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An efficient aerobic oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines

Bing Han, Zhengang Liu, Qiang Liu, Li Yang, Zhong-Li Liu* and Wei Yu*

National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, People's Republic of China

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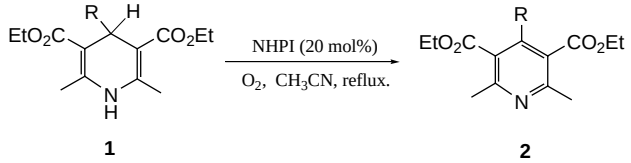
Abstract—4-Substituted Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were oxidized to the corresponding pyridines and pyrazoles, respectively, in high yields by molecular oxygen in the presence of catalytic amount of *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$ in acetonitrile at room temperature.

1. Introduction

Hantzsch 1,4-dihydropyridines (DHPs), a class of model compounds of NADH coenzyme,[1] have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process,[2] and their therapeutic functions for treatment of a variety of diseases,[3] such as cardiovascular disorders,[3a] cancer[3b] and AIDS.[3c] The oxidation of DHPs to the corresponding pyridine derivatives constitutes the principal metabolic route in biological systems,[1–2] as well as a facile access to the corresponding pyridine derivatives, which show antihypoxic and antiischemic activities,[4] from the easily available DHPs.[5] Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed.[6–8] Early works mostly used strong oxidants, such as HNO_3,[6b] $KMnO_4$,[6c] or CAN[6d] and I_2–MeOH.[6e] Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation[7] and catalytic aerobic oxidation using $RuCl_3$,[8a] Pd/C,[8b] activated carbon[8c] or $Fe(ClO_4)_3$[8d] as the catalyst.

1,3,5-Trisubstituted pyrazolines are important five-membered heterocyclic compounds, which can be easily prepared from phenylhydrazine and chalcone derivatives. The oxidative aromatization of these dihydroheteroaromatics provides the corresponding pyrazoles, which are known to possess diverse biological activities, including antiinflammatory, antiarrhythmic, antidiabetic and antibacterial activities.[9] For this oxidative conversion of pyrazolines, various methods have been reported, which employed reagents such as $Pb(OAc)_4$,[10] MnO_2,[11] $KMnO_4$,[12] $Zr(NO_3)_4$,[13] iodobenzene diacetate,[14] silver nitrate,[15] Pd/C[8b] and activated carbon.[8c]

On a continuance of our interest in the DHP based chemistry, we reported a photochemical approach for the aromatization of DHPs.[16] Very recently, we found that *N*-hydroxyphthalimide (NHPI) could effectively catalyze the aerobic oxidative aromatization of DHPs in CH_3CN at refluxing temperature (Scheme 1).[17] This NHPI–O_2 system, which was first used by Ishii et al. for oxygenation of hydrocarbons, provides a simple, mild, and highly efficient approach for the aromatization of DHPs. Subsequent investigation showed that the capacity of this approach could be enhanced significantly in the presence of catalytic amount of $Co(OAc)_2$. This method is also applicable to the oxidative aromatization of 1,3,5-trisubstituted pyrazolines. Herein, we wish to report this work in detail.



1 2

Scheme 1.

2. Results and discussion

As demonstrated by Ishii et al., NHPI is a very effective organic catalyst for the functionalization of hydrocarbons

Keywords: Hantzsch 1,4-dihydropyridines; 1,3,5-Trisubstituted pyrazolines; Aerobic oxidative aromatization; *N*-Hydroxyphthalimide; Cobalt diacetate.
* Corresponding authors. Fax: +86 931 8625657;
e-mail addresses: liuzl@lzu.edu.cn; yuwei@lzu.edu.cn

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Table 1. Catalytic aerobic aromatization of 1,4-dihydropyridines (**1**) by NHPI or NHPI–$Co(OAc)_2$

Entry	Method[a]	Substrate	R	Product[b]	Time (h)	Yield (%)[c]
1	A	**1a**	H	**2a**[8c]	0.5	99
2	B	**1a**	H	**2a**	0.5	99
3	A	**1b**	Me	**2b**[8c]	3	98
4	B	**1b**	Me	**2b**	4	98
5	A	**1c**	Ph	**2c**[8c,13]	4	99
6	B	**1c**	Ph	**2c**	4	99
7	A	**1d**	4-$MeOC_6H_4$	**2d**[6e]	1.5	98
8	B	**1d**	4-$MeOC_6H_4$	**2d**	3	99
9	A	**1e**	4-ClC_6H_4	**2e**[13]	5	96
10	B	**1e**	4-ClC_6H_4	**2e**	4	98
11	A	**1f**	2-Furyl	**2f**[6e]	7	93
12	B	**1f**	2-Furyl	**2f**, **2a**	3	91, 8
13	A	**1g**	4-$NO_2C_6H_4$	—	10	NR
14	B	**1g**	4-$NO_2C_6H_4$	**2g**[8c,13]	5	98

