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A General and Efficient Synthesis of Pyrazoles Catalyzed by $Sc(OTf)_3$ under Solvent-Free Conditions

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Pirazóis foram preparados em excelentes rendimentos via reação de condensação entre várias 1,3-dicetonas ($R^1COCHXCOCH_3$, R^1 = Me, Ph; X = H, Me, Cl) e hidrazinas, acilhidrazinas ou sulfonil hidrazinas, na presença de quantidades catalíticas de $Sc(OTf)_3$, a temperatura ambiente, na ausência de solventes. Adicionalmente, o catalisador foi facilmente recuperado após as reações e reutilizado sem perda evidente na atividade.

Pyrazoles were prepared in excellent yields via solventless condensation of various 1,3-diketones ($R^1COCHXCOCH_3$, R^1 = Me, Ph; X = H, Me, Cl) and hydrazines, acylhydrazines or sulfonyl hydrazines in the presence of a catalytic amount of $Sc(OTf)_3$ at room temperature. Additionally, the catalyst could be recovered easily after the reactions and reused without evident loss in activity.

Keywords: scandium(III) triflate, pyrazoles, 1,3-diketones, hydrazines, hydrazides, solvent-free

Introduction

Pyrazole and its derivatives constitute an important class of compounds, which exhibit various biological and pharmaceutical activities[1] ranging from antitumor[2] to antiinflammatory,[3] antipsychotic,[4] antimicrobial,[5] antiviral[6] and antifungal[7] activities. They are also useful intermediates for many industrial products.[8] It is therefore not surprising that many synthetic methods have been developed for the preparation of the heterocycles. The heterocycles can be synthesized via 1,3-dipolar cycloadditions of diazo compounds,[9] reaction of acetylenic ketones[10] or chalcones[11] and hydrazines, a four-component coupling of terminal alkynes, hydrazine, carbon monoxide, and aryl iodides.[12] Recently, a few efficient methods have been reported, too.[13] Moreover, pyrazoles can also be successfully obtained from the direct condensation of 1,3-diketones and hydrazines.[14] This is the most simple and straightforward procedure for their synthesis, a variety of catalysts such as H_2SO_4,[15] polystyrene supported sulfonic acid,[16] layered zirconium sulfophenyl phosphonate $[a\text{-}Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}]$,[17] have been employed to effect this transformation. Although these methods are suitable for certain synthetic conditions, sometimes, however, many of these procedures are associated with one or more disadvantages such as long reaction time, low yield, use of volatile organic solvents, requirement of excess of reagents or catalysts, special apparatus and harsh reaction conditions. And some of them need stoichiometric amount of acids which can be trapped by hydrazines in this condensation. Due to the importance of these compounds, the development of convenient, environmentally benign, high-yielding and clean approaches is highly desirable. To our knowledge, less attention has been paid to the synthesis of pyrazoles from 1,3-diketones and acylhydrazines/sulfonyl hydrazines in the presence of Lewis acid.

Metal triflates are unique Lewis acids that are currently of great research interest.[18] Firstly, metal triflates are air- and water- stable, thermal stable, less toxic, easily recovered and reused. In addition, metal triflates are still active in the coexistence of many substrates containing nitrogen, oxygen, phosphorous, and sulfur atoms. Due to these advantages, they are widely used in organic synthesis.[19] Recently, we have successfully applied metal triflates into several reactions.[20] In continuation of our interest in green chemistry and Lewis acid-catalyzed organic reactions,[21] we

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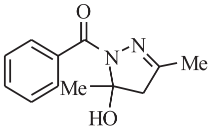
herein develop a green, simple and practical method for the synthesis of pyrazoles from 1,3-diketones with hydrazines, acylhydrazines and sulfonyl hydrazines catalyzed by Sc(OTf)$_3$ under solvent-free conditions.

Results and Discussion

To optimize the reaction conditions, we studied the condensation of pentane-2,4-dione with benzohydrazide in various reaction conditions and the results were summarized in Table 1.

Among the various catalyst such as Sc(OTf)$_3$, Cu(OTf)$_2$, Zn(OTf)$_2$, Yb(OTf)$_3$, InCl$_3$, ZrSO$_4$·4H$_2$O (Table 1, entries 1-6), Sc(OTf)$_3$ was found to be the most effective catalyst in terms of reaction yields and rate. Then, the reaction was performed in different amounts of Sc(OTf)$_3$. It was found that the yield was not significantly affected by adding amount of Sc(OTf)$_3$, and 2 mol % of Sc(OTf)$_3$ was sufficient, and excessive amount of catalyst did not increase the yield remarkably (Table 1, entries 1, 7 and 8). The use of 2 mol % Sc(OTf)$_3$ was optimal to ensure high reaction efficiency at room temperature in the absence of solvent. It was found that only the intermediate (5-hydroxy-3,5-dimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**4**) was observed when the mixture was stirred under similar conditions in the absence of Sc(OTf)$_3$, even after 1 h (Table 1, entry 9). It was proved that the catalyst did play an important role in this reaction.



4

The general efficiency of this protocol was then studied for the synthesis of a variety of pyrazoles and the results were summarized in Table 2.

