Acid Induced Reactions of a Sydnone Ketoxime [1]

Manouchehr Saljoughian*

Laboratory of Chemical Biodynamics, Lawrence Berkeley Laboratory, University of California, Berkeley, CA 94720 USA

Kenneth Turnbull*

Department of Chemistry, Wright State University, Dayton, OH 45435 USA

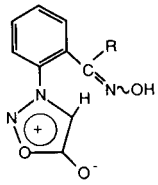
Received June 7, 1988

3-(2-Acetylphenyl)sydnone oxime **1a** reacts with acids (methanesulfonic-, *p*-toluenesulfonic, trifluoroacetic-acid or Amberlite IR 118) to give products apparently derived from protonation of the oxime oxygen or nitrogen atom followed by cyclization to the sydnone ring or interception by water.

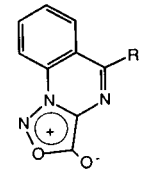
J. Heterocyclic Chem., **25**, 1817 (1988).

Recently, we reported our attempts to induce intramolecular cyclization upon the sydnone oximes **1a-b** by the use of electrophilic reagents [2]. While no direct cyclization (to *e.g.* **2**) was observed, thermolysis (on silica) of the mesylate, benzenesulfonate or tosylate derivatives of **1a** provided **2a** in extremely low yield.

The importance of the sydnoquinazoline **2a** to our research programme, coupled with the inefficiency of the synthetic route utilized for its preparation, prompted further investigations in this area.



1 a, R=Me; b, R=H



2 a, R=Me; b, R=H

It seemed likely that cyclization could also be effected by treatment of **1a** with acidic substances. Accordingly, **1a** was prepared as a mixture of isomers (3.4:1) by the procedure described previously [2-3]. Separation of the isomers was achieved by careful column chromatography but their spectral data did not permit unambiguous structural assignment. However, on steric grounds it is reasonable to assume that the major isomer has the (*E*) configuration and this premise has been employed throughout.

Initial results with sulfuric acid and several Lewis acids were not encouraging. With the former (neat or in benzene) a complex, inseparable product mixture was obtained whereas with the latter (borontrifluoride etherate, titantium tetrachloride or stannic chloride in dichloromethane) apparent reaction with the exocyclic oxygen atom of the sydnone ring occurred to form salts which hydrolyzed to the starting materials on aqueous "work-up". Similar reactivity with Meerwein's reagent [4] and triflic anhydride [5] has been reported previously.

Sluggish reaction was observed with phosphorus pentoxide. Reflux in benzene for 48 hours followed by "work-up" gave a complex mixture from which only 3-methylindazole **3** (12%) was isolated by column chromatography on silica gel. Utilization of a higher boiling solvent (toluene) shortened the reaction time but did not reduce the complexity of the product mixture. The isolation of **3** indicated that degradation of the sydnone ring had occurred, apparently triggered by initial reaction of the oxime functionality since 3-phenylsydnone was stable under these conditions.

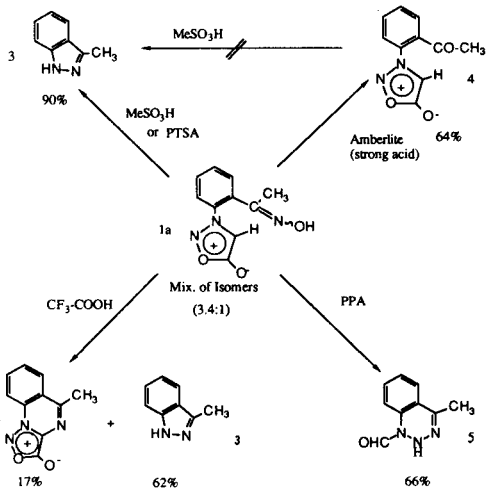
More intriguing results were obtained from the reactions of **1a** with other acids (see Scheme). Thus, the indazole **3** was also obtained, but in much better yield (>90%) by reaction of **1a** (one or a mixture of isomers) with methane- or *p*-toluenesulfonic acid in benzene for two days at room temperature. Initially, it seemed possible that **3** arose by initial hydrolysis to the ketone **4** and subsequent acid cleavage of the sydnone ring in the latter to form a hydrazine [6] which could then cyclize. However, this postulate was discounted by treatment of **4** with methanesulfonic acid (MSA) in benzene at room temperature; even after 14 days no reaction was observed. It is apparent that the sydnone ring is stable under these conditions and we now feel that the operative mechanism involves initial oxime nitrogen protonation and subsequent unprecedented cyclization from N-2 of the sydnone ring.

