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A Mild Thermal and Acid-Catalyzed Rearrangement of *O*-Aryl Ethers into *ortho*-Hydroxy Arenes

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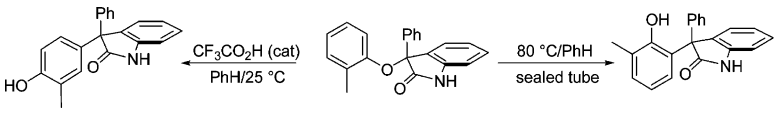
ABSTRACT



An unusual rearrangement of an *O*-aryl ether to an *ortho*-hydroxyaryl system was discovered during our studies on the synthesis of diazonamide A. We discuss the exploration of this rearrangement under mild thermal and both Brønsted and Lewis acid-catalyzed conditions.

The thermodynamic driving force of a large number of rearrangement processes involves the migration of an alkyl, acyl, or aryl group from attachment to a heteroatom (most frequently oxygen or nitrogen) to a carbon atom.[1] Two venerable reactions that fall under this broad classification are the well-known aromatic Claisen rearrangement[2] and the Fries rearrangement.[3] During our studies on the synthesis of diazonamide,[4] we discovered an unusual rearrangement that involves the mild thermal conversion of an *O*-aryl ether into an *ortho*-hydroxyaryl system. Warming **1** and **2** (ratio 1:1) converted them into **3** in 80% yield, and **4** was not observed.[5] There appears to be no immediate direct precedence for this rearrangement, although there is some analogy in the *O*-aryl glycoside to *C*-aryl glycoside conversion,[6] that is, the Lewis acid/Brønsted acid-catalyzed transformation of benzyl ethers of phenols into 2-hydroxydiphenylmethane derivatives,[7a−e] and it is known that *O*-trityl derivatives of phenols rearrange under acid-catalyzed conditions to *C*-tritylated products.[8] An unpublished thermal rearrangement of an *O*-cresyl ether into a *C*-cresol derivative[9] and the demonstrated antiproliferative activity of 3,3-diphenyl-1,3-dihydroindol-2-ones[10] provided the motivation to pursue the rearrangement chemistry described in Scheme 1.

To further explore the rearrangement depicted in Scheme 1, we first converted **5** and **8** into the corresponding *O*-aryl

(1) de Mayo, P. *Molecular Rearrangements: Parts 1 and 2*; Interscience: New York, 1963.

(2) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5, pp 827−866.

(3) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5, pp 745−760.

(4) For the correct structure of diazonamide A, see: (a) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765−4770. (b) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773.

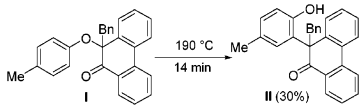
(5) Unpublished results.

(6) (a) Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1995**, *36*, 5807−5810. (b) Pinhey, J. T.; Xuan, P. T. *Aust. J. Chem.* **1988**, *41*, 69−80.

(7) (a) Dewar, M. J. S.; Puttnam, N. A. *J. Chem. Soc.* **1959**, 4080−4086, 4086−4090, 4090−4095. (b) de Mayo, P. *Molecular Rearrangements, Part 1 Aromatic Rearrangements*; Interscience: New York, 1963; pp 313−318. (c) Sprung, M. M.; Wallis, E, S. *J. Am. Chem. Soc.* **1934**, *56*, 1715−1720. (d) Tarbell, D. S.; Petropoulos, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 244−248. (e) Hart, H.; Elia, A. R. *J. Am. Chem. Soc.* **1954**, *76*, 3031−3032.

(8) (a) Baeyer, A.; Villiger, V. *Ber.* **1902**, *35*, 3013−3035. (b) Van Alphen, J. *Recl. Trav. Chim.* **1927**, *46*, 287−292. (c) Busch, M.; Knoll, R. *Ber.* **1927**, *60*, 2243−2257. (d) Schorigin, P. *Ber.* **1926**, *59*, 2502−2510; **1927**, *60*, 2373−2378; **1928**, *61*, 277−283. (e) Kharasch, M. S.; Reinmuth, O.; Mayo. F. R. *J. Chem. Educ.* **1936**, *13*, 7−12. (f) Iddles, H. A.; Chadwick, D. H.; Clapp, J. W.; Mart, R. T. *J. Am. Chem. Soc.* **1942**, *64*, 2154−2157. (g) Burton, H.; Cheeseman, G. W. H. *J. Chem. Soc.* **1953**, 832−837. (h) McKenzie, C. A.; Chuchani, G. *J. Org. Chem.* **1955**, *20*, 336−345.

