Regioselective Multicomponent Synthesis of Fully Substituted Pyrazoles and Bispyrazoles Catalyzed by Zinc Triflate

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Abstract: A variety of fully substituted pyrazoles were easily prepared through a three-component condensation of aldehydes, arylhydrazines, and ethyl acetoacetate in the presence of catalytic amounts of zinc triflate [$Zn(OTf)_2$] under solvent-free conditions. Selective synthesis of symmetrical and unsymmetrical bispyrazoles from dialdehydes in high yields can be considered as a notable advantage of this method.

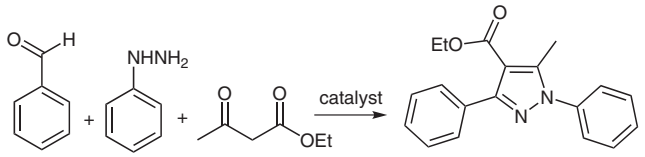
Key words: pyrazoles, aldehydes, arylhydrazines, zinc triflate, solvent-free

Pyrazoles and their derivatives have received special attention due to the wide range of useful biological activities and pharmacological properties, including antitumor,[1] anti-inflammatory,[2] antibacterial,[3] and hypolipidemic properties.[4] *N*-Arylpyrazoles have also emerged as estrogen receptor[5] and HIV protease inhibitors.[6] Known substituted pyrazole drugs are rimonabant (**I**) as an antiobesity drug[7] and lonazolac (**II**) as an anti-inflammatory drug[8] (Figure 1). These heterocycles are also employed as ligands for the transition-metal ions in coordination chemistry.[9] Due to the importance of pyrazole derivatives, several methods have been reported for the preparation of these heterocycles. In the most common synthetic methods, pyrazoles are constructed by cyclization of 1,3- diketones with hydrazines.[10] However with unsymmetrical 1,3-dicarbonyl compounds, the formation of two regioisomeric pyrazoles with poor selectivity and also difficulty in separation of these regioisomers are limitations of these methods.[11] Other methods have been employed including reaction of hydrazines with α,β-unsaturated carbonyl compounds[12] or β-keto nitriles,[13] reaction of hydrazones with activated alkenes[14] or alkynes,[15] reaction of arylhydrazines with 3-butynol,[16] coupling–cyclocondensation sequence of acid chlorides, terminal alynes and hydrazines,[17] palladium-catalyzed four-component coupling of terminal alkynes, hydrazines, aryl halides, and carbon monoxide or molybdenum hexacarbonyl,[18] and 1,3-dipolar cycloaddition of diazoalkanes with olefins or alkynes.[19]

Although a wide range of procedures have been devised for the synthesis of pyrazole derivatives, there are only a few reports dealing with the preparation of fully substituted pyrazoles.[20] Consequently, it is still critically needed to develop convenient and efficient methods for the synthesis of fully substituted pyrazoles. Recently, the synthesis of fully substituted pyrazoles has been reported via three-component reactions catalyzed by $Yb(PFO)_3$.[21]

During the recent years, multicomponent reactions (MCR) have received considerable attention because of

Table 1 Optimization of the Reaction Conditions for Synthesis of Pyrazole **4a**[a]



Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	$Ce(OTf)_3$ (2)	15	85
2	$Cu(OTf)_2$ (2)	15	83
3	$Bi(OTf)_3$ (2)	15	70
4	$Bi(TFA)_3$ (2)	15	25
5	$InCl_3{\cdot}4H_2O$ (2)	15	27
6	$ZrOCl_2{\cdot}8H_2O$ (2)	15	30
7	$ZnCl_2$ (2)	15	15
8	$Zn(OAc)_2$ (2)	15	20
9	$Zn(OTf)_2$ (2)	15	92
10	no catalyst	10 h	0
11[c]	$Zn(OTf)_2$ (2)	15	92
12	$Zn(OTf)_2$ (3)	15	92
13	$Zn(OTf)_2$ (2)	20	92
14[d]	$Zn(OTf)_2$ (2)	15	80
15	$Zn(OTf)_2$ (1)	15	68
16	$Zn(OTf)_2$ (2)	10	70

[a] Reaction conditions: aldehyde (1 mmol), phenylhydrazine (1 mmol), ethyl acetoacetate (1.5 mmol), under solvent-free conditions at 120 °C.
[b] Isolated yield.
[c] Reaction was performed at 130 °C.
[d] Reaction was performed at 110 °C.