[a] Method A: an CH_3CN solution (3 mL) of Hantzsch 1,4-dihydropyridine **1** (1 mmol) and NHPI (0.2 mmol) was refluxed under stirring and oxygen atmosphere (1 atm). Method B: a mixture of 1,4-dihydropyridine **1** (1 mmol), NHPI (0.1 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (0.005 mmol) in acetonitrile (3 mL) was stirred under an oxygen atmosphere (1 atm) at room temperature.

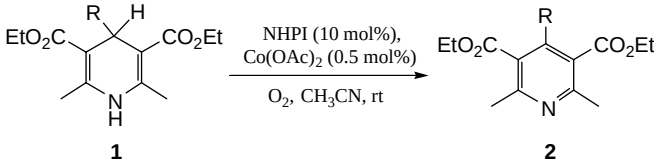
[b] The products were identified by comparing their ^1H, ^{13}C NMR and EI-MS spectral data and melting points with those reported in the cited references.

[c] Isolated yield.

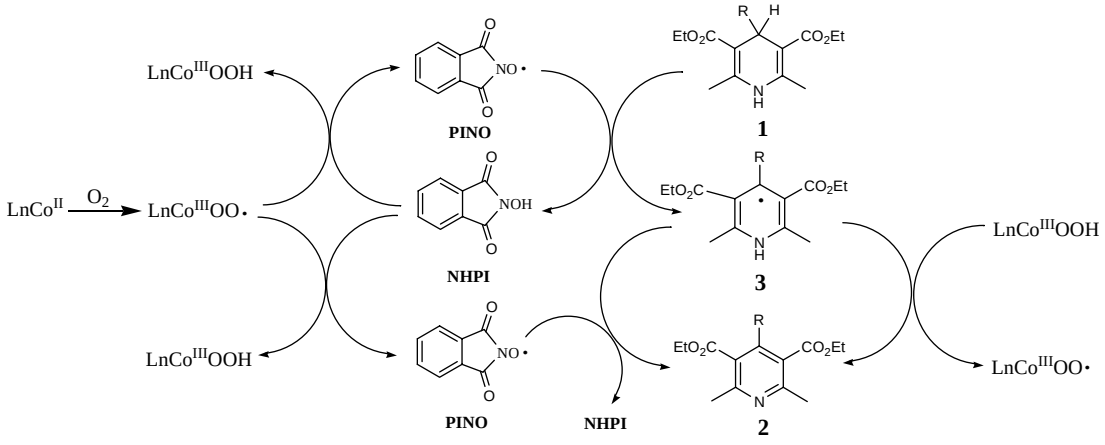
under O_2, NO, or NO_2 atmosphere to give oxygen-containing compounds, such as alcohols, ketones, carboxylic acids and nitroalkanes.[18] This process is believed to be via a NHPI mediated free radical mechanism. We envisioned that NHPI could also be used to catalyze the aerobic oxidation of DHPs. Indeed, when DHPs (**1**) was refluxed in acetonitrile under O_2 atmosphere in the presence of 20 mol% NHPI, the corresponding pyridine derivatives **2** was formed in excellent yields (Scheme 1, method A in Table 1). The only exception was **1g**, which gave no product after prolonged reflux (entry 13 in Table 1). Apparently, the strong electron-withdrawing nitro substituent renders **1g** unreactive.

It was found by Ishii et al. that the presence of a small amount of transition metals, such as Mn^{2+} and Co^{2+}, could significantly enhance the oxidizing capacity of the NHPI–O_2 system.[19] Accordingly, it was expected that the same effect could also be observed in our case for the oxidation of DHPs. Indeed, stirring substrate **1** with 10 mol% of NHPI and 0.5 mol% of $Co(OAc)_2$ in acetonitrile at room temperature for several hours led to the clean formation of pyridine product **2** in excellent yields (Scheme 2, method B in Table 1). By comparison, no appreciable reaction took place in the absence of $Co(OAc)_2$ under the otherwise same reaction conditions. Most significantly, even substrate **1g**, which was resistant to oxidation under the previous conditions,[17] was smoothly transformed to **2g** in 98% yield by this new treatment, demonstrating the high effectiveness of this NHPI–$Co(OAc)_2$–O_2 system (entry 14 in Table 1). In the case of **1f**, a small amount of C–C cleavaged product **2a** was formed along with the normal aromatization product **2f** (entry 12 in Table 1). This phenomenon was also observed in the previously reported aromatization of DHPs under other oxidative conditions.[16]

