A Novel Synthesis of Dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)one 5,5-Dioxides

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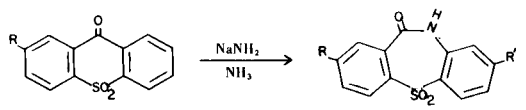
Treatment of thioxanthen-9-one 10,10-dioxides with sodium amide in liquid ammonia provided a novel one-step conversion to dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)one 5,5-dioxides. Some limitations and a possible mechanism for the reaction are discussed.

Recently, we reported (1) that thioxanthen-9-one 10,10-dioxides (I) undergo facile hydroxide displacement of the sulfone linkage exclusively on the more electrophilic ring to afford benzophenone-2′-sulfinic acids. Further, it was established that these sulfinic acids easily cyclize in alkaline media to give xanthones. This interesting cleavage reaction of I, and its ring substituted derivatives, prompted us to investigate the stability of this heterocyclic moiety toward other nucleophiles. Since amide ion is a strong nucleophile and takes part in a variety of important displacement reactions, its effect upon the hetero ring found in I appeared to be a worthwhile study.

Because our earlier findings (1) demonstrated that cleavage of I with hydroxide occurs exclusively at the sulfonyl linkage, with no evidence of Haller-Bauer type reaction (2) at the carbonyl group of the unique *ortho* keto-sulfonyl structure, we anticipated that reaction of I with amide ion might produce similar results. Indeed, the cleavage of diaryl sulfones with amide ion has been reported (3). In addition, because benzophenones undergo reaction with amide ion (4) at the carbonyl functionality, to give benzamides, anilines and hydrocarbons, comparable reaction of I was a possibility. We now wish to report that neither of these reactions occur when I is treated with sodium amide in liquid ammonia. Instead, reaction proceeds in a novel one-step conversion of thioxanthen-9-one 10,10-dioxides, I, to dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one 5,5-dioxides (VI).



I, R = H
II, R = CH_3
III, R = OCH_3
IV, R = Cl
V, R = NO_2

VI, R = R′ = H
VII, R = CH_3, R′ = H
VIII, R = H, R′ = OCH_3
IX, R = OCH_3, R′ = H

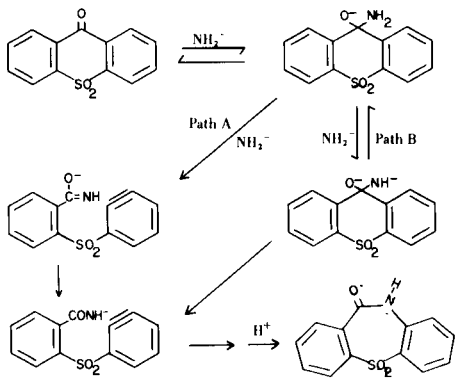
For this study, five thioxanthen-9-one 10,10-dioxides (I-V) were prepared as described in an earlier paper (1). Reaction of compounds I, II and III with sodamide in liquid ammonia (5), followed by acidification of the concentrated ammonia solution, afforded the corresponding dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)one 5,5-dioxides, VI, VII, and VIII.

However, attempts to promote reaction of IV in similar manner produced mixtures (attributable, at least in part, to reaction of the chloro group) from which pure materials could not be isolated. In addition, efforts to convert V to lactam product were not successful because acidification of the concentrated reaction system produced violent decomposition to non-organic containing materials.

Because our initial work confirmed the structures of lactams VI and VII by comparison to identical structures which were synthesized by independent routes, we anticipated that III would produce IX due to the similar ring activation of the methoxyl group relative to the methyl group. However, comparison of an authentic sample of IX (6) with the product obtained from reaction of III with sodium amide in liquid ammonia confirmed that III does not convert to IX in this reaction system, and ultimately the reaction product was shown to be VIII when comparisons were made with an authentic sample (see Experimental). The conversion of III to VIII suggests that this novel lactam formation from thioxanthen-9-one 10,10-dioxides does not proceed by formation of the more stable ring carbanion intermediate, or by initial attack of a negative species on the more electropositive ring, since for either of these reaction pathways IX would be the expected product. The formation of the lactam products can be explained, however, by the postulation that reaction proceeds through an aryne intermediate.

Scheme I depicts aryne formation *via* loss of a ring proton and a hydride ion from the amide nitrogen (Path A).

