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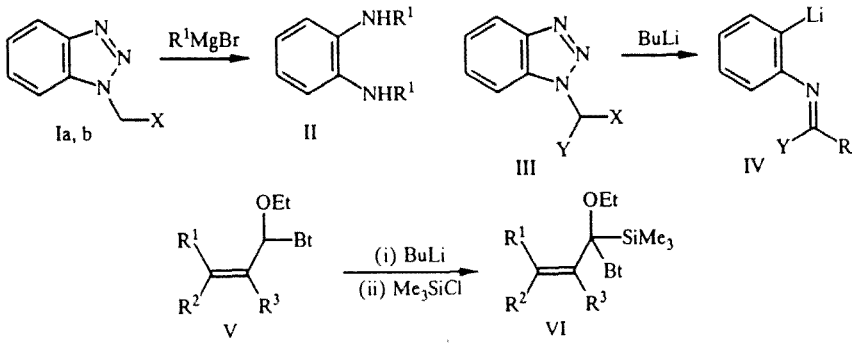
# FORMATION OF 1-(2-AMINOPHENYL)-5-ETHOXY-4-METHYL-3-PHENYLPYRAZOLE AND 4-METHYL-3-PHENYLPYRAZOLO-[5,1-*b*]BENZIMIDAZOLE VIA AN UNUSUAL ENZOTRIAZOLE RING OPENING

**Alan R. Katritzky, Zuoquan Wang, Hengyuan Lang, and Peter J. Steel**

*Successive treatment of N-[(1-ethoxy)alken-2-yl]benzotriazoles VII with butyllithium and trimethylsilyl chloride in THF at −78°C followed by refluxing in acidic acetone generated ring-opened 1-(2-aminophenyl)-5-ethoxy-4-methyl-3-phenylpyrazole VIII and 4-methyl-3-phenylpyrazolo[5,1-b]benzimidazole IX.*

Benzotriazole chemistry has been an area of intensive investigation in our group for the past few years, and from it has been developed a number of useful and versatile reagents for the transformations of many classes of organic compounds [1-4]. The benzotriazole ring is very stable to acids and bases, and also to oxidation and reduction under most reaction conditions. Rare cases have been observed of the opening of benzitriazole rings. Reactions of 1-(α-alkoxyalkyl)benzotriazoles (Ia) [5] and of benzotriazol-1-ylmethylammonium salts (Ib) [6] with Grignard reagents at high temperatures resulted in ring-opening to form *o*-phenylenediamine derivatives II. Another type of benzotriazole ring opening involves cleavage of the N-1 to N-2 bond in compound III followed by extrusion of nitrogen to form an *o*-iminophenyl anion of type IV, which then can be captured by an elecrophile [7]. In all of these cases, the reactions involve the loss of one or two nitrogen atoms. The only examples so far observed of the scission of the bond between the N-2 and N-3 atoms to form products which retain all the nitrogen atoms have included 1,2,3-benzotriazoline betaines [8].




Bt = benzotriazol-1-yl; Ia X = OR, b X = $N^+R_3$; III Y = OR, aryl etc.

Recently, we have developed benzotriazole-based acyl anion methodologies for the synthesis of a variety of alkenyl [9, 10], alkynyl [11], and aryl/heteroaryl [12] ketones. In particular, successive treatment of *N*-[(1-ethoxy)alken-2-yl]benzotriazoles V with butyllithium and trimethylsilyl chloride in THF at −78°C afforded the substituted derivatives VI, which underwent in situ hydrolysis to give rise to alkenoyl silanes in good yields [13]. We have now found that when the more sterically-hindered dimethyloctylsilyl chloride was used to react with deprotonated VII, two products VIII and IX in which the

