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Novel and Convenient Routes to Substituted Pyrroles and Imidazoles

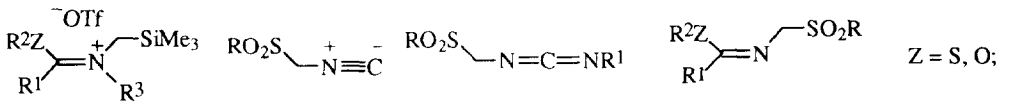
Alan R. Katritzky,* Lie Zhu, Hengyuan Lang, Olga Denisko and Zuoquan Wang

Center for Heterocyclic Compounds, Department of Chemistry,
University of Florida, Gainesville, FL 32611-7200, USA

Abstract: *S-Methyl N-(benzotriazol-1-ylmethyl)thioimidate* ***6*** *is obtained by lithiation of the corresponding N-(benzotriazol-1-ylmethyl)thioamide* ***5*** *and subsequent reaction with methyl iodide. Derivative* ***6*** *undergoes [2 + 3] cycloaddition reactions with α,β-unsaturated -esters, -ketones and -nitriles, and vinylpyridines which are followed by elimination of benzotriazole and the thioalkoxy group, to give 2,3,4-trisubstituted pyrroles. Lithiation of* ***6*** *followed by reactions with imines gives cyclized 4,5-dihydroimidazoles* ***14*** *which upon further treatment with* $ZnBr_2$ *or direct refluxing in toluene yield the 1,2,5-trisubstituted imidazoles* ***15*** *in good yields.*

1,3-Dipolar and 1,3-anionic cycloaddition reactions are two very efficient approaches for the construction of five-membered heterocyclic systems, as shown by comprehensive investigations of the preparation of a wide array of non-aromatic aza-, oxa- and thia- heterocycles.[1-4] However, the utilization of such [3 + 2] cyclizations for the synthesis of aromatic azoles is less documented. Padwa[5,6] and Vedejs[7] reported the alkylation of imidates or thioimidates with (trimethylsilyl)methyl triflate, followed by cesium fluoride desilylation of the resulting salts **1** (Z = O or S) which afforded transient azomethine ylides that underwent subsequent 1,3-dipolar cycloaddition to acetylene-carboxylates or -dicarboxylates, followed by loss of the alkoxy or thioalkoxy groups to produce 1,2,3-tri-, 1,2,4-tri-, and 1,2,3,4-tetra-substituted pyrroles.

A convenient approach to the synthesis of *N*-unsubstituted pyrroles, oxazoles and imidazoles by van Leusen *et al.* utilized tosyl-substituted isonitriles **2**,[8-11] carbodiimides **3**,[12] and imidates **4**[13-15] as 1,3-anionic (or 1,3-dipolar) synthon precursors. These synthons have been employed for the synthesis of different disubstituted and trisubstituted derivatives. Mannich condensation of *p*-toluenesulfinic acid, formaldehyde and an amide followed by methylation with methyl fluorosulfonate gave *N*-tosylmethylimidates **4** which cycloadd to electron-deficient olefins, aldehydes and imines to prepare 2,3,4-trisubstituted pyrroles, 2,5-disubstituted oxazoles and 1,2,5-trisubstituted imidazoles[13-15] in variable yields (14-98%). However, this procedure requires the use of hazardous methyl fluorosulfonate and yields are not always satisfactory.



1 **2** **3** **4**

*Submitted in honor of the 80th anniversary of our evergreen friend Hans Suschitzky.