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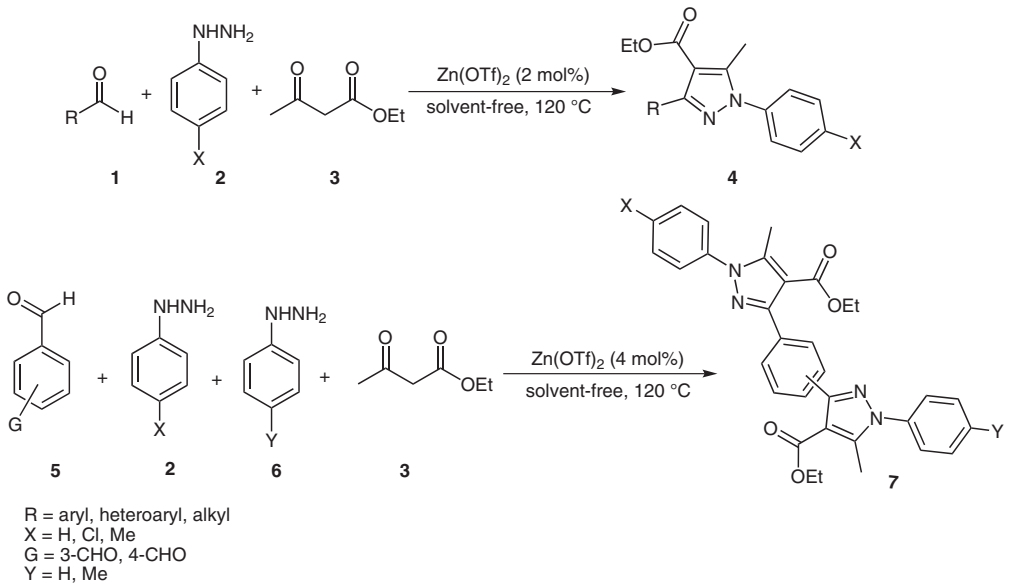
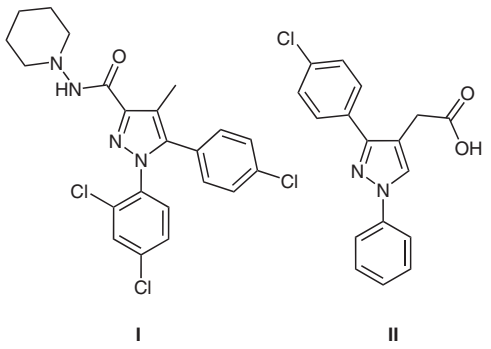


Scheme 1 Synthesis of fully substituted pyrazoles and bispyrazoles catalyzed by $Zn(OTf)_2$



I II

Figure 1 Structure of rimonabant (**I**) and lonazolac (**II**) – two pyrazole-based drugs

their wide range of applications in synthetic chemistry for the production of a broad spectrum of organic molecules. These reactions offer significant advantages over conventional bimolecular reactions, allowing the formation of several bonds and the construction of complex molecules from simple precursors in a single step without the need for isolation of intermediates. The use of MCR under solvent-free conditions provides even more benign processes.[22]

In continuation of our interest in the development of new and efficient protocols for the preparation of heterocyclic compounds,[23] here, we would like to report a facile one-pot synthesis of fully substituted pyrazoles and bispyrazoles from aldehydes, arylhydrazines, and ethyl acetoacetate catalyzed by $Zn(OTf)_2$ under solvent-free conditions at 120 °C (Scheme 1).

Initially, the reaction of benzaldehyde (1 mmol), phenylhydrazine (1 mmol), and ethyl acetoacetate (1.5 mmol) was carried out in the presence of different Lewis acids (2 mol%) at 120 °C under solvent-free conditions (Table 1, entries 1–9). The results showed that $Zn(OTf)_2$ was the most effective catalyst in this reaction (Table 1, entry 9).

It is noteworthy that in the absence of catalyst, the reaction failed to give the desired product, even after long reaction time (10 h, Table 1, entry 10). Then, the effect of temperature, the amount of catalyst, and the reaction time on the yield of the product were examined. Increasing either the temperature or the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entries 11–13), while reducing these factors led to a reduction in product yield (Table 1, entries 14–16). Therefore, 1:1:1.5:0.02 molar ratios of benzaldehyde, phenylhydrazine, ethyl acetoacetate, and $Zn(OTf)_2$ at 120 °C under solvent-free conditions were found to be the optimal conditions.

Under the optimized conditions, the aldehydes containing electron-withdrawing and electron-donating groups in the aromatic ring were reacted smoothly with arylhydrazines and ethyl acetoacetate in the presence of 2 mol% $Zn(OTf)_2$ to afford the corresponding fully substituted pyrazoles in high yields (Table 2, entries 1–8). The acid-sensitive aldehyde such as thiophene-2-carbaldehyde (Table 2, entry 9) and the aliphatic aldehyde such as heptanal (Table 2, entry 10) were also reacted efficiently to give the desired products in high yields. The reactions were generally clean and no side products such as pyrazolines were produced; in all cases, fully substituted pyrazoles were obtained as the sole products.[24] Comparison of the results obtained by this catalytic system with those reported using $Yb(PFO)_3$ catalyst[21a] show that in the presence $Zn(OTf)_2$ the yields of the products are higher and the reaction times are shorter. Also, only 2 mol% $Zn(OTf)_2$ is enough for successful reaction, whereas, reaction in the presence of $Yb(PFO)_3$ requires larger amount (10 mol%) of the catalyst. Therefore, this catalytic system can be used for novel and efficient three-component synthesis of fully substituted pyrazoles.

