Regioselective Synthesis of Polysubstituted Pyrazoles and Isoxazoles

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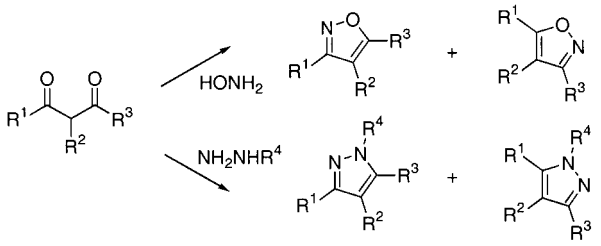
A regioselective synthesis has been developed for the preparation of unsymmetrical 1,3,5-triaryl-4-alkylpyrazolines and -pyrazoles by treatment of α-benzotriazolyl-α,*β*-unsaturated ketones with monosubstituted hydrazines followed by alkylation at the 4-position of the pyrazoline ring. Reaction of α-benzotriazolyl-α,*β*-unsaturated ketones with hydroxylamine gives 3,5-disubstituted isoxazoles regioselectively.

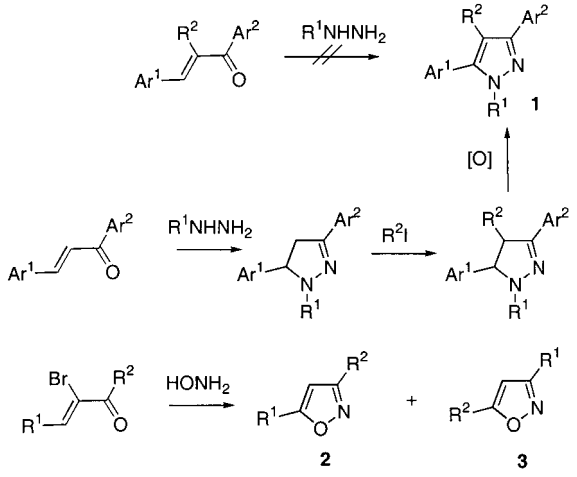
Introduction

The wide range of biological activities of pyrazoles[1a−f] and isoxazoles[1d,e,g,h] has made them popular synthetic targets. Numerous methods for the synthesis of these heterocycles involve approaches based on either (i) intermolecular [2 + 3] cycloadditions of 1,3-dipoles to alkynes,[1h,2a−c] or (ii) condensations of hydrazines[2a,d−g] or hydroxylamine[2a,g,h] with *β*-diketone equivalent three carbon 1,3-difunctionalized units bearing *sp* or sp^2 carbons, such as propargylic ketones. Although very frequently used, both those routes can give mixtures of regioisomers (Scheme 1).

Scheme 1



Scheme 2



Several regioselective methods exist for the preparation of pyrazoles;[1f,2d,i−l] however, the only regioselective synthesis of 1,3,5-triaryl-4-alkylpyrazoles **1** reported is the alkylation of the corresponding 1,3,5-triarylpyrazolines[1f] (Scheme 2). Previous regioselective syntheses of isoxazoles[3a,b] employ α-bromo-α,*β*-unsaturated ketones and hydroxylamine; the α-bromine atom behaves as a leaving group and allows for the direct transformation

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Scheme 3

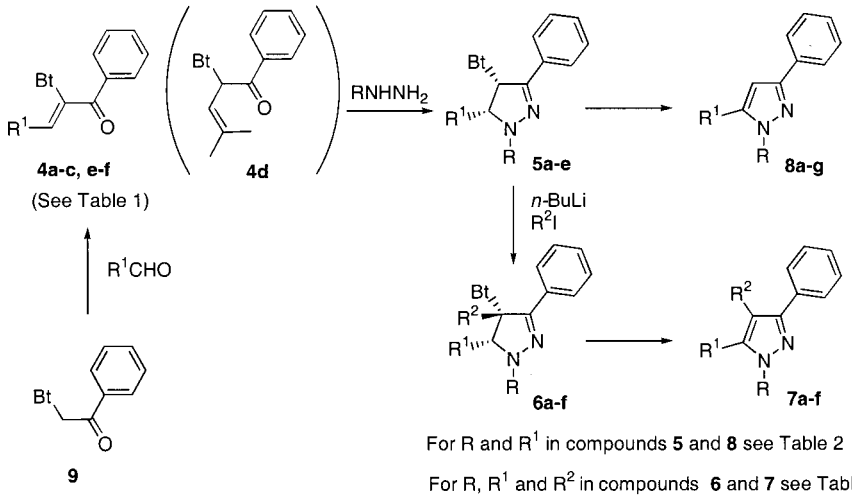

Table 1. α-Benzotriazolyl-α,β-unsaturated Ketones 4

entry	R^1	mp (°C)	yield (%)
4a	Ph	96−99	71
4b	*p*-Tol	145−146	66
4c	3-Py	114−116	55
4d	*i*-Pr	144−145	64
4e	4-$MeOC_6H_4$	−	64
4f	4-ClC_6H_4	121−122	59

