

Regiospecific preparation of 1,4,5-trisubstituted pyrazoles from 2-(1*H*-1,2,3-benzotriazol-1-yl)-3-(4-aryl)-2-propenals

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Abstract

Treatment of α -benzotriazolyl- α,β -unsaturated aldehydes with monosubstituted hydrazines followed by alkylation at the 4-position of the pyrazoline ring and elimination of the benzotriazole group affords 1,4,5-trisubstituted pyrazoles in overall yields of 52–79%.

Keywords: Pyrazoles, regiospecific synthesis, cyclization reaction

Introduction

Pyrazoles have attracted much attention in the last 30 years as their synthesis has become more accessible and their diverse properties appreciated.¹ Alongside the traditional pyrazole dyes,² couplers for photographic materials,³ herbicides,⁴ and luminescent and fluorescent substances,^{5a,b} pyrazoles with antiarrhythmic⁶ and cholesterol synthesis-inhibiting activities⁷ have appeared. Other pyrazoles (Figure 1) include effective antirheumatoidal (SC-58635 Celecoxib)⁸ and antiviral agents (Pyrazomycin),⁹ hormone oxytocin agonists (WAY-VNA-932)¹⁰ and selective Human C1s inhibitors.¹¹ Recently, pyrazoles became of interest as intermediates for fused pyrazoles,¹² and also as chiral catalysts,¹³ ligands¹⁴ or as moieties to enhance regio- and stereo-selectivity.¹⁵

Of the many reported syntheses of pyrazoles,¹⁶ three are especially widely applicable: (i) cyclocondensation of hydrazines with 2,3 dibromopropionitriles,¹⁷ propargyl aldehydes, 1,3-dicarbonyl compounds¹⁸ or their functional derivatives such as enol ethers, acetals, enamines;¹⁹ (ii) 1,3-dipolar cycloadditions of diazoalkanes to alkynes;^{16b} and (iii) eliminations of pyrazolines.²⁰

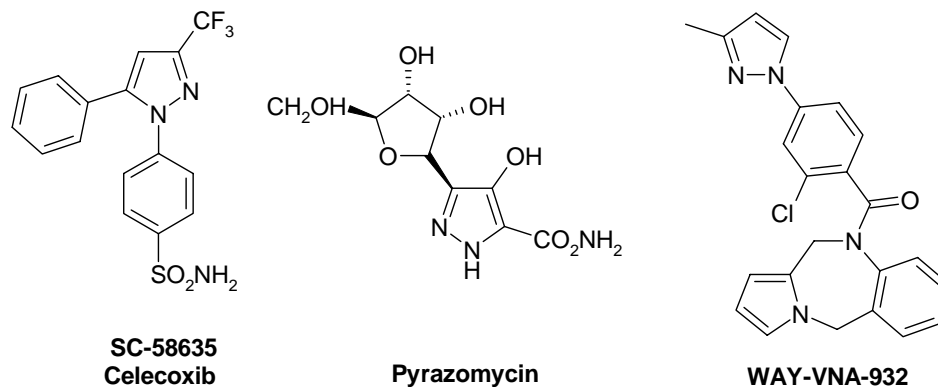


Figure 1. Bioactive molecules containing the pyrazole moiety.

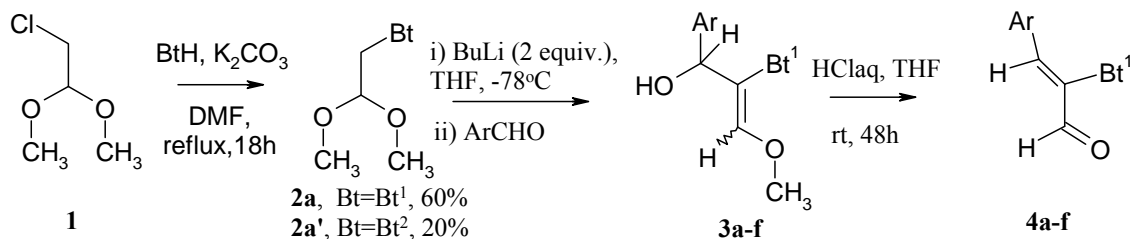
Unsymmetrical 1,3-dicarbonyls and hydrazines generally produce isomer mixtures.²¹ Sometimes this difficulty can be circumvented by the use of acetylenic-aldehydes or -ketones, where a hydrazone can be formed first by reaction at the carbonyl group then cyclised in a separate, second step.²² Using β -chloro- or β -alkoxy-enones²³ or sterically hindered enamines^{19a} as 1,3-dicarbonyl synthons also controls the regiochemistry of cyclization. We have previously prepared unsymmetrical 1,3,5-triaryl-4-alkylpyrazolines and -pyrazoles by treatment of α -benzotriazolyl- α,β -unsaturated ketones with hydrazines followed by alkylation at the 4-position of the pyrazoline ring.²⁴ We now report an alternative, convenient and regioselective route to 1,4,5-trisubstituted pyrazoles from α -benzotriazolyl- α,β -unsaturated aldehydes.

Results and Discussion

Synthesis of α -benzotriazolyl- α,β -unsaturated aldehydes (4a-f)

Previous preparations of α -benzotriazolyl- α,β -unsaturated aldehydes (**4**), in 43-68% yields, used four-steps from benzotriazole, 2-bromoacetate and various Grignard reagents.²⁵ We now report a simple and convenient method that provides a large variety of aldehydes (**4a-f**) in yields of 80-99% after a three-step reaction sequence.