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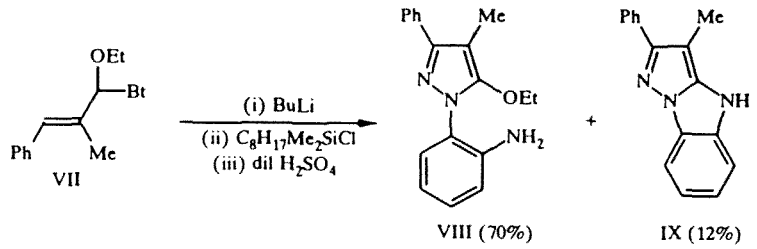
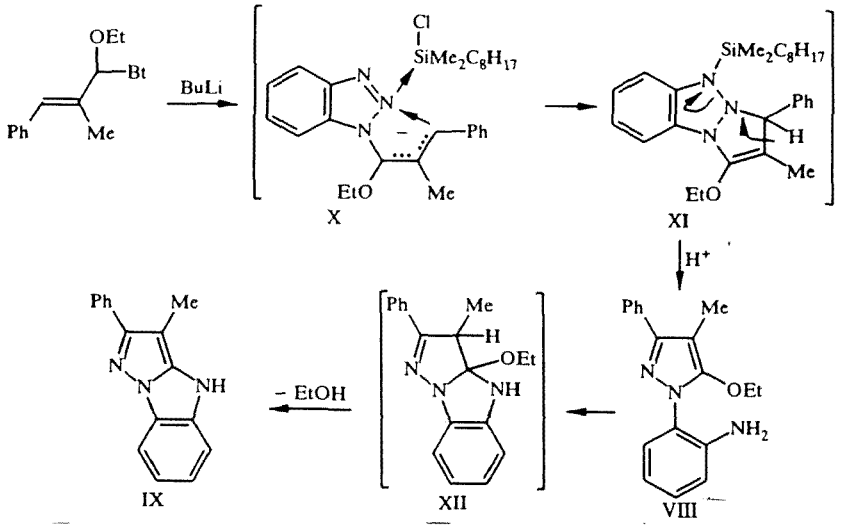
benzotriazole ring had opened, were generated in 70% and 12% yields, respectively. Their structures have been determined spectroscopically and by X-ray crystallography.

Scheme 1




Scheme 2




A possible pathway for the formation of compounds VIII and IX is shown in Scheme 2. Deprotonation of N-(1-ethoxy-2-methyl-3-phenyl-2-propenyl)benzotriazole VII gave the allylic anion X, which reacted with N-2 to undergo cyclization assisted by simultaneous reaction of N-3 with dimethyloctylsilyl chloride to give intermediate XI. Acidic cleavage of the N-2 and N-3 bond in intermediate XI with loss of the silyl group then produced the substituted pyrazole VIII. Upon further acid treatment, displacement of the ethoxy group in pyrazole VIII by the amino group via an addition-elimination mechanism of intermediate XII gives the ring-fused benzimidazole IX.

To confirm further the mechanism of the formation of benzimidazole IX, we refluxed pyrazole VIII in aqueous acetone under catalysis of sulfuric acid for 55 h to give the expected benzimidazole IX in 50% yield, along with the unreacted starting material VIII.

The X-ray crystal structures for compounds VIII and IX are shown in Figs. 1 and 2. In the structure of VIII the pyrazole ring is planar to within 0.005 Å and the aryl rings attached to N-1 and C-3 are inclined to the pyrazole plane at angles of 55.1(2) and 35.5(2)°, respectively. The $NH_2$ hydrogen atoms are both involved in bifurcated intermolecular hydrogen bonds to N-2 of an adjacent molecule. In the structure of IX the pyrazolo[5,1-*b*]benzimidazole ring system is planar to within 0.006 Å, with the C2 phenyl ring inclined to this plane at an angle of 41.5(1)°. The successful location and refinement of the potentially tautomeric N–H hydrogen atom, in combination with an inspection of the bonding geometry, clearly establish that this compound exists as the $N_4$-H tautomer, rather than the $N_1$-H tautomer. This hydrogen is also involved in a linear intermolecular hydrogen bond to N-4 of an adjacent molecule.

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus without correction. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Varian VXR 300 MHz. THF was distilled from sodium/benzophenone ketyl under nitrogen immediately before use.

