=6.2 Hz); 2.19 (s, 3H); 3.62 (s, 3H); 4.66 (sept, 1H, J=6.2 Hz); 5.41 (s, 1H). ^{13}C (CDCl$_3$): 14.4; 22.2; 35.4; 71.3; 90.6; 139.5; 161.2. ^{15}N (CDCl$_3$): −108 (CH$_3$); −200 (CH$_3$, H-4, N-CH$_3$). HRMS: Calcd for $C_8H_{14}N_2O+H$: 155.1184. Found: *m*/*z*, 155.1186.

4.2.38. 1,5-Dimethyl-4-iodo-3-isopropoxy-1H-pyrazole ***31b***

Obtained in a 56% yield as a solid still containing 2.5% of **32b** after a chromatography over silica gel (dichloromethane–cyclohexane 1:1). ^{1}H (CDCl$_3$): 1.36 (d, 6H, J=6.1 Hz); 2.24 (s, 3H); 3.71 (s, 3H); 4.81 (sept, 1H, J=6.1 Hz). ^{13}C (CDCl$_3$): 11.9; 22.2; 36.9; 46.8;

72.4; 141.1; 160.9. ^{15}N ($CDCl_3$): −108 (CH_3, N-CH_3); −197 (N-CH_3). HRMS: Calcd for $C_{18}H_{13}IN_2O+H$: 281.0151. Found: *m*/*z*, 281.0170.

4.2.39. *1,3-Dimethyl-4-iodo-5-isopropoxy-1H-pyrazole **32b***

Obtained in a 1.8% yield as an oil still containing 10% of **31b** in a second fraction of the chromatography described above. Again contrary to its isomer, this compound is barely detected by the UV monitor. ^{1}H ($CDCl_3$): 1.36 (d, 6H, *J*=6.1 Hz); 2.19 (s, 3H); 3.65 (s, 3H); 4.74 (sept, 1H, *J*=6.1 Hz). ^{13}C ($CDCl_3$): 11.9; 22.5; 34.5; 46.1; 77.8; 149.0; 152.7. ^{15}N ($CDCl_3$): −90 (CH_3, N-CH_3); −190 (N-CH_3). HRMS: Calcd for $C_{18}H_{13}IN_2O+H$: 281.0151. Found: *m*/*z*, 281.0188.

*Benzylation of **6***: Compound **6** (0.3 g, 2.14 mmol) was dissolved in dimethylformamide (25 mL, dried over 4 Å molecular sieves). To this solution was added sodium hydride (60% in mineral oil, 0.062 g, 2.57 mmol) and at the end of the hydrogen evolution benzylbromide (0.305 mL, 2.57 mmol) was added. The solution was stirred overnight at room temperature in a flask protected from moisture by a calcium chloride guard. It was then concentrated to dryness, the residue was absorbed on a small amount of silica, and purified by a chromatography over silica gel (cyclohexane–dichloromethane 95:5 to 0:100) to yield in order of elution, the N-1 benzylation product **33** (0.280 g, 57%, still containing 8% of **34**) and then its isomer **34** (0.16 g, 32%, still containing 5% of **33**) as described below.

4.2.40. *1-Benzyl-3-isopropoxy-5-methyl-1H-pyrazole **33***

^{1}H ($CDCl_3$): 1.35 (d, 6H, *J*=6.2 Hz); 2.10 (s, 3H); 4.73 (sept, 1H, *J*=6.2 Hz); 5.10 (s, 2H); 5.49 (s, 1H); 7.11 (m, 2H); 7.24 (m, 1H); 7.29 (m, 2H). ^{13}C ($CDCl_3$): 11.3; 22.2; 52.3; 71.2; 91.7; 126.6; 127.3; 128.6; 137.7; 139.7; 161.5. ^{15}N ($CDCl_3$): −109 (CH_2); −191 (CH_3, CH_2, H-4). HRMS: Calcd for $C_{14}H_{18}N_2O+H$: 231.1497. Found: *m*/*z*, 231.1540.

4.2.41. *1-Benzyl-5-isopropoxy-3-methyl-1H-pyrazole **34***

^{1}H ($CDCl_3$): 1.30 (d, 6H, *J*=6.2 Hz); 2.21 (s, 3H); 4.34 (sept, 1H, *J*=6.2 Hz); 5.08 (s, 2H); 5.33 (s, 1H); 7.24 (m, 3H); 7.31 (m, 2H). ^{13}C ($CDCl_3$): 14.6; 21.9; 50.2; 75.0; 85.4; 127.2; 127.4; 128.4; 137.7; 147.3; 153.9. ^{15}N ($CDCl_3$): −98 (CH_3, CH_2); −190 (CH_2, H-4). HRMS: Calcd for $C_{14}H_{18}N_2O+H$: 231.1497. Found: *m*/*z*, 231.1525.