2-Chloroacetaldehyde dimethylacetal (**1**) reacted with benzotriazole in DMF at reflux in the presence of one molar equivalent of potassium carbonate to give 1-(2,2-dimethoxyethyl)-1*H*-1,2,3-benzotriazole (**2a**) (42 %; 15% of the Bt² isomer (**2a'**) was also formed). When half a molar equivalent of potassium carbonate or one molar equivalent of potassium bicarbonate were used under the same reaction conditions, the Bt¹ and Bt² isomers were obtained (80%) in a ratio of (75:25). Lithiation of 1-(2,2-dimethoxyethyl)-1*H*-1,2,3-benzotriazole (**2**) with 2 molar equivalents of *n*-BuLi and then treatment with aromatic aldehydes gave vinylbenzotriazoles **3a-f**, as mixtures of E and Z isomers in an average ratio 7:3, which were isolated in 83-96% yield (Scheme 1).



Bt¹= benzotriazolyl-1-yl; Bt²= benzotriazolyl-2-yl

^a For designation of Ar in **3** and **4**, see Table 1.

Scheme 1^a

Reaction of **3a–f** with aqueous HCl in THF at room temperature for 48 h provided α,β -unsaturated aldehydes **4a–f** in 85–99% yield (Table 1). For comparison, compounds **4a,e** have been previously obtained in 43 and 63 % yields,²⁵ where our method allows the preparation of the intermediates **4a** and **4e** in 99 and 90% yields, respectively.

Table 1. Vinylbenzotriazoles **3** and α -Benzotriazolyl- α,β -unsaturated aldehydes **4**

Entry	Ar	Mp (°C)	Yield (%)
3a	Ph	102-103	83
3b	4-CH ₃ C ₆ H ₄	115-116	86
3c	C ₆ H ₅ (CH ₂) ₂	oil	85 ^a
3d	4-ClC ₆ H ₄	oil	92 ^a
3e	4-FC ₆ H ₄	100-101	88
3f	4-CH ₃ OC ₆ H ₄	oil	96 ^a
4a	Ph	Oil	99
4a'	Ph	81-82	87 ^b
4b	4-CH ₃ C ₆ H ₄	Oil	95
4c	C ₆ H ₅ (CH ₂) ₂	Oil	80
4d	4-ClC ₆ H ₄	106-108	85
4e	4-FC ₆ H ₄	92-93	90
4f	4-CH ₃ OC ₆ H ₄	119-120	94

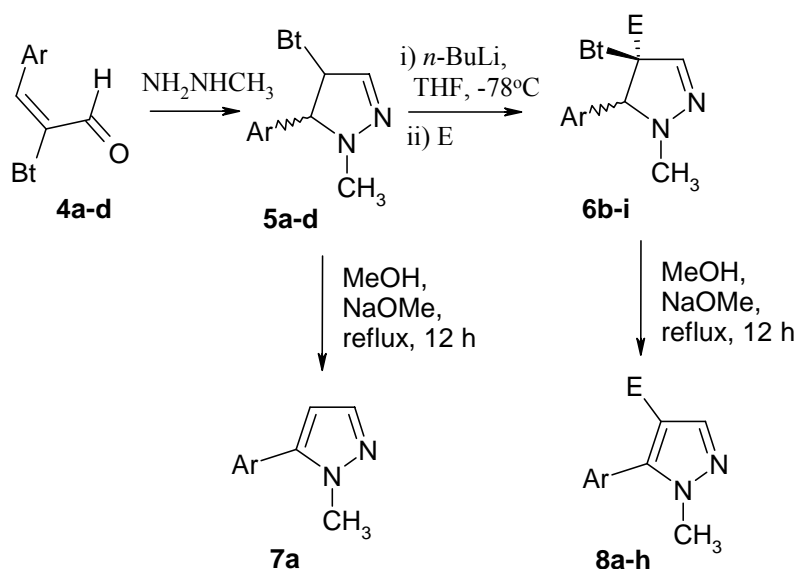
^aCompound was used for next step without purification and yield is given for the crude product.

^bBenzotriazol-2-yl derivative.

Preparation of substituted dihydropyrazoles 5–6 and pyrazoles 7–8

Compounds **4** react with *N*-methylhydrazine in ethanol under reflux in air for 4 h to form stable intermediates **5a–d** in 57–87% yield. This reaction yields a single 1,4,5-regioisomer **5**; no products of the alternative regiochemistry of addition were detected. Cyclization of α -benzotriazolyl- α,β -unsaturated aldehydes (**4**) with *N*-phenylhydrazine does not proceed under

the same reaction conditions and requires an application of base, which leads to undesirable elimination of the benzotriazolyl moiety. Dihydropyrazoles (pyrazolidines) **5a–c** can be converted further to 1,5-disubstituted pyrazoles **7** with sodium methoxide under reflux for 12 h in good (75% for **7a**) yield (Scheme 2).



^a For designation of R, Ar, E and Bt in **5-8** see Table 2.

Scheme 2^a

4,5-Dihydro-1*H*-pyrazoles **5** were functionalized further by alkylation or acylation at position 4 with alkyl iodides, bromides or alkylcarbonyl chlorides in the presence of $n\text{-BuLi}$ to afford **6** as mixtures of two diastereoisomers in 52–78% yields. Treatment of **6b–h** with NaOMe yielded the corresponding 1,4,5-trisubstituted pyrazoles **8b–h** in 52–79% yield (Scheme 2, Table 2). Final compound **8a** was prepared similarly from 4,5-dihydro-1*H*-pyrazole **5a** using crude intermediate **6a** in 63% overall yield. Use of sodium methoxide for elimination of BtH from 4-alkylcarbonyl substituted (4,5-dihydro-1*H*-pyrazol-4-yl)-1*H*-1,2,3-benzotriazole **6i** led to ring decomposition. On the other hand, the use of NaH resulted in cleavage of the alkylcarbonyl moiety.