As can be seen from Table 2, various hydrazines and acylhydrazines reacted efficiently with 1,3-diketones to afford the desired pyrazoles in good yields. A series of aromatic hydrazides bearing either electron-donating (Table 2, entries 1, 2, 9, 10, 13 and 14) or electron-withdrawing (Table 2, entries 4, 12, 16) groups on aromatic ring were investigated. The substitution group on the phenyl ring did not seem to affect the reaction significantly either in the yield of product or the rate of the reaction. Moreover, we also examined the condensation of aliphatic hydrazide with 1,3-diketone (Table 2, entry 5). Similarly, the corresponding product was obtained with good yields. Apart from the spectroscopic evidence, meanwhile, the structure of **3i** (Table 2, entry 9) was confirmed by a single crystal X-ray diffraction analysis (Figure 1).[22]

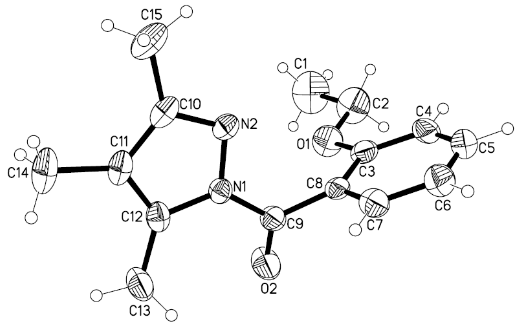
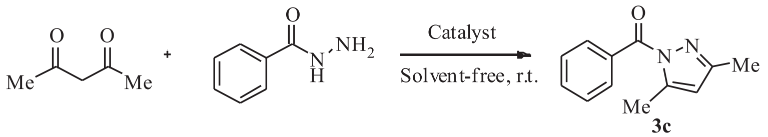


Figure 1. X-ray crystal structure of **3i**.

Furthermore, the advantage of the present protocol was also evidenced when less reactive hydrazines were used in the following reactions. Wang and Qin[15] reported that the

Table 1. The condensation of pentane-2,4-dione with benzohydrazide under different reaction conditions[a]

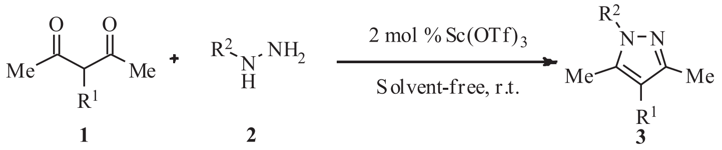


3c

Entry	Catalyst	Loading / (mol %)	Isolated yield / (%)
1	Sc(OTf)$_3$	5	93
2	Zn(OTf)$_2$	5	84
3	Cu(OTf)$_2$	5	71
4	Yb(OTf)$_3$	5	87
5	InCl$_3$	5	69
6	Zr(SO$_4$)$_2$·4H$_2$O	5	58
7	Sc(OTf)$_3$	2	92
8	Sc(OTf)$_3$	1	86
9	None	–	**4** (88)[b]

[a]Reactions performed with pentane-2,4-dione (1.0 mmol), benzohydrazide (1.0 mmol), and Sc(OTf)$_3$ (2 mol %) and mixed for 20 min at room temperature. [b]The product was the intermediate (5-hydroxy-3,5-dimethyl-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)methanone (**4**), and the yield was shown in parentheses.

Table 2. Synthesis of pyrazoles catalyzed by $Sc(OTf)_3$ under solvent-free conditions[a]