Table 2. Δ^2-Pyrazolines 5 and Pyrazoles 8

entry	R^1	R	mp (°C)	yield (%)
5a	Ph	Ph	220−221	80
5b	Ph	Me	129−130	51
5c	*p*-Tol	Ph	200−201	78
5d	*p*-Tol	Me	155−157	68
5e	3-Py	Ph	250−251	75
8a	Ph	Ph	139−140	84
8b	Ph	Me	59−61	90
8c	*p*-Tol	Ph	115−117	81
8d	*p*-Tol	Me	138−139	86
8e	3-Py	Ph	115−117	94
8f	*i*-Pr	Ph	oil	60
8g	*i*-Pr	Me	oil	50

of the initially formed isoxazolines into the aromatic isoxazoles **2** and **3** (Scheme 2). The ratio of the two products **2** and **3** depends on the substituents at the β-position of enones and the base used as a catalyst.[3b] The methods mentioned above offer variable versatility, convenience, and yields.

We now report that trisubstituted pyrazoles **8** can be conveniently prepared from α-benzotriazolyl-α,β-unsaturated ketones **4** and monosubstituted hydrazines *via* intermediates **5**. Advantageously, in addition to its leaving group ability, the benzotriazolyl moiety renders the α-hydrogen acidic and thus allows for its replacement using an electrophilic reagent,[4] so that **5** can be further functionalized to afford tetrasubstituted pyrazoles **7a**−**f** *via* intermediates **6a**−**f** (Scheme 3).

Results and Discussion

Preparation of α-benzotriazolyl-α,β-unsaturated Ketones (*Z*)-4a−f. The starting α-benzotriazolyl-α,β-unsaturated ketones *Z*-**4a**−**f** were generated stereoselectively in good yields from benzotriazolylacetophenone **9** and the corresponding aldehyde using piperidine as a base (Table 1, Scheme 3). The *Z*-configuration of the double bond was demonstrated by the X-ray crystal structure determination of **4c** (Supporting Information). In compound **4c,** the 3-pyridyl substituent is disordered over two conformations in the solid state. In the case of **4d**, the surprising shift of the double bond was evidenced by the ^{1}H NMR spectrum (δ 5.96 ppm, 1H, dt, J = 8.8, 1.5 Hz, olefinic proton; δ 1.82 and 1.84 ppm, s and d, J = 1.5 Hz, 2 × CH_3). This was explained by steric peculiarities of the structure of **4d** and also confirmed by X-ray crystallography (Supporting Information).

Preparation of Dihydropyrazoles 5a−e and Trisubstituted Pyrazoles 8a−g. Compounds **4a**−**c** react regio- and stereoselectively with *N*-phenyl- or *N*-methylhydrazine in the presence of a catalytic amount of NaOEt in ethanol to form the stable intermediates **5a**−**e** in 51−80% yields (Scheme 3, Table 2). We found that *N*-phenylhydrazine consistently gave higher yields than the more volatile *N*-methylhydrazine. This reaction yields a single 1,3,5-trisubstituted pyrazole regioisomer; no products of the alternative regiochemistry of addition were detected. According to ^{1}H NMR spectra and NOE experiments (Figure 1), the stereochemical relation of R^1 and Bt in **5** appears to be exclusively *syn*. Irradiation of H-4 at δ 6.72 ppm (d, J = 4.15 Hz, 1H) in **5c** (*N*-phenyl derivative) displays the correlation between H-4 and H-5 (δ 5.40 ppm, d, J = 4.15 Hz, 1H). Similar results were obtained for **5d** (*N*-methyl derivative) although the $J_{4,5}$ coupling constant is larger than that in **5c**. Thus, NOE correlation between H-4 (δ 6.65 ppm, d, J = 9.7 Hz) and H-5 (4.61 ppm, d, J = 9.7 Hz) was observed on the irradiation of H-4 in **5d**. The formation of these *syn* products may be explained by the *cis* stereochemistry of the starting material **4**. The observed diastereoselective protonation rules out an enamine intermediate which could easily be protonated from either face.