In conclusion we have used easily available α -benzotriazolyl- α,β -unsaturated aldehydes to prepare pyrazole derivatives regiospecifically. This method will be useful as a general route to either 1,5-di- or 1,4,5-trisubstituted pyrazoles, which are compounds of major synthetic, biological, and medicinal importance.

Table 2. Dihydropyrazoles **5–6** and pyrazoles **7–8**

Entry	Ar	E	Yield (%)
5a	Ph	-	57
5b	4-CH ₃ C ₆ H ₄	-	87
5c'	C ₆ H ₅ (CH ₂) ₂		60 ^a
5d'	4-ClC ₆ H ₄	-	68 ^a
6b	4-CH ₃ C ₆ H ₄	CH ₃	73
6c	4-CH ₃ C ₆ H ₄	C ₄ H ₉	55
6d'	C ₆ H ₅ (CH ₂) ₂	CH ₃	52 ^a
6e'	C ₆ H ₅ (CH ₂) ₂	(CH ₃) ₂ CH(CH ₂) ₂	78 ^a
6f'	C ₆ H ₅ (CH ₂) ₂	C ₆ H ₁₃	65 ^a
6h'	C ₆ H ₅ (CH ₂) ₂	C ₆ H ₅ CH ₂	45 ^a
6i	4-CH ₃ C ₆ H ₄	C ₄ H ₉ CO	60
7a	Ph	-	75
8a	Ph	CH ₃	63
8b	4-CH ₃ C ₆ H ₄	CH ₃	79
8c	4-CH ₃ C ₆ H ₄	C ₄ H ₉	52
8d	C ₆ H ₅ (CH ₂) ₂	CH ₃	60
8e	C ₆ H ₅ (CH ₂) ₂	(CH ₃) ₂ CH(CH ₂) ₂	53
8f	C ₆ H ₅ (CH ₂) ₂	C ₆ H ₁₃	57
8g	C ₆ H ₅ (CH ₂) ₂	C ₂ H ₅	58
8h	C ₆ H ₅ (CH ₂) ₂	C ₆ H ₅ CH ₂	55

^a Benzotriazol-2-yl derivative.

Experimental Section

General Procedures. Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded in CDCl₃ (with tetramethylsilane as the internal standard), unless otherwise stated. Elemental analyses were performed on a Carlo Erba EA-1108 instrument. THF was distilled from sodium-benzophenone ketal prior to use. Column chromatography was performed on silica gel 200-425 mesh.

General procedure for preparation of **2a** and **2a'**

A mixture of benzotriazole (21.4 g, 0.18 mol), potassium bicarbonate (18.0 g, 0.18 mol) and 2-chloroacetaldehyde dimethylacetal (20.5 mL, 0.18 mol) in 180 mL of DMF was refluxed for 18 h. The reaction mixture was cooled, diluted with 180 mL of water and extracted with ether. The combined organic layers were washed with water, brine and dried over MgSO₄. After

evaporation of the solvent under vacuum, the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to afford the pure **2a** and **2a'**.

2-(1H-1,2,3-Benzotriazol-1-yl)-1-ethoxyethyl methyl ether (2a). Colorless oil (60%); ¹H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51–7.46 (m, 1H), 7.38–7.33 (m, 1H), 4.81–4.73 (m, 3H), 3.38 (s, 6H); ¹³C NMR δ 145.7, 133.6, 127.3, 123.7, 119.6, 110.1, 103.1, 55.0, 50.1. Anal. Calcd for C₁₀H₁₃N₃O₂: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.97; H, 6.03; N, 20.48.

2-(1H-1,2,3-Benzotriazol-2-yl)-1-ethoxyethyl methyl ether (2a'). Colorless oil (20%); ¹H NMR δ 7.89–7.86 (m, 2H), 7.40–7.37 (m, 2H), 5.10 (t, *J* = 5.6 Hz, 1H), 4.85 (d, *J* = 5.6 Hz, 2H), 3.41 (s, 6H); ¹³C NMR δ 144.4, 126.4, 118.0, 102.0, 57.3, 53.9. Anal. Calcd for C₁₀H₁₃N₃O₂: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.98; H, 6.41; N, 20.51.

General procedure for preparation of **3a–f**

A solution of **2** (5.0 mmol) in anhydrous THF (50 mL) was cooled to –78 °C and then treated dropwise with *n*-BuLi (6.4 mL of 1.6 M in hexane, 10 mmol) and stirred at this temperature for 1 h. A solution of aldehyde (6.0 mmol) in 5 mL of THF was added slowly to the reaction mixture at –78 °C. The reaction mixture was allowed to stir and warm to room temperature during 2 h, quenched by the addition of saturated NH₄Cl, and extracted with ether. The organic extracts were washed with brine, dried over MgSO₄ and concentrated under vacuum. The residue was chromatographed on a silica gel eluted with EtOAc/hexanes 1:4 to give **3a, b, e** as isomeric mixtures. The residues isolated from the reaction mixtures for compounds **3c–d, f** were used for the next step without purification.

