Preparation of 1,2-Diaryl(heteroaryl)pyrroles and -3-methylpyrroles from *N*-Allylbenzotriazole

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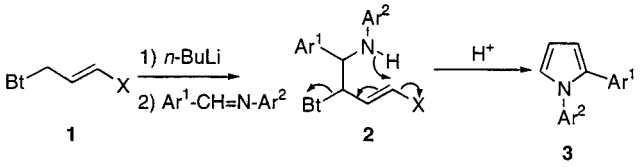
Numerous 1,2-diaryl(heteroaryl)pyrroles and -3-methylpyrroles were prepared in a two-step procedure from *N*-allylbenzotriazoles via intramolecular oxidative cyclization in the presence of Pd(II) catalyst.

Although 1,2-diarylpyrroles have long been known,[1] their chemistry remained undeveloped until recently when their biological properties attracted attention from medicinal and industrial chemists. 1,2-Diarylpyrroles have potential application as fungicides and bactericides[2] and as active components of nonsteroidal antiinflammatory drugs inhibiting human cyclooxygenase-2.[3,4]

The following procedures are available for the preparation of 1,2-diarylpyrroles: (i) low-yielding (20−30%) base-catalyzed condensations of 2-(*N*-phenylamino)-2-arylacetonitriles with acrolein under mild conditions;[1,4,5] (ii) Paal−Knorr reactions, which provide various 1,2-diarylpyrroles (in 45−70% yields),[3,6] although preparation of the starting 3-aroylpropionaldehyde (or its acetal) is usually a multistep synthesis with overall yields in the range 35−50%; (iii) a two-step procedure involving S-methylation of *N*-allyl-*N*-phenylthiobenzamide with subsequent treatment of the resulting thioimidate salt with LiHMDS,[7] which was applied to the preparation of 1,2-diphenylpyrrole; and (iv) cyclization of *N*-aryl-γ-ketoamides upon treatment with Lawesson's reagent, which affords 1,2-diarylpyrroles in modest yields (30−48%).[8]

The strong electron-withdrawing ability and nucleofugicity of the benzotriazolyl group have been used successfully for the preparation of a number of 1,2-diarylpyrroles.[9,10] It was shown that *N*-allylbenzotriazoles **1** of the general formula $BtCH_2CH{=}CHX$, where X is a second leaving group, easily undergo lithiation at the allylic carbon. The reaction of the anion obtained with a diarylimine and subsequent acid-catalyzed cyclization

Scheme 1



with the elimination of both benzotriazolyl and X groups affords 1,2-diarylpyrroles **3** in moderate yields (Scheme 1). The nature of the leaving group X (OEt[9] or morpholino[10]) does not affect the yield of the final product significantly.

In the absence of the leaving group X (**4** ≡ **1**, X = H), the cyclization of the reaction intermediate **5** in the way shown in Scheme 2 should lead to 2,5-dihydro-1,2-diarylpyrroles **A** for which methods for oxidation to the corresponding pyrroles are known using DDQ[11] or Cu(II) salts.[12] Cyclization **5** → **6** does not occur under acid-catalyzed conditions; but we showed recently that *N*-allylbenzotriazoles undergo intermolecular γ-amination in the presence of Pd(II) or Pd(0) catalysts and a weak base such as potassium carbonate.[13] Applying this procedure to the similar intramolecular reaction with simultaneous oxidation of the intermediate Δ^3-pyrroline has now provided a convenient approach to the synthesis of 1,2-diaryl(heteroaryl)pyrroles **6**.

Results and Discussion

Several (2-benzotriazolyl-1-arylbut-3-en)anilines **5a**−**h** and (2-benzotriazolyl-1-heteroarylbut-3-en)anilines **5i**−**l** were synthesized in moderate to high yields by the known procedure[10] of treating unsubstituted *N*-allylbenzotriazole (**4**) with *n*-butyllithium followed by a diarylimine or *N*-aryl-heteroarylimine, respectively (Scheme 2). Subsequently heating the compounds **5a**−**l** in the presence of a system $Pd(OAc)_2-PPh_3-CuCl_2-K_2CO_3$ in THF gave the targeted 1,2-diaryl(heteroaryl)pyrroles **6a**−**l** (Scheme 2). The yields of the products **6a**−**h** depend dramatically on the nature of the substituents in the both aromatic