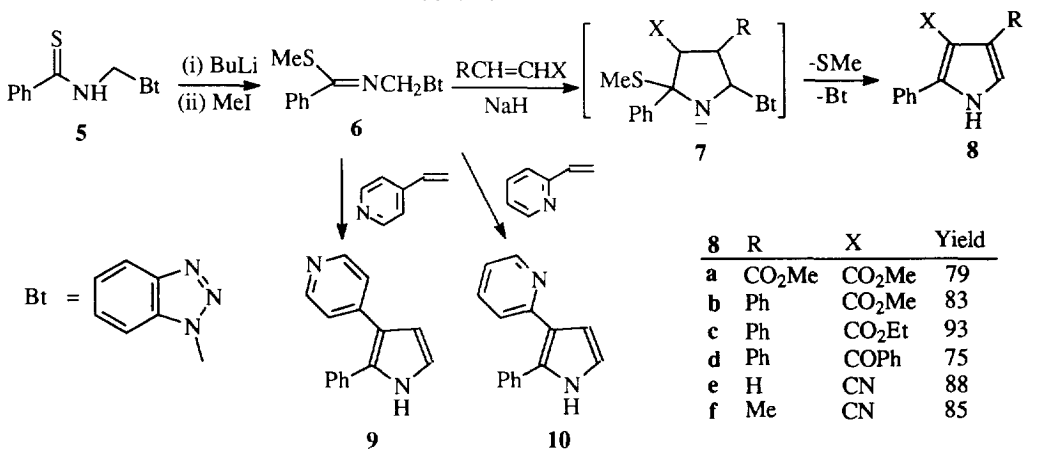
Work in our group has shown that benzotriazole is a good activating and leaving group.[16-19] In particular, benzotriazolylmethylaminomethylsilanes, the condensation products of benzotriazole, formaldehyde and (aminomethyl)silanes, are convenient precursors of azomethine ylides, which can undergo stereospecific cycloadditions with dipolarophiles to give 3,4-disubstituted pyrrolidines or 2,5-dihydropyrroles in good yield.[20] We have also shown that *N*-(benzotriazol-1-ylalkyl)thioamides can be prepared in high yields either from direct Mannich condensation of benzotriazole, an aldehyde and a thioamide or *via* lithiation of formaldehyde condensation products of type $BtCH_2NHCSR$. Subsequent displacement of benzotriazole provides a novel route for the *N*-alkylation of thioamides.[21-23] We have now found that treatment of the *N*-(benzotriazol-1-ylmethyl)thioamides with one equivalent of BuLi at - 78 °C in THF, followed by reaction with alkyl iodides affords the thioimidates in excellent yields. These thioimidates undergo cycloaddition reactions with Michael acceptors, including α,β-unsaturated esters, ketones and nitriles, and vinyl pyridines: in each case the addition was followed by elimination of benzotriazole and the thioalkoxy group, to give 2,3,4-trisubstituted pyrroles. Lithiation of **6** followed by reaction with imines gave cyclized 4,5-dihydro-1,3-imidazoles, which upon further treatment with $ZnBr_2$, or direct refluxing in toluene generated 1,2,5-trisubstituted imidazoles in good yields.

RESULTS AND DISCUSSION

N-(Benzotriazol-1-ylmethyl)thiobenzamide **5** was readily obtained by Mannich condensation of thiobenzamide, formaldehyde and benzotriazole according to the literature.[21-22] Treatment of **5** with one equivalent of BuLi in THF at -78 °C, followed by reaction with methyl iodide gave *S*-methyl thioimidate **6** in 87% yield. Pure **6** was obtained by washing the crude product after workup with a mixture of hexane and ethyl acetate. Compound **6** is stable to storage at ambient temperature indefinitely without special precautions.

Reactions of thioimidates **6** with a Michael acceptor in the presence of NaH gave the 2,3,4-trisubstituted pyrroles **8a-f** in 75-93% yields. Thus, stirring a mixture of **6**, dimethyl maleate and sodium hydride in THF and DMSO at 30-40 °C for 2 h, gave the expected 3,4-dimethoxycarbonyl-2-phenylpyrrole **8a** in 79% yield. The intermediates **7**, which cannot be isolated, underwent spontaneous elimination of BtH and MeS^- to generate the pyrroles **8**. The pyrrole derivatives **8b-f** were similarly prepared in good to excellent yields. When 4-vinylpyridine and 2-vinylpyridine were used, the expected 2-phenyl-3-(pyridin-4-yl)- **9** and 2-phenyl-3-(pyridin-2-yl)-pyrroles **10** were obtained in 64% and 36% yields, respectively. These reactions proceeded regiospecifically without formation of other isomers. However, when methyl vinyl ketone was