When **4d** (β,γ-unsaturated ketone) was treated with hydrazines, the reaction proceeded directly to the corresponding pyrazoles **8f** and **8g** with no intermediate pyrazolines **5f** and **5g** observed. Dihydropyrazoles (pyrazolines) **5a**−**e** can be further converted to trisubstituted pyrazoles **8a**−**e** by treatment with a mild base in 81−94% yields. The structures of **8a**,[5] **8b**,[6] **8c**,[7] **8d**,[8] and **8e**[5]

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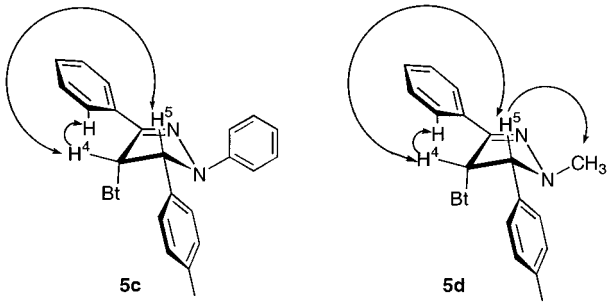
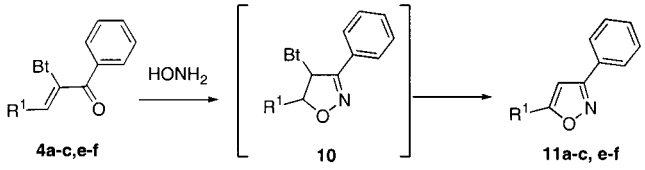


Figure 1. NOE correlations of **5c** and **5d**.

Table 3. Δ²-Pyrazolines 6 and Pyrazoles 7

entry	R	R¹	R²	mp (°C)	yield (%)
6a	Ph	Ph	Me	184−185	88
6b	Ph	*p*-Tol	Me	184−186	73
6c	Me	*p*-Tol	Me	138−140	95
6d	Ph	*p*-Tol	*n*-Bu	171−172	87
6e	Ph	*p*-Tol	allyl	195−196	84
6f	Ph	*p*-Tol	benzyl	155−157	91
7a	Ph	Ph	Me	123−124	91
7b	Ph	*p*-Tol	Me	134−135	85
7c	Me	*p*-Tol	Me	98−99	99
7d	Ph	*p*-Tol	*n*-Bu	−	95
7e	Ph	*p*-Tol	allyl	−	93
7f	Ph	*p*-Tol	benzyl	129−130	95

Scheme 4



were assigned by comparison with their literature spectroscopic data.

Tetrasubstituted Pyrazoles 7a−f. Compounds **5a−c** were further functionalized by alkylation at the 4-position with alkyl iodides in the presence of *n*-BuLi to afford derivatives **6a−f** in 73−95% yields. The structure of **6b** was initially assigned by NOE experiments; the regio- and stereochemistry were established unambiguously by X-ray structure determination (Supporting Information). Apparently, the alkylations take place with retention of the stereochemistry at C-4. Treatment of **6a−f** with NaOEt or *t*-BuOK yielded the desired 1,3,4,5-tetrasubstituted pyrazoles **7a**[9] and **7b−f** in 85−99% yields (Table 3).

Preparation of Isoxazoles 11a−c,e−f. In an extension of this methodology to the synthesis of trisubstituted isoxazoles, a number of disubstituted isoxazoles **11** were regioselectively prepared in 55−81% yields by treatment of **4** with hydroxylamine in THF (Scheme 4, Table 4). The structures of **11c**[10] and **11f**[10a,11] were examined by single-crystal X-ray crystallography. Surprisingly, the isoxazole **11c** crystallizes with the molecule lying on a crystallographic 2-fold rotation axis. As the result, the N/O atoms and the phenyl/pyridyl rings are each superimposed in the asymmetric unit. Hence the X-ray determination does not distinguish between the two isomeric possibilities for this compound, despite the excellent level of data refinement. No such problem exists for **11f**, which crystallizes with a whole molecule in the asymmetric unit, and the structure is unambiguously established as the 5-(4-chlorophenyl) isomer (Supporting Information).

Table 4. 3-Phenylisoxazoles 11

entry	R¹	mp (°C)	yield (%)
11a	Ph	140−141	61
11b	*p*-Tol	135−136	79
11c	3-Py	143−144	81
11e	4-$MeOC_6H_4$	126−127	71
11f	4-ClC_6H_4	177−179	55

In contrast to the preparation of pyrazoles, no stable adduct **10** was isolated and the reaction proceeded directly to **11**. The lower stability of **10** in comparison with that of **5** may be explained by the ease of BtH elimination due to the greater acidity of H-5 of the ring.

In conclusion, tri- and tetrasubstituted pyrazolines and pyrazoles and disubstituted isoxazoles are readily available from α-benzotriazolyl-α,β-unsaturated ketones in regio- and stereoselective and efficient fashion.

Experimental Section

General Methods. Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) and ^{13}C (75 MHz) NMR. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere. Column chromatography was conducted with silica gel (230−400 mesh).

General Procedure for the Preparation of Compounds 4a−f. To a solution of an aldehyde (2.55 mmol) and piperidine (0.11 g, 1.25 mmol) in ethanol (20 mL) was added 2-(benzotriazol-1-yl)-1-phenylethanone **9** (0.59 g, 2.5 mmol) to give a suspension. The reaction was monitored by TLC and completed in about 40 h. Ethanol was removed under reduced pressure, and the desired product was purified by column chromatography (hexane:ethyl acetate 4:1).

