Tetrahedron Letters, Vol. 34, No. 45, pp. 7247-7250, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

HETEROAROMATIC N-OXIDE REARRANGEMENTS. REINVESTIGATION OF 1,3 TOSYLOXY MIGRATION IN THE REACTION OF ISOQUINOLINE N-OXIDE WITH TOSYL CHLORIDE

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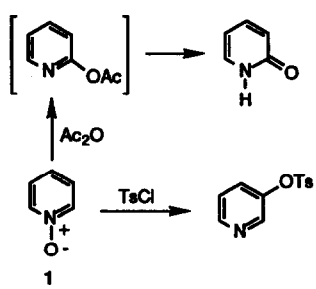
Summary: Isoquinoline N-oxide (2) reacts with ^{18}O-enriched tosyl chloride to furnish ^{18}O-labeled 4-tosyloxyisoquinoline (4), which was assessed for oxygen isotopic enrichment by NMR and mass spectrometry. The 30-45% ^{18}O incorporation at the bridging oxygen is inconsistent with a high level of the intramolecular tight-ion-pair ("sliding") mechanism. A combination of two intramolecular mechanisms is probably operative.

Acylation and sulfonylation of heteroaromatic N-oxides, in the absence of an added base, result in rearrangement products, which formally arise via oxygen migration from nitrogen to carbon.[1] Thus, N-oxides of pyridine (1), isoquinoline (2), and acridine (3) generate C-acyloxy-derived or C-sulfonyloxy compounds, as depicted in Schemes 1-3.

Scheme 1:



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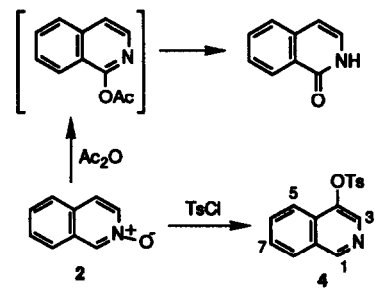
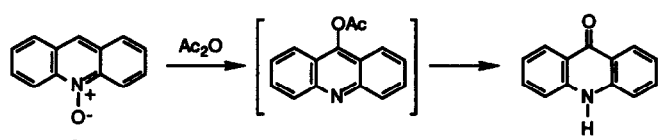
Scheme 2:



2 4

Scheme 3:



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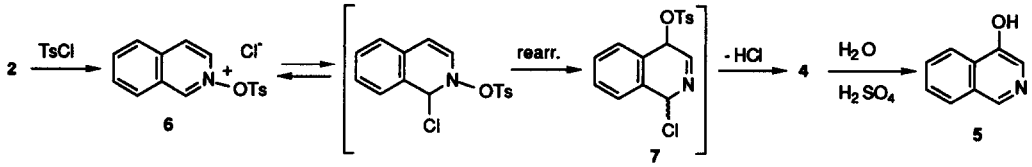
This type of rearrangement has attracted mechanistic attention.[1] For example, reactions of pyridine N-oxides with Ac_2O were determined to involve an intermolecular rearrangement mechanism by kinetics and oxygen-labeling studies.[1a,1b] However, oxygen isotope-tracer experiments with acridine N-oxide (3) indicated a more complex situation, in which two types of intramolecular rearrangement pathways occurred depending on concentration and solvent:[1a,1b,2] (1) a tight-ion-pair ("sliding") mechanism that *retained* the original oxygen atom attached to the heterocycle during rearrangement and (2) a "cyclic" mechanism that *completely exchanged* the originally attached oxygen atom. A representative sulfonylation example was the

reaction of isoquinoline N-oxide (**2**) with *p*-toluenesulfonyl chloride (tosyl chloride; TsCl), which gives 4-tosyloxyisoquinoline (**4**) in a reasonably good yield.[3] The rearrangement was postulated to proceed almost exclusively by a "sliding" mechanism, on the basis of ^{18}O-labeling, kinetics, and crossover studies.[1a,3]