2-(1H-1,2,3-Benzotriazol-1-yl)-1-phenyl-3-methoxy-2-propen-1-ol (3a). White microcrystals (83%); mp 102–103 °C; ¹H NMR δ (mixture of two isomers in the ratio 7:3): 7.91–7.87 (m, 1H), 7.37–7.04 (m, 8H), 6.56 (s, 0.7H), 6.54 (s, 0.3H), 6.26 (s, 0.7H), 5.75 (s, 0.3H), 4.40 (br s, 0.3H), 3.92 (br s, 0.7H), 3.80 (s, 2.1H), 3.61 (s, 0.9H); ¹³C NMR δ 149.6, 145.9, 145.0, 144.8, 140.7, 140.4, 135.1, 133.8, 128.3, 128.2, 127.8, 127.7, 127.5, 126.2, 125.6, 123.9, 123.8, 119.9, 119.5, 119.4, 117.4, 111.3, 110.7, 73.3, 68.6, 61.5, 61.2, 60.4. Anal. Calcd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.44; H, 5.25; N, 14.99.

2-(1H-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)-3-methoxy-2-propen-1-ol (3b). White microcrystals (86%); mp 115–116 °C; ¹H NMR δ (mixture of two isomers in the ratio 6:4): 7.95–7.90 (m, 1H), 7.39–7.17 (m, 3.8H), 7.04 (d, *J* = 7.8 Hz, 1.2H), 6.98 (d, *J* = 7.8 Hz, 0.8H), 6.92 (d, *J* = 7.8 Hz, 1.2H), 6.58 (s, 0.6H), 6.50 (s, 0.4H), 6.21 (s, 0.6H), 5.70 (s, 0.4H), 3.98 (br s, 0.4H), 3.84 (s, 1.8H), 3.65 (s, 1.2H), 3.55 (br s, 0.6H), 2.21 (s, 1.2H), 2.19 (s, 1.8H); ¹³C NMR δ 149.1, 145.5, 144.9, 144.7, 137.5, 137.3, 137.1, 137.0, 134.9, 133.6, 128.9, 128.8, 127.5, 127.3, 125.9, 125.3, 123.7, 123.7, 119.9, 119.5, 117.3, 111.3, 110.5, 73.1, 68.6, 61.3, 61.0, 20.9. Anal. Calcd for C₁₇H₁₇N₃O₂: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.93; H, 5.90; N, 14.10.

2-(1H-1,2,3-Benzotriazol-1-yl)-1-(4-fluorophenyl)-3-methoxy-2-propen-1-ol (3e). White microcrystals (88%); mp 100–101 °C; ¹H NMR δ (mixture of two isomers in the ratio 6:4): 7.93–7.89 (m, 1H), 7.38–7.12 (m, 5H), 6.87–6.77 (m, 2H), 6.59 (s, 0.6H), 6.57 (s, 0.4H), 6.24 (s, 0.6H), 5.74 (s, 0.4H), 4.47 (brs, 0.4H), 3.95 (s, 0.6H), 3.84 (s, 1.8H), 3.66 (s, 1.2H); ¹³C NMR δ

163.6, 160.3, 149.5, 145.6, 144.8, 144.6, 136.4, 136.3, 136.0, 134.9, 133.5, 127.7, 127.6, 127.5, 127.2, 127.0, 123.9, 123.8, 119.5, 119.4, 117.1, 115.1, 115.0, 114.9, 114.8, 111.1, 110.3, 72.6, 67.9, 61.4, 61.1. Anal. Calcd for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.71; N, 14.04. Found: C, 64.12; H, 4.53; N, 13.79.

General Procedure for Preparation of 4a–f

Aqueous HCl (19 mL, 10 % solution in water) was added dropwise to a stirred solution of **3** (3.6 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 48 h, and then extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give **4**.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-phenyl-2-propenal (4a). Colorless oil (75%); bp 109–111 °C/0.1 mmHg (lit.²⁵ bp 110 °C/0.1 mmHg); 1H NMR δ 9.85 (s, 1H), 8.17–8.14 (m, 1H), 7.92 (s, 1H), 7.63–7.28 (m, 3H), 7.22–7.17 (m, 3H), 6.94–6.91 (m, 2H); ^{13}C NMR δ 187.3, 148.0, 145.4, 133.1, 132.6, 132.6, 130.9, 130.7, 129.3, 128.8, 125.0, 120.1, 110.3.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-phenyl-2-propenal (4a'). White microcrystals (87%); mp 81–82 °C; 1H NMR δ 9.80 (s, 1H), 7.99–7.94 (m, 2H), 7.79 (s, 1H), 7.50–7.45 (m, 2H), 7.40–7.35 (m, 1H), 7.25–7.20 (m, 2H), 6.87–6.85 (m, 2H); ^{13}C NMR δ 186.3, 145.4, 145.2, 137.1, 132.4, 130.9, 130.2, 129.1, 127.5, 118.7. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.32; H, 4.39; N, 17.09.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(4-methylphenyl)-2-propenal (4b). White prisms (95%); mp 93–94 °C; 1H NMR δ 9.80 (s, 1H), 8.16–8.14 (m, 1H), 7.83 (s, 1H), 7.47–7.38 (m, 2H), 7.21–7.18 (m, 1H), 7.00 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR δ 187.1, 147.8, 145.7, 143.6, 132.9, 131.7, 130.9, 129.9, 128.4, 127.8, 124.4, 120.1, 110.0, 21.5. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.30; H, 4.95; N, 16.02.