(*Z*)-2-(Benzotriazol-1-yl)-1,3-diphenyl-2-propen-1-one (4a). Yellow plates from methanol (71%), mp 96−99 °C; ^1H NMR δ 8.12−8.09 (dd, J = 8.3, 1.1 Hz, 1H), 7.82−7.79 (m, 3H), 7.58−7.11 (m, 9H), 6.85 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 191.4, 146.0, 142.2, 136.9, 133.4, 133.2, 131.6, 131.5, 131.4, 130.5, 129.4, 129.2, 128.9, 128.6, 124.6, 120.4, 110.3. Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.51; H, 4.63; N, 12.57.

(*Z*)-2-(Benzotriazol-1-yl)-3-(4-methylphenyl)-1-phenyl-2-propen-1-one (4b). Yellow microcrystals from ethanol (66%), mp 145−146 °C; ^1H NMR δ 8.09−8.05 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.50 (dd, J = 7.6, 7.3 Hz, 1H), 7.40−7.27 (m, 4H), 7.21 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.67 (d, J = 8.3 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR δ 190.8, 145.4, 142.3, 141.9, 136.5, 132.8, 132.4, 130.0, 129.9, 129.3, 128.7, 128.2, 128.0, 127.9, 123.9, 119.6, 109.7, 21.1. Anal. Calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.47; H, 5.03; N, 12.33.

(*Z*)-2-(Benzotriazol-1-yl)-1-phenyl-3-(3-pyridinyl)-2-propen-1-one (4c). Yellow microcrystals from methanol−chloro-

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form (55%), mp 114−116 °C; ^{1}H NMR δ 8.41−8.40 (m, 1H), 8.29 (s, 1H), 8.06−8.03 (m, 1H), 7.82−7.79 (m, 3H), 7.53−7.40 (m, 1H), 7.38−7.21 (m, 5H), 6.99−6.90 (m, 2H); ^{13}C NMR δ 189.9, 150.9, 150.7, 145.2, 137.4, 135.6, 135.5, 132.7, 132.4, 132.3, 128.6, 128.5, 128.2, 127.0, 124.0, 123.1, 119.7, 109.4. Anal. Calcd for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.75; H, 4.34; N, 17.35.

Crystal data for 4c: $C_{20}H_{14}N_4O$, MW 326.35, monoclinic, space group $P2_1/c$, a = 11.063(5), b = 12.156(6), c = 12.200(6) Å, β = 97.391(5) °, V = 1627(1) Å^3, F(000) = 680, Z = 4, T = −105 °C, μ (Mo Kα) = 0.086 mm^{-1}, D_{calcd} = 1.332 g cm^{-3}, $2\theta_{max}$ 53° (CCD area detector, Mo Kα radiation), GOF = 1.02, $wR(F^2)$ = 0.1079 (all 3351 data), R = 0.0401 (2873 data with $I > 2\sigma I$).

(*Z*)-2-(Benzotriazol-1-yl)-4-methyl-1-phenyl-3-penten-1-one (4d). Colorless needles from hexanes−ethyl acetate (64%), mp 144−145 °C; ^{1}H NMR δ 8.05−8.02 (m, 3H), 7.62−7.55 (m, 2H), 7.49−7.41 (m, 3H), 7.37−7.30 (m, 2H), 5.98−5.94 (dt, J = 8.8, 1.5 Hz, 1H), 1.84 (s, 3H), 1.82 (d, J = 1.5 Hz, 3H); ^{13}C NMR δ 193.1, 146.3, 143.5, 134.0, 133.9, 132.6, 128.8, 127.3, 123.8, 119.9, 115.9, 111.2, 62.8, 25.8, 18.5. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.25; H, 6.01; N, 14.54.

Crystal data for 4d: $C_{18}H_{17}N_3O$, MW 291.35, monoclinic, space group $P2_1/c$, a = 17.387(7), b = 8.447(3), c = 10.587(4) Å, β = 100.016(5)°, V = 1531(1) Å^3, F(000) = 616, Z = 4, T = −105 °C, μ (Mo Kα) = 0.081 mm^{-1}, D_{calcd} = 1.264 g cm^{-3}, $2\theta_{max}$ 53° (CCD area detector, Mo Kα radiation), GOF = 0.999, $wR(F^2)$ = 0.0997 (all 3097 data), R = 0.0379 (2189 data with $I > 2\sigma I$).

(*Z*)-2-(Benzotriazol-1-yl)-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one (4e). Foam (64%); ^{1}H NMR δ 8.10−8.07 (d, J = 8.2 Hz, 1H), 7.81−7.76 (m, 3H), 7.52−7.47 (t, J = 6.2 Hz, 1H), 7.41−7.29 (m, 4H), 7.25−7.20 (m, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 3.60 (s, 3H); ^{13}C NMR δ 190.9, 161.8, 145.4, 142.6, 136.7, 132.8, 132.3, 132.2, 128.6, 128.5, 128.2, 128.0, 124.0, 123.1, 119.6, 114.1, 109.7, 54.9. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.29; H, 5.01; N, 11.53.