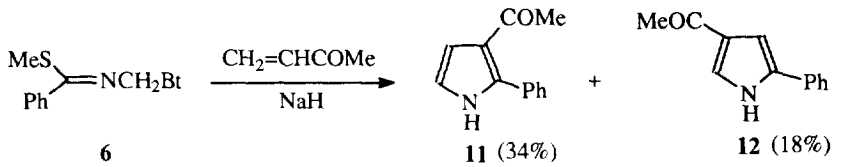
Scheme 1



8	R	X	Yield
a	CO_2Me	CO_2Me	79
b	Ph	CO_2Me	83
c	Ph	CO_2Et	93
d	Ph	COPh	75
e	H	CN	88
f	Me	CN	85

reacted with thioimidate **6** under similar conditions, two regioisomers **11** and **12** were generated in the ratio of *ca.* 1.5:1 (total yield 54%). Compounds of type **8** have been previously prepared by cycloaddition of *N*-(tosylmethyl)imino compounds of type **4** with Michael acceptors,[14] or by multi-step manipulation of aryl cyclopropyl ketones,[24] or *via* reaction of alkynes with aryloxazolones,[24] or by reaction of β-aminoenones with phenacylamine hydrochloride.[25-26] Comparing with these methods, the present approach gave higher yields and utilizes a short procedure.

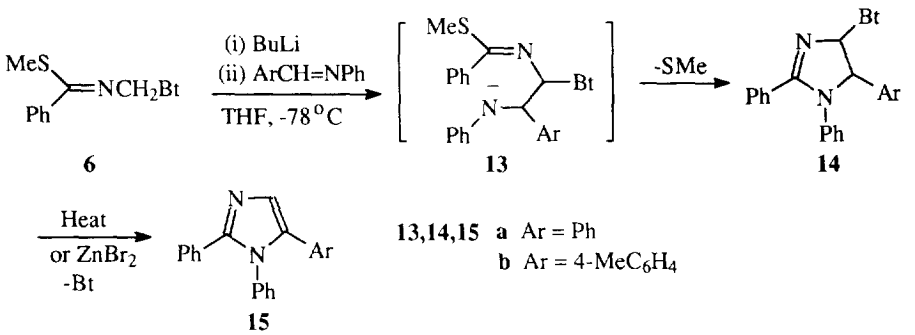
Scheme 2



6 **11** (34%) **12** (18%)

Under similar conditions, reaction of compound **6** with an imine does not produce the expected imidazoles. However, treatment of thioimidate **6** with BuLi in THF, followed by reaction with imine (PhCH=NPh) at room temperature gave 4,5-dihydroimidazole **14a** in 65% yield. Further treatment of this compound with $ZnBr_2$ in refluxing THF or direct refluxing in toluene afforded the expected 1,2,5-trisubstituted imidazole **15a** in 90% yield. Compound **15b** was similarly prepared in 70% overall yield.

Scheme 3



6 **13** **14** **15**

The structures of all products obtained were confirmed by ^1H, ^{13}C NMR spectra and elemental analysis or high resolution mass spectra. Data for known compounds have been compared with those reported in the literature. In cases of **8a-f, 9-12**, broad peaks for pyrrole NH were observed at 8.60-12.0 ppm, and their chemical shifts were affected by the concentration and existence of a small amount of water.

In conclusion, novel and convenient [2 + 3] cycloaddition precursors have been developed for the preparation of 2,3,4-trisubstituted, 2,3-disubstituted, and 2,5-disubstituted pyrroles, and for 1,2,5-trisubstituted imidazoles. Compared with preexisting literature methods, the present approach which employs inexpensive, non-hazardous (avoiding methyl fluorosulfonate) and readily available starting materials, and proceeds with higher yields, presents a viable alternative. However, the present method is restricted to aryl thioamides.

EXPERIMENTAL

General Comments. Melting points were determined on a hot stage apparatus. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini-300 spectrometer in $CDCl_3$ (unless otherwise stated) with TMS or $CDCl_3$, respectively, as the internal reference. Elemental analyses were performed using a Carlo Erba 1106 elemental analyzer. High resolution mass spectra were measured on an AEI-30 mass spectrometer. Column chromatography was carried out on MCB silica gel (230-400 mesh). Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone. Lithiation reactions were carried out under the protection of dry nitrogen.