2-Benzotriazol-1-yl-5-phenyl-pent-2-enal (4c). Yellow oil (80%); 1H NMR δ 9.65 (s, 1H); 8.11 (d, J = 8.1 Hz, 1H); 7.50–7.36 (m, 2H); 7.24–7.15 (m, 4H); 7.11–7.08 (m, 3H); 2.89 (t, J = 7.4 Hz, 2H); 2.69 (q, J = 7.4 Hz, 2H); ^{13}C NMR δ 186.0, 153.3, 145.5, 139.3, 137.2, 133.3, 128.6, 128.2, 126.6, 124.2, 120.0, 110.3, 109.6, 34.1, 30.2. HRMS Calcd for $C_{17}H_{16}N_3O$: 278.1287. Found: 278.1284.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-2-propenal (4d). Yellow microcrystals (85%) mp 106–108 °C (lit.²⁵ bp 122 °C/1 mmHg); 1H NMR δ 9.82 (s, 1H), 8.16 (dd, J = 7.4 Hz, J = 1.8 Hz, 1H), 7.81 (s, 1H), 7.50–7.41 (m, 2H), 7.21–7.18 (m, 3H), 6.87 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 186.8, 145.8, 145.5, 138.6, 132.8, 132.7, 131.8, 129.5, 129.0, 128.7, 124.6, 120.3, 109.9; Anal. Calcd for $C_{15}H_{10}ClN_3O$: C, 63.50; H, 3.55. Found: C, 63.21; H, 3.62.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(4-fluorophenyl)-2-propenal (4e). Colorless needles (90%); mp 92–93 °C (lit.²⁵ mp 93–94 °C); 1H NMR δ 9.82 (s, 1H), 8.17–8.14 (m, 1H), 7.84 (s, 1H), 7.49–7.39 (m, 2H), 7.22–7.19 (m, 1H), 6.97–6.87 (m, 4H); ^{13}C NMR δ 186.9, 164.6 (d, J = 255.0 Hz, 1C), 146.1, 145.7, 133.1 (d, J = 9.2 Hz, 1C), 132.7, 132.2, 128.6, 126.9 (d, J = 3.4 Hz, 1C), 124.5, 120.2, 116.5 (d, J = 21.6 Hz, 1C), 109.9.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(4-methoxyphenyl)-2-propenal (4f). White microcrystals (94%); mp 119–120 °C; 1H NMR δ 9.78 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.79 (s, 1H), 7.49–

7.40 (m, 2H), 7.27–7.21 (m, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 8.8$ Hz, 2H), 3.75 (s, 3H); ^{13}C NMR δ 187.0, 163.0, 147.7, 145.8, 133.3, 132.9, 130.4, 128.4, 124.4, 123.2, 120.2, 114.7, 110.0, 55.4. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.47; H, 4.65; N, 14.90.

General Procedure for Preparation of 5

Hydrazine (3.1 mmol) was added to a stirred solution of **7** (3.1 mmol) in 15 mL of ethanol. The reaction mixture was heated under reflux for 4 h, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluted with EtOAc/hexane 1:9 to give pure **5**.

1-(1-Methyl-5-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-1H-1,2,3-benzotriazole (5a). Colorless oil (57%); ^1H NMR δ (mixture of 2 isomers 6:4): 8.12–8.09 (m, 0.4H), 8.00 (d, $J = 8.2$ Hz, 0.6H), 7.71 (d, $J = 8.4$ Hz, 0.6H), 7.63–7.60 (m, 1.2H), 7.44–7.20 (m, 6.2H), 6.99 (d, $J = 1.1$ Hz, 0.4H), 6.91 (dd, $J = 10.6, 2.7$ Hz, 0.6H), 6.12 (dd, $J = 12.1, 1.4$ Hz, 0.4H), 4.46 (d, $J = 12.1$ Hz, 0.4H), 3.80 (dd, $J = 12.0, 2.6$ Hz, 0.6H), 3.54–3.47 (m, 0.6H), 3.18 (s, 1.8H), 2.97 (s, 1.2H); ^{13}C NMR δ (mixture of 2 isomers 6:4): 146.7, 146.5, 145.2, 137.2, 136.3, 132.4, 131.0, 130.3, 129.1, 129.0, 128.8, 128.7, 127.9, 127.7, 127.3, 125.7, 124.3, 124.2, 120.4, 119.8, 110.9, 109.6, 77.9, 73.6, 63.8, 60.6, 42.4, 41.4. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5$: C, 69.30; H, 5.45; N, 25.25. Found: C, 69.54; H, 5.54; N, 24.89.

1-(1-Methyl-5-*p*-tolyl-4,5-dihydro-1H-pyrazol-4-yl)-1H-benzotriazole (5b). Colorless oil (75%); ^1H NMR δ 8.12–8.08 (m, 1H), 7.44–7.36 (m, 2H), 7.26–7.23 (m, 1H), 7.16–7.10 (m, 4H), 6.98 (d, $J = 1.2$ Hz, 1H), 6.10 (dd, $J = 12.1, 1.4$ Hz, 1H), 4.42 (d, $J = 12.1$ Hz, 1H), 2.95 (s, 3H), 2.35 (s, 3H); ^{13}C NMR δ 146.4, 138.6, 136.3, 134.0, 132.4, 129.7, 127.6, 127.2, 124.3, 120.3, 109.7, 77.7, 73.6, 41.3, 21.1. HRMS calcd for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{Na}$: 314.1376. Found: 314.1378.