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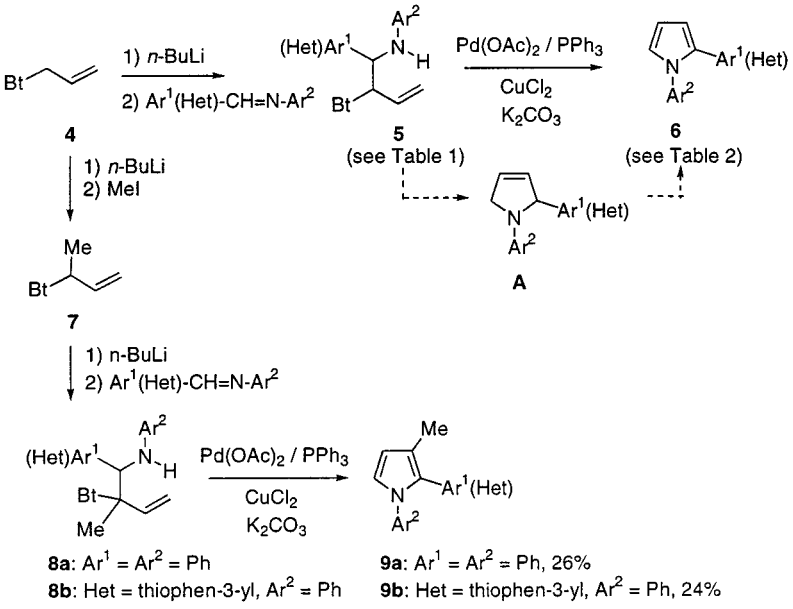
Scheme 2



rings. Electron-withdrawing substituents, such as halogen, in the para or meta position facilitate the reaction significantly; thus, the pyrroles **6b**,**d** were obtained in 79% and 78% yields, respectively [compare to 46% for 1,2-diphenylpyrrole (**6a**)]. The introduction of a strong electron-donor substituent shows the opposite effect, and so, for example, pyrrole **6h** with $Ar^1 = 4\text{-}MeOC_6H_4$ was obtained in only 21% yield.

A heterocyclic moiety, such as pyrid-3-yl, thiophen-3-yl, or even acid-sensitive furan-2-yl fragment, could be successfully used in place of the Ar^1 substituent, which enabled the synthesis of previously unknown bis-heterocyclic systems **6i**−**l**. Interestingly, in contrast to the case of 1,2-diarylpyrroles discussed above, the electron-donating (or electron-withdrawing) properties of a heterocyclic moiety do not have a significant effect on the yield of the resulting pyrrole derivative. Thus, the cyclization reactions of thiophen-3-yl-substituted allylbenzotriazole **5j** and pyrid-3-yl-substituted allylbenzotriazole **5l** gave the 2-heteroarylpyrroles **6j** and **6l**, respectively, in similar yields.

Introduction of a methyl group into the α-position to the benzotriazolyl group in the starting *N*-allylbenzotriazole caused some complications, probably for steric reasons. Thus, compounds **8a**,**b**, obtained by lithiation of 2-(buten-3-yl)benzotriazole (**7**) and subsequent reaction with an imine, were difficult to purify, but could be used crude in the subsequent cyclization reaction (analogous to that used for the preparation of 1,2-disubstituted pyrroles), thus affording 1,2,3-trisubstituted pyrroles **9a**,**b** in low yields [calculated on the starting 2-(buten-3-yl)benzotriazole (**7**)]. Products **9a**,**b** possess R_f values close to that of triphenylphosphine, which hinders their separation. Modification of the cyclization procedure by applying polymer-supported triphenylphosphine instead of the monomeric reagent improved the quality of **9a**,**b** after chromatographic purification without affecting the yields.

The presence of an oxidizing agent, $CuCl_2$, is crucial for the reaction. Thus, we showed that no cyclization occurs when Pd(II) catalyst is used alone. The use in the present work of readily available *N*-allylbenzotriazole (**1**, X = H) as a starting material is more convenient than the earlier utilization of **1** (X = OEt) or **1** (X = morpholino) which requires multistep preparation.