The NHPI catalyzed aerobic oxidation of DHPs was supposed to be following a free radical chain process,[17] similar to that proposed previously by Ishii et al.[18a] The initiation step was the generation of phthalimide-*N*-oxyl radical (PINO) by the hydrogen transfer from NHPI to O_2. Co^{2+} could accelerate this step by binding with O_2 to form a Co^{3+}–oxygen complex, which can abstract the hydrogen from NHPI much more effectively than oxygen (Scheme 3).[18a] Consequently, the whole process was remarkably accelerated in the presence of $Co(OAc)_2$, as demonstrated by the present result, as well as those observed



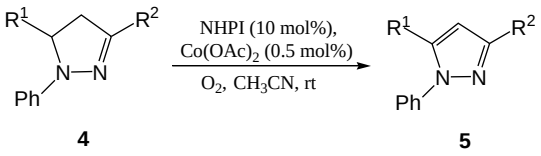
Scheme 2.



Scheme 3.

by others.[18] In the subsequent propagation step, PINO abstracted hydrogen from DHP to produce radical **3**. Generally, alkyl radicals would react with oxygen to form alkyl peroxyl radicals, which in turn, would produce oxygenated products. In the present case, however, the strong driving force of aromatization made the second hydrogen abstraction from radical **3** by PINO and/or Co^{3+}–oxygen complex very effective. Therefore, the pyridine derivative formed exclusively rather than the oxygenated products.

Having successfully achieved the aromatization of DHPs, we applied this method to the oxidative aromatization of 1,3,5-trisubstituted pyrazolines (Scheme 4, Table 2). As shown in Table 2, treatment of 1,3,5-trisubstituted pyrazolines (**4**) with the above mentioned procedure led to the formation of the corresponding pyrazoles (**5**) in high yields.



4 **5**

Scheme 4.

Table 2. Catalytic aerobic aromatization of 1,3,5-trisubstituted pyrazolines with NHPI–$Co(OAc)_2$[a]

Entry	Substrate	R^1	R^2	Time (h)	Product[b]	Yield (%)[c]
1	**4a**	Ph	Ph	7	**5a**[8c,13]	90
2	**4b**	4-$MeOC_6H_4$	Ph	9	**5b**[8c,13]	95
3	**4c**	4-ClC_6H_4	Ph	9	**5c**[8c,13]	88
4	**4d**	4-$NO_2C_6H_4$	Ph	7	**5d**[8c,13]	91
5	**4e**	Ph	Me	6	**5e**	89
6	**4f**	4-$MeOC_6H_4$	Me	6	**5f**	91

[a] Reaction condition: a mixture of 1,3,5-trisubstituted pyrazolines **4** (1 mmol), NHPI (0.1 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (0.005 mmol) in acetonitrile (5 mL) was stirred under an oxygen atmosphere (1 atm) at room temperature.
[b] Compounds **5a–5d** were identified by comparing their ^1H, ^{13}C NMR and EI-MS spectral data and melting points with those reported in the cited references. **5e** and **5f** were two new compounds characterized by ^1H, ^{13}C NMR, EI-MS and HRMS spectra.
[c] Isolated yields.

In conclusion, the oxidative aromatization of substituted Hantzsch dihydropyridines and pyrazolines was achieved efficiently by using molecular oxygen as the terminal oxidant with NHPI and $Co(OAc)_2$ as the co-catalysts at room temperature. Extension of this method to the preparation of other heterocyclic compounds is under way in this laboratory.

3. Experimental

N-Hydroxyphthalimide (NHPI) (purity > 98%) was purchased from ALDRICH.

^1H and ^{13}C NMR spectra (300 and 75.5 MHz, respectively) were recorded on a Varian Mercury plus-300 spectrometer with TMS as the internal standard in $CDCl_3$. EI-MS spectra were measured on an HP 5988A spectrometer by direct inlet at 70 eV. The high resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 47e spectrometer by ESI.

3.1. A typical procedure for the aromatization of 4-Hantzsch 1,4-dihydropyridines (1)

A mixture of 1,4-dihydropyridine **1a** (253 mg, 1.00 mmol), NHPI (16 mg, 0.10 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.005 mmol) in acetonitrile (3 mL) was stirred under an oxygen atmosphere at room temperature for 4 h. After removal of the solvent under reduced pressure, the residue was column chromatographed (over silica gel) to afford the corresponding pyridine derivative **2a** 249 mg. Yield: 99%.