2-(1-Methyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (5c'). Yellow oil (60%); ^1H NMR δ 7.92–7.87 (m, 2H); 7.46–7.41 (m, 2H); 7.23–7.12 (m, 3H); 7.04–7.02 (m, 2H); 6.85 (br s, 1H); 6.04 (dd, $J = 10.6, 1.1$ Hz, 1H); 3.78–3.70 (m, 1H); 3.00 (s, 3H); 2.80–2.70 (m, 1H); 2.63–2.52 (m, 1H); 2.31–2.08 (m, 2H); ^{13}C NMR δ 144.6, 140.8, 136.7, 128.4, 128.1, 126.9, 126.1, 118.2, 76.9, 73.3, 41.8, 33.2, 31.3. HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{N}_5$: 306.1713. Found: 306.1732.

2-[5-(4-Chloro-phenyl)-1-methyl-4,5-dihydro-1H-pyrazol-4-yl]-2H-benzotriazole (5d'). Yellow oil (68%); ^1H NMR δ 7.90–7.86 (m, 2H); 7.43–7.40 (m, 2H); 7.31 (d, $J = 8.4$ Hz, 2H); 7.24 (d, $J = 8.5$ Hz, 2H); 6.91 (s, 1H); 6.09 (d, $J = 11.9$ Hz, 1H); 4.70 (d, $J = 11.8$ Hz, 1H); 2.93 (s, 3H); ^{13}C NMR δ 144.5, 136.3, 135.7, 134.3, 129.1, 128.7, 126.9, 118.1, 79.9, 77.4, 41.4. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{ClN}_5$: C, 61.64; H, 4.53. Found: C, 61.78; H, 4.62.

General procedure for preparation of 6

To a stirred solution of **5** (1.7 mmol) in anhydrous THF (20 mL) at -78 °C, *n*-BuLi (1.1 mL of 1.6 M in hexane, 1.7 mmol) was added dropwise and stirring was continued for 0.5 h at -78 °C. A solution of methyl iodide (0.12 mL, 1.9 mmol) was then added. The reaction mixture was allowed to warm to room temperature while stirring for 2 h, quenched by the addition of saturated NH_4Cl , and extracted with ether. The combined extracts were washed with brine, dried

over MgSO₄ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc/hexane 1:9 to give **6b–i**. The residue isolated from the column chromatography for compound **6g'** contained about 10% of final product **8g** due to easy elimination of Bt² moiety on silica gel and was used for the next step without additional purification.

1-[1,4-Dimethyl-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-4-yl]-1H-1,2,3-benzotriazole (6b). Colorless oil (73%); ¹H NMR δ 8.13 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.50–7.38 (m, 2H), 7.14–7.10 (m, 3H), 6.94 (d, *J* = 7.7 Hz, 2H), 4.40 (s, 1H), 2.95 (s, 3H), 2.34 (s, 3H), 1.63 (s, 3H); ¹³C NMR δ 146.9, 142.4, 138.3, 131.9, 129.7, 129.2, 127.7, 127.0, 124.0, 120.4, 111.6, 79.9, 76.3, 40.8, 21.0, 18.3. Anal. Calcd for C₁₈H₁₉N₅: C, 70.79; H, 6.27. Found: C, 70.39; H, 6.42.

1-(4-Butyl-1-methyl-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-4-yl)-1H-benzotriazole (6c). Colorless crystals (55%), mp 110–112 °C; ¹H NMR δ 7.89–7.87 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.30–7.20 (m, 3H), 6.72 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.11 (s, 1H), 3.00–2.88 (m, 1H), 2.43–2.33 (m, 1H), 2.12 (s, 3H), 1.52–1.38 (m, 3H), 1.32–1.22 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H); ¹³C NMR δ 146.2, 139.2, 138.3, 133.2, 129.6, 128.8, 127.3, 127.0, 123.2, 119.5, 111.9, 79.4, 78.5, 40.5, 36.6, 27.2, 22.8, 21.0, 13.9. Anal. Calcd for C₂₁H₂₅N₅: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.84; H, 7.34; N, 20.44.

2-(1,4-Dimethyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (6d'). Colorless oil (52%); ¹H NMR δ 7.92–7.88 (m, 2H); 7.45–7.40 (m, 2H); 7.19–7.11 (m, 3H); 6.96–6.94 (m, 3H); 3.54 (dd, *J* = 8.7, 4.8, Hz, 1H); 2.94 (s, 3H); 2.69–2.59 (m, 1H); 2.47–2.36 (m, 1H); 2.27–2.05 (m, 2H); 1.98 (s, 3H); ¹³C NMR δ 144.1, 143.6, 141.0, 128.3, 128.0, 126.7, 126.0, 118.2, 79.6, 75.8, 41.8, 32.1, 28.6, 16.8. Anal. Calcd for C₁₉H₂₁N₅: C, 71.45; H, 6.63; N, 21.93. Found: C, 71.42; H, 6.44; N, 21.58.

2-[1-Methyl-4-(3-methyl-butyl)-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl]-2H-benzotriazole (6e'). Yellow oil (78%); ¹H NMR δ 7.93–7.88 (m, 2H); 7.44–7.39 (m, 2H); 7.25 (s, 1H); 7.21–7.09 (m, 3H); 7.03–7.01 (m, 2H); 3.13 (dd, *J* = 7.3, 5.1 Hz, 1H); 2.89 (s, 3H); 2.89–2.78 (m, 1H); 2.71–2.54 (m, 2H); 2.44–2.32 (m, 1H); 2.23–2.05 (m, 2H); 1.63–1.50 (m, 1H); 1.32–1.15 (m, 1H); 1.09–0.95 (m, 1H); 0.88 (d, *J* = 2.9 Hz, 3H); 0.86 (d, *J* = 2.9 Hz, 3H); ¹³C NMR δ 143.9, 142.3, 141.2, 128.3, 128.1, 126.5, 126.0, 118.3, 82.6, 76.9, 42.1, 32.8, 32.2, 29.4, 28.4, 28.3, 22.4, 22.3. Anal. Calcd for C₂₃H₂₉N₅: C, 73.57; H, 7.78. Found: C, 73.49; H, 7.85.

