Synthesis of 1,2,3-Triarylpyrroles from 1-Benzylbenzotriazoles *via* [1 + 2 + 2] Annulation

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1,2,3-Triarylpyrroles **7** have been synthesized by sequential lithiation and alkylation of 1-benzylbenzotriazoles **1** with 2-bromoacetaldehyde diethyl acetal (**2**) and *N*-benzylideneaniline (**4**), followed by treatment with formic acid in ethanol.

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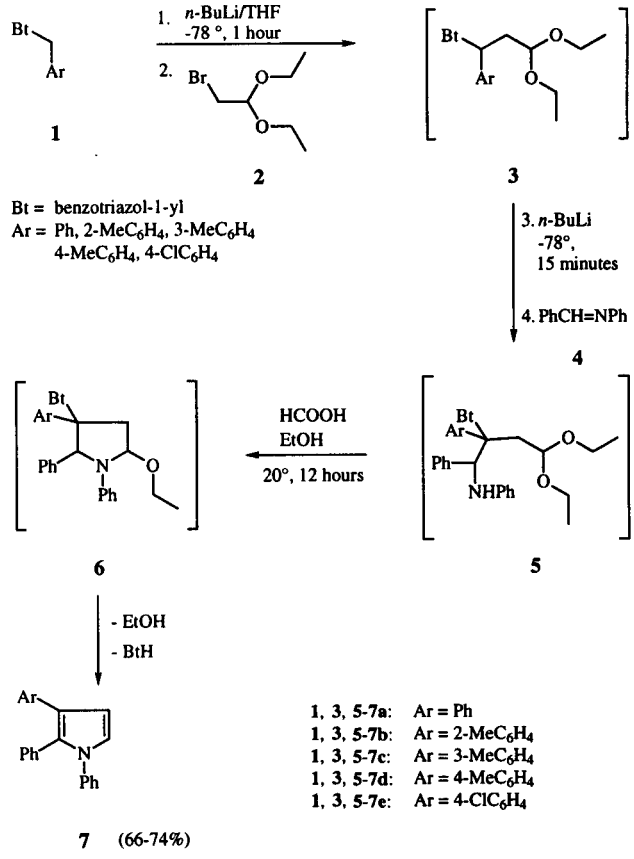
Introduction.

Three component annulations are of interest in the construction of heterocyclic rings. Although many classical methods for the syntheses of furans *via* [1 + 2 + 2] cyclizations have been documented, pyrrole ring syntheses involving formation of the C(2)-C(3), C(3)-C(4) and C(5)-*N* bonds has received little attention [1].

Typical methods for the synthesis of 1,2,3-triphenylpyrroles include: i) condensation of aniline, benzoin and an aldehyde [2]; ii) condensation of desylaniline with methyl propionate followed by decarboxylation with copper chromite [3]. We now report a method for the preparation of 1,2,3-triarylpyrroles **7a-c**, with a variety of 3-aryl substituents, using [1 + 2 + 2] annulation of 1-benzylbenzotriazoles **1** with 2-bromoacetaldehyde diethyl acetal (**2**) and *N*-benzylideneaniline (**4**) *via* sequential lithiation and alkylation, followed by the treatment with formic acid (Scheme 1).

Scheme 1



Results and Discussion.

1-Benzylbenzotriazoles **1a** [4], **1d** [5] and **1e** [6] were prepared by previously reported methods. Analogs **1b,c** were obtained from the reactions of benzotriazole with 2-methylbenzyl bromide or 3-methylbenzyl chloride in the presence of sodium hydroxide in ethanol at room temperature for 24 hours.

The reactions of 1-benzylbenzotriazoles **1** with 1 equivalent of *n*-butyllithium generated α-lithiobenzylbenzotriazoles, which were treated with 2-bromoacetaldehyde diethyl acetal (**2**) to give 3-(benzotriazol-1-yl)-3- arylpropanal diethyl acetals **3** in almost quantitative yields based on ^{1}H nmr. The intermediates **3**, were treated without isolation, in one-pot transformation, with a second equivalent of *n*-butyllithium followed by the reaction with *N*-benzylideneaniline (**4**) to afford the adducts **5a-e**. After aqueous workup, the crude diastereomeric mixtures **5a-e** were treated with formic acid in ethanol at room temperature: intramolecular cyclization and subsequent elimination of ethanol and benzotriazole formed the 1,2,3-triarylpyrroles **7a-e** in good yields. Products **7a-e** were characterized by ^{1}H and ^{13}C nmr and elemental analyses.