It is interesting that **1a** was slowly (4-5 days) converted to the ketone **4** by stirring with the strongly acidic, ion exchange resin, Amberlite IR 118, in benzene at room temperature. The conversion could be expedited (2-3 hours) by heating at 65°. This divergent result with a reagent which also contains sulfonic acid groups, may reflect the presence of water bound to the surface of the polymer. Thus, when the oxime is protonated on the nitrogen atom, interception by bound water apparently precedes cyclization from the sydnone ring nitrogen atom.

Surprisingly, when **1a** was treated with polyphosphoric acid (PPA) [benzene, room temperature, 2 days] only the major oxime isomer (putatively the *E*) reacted and the product obtained (66% based on the isomeric mixture) was apparently the *N*-formylbenzotriazine **5**, mp 197-198°. The latter can be rationalized as arising from initial pro-

tonation on the oxime oxygen atom followed by attack from N-2 of the sydnone ring. The reaction of only one isomer is intriguing and this strongly suggests that steric hindrance from the reagent is a controlling factor.

Scheme



Lastly, when **1a** (isomeric mixture) was reacted with trifluoroacetic acid (TFA) [in benzene or neat] for several days at room temperature a mixture of the indazole **3** (62%) and sydnoquinazoline **2a** (17%) was obtained. The same products were isolated with the individual oxime isomers but the relative amounts were quite different. Thus, the major isomer (probably *E*) gave **3** and **2a** in 47% and 11% yield respectively, whereas the minor isomer (probably *Z*) afforded the two in 25% and 32% yield, respectively. It is clear that the yield of the desired sydnoquinazoline **2a** is substantially better than previously obtained [2]. However, it is disappointing (and surprising) that it should be formed in greater quantity from the minor isomer. This, notwithstanding, the present isomeric content (3.4:1) almost certainly represents a thermodynamic distribution and it should be possible to favour the minor isomer by exercising kinetic control.

Work to assess this last point and the generality of the reactions described is presently underway in our laboratory.

EXPERIMENTAL [8]

Preparation and Separation of the Sydnone Oxime Isomers **1a**.

The mixture of oxime isomers was prepared as described previously [2]. Separation was effected by repeated column chromatography (silica gel) using dichloromethane-methanol (20:1) as eluant. The upper (by tlc) oxime isomer (major, putatively *E*) was recrystallized from dichloromethane-petroleum ether (30-60°) as colourless needles, mp 115-116°; ir (potassium bromide): 3276, 3127, 1715, 2847, 1440 cm^{-1}; nmr (deuteriochloroform/deuteriodimethyl sulfoxide): δ 2.10 (s, 3H), 6.63 (s, 1H), 7.70 (s, 4H), 10.96 (s, 1H). The lower (by tlc) oxime isomer (minor, putatively *Z*) was recrystallized from dichloromethane-petroleum ether (30-60°) as colourless needles, mp 137-138°; ir (potassium bromide): 3269, 3135, 1729, 2987, 766 cm^{-1}; nmr (deuteriochloroform-deuteriodimethyl sulfoxide): δ 2.20 (s, 3H), 6.80 (s, 1H), 7.70 (s, 4H), 10.73 (s, 1H).

Reaction of **1a** with *p*-toluenesulfonic Acid or Methanesulfonic Acid.

To the mixture of oxime isomers **1a** (0.20 g, 0.91 mmole) in benzene (10 ml) was added *p*-toluenesulfonic acid monohydrate (0.8 g, 4.2 mmoles) with stirring. After 2.5 days at room temperature the mixture was quenched with ice-water then dilute aqueous sodium bicarbonate solution. The benzene layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield a tan solid which crystallized from petroleum ether (30-60°) as colourless needles, (0.113 g, 94%), mp 109-110°, identical in all respects to an authentic [9] sample of 3-methylindazole **3**.

