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An unexpected chemical behavior of 5-*N*-(benzotriazol-1-ylmethyl)amino-3-*tert*-butyl-1-phenylpyrazole

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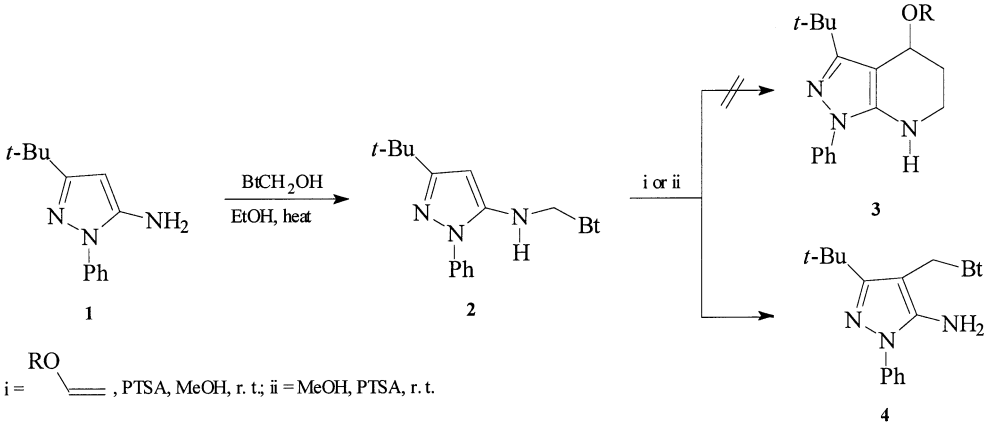
Abstract—A rearrangement product or a pyrazolic Tröger's base were unexpectedly obtained when 5-*N*-(benzotriazol-1-ylmethyl)amino-3-*tert*-butyl-1-phenylpyrazole was treated with electron-rich alkenes with well protic or Lewis acid catalyst, respectively, when tetrahydropyrazolopyridines were expected according with the benzotriazole methodology. The structure of the products was confirmed by NMR and X-ray diffraction techniques. Mechanisms for their formation are also proposed. © 2002 Elsevier Science Ltd. All rights reserved.

In recent works we[1] and others[2] have successfully used 5-aminopyrazoles as starting materials for the synthesis of diverse fused heterocyclic compounds. For example, we have reported the reaction of 5-amino-3-methyl-1-phenylpyrazole with chalcones and β-dimethylamino-propiophenone-hydrochlorides as versatile methods for the synthesis of new pyrazolopyridine derivatives.[3] Some of these compounds have displayed interesting biological activities.[4]

Continuing with our ongoing studies on the synthesis of pyrazolopyridine derivatives and in an attempt to obtain the new tetrahydropyrazolopyridines **3** using benzotriazole methodology,[5] the benzotriazolyl deriva-



Scheme 1. (Bt = Benzotriazol-1-yl).

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tive **2** was prepared from the 5-aminopyrazole **1** and 1-hydroxymethylbenzotriazole as a white solid in 84% yield (Scheme 1).[6]

Treatment of compound **2** with electron-rich alkenes to afford product **3** with PTSA as catalyst yielded the unexpected isomeric compound **4** in 90% yield instead of the expected **3**. The same rearrangement product was obtained without the presence of the alkenes. Compounds **2** and **4** were completely characterized by spectroscopic (IR, NMR, and mass spectrometry) and analytical measurements, and by X-ray diffraction for both compounds.[6–9]

The rearrangement from **2** to **4** can be explained based mainly on the higher nucleophilicity of the pyrazole ring versus the alkene, and on the cation-stabilizing character of the Bt moiety.[10] So, the *p*-toluenesulfonic acid helps the migration of the $BtCH_2^+$ fragment from 5-NH to 4-C positions through the cationic species **5**, as shown in Scheme 2. The high yield obtained for **4** indicates no competitive reaction of the vinyl ether due to its lower reactivity.

The results indicate that compound **2** is the kinetic product while **4** is the thermodynamic one. We also observed that compound **2** slowly converts into **4** even in the neutral alcoholic solution; the rate speeds up when the acid is added. It is worth mentioning that attempts to cyclize compound **4** under (i) conditions were also unsuccessful.