Table 2 Synthesis of Fully Substituted Pyrazoles Catalyzed by $Zn(OTf)_2$[a]

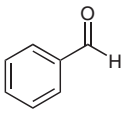
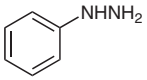
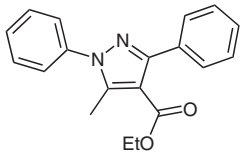
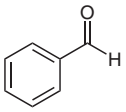
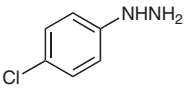
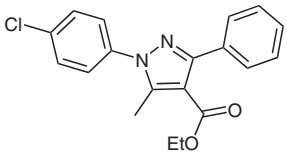
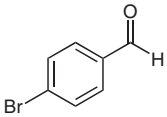
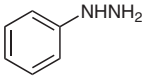
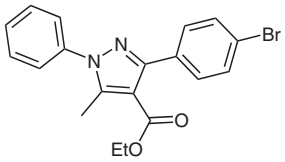
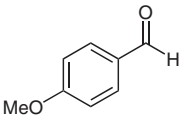
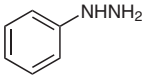
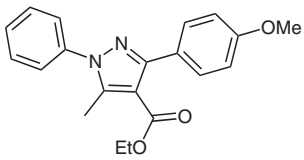
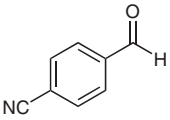
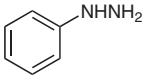
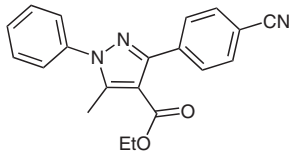
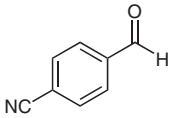
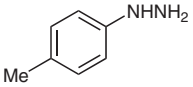
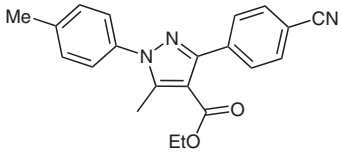
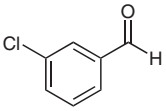
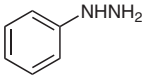
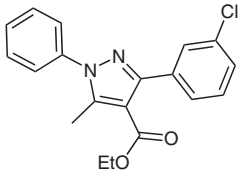
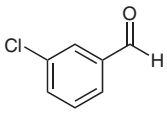
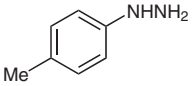
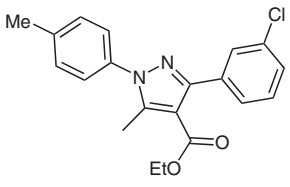
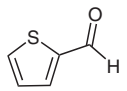
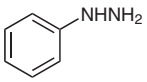
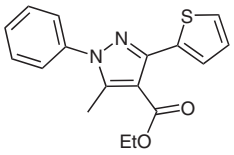
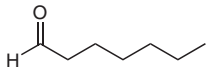
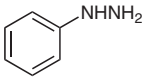
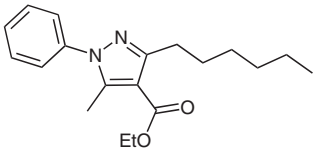
Entry	Aldehyde **1**	Arylhydrazine **2**	Pyrazole **4**	Time (min)	Yield (%)[b]
1			 **4a**	15	92
2			 **4b**	15	93
3			 **4c**	15	90
4			 **4d**	10	90
5			 **4e**	75	84
6			 **4f**	75	88
7			 **4g**	20	87
8			 **4h**	15	91

Table 2 Synthesis of Fully Substituted Pyrazoles Catalyzed by $Zn(OTf)_2$[a] (continued)

Entry	Aldehyde **1**	Arylhydrazine **2**	Pyrazole **4**	Time (min)	Yield (%)[b]
9			 **4i**	15	84
10			 **4j**	15	83

[a] Reaction conditions: aldehyde **1** (1 mmol), arylhydrazine **2** (1 mmol), ethyl acetoacetate **3** (1.5 mmol), catalyst (2 mol%), under solvent-free conditions at 120 °C.
[b] Isolated yield.

In order to further expand the scope of this new MCR and due to the extensive applications of bispyrazoles as ligands in chemistry,[25] the synthesis of fully substituted bispyrazoles was also examined. As shown in Table 3, the reaction of dialdehydes such as terephthaldialdehyde and isophthaldialdehyde with arylhydrazines and ethyl acetoacetate in the presence of catalytic amounts of $Zn(OTf)_2$ proceeded efficiently to furnish the corresponding symmetrical and unsymmetrical fully substituted bispyrazoles in high yields.[26] To the best of our knowledge, there is no report on the synthesis of fully substituted bispyrazoles through the MCR of dialdehydes, arylhydrazines, and ethyl acetoacetate and therefore, such a synthesis can be considered as a useful practical achievement in the preparation of pyrazole derivatives.

The structure of the products was identified by their IR, MS, ^{1}H NMR, and ^{13}C NMR spectra and by their elemental analysis. Furthermore, the structure of **7b** was confirmed by X-ray crystallographic analysis[27] (CCDC 817131, Figure 2).