Experimental Section

General Comments. Melting points were measured on a hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR data were recorded on 300 MHz NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ as a solvent and with TMS as an internal standard. Column chromatography was carried out on silica gel (activated, neutral, 50−200 micron). Tetrahydrofuran was purified by distillation from Na/benzophenone under nitrogen. Diarylimines and *N*-aryl-heteroarylimines were prepared according to procedure described.[14] *N*-Allylbenzotriazole (**4**) and 2-(buten-3-yl)benzotriazole (**7**) were prepared by the known procedures.[15]

General Procedure for the Synthesis of *N*-Aryl-2-(benzotriazol-1-yl)-1-aryl(heteroaryl)buten-3-ylamines (5). A solution of *N*-allylbenzotriazole (**4**) (1.59 g, 0.01 mol) in dry THF (60 mL) was cooled under nitrogen to −78 °C, and a 1.5 M solution of *n*-butyllithium in hexanes (6.6 mL, 0.01 mol) was added dropwise at this temperature during 20 min. The reaction mixture was stirred at −78 °C for another 30 min, and then a solution of a corresponding diarylimine (or *N*-aryl-heteroarylimine) (0.01 mol) in dry THF (20 mL) was added dropwise. The resulting solution was stirred at −78 °C for an additional 1 h and then quenched with water. The product was extracted with chloroform, and the chloroform extracts were filtered and washed with water. Removal of the solvent gave a crude product, which was additionally purified by recrystallization from methanol.

***N*-Phenyl-2-(benzotriazol-1-yl)-1-phenylbuten-3-ylamine (5a):** white plates; mp 164−165 °C; yield 85%; ^1H NMR δ 8.00−7.95 (m, 1H), 7.31−7.22 (m, 2H), 7.14−7.03 (m, 8H), 6.71−6.54 (m, 4H), 5.49−5.33 (m, 3H), 5.01 (d, J = 7.6 Hz, 1H), 4.72 (br s, 1H); ^{13}C NMR δ 146.4, 145.3, 139.0, 132.8, 132.4, 129.0, 128.5, 127.8, 127.1, 126.7, 123.8, 121.5, 119.8, 118.3, 114.0, 109.2, 67.4, 61.6. Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.61; H, 5.93; N, 16.47. Found: C, 77.36; H, 6.23; N, 16.69.

***N*-Phenyl-2-(benzotriazol-1-yl)-1-(4-fluorophenyl)buten-3-ylamine (5b):** white needles; mp 165−166 °C; yield 71%; ^1H NMR δ 7.99 (dd, J = 6.8, 1.7 Hz, 1H), 7.33−7.25 (m, 2H),

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Table 1. *N*-Aryl-2-(benzotriazolyl)-1-aryl(heteroaryl)buten-3-ylamines (5)

compd	Ar^1(Het)	Ar^2	mp, °C	yield, %
5a	Ph	Ph	164−165	85
5b	4-FC_6H_4	Ph	165−166	71
5c	Ph	2-ClC_6H_4	194−195	81
5d	Ph	3-ClC_6H_4	159−160	52
5e	Ph	4-ClC_6H_4	60−62	65
5f	4-ClC_6H_4	Ph	171−172	80
5g	4-MeC_6H_4	Ph	167−168	76
5h	4-$MeOC_6H_4$	Ph	176−178	75
5i	2-furyl	Ph	118−120	46
5j	3-thiophenyl	Ph	143−144	66
5k	3-pyridyl	Ph	173−174	71
5l	3-pyridyl	4-ClC_6H_4	189−190	48

Table 2. 1-Aryl-2-aryl(heteroaryl)pyrroles (6) and 1-Aryl-2-aryl(heteroaryl)-3-methylpyrroles (9)

compd	Ar^1(Het)	Ar^2	reaction time, h	mp, °C	yield, %
6a	Ph	Ph	24	68−70 (82−83)	46
6b	4-FC_6H_4	Ph	12	73−74	79
6c	Ph	2-ClC_6H_4	12	72−74	52
6d	Ph	3-ClC_6H_4	16	liquid	78
6e	Ph	4-ClC_6H_4	6	74−75	72
6f	4-ClC_6H_4	Ph	8	110−112	76
6g	4-MeC_6H_4	Ph	24	liquid	76
6h	4-$MeOC_6H_4$	Ph	12	liquid	21
6i	2-furyl	Ph	16	71−73	56
6j	3-thiophenyl	Ph	15	86−88	70
6k	3-pyridyl	Ph	16	liquid	56
6l	3-pyridyl	4-ClC_6H_4	24	78−80	68
9a	Ph	Ph	16	liquid	26[a]
9b	3-thiophenyl	Ph	24	liquid	24[a]

[a] Total yield, based on 2-(buten-3-yl)benzotriazole (**7**).