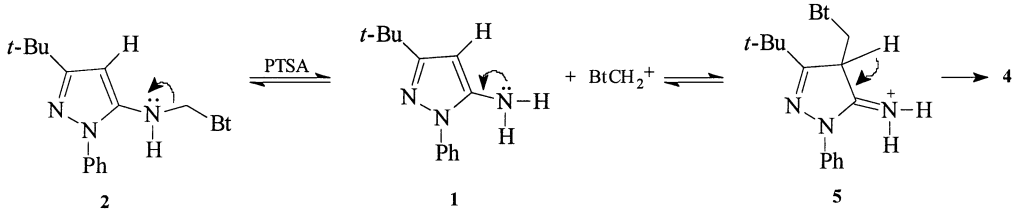
A Lewis, like Ag^+ ion was used instead of a protic acid in order to obtain the product **3** (it reacts fast and easily with BtH and Bt derivatives to produce an insoluble white precipitate of AgBt),[11] then compound **2** was treated at room temperature with a methanolic solution of $AgNO_3$ (1 equiv.) and dodecylvinylether (1 equiv.) (Scheme 3). This experiment was carried out with the purpose of removing selectively the Bt^- ion and trapping the cationic species **6** formed (Scheme 4) with an electron-rich alkene that would yield **3**.

On the contrary, a white solid mixture of two compounds, one of them AgBt, was isolated. After removing the AgBt, spectroscopical and analytical analyses of the remaining product indicate that the structure of the white solid surprisingly corresponded to the pyrazolic Tröger's base **9** (75% yield based on **1**) (Scheme 3). No expected product **3** was isolated, but traces of free pyrazole **1** were detected by TLC in the reaction mixture. Recently, we have obtained compound **9** (and analogues) from the reaction of pyrazole **1** and formaldehyde in ethanol and acetic acid as catalyst.[12]

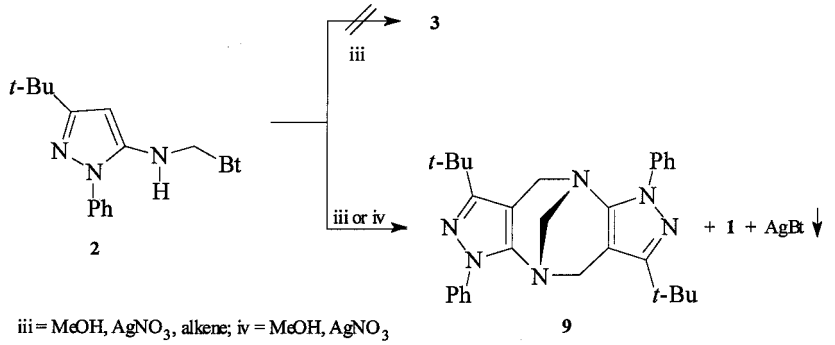
Formation of compound **9** could occur according to the mechanism shown in Scheme 4.

In this sequence, compound **9** could be formed from a first dimerization of the cationic species **6** to form the intermediate diazocinic **7** which reacts with a third species **6** to yield the intermediate **8**. Compound **8** can lose a molecule of pyrazole **1** by an intramolecular nucleophilic attack (catalyzed by the HNO_3 formed in situ), affording the Tröger's base **9**. It is worth emphasizing that pyrazole **1** was detected by TLC of the reaction mixture. Alternatively, intermediate **7** could react with a molecule of **2** to afford **9**, previous elimination of both BtH (trapped by Ag^+) and pyrazole **1** molecules. Formation of Tröger's bases by benzotriazole methodology has not already been reported.

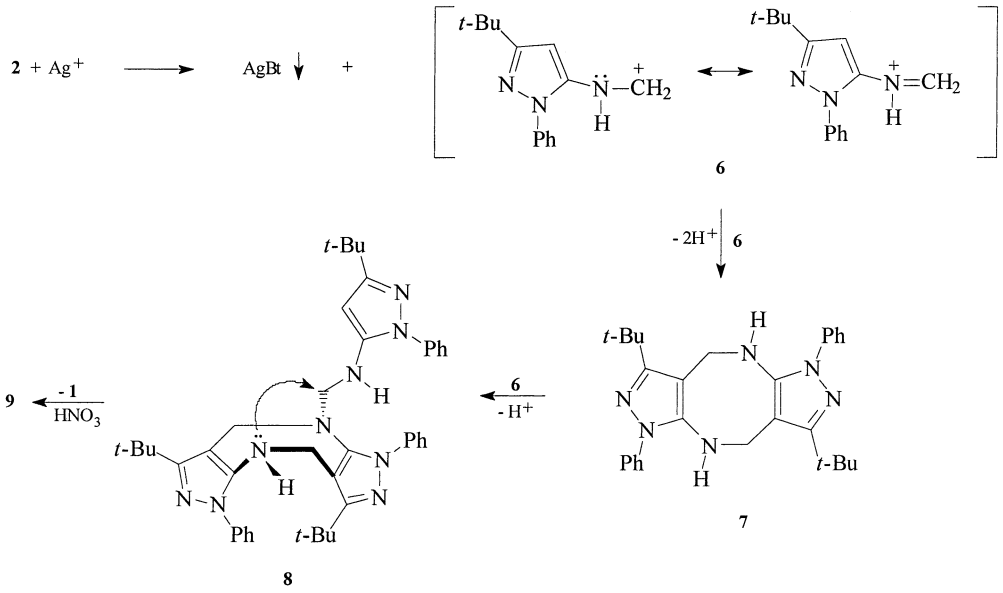
In conclusion, the benzotriazolyl-derivative **2** behaves in an unusual manner under the present reaction conditions, compared with their anilino, diazepino and indolino analogues previously reported as effective starting materials for the synthesis of interesting fused heterocyclic compounds,[5] due to its higher nucleophilic character.