Preparation of N-(Benzotriazol-1-ylmethyl)-α-(methylthio)phenylimine (6): To a solution of *N*-(benzotriazol-1-ylmethyl)thiobenzoamide **5** (10 mmol) in THF (70 mL) was added *n*-butyllithium (2 *M* in cyclohexane, 5 mL, 10 mmol) at -78 °C. The solution was stirred at this temperature for 10 min, then methyl iodide (1.42 g, 10 mmol) was added. The solution was kept at this temperature for another 30 min. After addition of water (50 mL), the solution was extracted with diethyl ether (150 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a lemon yellow solid which was washed with hexane/ethyl acetate (3:1) to give 2.56 g pure product (87% yield). This product is a mixture of *trans*- and *cis*- isomers (ratio of two isomers: *ca.* 1.5:1 from NMR). mp 133-134 °C. ^1H NMR δ 2.29 (s) and 2.33 (s) (total 3 H), 6.11 (s) and 6.33 (s) (total 2 H), 7.35-7.56 (m, 7 H), 7.65-7.68 (m, 1 H), 8.06-8.09 (m, 1 H); ^{13}C NMR δ 13.8 (16.9), 65.5 (65.6), 110.2 (110.4), 119.8, 123.9 (123.8), 126.8 (127.3), 128.1, 128.5 (128.9), 130.0 (130.2), 132.9 (133.0), 135.5 (136.7), 146.3 (146.4), 168.2 (171.5). Anal. Calcd for $C_{15}H_{14}N_4S$: C, 63.80; H, 5.00; N, 19.84. Found: C, 63.97; H, 5.02; N, 19.73.

General Procedure for the Preparation of Compounds 8a-f and 9-12: Sodium hydride (0.39 g, 95%, 15 mmol) was added to the solution of *N*-(benzotriazol-1-ylmethyl)-α-(methylthio)phenylimine **6** (1.45g, 5 mmol) and the appropriate Michael acceptor (6 mmol) at room temperature under nitrogen in a mixture of THF (20 ml) and DMSO (5 ml). The reaction mixture was stirred for 2 h at room temperature (**8b** and **8d**) or at 30 - 40 °C (**8a,c,e,f** and **9-12**). Then it was treated with water (30 ml), extracted with diethyl ether (200 ml) and dried over Mg_2SO_4. After evaporation of the solvents, the residue was chromatographed on silica gel with hexane/ethyl acetate (3:1) to give the expected product.

Dimethyl 2-phenylpyrrole-3,4-dicarboxylate (8a): yield 79%; mp 99-102 °C (Lit[24] mp 103-105 °C); ^1H NMR δ 3.77 (s, 3 H), 3.78 (s, 3 H), 7.22 (d, 1 H, *J* = 2.7 Hz), 7.27-7.41 (m, 5 H), 9.55-9.65 (br s, 1 H); ^{13}C NMR δ 51.4, 52.2, 113.5, 115.9, 124.3, 127.2, 128.2, 128.6, 130.7, 134.0, 164.3, 167.4.

Methyl 2,4-diphenylpyrrole-3-carboxylate (8b): yield 83%; mp 138-140 °C (Found: HRMS M^+ = 277.1129; $C_{18}H_{15}NO_2$ requires M = 277.1181); ^1H NMR δ 3.52 (s, 3 H), 6.64 (d, 1 H, *J* = 2.6 Hz), 7.20-7.48 (m, 11 H), 8.68-8.72 (br s, 1H); ^{13}C NMR δ 50.9, 117.5, 126.4, 127.6, 127.8, 128.1, 128.2, 128.5, 128.8, 132.3, 135.3, 137.0, 166.4.

Ethyl 2,4-diphenylpyrrole-3-carboxylate (8c). Obtained as an oil; yield 93%; ^1H NMR δ 0.94 (t, 3 H, *J* = 7.2 Hz), 4.00 (q, 2 H, *J* = 7.2 Hz), 6.59 (d, 1 H, *J* = 2.5), 7.20-7.48 (m, 10 H), 8.80-8.88 (br s, 1 H); ^{13}C NMR δ 13.6, 59.9, 117.4, 126.3, 127.5, 127.7, 127.9, 128.0, 128.7, 128.9, 132.4, 135.4, 136.9, 166.0. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.89; N, 4.81. Found: C, 78.10; H, 6.31; N, 4.98.

3-Benzoyl-2,4-phenylpyrrole (8d): yield 75%; mp. 179-181 °C, (Lit[25] 183-184 °C); ^1H NMR δ 6.99 (d, 1 H, *J* = 2.6 Hz), 7.08-7.40 (m, 13 H), 7.76 (d, 2 H, *J* = 7.0 Hz), 8.52-8.60 (br s, 1 H); ^{13}C NMR δ 115.6, 124.0, 124.7, 125.4, 126.0, 126.1, 126.3, 126.4, 126.5, 128.0, 130.5, 130.6, 132.6, 133.6, 137.2, 193.3.