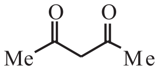
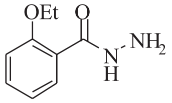
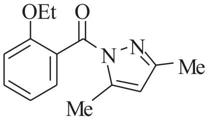
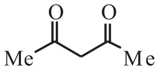
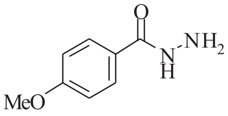
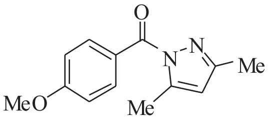
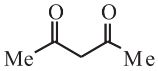
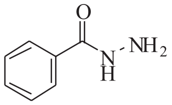
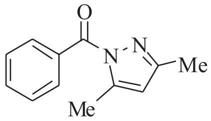
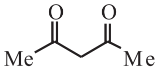
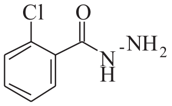
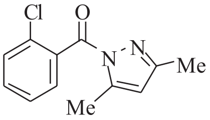
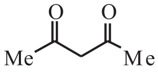
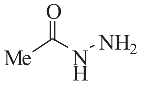
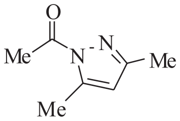
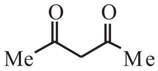
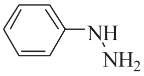
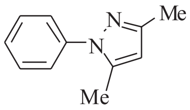
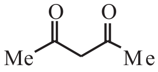
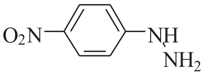
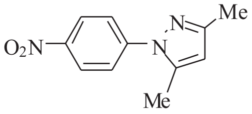
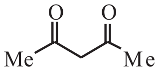
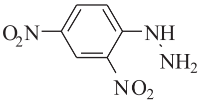
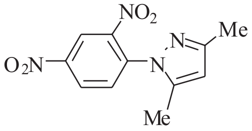
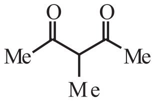
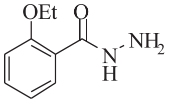
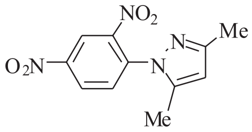
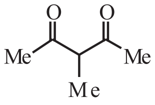
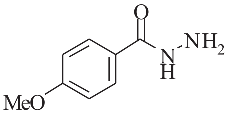
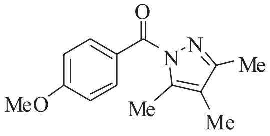
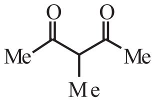
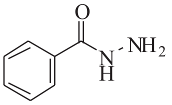
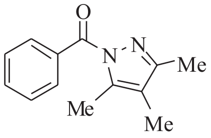
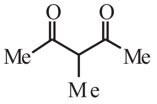
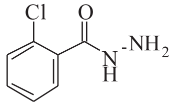
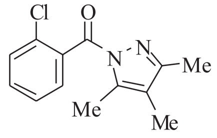
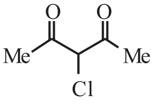
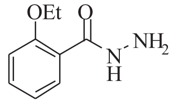
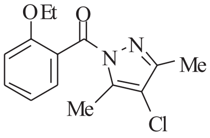
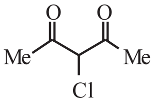
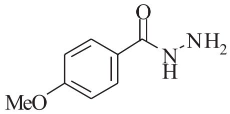
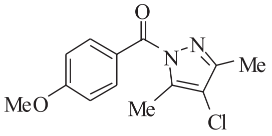
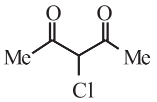
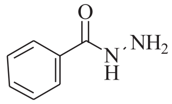
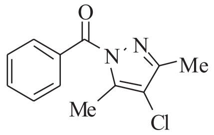
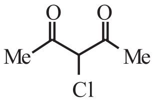
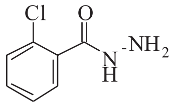
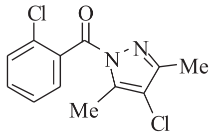
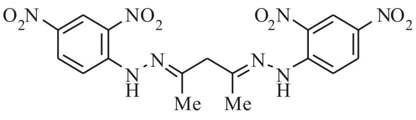
Entry	Diketone	Hydrazine/Hydrazide	Product	Yield[b] / (%)
1[c]			 **3a**	92, 94, 95
2			 **3b**	86
3			 **3c**	92
4			 **3d**	99
5			 **3e**	86
6			 **3f**	94
7[d]			 **3g**	84
8[d]			 **3h**	99
9			 **3i**	95
10			 **3j**	87
11			 **3k**	85

Table 2. Synthesis of pyrazoles catalyzed by Sc(OTf)$_3$ under solvent-free conditions[a]

Entry	Diketone	Hydrazine/Hydrazide	Product	Yield[b] / (%)
12			 **3l**	99
13			 **3m**	92
14[d]			 **3n**	78
15[d]			 **3o**	76
16[d]			 **3p**	88

[a]Reactions performed with 1,3-diketones (1.0 mmol), hydrazines/hydrazides (1.0 mmol), and Sc(OTf)$_3$ (2 mol %) and mixed for 20 min at room temperature. [b]Isolated yields. [c]Sc(OTf)$_3$ was recovered and reused three times. [d]Reaction run at 60 °C.



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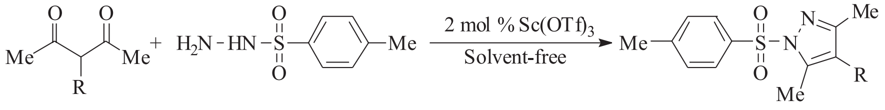
solventless condensation of 2,4-dinitrophenylhydrazine with 2,4-pentanedione only afforded hydrazone derivative 2,2'-(pentane-2,4-diylidene)bis(1-(2,4-dinitrophenyl) hydrazine) (**5**) in the presence of sulfuric acid. However, 2,4-dinitrophenyl hydrazine smoothly reacted with 2,4-pentanedione to afford the desired pyrazole derivative (**3h**) in excellent yield (99%) using the present protocol (Table 2, entry 8). And other less reactive hydrazines such as 4-nitro-phenyl hydrazinecan also smoothly reacted with 1,3-diketones to afford the desired product in high yields (Table 2, entry 7). It is noteworthy that we also examined the activity of recycled Sc(OTf)$_3$ catalyst. The reaction mixture was washed with water, extracted with ethyl acetate, and the aqueous phase was dried at 140 °C for 4 h. The residue could be reused for the next batch reaction. It was found that Sc(OTf)$_3$ could be reused three times without evident loss of activity (with the yields of the corresponding product being 95%, 94%, and 92%, respectively); Table 2, entry 1.

Next, we examined the condensation reactions of 1,3-diketones with *p*-toluenesulfonylhydrazide (Scheme 1). 3,5-Dimethyl-1-tosyl-1H-pyrazole (**3q**) and 4-chloro-3,5-dimethyl-1-tosyl-1H-pyrazole (**3r**) were obtained in 99%, and 82% yields respectively when the reaction was performed at 60 °C in the presence of Sc(OTf)$_3$. Nevertheless, trace product was obtained in the absence of catalysts, which also further proved that Sc(OTf)$_3$ did play an important role in this reaction.

