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Thermal and Acid-Catalyzed Hofmann–Martius Rearrangement of 3-*N*-Aryl-2-oxindoles into 3-(Arylamino)-2-oxindoles

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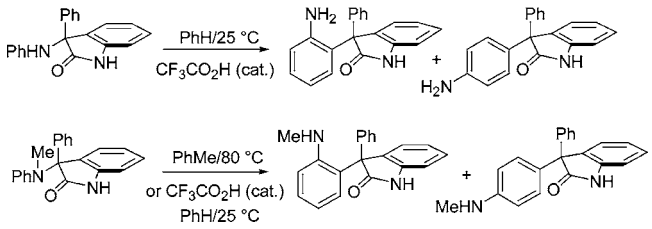
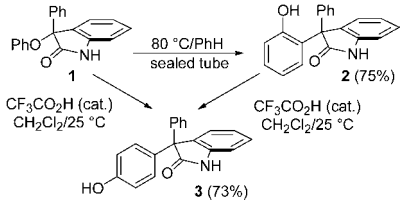
ABSTRACT



The Hofmann–Martius rearrangement of 3-*N*-aryl-2-oxindoles into 3-(arylamino)-2-oxindoles under thermal and acid-catalyzed conditions is described.

Recently, we reported the unusual thermal and acid-catalyzed rearrangement of 3-aryloxy-2-oxindoles into 3-(arylhydroxy)-2-oxindoles.[1] For example, heating **1** at 80 °C resulted in rearrangement to the ortho isomer **2**, Scheme 1, whereas

Scheme 1. Rearrangement of 3-Phenoxy-2-oxindoles



treatment of **1** with CF_3CO_2H (cat.) at 25 °C gave the para isomer **3**. Furthermore, to emphasize the thermodynamic driving force in these transformations, exposure of **2** to CF_3CO_2H (cat.) at 25 °C converted it into **3**.

Since compounds similar to **2** and **3** have found applications as antiproliferatives[2] and calcium-dependent potassium channel openers,[3] we decided to examine the nitrogen analogue (aniline) version of this rearrangement chemistry. The conversion of *N*-alkylanilines into *C*-alkylanilines under acidic conditions is known as the Hofmann−Martius rearrangement.[4,5]

(1) Goldberg, F. W.; Magnus, P.; Turnbull, R. *Org. Lett.* **2005**, *7*, 4531−4534.

(2) Natarajan, A.; Fan, Y.-H.; Chen, H.; Guo, Y.; Iyasere, J.; Harbinski, F.; Christ, W. J.; Aktas, H.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 1882−1885.

(3) Hewawasam, P.; Erway, M.; Moon, S.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487−1499.

(4) Hofmann, A. W.; Martius, C. A. *Ber* **1871**, *4*, 742−748. Hofmann, A. W. *Ber* **1872**, *5*, 720−722. Reilly, J.; Hickinbottom, W. J. *J. Chem. Soc.* **1920**, 103−137. Hickinbottom, W. J. *J. Chem. Soc.* **1937**, 404−406. Willenz, J. *J. Chem.* Soc. **1955**, 1677−1682. Hart, H.; Kosak, J. R. *J. Org. Chem.* **1962**, *27*, 116−127. For a more recent example of this type of rearrangement, see: Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542−14543.

(5) Banthorpe, D. V. Rearrangments involving amino groups. In *The chemistry of the amino group*; Patai, S., Ed.; Interscience: New York, 1968; pp 585−667.

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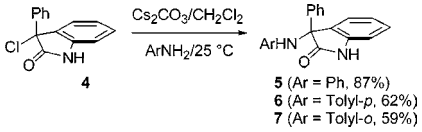
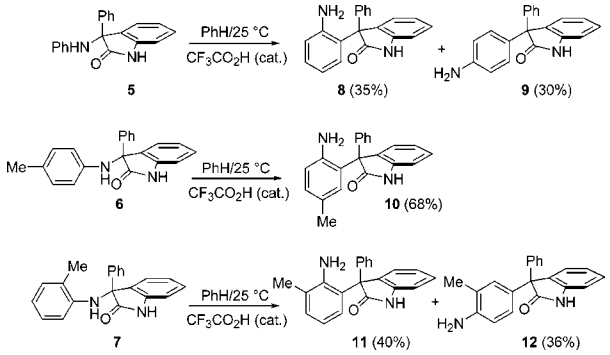
Treatment of **4**[6] with aniline, *p*-toluidine, and *o*-toluidine, respectively, in CH_2Cl_2 at 25 °C in the presence of Cs_2CO_3 gave **5** (87%), **6** (62%), and **7** (59%), Scheme 2.