(*Z*)-2-(Benzotriazol-1-yl)-3-(4-chorophenyl)-1-phenyl-2-propen-1-one (4f). Yellow microcrystals from methanol (59%), mp 121−122 °C; ^{1}H NMR δ 8.14−8.11 (m, 1H), 7.80−7.74 (m, 3H), 7.62−7.53 (m, 1H), 7.45−7.36 (m, 4H), 7.20−7.12 (m, 3H), 6.77 (d, J = 0.6 Hz, 2H); ^{13}C NMR δ 190.8, 145.7, 140.1, 1347.4, 136.4, 133.0, 132.9, 131.5, 131.3, 129.7, 129.2, 129.0, 128.6, 128.5, 124.5, 120.3, 109.8. Anal. Calcd for $C_{21}H_{14}ClN_3O$: C, 70.10; H, 3.92; N, 11.68. Found: C, 70.04; H, 3.80; N, 11.66.

General Procedure for the Preparation of Compounds 5a−e. To a freshly prepared solution of NaOEt in ethanol (by dissolving 10 mg of sodium metal in 20 mL of ethanol) was added a hydrazine (3 mmol) followed by the corresponding **4** (2 mmol). The reaction mixture was heated under reflux overnight. Subsequent workup and purification by column chromatography afforded **5a**−**e**.

***cis*-1-(1,3,5-Triphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)benzotriazole (5a).** Yellow needles from methanol (80%), mp 220−221 °C; ^{1}H NMR δ 8.07−8.04 (m, 1H), 7.68−7.65 (m, 2H), 7.40−7.18 (m, 15H), 6.93−6.88 (m, 1H), 6.75 (d, J = 3.9 Hz, 1H), 5.45 (d, J = 3.9 Hz, 1H); ^{13}C NMR δ 147.0, 142.5, 140.9, 137.8, 131.0, 130.4, 129.7, 129.3, 129.0, 128.8, 128.7, 128.5, 125.8, 125.5, 124.5, 120.5, 120.4, 113.5, 109.8, 71.9, 70.2. Anal. Calcd for $C_{27}H_{21}N_5$: C, 78.05; H, 5.09; N, 16.86. Found: C, 78.16; H, 4.97; N, 16.76.

***cis*-1-(1-Methyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)benzotriazole (5b).** Colorless needles from methanol (51%), mp 129−130 °C; ^{1}H NMR δ 8.07−8.04 (d, J = 7.8 Hz, 1H), 7.52−7.49 (m, 1H), 7.42−7.31 (m, 7H), 7.22−7.19 (m, 2H), 7.16−7.13 (m, 3H), 6.67 (d, J = 9.8 Hz, 1H), 4.63 (d, J = 9.7 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR δ 146.6, 142.8, 137.2, 131.5, 130.6, 129.1, 128.7, 128.6, 127.8, 126.9, 124.9, 124.2, 120.4, 110.0, 77.0, 72.8, 40.5. Anal. Calcd for $C_{29}H_{25}N_5$: C, 74.77; H, 5.42; N, 19.82. Found: C, 74.85; H, 5.12; N, 19.49.

***cis*-1-[5-(4-Methylphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (5c).** White needles from methanol (78%), mp 200−201 °C; ^{1}H NMR δ 8.06−8.03 (m, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.33−7.15 (m, 14H), 6.92−6.88 (m, 1H), 6.72 (d, J = 4.2 Hz, 1H), 5.40 (d, J = 4.2 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR δ 146.9, 142.5, 140.8, 138.5, 134.8, 130.9, 130.4, 130.3, 129.2, 128.9, 128.7, 128.4, 125.6, 125.4, 124.4, 120.4, 120.3, 113.5, 109.8, 72.0, 70.0, 21.1. Anal. Calcd for $C_{28}H_{23}N_5$: C, 78.30; H, 5.40; N, 16.30. Found: C, 78.29; H, 5.76; N, 16.29.

***cis*-1-[1-Methyl-5-(4-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (5d).** White needles from methanol (68%), mp 155−157 °C; ^{1}H NMR δ 8.06 (d, J = 8.0 Hz, 1H), 7.52−7.49 (d, J = 8.0 Hz, 1H), 7.42−7.34 (m, 4H), 7.17−7.08 (m, 7H), 6.65 (d, J = 9.7 Hz, 1H), 4.61 (d, J = 9.8 Hz, 1H), 3.08 (s, 3H), 2.35 (s, 3H); ^{13}C NMR δ 146.7, 142.8, 138.5, 134.2, 131.5, 130.7, 129.8, 128.6, 127.8, 126.9, 124.9, 124.2, 120.3, 110.1, 76.5, 72.8, 40.9, 21.1. Anal. Calcd for $C_{23}H_{21}N_5$: C, 75.18; H, 5.76; N, 19.06. Found: C, 75.28; H, 5.98; N, 19.18.