We had occasion to conduct the synthesis of **4** from **2**, and thereby became interested in the rearrangement mechanism. Oae and coworkers reacted **2** with ^{18}O-enriched TsCl and found that the bridging oxygen in product **4** lacked ^{18}O incorporation.[3] The oxygen isotopic composition of **4** was obtained by an indirect method requiring hydrolysis of **4** to 4-hydroxyisoquinoline (**5**) with aqueous sulfuric acid. To address the possibility of oxygen exchange in **5**, which would dilute any potential ^{18}O content derived from the rearrangement, Oae and coworkers performed a control experiment. Thus, they treated **5** with ^{18}O-labeled water and sulfuric acid and found that ^{18}O was not incorporated, in support of the "sliding" mechanism.



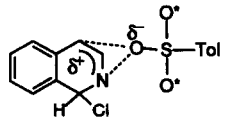
A weakness of the control experiment is that it only tested the isotopic fate of product **5** after it had been formed. We wondered what would happen if the control experiment were expanded in scope, by applying it to the hydrolytic conversion of **4** to **5**. In fact, hydrolysis of **4** with ^{18}O-enriched water (20 atom % ^{18}O) and sulfuric acid provided **5** *with a significant incorporation of the the heavy isotope*, reflective of 55% exchange (based on CI-MS, CH_4). Since this outcome casts doubt on the quantitative results for the earlier mechanistic conclusion, we decided to reinvestigate the reaction of **2** with heavy oxygen-enriched TsCl and determine the isotope composition of **4** directly, by NMR and MS.

We hoped at first to use ^{17}O NMR to approach this problem, but the signals for the bridging and sulfonyl oxygens of **4**, and its HCl salt, were not resolvable; also, there was no resolution under the influence of a dysprosium NMR shift reagent.[4] Consequently, we switched to ^{13}C NMR, capitalizing on the ^{18}O isotope-induced shift of the attached carbon resonance.[5] Compound **2** was treated with TsCl-$^{18}O_2$[6] in $CHCl_3$ at 0-5 °C, then warmed to 25 °C (1 h) and 45 °C (1 h); product **4** was isolated in 53% yield by flash chromatography (silica gel; hexane-EtOAc, 2:1): mp 91-92 °C; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 151.19 (C_1), 145.90 (4'), 141.94 (C_4), 135.81 (C_3), 131.95 (1'), 131.11 (C_6), 130.38 (C_{4a}), 129.90 (3'), 129.70 (C_{8a}), 128.53 (2'), 128.11 (C_7), 127.17 (C_8), 121.06 (C_5), 21.68 (Me).[7] Incorporation of ^{18}O at the bridging position in some, but not all, of the molecules of **4** doubled the C_4 resonance, with an isotope-induced shift of 2.9 Hz (Fig. 1). Spectral deconvolution and integration provided an $^{16}O/^{18}O$ ratio for the bridging oxygen of 73:27.

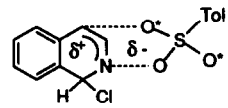
Further substantiation of the isotopic content was obtained by mass spectrometry. Under negative-ion CI (CH_4), **4** produces two key fragments by cleavage of the bridging S-O bond (Fig. 2). Analysis of one of these fragments, m/z 144/146, afforded an $^{16}O/^{18}O$ ratio for the bridging oxygen of 69.2:30.8, which is reasonably consistent with the NMR-derived value.[8]

The conversion of **2** to **4** first involves the formation of *N*-tosyloxyisoquinolinium (**6**) chloride, which has been isolated as a perchlorate salt by addition of $LiClO_4$ to the reaction.[3b] Salt **6** undergoes chloride addition at C-1 and subsequent 1,3 rearrangement to give **7**. This chemistry can be simulated by addition of