3.1.1. Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (2a). Pale yellow solid; mp 70–71 °C (lit.[8c] 71–72 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (t, 6H, $J = 7.2$ Hz), 2.85 (s, 6H), 4.40 (q, 4H, $J = 7.2$ Hz), 8.68 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.2$, 24.8, 61.3, 123.0, 140.8, 162.1, 165.8.

EI-MS: *m/z* (rel int., %) = 251 (39.8), 206 (100), 195 (19.6), 178 (53.8), 150 (29.0), 106 (21.6).

3.1.2. Diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate (2b). Pale yellow oil (lit.[8c]).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, 6H, $J = 7.2$ Hz), 2.27 (s, 3H), 2.52 (s, 6H), 4.41 (q, 4H, $J = 7.2$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.1$, 16.9, 22.8, 61.5, 127.5, 142.0, 154.8, 168.3.

EI-MS: *m/z* (rel int., %) = 265 (31.4), 236 (45.9), 220 (100), 208 (43.2), 192 (25.9), 77 (34.5).

3.1.3. Diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (2c). Pale yellow solid; mp 61–62 °C (lit.[8c] 60–61 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, 6H, $J = 7.2$ Hz), 2.60 (s, 6H), 4.00 (q, 4H, $J = 7.2$ Hz), 7.2–7.4 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.4$, 22.8, 61.2, 126.8, 127.9, 128.0, 128.3, 136.4, 146.0, 155.3, 167.7.

EI-MS: *m/z* (rel int., %) = 327 (71.2), 282 (48.1), 254 (42.4), 236 (100), 209 (29.4), 139 (33.8).

3.1.4. Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2d). Pale yellow solid; mp 49–50 °C (lit.[6e] 51–53 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, 6H, $J = 7.2$ Hz), 2.50 (s, 6H), 3.72 (s, 3H), 3.96 (q, 4H, $J = 7.2$ Hz), 6.80 (d, 2H, $J = 6.9$ Hz), 7.10 (d, 2H, $J = 6.9$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.8, 22.9, 55.4, 61.4, 113.7, 127.4, 128.8, 129.6, 146.0, 155.3, 160.0, 168.2.

EI-MS: *m*/*z* (rel int., %)=357 (100), 312 (25.1), 282 (27.9), 266 (83.5), 135 (31.8), 84 (51.1).

3.1.5. Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2e). Pale yellow solid; mp 65–66 °C (lit.[13] 65–66 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (t, 6H, J=7.2 Hz), 2.59 (s, 6H), 4.03 (q, 4H, J=7.2 Hz), 7.19 (d, 2H, J=8.4 Hz), 7.35 (d, 2H, J=8.4 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 22.8, 61.4, 126.7, 128.2, 129.5, 134.6, 134.9, 144.7, 155.5, 167.5.

EI-MS: *m*/*z* (rel int., %)=363 (36.2), 361 (100), 316 (49.3), 288 (32.9), 270 (34.3), 139 (24.5), 43 (19.1).

3.1.6. Diethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2f). Pale yellow oil (lit.[6e]).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 6H, J=6.9 Hz), 2.49 (s, 6H), 4.18 (q, 4H, J=6.9 Hz), 6.39 (d, 1H, J=3.3 Hz), 6.54 (d, 1H, J=3.3 Hz), 7.42 (br s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.7, 22.5, 61.5, 111.6, 111.7, 124.5, 133.5, 143.7, 147.8, 155.4, 167.9.

EI-MS: *m*/*z* (rel int., %)=317 (71.5), 272 (52.3), 243 (38.1), 214 (100), 95 (45.3).

3.1.7. Diethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2g). Pale yellow solid; mp 114–115 °C (lit.[8c] 115–116 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, 6H, J=6.9 Hz), 2.64 (s, 6H), 4.05 (q, 4H, J=6.9 Hz), 7.47 (d, 2H, J=9.0 Hz), 8.27 (d, 2H, J=9.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.6, 23.0, 61.6, 123.1, 126.1, 129.3, 143.3, 143.9, 147.7, 156.1, 167.0.

EI-MS: *m*/*z* (rel int., %)=372 (48.8), 355 (29.5), 327 (100), 299 (39.5), 281 (32.5), 139 (23.2).

