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Studies towards understanding the mechanism of the unusual rearrangement of certain 5-propargyloxyindoles

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Abstract

A mechanism of the rearrangement of 5-propargyloxyindoles is proposed and supported by the formation of a novel tetracyclic indole derivative **12** as the major product in the cyclization of 5-propargyloxytryptophol **10**.

Keywords: indole; pyrano[3,2-*e*]indole; Claisen rearrangement; conformationally restricted serotonin analogs; conformationally restricted tryptamines.

Our work has shown dihydropyrano[3,2-*e*]indole to be a rotationally restricted phenolic replacement for the 5-hydroxyindole portion in certain agonists for serotonin 5-HT_2 receptors.[1] This structural feature imparts significant 5-HT_2 versus 5-HT_1 receptor potency and selectivity within a series of tryptamine analogs.[1] During the course of our efforts to improve the synthesis of a 5-HT_2 receptor selective analog (**1**) of the neurotransmitter serotonin (Scheme 1, Fig. 1), we explored the use of the rearrangement of the 5-propargyloxyindole **2** as a direct means to access the desired pyrano[3,2-*e*]indole framework exemplified in **1**.[2] While there have been a limited number of reports of this type of transformation with simple benzene rings,[3] this reaction had not been generally applied to indoles.[4] Furthermore, during the formation of **1** from **2**, an unusual tetracyclic by-product (**3**) was also formed (Scheme 1).[2]

Because of the dearth of reports of this transformation with indoles and hoping to explain the formation of the unusual product **3**, we have embarked on an investigation of the mechanism of the rearrangement of 5-propargyloxyindoles. We endeavor to explain the formation of **1** and **3** and to understand the generality of the transformation which gave rise to **3**. This communication summarizes our preliminary results in this area.

In our original work that gave rise to the unusual tetracyclic indole derivative **3**, characterization of the compound by NMR was made difficult because of the presence of the *N*-carbobenzyloxy

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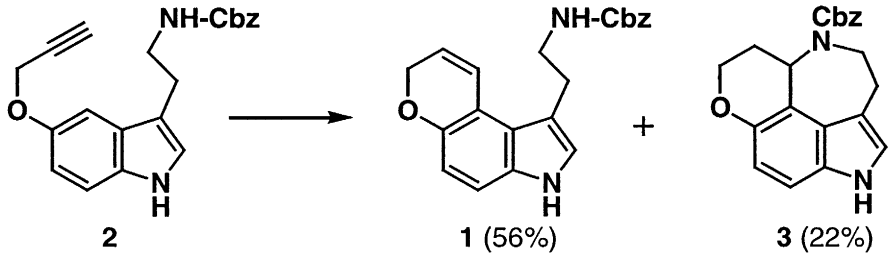
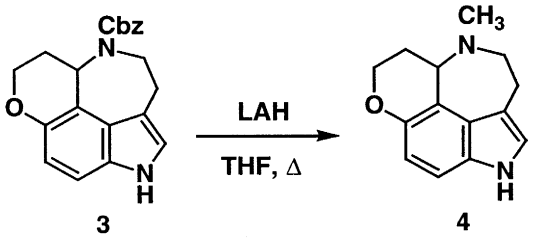


Scheme 1.

Fig. 1.

group (*N*-Cbz). Thus, the -Cbz group was reduced by LAH to form a crystalline amine **4** (Scheme 2) which was characterized by a combination of NMR, IR and elemental analysis.[2] Because of its highly unusual structure and unexplained formation, we have reprepared **4** for X-ray crystallographic analysis and confirmation. This experiment[5] unequivocally confirmed the structure of **4** as a unique, fully conformationally restricted analog of serotonin (Fig. 2).



Scheme 2.