3-(Benzotriazol-1-yl)-3-arylpropanal diethyl acetals **3a-e** can be isolated by distillation. A similar method for the synthesis of pyrroles using 3-(*p*-toluenesulfonyl)propanal ethylene acetal derivatives and *N*-methylene-*p*-toluenesulfonamide has been reported [7,8], but appears to be limited to reactive imines such as *N*-tosylimines. In addition, the starting 3-(*p*-toluenesulfonyl)propanal ethylene acetal derivatives are not easily available [7,8]. The present method allows an aryl group at the 3-position of pyrrole ring and offers an alternative way for accessing 1,2,3-triarylpyrroles **7** using readily available starting materials *via* a simple procedure.

EXPERIMENTAL

Melting points were determined on a hot-stage microscope and are uncorrected. The ^1H nmr spectra were recorded on a 300 MHz spectrometer using tetramethylsilane as the internal standard and deuteriochloroform (or dimethyl-d_6 sulfoxide for **7e**) as the solvent. The ^{13}C nmr spectra were recorded at 75 MHz on the same instrument with the solvent peak (deuteriochloroform or dimethyl-d_6, sulfoxide for **7e**) as the reference. Elemental analyses (C, H, N) were carried out within the department.

General Procedure for the Preparation of 1-Benzylbenzotriazoles **1b,c**.

To a solution of benzotriazole (3.21 g, 26.21 mmoles) in ethanol (50 ml) was added a solution of sodium hydroxide (1.07 g, 26.21 mmoles) in water (3 ml) at 0°. After being stirred for 10 minutes, a solution of 2-methylbenzyl bromide (4.95 g, 26.21 mmoles) or 3-methylbenzyl chloride (4.39 g, 26.21 mmoles) in ethanol (5 ml) was added and the reaction mixture was stirred at room temperature for 24 hours. Diethyl ether (200 ml) and a solution of sodium hydroxide (1*N*, 100 ml) were added. The organic phase was separated, washed with brine (3 x 100 ml) and dried over magnesium sulfate. After the solvent was removed, the oily residue was subjected to column chromatography using ethyl acetate:hexane (1:6) as the eluent to give the product **7b** or **7c**.

1-(2-Methyl)benzylbenzotriazole (**1b**).

This compound was obtained as white prisms, 74%, yield, mp 81-83°; ^1H nmr: δ 2.32 (s, 3H), 5.82 (s, 2H), 7.03 (d, 1H. J = 7.5 Hz), 7.12-7.38 (m, 6H), 8.04 (d, 1H. J = 8.4 Hz); ^{13}C nmr: δ 19.1, 50.6, 109.7, 119.8, 123.7, 126.3, 127.2, 128.3, 128.5, 130.8, 132.4, 132.8, 136.4, 146.1.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82 Found: C, 75.47; H, 6.23; N, 19.02.

1-(3-Methyl)benzylbenzotriazole (**1c**).

This compound was obtained as white prisms, 59% yield, mp 127-129°; ^1H nmr: δ 2.29 (s, 3H), 5.79 (s, 2H), 7.05-7.11 (m, 3H), 7.18-7.23 (m, 1H), 7.30-7.39 (m, 3H), 8.05 (d, 1H. J = 8.1 Hz); ^{13}C nmr: δ 21.3, 52.1, 109.7, 119.9, 123.8, 124.6, 127.3, 128.2, 128.7, 129.1, 132.7, 134.6, 138.7, 146.2.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.43; H, 6.24; N, 19.01.

General Procedure for the Preparation of 1,2,3-Triarylpyrroles **7**.

To a solution of an appropriate 1-benzylbenzotriazole **1** (5 mmoles) in tetrahydrofuran (80 ml) was added a solution of *n*-butyllithium (3.2 ml, 5 mmoles 1.6 *M* in hexane) at -78°. The mixture was stirred at -78° for l hour before adding a solution of 2-bromoacetaldehyde diethyl acetal (**2**) (0.99 g, 5 mmoles) in tetrahydrofuran (5 ml). The reaction solution was allowed to warm to room temperature overnight before being recooled to -78°. A solution of *n*-butyllithium (3.2 ml, 5 mmoles, 1.6 *M* in hexane) was added and the reaction mixture was stirred at -78° for 15 minutes. A solution of *N*-benzylideneaniline (**4**) (0.91 g, 5 mmoles) in tetrahydrofuran (10 ml) was added. After being stirred for 3 hours at -78°, the reaction was quenched with saturated ammonium chloride solution (100 ml) and extracted with diethyl ether (3 x 50 ml). The organic phase was separated, washed with brine (3 x 50 ml), and dried over magnesium sulfate. After removal of the solvent, the residue was dissolved in ethanol (80 ml) and formic acid (20 ml, 88%) was added. The reaction mixture was stirred overnight at room temperature and quenched with saturated sodium bicarbonate, and extracted with diethyl ether (3 x 50 ml). The organic layer was separated, washed with brine (3 x 50 ml), and dried over magnesium sulfate. After removal of the solvent, the residue was subjected to a short column chromatography on silica gel using ethyl acetate:hexane (1:30) as the eluent to afford the products **7**.