***cis*-1-[1,3-Diphenyl-5-(3-pyridinyl)-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (5e).** White needles from methanol−chloroform (75%), mp 250−251 °C; ^{1}H NMR δ 8.63 (m, 2H), 8.07−8.04 (m, 1H), 7.68−7.65 (m, 2H), 7.58−7.55 (m, 1H), 7.34−7.16 (m, 11H), 6.93 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 3.9 Hz, 1H), 5.5 (d, J = 3.8 Hz, 1H); ^{13}C NMR δ 150.2, 147.9, 146.9, 142.1, 141.0, 133.5, 130.8, 129.9, 129.4, 129.2, 128.8, 128.6, 125.5, 124.5, 124.2, 120.9, 120.4, 113.5, 109.5, 71.5, 68.0. Anal. Calcd for $C_{26}H_{20}N_6$: C, 74.98; H, 4.84; N, 20.18. Found: C, 74.87; H, 4.95; N, 20.10.

General Procedure for the Preparation of Compounds 8f and 8g. To a freshly prepared solution of NaOEt in ethanol (by dissolving 5 mg of sodium metal in 20 mL of ethanol) was added the corresponding hydrazine (1.5 mmol) followed by **4d** (1.2 mmol). The reaction mixture was heated under reflux overnight. Then ethanol was evaporated *in vacuo* to dryness. Purification of the residue by column chromatography afforded **8f** and **8g** in 50−60% yields.

5-Isopropyl-1,3-diphenyl-1*H*-pyrazole (8f). Oil (60%); ^{1}H NMR δ 7.28−7.19 (m, 10H), 6.34 (s, 1H), 3.10 (m, 1H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR δ 159.7, 143.2, 140.1, 130.8, 128.7, 128.5, 128.2, 127.8, 126.8, 125.0, 104.7, 27.8, 22.8. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.20; H, 7.10; N, 10.98.

5-Isopropyl-1-methyl-3-phenyl-1*H*-pyrazole (8g). Oil (50%); ^{1}H NMR δ 7.60−7.52 (m, 5H), 6.29 (s, 1H), 3.99 (s, 3H), 3.19 (m, 1H), 1.48 (d, J = 7.0 Hz, 6H); ^{13}C NMR δ 157.9, 143.7, 130.7, 128.3, 128.2, 127.9, 102.4, 36.8, 27.6, 22.7. HRMS (FAB) Calcd for $C_{13}H_{16}N_2$ $[M + 1]^+$: 201.1391. Found: 201.1382.

General Procedure for the Preparation of Compounds 6a−f. To a solution of a compound **5a**−**c** (0.5 mmol) in THF (20 mL) was added *n*-BuLi solution (1.5 M, 0.34 mL, 0.5 mmol) dropwise at −78 °C. After 10 min, R^2I (0.5 mmol) was added. The reaction mixture was stirred and allowed to warm up to room-temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with H_2O, and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to dryness. The residue was purified by column chromatography affording the corresponding products **6a**−**f** in 73−95% yields.

***cis*-1-(4-Methyl-1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)benzotriazole (6a).** White needles from methanol (88%), mp 184−185 °C; ^{1}H NMR δ 7.77−7.74 (m, 1H), 7.43 (d, J = 7.8 Hz, 2H), 7.34−7.31(m, 1H), 7.23−7.09 (m, 10H), 6.92−6.78 (m, 5H), 5.30 (s, 1H), 2.66 (s, 3H); ^{13}C NMR δ 146.3, 143.8, 132.5, 130.5, 128.9, 128.7, 128.3, 127.8, 127.0, 126.5, 125.8, 123.5, 120.8, 119.4, 114.8, 112.4, 75.9, 27.2. Anal. Calcd for $C_{28}H_{23}N_5$: C, 78.30; H, 5.40; N, 16.30. Found: C, 78.42; H, 5.81; N, 15.92.

***cis*-1-[4-Methyl-5-(4-methylphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (6b).** Yellow needles from methanol (73%), mp 184−186 °C; ^{1}H NMR δ 8.13 (d, J = 8.3 Hz, 1H), 7.45−7.42 (d, J = 8.4 Hz, 1H), 7.36−7.29 (m, 4H), 7.26−7.13 (m, 10H), 6.92 (t, J = 7.1 Hz, 2H), 5.37 (s, 1H), 2.34 (s, 3H), 1.91 (s, 3H); ^{13}C NMR δ 147.2, 146.2, 144.1, 138.4, 131.9, 131.3, 130.1, 129.7, 128.9, 128.9, 128.6, 127.9, 127.2, 125.6, 124.4, 120.9, 120.4, 115.2, 111.2, 76.2, 75.9, 21.3, 21.2. Anal. Calcd for $C_{29}H_{25}N_5$: C, 78.53; H, 5.68; N, 15.79. Found: C, 78.17; H, 5.67; N, 15.82.