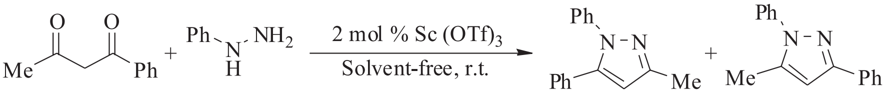
Finally, to extend the scope of triflate-catalyzed method of pyrazoles formation, an unsymmetrical diketone such as 1-phenylbutane-1,3-dione was employed. As shown in Scheme 2, the reaction was also performed smoothly and a very good regioselectivity was also observed (**3s** : **3s′** = 13 : 1, ratio based on its ^{1}H NMR spectrum).

In summary, a new catalytic protocol to synthesize pyrazoles has been developed. Compared to previous reported methodologies, the present protocol features simple work-up, short reaction time, environmentally benign, easy recovery and reuse of metal triflate and mild reaction conditions with excellent yield. Currently, studies on the extension of this protocol are ongoing in our laboratory.



R = H, yield 99% **3q**
R = Cl, yield 82% **3r**

Scheme 1.



3s **3s'**

Yield 96% (**3s** : **3s'**=13 : 1)

Scheme 2.

Experimental

All reagents were commercial available and used without any purification. Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. IR spectra were recorded on a Bruker-EQUINOX55 spectrometer. Mass spectra (EI, 70 eV) were measured with SHIMADZU GCMS-QP2010 Plus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC 300 instrument using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts were given in δ relative to TMS, the coupling constants *J* are given in Hz. Elemental analysis was determined on a Carlo-Erba 1108 instrument. X-ray diffraction data were collected on a Bruker Smart Apex diffractometer with graphite-monochromated (Mo Ka, λ 0.70173Å) radiation using SMART. All reactions were conducted using standard Schlenk techniques. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

General procedure for the preparation of pyrazoles

The hydazines/hydrazides (1.0 mmol) and Sc(OTf)$_3$ (2 mol %) were placed in a Schlenk reaction tube with efficient stirring or mixing, then 1,3-diketone (1.0 mmol) was added. The mixture was stirred for 20 min at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with water, extracted with ethyl acetate, the organic phase was separated and dried over anhydrous sodium sulfate, filtered and the solvent was removed under vacuum. Then, the residue was purified by flash column chromatography on a silica gel to give the corresponding product.

The spectral and analytical data of some representative compounds are given below.

*(3,5-Dimethyl-1H-pyrazol-1-yl)(2-ethoxyphenyl) methanone (**3a**)*

White solid, mp 70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.19 (t, 3H, *J* 7.0 Hz, CH_3), 2.16 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.02 (q, 2H, *J* 7.0 Hz, CH_2), 6.00 (s, 1H, CH), 6.93-7.03 (m, 2H, ArH), 7.40-7.46 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.9, 14.2, 14.6 ($3CH_3$), 64.2 (CH_2), 110.9 (C4), 112.7, 120.2, 125.2, 129.7, 132.1 (5C, Ph), 144.0 (C5), 151.9 (C3), 156.9 ($\underline{C}$-OEt, Ph), 168.6 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3068, 2974, 2928, 2890, 1709, 1587, 1485, 1401, 1336, 1250, 1038, 900, 664; MS (EI, 70 eV): *m/z* (%) = 244 (M$^+$, 1), 199 (67), 149 (28), 121 (100), 93 (21), 65 (19). Anal. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.75; H, 6.64; N, 11.52.

*(3,5-Dimethyl-1H-pyrazol-1-yl)(4-methoxyphenyl) methanone (**3b**)*

White solid, mp 48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 5.99 (s, 1H, CH), 6.91 (d, 2H, *J* 8.3 Hz, ArH), 8.03 (m, 2H, *J* 8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.8, 14.2 ($2CH_3$), 55.4 (OCH_3), 110.7 (C4), 113.3, 125.3, 134.0 (3C, Ph), 144.9 (C5), 151.6 (C3), 163.2 ($\underline{C}$-OMe, Ph), 167.4 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3033, 2928, 1689, 1602, 1342, 1262, 669; MS (EI, 70 eV): *m/z* (%) = 230 (M$^+$, 7), 135 (100), 107 (10), 92 (10), 77 (15). Anal. Calc. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.88; H, 6.26; N, 12.19.

*(3,5-Dimethyl-1H-pyrazol-1-yl)(phenyl)methanone (**3c**)*[15]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.05 (s, 3H, CH), 7.42-7.54 (m, 3H, ArH), 7.98 (d, 2H, *J* 7.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.9, 14.4 ($2CH_3$), 111.1 (C4), 127.9, 131.4, 132.4, 133.4 (6C, Ph), 145.1 (C5), 152.1 (C3), 168.4 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3063, 2976, 2928, 1698, 1586, 1340, 918, 705.

*(2-Chlorophenyl)(3,5-dimethyl-1H-pyrazol-1-yl) methanone (**3d**)*[23]

Colorless oil; ^1H NMR (300MHz, $CDCl_3$): δ (ppm) 2.13 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 6.03 (s, 1H, CH), 7.29-7.47 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.9, 14.2 ($2CH_3$), 111.9 (C4), 126.4, 129.3, 129.6, 131.2, 131.5, 135.2 (6C, Ph), 144.4 (C5), 153.2 (C3), 167.4 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3066, 2978, 2929, 1712, 1587, 1346, 967, 918, 746, 652.