2-Phenylpyrrole-3-carbonitrile (8e): yield, 88%; mp 166-167 °C; ^1H NMR (DMSO-d_6) δ 6.96 (d, 1 H, *J* = 1.6 Hz), 7.28 (t, 1 H, *J* = 7.4 Hz), 7.35-7.48 (m, 2 H), 7.68-7.74 (m, 3 H), 8.80-9.00 (br s, 1 H); ^{13}C

NMR (DMSO-d_6) δ 92.8, 108.3, 117.5, 124.6, 127.4, 128.3, 129.2, 131.3, 133.4. Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.88; H, 4.76; N, 16.71.

4-Methyl-2-phenylpyrrole-3-carbonitrile (8f): yield 85%; mp 140-142 °C (lit[14] 141-144.5 °C); ^{1}H NMR δ 2.32 (s, 3 H), 7.26 (d, 1 H, *J* = 3.3 Hz)), 7.26-7.34 (m, 1 H), 7.38-7.42 (m, 4 H), 8.68-8.78 (br s, 1 H); ^{13}C NMR δ 10.7, 95.6, 116.8, 118.5, 124.8, 126.7, 127.3, 128.8, 129.5, 131.6.

2-Phenyl-3-(pyridin-4-yl)pyrrole (9): yield 64%; mp 215-216 °C; ^{1}H NMR (DMSO-d_6) δ 7.12 (d, 1 H, *J* = 1.8), 7.18-7.25 (m, 1 H), 7.41 (t, 1 H, *J* = 7.5 Hz), 7.60-7.65 (m, 3 H), 7.73 (d, 2 H, *J* = 7.2 Hz), 8.47 (d, 2 H, *J* = 6.1 Hz), 11.6-12.0 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 103.4, 119.0, 122.1, 123.6, 126.11, 128.7, 132.3, 133.0, 142.9, 149.7. Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.99; H, 5.49; N, 12.76.

2-Phenyl-3-(pyridin-4-yl)pyrrole (10): yield 36%; mp °C (Found: HRMS M^+ = 220.1001; $C_{15}H_{12}N_2$ requires M = 220.1000); ^{1}H NMR δ 6.92 (t, 1 H, *J* = 6.3 Hz), 7.01-7.11 (m, 2 H), 7.17-7.22 (m, 2 H), 7.29 (s, 1 H), 7.39-7.51 (m, 4 H), 8.44 (d, 1 H, *J* = 4.1 Hz), 10.22 (br s, 1 H); ^{13}C NMR δ 103.9, 118.7, 119.2, 120.2, 123.7, 125.7, 126.1, 128.6, 132.2, 133.3, 136.5, 148.7, 154.3.

3-Acetyl-2-phenylpyrrole (11): yield 34%; mp 178-179 °C (Found: HRMS M^+ + 1 = 186.0919; $C_{12}H_{11}NO$ requires M + 1 = 186.0919); ^{1}H NMR δ 2.45 (s, 3 H), 6.91 (dd, 1 H, *J* = 2.7, 1.6 Hz), 7.20-7.27 (m, 1 H), 7.33-7.39 (m, 2 H), 7.46 (dd, 1 H, *J* = 3.1, 1.6 Hz), 7.50-7.54 (m, 2 H), 9.75-9.85 (br s, 1 H); ^{13}C NMR δ 27.1, 105.4, 111.2, 124.2, 124.6, 127.1, 127.3, 129.0, 131.6, 133.9, 194.3.

4-Acetyl-2-phenylpyrrole (12): yield 18%; mp 116-118 °C; ^{1}H NMR δ 2.29 (s, 3 H), 6.68 (dd, 1 H, *J* = 3.0, 2.8 Hz), 6.72 (dd, 1 H, *J* = 3.0, 2.5 Hz), 7.34-7.42 (m, 3 H), 7.50-7.54 (m, 2 H), 8.80-8.90 (br s, 1 H); ^{13}C NMR δ 29.0, 111.8, 117.8, 121.7, 128.3, 128.5, 129.1, 132.5, 136.4, 194.7. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.18; H, 6.25; N, 7.39.

Preparation of 4-(Benzotroazol-1-yl)-1,2,5-triaryl-4,5-dihydroimidazoles (14a,b): To a solution of *N*-(benzotriazol-1-ylmethyl)-(methylthio)phenylimine **6** (1.41g, 5 mmol) in THF (40 mL) was added *n*-butyllithium (2 *M* in cyclohexane, 2.5 mL, 5 mmol) at -78 °C. The solution was stirred at this temperature for 5 min, then the appropriate imine (5 mmol) was added. The solution was kept at this temperature for another 30 min. After addition of water (50 mL), the solution was extracted with diethyl ether (3 x 50 mL), and dried over $MgSO_4$. Evaporation of the solvent gave the crude product which was purified by recrystallization from hexane/ethyl acetate (3:1).