Crystal data for 6b: $C_{29}H_{25}N_5$, MW 443.54, monoclinic, space group $P2_1/c$, a = 10.349(3), b = 12.211(3), c = 17.921(4)

Å, $\beta = 97.260(4)^{\circ}$, $V = 2247(1)$ Å^3, $F(000) = 936$, $Z = 4$, $T = -110$ °C, μ (Mo Kα) = 0.080 mm^{-1}, $D_{calcd} = 1.311$ g cm^{-3}, $2\theta_{max}$ 50° (CCD area detector, Mo Kα radiation), GOF = 1.06, $wR(F^2) = 0.1268$ (all 3959 data), $R = 0.0467$ (2837 data with $I > 2\sigma I$).

***cis*-1-[1,4-Dimethyl-5-(4-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (6c).** Needles from methanol (95%), mp 138−140 °C; ^{1}H NMR δ 8.13−8.11 (m, 1H), 7.69−7.67 (m, 1H), 7.35−7.10 (m, 9H), 6.80 (m, 2H), 4.65 (s, 1H), 3.07 (s, 3H), 2.33 (s, 3H), 1.85 (s, 3H); ^{13}C NMR δ 148.4, 147.1, 138.4, 132.0, 130.1, 129.8, 129.3, 128.8, 128.5, 127.6, 127.3, 125.0, 124.1, 120.4, 111.9, 81.4, 76.3, 41.1, 21.1, 18.6. Anal. Calcd for $C_{24}H_{23}N_5$: C, 75.56; H, 6.08; N, 18.36. Found: C, 75.83; H, 6.38; N, 17.96.

***cis*-1-[4-Butyl-5-(4-methylphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (6d).** Needles from methanol (87%), mp 171−172 °C; ^{1}H NMR δ 7.75−7.72 (m, 1H), 7.46 (d, $J = 7.9$ Hz, 2H), 7.39−7.37 (m, 1H), 7.24−7.07 (m, 9H), 6.88 (t, $J = 7.0$ Hz, 1H), 6.74 (br s, 2H), 6.55 (br s, 2H), 5.35 (s, 1H), 3.30−3.22 (m, 1H), 3.07−2.99 (m, 1H), 1.98 (s, 3H), 1.53−1.26 (m, 4H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ 146.2, 143.6, 137.8, 133.4, 131.2, 129.7, 128.9, 128.6, 128.2, 126.8, 126.4, 125.3, 123.3, 120.5, 119.3, 114.7, 112.7, 112.1, 79.6, 73.6, 37.9, 26.5, 22.6, 20.8, 13.7. Anal. Calcd for $C_{32}H_{31}N_5$: C, 79.14; H, 6.43; N, 14.42. Found: C, 79.18; H, 6.57; N, 14.55.

***cis*-1-[4-Allyl-5-(4-methylphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (6e).** Needles from methanol (84%), mp 195−196 °C; ^{1}H NMR δ 7.78−7.75 (m, 1H), 7.44−7.40 (m, 3H), 7.23−7.08 (m, 9H), 6.87 (t, $J = 7.0$ Hz, 1H), 6.72 (br s, 2H), 6.58 (br s, 2H), 5.76−5.66 (m, 1H), 5.46 (s, 1H), 5.36 (d, $J = 6.9$ Hz, 1H), 5.23 (d, $J = 9.9$ Hz, 1H), 4.07−3.99 (m, 1H), 3.80 (d, $J = 4.6$ Hz, 1H), 3.76 (d, $J = 4.9$ Hz, 1H), 1.99 (s, 3H); ^{13}C NMR δ 146.2, 143.6, 143.3, 137.8, 133.5, 131.7, 130.9, 129.6, 128.8, 128.7, 128.3, 127.0, 126.4, 125.5, 123.4, 121.7, 120.6, 119.3, 114.8, 78.6, 72.5, 42.1, 20.8. Anal. Calcd for $C_{31}H_{27}N_5$: C, 79.29; H, 5.80; N, 14.91. Found: C, 79.39; H, 5.72; N, 15.02.

***cis*-1-[4-Benzyl-5-(4-methylphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl]benzotriazole (6f).** Needles from methanol−chloroform (91%), mp 155−157 °C; ^{1}H NMR δ 7.76 (d, $J = 7.9$ Hz, 1H), 7.47−7.44 (m, 2H), 7.28−7.03 (m, 14H), 6.86 (d, $J = 8.2$ Hz, 2H), 6.79−6.72 (m, 3H), 6.55 (d, $J = 7.6$ Hz, 2H), 5.56 (s, 1H), 4.67 (d, $J = 14.0$ Hz, 1H), 4.39 (d, $J = 14.3$ Hz, 1H), 1.97 (s, 3H); ^{13}C NMR δ 146.3, 143.0, 142.8, 137.8, 134.3, 133.6, 131.8, 130.9, 129.8, 128.8, 128.6, 128.3, 127.5, 126.7, 126.4, 125.6, 123.4, 120.3, 119.2, 114.3, 113.0, 80.3, 72.3, 42.9, 20.8. Anal. Calcd for $C_{35}H_{29}N_5$: C, 80.90; H, 5.62; N, 13.48. Found: C, 80.76; H, 5.58; N, 13.67.