Table 3 Synthesis of Fully Substituted Bispyrazoles Catalyzed by $Zn(OTf)_2$

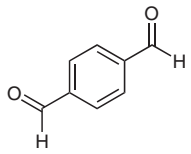
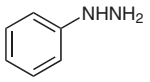
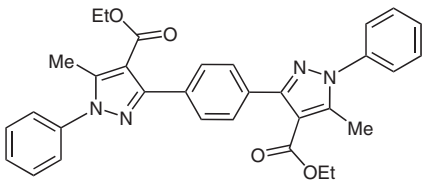
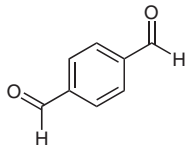
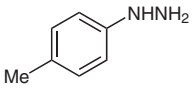
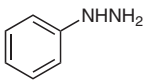
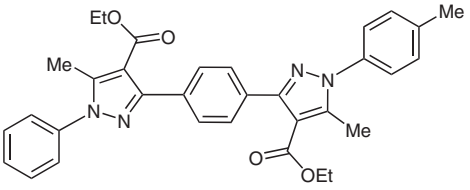
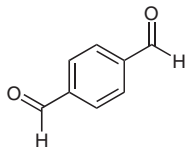
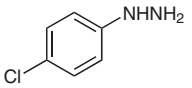
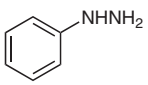
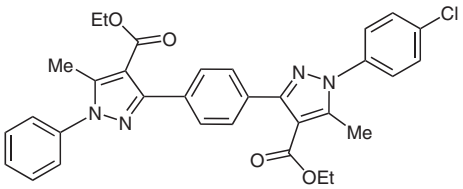
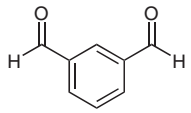
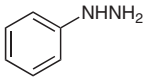
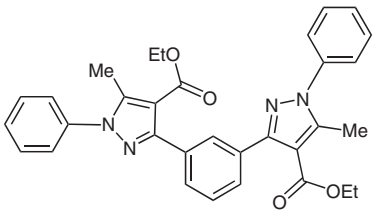
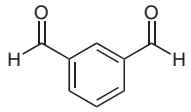
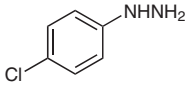
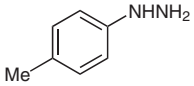
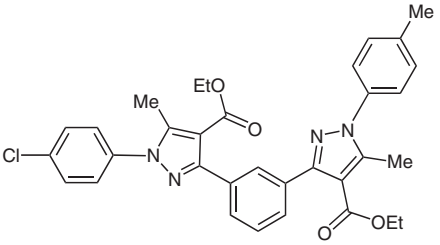
Entry	Dialdehyde **5**	Arylhydrazine **2**	Arylhydrazine **6**	Bispyrazole **7**	Time (min)	Yield (%)[a]
1[b]			–	 **7a**	25	89
2[c]				 **7b**	25	90
3[c]				 **7c**	25	86

Table 3 Synthesis of Fully Substituted Bispyrazoles Catalyzed by $Zn(OTf)_2$ (continued)

Entry	Dialdehyde **5**	Arylhydrazine **2**	Arylhydrazine **6**	Bispyrazole **7**	Time (min)	Yield (%)[a]
4[b]			–	 **7d**	25	80
5[c]				 **7e**	25	82

[a] Isolated yield.
[b] Reaction conditions: dialdehyde **5** (1 mmol), arylhydrazine **2** (2 mmol), ethyl acetoacetate **3** (4 mmol), catalyst (4 mol%), under solvent-free conditions at 120 °C.
[c] Reaction conditions: dialdehyde **5** (1 mmol), arylhydrazine **2** (1 mmol), arylhydrazine **6** (1 mmol), ethyl acetoacetate **3** (4 mmol), catalyst (4 mol%), under solvent-free conditions at 120 °C.

A plausible mechanism for this MCR is illustrated in Scheme 2. First, $Zn(OTf)_2$ catalyzes the keto–enol tautomerization of ethyl acetoacetate and also activates the hydrazone to give **8** and **9**, respectively. Then, cyclization of **8** with **9** gives the intermediate (5-hydroxypyrazolidine) **10**, which upon dehydration affords the pyrazoline **11**. Finally, aromatization of **11** under ambient atmosphere in the presence of catalyst produces the corresponding fully substituted pyrazole **4** as a desired product. To confirm the suggested mechanism, a radical scavenger such as acrylamide was added to the reaction mixture. Under these conditions, no change in the yield of the product was observed. This shows that no radical species is present in the reaction, which has been reported by Cao et al. in the synthesis of fully substituted pyrazoles catalyzed by $Yb(PFO)_3$.[21] Then the model reaction was performed