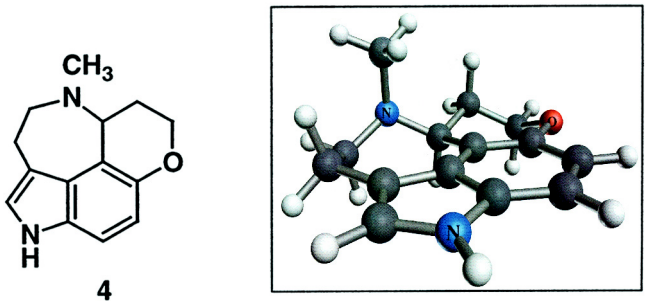
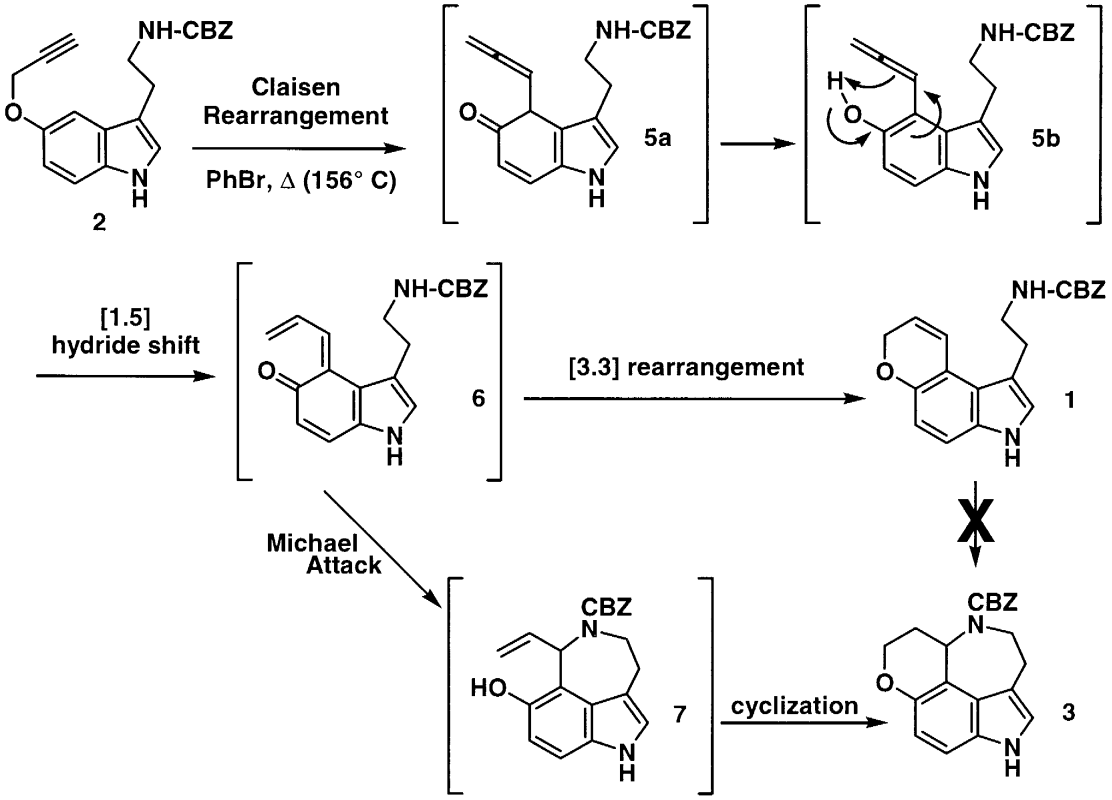


Fig. 2.

The question of whether tetracycle **3** arose from an additional cyclization of pyranoindole **1** was immediately addressed. While the transformation of **2** to the combination of **1** and **3** occurred in three days in refluxing bromobenzene (156°C, Scheme 1), continued heating of **1** (purified from the reaction

and again subjected to bromobenzene reflux) *did not* afford any additional tetracycle **3**. Only returned **1** and decomposition were observed in this reaction (Scheme 3). This result leads to the conclusion that, while **1** and **3** may have come from a common intermediate in the reaction mechanism, the unusual tetracyclic indole **3** *did not* come from the pyrano[3,2-*e*]indole **1**.