7.12−7.06 (m, 5H), 6.78−6.52 (m, 6H), 5.52−5.39 (m, 3H), 5.00 (dd, J = 7.8, 3.3 Hz, 1H), 4.66 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 162.1 (d, J = 246.8 Hz), 146.2, 145.3, 134.8, 132.7, 132.4, 129.0, 128.3 (d, J = 8.1 Hz), 127.3, 123.9, 121.7, 119.8, 118.5, 115.4 (d, J = 21.2 Hz), 114.0, 109.1, 67.4, 60.8. Anal. Calcd for $C_{22}H_{19}FN_4$: C, 73.72; H, 5.34; N, 15.63. Found: C, 73.78; H, 5.52; N, 15.79.

***N*-Phenyl-2-(benzotriazol-1-yl)-1-(thiophen-3-yl)buten-3-ylamine (5j):** white needles; mp 143−144 °C; yield 66%; ^{1}H NMR δ 8.01 (d, J = 6.8 Hz, 1H), 7.35−7.24 (m, 2H), 7.15−7.02 (m, 4H), 6.88 (d, J = 2.4 Hz, 1H), 6.71 (t, J = 6.9 Hz, 2H), 6.64−6.52 (m, 3H), 5.54−5.37 (m, 3H), 5.18 (d, J = 7.3 Hz, 1H), 4.55 (br s, 1H); ^{13}C NMR δ 146.4, 145.4, 140.3, 132.9, 132.6, 129.1, 127.2, 126.3, 125.6, 123.8, 122.5, 121.4, 119.8, 118.5, 113.9, 109.4, 67.0, 57.6. Anal. Calcd for $C_{20}H_{18}N_4S$: C, 69.34; H, 5.24; N, 16.17. Found: C, 68.98; H, 5.26; N, 16.31.

General Procedure for the Synthesis of 1,2-Diaryl-(heteroaryl)pyrroles (6). A mixture of an amino-substituted allylbenzotriazole (**5**) (26.4 mmol), anhydrous $CuCl_2$ (0.71 g, 52.8 mmol), potassium carbonate (0.73 g, 52.8 mmol), triphenylphosphine (0.14 g, 0.5 mmol), and catalytic amount (30 mg) of palladium(II) acetate in dry THF (50 mL) was heated under reflux under nitrogen (for the reaction time required, see Table 2). The residue obtained after the solvent removal was subjected to column chromatography (SiO_2, hexane/chloroform = 7:3) to give the corresponding 1,2-diaryl(heteroaryl)pyrrole.

1-Phenyl-2-(4-fluorophenyl)pyrrole (6b): white microcrystals; mp 73−74 °C; yield 79%; ^{1}H NMR δ 7.20−7.08 (m, 3H), 7.04−6.92 (m, 4H), 6.82−6.72 (m, 3H), 6.27 (dd, J = 3.7, 1.8 Hz, 1 H), 6.23 (t, J = 3.1 Hz, 1H); ^{13}C NMR δ 161.5 (d, J = 245.8 Hz), 140.2, 132.7, 129.8 (d, J = 8.1 Hz), 129.1, 129.0, 126.6, 125.6, 124.2, 115.0 (d, J = 21.7 Hz), 110.5, 109.2. Anal. Calcd for $C_{16}H_{12}FN$: C, 80.98; H, 5.10; N, 5.91. Found: C, 80.87; H, 4.88; N, 5.83.

1-Phenyl-2-(furan-2-yl)pyrrole (6i): white needles; mp 71−73 °C; yield 56%; ^{1}H NMR δ 7.35−7.18 (m, 6H), 6.76 (t, J = 2.0 Hz, 1H), 6.51 (dd, J = 3.6, 1.9 Hz, 1H), 6.24 (t, J = 3.0 Hz, 1H), 6.15 (dd, J = 2.2, 1.7 Hz, 1H), 5.56 (d, J = 3.4 Hz, 1H); ^{13}C NMR δ 147.3, 140.9, 140.3, 129.0, 127.5, 126.2, 125.2, 124.3, 110.7, 109.7, 109.2, 105.5. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.07; H, 5.39; N, 6.88.