4-(Benzotriazol-1yl)-1,2,5-triphenyl-4,5-dihydroimidazole (14a): yield 65%; mp 147-149 °C; ^{1}H NMR (DMSO-d_6) δ 5.76 (d, 1 H, *J* = 4.9 Hz), 6.88 (d, 1 H, *J* = 5.0 Hz), 6.94 (d, 2 H, *J* = 7.3 Hz), 7.06-7.30 (m, 4 H), 7.40-7.55 (m, 8 H), 7.60-7.70 (m, 3 H), 7.96 (d, 1 H, *J* = 8.3 Hz), 8.15 (d, 1 H, *J* = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 73.1, 85.9, 110.8, 119.5, 124.3, 124.6, 125.4, 126.7, 127.8, 128.3, 128.4, 129.0, 129.7, 130.9, 131.9, 140.2, 140.9, 145.8, 165.4. Anal. Calcd for $C_{27}H_{21}N_5$: C, 78.05; H, 5.09; N, 16.86. Found: C, 78.13; H, 5.19; N, 16.47.

4-(Benzotriazol-1yl)-1,2-diphenyl-5-(4-methylphenyl)-4,5-dihydroimidazole (14b): yield 97%; mp 135-136 °C (Found: HRMS M^+ + 1 = 430.2024; $C_{28}H_{23}N_5$ requires M + 1 = 430.2031); ^{1}H NMR δ 2.38 (s, 3 H), 5.53 (d, 1 H, *J* = 4.7 Hz), 6.70 (d, 1 H, *J* = 4.7 Hz), 6.89-6.92 (m, 2 H), 7.03-7.15 (m, 3 H), 7.23-7.50 (m, 9 H), 7.67-7.70 (m, 3 H), 8.08 (d, 1 H, *J* = 8.3 Hz); ^{13}C NMR δ 21.2, 74.2, 86.8, 110.2, 120.1, 124.0, 125.0, 125.8, 126.5, 127.5, 128.4, 129.0, 129.5, 129.8, 130.1, 131.0, 132.4, 137.8, 138.4, 141.6, 146.6, 150.6, 166.7.

Preparation of 1,2,5-Triarylimidazoles (15a,b). Method A: Compound **14a** or **14b** (5 mmol) was refluxed in toluene (20 mL) under N_2 for 12 h. Diethyl ether (150 mL) was added. The solution was washed with saturated Na_2CO_3 solution (2 x 100 mL), and dried over Mg_2SO_4. Evaporation of the solvents afforded the pure compound. *Method B:* Zinc bromide (1.13 g, 5 mmol) was added to the solution of **14a** or **14b** (5

mmol) in THF (30 mL). The reaction mixture was refluxed for 3 h. Then the solution was treated with water (30 ml), extracted with diethyl ether (3 x 100 mL), washed with saturated Na_2CO_3 solution (2 x 100 mL), and dried over Mg_2SO_4. Evaporation of the solvents gave the pure compound.

1,2,5-Triphenylimidazole (15a): yield 90%; mp 254.5-255 °C (Lit[13] mp 251-252.5 °C); ^{1}H NMR δ 7.11-7.16 (m, 4 H), 7.23-7.30 (m, 6 H), 7.35-7.40 (m, 6 H); ^{13}C NMR δ 127.3, 128.0, 128.1, 128.2, 128.3, 128.5, 128.8, 129.3, 129.8, 130.6, 135.1, 137.2, 148.0.

1,2-Diphenyl-5-(4-methylphenyl)imidazole (15b): yield 72%; mp 221.5-223 °C (Found: HRMS M^+ = 310.1427; $C_{22}H_{18}N_2$ requires M = 310.1470); ^{1}H NMR δ 2.29 (s, 3 H), 6.95-7.04 (m, 4 H), 7.08-7.12 (m, 2 H), 7.20-7.26 (m, 3 H), 7.30-7.37 (m, 6 H); ^{13}C NMR δ 21.1, 126.9, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.7, 128.9, 129.3, 130.7, 135.2, 137.1, 137.3, 147.8.

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