(9) Bould. L. Studies on the synthesis of tetracycline. Ph.D. Thesis. Imperial College, London, 1968; p 150. The conversion of **I** into **II** is described.



I II (30%)

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

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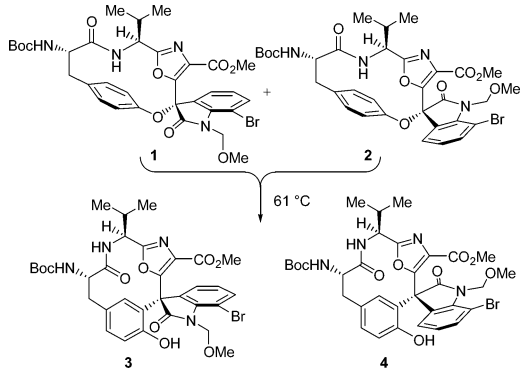
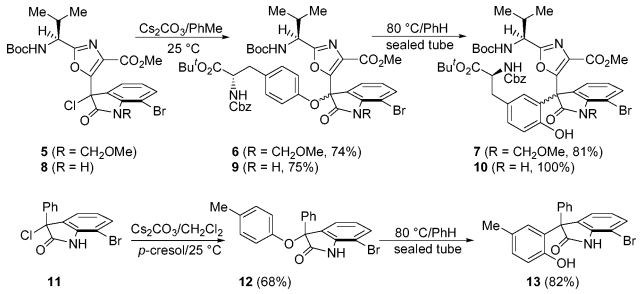
Scheme 1. Thermal Rearrangement in the Diazonamide Series



derivatives **6** and **9**, respectively, by treatment with Cbz-Tyr-O*t*Bu/Cs_2CO_3 (Scheme 2).[11] Heating **6** and **9** (ca. 1:1 mixture of diastereomers for each) in a sealed tube at 80 °C resulted in **7** and **10** (ca. 1:1 mixture of diastereomers for each), respectively. While the standard spectral information of the above compounds was in agreement with the proposed structural changes, we were not able to obtain X-ray crystallographic data to confirm this. Consequently, the conversion of **11** into **12** (see X-ray structure in Supporting Information) and its rearrangement into **13** (see X-ray structure in Supporting Information) was carried out for verification of the previous structural assignments (Scheme 2).

Scheme 2. Model Thermal Rearrangements



To examine the above rearrangement in more detail, we treated **14**[12] with a variety of phenols in CH_2Cl_2 at 25 °C in the presence of Cs_2CO_3, or refluxing CH_2Cl_2/Et_3N in the case of **15i** (Scheme 3, Table 1). In the cases of **15a**−**f** and **15h**, the *O*-aryl ether was the main product. For the substrates

Scheme 3. Thermal Rearrangements

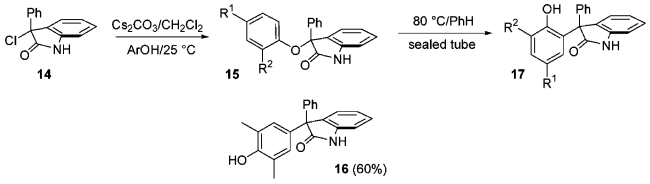


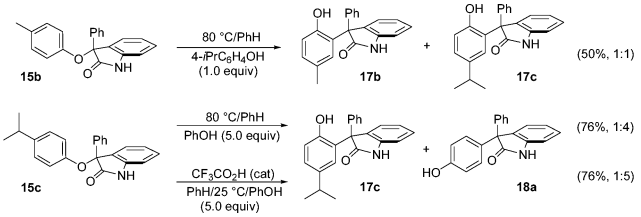
Table 1.