*Alternative preparation of compound **34***: As the comparison of the ^{15}N–^{1}H long distance correlation spectra of **33** and **34** were of little help in their structural assignment, we prepared compound **34** in 62% as follow.[1] Thus, isopropylacetoacetate (0.23 g, 1.59 mmol) and benzylhydrazine dihydrochloride (0.32 g, 1.64 mmol) were refluxed in isopropanol (50 mL) for 2 h. This was then concentrated to dryness and the residue dispersed in water, made basic with solid sodium hydrogenocarbonate, and extracted with dichloromethane. The organic phase was washed with 1 N sodium hydrogenocarbonate, dried over sodium sulfate and concentrated to dryness. The resulting residue was further purified by a chromatography over silica gel (cyclohexane–ethyl acetate 1:1) to yield a product identical with compound **34** as an oil (0.23 g, 62%; weakly visible in UV).

4.2.42. *1,2-Dibenzyl-3-ethoxy-5-methyl-1H-pyrazol-2-ium **35***

In a Biotage 10 ml microwave-adapted vial, compound **6** (0.4 g, 2.85 mmol) was dissolved in acetonitrile (5 mL, dried over 4 Å molecular sieves). Potassium carbonate (0.79 g, 5.7 mmol) and benzylbromide (0.68 mL, 5.7 mmol) were added and the vial was sealed. This was submitted to a microwave-based heating (140 °C for 7 mn) and the resulting suspension was diluted in dichloromethane, washed with brine dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified by a chromatography over silica gel (dichloromethane–ethanol 9:1) to yield compound **35** (0.37 g, 53%) as an oil. ^{1}H ($CDCl_3$): 1.47 (d, 6H, *J*=6.1 Hz); 2.53 (s, 3H); 5.01 (sept, 1H, *J*=6.1 Hz); 5.52 (s, 2H); 5.73 (s, 2H); 6.64 (s, 1H); 6.80 (m, 3H); 7.05 (m, 2H); 7.16 (m, 6H). ^{13}C ($CDCl_3$): (one signal overlapped); 13.6; 22.3; 49.3; 51.5; 79.9; 95.9; 126.1; 127.4; 128.9; 129.2; 129.5; 129.6; 132.5; 150.2; 157.1. ^{15}N ($CDCl_3$): −195 (2CH_2, H-4 and CH_3). HRMS: Calcd for $C_{21}H_{25}N_2O$: 321.1967. Found: *m*/*z*, 321.1986.

Acknowledgements

This work was supported by the Medicen initiative (Chemical Library Project; grant of the Région Ile de France no. I 06-222/R, which included a fellowship for S.G.). Dr. Daniel Larzul as well as Dr. Emile Bisagni are also acknowledged for their interest and support.