1-Phenyl-2-(thiophen-3-yl)pyrrole (6j): white plates; mp 86−88 °C; yield 70%; ^{1}H NMR δ 7.28−7.20 (m, 3H), 7.14−7.11 (m, 2H), 7.03 (dd, J = 5.1, 2.9 Hz, 1H), 6.80−6.74 (m, 2H), 6.64 (dd, J = 2.9, 1.2 Hz, 1H), 6.35 (dd, J = 3.4, 1.7 Hz, 1H), 6.23 (t, J = 3.2 Hz, 1H); ^{13}C NMR δ 140.4, 133.4, 129.4, 129.0, 127.7, 127.0, 126.1, 124.7, 123.7, 120.3, 109.8, 108.9. Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.38; H, 4.75; N, 6.24.

General Procedure for the Synthesis of 1,2-Diaryl-(heteroaryl)-3-methylpyrroles (9). 2-(Buten-3-yl)benzotriazole (**7**) (1.74 g, 0.01 mol) in dry THF (60 mL) was cooled under nitrogen to −78 °C, and 1.5 M solution of *n*-butyllithium in hexanes (6.6 mL, 0.01 mol) was added dropwise at this temperature during 20 min. The reaction mixture was stirred at −78 °C for another 30 min, and then the corresponding diarylimine (or *N*-aryl-heteroarylimine) (0.01 mol) in dry THF (20 mL) was added dropwise. The resulting solution was stirred at −78 °C for an additional 1 h and then quenched with water. The product was extracted with chloroform, and the chloroform extracts were filtered and washed with water. Removal of the solvent gave a viscous oil which was subjected to flash column chromatography (SiO_2, hexane/ethyl acetate = 7:3). The crude product **8** so obtained was used in the next step.

A mixture of crude **8** (18.8 mmol), prepared as described above, anhydrous $CuCl_2$ (0.51 g, 37.6 mmol), potassium carbonate (0.52 g, 37.6 mmol), and catalytic amounts of palladium(II) acetate (30 mg) and polymer-supported triphenylphosphine (178 mg) in dry THF (50 mL) was heated under reflux under nitrogen (for the reaction time required, see Table 2). The residue obtained after solvent removal was subjected to column chromatography (SiO_2, hexane/chloroform = 7:3) to give the corresponding 1,2-diaryl(heteroaryl)-3-methylpyrrole.

1,2-Diphenyl-3-methylpyrrole (9a): colorless liquid, yield 26% (total yield, based on 2-(buten-3-yl)benzotriazole); ^{1}H NMR δ 7.56−7.06 (m, 8H), 6.94 (dd, J = 2.9, 1.2 Hz, 1H), 6.84 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 4.9, 1.2 Hz, 1H), 6.22 (d, J = 2.9 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR δ 140.7, 132.6, 131.0, 129.1, 128.9, 128.8, 128.5, 126.2, 125.3, 124.3, 122.9, 122.8, 121.9, 110.9, 12.3; HRMS (FAB) calcd for $C_{17}H_{16}N$ (M + 1) 234.1283, found 234.1263. Anal. Calcd for $C_{17}H_{15}N$: N, 6.00. Found: N, 5.92.

1-Phenyl-2-(thiophen-3-yl)-3-methylpyrrole (9b): colorless liquid; yield 24% (total yield, based on 2-(buten-3-yl)-benzotriazole); ^{1}H NMR δ 7.58−7.46 (m, 1H), 7.32−7.20 (m, 2H), 7.18−7.08 (m, 3H), 6.93 (d, J = 2.9 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.69 (d, J = 5.0 Hz, 1H), 6.22 (d, J = 2.8 Hz, 1H); ^{13}C NMR δ 140.7, 132.8, 131.0, 128.9, 128.8, 126.2, 125.3, 124.3, 122.9, 121.9, 119.0, 110.9, 12.3; HRMS (FAB) calcd for $C_{15}H_{14}NS$ (M + 1) 240.0847, found 240.0853. Anal. Calcd for $C_{15}H_{13}NS$: N, 5.85. Found: N, 5.97.

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Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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