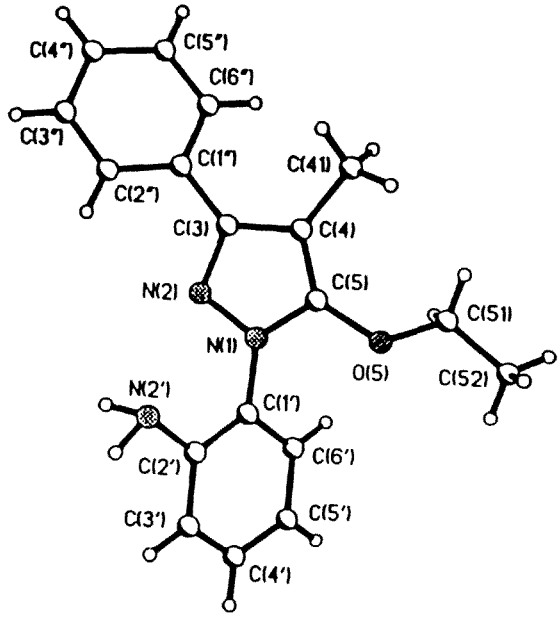



Fig. 1. Perspective view and atom labeling of the X-ray structure of VIII.

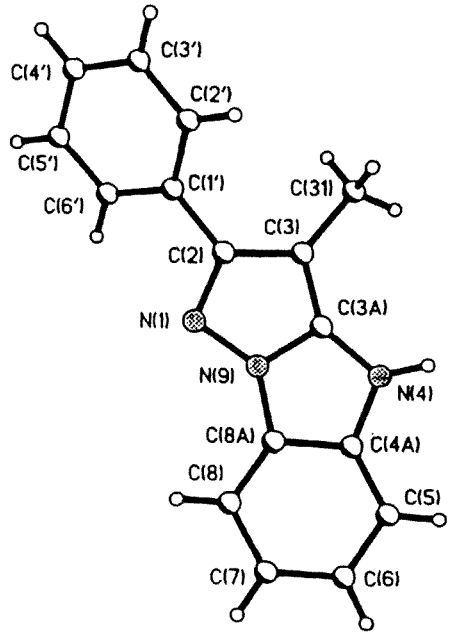



Fig. 2. Perspective view and atom labeling of the X-ray structure of IX.

Compound VII was prepared according to the previously published procedure [13].

**Preparation of 1-(2-Aminophenyl)-5-ethoxy-4-methyl-3-phenylpyrazole VIII and 4-Methyl-3-phenylpyrazolo[5,1-*b*]benzimidazole IX:** To a solution of *N*-[(1-ethoxy)-2-methyl-3-phenyl-2-propenyl]benzotriazole (VII) (1 g, 3.4 mmol) in THF (40 ml) at −78°C were added octyldimethylsilyl chloride (0.76 g, 3.57 mmol) and butyllithium (2M in hexane, 1.8 ml, 3.6 mmol). The solution was kept at −78°C for 1 h and then at room temperature overnight. Water (20 ml) was added and the solvents were removed under reduced pressure. Toluene (40 ml), water (10 ml), and conc. sulfuric acid (0.25 g) were added to the residue and the resulting mixture was refluxed for 4 h. The solvents were removed again under reduced pressure and the residue was extracted with diethyl ether (3 × 50 ml) and dried with $MgSO_4$. Evaporation of the solvents and separation by column chromatography gave the compounds VIII (0.7 g, 70%) and IX (0.1 g, 12%).

**Conversion of 1-(2-Aminophenyl)-5-ethoxy-4-methyl-3-phenylpyrazole VIII to 4-Methyl-3-phenylpyrazolo[5,1-*b*]benzimidazole IX:** A mixture of 1-(2-aminophenyl)-5-ethoxy-4-methyl-3-phenylpyrazole VIII (0.29 g, 1 mmol), acetone (30