Scheme 2.



Scheme 3.



Scheme 4.

In an ongoing experiment, we are planning to block or deactivate 5-amino group by alkylation or acetylation, respectively, of compound **1**, and in this way to try to prevent the formation of compounds **4** or **9** and so to induce the reaction with the vinyl ethers to form compounds **3**. Compound **4** is also synthetically interesting and we will try in a future work to find its synthetic applicability.

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6. **5-*N*-(Benzotriazol-1-ylmethyl)amino-1-phenyl-3-*tert*-butylpyrazole 2**. A solution of 5-amino-1-phenyl-3-*tert*-butylpyrazole **1** (1.0 g, 4.65 mmol), 1-hydroxymethylbenzotriazole (0.7 g, 4.69 mmol) and 5 mL of ethanol was heated to reflux for 3 min. After cooling, the precipitate formed was filtered and washed with ethanol. White solid (84% yield; mp 180°C). IR (cm^{-1}) 3286 (NH); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.17 (s, 9H), 5.74 (s, 1H, 4-H), 6.00 (d, $J=9.0$ Hz, 2H, CH_2), 7.11 (t, $J=9.0$ Hz, 1H, NH), 7.32–7.53 (m, 7H), 7.99 (br d, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 30.0, 31.8, 58.5 (CH_2), 85.8 (4-C), 111.2, 119.0, 123.6, 124.0, 126.5, 127.2, 129.1, 132.2, 138.7, 145.4 (two C), 160.8; MS: (70 eV) m/z (%) 346 (0.5, M^+), 229 (52), 212 (100); Anal. calcd for $C_{20}H_{22}N_6$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.28; H, 6.43; N, 24.23.
7. **5-Amino-4-(benzotriazol-1-ylmethyl)-1-phenyl-3-*tert*-butylpyrazole 4**. To a solution of 0.3 g (0.867 mmol) of **1** in 15 mL of absolute methanol were added 20–30 mg of *p*-toluenesulfonic acid, and the mixture was stirred at room temperature for 1 h (TLC control). The solvent was removed under reduced pressure, the residue was re-dissolved in ethyl acetate, washed with a 10% NaOH solution and dried with anhydrous sodium sulfate. The solution was concentrated and purified by column chromatography on silica gel with a mixture 80:20 (hexane:ethyl acetate) as eluent, yielding 0.27 g (90%) of compound **4** as white crystals (mp 124°C). IR (cm^{-1}) 3401, 3293 (5-NH_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 4.38 (br s, 2H, 5-NH_2), 5.70 (s, 2H, CH_2), 7.15–7.82 (m, 8H), 8.01 (d, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.0, 33.5, 43.8 (CH_2), 94.6 (4-C), 110.3, 120.4, 124.3, 124.6, 126.2, 129.8 (two C), 132.9, 138.7, 146.0 (two C), 158.1; MS: (70 eV) m/z (%) 346 (70,

M^+), 227 (100), 212 (20); Anal. calcd for $C_{20}H_{22}N_6$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.30; H, 6.38; N, 24.24.

8. For X-ray structure of compound **2**, see: Glidewell, Ch.; Low, J. N.; Cobo, J.; Nogueras, M.; Sánchez, A.; Rengifo, E.; Abonia, R. *Acta Crystallogr*. **2002**, *C58*, 314–317.
9. For X-ray structure of compound **4**, see: Low, J. N.; Cobo, J.; Nogueras, M.; Sánchez, A.; Rengifo, E.; Abonia, R. *Acta Crystallogr*. **2002**, *E58*, o53–o54.
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