General Procedure for the Preparation of Compounds 7a−f. To a freshly prepared solution of NaOEt in ethanol (12 mg of sodium metal in 10 mL of ethanol) or *t*-BuOK (58 mg, 0.52 mmol) in toluene (10 mL) was added the corresponding compound **6a−f** (0.26 mmol). The reaction mixture was refluxed (in the case of EtONa/EtOH) or heated at 70 °C (for *t*-BuOK/toluene) overnight and then evaporated *in vacuo* to dryness. The residue was purified by column chromatography affording **7a−f** in 85−99% yields.

4-Methyl-5-(4-methylphenyl)-1,3-diphenyl-1*H*-pyrazole (7b). Needles from ethanol (85%), mp 134−135 °C; ^{1}H NMR δ 7.80 (d, $J = 7.0$ Hz, 2H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.37−7.10 (m, 10H), 2.36 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 151.1, 141.4, 140.2, 137.9, 133.8, 129.8, 129.1, 128.6, 128.3, 127.8, 127.5, 126.6, 125.7, 125.2, 124.7, 113.9, 21.3, 10.2. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.35; H, 6.47; N, 8.69.

1,4-Dimethyl-5-(4-methylphenyl)-3-phenyl-1*H*-pyrazole (7c). Needles from ethanol (99%), mp 98−99 °C; ^{1}H NMR δ 7.72 (d, $J = 8.4$ Hz, 2H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.34−7.23 (m, 5H), 3.79 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H); ^{13}C NMR δ 149.1, 142.4, 138.3, 134.2, 129.7, 129.3, 128.3, 127.5, 127.4, 127.1, 111.9, 37.1, 21.2, 10.0. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.33; H, 7.30; N, 10.26.

4-Butyl-5-(4-methylphenyl)-1,3-diphenyl-1*H*-pyrazole (7d). Oil (95%); ^{1}H NMR δ 7.79−7.75 (m, 2H), 7.47−7.41 (m, 2H), 7.38−7.09 (m, 10H), 2.62 (t, $J = 7.8$ Hz, 2H), 2.36 (s, 3H), 1.43−1.33 (m, 2H), 1.25−1.15 (m, 2H), 0.75 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR δ 150.9, 141.4, 140.1, 137.9, 134.2, 129.9, 129.2, 128.5, 128.3, 127.9, 127.8, 127.5, 126.5, 124.6, 119.4, 32.8, 23.4, 22.5, 21.3, 13.6. Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.20; H, 7.17; N, 7.65. Found: C, 85.05; H, 6.94; N, 7.72.

4-Allyl-5-(4-methylphenyl)-1,3-diphenyl-1*H*-pyrazole (7e). Oil (93%); ^{1}H NMR δ 7.75 (dd, $J = 8.5$, 1.4 Hz, 2H), 7.38−7.06 (m, 12H), 5.98−5.89 (m, 1H), 5.06−4.92 (m, 2H), 3.27−3.24 (m, 2H), 2.28 (s, 3H); ^{13}C NMR δ 151.4, 142.0, 140.2, 138.2, 137.7, 133.6, 129.7, 129.1, 128.6, 128.3, 127.9, 127.6, 127.5, 126.7, 124.7, 115.8, 115.7, 28.2, 21.3. Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.66; H, 6.34; N, 7.99. Found: C, 85.33; H, 6.60; N, 7.93.

4-Benzyl-5-(4-methylphenyl)-1,3-diphenyl-1*H*-pyrazole (7f). Needles from hexanes−ethyl acetate (95%), mp 129−130 °C; ^{1}H NMR δ 7.66 (d, $J = 6.7$ Hz, 2H), 7.36−7.11 (m, 13H), 7.07−6.99 (m, 4H), 3.99 (s, 2H), 2.31 (s, 3H); ^{13}C NMR δ 151.6, 142.4, 141.4, 140.2, 138.2, 133.6, 129.7, 129.2, 128.6, 128.3, 128.1, 127.8, 127.6, 127.5, 126.7, 125.8, 124.7, 116.5, 29.8, 21.2. Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.96; H, 6.05; N, 7.00. Found: C, 86.75; H, 6.27; N, 7.07.

Supporting Information Available: Experimental procedures and characterization data for compounds **8a−e**, **7a**, **11a−c**, and **11e−f**; X-ray data for **4c−d**, **6b** and **11c**, **f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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