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

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Abstract
Treatment of α-benzotriazolyloxy-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,5ab pyrazoles with antiarrhythmic6 and cholesterol synthesis-inhibiting activities7 have appeared. Other pyrazoles (Figure 1) include effective antirheumatomatoidal (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
Unsymmetrical 1,3-dicarbonyls and hydrazines generally produce isomer mixtures.\textsuperscript{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.\textsuperscript{22} Using β-chloro- or β-alkoxy-enones\textsuperscript{23} or sterically hindered enamines\textsuperscript{19a} as 1,3-dicarbonyl synths 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.\textsuperscript{24} We now report an alternative, convenient and regioselective route to 1,4,5-trisubstituted pyrazoles from α-benzotriazolyl-α,β-unsaturated aldehydes.

**Figure 1.** Bioactive molecules containing the pyrazole moiety.

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.\textsuperscript{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)-1H-1,2,3-benzotriazole (2a) (42 %; 15% of the Bt\textsuperscript{2} 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 Bt\textsuperscript{1} and Bt\textsuperscript{2} isomers were obtained (80%) in a ratio of (75:25). Lithiation of 1-(2,2-dimethoxyethyl)-1H-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).
Scheme 1a

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

<table>
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<th>Entry</th>
<th>Ar</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
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<tr>
<td>3a</td>
<td>Ph</td>
<td>102-103</td>
<td>83</td>
</tr>
<tr>
<td>3b</td>
<td>4-CH₃C₆H₄</td>
<td>115-116</td>
<td>86</td>
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<tr>
<td>3c</td>
<td>C₆H₅(CH₂)₂</td>
<td>oil</td>
<td>85a</td>
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<tr>
<td>3d</td>
<td>4-ClC₆H₄</td>
<td>oil</td>
<td>92a</td>
</tr>
<tr>
<td>3e</td>
<td>4-FC₆H₄</td>
<td>100-101</td>
<td>88</td>
</tr>
<tr>
<td>3f</td>
<td>4-CH₃OC₆H₄</td>
<td>oil</td>
<td>96a</td>
</tr>
<tr>
<td>4a</td>
<td>Ph</td>
<td>Oil</td>
<td>99</td>
</tr>
<tr>
<td>4a'</td>
<td>Ph</td>
<td>81-82</td>
<td>87b</td>
</tr>
<tr>
<td>4b</td>
<td>4-CH₃C₆H₄</td>
<td>Oil</td>
<td>95</td>
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<tr>
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<td>Oil</td>
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<td>4d</td>
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<td>85</td>
</tr>
<tr>
<td>4e</td>
<td>4-FC₆H₄</td>
<td>92-93</td>
<td>90</td>
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<tr>
<td>4f</td>
<td>4-CH₃OC₆H₄</td>
<td>119-120</td>
<td>94</td>
</tr>
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</table>

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).

Scheme 2

4,5-Dihydro-1H-pyrazoles 5 were functionalized further by alkylation or acylation at position 4 with alkyl iodides, bromides or alkylcarbonyl chlorides in the presence of n-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-1H-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-1H-pyrazol-4-yl)-1H-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

<table>
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<tr>
<th>Entry</th>
<th>Ar</th>
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<th>Yield (%)</th>
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<td>-</td>
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<tr>
<td>5b</td>
<td>4-CH₃C₆H₄</td>
<td>-</td>
<td>87</td>
</tr>
<tr>
<td>5c'</td>
<td>C₆H₅(CH₂)₂</td>
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<tr>
<td>5d'</td>
<td>4-ClC₆H₄</td>
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<td>68</td>
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<td>6b</td>
<td>4-CH₃C₆H₄</td>
<td>CH₃</td>
<td>73</td>
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<tr>
<td>6c</td>
<td>4-CH₃C₆H₄</td>
<td>C₄H₉</td>
<td>55</td>
</tr>
<tr>
<td>6d'</td>
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<td>CH₃</td>
<td>52</td>
</tr>
<tr>
<td>6e'</td>
<td>C₆H₅(CH₂)₂</td>
<td>(CH₃)₂CH(CH₂)₂</td>
<td>78</td>
</tr>
<tr>
<td>6f'</td>
<td>C₆H₅(CH₂)₂</td>
<td>C₆H₁₃</td>
<td>65</td>
</tr>
<tr>
<td>6h'</td>
<td>C₆H₅(CH₂)₂</td>
<td>C₆H₃CH₂</td>
<td>45</td>
</tr>
<tr>
<td>6i</td>
<td>4-CH₃C₆H₄</td>
<td>C₄H₉CO</td>
<td>60</td>
</tr>
<tr>
<td>7a</td>
<td>Ph</td>
<td>-</td>
<td>75</td>
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<tr>
<td>8a</td>
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<td>63</td>
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<td>8b</td>
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<td>8d</td>
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<td>CH₃</td>
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<tr>
<td>8e</td>
<td>C₆H₅(CH₂)₂</td>
<td>(CH₃)₂CH(CH₂)₂</td>
<td>53</td>
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<tr>
<td>8f</td>
<td>C₆H₅(CH₂)₂</td>
<td>C₆H₁₃</td>
<td>57</td>
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<td>C₆H₅(CH₂)₂</td>
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<td>58</td>
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<tr>
<td>8h</td>
<td>C₆H₅(CH₂)₂</td>
<td>C₆H₃CH₂</td>
<td>55</td>
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</table>