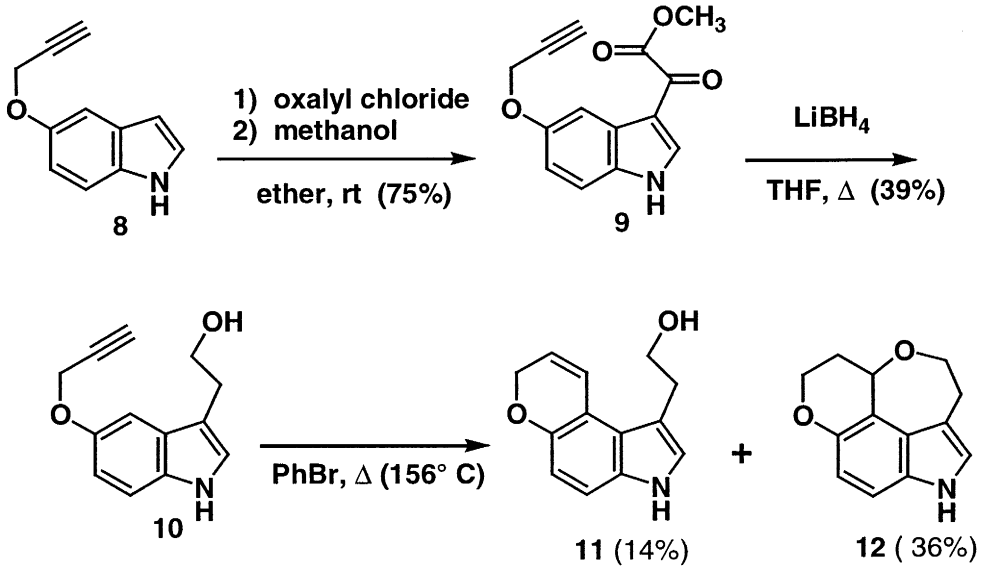


Scheme 3.

This result has led us to a working hypothesis for the reaction mechanism which attempts to explain the formation of both **1** and **3** (Scheme 3). In this hypothesized reaction mechanism, the propargyloxyindole **2** undergoes a Claisen rearrangement to afford allene **5a**. Most reaction mechanisms used to explain the propargyloxybenzene analog of this reaction also utilize this as the first step in the process.[3] Tautomerization of **5a** to phenol **5b**, followed by a [1.5] hydride shift would afford diene **6**. Compound **6** represents the common intermediate for both the pyrano[3,2-*e*]indole **1** and the tetracyclic indole **3**. A [3.3] electrocyclic rearrangement of **6** would lead to rearomatization of the indole and to the formation of the pyranoindole **1**. Alternatively, **6** represents a highly electrophilic Michael acceptor, and the amide of the -NH-Cbz could add forming **7**. This phenolic olefin is ideally situated for cyclization as previously described by Evans and Kirby.[6] This cyclization would lead to the tetracyclic indole product **3**.

Using this working hypothesis, one would predict that a 5-propargyloxyindole derivative in which the pendent nucleophile was either more nucleophilic or less sterically encumbered than the amide in **2** would afford a greater proportion of the tetracyclic product analogous to **3**. Following this logic, tryptophol **10** was prepared using standard indole methodologies (Scheme 4). Heating the alcohol **10** in refluxing bromobenzene[7] for three days afforded a mixture of the pyranoindole **11** (14%) and the tetracyclic indole **12** (36%).[8] Clearly in this reaction sequence, a greater proportion of the tetracyclic

indole was obtained (i.e., >2:1 [**12**:**11**] versus <1:2 [**3**:**1**]). This result supports our hypothesized reaction mechanism indicating that the nucleophilicity and/or steric nature of the pendant nucleophile can have a significant effect on the outcome of this unusual rearrangement. It should be noted that the overall yield of isolated products (i.e., **12** and **11**, 50%) was lower for the tryptophol **10** than for the amide **2** (i.e., **3** and **1**, 78%). This demonstrates a weakness in this methodology: the 5-propargyloxyindole derivative and its products need to be stable to the rather severe reaction conditions (i.e., three days heating at 156°C).



