A Novel Rearrangement to 1,2,4-Triazolo[1,5-*a*]quinoxalines

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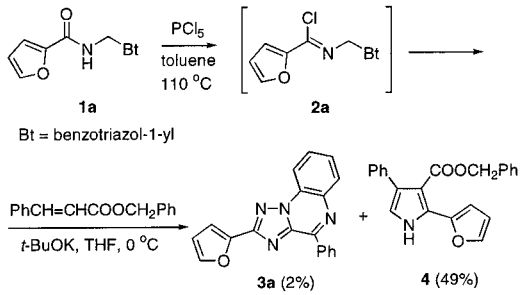
Abstract: Reactions of benzyl bromide or benzyl cinnamate with *N*-(benzotriazol-1-ylmethyl)arylimidoyl chlorides (**2a**,**b**) in the presence of *t*-BuOK occur with opening of the benzotriazole ring affording 1,2,4-triazolo[1,5-*a*]quinoxalines (**3a**,**b**). A possible reaction mechanism is discussed.

1,2,4-Triazolo[1,5-*a*]-pyrazines and -quinoxalines possess a broad spectrum of physiological and biological activities, which have attracted much recent attention from medicinal chemists. Thus, Cecchi et al. showed 1,2,4-triazolo[1,5-*a*]quinoxalines to be potent benzodiazepine receptor ligands,[1] adenosine receptor ligands,[2] and highly selective glycine/NMDA and AMPA receptor antagonists.[3]

The rather limited synthetic approaches to such polycycles include (i) simultaneous formation of both triazole and pyrazine heterorings on treatment of 2-aza-1,3-diene-1,1-dicarbonitriles with hydrazides,[4] (ii) pyrazine ring formation by intramolecular reductive cyclization of 1-(2-nitroaryl)-2-alkoxycarbonyl-1,2,4-triazoles, themselves prepared in four steps from the corresponding *o*-nitroanilines,[1,3,5] (iii) triazole ring formation by acid-induced intramolecular cyclization of quinoxaline amidine or formamidoxime,[6] and (iv) substituent modification of the already existing bis(heterocyclic) core system, preliminarily obtained by aforementioned methods.[2,6,7]

Intramolecular benzotriazole ring opening−ring closure without elimination of nitrogen is a powerful tool for the preparation of nitrogen-containing fused heterocyclic systems such as pyrazolo[5,1-*b*]benzimidazoles[8] and tetrazolo[1,5-*e*][1,2,5]triazepines.[9] We now demonstrate its applicability to 1,2,4-triazolo[1,5-*a*]quinoxalines.

Scheme 1



Following earlier work,[10] we reacted benzyl cinnamate with *N*-(benzotriazol-1-ylmethyl)furylimidoyl chloride (**2a**), prepared in situ from the corresponding α-benzotriazolyl amide **1a**, in the presence of potassium *tert*-butoxide and obtained, along with the expected pyrrole **4**[10] (49%), 2-furyl-4-phenyl-1,2,4-triazolo[1,5-*a*]quinoxaline (**3a**) as a minor product (2%) (Scheme 1). Structure **3a**, assigned on the basis of ^{1}H and ^{13}C NMR data,[2,4] was confirmed by X-ray crystallography.

Apparently, only one nonaromatic carbon of the original benzyl cinnamate molecule is retained in the structure **3a**. From this, we hypothesized that an early step in the formation of **3a** was benzylation of an α-amino carbanion, formed by deprotonation of the intermediate *N*-(benzotriazol-1-ylmethyl)furylimidoyl chloride (**2a**); this affords the α-benzylated product of type **5** and potassium cinnamate. Indeed, treatment of *N*-(benzotriazol-1-ylmethyl)aryl(heteroaryl)imidoyl chlorides **2a**,**b** (prepared in situ) with the more efficient benzyl group donor, benzyl bromide, and *t*-BuOK in THF under reflux smoothly gave 1,2,4-triazolo[1,5-*a*]quinoxalines **3a**,**b** in 25−31% yields. These reactions also proceed at 0 °C, but in lower yields. Compounds **3a**,**b** give blue fluorescent spots on TLC plates under UV irradiation and are easily monitored during purification by column chromatography. The structure of compound **3b** is assigned by analogy and by comparison of its NMR data with those of **3a**.

The mechanism of the transformation **5** → **3** suggested in Scheme 2 is speculative. Ring closure of **5** induced by participation of the benzotriazole N-2 electron lone pair could give **6**, which ring opens to the eight-membered 1,2,4,6-tetrazocane **7**. The latter rearranges to the enamine form **8**. Further ring closure−ring opening, possibly via **9**, would result in the 4,5-dihydro-1,2,4-triazolo[1,5-*a*]quinoxaline **10**, which is oxidatively aromatized into 1,2,4-triazolo[1,5-*a*]quinoxaline **3**.