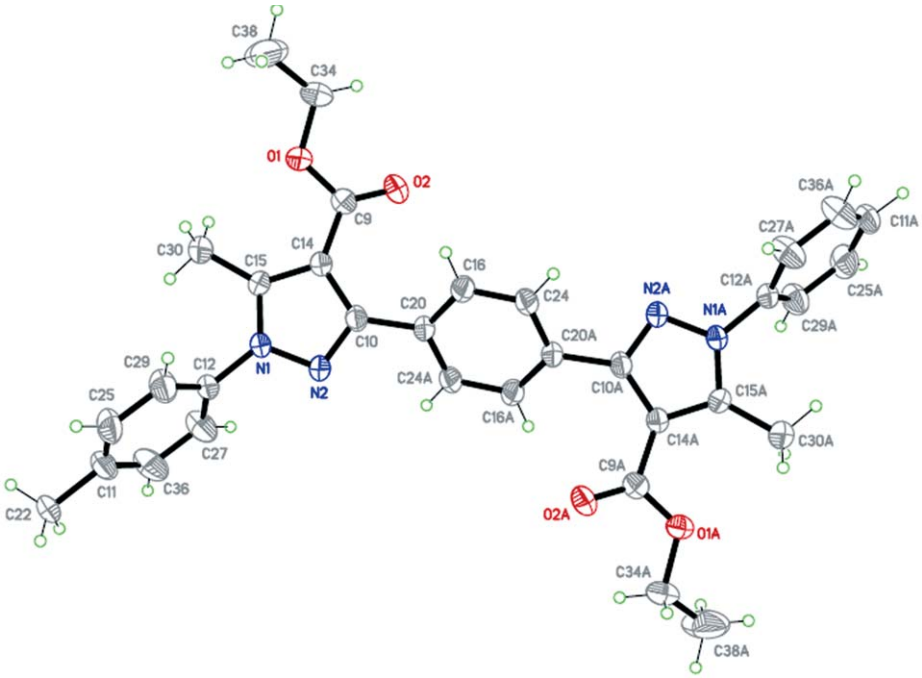
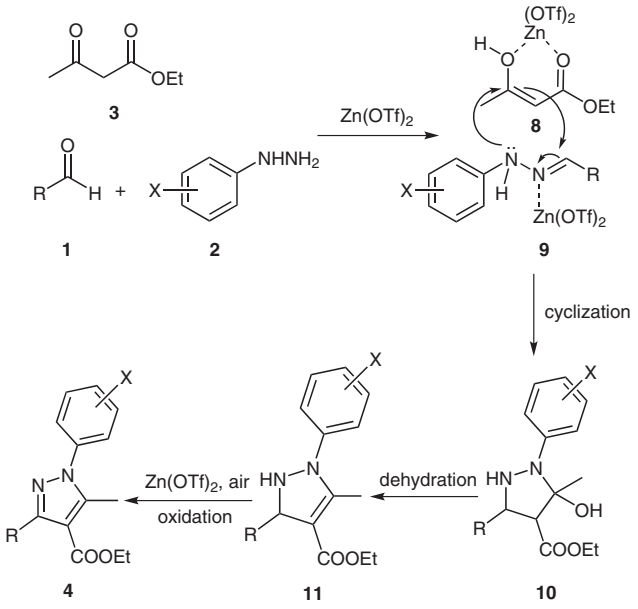


Figure 2 X-ray crystal structure of **7b**

under argon atmosphere, and the product yield was reduced considerably under these conditions. It is also noteworthy that bubbling of the O_2 gas into the reaction mixture accelerated the reaction. These results show that the presence of oxygen is essential and therefore, according to the published results,[28] the oxygen provided from air in the presence of $Zn(OTf)_2$ catalyst can act as oxidizing agent. All these observations showed that the proposed mechanism is reasonable.



Scheme 2 A plausible mechanism

In summary, we have demonstrated an efficient and novel multicomponent synthesis of fully substituted pyrazoles, symmetrical and unsymmetrical bispyrazoles under solvent-free conditions using $Zn(OTf)_2$ as catalyst. Short reaction times, high yields of products, convenient procedure avoiding toxic organic solvents, and operational simplicity are notable advantages of the present method which makes it a useful and attractive process for the the synthesis of pyrazole derivatives.

Ethyl 5-Methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (4a)[21a]
Mp 100–102 °C. IR (KBr): 3069, 2983, 1710, 1596, 1501, 1310, 1146, 1089, 773, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 2.60 (s, 3 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 7.38–7.42 (m, 3 H), 7.45–7.54 (m, 5 H), 7.67–7.69 (m, 2 H). MS: *m/z* = 308.05 (10.71) $[M + 2]^+$, 306.01 (89.39) $[M]^+$, 260.99 (89.39), 234.01 (69.39), 129.90 (59.18), 117.86 (86.53), 76.81 (100.00), 50.83 (89.39).

Ethyl 1-(4-Chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazole-4-carboxylate (4b)
Mp 68–70 °C. IR (KBr): 3071, 2982, 1697, 1500, 1254, 1178, 1085, 835, 687 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3 H), 2.59 (s, 3 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 7.38–7.43 (m, 3 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 7.64–7.67 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.73, 14.07, 60.08, 111.04, 127.01, 127.70, 128.35, 129.43, 129.46, 132.98, 134.57, 137.36, 144.78, 153.89, 164.04. MS: *m/z* = 341.90 (71.37) $[M + 2]^+$, 339.95 (100.00) $[M]^+$, 294.90 (83.93), 267.89 (76.03), 230.93 (60.73), 151.79 (87.23), 110.73 (100), 101.79 (82.32), 76.78 (85.93), 56.87 (80.27). Anal. Calcd for $C_{19}H_{17}ClN_2O_2$ (340.78): C, 66.96; H, 5.03; N, 8.22. Found: C, 66.69; H, 5.10; N, 8.15.