With methanesulfonic acid (1.48 g, 15.4 mmoles), under the same conditions, **3** was obtained in 91% yield. Clean conversion of each individual isomer to **3** was also effected in high yield with *p*-toluenesulfonic acid or methanesulfonic acid.

Reaction of **1a** with Amberlite IR 118.

The mixture of oxime isomers **1a** (0.20 g, 0.91 mmole) in benzene (30 ml) was stirred with Amberlite IR 118 (1.2 g) for 5 days at room temperature. After filtration the solvent was removed *in vacuo* and the residue was chromatographed (by tlc) using dichloromethane/acetone (20:1) as eluant to yield ketone **4** which was recrystallized from dichloromethane/petroleum ether (25:5) as colourless needles, (0.12 g, 64%), mp 112-114°, lit mp 113-115°. Further elution afforded unreacted starting material (0.035 g). Similar results were obtained with each individual isomer.

Reaction of **1a** with Trifluoroacetic Acid.

The mixture of oxime isomers **1a** (0.20 g, 0.91 mmole) in trifluoroacetic acid (10 ml) was stirred for 10 days at room temperature. The solvent was removed under a stream of nitrogen and the residue was chromatographed (by tlc) using dichloromethane-methanol (20:1) as eluant. The first eluted compound (0.032 g, 17%) was identified as the sydnoquinazoline **2a**, mp 244-245°, lit [2] mp 242-243°. Further elution afforded indazole **3** (0.074 g, 62%).

Repetition of the experiment with the individual oxime isomers gave: **2a** (11%) and **3** (47%) [from the upper (tlc) isomer] and **2a** (32%) and **3** (25%) [from the lower (tlc) isomer].

Reaction of **1a** with Polyphosphoric Acid.

The mixture of oxime isomers **1a** (0.20 g, 0.91 mmole) in benzene (10 ml) was stirred with polyphosphoric acid (2.00 g) for 3 days at room temperature, whereupon sufficient saturated sodium bicarbonate solution was added to effect neutralization. The benzene layer was separated and the aqueous layer was further extracted with dichloromethane (2 × 15 ml). The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo* to yield a dark brown solid. Recrystallzation from dichloromethane-petroleum ether gave a tan, microcrystalline solid (2 crops) (0.105 g, 66%), mp 197-198°; ir (potassium bromide): 3219, 3183, 3109, 3042, 3010, 2982, 1639, 1500, 1370, 747 cm^{-1}; nmr (deuteriochloroform-deuteriodimethyl sulfoxide): δ 1.82 (s, 3H), 6.58 (m, 1H), 6.94 (m, 2H), 7.87 (dd, 1H), 8.35 (s, 1H), 9.07 (brd s, 1H).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.71; H, 5.14; N, 24.00. Found: C, 61.70; H, 5.21; N, 23.93.

Evaporation of the mother liquor and chromatography (silica gel) using dichloromethane-methanol (20:1) as eluant gave the lower oxime isomer **1a** (putatively *Z*) (0.035 g, 18%), mp 135-137°, identical in all respects to an authentic sample.

Repetition of the experiment with the individual oxime isomers confirmed these finding.

Acknowledgement.

This work was supported by the WSU Chemistry Department and in part by NIH Contract No. RRZ1237-05.

REFERENCES AND NOTES

[1] Presented at the ACS 18th Central Regional Meeting, Bowling Green University, Ohio, USA, June 1-5 (1986).

[2] J. D. Lowe and K. Turnbull, *J. Heterocyclic Chem.*, **23**, 125 (1986).

[3] The experiments described in this communication were performed on the mixture of isomers unless otherwise stated.

[4] K. T. Potts, E. Houghton and S. Husain, *J. Chem. Soc., Chem. Commun.*, 1025 (1970).

[5] S. Araki, J. Mizuya and Y. Butsugan, *Chem. Letters*, 1045 (1984).

[6] Sydnones are known to form hydrazines *via* hydrolysis with aqueous acid [7].

[7] W. Baker and W. D. Ollis, *Quart. Rev.*, **11**, 15 (1957).

[8] All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra (potassium bromide) were measured on a Perkin Elmer 1330 and nuclear magnetic resonance spectra on a Varian EM 360 with tetramethylsilane as the internal standard, chemical shifts reported in ppm (δ).

[9] P. D. Croce and C. La Rosa, *Synthesis*, 982 (1984).