1,2,3-Triphenylpyrrole (**7a**).

This compound was obtained as white prisms (ethyl acetate:hexane), 68% yield, mp 181-182°; ^1H nmr: δ 6.57 (d, 1H. J = 3.0 Hz), 6.99 (d, 1H, J = 3.0 Hz), 7.05-7.36 (m, 15H); ^{13}C nmr: δ 109.9, 123.0, 124.2, 125.4, 125.9, 126.4, 126.9, 128.0, 128.1, 128.3, 128.7, 129.9, 131.1, 132.3, 136.4, 140.3.

Anal. Calcd. for $C_{22}H_{17}N_1$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.35; H, 5.76; N, 4.73.

1,2-Diphenyl-3-(2-methyl)phenylpyrrole (**7b**).

This compound was obtained as white prisms (ethyl acetate:hexane), 71% yield, mp 130-132°; ^1H nmr: δ 2.05 (s, 3H), 6.37 (d, 1H. J = 3.0 Hz), 6.84-6.88 (m, 2H), 6.97 (d, 1H. J = 3.0 Hz), 7.01-7.29 (m, 12H); ^{13}C nmr: δ 20.4, 111.4, 122.6, 124.6, 125.3, 125.7, 126.1, 126.3, 126.4, 127.7, 128.8, 129.8, 130.0, 130.3, 131.2, 132.5, 136.5, 136.8, 140.6.

Anal. Calcd. for $C_{23}H_{19}N_1$: C, 89.28; H, 6.19; N, 4.53. Found: C, 89.09; H, 6.41; N, 4.43.

1,2-Diphenyl-3-(3-methyl)phenylpyrrole (**7c**).

This compound was obtained as white prisms (ethyl acetate:hexane), 71% yield, mp 114-116°; ^1H nmr: δ 2.25 (s, 3H), 6.54 (d, 1H, J = 2.75 Hz), 6.94-6.98 (m, 3H), 7.05-7.27 (m, 12H); ^{13}C nmr: δ 21.4, 109.9, 122.9, 124.4, 125.5, 126.0, 126.2, 126.4, 126.9, 127.9, 128.0, 128.7, 129.1, 130.0, 131.1, 132.5, 136.4, 137.5, 140.4

Anal. Calcd. for $C_{23}H_{19}N_1$: C, 89.28; H, 6.19; N, 4.53. Found: C, 89.29; H, 6.52; N, 4.47.

1,2-Diphenyl-3-(4-methyl)phenylpyrrole (**7d**).

This compound was obiained as white powder (ethyl acetate:hexane), 74% yield, mp 167-168°; ^1H nmr: δ 2.29 (s, 3H), 6.53 (d, 1H, J = 3.0 Hz), 6.96 (d, 1H, J = 3.0 Hz), 7.00-7.26 (m, 14H); ^{13}C nmr: δ 21.1, 109.9, 122.9, 124.2, 125.9, 126.4, 126.8, 128.0, 128.2, 128.7, 128.8, 129.7, 131.1, 132.5, 133.5, 134.9, 140.4.

Anal. Calcd. for $C_{23}H_{19}N_1$: C, 89.28; H, 6.19; N, 4.53. Found: C, 89.27; H, 6.24; N, 4.45.

1,2-Diphenyl-3-(4-chloro)phenylpyrrole (**7e**).

This compound was obtained as white prisms (ethyl acetate:hexane), 66% yield, mp 190-191°; ^1H nmr: δ 6.58 (d, 1H. J = 3.0 Hz), 6.80-7.62 (m, 15H); ^{13}C nmr: δ 109.4, 122.1, 123.5, 125.8, 126.8, 127.5, 128.1, 128.3, 128.9, 129.2, 129.6, 129.9, 130.8, 131.8, 134.9, 139.5.

Anal. Calcd. for $C_{22}H_{16}Cl_1N_1$: C, 80.11; H, 4.89; N, 4.25. Found: C, 80.09; H, 5.14; N, 4.29.

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