Ethyl 3-(4-Bromophenyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (4c)[21a]
Mp 62–64 °C. IR (KBr): 3064, 2979, 1705, 1596, 1500, 1435, 1304, 1086, 835, 764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.58 (s, 3 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 7.46–7.51 (m, 5 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H). MS: *m/z* = 386.31 (100.00) $[M + 2]^+$, 384.31 (100.00) $[M]^+$, 338.83 (100.00), 311.85 (87.06), 230.94 (85.10), 117.82 (100), 76.33 (100), 50.82 (96.47).

Ethyl 3-(4-Methoxyphenyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (4d)[21a]
Mp 84–85 °C. IR (KBr): 3064, 2967, 1707, 1607, 1504, 1249, 1151, 838, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.57 (s, 3 H), 3.84 (s, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 7.44–7.52 (m, 5 H), 7.64 (d, *J* = 8.6 Hz, 2 H). MS: *m/z* = 338.07 (15.64) $[M + 2]^+$, 336.01 (94.02) $[M]^+$, 291.00 (83.27), 264.04 (42.23), 129.88 (47.41), 117.81 (95.62), 76.80 (100.00), 50.82 (83.27).

Ethyl 3-(4-Cyanophenyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (4e)
Mp 111–112 °C. IR (KBr): 3074, 2978, 2223, 1707, 1591, 1498, 1434, 1309, 1154, 1087, 850, 769 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 2.60 (s, 3 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 7.46–7.56 (m, 5 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.83 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.85, 14.16, 60.28, 110.73, 111.68, 118.98, 125.75, 129.02, 129.38, 130.22, 131.42, 137.87, 138.49, 145.33, 151.66, 163.60. MS: *m/z* = 333.05 (8.64) $[M + 2]^+$, 331.03 (97.66) $[M]^+$, 286.00 (93.13), 259.06 (53.76), 129.93 (32.24), 117.91 (66.82), 101.88 (28.62), 76.88 (100.00), 50.92 (80.37). Anal. Calcd for $C_{20}H_{17}N_3O_2$ (331.34): C, 72.49; H, 5.17; N, 12.68. Found: C, 72.57; H, 5.14; N, 12.66.

Ethyl 3-(4-Cyanophenyl)-5-methyl-1-*p*-tolyl-1*H*-pyrazole-4-carboxylate (4f)
Mp 96–98 °C. IR (KBr): 3072, 2981, 2224, 1705, 1608, 1514, 1454, 1306, 1159, 824, 784 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 2.43 (s, 3 H), 2.56 (s, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 7.30–7.34 (m, 4 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.82 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.78, 14.15, 21.20, 60.25, 110.58, 111.76, 119.02, 125.62, 129.94, 130.23, 131.45, 136.07, 137.99, 139.22, 145.33, 151.58, 163.72. MS: *m/z* = 346.94 (16.91) $[M + 2]^+$, 344.94 (100.00) $[M]^+$, 299.94 (98.68), 272.98 (78.23), 131.94 (75.24), 101.89 (68.02), 90.92 (89.75), 76.92 (51.64), 64.96 (79.51). Anal. Calcd for $C_{21}H_{19}N_3O_2$ (345.36): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.92; H, 5.60; N, 12.04.

Ethyl 3-(3-Chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (4g)
Mp 78–80 °C. IR (KBr): 3067, 2980, 1703, 1595, 1500, 1436, 1310, 1154, 1094, 764, 686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 2.56 (s, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 7.36–7.31 (m, 2 H), 7.47 (d, *J* = 7.1 Hz, 1 H), 7.51–7.54 (m, 4 H), 7.57 (d, *J* = 7.1 Hz, 1 H), 7.70 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.71, 14.05, 60.14, 110.65, 125.83, 127.74, 128.27, 128.85, 128.89, 129.32, 129.71, 133.49, 134.97, 138.70, 145.16, 152.14, 163.92. MS: *m/z* = 341.97 (26.99) $[M + 2]^+$, 339.96 (100.00) $[M]^+$, 294.94 (100.00), 267.98 (74.48), 130.02 (77.78), 118.00 (80.75), 110.93 (51.88), 77.00 (87.03), 51.04 (76.15). Anal. Calcd for $C_{19}H_{17}ClN_2O_2$ (340.78): C, 66.96; H, 5.03; N, 8.22. Found: C, 66.52; H, 5.15; N, 8.08.

Ethyl 3-(3-Chlorophenyl)-5-methyl-1-*p*-tolyl-1*H*-pyrazole-4-carboxylate (4h)
Mp 70–72 °C. IR (KBr): 3033, 2928, 1706, 1525, 1439, 1164, 1093, 1014, 834, 784, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 2.43 (s, 3 H), 2.57 (s, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 7.30–7.36 (m, 6 H), 7.57–7.69 (m, 1 H), 7.70 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.69, 14.08, 21.20, 60.10, 110.42, 125.64, 127.76, 128.72, 128.88, 129.71, 129.87, 133.46, 135.05, 136.20, 138.96, 145.16, 151.97, 163.96. MS: *m/z* = 356.94 (79.22) $[M + 2]^+$, 354.92 (100.00) $[M]^+$, 309.01 (99.61), 282.90 (83.14), 131.90 (96.08), 110.83 (87.84), 90.88 (99.61), 64.90 (95.29). Anal. Calcd for $C_{20}H_{19}ClN_2O_2$ (354.81): C, 67.70; H, 5.40; N, 7.89. Found: C, 67.41; H, 5.47; N, 7.79.