TABLE 1. Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$) for VIII

| Atom | $10^4x$ | $10^4y$ | $10^4z$ | $10^3U_{eq}$ |
|---|---|---|---|---|
| N(1) | 3595(3) | 2712(8) | 2926(3) | 60(2) |
| N(2) | 3846(4) | 2829(8) | 2389(3) | 68(2) |
| C(3) | 3155(5) | 2805(9) | 2080(4) | 66(2) |
| C(4) | 2484(5) | 2668(10) | 2425(3) | 65(2) |
| C(5) | 2788(4) | 2638(10) | 2940(4) | 67(2) |
| C(1') | 4169(5) | 2699(11) | 3372(4) | 59(2) |
| C(2') | 4757(5) | 1556(11) | 3389(4) | 65(2) |
| C(3') | 5287(5) | 1573(12) | 3835(5) | 80(3) |
| C(4') | 5215(6) | 2652(14) | 4251(5) | 95(3) |
| C(5') | 4628(6) | 3838(14) | 4257(4) | 97(3) |
| C(6') | 4102(5) | 3864(10) | 3804(4) | 71(3) |
| N(2') | 4784(4) | 356(11) | 2969(4) | 84(2) |
| C(1") | 3225(6) | 2929(11) | 1487(4) | 68(2) |
| C(2") | 3862(5) | 2193(12) | 1218(4) | 81(3) |
| C(3") | 3916(6) | 2373(12) | 659(5) | 94(3) |
| C(4") | 3366(7) | 3220(13) | 356(4) | 100(3) |
| C(5") | 2740(6) | 3932(12) | 641(5) | 100(3) |
| C(6") | 2665(6) | 3807(12) | 1195(4) | 90(3) |
| C(41) | 1641(4) | 2452(10) | 2256(3) | 83(3) |
| O(5) | 2450(3) | 2385(6) | 3467(2) | 71(2) |
| C(51) | 1813(5) | 3465(11) | 3620(4) | 103(3) |
| C(52) | 1600(6) | 3332(13) | 4201(4) | 142(5) |

TABLE 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$) for IX

| Atom | $10^4x$ | $10^4y$ | $10^4z$ | $10^3U_{eq}$ |
|---|---|---|---|---|
| N(1) | 3612(1) | 1137(1) | 8053(1) | 45(1) |
| C(2) | 2847(1) | 1847(2) | 8383(1) | 41(1) |
| C(3) | 1712(1) | 1969(2) | 8129(1) | 44(1) |
| C(3A) | 1812(1) | 1280(2) | 7613(1) | 42(1) |
| N(4) | 1212(1) | 858(2) | 7123(1) | 50(1) |
| C(4A) | 1988(1) | 126(2) | 6779(1) | 42(1) |
| C(5) | 1829(1) | -500(2) | 6245(1) | 51(1) |
| C(6) | 2779(2) | -1171(2) | 6015(1) | 58(1) |
| C(7) | 3860(2) | -1223(2) | 6301(1) | 62(1) |
| C(8) | 4031(1) | -591(2) | 6832(1) | 55(1) |
| C(8A) | 3086(1) | 78(2) | 7064(1) | 42(1) |
| N(9) | 2934(1) | 800(1) | 7578(1) | 43(1) |
| C(1') | 3259(1) | 2364(2) | 8952(1) | 44(1) |
| C(2') | 2977(2) | 3621(2) | 9134(1) | 61(1) |
| C(3') | 3384(2) | 4106(2) | 9662(1) | 76(1) |
| C(4') | 4084(2) | 3360(2) | 10021(1) | 73(1) |
| C(5') | 4390(2) | 2113(2) | 9850(1) | 64(1) |
| C(6') | 3966(2) | 1615(2) | 9320(1) | 52(1) |
| C(31) | 624(1) | 2633(2) | 8365(1) | 61(1) |

ml), water (20 ml), and sulfuric acid (0.2 g) was heated under reflux for 55 h. The solvents were removed under reduced pressure and the residue was extracted with diethyl ether (3 × 50 ml) and dried with $MgSO_4$. Evaporation of the solvents and separation by column chromatography gave IX (0.12 g, 50%).

**1-(2-Aminophenyl)-5-ethoxy-4-methyl-3-phenylpyrazole (VIII):** Mp 95-97°C. $^1H$ NMR ($CDCl_3$): 1.17 (3 H, t, $J$ = 7.1 Hz, $CH_3$), 2.19 (3 H, s, $CH_3$), 3.90 (2 H, q, $J$ = 7.1 Hz, $CH_2$), 4.35 (2 H, s, $NH_2$), 6.73-6.78 (2 H, m), 7.08-7.14 (1 H, m), 7.26-7.37 (2 H, m), 7.40-7.42 (2 H, m), 7.72-7.75 (2 H, m). $^{13}C$ NMR ($CDCl_3$): 8.5, 15.0, 70.4, 99.9, 116.8, 117.8, 124.1, 126.6, 127.1, 127.4, 128.2, 134.1, 142.3, 149.8, 151.8. Found, %: C, 73.99; H, 6.55; N, 14.36. $C_{18}H_{19}N_3O$. Calculated, %: C, 73.70; H, 6.53; N, 14.32.