*1-(3,5-Dimethyl-1H-pyrazol-1-yl)ethanone (**3e**)*[15]

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 5.92 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.8, 14.6 ($2CH_3$), 23.5 ($\underline{C}H_3CO$) , 111.1 (C4), 144.0 (C5), 152.0 (C3), 171.5 (C=O); IR (KBr) ν_{max}/cm^{-1}: 2924, 2859, 1730, 1666, 1457, 1142, 647.

*3,5-Dimethyl-1-phenyl-1H-pyrazole (**3f**)*[15]

Yellow oil; ^1H NMR (300MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.96 (s, 1H, CH), 7.28-7.40 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 12.3, 13.5 ($2CH_3$), 107.0 (C4), 124.6, 127.2, 128.9, 139.3 (6C, Ph), 139.9 (C5), 148.9 (C3); IR (KBr) ν_{max}/cm^{-1}: 3059, 2923, 1598, 1555, 1501, 1421, 1376, 778, 693.

*3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazole (**3g**)*[24]

Yellow solid, mp 100-101 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.06 (s, 1H, CH), 7.66 (d, 2H, *J* 7.3 Hz, ArH), 8.30 (d, 2H, *J* 7.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.2, 13.5 ($2CH_3$), 109.4 (C4), 123.5, 124.8 (4C, Ph), 139.9 (C5), 145.0 (C-NO_2, Ph), 145.5 (C-N, Ph), 150.9 (C3); IR (KBr) ν_{max}/cm^{-1}: 3102, 2977, 2923, 1660, 1598, 1513, 1331, 1103, 852.

*1-(2,4-Dinitrophenyl)-3,5-dimethyl-1H-pyrazole (**3h**)*[24]

Yellow solid, mp 122-123 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.69 (d, 1H, *J* 8.7 Hz, ArH), 8.52 (dd, 1H, J_1 8.7 Hz, J_2 2.0 Hz, ArH), 8.78 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 11.6, 13.5 ($2CH_3$), 108.9 (C4), 121.0, 127.3, 129.3, 137.9 (4C, Ph), 140.9 (C5), 145.6 , 146.2 (2C-NO_2, Ph), 152.4 (C3); IR (KBr) ν_{max}/cm^{-1}: 3120, 3077, 2928, 2865, 1612, 1532, 1432, 1344, 1124, 1025, 973, 903, 671.

*(2-Ethoxyphenyl)(3,4,5-trimethyl-1H-pyrazol-1-yl) methanone (**3i**)*

White solid, mp 60 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.17 (t, 3H, *J* 7.0 Hz, CH_3), 1.91 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.99 (q, 2H, *J* 7.0 Hz, CH_2), 6.90-6.99 (m, 2H, ArH), 7.35-7.41 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 7.7, 12.4, 12.5, 14.6 ($4CH_3$), 64.2 (CH_2), 112.7 (C4), 117.3, 120.1, 125.6, 129.6, 131.8 (5C, Ph), 139.5 (C5), 152.3 (C3), 156.7 ($\underline{C}$-OEt, Ph), 168.4 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3047, 2981, 2927, 2881, 1717, 1593, 1488, 1442, 1386, 1343, 901,753, 655; MS (EI, 70 eV): *m/z* (%) = 258 (M^+, 1), 213 (75), 149 (28), 121 (100), 93 (22), 65 (18). Anal. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.78; H, 6.97; N, 10.89.

*(4-Methoxyphenyl)(3,4,5-trimethyl-1H-pyrazol-1-yl) methanone (**3j**)*

Yellow solid, mp 80-81 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.93 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 6.92 (d, 2H, *J* 8.9 Hz, ArH), 8.00 (d, 2H, *J* 8.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 7.7, 12.4, 12.5 ($3CH_3$), 55.4 (OCH_3), 113.2 (C4), 117.1, 125.7, 133.9 (5C, Ph), 140.4 (C5), 152.0 (C3), 163.0 ($\underline{C}$-OMe, Ph), 167.5 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3031, 2924, 2846, 1677, 1601, 1501, 1340, 1256, 906, 617; MS (EI, 70 eV): *m/z* (%) = 244 (M^+, 8), 135 (100), 107 (10), 92 (10), 77 (15). Anal. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.90; H, 6.53; N, 11.52.

*Phenyl(3,4,5-trimethyl-1H-pyrazol-1-yl)methanone (**3k**)*[25]

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.95 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.41-7.53 (m, 3H, ArH), 7.95 (d, 2H, *J* 8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 7.7, 12.4, 12.6 ($3CH_3$), 117.5 (C4), 127.8, 131.3, 132.2, 133.7 (6C, Ph), 140.5 (C5), 152.5 (C3), 168.4 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3063, 2925, 2863, 1692, 1601, 1343, 910, 708.