Ethyl 5-Methyl-1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxylate (4i)
Mp 73–74 °C. IR (KBr): 3109, 2978, 1702, 1593, 1499, 1470, 1226, 1117, 777, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.1 Hz, 3 H), 2.55 (s, 3 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 7.09 (dd, ^1J = 5.0 Hz, ^2J = 3.7 Hz, 1 H), 7.33 (dd, ^1J = 5.0 Hz, ^2J = 1.0 Hz, 1 H), 7.53–7.46 (m, 5 H), 7.81 (dd, ^1J = 3.7 Hz, ^2J = 1.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.00, 14.32, 60.25, 110.20, 125.96, 126.13, 127.00, 128.55, 128.80, 129.27, 134.47, 138.68, 145.00, 147.27, 163.97. MS: *m/z* = 315.91 (2.52) $[M + 4]^+$, 313.90 (77.25) $[M + 2]^+$, 311.94 (100.00) $[M]^+$, 266.92 (100.00), 239.90 (86.27), 148.81 (57.25), 133.82 (93.73), 117.89 (95.29), 76.87 (96.08), 50.92 (83.53). Anal. Calcd for $C_{17}H_{16}SN_2O_2$ (312.39): C, 65.36; H, 5.17; N, 8.97; S, 10.26. Found: C, 64.98; H, 5.24; N, 8.86; S, 10.54.

Ethyl 3-Hexyl-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (4j)
Oil. IR (neat): 3052, 2928, 1705, 1597, 1547, 1449, 1250, 1099, 764, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.9 (m, 5 H), 1.26–1.42 (m, 7 H), 1.66–1.72 (m, 2 H), 2.52 (s, 3 H), 2.89 (t, *J* = 7.7 Hz, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 7.39–7.50 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.66, 14.09, 14.41, 22.65, 28.49, 29.44, 29.46, 31.72, 59.71, 110.26, 125.74, 128.36, 129.18, 138.97, 144.52, 155.67, 164.54. MS: *m/z* = 316.09 (3.42) $[M + 2]^+$, 314.08 (72.40) $[M]^+$, 271.04 (60.40), 244.01 (91.60), 171.95 (100.00), 117.86 (83.60), 76.84 (94.00), 50.86 (50.00).

Diethyl 3,3′-(1,4-Phenylene)-bis(5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate) (7a)
Mp 160–162 °C. IR (KBr): 3089, 2975, 1702, 1594, 1499, 1441, 1153, 1086, 769 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 6 H), 2.59 (s, 6 H), 4.26 (q, *J* = 7.1 Hz, 4 H), 7.43–7.52 (m, 10 H), 7.74 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.71, 14.20, 60.05, 110.82, 125.85, 128.67, 128.78, 129.27, 133.04, 138.88, 144.92, 153.17, 164.33. MS: *m/z* = 533.97 (3.63) $[M]^+$, 388.95 (6.37), 300.65 (18.87), 284.85 (32.08), 230.68 (6.60), 129.24 (29.83), 76.77 (100.00). Anal. Calcd for $C_{32}H_{30}N_4O_4$ (534.61): C, 71.89; H, 5.66; N, 10.48. Found: C, 71.65; H, 5.65; N, 10.43.

Ethyl 3-{4-[4-(Ethoxycarbonyl)-5-methyl-1-*p*-tolyl-1*H*-pyrazol-3-yl]phenyl}-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (7b)
Mp 140–142 °C. IR (KBr): 3081, 2972, 1692, 1517, 1430, 1300, 1180, 1082, 849, 694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 6 H), 2.43 (s, 3 H), 2.56 (s, 3 H), 2.59 (s, 3 H), 4.23–4.27 (m, 4 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 7.45–7.53 (m, 5 H), 7.73 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.64, 12.67, 14.20, 21.18, 59.99, 60.03, 110.61, 110.84, 125.68, 125.86, 128.64, 128.75, 128.78, 129.26, 129.80, 132.98, 133.14, 136.42, 138.72, 138.92, 144.89, 153.00, 153.19, 164.34, 164.37. MS: *m/z* = 550.28 (10.24) $[M + 2]^+$, 548.22 (100.00) $[M]^+$, 503.20 (6.22), 457.12 (20.00), 404.15 (11.67), 237.10 (10.83), 132.01 (16.43), 117.96 (22.02), 90.95 (43.81), 76.95 (53.33). Anal. Calcd for $C_{33}H_{32}N_4O_4$ (548.63): C, 72.24; H, 5.88; N, 10.21. Found: C, 71.98; H, 5.92; N, 10.09.