**4-Methyl-3-phenylpyrazolo[5,1-*b*]benzimidazole (IX):** Mp 252-254°C. $^1$H NMR (DMSO): 2.37 (3 H, s, $CH_3$), 7.19-7.53 (6 H, m), 7.79-7.84 (3 H, m), 11.5 (1 H, br s, NH). $^{13}$C NMR (DMSO): 8.7, 86.5, 109.5, 111.7, 119.8, 123.0, 125.7, 127.2, 127.3, 128.3, 134.8, 135.3, 143.9, 153.3.

**Crystallography:** Intensity data were collected with a Nicolet P4s four-circle diffractometer using graphite-monochromatized Mo Kα radiation (λ 0.7107 Å). Cell parameters were determined by least-squares refinement using the setting angles of at least 17 accurately centered reflections ($2\theta > 24°$). Throughout data collections ($\omega$ scans) the intensities of three standard reflections were monitored and this showed no significant crystal decomposition. The intensities were corrected for Lorentz and polarization effects but no corrections for absorption were deemed necessary.

Both structures were solved by direct methods using SHELXS-90 and refined on $F^2$ by full-matrix least squares procedures using SHELXL-93. All non-hydrogen atoms were refined with anisotropic displacement parameters. The C−H hydrogens were included in calculated positions with the rotational orientations of the methyl groups deduced from circular Fourier syntheses. The N−H hydrogens were located from difference Fourier maps and their positions refined. All hydrogens were assigned isotropic displacement parameters 1.3 times the isotropic equivalent of their carrier carbons. All data were used in the refinements; the functions minimized were

$$\sum w(F^2_o - F^2_c),$$

with

$$w = [\sigma^2(F^2_o) + aP^2)]^{-1},$$

where

$$P = [\max(F^2_o) + 2F^2_c]/3.$$

Final Fourier syntheses showed no residual electron density $>0.19$ e/Å$^3$.

Final atomic coordinates and equivalent isotropic displacement parameters (defined as one third of the trace of the orthogonalized $U_{ij}$ tensor) for VIII and IX are given in Tables 1 and 2, respectively. Tabulations of structure factors, bond lengths and angles, hydrogen atom coordinates, and anisotropic displacement parameters are available from the author PJS.

**Crystal Data for VIII.** $C_{18}H_{19}N_3O$, *M* 293.4, orthorhombic, space group Pbca, *a* 16.86(2), *b* 8.070(6), *c* 24.11(2) Å, *V* 3280(5) Å$^3$, *F*(000), 1248, *Dc* (Z = 8) 1.188 g·cm$^{-1}$, *T* 300 K, $\mu$(Mo Kα) 0.76 cm$^{-1}$, approximate crystal dimensions 0.74 by 0.66 by 0.02 mm, $2\theta_{max}$ 46°, *w*R (all 2274 data, *a* = 0.0869) 0.257, conventional R [612 data with $I > 2\sigma(I)$] 0.075 for 207 parameters.

**Crystal Data for IX.** $C_{16}H_{13}N_3$, *M* 274.3, orthorhombic, space group Pbca, *a* 11.302(4), *b* 10.220(5), *c* 22.683(8) Å, *V* 2620(2) Å$^3$, *F*(000), 1040, *Dc* (Z = 8) 1.254 g·cm$^{-1}$, $\mu$(Mo Kα) 0.77 cm$^{-1}$, *T* 300 K, approximate crystal dimensions 0.79 by 0.55 by 0.38 mm, $2\theta_{max}$ 54°, *w*R (all 2681 data, *a* = 0.0524) 0.098, conventional R [1443 data with $I > 2\sigma(I)$] 0.039 for 177 parameters.

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