3.2. A typical procedure for the aromatization of 1,3,5-trisubstituted pyrazolines (4)

A mixture of 1,3,5-triphenylpyrazoline (**4a**) (298 mg, 1.00 mmol), NHPI (16 mg, 0.10 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.005 mmol) in acetonitrile (5 mL) was stirred under an oxygen atmosphere at room temperature for 7 h. After removal of the solvent under reduced pressure, the residue was column chromatographed (over silica gel) to afford 1,3,5-triphenylpyrazole (**5a**) 267 mg. Yield: 90%.

3.2.1. 1,3,5-Triphenylpyrazole (5a). Pale yellow solid; mp 141–142 °C (lit.[13] 139–140 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.83 (s, 1H), 7.3–7.5 (m, 13H), 7.93 (d, 2H, J=7.7 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=105.2, 125.3, 125.8, 127.4, 128.0, 128.3, 128.4, 128.6, 128.7, 128.9, 130.5, 133.0, 140.0, 144.3, 151.9.

EI-MS *m*/*z* (rel int., %): 296 (48.6), 86 (64.2), 84 (100), 77 (91.5), 51 (55.2).

3.2.2. 1,3-Diphenyl-5-(4-methoxyphenyl)pyrazole (5b). Pale yellow solid; mp 79–80 °C (lit.[13] 78 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=3.81 (s, 3H), 6.78 (s, 1H), 6.85 (d, 2H, J=9.0 Hz), 7.21 (d, 2H, J=9.0 Hz), 7.3–7.5 (m, 8H), 7.93 (d, 2H, J=7.5 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=55.2, 104.7, 113.9, 122.9, 125.3, 125.7, 127.3, 127.9, 128.6, 128.9, 130.0, 133.0, 140.2, 144.2, 151.8, 159.5.

EI-MS *m*/*z* (rel int., %): 326 (23.1), 325 (4.1), 152 (14.5), 105 (61.5), 86 (100), 77 (36.6), 49 (61.4).

3.2.3. 5-(4-Chlorophenyl)-1,3-diphenylpyrazole (5c). Pale yellow solid; mp 113–114 °C (lit.[13] 114–115 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.83 (s, 1H), 7.2–7.5 (m, 12H), 7.91 (d, 2H, J=8.1 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=105.2, 125.2, 125.7, 127.6, 128.0, 128.6, 128.7, 128.9, 129.0, 129.9, 132.7, 134.3, 139.8, 143.1, 151.9.

EI-MS *m*/*z* (rel int., %): 332 (13.0), 330 (38.8), 329 (20.7), 105 (27.4) 84 (71.4), 77 (100), 51 (57.7).

3.2.4. 1,3-Diphenyl-5-(4-nitrophenyl)pyrazole (5d). Pale yellow solid; mp 142–144 °C (lit.[13] 142–143 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (s, 1H), 7.3–7.5 (m, 10H), 7.92 (d, 2H, J=8.4 Hz), 8.18 (d, 2H, J=8.4 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=106.2, 123.8, 125.4, 125.8, 128.2, 128.3, 128.7, 129.2, 129.3, 132.4, 136.7, 139.5, 141.9, 147.2, 152.4.

EI-MS *m*/*z* (rel int.): 341 (20), 294 (30.1), 191 (11.5), 163 (13.2), 105 (63.8), 77 (100), 51 (21.8).

3.2.5. 1,5-Diphenyl-3-methyl-pyrazole (5e). Pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ=2.38 (s, 3H), 6.31 (s, 1H), 7.1–7.3 (m, 10H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 107.7, 125.0, 127.0, 128.0, 128.3, 128.5, 128.8, 130.6, 140.0, 143.6, 149.4.

EI-MS *m*/*z* (rel int., %): 234 (100), 218 (14.3), 192 (13.8), 77 (31.5), 51 (20.5).

ESI-HRMS: *m*/*z* Calcd for $C_{16}H_{14}N_2+H^+$: 235.1230; found: 235.1228.

3.2.6. 1-Phenyl-3-methyl-5-(4-methoxyphenyl)pyrazole (5f). Pale yellow solid; mp 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H), 3.77 (s, 3H), 6.25 (s, 1H), 6.80 (d, 2H, J=8.7 Hz), 7.13 (d, 2H, J=8.7 Hz), 7.2–7.4 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 55.1, 107.1, 113.8, 123.1, 125.0, 126.9, 128.7, 129.8, 140.2, 143.4, 149.3, 159.3.

MS *m/z* (rel int., %): 264 (100), 249 (39.5), 115 (18.4), 77 (58.1), 51 (28.7).

ESI-HRMS: *m/z* Calcd for $C_{17}H_{16}N_2O+H^+$: 265.1335; found: 265.1335.

Acknowledgements

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