Scheme 4.

We continue to prepare 5-propargyloxyindole derivatives that can be used to provide additional insight into this unusual reaction sequence. Results from these studies will be reported in due course.

References

1. Macor, J. E.; Fox, C. B.; Johnson, C. J.; Koe, B. K.; Lebel, L. A.; Zorn, S. H. *J. Med. Chem.* **1992**, *35*, 3625.
2. Macor, J. E. *Tetrahedron Lett.* **1995**, *36*, 7019.
3. Kakigami, T.; Baba, K.; Usui, T. *Heterocycles* **1998**, *48*, 2611 and references cited therein.
4. To our knowledge, only three reports of this transformation with indoles exist: (a) Ref. 2; (b) Macor, J. E.; Blank, D. H.; Post, R. J. *Tetrahedron Lett.* **1994**, *35*, 45; (c) Plug, J. P. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron Lett.* **1992**, *33*, 2179.
5. Crystallographic data for **4**: $C_{14}H_{16}N_2O$; beige plates from methanol; cell parameters (T=−53°C) *a*=5.940(1) Å, *b*=15.089(2) Å, *c*=12.910(2) Å; β=100.27(1)°, *V*=1138.6(6) Å^3; space group: P2$_1$/c, *Z*=4; *R*=0.053, *R*w=0.065 for refinements based on 1601 observed [$I>3\sigma(I)$] reflections. In the solid state molecular conformation of **4**, the methyl group on the azepine nitrogen is in the axial position, and the equatorial lone pair of electrons from the azepine nitrogen is intermolecularly H-bonded to an adjacent indole -NH-.
6. Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1259.
7. The best yields for all of the cyclization reactions described in this paper were obtained when the reaction solution was thoroughly deoxygenated prior to heating under nitrogen.
8. The spectral and physical properties of **12** are as follows: mp 151–153°C; IR (KBr) 3260, 1490, 1420 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 8.00 (br, 1H), 7.12 (d, *J*=8.8 Hz, 1H), 6.98 (s, 1H), 6.69 (d, *J*=8.4 Hz, 1H), 4.87 (dd, *J*=5.7 and 10.5 Hz, 1H), 4.55–4.50 (m, 1H), 4.43–4.39 (m, 1H), 4.30 (dt, *J*=3.1 and 11.4 Hz, 1H), 3.82 (dt, *J*=4.0 and 11.4 Hz, 1H), 3.17–3.05 (m, 2H), 2.39–2.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 147.1, 131.2, 125.2, 121.8, 117.2, 114.5, 112.3, 111.0, 78.4, 73.2, 65.5, 30.0, 29.4; LRMS *m/z* (relative intensity) 216 (100, [MH$^+$]). Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.39; H, 6.04; N, 6.31. Crystallographic data for **12**: $C_{13}H_{13}NO_2$; beige prisms from ethyl acetate/hexanes;

cell parameters (T=22°C) a=8.946(2) Å, b=11.378(2) Å, c=10.212(2) Å; β=93.86(2)°, V=1037.1(4) Å^3; space group: $P2_1/n$, Z=4, R=0.050, Rw=0.066 for refinements based on 1489 observed [$I>3\sigma(I)$] reflections. The solid state molecular conformation of **12** was similar to that of **4**. However, whereas the *equatorial* lone pair of electrons from the azepine nitrogen in **4** is intermolecularly H-bonded to the indole -NH-, the *axial* lone pair of electrons from the oxygen in the oxepine ring in **12** is intermolecularly H-bonded to the indole -NH-. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).