*(2-Chlorophenyl)(3,4,5-trimethyl-1H-pyrazol-1-yl) methanone (**3l**)*

White solid, mp 96-97 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.97 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.35-7.47 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 7.7, 12.5, 14.2 ($3CH_3$), 118.3 (C4), 126.4, 129.2, 129.7, 131.0, 131.6, 135.5 (6C, Ph), 139.8 (C5), 153.7 (C3), 167.3 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3042, 2926, 1699, 1604, 1348, 1050, 907, 756, 637; MS (EI, 70 eV): *m/z* (%) = 248 (M^+, 1), 213 (100), 139 (84), 111 (39), 75 (17). Anal. Calc. for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26. Found: C, 62.81; H, 5.22; N, 11.33.

*(4-Chloro-3,5-dimethyl-1H-pyrazol-1-yl)(2-ethoxyphenyl) methanone (**3m**)*

Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.22 (t, 3H, *J* 7.0 Hz, CH_3), 2.21 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.05 (q, 2H, *J* 7.0 Hz, CH_2), 6.96-7.07 (m, 2H, ArH), 7.44-7.50 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 11.8, 12.2, 14.6 (3CH$_3$), 64.2 (CH$_2$), 112.6 (C4), 114.4, 120.2, 124.2, 129.8, 132.5 (5C, Ph), 139.3 (C5), 149.3 (C3), 156.9 ($\underline{\text{C}}$-OEt, Ph), 168.2 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3069, 2981, 2929, 1717, 1595, 1488, 1449, 1340, 1254, 928, 755, 673; MS (EI, 70 eV): *m/z* (%) = 278 (M$^+$, 2), 233 (35), 149 (54), 121 (100), 93 (19), 65 (17). Anal. Calc. for C$_{14}$H$_{15}$ClN$_2$O$_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.26; H, 5.39; N, 10.11.

*(4-Chloro-3,5-dimethyl-1H-pyrazol-1-yl)(4-methoxyphenyl) methanone (**3n**)*

White solid, mp 125-126 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.29 (s, 3H, CH$_3$), 2.62 (s, 3H, CH$_3$), 3.89 (s, 3H, CH$_3$), 6.98 (d, 2H, *J* 8.4 Hz, ArH), 8.03 (d, 2H, *J* 8.5 Hz, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 11.8, 12.3 (2CH$_3$), 55.5 (OCH$_3$), 113.4 (C4), 114.1, 124.4, 134.0 (5C, Ph), 140.3 (C5), 149.0 (C3), 163.4 ($\underline{\text{C}}$-OMe, Ph), 167.0 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3079, 2928, 2843, 1689, 1602, 1504, 1454, 1344, 1266, 696; MS (EI, 70 eV): *m/z* (%) = 264 (M$^+$, 5), 135 (100), 107 (9), 92 (10), 77 (14). Anal. Calc. for C$_{13}$H$_{13}$ClN$_2$O$_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 59.02; H, 4.89; N, 10.65.

*(4-Chloro-3,5-dimethyl-1H-pyrazol-1-yl)(phenyl) methanone (**3o**)*[26]

White solid, mp 48-49 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.29 (s, 3H, CH$_3$), 2.66 (s, 3H, CH$_3$), 7.47-7.61 (m, 3H, ArH), 7.97-8.00 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 11.8, 12.4 (2CH$_3$), 114.9 (C4), 128.0, 131.4, 132.5, 132.7 (6C, Ph), 140.4 (C5), 149.6 (C3), 167.9 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3066, 2926, 1700, 1588, 1487, 1447, 1343, 1272, 686.

*(4-Chloro-3,5-dimethyl-1H-pyrazol-1-yl)(2-chlorophenyl) methanone (**3p**)*

White solid, mp 81-82 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.17 (s, 3H, CH$_3$), 2.66 (s, 3H, CH$_3$), 7.35-7.45 (m, 4H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 11.8, 12.2 (2CH$_3$), 115.5 (C4), 126.4, 129.4, 129.7, 131.5, 131.8, 134.3 (6C, Ph), 139.7, (C5), 150.7 (C3), 167.0 (C=O); IR (KBr) ν_{max}/cm^{-1}: 3065, 2969, 2922, 2855, 1715, 1587, 1335, 924, 734, 651; MS (EI, 70 eV): *m/z* (%) = 268 (M$^+$, 1), 233 (50), 139 (100), 111 (38), 75 (21). Anal. Calc. for C$_{12}$H$_{10}$Cl$_2$N$_2$O: C, 53.55; H, 3.75; N, 10.41. Found: C, 53.61; H, 3.79; N, 10.34.

*3,5-Dimethyl-1-tosyl-1H-pyrazole (**3q**)*[27]

White solid, mp 95 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.20 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 2.49 (s, 3H, CH$_3$), 5.90 (s, 1H, CH), 7.30 (d, 2H, *J* 8.1 Hz, ArH), 7.83 (d, 2H, *J* 8.2 Hz, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 13.1, 13.8, 21.6 (3CH$_3$), 110.8 (C4), 127.5, 129.9, 135.3, 144.1 (6C, Ph), 145.2 (C5), 153.4 (C3); IR (KBr) ν_{max}/cm^{-1}: 3041, 2928, 2863, 1656, 1580, 1372, 1292, 1186, 1120, 809, 668, 591, 534.