References and notes

1. Guillou, S.; Bonhomme, F. J.; Janin, Y. L. *Synthesis* **2008**, 3504–3508.
2. Stolz, F. *J. Prakt. Chem.* **1897**, *55*, 145–171.
3. Mayer, K. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 717–718.
4. Michaelis, A. *Justus Liebigs Ann. Chem.* **1905**, *338*, 267–321.
5. Elguero, J.; Jacquier, R.; Tarrago, G. *Bull. Soc. Chim. Fr.* **1967**, 3780–3794.
6. Kornet, M. J.; Ong, T. H.; Thio, P. A. *J. Heterocycl. Chem.* **1971**, *8*, 999–1003.
7. Harries, C.; Loth, G. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 513–520.
8. Bellamy, A. J.; Innes, D. I.; Hillson, P. J. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1599–1604.
9. Vogelbacher, U. J.; Keil, M.; Klintz, R.; Wahl, J.; Wingert, H.; Konig, H.; Rack, M.; Gotz, R.; Teles, J. H. Patent WO 98027062; see *Chem. Abstr.* **1998**, *129*, 81726.
10. Axford, A. J.; Kendall, J. D. *Sci. Ind. Photogr.* **1953**, *24*, 467–468; see *Chem. Abstr.* *48*, 2916.
11. Lecher, H. Z.; Parker, R. P.; Conn, R. C. *J. Am. Chem. Soc.* **1944**, *66*, 1959–1963.
12. Ainsworth, D. P.; Suschitzky, H. *J. Chem. Soc. C* **1967**, 1003–1006.
13. Yamamoto, Y.; Shirakawa, N.; Takano, S.; Kawai, Y. U.S. Patent 5,663,365; see-*Chem. Abstr.* **1997**, *127*, 262675.
14. Effenberger, F.; Hartmann, W. *Chem. Ber.* **1969**, *102*, 3260–3267.
15. Effenberger, F.; Hartmann, W. *Angew. Chem.* **1964**, *76*, 188.
16. Nakamura, N.; Kishida, Y.; Ishida, N. *Chem. Pharm. Bull.* **1971**, *19*, 1389–1394.
17. Bourrain, S.; Ridgill, M.; Collins, I. *Synlett* **2004**, 795–798.
18. Venturello, C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 681–685.
19. Venturello, C.; D'Aloisio, R. *Synthesis* **1979**, 283–287.
20. Almerico, A. M.; Boulton, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 204–205.
21. Downs, J. R.; Pastine, S. J.; Townsend, J. D.; Greer, H. A.; Kelley, W.; Schady, D. A.; Lentz McConaughy, T.; Metz, C. R.; Beam, C. F. *J. Heterocycl. Chem.* **2001**, *39*, 695–701.
22. Guillou, S.; Nesmes, O.; Ermolenko, M. S.; Janin, Y. L. *Tetrahedron*, in press.
23. Rossiter, S.; Woo, C. K.; Hartzoulakis, B.; Wishart, G.; Stanyer, L.; Labadie, J. W.; Selwood, D. L. *J. Comb. Chem.* **2004**, *6*, 385–390.
24. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
25. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
26. Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.
27. Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892–7897.
28. Lan, J. B.; Chen, L.; Yu, X. Q.; You, J. S.; Xie, R. G. *Chem. Commun.* **2004**, 188–189.
29. Strouse, J. J.; Jeselnik, M.; Tapaha, F.; Jonsson, C. B.; Parker, W. B.; Arterburn, J. B. *Tetrahedron Lett.* **2005**, *46*, 5699–5702.
30. Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 205–240.
31. Khan, M. A. *Rec. Chem. Prog.* **1970**, *31*, 43–50.
32. Kiyomori, J. F.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.
33. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
34. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
35. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
36. Antilla, J. C.; Baskin, J. M.; Barders, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.
37. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607–5622.
38. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695–709.
39. Kuil, M.; Bedekam, E. K.; Visser, G. M.; van den Hoogband, A.; Terpstra, J. W.; Kamer, P. C. J.; van Leewen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405–2409.
40. Alcade, E.; Dinarès, I.; Rodriguez, S.; Garcia de Miguel, C. *Eur. J. Org. Chem.* **2005**, 1637–1643.
41. Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553–6560.
42. Correa, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2673–2676.
43. Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.
44. Kantam, M. L.; Venkanna, G. T.; Sridhar, C.; Sreedhar, B.; Choudary, B. M. *J. Org. Chem.* **2006**, *25*, 9522–9524.
45. Bekolo, H. *Can. J. Chem.* **2007**, *85*, 42–46.

46. Yang, D.; Fu, N.; Luiu, Z.; Li, Y.; Chen, B. *Synlett* **2007**, 278–282.
47. O'Brien, D. F.; Gates, J. W. *J. Org. Chem.* **1966**, *31*, 1538–1542.
48. L'abbé, G.; Emmers, S.; Dehaen, W.; Dyall, L. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2553–2558.
49. Rodríguez-Franco, M. I.; Dorronsoro, I.; Hernández-Higueras, A. I.; Antequera, G. *Tetrahedron Lett.* **2001**, *42*, 863–865.
50. Bieringer, S.; Holzer, W. *Heterocycles* **2006**, *68*, 1825–1836.
51. Stanovik, E.; Svete, J. In *Product Class 1: Pyrazoles*; Neier, R., Ed.; Science of Synthesis; Thieme: Stuttgart, 2002; Vol. 12, pp 15–225.
52. Varvounis, G.; Fiamegos, Y.; Pilidis, G. In *Pyrazol-3-ones, Part 1: Synthesis and Applications*; Katritzky, A. R., Ed.; Advances in Heterocyclic Chemistry; Academic: London, 2001; Vol. 80, pp 74–144.
53. Castagnolo, D.; De Logu, A.; Radi, M.; Bechi, B.; Manetti, F.; Magnani, M.; Supino, S.; Meleddu, R.; Chisu, L.; Botta, M. *Bioorg. Med. Chem.* **2008**, *16*, 8587–8591.