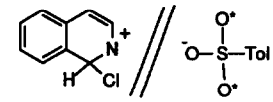
chloride to the perchlorate of **6**. The rearrangement can proceed by three possible pathways: (1) intramolecular tight ion-pair ("sliding") mechanism, (2) intramolecular [3,3] sigmatropic migration, and (3) intermolecular, solvent-separated ion-pair mechanism. By using TsCl-$^{18}O_2$ and assaying the bridging oxygen in **4**, the isotope-tracer results for these individual processes would be: (1) 100% ^{16}O, (2) 0% ^{16}O, and (3) 33% ^{16}O (scrambling). The reported[3] results of 85-100% ^{16}O are consistent with a high level of mechanism 1; however, this is not an accurate picture. Our reinvestigation ($CHCl_3$ data) indicates 70% ^{16}O retention, which requires a combination of mechanism 1 with mechanism 2 (30%) or 3 (45%), or a mixture of all three.



tight ion pair (#1)
100 % ^{16}O



cyclic [3,3] mechanism (#2)
0 % ^{16}O



solvent-separated ion pair (#3)
33 % ^{16}O

The rearrangement was studied in different solvents. Thus, ^{18}O incorporation increased in small steps from $CHCl_3$ (30.8%) to benzene (33.6%) to HMPA (34.2%) to MeCN (37.6%) to MeCN-water (44.6%).[9] Polar solvents would be expected to enhance the contribution of mechanism 3; however, the effect of polar solvent on the amount of ^{18}O incorporation is minimal. These data suggest that mechanism 3 is insignificant.

Fig. 1

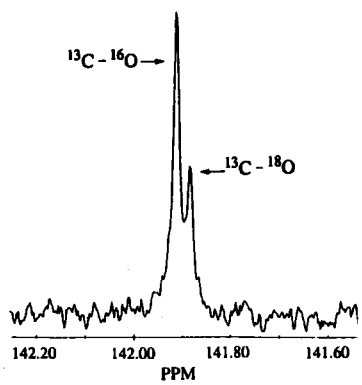
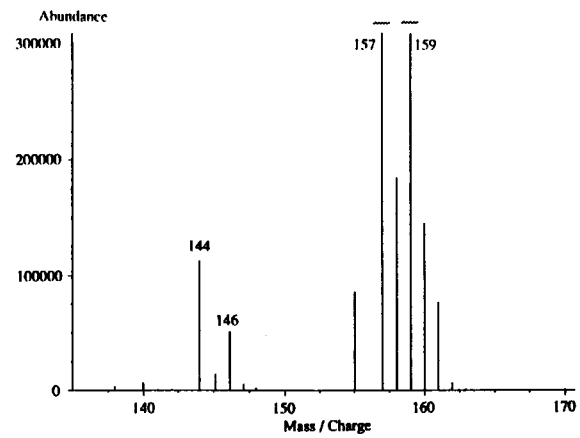


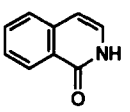
Fig. 2



To clarify the mechanism further, we can refer to the reported kinetics and crossover experiments.[1a] Rate studies involving solvent, substituent, and hydrogen isotope effects indicate cleavage of the N-O bond in the rate-determining step. An activation entropy ($\Delta S^{\neq}$) of -40.2 eu points to a highly ordered transition state. Also, negligible oxygen isotope scrambling in a doping experiment with unlabeled TsO^- rules out intermolecular exchange. Since no original data were published for this crossover result, we performed crossover experiments with NaOTs. For example, a solution of TsCl-$^{18}O_2$ (1 mol equiv) in HMPA was added dropwise to a solution of NaOTs (1 mol equiv) and **2** (1.6 mol equiv) in HMPA at 0 °C, followed by warming (25 °C, 1 h;

45 °C, 1 h), to give **4** with 33.2% ^{18}O incorporation (vs. 34.2% without NaOTs present).[10] This reflects a very low level of crossover. Standard EI-MS analysis of the product mixture revealed 2.3% of the 4-$^{16}O_3$ species. The product from the non-crossover ^{18}O-labeling reaction showed 0.7% of 4-$^{16}O_3$, resulting in an actual amount of 4-$^{16}O_3$ from crossover of 1.6% (out of a maximum of ca. 50%). Thus, in the crossover experiment mechanism 3 is quite minor (ca. 3%), even though excess NaOTs was present during the reaction.