*4-Chloro-3,5-dimethyl-1-tosyl-1H-pyrazole (**3r**)*

White solid, mp 126-127 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.17 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 7.29 (d, 2H, *J* 8.2 Hz, ArH), 7.80 (d, 2H, *J* 8.4 Hz, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 11.2, 11.9, 21.7 (3CH$_3$), 113.5 (C4), 127.7, 130.1, 134.7, 139.3 (6C, Ph), 145.7 (C5), 150.9 (C3); IR (KBr) ν_{max}/cm^{-1}: 3067, 2927, 2859, 1581, 1451, 1374, 1188, 1151, 669; MS (EI, 70 eV): *m/z* (%) = 284 (M$^+$, 4), 220 (30), 129 (8), 91 (100), 65 (30). Anal. Calc. for C$_{12}$H$_{13}$ClN$_2$O$_2$S: C, 50.61; H, 4.60; N, 9.84. Found: C, 50.63; H, 4.65; N, 9.87.

*(5-Hydroxy-3,5-dimethyl-4,5-dihydro-1H-pyrazol-1-yl) (phenyl)methanone (**4**)*[28]

Colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 1.92 (s, 3H, CH$_3$), 1.94 (s, 3H, CH$_3$), 2.76 (d, 1H, *J* 18.4 Hz, CH$_2$), 2.99 (d, 1H, *J* 18.4 Hz, CH$_2$), 5.30 (s, 1H, OH), 7.33-7.44 (m, 3H, ArH), 7.82-7.84 (m, 2H, ArH); IR (KBr) ν_{max}/cm^{-1}: 3445, 3063, 2983, 2930, 1695, 1626, 1438, 1340, 1224, 1120, 918, 706.

*3-Methyl-1,5-diphenyl-1H-pyrazole (**3s**) and 5-methyl-1,3-diphenyl-1H-pyrazole (**3s'**)*[15]

(**3s**): colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.39(s, 3H, CH$_3$), 6.31 (s, 1H, CH$_3$), 7.21-7.30 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 13.6 (CH$_3$), 107.8 (C4), 125.1, 127.1, 128.1, 128.4, 128.7, 128.9, 130.8, 140.2 (12C, 2Ph), 143.7 (C5), 149.5 (C3); IR (KBr) ν_{max}/cm^{-1}: 3057, 2925, 2866, 1597, 1550, 1500, 1450, 1419, 1369, 763, 694.; (**3s'**): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.38(s, 3H, CH$_3$), 6.41 (s, 1H, CH$_3$), 7.30-7.39 (m, 10H, ArH).

Acknowledgments

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

References

1. Elguero, J.; In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., eds.; Pergamon-

Elsevier Science: Oxford, 1996, p.1; Behr, L. C.; Fusco, R.; Jarboe, C. H. In *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Wiley, R. H., ed., Interscience Publishers: New York, 1967; McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. ; *Curr. Top. Med. Chem.* **2006**, *6*, 1193; Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A.M.S.; *Targets Heterocycl. Syst*. **2002**, *6*, 52.