2-(4-Hexyl-1-methyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (6f'). Yellow oil (65%); ¹H NMR δ 7.96–7.90 (m, 2H); 7.42–7.36 (m, 2H); 7.23–7.09 (m, 4H); 6.99–6.97 (m, 2H); 3.05 (dd, *J* = 3.8 Hz, 8.5 Hz, 1H); 2.94 (s, 3H); 2.92–2.80 (m, 2H); 2.37–2.27 (m, 2H); 1.71–1.60 (m, 1H), 1.39–1.18 (m, 8H); 1.09–0.96 (m, 1H); 0.88 (t, *J* = 6.7 Hz, 3H); ¹³C NMR δ 144.1, 141.2, 140.6, 128.4, 128.2, 126.5, 126.0, 118.4, 82.4, 73.6, 41.3, 37.3, 32.0, 31.5, 29.3, 28.7, 25.1, 22.5, 14.0. Anal. Calcd for C₂₄H₃₁N₅: C, 74.00; H, 8.02; N, 17.98. Found: C, 74.32; H, 8.37; N, 17.59.

2-(4-Benzyl-1-methyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (6h'). Yellow oil (45%); ¹H NMR δ 7.97–7.91 (m, 2H); 7.43–7.38 (m, 2H); 7.23–7.13 (m, 6H); 7.05–6.98 (m,

5H); 4.35 (d, $J = 14.0$ Hz, 1H); 3.66 (d, $J = 14.1$ Hz, 1H); 3.19 (dd, $J = 8.2, 4.0$ Hz, 1H); 2.99–2.82 (m, 1H); 2.85 (s, 3H); 2.44–2.34 (m, 1H); 1.75–1.63 (m, 1H); 1.18–1.05 (m, 1H); ^{13}C NMR δ 144.5, 141.6, 140.8, 135.3, 131.0, 129.0, 128.9, 128.7, 127.7, 127.1, 126.5, 118.9, 83.3, 73.8, 43.6, 41.6, 32.5, 29.3. Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{N}_5$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.32; H, 6.23; N, 17.65.

1-(4-Benzotriazol-1-yl-1-methyl-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-4-yl)-pentan-1-one (6i). Yellow microcrystals (60%), mp 95–97 °C; ^1H NMR δ 8.06 (d, $J = 8.4$ Hz, 1H), 7.74–7.71 (m, 2H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.44–7.38 (m, 1H), 7.15 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 8.0$ Hz, 2H), 5.50 (s, 1H), 2.95 (s, 3H), 2.75–2.65 (m, 1H), 2.51–2.41 (m, 1H), 2.24 (s, 3H), 1.68–1.58 (m, 2H), 1.40–1.31 (m, 2H), 0.88 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR δ 172.2, 146.1, 138.3, 134.7, 131.9, 129.4, 128.6, 126.5, 124.8, 123.7, 120.4, 112.3, 110.6, 75.1, 47.6, 32.2, 26.7, 22.3, 21.0, 13.7. Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.43; H, 6.82; N, 18.83.

General procedure for preparation of 7

A solution of **4** (1.0 mmol) and hydrazine (1.0 mmol) in 5 mL of ethanol was heated at 78 °C for 12 h. After cooling, sodium (0.05 g, 2.1 mmol) was added and the reaction mixture was heated under reflux again for additional 12 h. After evaporation of solvent, the residue was chromatographed on silica gel eluted with EtOAc/hexane 1:19 to give pyrazole **7**.

1-Methyl-5-phenyl-1H-pyrazole (7a). Colorless oil (75%); bp 91–93 °C/1.5 mmHg (lit.²⁶ bp 90–95 °C/1.5 mmHg); ^1H NMR δ 7.51 (d, $J = 1.8$ Hz, 1H), 7.47–7.37 (m, 5H), 6.30 (d, $J = 1.8$ Hz, 1H), 3.89 (s, 3H); ^{13}C NMR δ 143.5, 138.4, 130.7, 128.7, 128.6, 128.3, 106.0, 37.4.

General procedure for preparation of 8 from 5

A solution of **5a** (1.1 mmol) in anhydrous THF (20 mL) was cooled to –78 °C and then treated dropwise with *n*-BuLi (0.75 mL of 1.6 M in hexane, 1.2 mmol) and stirred at this temperature for 0.5 h. A solution of methyl iodide (0.08 mL, 1.3 mmol) in 5 mL of THF was added slowly at –78 °C. The reaction mixture was allowed to warm to room temperature while stirring for 2 h, quenched by the addition of saturated NH_4Cl , and extracted with ether. The organic extracts were washed with brine, dried over MgSO_4 and concentrated under vacuum. The residue was dissolved in MeOH (10 mL) and MeONa (0.21 g, 0.0038 mol) was added. The reaction mixture was heated under reflux for 12 h. The solvent was evaporated and the residue was dissolved in EtOAc (15 mL). The solution was washed with water, brine, dried over MgSO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/hexane (1:9) to give pure **8a**.