Three by-products, **8**[11] (11%), **9**[11] (13%), and **10** (8%), were isolated directly from the rearrangement mixture in $CHCl_3$ (no aqueous work-up; assigned by ^1H NMR, MS, IR, mp). No ^{18}O was found in either **8** or **10** by MS analysis. The ratio of by-products varied according to solvent employed, with 62% of **8** being formed with MeCN-water.



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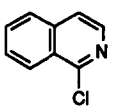

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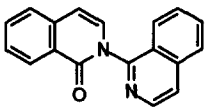

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In conclusion, the rearrangement of isoquinoline N-oxide (**2**) with tosyl chloride to **4** does not occur almost exclusively by an intramolecular tight-ion-pair ("sliding") mechanism, as indicated previously.[1a,3] The rearrangement proceeds in $CHCl_3$ by a combination of two mechanistic pathways, a significant component of which is the intramolecular tight-ion-pair mechanism (ca. 70% mechanism 1 and ca. 30% mechanism 2). It is interesting that heterocyclic N-oxide rearrangements can proceed by any of the three mechanistic pathways, or a combination thereof, depending on the system, electrophilic reagent, or reaction conditions.

References and Notes

1. Reviews: (a) Oae, S. *Heterocycles* **1977**, *6*, 583-675. (b) Traynelis, V. J. in *Mechanisms of Molecular Migrations*, Vol. 2, Thygarajan, B. S., Ed., John Wiley & Sons: New York, 1969, pp 1-42. (c) Scriven, E. F. V. in *Comprehensive Heterocyclic Chemistry*, Vol. 2, Boulton, A. J.; McKillop, A, Eds., Pergamon Press: Oxford, 1984, pp 224-229. (d) Uff, B. C. in *Comprehensive Heterocyclic Chemistry*, Vol. 2, Boulton, A. J.; McKillop, A., Eds., Pergamon Press: Oxford, 1984, p 355. (e) Dyke, S. F.; Kinsman, R. G. in *Chemistry of Heterocyclic Compounds--Isoquinolines*, Part 1, Grethe, G., Ed., John Wiley & Sons: New York, 1981, pp 89-92.
2. Oae, S.; Kozuka, S.; Sakaguchi, Y.; Hiramatsu, K. *Tetrahedron* **1966**, *22*, 3143.
3. (a) Oae, S.; Kitao, T.; Kitaoka, Y. *Tetrahedron* **1963**, *19*, 827. (b) Oae, S.; Ogino, K.; Tamagaki, S.; Kozuka, S. *Ibid.* **1969**, *25*, 5761.
4. Dahn, H.; Toan, V. V.; Ung-Truong, M.-N. *Magn. Reson. Chem.* **1991**, *29*, 897. The ratios of 4/Dy reagent used were 100:1, 25:1, and 4:1.
5. Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* **1988**, *29*, 93. An ^{18}O atom in the bridging position should cause a 3-4 Hz upfield shift of the directly bonded ^{13}C nucleus.
6. Prepared from toluenethiol and 97-98 atom % $H_2{}^{18}O$ (ref 3a and Dietze, P. E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240). The ^{18}O-enriched TsCl had mp 67-68 °C; CI-MS (CH_4) analysis indicated 96% ^{18}O content.
7. (a) Signal assignments are based on connectivities obtained from an HMBC experiment (60-ms evolution delay). See: Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093. (b) Primes are for Ts.
8. Analysis of the companion fragment, m/z 157/159, was less reliable for quantitation. Under the negative-ion CI conditions, the molecular ion was miniscule.
9. From MS analysis. Corresponding isolated yields of **4**: 53%, 44%, 47%, 38%, 20% (based on TsCl).
10. From MS analysis. A control experiment indicated that the rate of formation of Ts_2O was very slow.
11. Ochiai, E.; Ikehara, M. *Pharm. Bull. (Tokyo)* **1955**, *3*, 454.

(Received in USA 16 July 1993; accepted 10 September 1993)