2. Lin, R.; Chiu, G.; Yu, Y.; Connolly, P. J.; Li, S.; Lu, Y.; Adams, M.; Fuentes-Pesquera, A. R.; Emanuel, S. L.; Greenberger, L. M.; *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4557; Hatheway, G.. J.; Hansch, C.; Kim, K. H.; Milstein, S. R.; Schimidt, L.; Smith, R. N.; Quin, F. R.; *J. Med. Chem.* **1978**, *21*, 563; Katayama, H.; Oshiyama, T.; *Can. J. Chem.* **1997**, *75*, 913.
3. Gokhan-Kelekci, N.; Yabanoglu, S.; Kupeli, E.; Salgin, U.; Ozgen, O.; Ucar, G.; Yesilada, E.; Kendi, E.; Yesilada, A.; Bilgin, A. A.; *Bioorg. Med. Chem.* **2007**, *15*, 5775; Badawey, E.; El-Ashmawey, I. M.; *Eur. J. Med. Chem*. **1998**, *33*, 349.
4. Barceló , M.; Raviña, E.; Masaguer, C. F.; Domínuez, E.; Areias, F. M.; Brea, J.; Loza, M. I.; *Bioorg. Med. Chem.Lett.* **2007**, *17*, 4873.
5. Farag, A. M.; Mayhoub, A. S.; Barakat, S. E.; Bayomi, A. H.; *Bioorg. Med. Chem.* **2008**, *16*, 4569; Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S.; *J. Indian Chem. Soc.* **1991**, *68*, 245.
6. Larsen, J. S.; Zahran, M. A.; Pedersen, E. B.; Nielsen, C.; *Monatsh. Chem.* **1999**, *130*, 1167.
7. Prakash, O.; Kumar, R.; Parkash, V.; *Eur. J. Med. Chem.* **2008**, *43*, 435.
8. Cativiela, C.; Serrano, J. L.; Zurbano, M. M.; *J. Org. Chem.* **1995**, *60*, 3074; Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K.; Hori, V.; *J. Med. Chem.* **1977**, *20*, 80.
9. Aggarwal, V. K.; Vicente, D. V.; Bonnert, R. V.; *J. Org. Chem.* **2003**, *68*, 5381; Padwa, A.; *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984.
10. Bishop, B. C.; *Synthesis* **2004**, *1*, 43.
11. Bhat, B. A.; Puri, S. C.; Qurishi, M. A.; Dhar, K. L.; Qazi, G. N.; *Synth. Commun.* **2005**, *35*, 1135.
12. Ahmed, M. S. M.; Kobayashi, K.; Mori, A.; *Org. Lett.* **2005**, *7*, 4487.
13. Heller, S. T.; Natarajan, S. R.; *Org. Lett.* **2006**, *8*, 2675; Deng, X.; Mani, N. S.; *Org. Lett.* **2006**, *8*, 3505; Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D.; *Org. Lett.* **2005**, *7*, 713; Alex, K.; Tillack, A.; Schwarz, N.; Beller, M.; *Org. Lett.* **2008**, *10*, 2377.; Borges, J. C.; De Oliveira, C. D.; Pinheiro, L. C. S.; Marra, R. K. F.; Khan, M. A.; Wardell, J. L.; Wardell, S. M. S. V.; Bernardino, A. M. R.; *J. Braz. Chem. Soc.* **2007**, *18*, 1571.
14. Fustero, S.; Román, R.; Sanz-Cervera, J. F.; X Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M.; *J. Org. Chem.* **2008**, *73*, 3523; Katritzky, A. R.; *Handbook of Heterocyclic Chemistry*; Pergamon; New York, 1985, p. 416.
15. Wang, Z.; Qin, H.; *Green Chem.* **2004**, *6*, 90.
16. Polshettiwar, V.; Varma, R. S.; *Tetrahedron Lett.* **2008**, *49*, 397.
17. Curini, M.; Rosati, O.; Campagna, V.; Montanari, F.; Cravotto, G.; Boccalini, M.; *Synlett* **2005**, *19*, 2927;
18. Curini, M.; Epifano, F.; Genovese, S.; Marcotullio, M. C.; Rosati, O.; *Org. Lett.* **2005**, *7*, 1331; Evans, D. A.; Fandrick, K. R.; Song, H. J.; *J. Am. Chem. Soc.* **2005**, *127*, 8942; Morris, W. J.; Custar, D. W.; Scheidt, K. A.; *Org. Lett.* **2005**, *7*, 1113; Deng, X. M.; Sun, X. L.; Tang, Y.; *J. Org. Chem.* **2005**, *70*, 6537; Lacey, J. R.; Anzalone, P. W.; Duncan, C. M.; Hackert, M. J.; Mohan, R. S.; *Tetrahedron Lett.* **2005**, *46*, 8507; Ollevier, T.; Nadeau, E.; *Synlett.* **2006**, *2*, 219; Kang, Y. B.; Tang, Y.; Sun, X. L.; *Org. Biomol. Chem*. **2006**, *4*, 299; Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K.; *Org. Lett*. **2005**, *7*, 4729.
19. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L.; *Chem. Rev*. **2002**, *102*, 2227.
20. Chen, J. X.; Wu, H. Y.; Zheng, Z. G.; Jin, C.; Zhang, X. X.; Su, W. K.; *Tetrahedron Lett.* **2006**, *47*, 5383; Su, W. K.; Chen, J. X.; Wu, H. Y.; Jin, C.; *J. Org. Chem.* **2007**, *72*, 4524; Su, W. K.; Hong, Z.; Shan, W. G.; Zhang, X. X.; *Eur. J. Org. Chem.* **2006**, 2723; Su, W. K.; Li, J. J.; Zheng, Z. G.; Shen, Y. C.; *Tetrahedron Lett.* **2005**, *46*, 6037; Yu, C. M.; Dai, X. P.; Su, W. K.; *Synlett* **2007**, 646; Su, W. K.; Jin, C.; *Org. Lett.* **2007**, *9*, 993; Chen, J. X.; Wu, D. Z.; He, F.; Liu, M. C.; Wu H. Y.; Ding, J. C.; Su, W. K.; *Tetrahedron Lett.* **2008**, *49*, 3814.
21. Chen, J. X.; Wu, H. Y.; Jin, C.; Zhang, X. X.; Xie, Y. Y.; Su, W. K.; *Green Chem*. **2006**, *8*, 330; Chen, X. A.; Zhang, C. F.; Wu, H. Y.; Yu, X. C.; Su, W. K.; Ding, J. C.; *Synthesis* **2007**, *20*, 3233. Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C.; *Green Chem.* **2007**, *9*, 972; Chen, J. X.; Liu, M. C.; Yang, X. L.; Ding, J. C.; Wu, H. Y.; *J. Braz. Chem. Soc.* **2008**, *19*, 877.
22. Crystallographic data for structure 5f, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center (CCDC 699093). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
23. Sharma, R. S.; Pathak, R. B.; Bahel, S. C.; *J. Indian Chem. Soc.* **1985**, *62*, 625.
24. Claramunt, R. M.; Marıa, M. D. S.; Sanz, D.; Alkorta, I.; Elguero, J.; *Magn. Reson. Chem*. **2006**, *44*, 566.
25. Papadopoulos, S.; Stephanidou-Stephanatou, J.; *Liebigs Ann. Chem*. **1985**, 1697.
26. Zhao, Z. G.; Wang, Z. X.; *Synth. Commun*. **2007**, *37*, 137.
27. Ege, G; Franz, H.; *J. Heterocycl. Chem.***1984**, *21*, 689.
28. Hedbom, C.; Helgstrand, E.; *Acta Chem. Scand*. **1970**, *24*, 1744.

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