1,4-Dimethyl-5-phenyl-1H-pyrazole (8a). Colorless oil (63%); (lit.²⁷ bp 112–114 °C/1 mmHg); ^1H NMR δ 7.69–7.66 (m, 2H), 7.43–7.27 (m, 3H), 7.20 (s, 1H), 3.90 (s, 3H), 2.23 (d, $J = 0.6$ Hz, 3H); ^{13}C NMR δ 130.7, 128.6, 128.4, 127.3, 127.1, 125.5, 113.8, 38.8, 10.0. HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2$: 173.1073. Found: 173.1077.

General procedure for preparation of 8 from 6

MeONa (0.06 g, 1.1 mmol) was added to a stirred solution of **6** (0.33 mmol) of methanol (10 mL). The reaction mixture was heated under reflux for 12 h. The solvent was evaporated and the

residue was dissolved in EtOAc (15 mL). The solution was washed with water, brine, dried over MgSO_4 and the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give pure **8b-h**.

1,4-Dimethyl-5-(4-methylphenyl)-1H-pyrazole (8b). Colorless oil (79%); ^1H NMR δ 7.37 (s, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 3.75 (s, 3H), 2.41 (s, 3H), 2.00 (s, 3H); ^{13}C NMR δ 140.7, 138.7, 138.1, 129.4, 129.2, 127.3, 114.2, 37.2, 21.2, 9.0. HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2$: 187.1229. Found: 187.1227.

1-Methyl-4-butyl-5-(4-methylphenyl)-1H-pyrazole (8c). Colorless oil (52%); ^1H NMR δ 7.39 (s, 1H); 7.27 (d, $J = 7.8$ Hz, 2H); 7.18 (d, $J = 8.1$ Hz, 2H); 3.73 (s, 3H); 2.42 (s, 3H); 2.35 (t, $J = 7.4$ Hz, 2H); 1.51–1.40 (m, 2H); 1.34–1.21 (m, 2H); 0.84 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR δ 140.5, 138.2, 138.0, 129.6, 129.3, 127.6, 120.0, 37.1, 33.1, 23.6, 22.3, 21.3, 13.8. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.65; H, 9.05; N, 12.45.

1,4-Dimethyl-5-phenethyl-1H-pyrazole (8d). Yellow oil (60%); ^1H NMR δ 7.30–7.22 (m, 4H); 7.08–7.05 (m, 2H); 3.56 (s, 3H); 2.89–2.77 (m, 4H); 1.87 (s, 3H); ^{13}C NMR δ 140.5, 138.5, 138.3, 128.5, 128.4, 126.3, 113.5, 36.1, 35.1, 26.2, 8.5. HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2$: 201.1386. Found: 201.1384.

1-Methyl-4-(3-methyl-butyl)-5-phenethyl-1H-pyrazole (8e). Yellow oil (53%); ^1H NMR δ 7.30–7.18 (m, 4H), 7.09–7.06 (m, 2H), 3.58 (s, 3H), 2.89–2.76 (m, 4H), 2.28–2.22 (m, 2H), 1.56 (septet, $J = 6.6$ Hz, 1H), 1.40–1.33 (m, 2H), 0.91 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR δ 140.5, 128.0, 138.0, 137.4, 128.5, 128.4, 126.3, 119.1, 40.0, 36.1, 35.5, 27.6, 26.3, 22.4, 21.6. Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.45; H, 9.75; N, 10.75.

4-Hexyl-1-methyl-5-phenethyl-1H-pyrazole (8f). Yellow oil (57%); ^1H NMR δ 7.31–7.19 (m, 4H); 7.10–7.07 (m, 2H); 3.57 (s, 3H); 2.89–2.76 (m, 4H); 2.26 (t, $J = 7.3$ Hz, 2H); 1.50–1.45 (m, 2H); 1.33–1.25 (m, 6H); 0.91–0.86 (m, 3H); ^{13}C NMR δ 140.6, 138.1, 137.6, 128.5, 128.4, 126.3, 119.0, 36.1, 35.6, 31.7, 30.8, 29.1, 26.2, 23.8, 22.6, 14.1. Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.73; H, 10.04; N, 10.57.

4-Ethyl-1-methyl-5-phenethyl-1H-pyrazole (8g). Yellow oil (58%); ^1H NMR δ 7.30–7.19 (m, 4H); 7.10–7.07 (m, 2H); 3.58 (s, 3H); 2.90–2.77 (m, 4H); 2.30 (q, $J = 7.7$ Hz, 2H); 1.13 (t, $J = 7.7$ Hz, 3H); ^{13}C NMR δ 140.5, 137.9, 137.1, 128.5, 128.5, 126.4, 120.6, 36.1, 35.5, 26.2, 17.0, 15.2. Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.39; H, 8.82; N, 12.88.

4-Benzyl-1-methyl-5-phenethyl-1H-pyrazole (8h). Yellow oil (55%); ^1H NMR δ 7.30–7.14 (m, 9H); 7.00–6.98 (m, 2H); 3.64 (s, 2H); 3.59 (s, 3H); 2.81 (t, $J = 7.4$ Hz, 2H); 2.63 (t, $J = 7.3$ Hz, 2H); ^{13}C NMR δ 141.1, 140.5, 138.8, 138.5, 128.5, 128.45, 128.4, 128.36, 126.3, 126.0, 117.5, 36.2, 35.1, 30.2, 26.4. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.23; H, 7.54; N, 10.21.

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