Ethyl 1-(4-Chlorophenyl)-3-{4-[4-(ethoxycarbonyl)-5-methyl-1-phenyl-1*H*-pyrazol-3-yl]phenyl}-5-methyl-1*H*-pyrazole-4-carboxylate (7c)
Mp 140 °C. IR (KBr): 3080, 2972, 1594, 1500, 1430, 1297, 1180, 1083, 837, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21–1.25 (m, 6 H), 2.59 (s, 6 H), 4.23–4.28 (m, 4 H), 7.44–7.52 (m, 9 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.67, 12.69, 14.17, 14.18, 60.04, 60.12, 110.83, 111.20, 125.87, 127.01, 128.67, 128.72, 128.82, 129.27, 129.47, 132.81, 133.18, 134.55, 137.41, 138.89, 144.91, 153.13, 153.45, 164.16, 164.30. MS: *m/z* = 570.32 (4.30) $[M + 2]^+$, 568.30 (10.97) $[M]^+$, 477.18 (2.93), 424.20 (2.80), 191.11 (2.16), 151.98 (11.04), 129.98 (29.60), 117.96 (14.23), 110.94 (18.57), 90.94 (33.23), 76.94 (79.70), 55.01 (100.00). Anal. Calcd for $C_{32}H_{29}ClN_4O_4$ (569.09): C, 67.54; H, 5.14; N, 9.85. Found: C, 67.51; H, 5.17; N, 9.80.

Diethyl 3,3′-(1,3-Phenylene)-bis(5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate) (7d)
Oil. IR (neat): 3064, 2924, 1704, 1595, 1500, 1430, 1254, 1088, 1017, 766, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 6 H), 2.59 (s, 6 H), 4.22 (q, *J* = 7.1 Hz, 4 H), 7.41–7.52 (m, 11 H), 7.69 (d, *J* = 1.7 Hz, 1 H), 7.70 (d, *J* = 1.7 Hz, 1 H), 8.00 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.65, 14.00, 60.00, 110.72, 125.80, 126.81, 128.56, 129.16, 129.43, 130.60, 132.74, 138.93, 144.84, 153.33, 164.33. MS: *m/z* = 536.16 (11.66) $[M + 2]^+$, 534.15 (100.00) $[M]^+$, 442.01 (77.58), 390.05 (92.83), 230.27 (53.81), 117.96 (76.23), 76.95 (89.24). Anal. Calcd for $C_{32}H_{30}N_4O_4$ (534.61): C, 71.89; H, 5.66; N, 10.48. Found: C, 71.65; H, 5.60; N, 10.39.

Ethyl 1-(4-Chlorophenyl)-3-{3-[4-(ethoxycarbonyl)-5-methyl-1-*p*-tolyl-1*H*-pyrazol-3-yl]phenyl}-5-methyl-1*H*-pyrazole-4-carboxylate (7e)
Mp 66–68 °C. IR (KBr): 3085, 2978, 1702, 1499, 1435, 1253, 1088, 1010, 831, 784, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.15–1.19 (m, 6 H), 2.42 (s, 3 H), 2.56 (s, 3 H), 2.58 (s, 3 H), 4.20 (q, *J* = 7.1 Hz, 4 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.04–7.48 (m, 5 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.70 (d, *J* = 7.7 Hz, 1 H), 7.97 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.64, 13.98, 14.01, 21.17, 59.96, 60.10, 110.47, 111.08, 125.61, 126.83, 126.93, 129.33, 129.40, 129.58, 129.75, 130.42, 130.52, 130.63, 132.48, 132.87, 134.48, 136.41, 137.39, 138.60, 144.85, 153.10, 153.61, 164.18, 164.34. MS: *m/z* = 584.16 (25.69) $[M + 2]^+$, 582.13 (63.97) $[M]^+$, 491.08 (20.24), 438.09 (79.69), 319.99 (3.05), 263.99 (6.74), 244.10 (35.16), 151.98 (22.02), 110.96 (46.88), 91.00 (100.00). Anal. Calcd for $C_{33}H_{31}ClN_4O_4$ (583.08): C, 67.98; H, 5.36; N, 9.61. Found: C, 67.82; H, 5.30; N, 9.69.

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(24) **General Procedure for the Synthesis of Fully Substituted Pyrazoles**
A mixture of aldehyde **1** (1 mmol) and arylhydrazine **2** (1 mmol) was stirred for 20 min, then ethyl acetoacetate **3** (1.5 mmol) and $Zn(OTf)_2$ (0.02 mmol) were added, and the mixture was stirred at 120 °C for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane–EtOAc, 10:1). After completion of the reaction, the mixture was cooled to r.t., and the crude product was purified by chromatography on silica gel (eluent: *n*-hexane–EtOAc, 10:1) or by recrystallization from EtOH to afford the pure product.
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(26) **General Procedure for the Synthesis of Fully Substituted Bispyrazoles**
A mixture of dialdehyde **5** (1 mmol) and arylhydrazine **2** (2 mmol) was stirred for 20 min (for unsymmetrical bispyrazoles, a mixture of dialdehyde **5** (1 mmol) and arylhydrazine **2** (1 mmol) was stirred for 20 min, then

arylhydrazine **6** (1 mmol) was added and stirred for further 20 min). Ethyl acetoacetate **3** (4 mmol) and $Zn(OTf)_2$ (0.04 mmol) were added, and the mixture was heated at 120 °C for the appropriate time (Table 3). The progress of the reaction was monitored by TLC (eluent: *n*-hexane–EtOAc, 10:1). After completion of the reaction, the mixture was cooled to r.t., and the crude product was purified by chromatography on silica gel (eluent: *n*-hexane–EtOAc, 10:1) or by recrystallization from EtOH to give the pure product.

(27) CCDC 817131 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].
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