15	R^1	R^2	yield (%)	**17**	R^1	R^2	yield (%)
15a	H	H	73	**17a**	H	H	75
15b	Me	H	76	**17b**	Me	H	68
15c	^{i}Pr	H	64	**17c**	^{i}Pr	H	63
15d	NO_2	H	79	**17d**	NO_2	H	73
15e	Cl	H	76	**17e**	Cl	H	71
15f	MeCO	H	78	**17f**	MeCO	H	68
15g	OMe	H	n/a	**17g**	OMe	H	50
15h	H	Me	74	**17h**	H	Me	85
15i	H	OMe	n/a	**17i**	H	OMe	55

15g and **15i**, only the *C*-arylated products **17g** and **17i** were isolated. When a hindered 2,6-dimethyl phenol was used, only the *C*-arylated **16** was observed.

Heating **15a**−**f** and **15h** in benzene at 80 °C resulted in clean rearrangement to the 2-hydroxy isomers **17a**−**f** and **17h**, respectively. It is noteworthy that the phenol ether **15a** gave only the 2-hydroxy isomer **17a** and none of the 4-hydroxy isomer **18a**. The next experiments were to establish whether the rearrangement exhibited crossover. Subjecting **15b** to the same thermal conditions for the rearrangement but now in the presence of 4-*i*PrC_6H_4OH gave **17b** and **17c** as a 1:1 mixture (Scheme 4).

Scheme 4. Crossover Experiments



Clearly, this is classical evidence for the dissociative S_N1 mechanism, and as such, should be responsive to both Brønsted and Lewis acid catalysis.[13] This is indeed the case. A trace of trifluoroacetic acid caused the rearrangement of **15a** to **18a** to take place at 25 °C within a few hours, and exposure of **15a** to Lewis acids ($Cu(OTf)_2$, AgOTf, $TiCl_4$) at 25 °C also gave **18a**.

At first sight, it seems strange that the thermal dissociation of **15a** should give only *ortho*-substitution, yet the rearrangement exhibits crossover. Consequently, we examined the acid-catalyzed rearrangement of **15** and performed further crossover experiments. Treatment of **15a** and **15h** in benzene

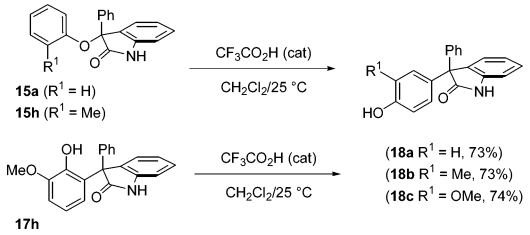
(11) For references to azaxylylene intermediates formed from 1,4-elimination, see: (a) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928−1931. (b) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068−5069. (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677−680. (d) Avemaria, F.; Vanderheiden, S.; Braese, S. *Tetrahedron* **2003**, *59*, 6785−6796.

(12) Sutcliffe, B. *J. Chem. Soc.* **1957**, 4789−4792.

(13) Alder, R. W.; Baker, R.; Brown, J. M. *Mechanisms in Organic Chemistry, Dissociative Processes*; Wiley-Interscience: New York, 1971; pp 78−179.

at 25 °C with a catalytic amount of CF_3CO_2H resulted in the *para*-substituted rearrangement products **18a** and **18b** and no trace (^{1}H NMR and TLC) of **17a** or **17b**. It was also noted that treatment of **17h** under the same conditions gave **18c** presumably via *ipso*-protonation (Scheme 5).

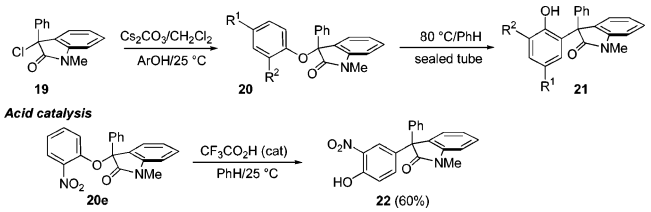
Scheme 5. Acid-Catalyzed Rearrangements



Thermal rearrangement of **15c** in the presence of phenol (5 equiv) gave **17c** and **18a** (1:4). The *ortho*-isomer **17a** was not detected. Similarly, CF_3CO_2H-catalyzed rearrangement of **15c** in the presence of phenol (5 equiv) gave **17c** and **18a** (1:5). These results point to two clear mechanistic pathways for the rearrangement (see later).