Scheme 2. 3-NHAr-2-oxindoles



Somewhat surprisingly, the adduct **5** did not rearrange to either **8** or **9** (Scheme 3) under thermal reaction conditions

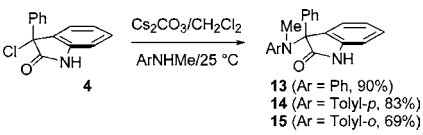
Scheme 3. Acid-Catalyzed Rearrangement



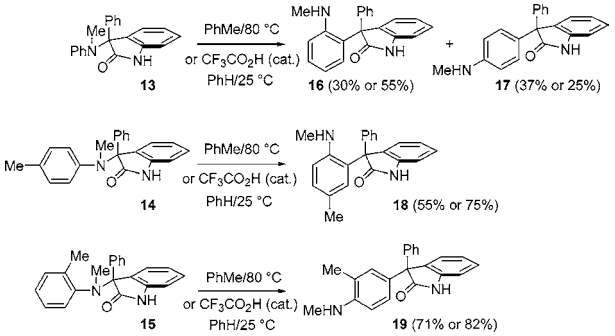
(80 °C/PhH, sealed tube) that had sufficed for the phenoxy adduct **1**. Heating **5** in *o*-dichlorobenzene at 180 °C resulted in decomposition with no trace of **8** or **9**.[7] It is speculated that at higher temperatures the compounds **5**−**7** undergo homolysis[8] to an *N*-centered aniline radical and a 2-oxindole radical.[9] Indeed, melting **5** and heating neat at 220 °C for 2 h resulted in a complex mixture of products derived from homolysis. Consequently, we examined acidic reaction conditions to effect the rearrangement. Treatment of **5** with CF_3CO_2H (cat.) in benzene at 25 °C for 18 h produced the ortho product **8** and para product **9** in 35% and 30% yield, respectively, Scheme 3. Similarly, under the acidic reaction conditions, **6** was converted into **10** (68%), and **7** gave **11** (40%) and **12** (36%).

The *N*-methyl analogues **13**−**15** were made from **4** and the corresponding *N*-methylanilines using Cs_2CO_3 as the base, Scheme 4. These compounds were thermally labile and rearranged under the same conditions as the phenolic ethers. For example, heating **13** in toluene at 80 °C gave **16** (30%)

Scheme 4. 3-NMeAr-2-oxindoles



Scheme 5. Thermal and Acid-Catalyzed Rearrangement

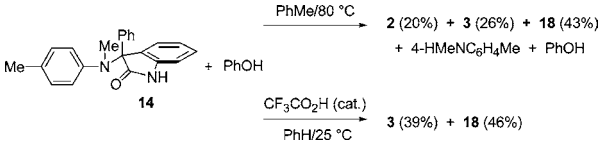


and **17** (37%), Scheme 5. Likewise, heating **14** gave **18** (55%), and **15** gave only the para isomer 1**9** (71%).

The acid-catalyzed rearrangement of the *N*-methyl series using CF_3CO_2H (cat.) in benzene at 25 °C for 18 h converted **13** into **16** (55%) and **17** (25%), **14** into **18** (75%), and **15** into **19** (82%), Scheme 5.

To demonstrate the dissociative[10] reversible nature of these rearrangements we conducted two crossover experiments. Treatment of **14** with phenol (1.0 equiv) in toluene at 80 °C gave **2** (20%), **3** (26%), and **18** (43%) along with *N*-methyl *p*-toluididne and phenol, Scheme 6. Conducting the same

Scheme 6. Crossover Experiments



experiment under the acidic reaction conditions of CF_3CO_2H (cat.) in benzene at 25 °C for 18 h gave **3** (39%) and **18** (46%). The ortho product **2** was not detected. This information is consistent with the mechanism suggested for the phenol rearrangement,[1] Scheme 1.

We attribute the thermal stability of the NH series (**5**−**7**) to the presence of intramolecular hydrogen bonds: X-ray crystallography shows intermolecular H-bonding in a dimeric fashion between the NH (aniline) and the amide carbonyl groups (Figure 1).