*aBenzotriazol-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. ^1^H NMR (300 MHz) and ^13^C 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%); \(^{1}\)H NMR \(\delta 8.04\) (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); \(^{13}\)C NMR \(\delta 145.7, 133.6, 127.3, 123.7, 119.6, 110.1, 103.1, 55.0, 50.1\). Anal. Calcd for C\(_{10}\)H\(_{13}\)N\(_{3}\)O\(_{2}\): 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%); \(^{1}\)H NMR \(\delta 7.89–7.86\) (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); \(^{13}\)C NMR \(\delta 144.4, 126.4, 118.0, 102.0, 57.3, 53.9\). Anal. Calcd for C\(_{10}\)H\(_{13}\)N\(_{3}\)O\(_{2}\): 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 NH\(_4\)Cl, and extracted with ether. The organic extracts were washed with brine, dried over MgSO\(_4\) 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; \(^{1}\)H NMR \(\delta\) (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); \(^{13}\)C NMR \(\delta 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 C\(_{16}\)H\(_{15}\)N\(_{3}\)O\(_{2}\): 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; \(^{1}\)H NMR \(\delta\) (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); \(^{13}\)C NMR \(\delta 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, 119.9, 119.5, 117.3, 111.3, 110.5, 73.1, 68.6, 61.3, 61.0, 20.9. Anal. Calcd for C\(_{17}\)H\(_{15}\)N\(_{3}\)O\(_{2}\): 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; \(^{1}\)H NMR \(\delta\) (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); \(^{13}\)C NMR \(\delta\).
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}F_{3}O_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-(1H-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); \(^1\)H 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-(1H-1,2,3-Benzotriazol-1-yl)-3-phenyl-2-propenal (4a'). White microcrystals (87%); mp 81–82 °C; \(^1\)H 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-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-methylphenyl)-2-propenal (4b). White prisms (95%); mp 93–94 °C; \(^1\)H 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%); \(^1\)H 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_2O: 278.1287. Found: 278.1284.

2-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-2-propenal (4d). Yellow microcrystals (85%) mp 106–108 °C (lit.\(^{25}\) mp 122 °C/1 mmHg); \(^1\)H 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, 138.3, 128.8, 123.7, 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-(1H-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); \(^1\)H 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-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-methoxyphenyl)-2-propenal (4f). White microcrystals (94%); mp 119–120 °C; \(^1\)H 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 C$_{16}$H$_{13}$N$_{3}$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%); $^1$H 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, 125.0, 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 C$_{16}$H$_{15}$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%); $^1$H 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, 124.2, 120.3, 109.7, 77.7, 73.6, 41.3, 21.1. HRMS calcd for C$_{17}$H$_{17}$N$_{5}$Na: 314.1376. Found: 314.1378.

**2-(1-Methyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (5c').** Yellow oil (60%); $^1$H NMR δ 7.92–7.87 (m, 2H); 7.46–7.36 (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 144.6, 138.6, 136.3, 134.0, 132.4, 129.7, 127.6, 127.2, 124.3, 124.0, 109.7, 77.7, 73.6, 41.3, 21.1. HRMS calcd for C$_{18}$H$_{20}$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%); $^1$H NMR δ 7.90–7.86 (m, 2H); 7.43–7.40 (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 C$_{16}$H$_{14}$ClN$_{5}$: 306.1713. Found: 306.1732.

**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$_4$Cl, 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 Br² 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 ºC; 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); 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 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, 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 C₂₄H₃₁N₅: C, 73.57; H, 7.78. Found: C, 73.49; H, 7.85.

2-(4-Benzyl-1-methyl-5-phenethyl-4,5-dihydro-1H-pyrazol-4-yl)-2H-benzotriazole (6g').
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);

13C 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 C25H25N5: 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 ºC; 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); 13C 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 C22H25N5O: 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 ºC 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 ºC/1.5 mmHg (lit.26 bp 90–95 ºC/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); 13C NMR δ 143.5, 138.4, 130.7, 128.7, 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 C11H13N2: 173.1073. Found: 173.1077.

General procedure for preparation of 8 from 5
A solution of 5a (1.1 mmol) in anhydrous THF (20 mL) was cooled to –78 ºC 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 ºC. The reaction mixture was allowed to warm to room temperature while stirring for 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 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 MgSO4 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 ºC/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); 13C NMR δ 130.7, 128.6, 128.4, 127.3, 127.1, 125.5, 113.8, 38.8, 10.0. HRMS calcd for C11H13N2: 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 MgSO₄ 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); ¹³C 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 C₁₂H₁₅N₂: 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); ¹³C 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 C₁₅H₂₀N₂: 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); ¹³C 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 C₁₃H₁₇N₂: 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); ¹³C NMR δ 140.5, 128.0, 138.0, 137.4, 128.5, 128.4, 126.3, 119.1, 40.0, 36.1, 35.7, 27.6, 26.3, 22.4, 21.6. Anal. Calcd for C₁₇H₂₄N₂: 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); 2.90–2.77 (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); ¹³C NMR δ 140.6, 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. Anal. Calcd for C₁₈H₂₆N₂: 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); ¹³C 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 C₁₄H₁₈N₂: 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); ¹³C 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 C₁₉H₂₀N₂: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.23; H, 7.54; N, 10.21.

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