It was of some interest to see if the same chemistry described above was applicable to the NMe series, where the azaxylylene intermediate would be positively charged (as in Scheme 8, **27**). Treatment of **19** with phenol, *p*-cresol, and *o*-cresol in CH_2Cl_2 at 25 °C in the presence of Cs_2CO_3 did not give **20a**, **20b**, or **20d**, respectively. Instead, the *C*-arylated products **21a**, **21b**, and **21d** were formed directly (Scheme 6, Table 2). However, *p*-nitrophenol and *o*-nitro-

Scheme 6. NMe Rearrangements



phenol gave **20c** and **20e**, respectively, which rearranged upon heating at 80 °C in benzene to give **21c** and **21e**.

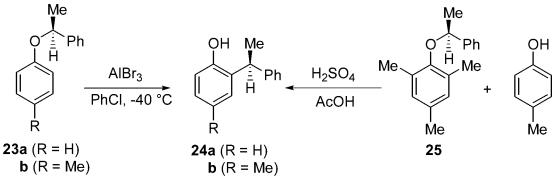
Table 2.

20	R^1	R^2	yield (%)	**21**	R^1	R^2	yield (%)
20a	H	H	n/a	**21a**	H	H	63
20b	Me	H	n/a	**21b**	Me	H	68
20c	NO_2	H	60	**21c**	NO_2	H	67
20d	H	Me	n/a	**21d**	H	Me	57
20e	H	NO_2	72	**21e**	H	NO_2	77

Exposure of **20e** to a catalytic amount of CF_3CO_2H in CH_2Cl_2 at 25 °C resulted in rearrangement to the *p*-isomer **22**.

The key results from Sprung,[7c] Tarbell,[7d] and Hart[7e] showed that **23** rearranged into **24** with 76% retention of absolute configuration. Treatment of **25** with *p*-cresol in H_2SO_4/AcOH gave racemic **24** (Scheme 7). Dewar[7a] concluded

Scheme 7. Inter- and Intramolecular Rearrangement

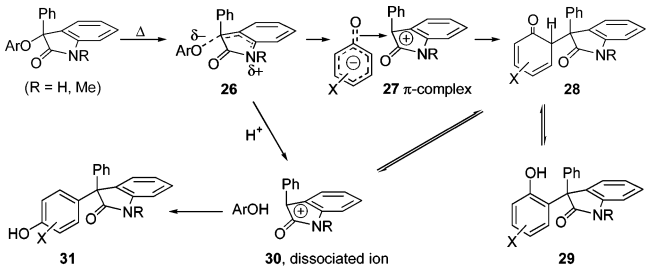


from these results and his own studies that "the rearrangement of alkyl aryl ethers to alkyl phenols can take place by two routes, one intermolecular and one intramolecular". He postulated that the reactions proceed via an *ortho*-π-complex to explain the predominate formation of **24** rather than its *p*-isomer. All of the rearrangements described in the above literature and in references[6,8] are conducted using Lewis acids or Brønsted acids. There are no reported thermal versions.

Under neutral conditions, the *O*-aryl ether begins to dissociate (**26**) and forms a π-complex **27**, which can be regarded as a cationic azaxylylene intermediate (Scheme 8). It is noteworthy that the azaxylylene intermediates described in ref 10 were neutral as they were derived from N−H precursors. This is the first reported example of the formation of cationic azaxylylene intermediates derived from *N*-alkyl precursors.

The π-complex (**27**) can rearrange to give **28**[14] and subsequently tautomerize to **29**. When these reactions are conducted in the presence of a Brønsted acid, the initial partially dissociated adduct **26** can completely ionize to give **30** (which is also accessible from **29** through *ipso*-protonation to give **28**, see the conversion of **17h** into **18c**), which results in the thermodynamically more stable *p*-substituted product **31** (Scheme 8). The original Dewar mechanism provides the

Scheme 8. Proposed Mechanism of Rearrangement



most plausible explanation and is a reminder of the powerful effects of ion pairing.[15]

(14) Principle of least motion: (a) Rice, F. O.; Teller, E. *J. Chem. Phys.* **1938**, *6*, 489−496. (b) Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1−61.
(15) Szwarc, M. *Ions and Ion-Pairs in Organic Reactions*; Wiley: New York, 1972.

In conclusion, this subtle and unexpected reaction and its relationship to the Dewar studies illustrates that natural product synthesis continues to be one of the central vehicles for the discovery of new chemistry.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. X-ray crystallographic data for **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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