The NMe series behaves "normally" and thermally ionizes in the same manner as the phenolic ethers. The thermal rearrangement of **13** proceeds to the ion pair **20** which appears to dissociate to **23** rather than form the π-complex **21** which would lead exclusively to **16** via **22** (cf. Scheme

(6) Bruce, J. M.; Sutcliffe, F. K. *J. Chem. Soc.* **1957**, 4789−4798.
(7) If **8** and/or **9** had been formed they would have been stable to the reaction conditions.
(8) Magnus, P.; Venable, J. D.; Shen, L.; Lynch, V. *Tetrahedron Lett.* **2005**, *46*, 707−710.
(9) Akira. I.; Yutaka, M. *Heterocycles* **1982**, *19*, 2139−2142.
(10) Alder, R. W.; Baker, R.; Brown, J. M. Dissociative Processes. In *Mechanisms in Organic Chemistry*; Wiley-Interscience: New York, 1971; pp 78−179.

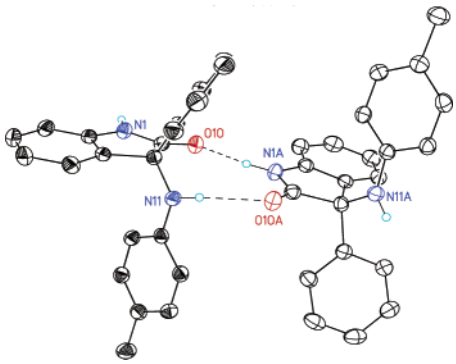
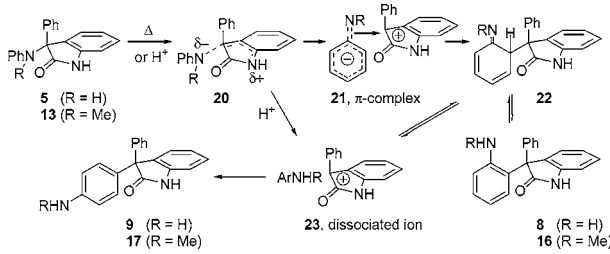


Figure 1. ORTEP representation of dimeric **6** X-ray structure.

1), Scheme 7. The dissociated intermediate **23** can form both **16** and **17**,[11] which is what we observe. The acid-catalyzed rearrangement gives the same product distribution as the thermal version and proceeds via **23**. The only noticeable difference between the NH and NMe series is that **7** gave a mixture of the ortho and para adducts **11** and **12**, respectively, whereas **15** only gave the para adduct **19**.

Scheme 7. Proposed Mechanism of Rearrangement



Because of the structural relationship of these adducts to the core of diazonamide[12] and physostigmine[13] analogues, we attempted to reduce the amide carbonyl group of some of the rearrangement products. It was found that treatment

(11) For structures analogous to 17 see: Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677−680.

(12) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765−4770. Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773.

(13) Stedman, E.; Barger, G. *J. Chem. Soc.* **1925**, *127*, 247−258.

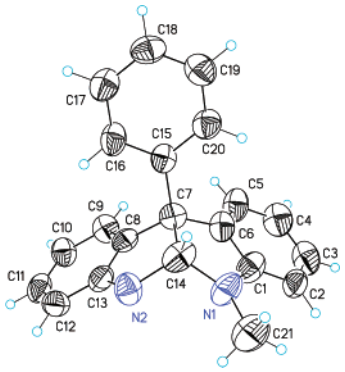
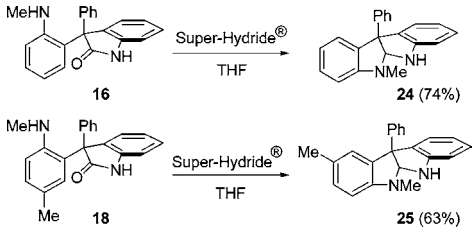


Figure 2. ORTEP representation of **24** X-ray structure.

of **16** and **17** with Super-Hydride in THF gave the aminals **24** (74%, structure by X-ray, Figure 2) and **25** (63%), Scheme 8.

Scheme 8. Formation of the Tetrahydroindolo[2,3-*b*]indole Aminal



In conclusion, we have demonstrated the versatility of the rearrangement reaction and have shown that it has potential applications in the synthesis of natural product analogues.

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Supporting Information Available: Experimental procedures, spectral data, and characterization of all new compounds. X-ray crystallographic data for compounds **6** and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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