Scheme I



Since the orientation of formation of an aryne relative to substituents present, depending as it does on the hydrogen acidities, appears to be essentially controlled by the inductive effect of the substituents (7), the general mode of aryne formation shown by Path A would be consistant with the expected substituent effects leading to the observed reaction products, VII and VIII.

A less feasible alternative pathway leading to aryne formation is shown in Scheme I and involves loss of a proton from the amide nitrogen and a hydride ion from the aromatic ring (Path B). Although this type of proton loss from an amide nitrogen has been suggested for some Haller-Bauer cleavage reactions (4), the expected substituent effects of methyl and methoxyl groups towards loss of a ring hydride ion should not favor proper aryne orientation to allow formation of the observed products.

Although our observations are satisfactorily interpreted with respect to an aryne mechanism, the precise nature of this reaction is not presently known and efforts to elucidate the mechanistic pathway of this reaction are in progress.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Thioxanthen-9-one 10,10-Dioxides (I-V).

Compounds I through V were prepared as described in an earlier paper (1) and were identified by satisfactory elemental analysis, melting points and ir and nmr data.

Reactions in Liquid Ammonia.

The thioxanthen-9-one 10,10-dioxides were allowed to react at reflux, with continuous stirring, with sodium amide in 150 ml. of dry liquid ammonia for a given time. Following reaction, the solutions were concentrated by evaporation to about 25 ml. before the addition of 75 ml. of water. The aqueous solutions were filtered, acidified with dilute hydrochloric acid, and the solid products collected and purified.

Dibenzo[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-Dioxide (VI).

As described above, reaction of I (2.0 g., 0.008 mole) with sodium amide (1.0 g., 0.026 mole) in liquid ammonia for 2 hours gave VI (1.74 g., 83% from ethanol), m.p. 290-292°; lit. m.p. 290-292° (8).

Mixture melting point determination and ir spectral comparison showed VI to be identical with an authentic sample which was prepared from 2-amino-2′-carboxydiphenyl sulfide (9) following the procedure of McClelland and Peters (8).

The *N*-methyl derivative of VI was prepared by dissolving VI (1.0 g., 0.00384 mole) in 50 ml. of 10% aqueous sodium hydroxide solution. To this stirred solution, 0.85 g. (0.00675 mole) of dimethyl sulfate was added over a five minute period with continuous formation of a solid precipitate. Following an additional hour of reaction at 40°, the solid was collected and recrystallized from ethanol to give 0.97 g. (95%) of 10-methyldibenzo[*b,f*][1,4]-thiazepin-11(10*H*)one 5,5-dioxide, m.p. 220-222°.

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.54; H, 4.03; N, 5.13; S, 11.72. Found: C, 61.35; H, 3.99; N, 5.09; S, 11.66.

2-Methyldibenzo[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-Dioxide (VII).

The procedure used was identical to that described above for the preparation of VI. Reaction of II (5.0 g., 0.02 mole) with sodium amide (2.0 g., 0.05 mole) in liquid ammonia for eight hours gave VII and 3.4 g. of unreacted II. Recrystallization from acetic acid-water gave 1.5 g. (89%) of pure VII as white needles, m.p. 273-275°.

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.54; H, 4.03; N, 5.13; S, 11.72. Found: C, 61.37; H, 3.98; N, 4.98; S, 11.64.

The procedure used for the preparation of the N-methyl derivative of VI was utilized for the preparation of the N-methyl derivative of VII. Reaction of VII (1.0 g., 0.0037 mole) with 0.96 g. (0.0074 mole) of dimethyl sulfate in 50 ml. of 10% aqueous sodium hydroxide afforded 0.91 g., (86% from ethanol of 2-methyl-10-methyldibenzo[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-Dioxide, m.p. 194-196°.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.72; H, 4.53; N, 4.88; S, 11.15. Found: C, 62.80; H, 4.61; N, 4.85; S, 10.99.

8-Methoxydibenzo[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-Dioxide (VIII).

Using the procedure described above, reaction of III (2.0 g., 0.0073 mole) with sodium amide (2.0 g., 0.052 mole) in liquid ammonia for two hours gave VIII and 1.0 g. of unreacted III. Recrystallization from acetic acid-water gave 1.0 g. (95%) of pure VIII as white needles, m.p. 237-239°.

Anal. Calcd. for $C_{14}H_{11}NO_4S$: C, 58.13; H, 3.81; N, 4.84; S, 11.07. Found: C, 58.27; H, 3.86; N, 4.75; S, 11.12.