In conclusion, we have shown that benzylation of *N*-(benzotriazol-1-ylmethyl)-substituted imidoyl chlorides under basic conditions induces an unusual rearrangement, accompanied by benzotriazole ring opening, with

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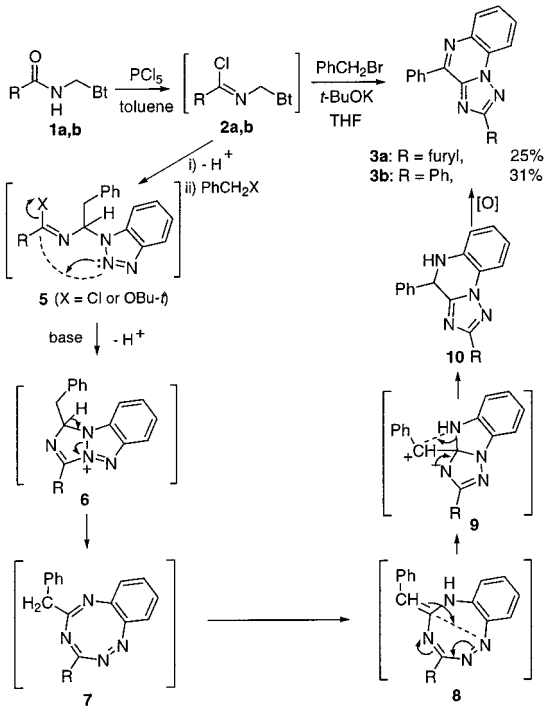
Scheme 2



the formation of 1,2,4-triazolo[1,5-*a*]quinoxalines. A possible mechanism of the rearrangement is discussed.

Experimental Section

General Comments. Melting points were measured on a hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR data were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ as a solvent and with TMS (for ^{1}H) or the solvent (for ^{13}C) as an internal standard. Column chromatography was carried out on silica gel (activated, neutral, 50−200 μm). Tetrahydrofuran was purified by distillation from Na/benzophenone under nitrogen. *N*-(Benzotriazol-1-ylmethyl) amides **1a**,**b** were prepared as described previously.[11]

General Procedure for the Preparation of 1,2,4-Triazolo[1,5-*a*]quinoxalines 3 from *N*-(Benzotriazolylmethyl) Amides 1a,b and Benzyl Bromide. *N*-(Benzotriazol-1-ylmethyl)furylcarboxamide **1a** (1.21 g, 5 mmol) was dissolved in toluene (100 mL) and treated with phosphorus pentachloride (1.25 g, 6 mmol). The reaction mixture was heated at 90−100 °C for 3 h and then filtered, and the solvent was removed under reduced pressure. The crude imidoyl chloride **2a** obtained was used in the subsequent reaction without additional purification. A mixture of crude imidoyl chloride **2a** (0.83 g, 3 mmol) and benzyl bromide (0.62 g, 3.6 mmol) in dry tetrahydrofuran (30 mL) was treated with potassium *tert*-butoxide (1.12 g, 10 mmol). The reaction mixture was stirred for 0.5 h at room temperature, heated under reflux for an additional 4 h, allowed to cool, and filtered. The residue obtained after solvent evaporation was purified by column chromatography (eluting with 50/1 hexane/EtOAc) to give 2-furyl-4-phenyl-1,2,4-triazolo[1,5-*a*]quinoxaline **3a** (0.23 g, 25%) as pale yellow needles.

2-Furyl-4-phenyl-1,2,4-triazolo[1,5-*a*]quinoxaline 3a: pale yellow needles (25%), mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 6.61 (dd, J = 3.5, 1.7 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.55−7.74 (m, 6H), 8.21 (dd, J = 8.1, 1.5 Hz, 1H), 8.50 (dd, J = 8.1, 1.7 Hz, 1H), 8.83−8.87 (m, 2H); ^{13}C NMR δ 111.8, 112.1, 115.4, 127.4, 127.6, 128.6(2), 129.6(2), 129.7, 130.2, 131.1, 135.1, 136.4, 144.0, 144.4, 146.0, 148.5, 156.7. Anal. Calcd for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.87; N, 17.94. Found: C, 72.79; H, 3.74; N, 18.00.

2,4-Diphenyl-1,2,4-triazolo[1,5-*a*]quinoxaline 3b: colorless needles (31%), mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.50−7.65 (m, 6H), 7.70 (t, J = 7.7 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.46 (dd, J = 8.0, 1.4 Hz, 2H), 8.54 (d, J = 8.0 Hz, 1H), 8.95 (dd, J = 8.0, 1.6 Hz, 2H); ^{13}C NMR δ 115.4, 127.4, 127.5(2), 127.8, 128.6(2), 128.8(2), 129.6, 129.7(2), 130.2, 130.3, 130.4, 131.1, 135.4, 136.4, 144.3, 148.6, 164.0. Anal. Calcd. for $C_{21}H_{14}N_4$: C, 78.24; H, 4.38; N, 17.38. Found: C, 77.87; H, 4.73; N, 17.14.

Supporting Information Available: Perspective view of the X-ray crystal structure of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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