In similar manner to that described before, reaction of VIII (1.0 g., 0.0035 mole) with 0.87 g. (0.007 mole) of dimethyl sulfate in 50 ml. of 10% aqueous sodium hydroxide gave 0.97 g. (93% from ethanol) of 8-methoxy-10-methyldibenzo[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-dioxide, m.p. 172-173°.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.29; N, 4.62; S, 10.57. Found: C, 59.36; H, 4.28; N, 4.57; S, 10.46.

A. Independent Synthesis of VII.

2-Carbomethoxy-4-methyl-2′-nitrodiphenyl Sulfide (X).

The required precursor of X, methyl 5-methylthiosalicylate, m.p. 58-60° (ethanol water), lit. m.p. 61-62° (10) was obtained utilizing the known diazonium replacement reaction for the conversion of 5-methylanthranilic acid to 5-methylthiosalicylic acid, m.p. 155-157° (ethanol water), lit. m.p. 155-157° (10), followed by sulfuric acid catalyzed esterification with methanol.

A mixture of 18.2 g. (0.101 mole) of methyl 5-methylthiosalicylate, 25.0 g. (0.101 mole) of 1-iodo-2-nitrobenzene, 5.5 g. (0.101 mole) of sodium methoxide, 0.1 g. of copper powder and 500 ml. of xylene was refluxed for twenty-four hours then steam distilled to remove the xylene. Collection of the solid from the cooled solution and recrystallization from ethanol gave 15.2 g. (50%) of X as yellow needles, m.p. 109-110°.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.29. Found: C, 59.57; H, 4.46.

2-Carboxy-4-methyl-2′-nitrodiphenyl Sulfide (XI).

A mixture of 12.0 g. (0.040 mole) of X, 125 ml. of 20% aqueous sodium hydroxide and 125 ml. of 95% ethanol was heated at reflux for one hour. The hot solution was filtered and the ethanol removed from the cooled filtrate by evaporation *in vacuo*. The remaining solution was acidified with 10% hydrochloric acid and the collected precipitate recrystallized from ethanol-water afforded 10.3 g. (90%) of XI, m.p. 173-174°.

Anal. Calcd. for $C_{14}H_{11}NO_4S$: C, 58.13; H, 3.81. Found: C, 58.18; H, 4.00.

2′-Amino-2-carboxy-4-methyldiphenyl Sulfide (XII).

A solution of 9.0 g. (0.031 mole) of XI dissolved in 125 ml. of ammonium hydroxide (1.23*N*) was added to a stirred boiling solution of 68.8 g. (0.18 mole) of ferrous ammonium sulfate hexahydrate in 125 ml. of water. The thick mixture was diluted with 50 ml. of water and boiled for five minutes while adding 50 ml. of concentrated ammonium hydroxide. The cooled mixture was filtered and the filtrate concentrated to about 100 ml. before careful acidification with glacial acetic acid. Collection of the solid from the chilled solution and recrystallization from acetic acid-water gave 4.85 g. (60%) of XII as tan needles, m.p. 168-169°.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.02. Found: C, 64.75; H, 5.16.

2-Methyldibenzo[*b,f*][1,4]thiazepin-11(10*H*)one (XIII).

To a stirred solution of 4.4 g. (0.31 mole) of phosphorus pentoxide in 125 ml. of xylene was added 4.0 g. (0.155 mole) of XII and the reaction system refluxed for five hours. The hot solution was filtered and the solid that was collected from the cooled filtrate was recrystallized from acetic acid-water to give 3.0 g. (79%) of XIII as brown crystals, m.p. 237-238°; lit. m.p. 239-240° (11).

Oxidation of XIII to VII.

A mixture of 2.0 g. (0.0083 mole) of XIII, 50 ml. of glacial acetic acid and 10 ml. of 30% hydrogen peroxide was refluxed for two hours. The precipitate was collected from the cold reaction mixture and recrystallized from acetic acid to give 2.03 g. (89%) of VII, m.p. 273-275°. This material was shown by ir spectral comparison and mixture melting point determination to be identical with the compound prepared above from the reaction of II with sodium amide in liquid ammonia.

B. Independent Synthesis of VIII.

The product obtained from the reaction of III with sodium amide in liquid ammonia was shown not to be 2-methoxydibenzo-[*b,f*][1,4]thiazepin-11(10*H*)one 5,5-dioxide (IX) by ir and mixture melting point comparison with an authentic sample (6) of IX. Thus, to confirm the structure of this product as VIII, this compound was prepared by an independent procedure.

2′-Carboxy-4-methoxy-2-nitrodiphenyl Sulfide (XIV).

A required precursor of XIV, 4-iodo-3-nitroanisole, was prepared from 4-amino-3-nitroanisole following the literature procedure, m.p. 57-59°, lit. m.p. 62° (12).

A mixture of 15.3 g. (0.091 mole) of methyl thiosalicylate, 25.0 g. (0.091 mole) of 4-iodo-3-nitroanisole, 4.5 g. (0.083 mole) of sodium methoxide, 0.1 g. of copper powder and 500 ml. of xylene was refluxed for twenty-four hours and then steam distilled to remove the xylene. To the remaining solution was added 75 ml. of 20% sodium hydroxide and 75 ml. of 95% ethanol and the solution heated at reflux for one hour. Following filtration of the hot reaction mixture, the ethanol was removed by distillation and the cool solution acidified with 10% hydrochloric acid. Collection of the precipitate and recrystallization from ethanol-water gave 21.5 g. (79%) of XIV as yellow crystals, m.p. 223-225°.

Anal. Calcd. for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.61. Found: C, 54.94; H, 3.56.

2-Amino-2′-carboxy-4-methoxydiphenyl Sulfide (XV).

A solution of 20.0 g. (0.066 mole) of XIV dissolved in 125 ml. of ammonium hydroxide (1.23*N*) was added to a stirred boiling solution of 137.6 g. (0.36 mole) of ferrous ammonium sulfate hexahydrate in 175 ml. of water. The thick mixture was diluted with 50 ml. of water and boiled for five minutes while adding 50 ml. of concentrated ammonium hydroxide. The cooled mixture was filtered and the filtrate concentrated to about 100 ml. before careful acidification with glacial acetic acid. Collection of the solid from the cold solution and recrystallization from acetic acid-water gave 9.5 g. (53%) of XV as tan needles, m.p. 205-207° dec.

Anal. Calcd. for $C_{14}H_{13}NO_3S$: C, 61.11; H, 4.73. Found: C, 60.92; H, 4.76.

8-Methoxydibenzo[*b,f*][1,4]thiazepin-11(10*H*)one (XVI).

Heating 2.0 g. (0.0073 mole) of XV *in vacuo* (1 mm) at 200° for five hours gave impure XVI. Recrystallization from acetic acid-water afforded 1.5 g. (80%) of XVI as tan crystals, m.p. 212-214°.

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.37; H, 4.28. Found: C, 65.10; H, 4.38.

Oxidation of XVI to VIII.

A mixture of 1.1 g. (0.0043 mole) of XVI, 25 ml. of glacial acetic acid and 5 ml. of 30% hydrogen peroxide was refluxed for two hours. The precipitate was collected from the cold reaction mixture and recrystallized from acetic acid-water to give 1.0 g. (81%) of VIII, m.p. 238-240°. This material was shown by ir spectral comparison and mixture melting point determination to be identical with the compound prepared above from the reaction of III with sodium amide in liquid ammonia.

NOTES AND REFERENCES

(1) O. F. Bennett, M. J. Bouchard, R. Malloy, P. Dervin and G. Saluti, *J. Org. Chem.*, 37, 1356 (1972).

(2) K. E. Hamlin and A. W. Weston, "Organic Reaction", Vol. 9, J. Wiley and Sons, Inc., New York, N.Y., 1957, p. 1.

(3) J. F. Bunnett and T. K. Brotherton, *Chem. Ind.* (London), 80 (1957).

(4) J. F. Bunnett and B. F. Hrutfiord, *J. Org. Chem.*, 27, 4152 (1962).

(5) Attempts to promote similar reaction of I with sodium amide in refluxing toluene or xylene were not successful.

(6) O. F. Bennett, J. Johnson and J. Tramondozzi, Org. Prep. and Proc. Int., 6 (6), 287 (1974).

(7) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier Co., New York, N.Y., 1968, p. 53.

(8) E. W. McClelland and R. H. Peters, *J. Chem. Soc.*, 1229 (1947).

(9) F. Mayer, *Ber.*, 42, 3046 (1909).

(10) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 747 (1951).

(11) A. Wander, Netherlands Application 6,411,504., April 12, 1965; *Chem. Abstr.*, 64, 8223b (1966).

(12) K. Hata, K. Tatematsu and B. Kubota, *Bull. Chem. Soc.*, Japan, 10, 425 (1935).