Preparation of *N*-(Thioalkyl and -Thioaryl)amides[1]

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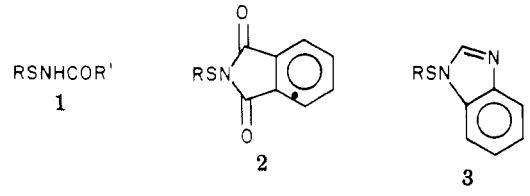
Received April 10, 1979

As part of a program on the desulfurization[2] of organosulfur compounds, we required various *N*-thioalkyl/-aryl amides[3] (1). A variety of approaches are possible based on synthesis of the analogous thioimides **2**[4] and thioazoles **3**.[5]



1 2 3

The first method involves the reaction of a sulfenyl chloride with an amide in the presence of Et_3N.[4c] In the

$$RSCl + CH_3CONH_2 \xrightarrow{Et_3N} RSNHCOCH_3$$

case of R = C_6H_5 only a 6% yield of **1a** was obtained; when R = *n*-propyl (**1b**) no amide could be isolated. Only phenyl disulfide was isolated when benzenethiol was treated at 0 °C in acetone with *N*-bromoacetamide.[4b]

$$RSH + BrNHCOCH_3 \rightarrow RSNHCOCH_3 + HBr$$

$$RSH + RSNHCOCH_3 \rightarrow RSSR + H_2NCOCH_3$$

Evidently when **1a** was formed it condensed with unreacted thiol.[6] A somewhat more successful approach involved reacting the trimethylsilyl thiol[7] derivative with the *N*-bromoamide; when R = C_6H_5 a 52% yield of **1a** was obtained although when R = *n*-propyl again no **1b** could be isolated.

$$RSSi(CH_3)_3 + BrNHCOCH_3 \rightarrow \underset{1}{RSNHCOCH_3}$$

Table I

$(Me)_3SiNHCOCH_3 + RSCl \rightarrow RSNHCOCH_3 + (Me)_3SiCl$

R	yield	mp, °C	solvent	T, °C
C_6H_5	85	101-103	hexane	25
$C_6H_5CH_2$	46	85-87	hexane	25
p-$CH_3C_6H_4$	86	102-105	hexane	15
o-$NO_2C_6H_4$	81	184-186	CH_3CN	25
$EtOOCCH_2$	36	45-47	CCl_4	25

The most generally useful method for preparing **1** was found in the reaction of the appropriate sulfenyl chloride[4b,8] with the trimethylsilyl derivative of the amide[9] (Table I).

$$RSCl + (CH_3)_3SiNHCOCH_3 \rightarrow \underset{1}{RSNHCOCH_3} + (CH_3)_3SiCl$$

Under these conditions yields of over 80% were obtained for the arenesulfenyl derivatives; the aliphatic examples were formed in about 40% yield. In the case of *p*-tolylsulfenyl chloride the resulting amide, **1c**, was apparently nucleophilic enough to react with another mole of sulfenyl chloride to produce the disubstituted acetamide **4** (34%).

$$\underset{4}{(p\text{-}CH_3C_6H_4S)_2NCOCH_3}$$

By adding sulfenyl chloride at 15 °C, we isolated a yield of 86% of the monosubstituted amide **1c** (R = *p*-tolyl); at 0 °C no reaction took place.

Oxidation of **1** with *m*-chloroperbenzoic acid in $CHCl_3$ cleanly produced the *N*-sulfinyl compounds **5** in 80% yield.

$$\underset{1}{RSHNCOCH_3} \xrightarrow[m\text{-}ClC_6H_4CO_3H]{} \underset{3}{RSONHCOCH_3}$$

R = C_6H_5, $CH_2CO_2CH_2CH_3$

These compounds are stable and are analogous to the *N*-(alkyl- and -arylsulfinyl)phthalimides previously reported.[10]

Experimental Section[11]

Sulfenyl chlorides were prepared by one of two methods.[8] (1) The thiol (10 mmol) in CCl_4 solution was added to a suspension of *N*-chlorosuccinimide (10 mmol) in CCl_4. The precipitated succinimide was collected, and the resulting yellow solution used directly. (2) The disulfide (10 mmol) in 30 mL of CCl_4 was cooled to 0 °C. One drop of triethylamine was added, and 10 mmol of SO_2Cl_2 was added dropwise with stirring. The product was purified by distillation except in the case of the alkanesulfenyl chlorides which were used directly.

***N*-(Thio)amides.** A solution of the sulfenyl chloride in 15 mL of hexane was added dropwise to a stirred solution of *N*-(trimethylsilyl)acetamide in 25 mL of hexane. After addition was complete, the reaction was stirred for 0–5 h and the solvent evaporated. The solid residue was dissolved in CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. The product was crystallized from hexane.

***N*-(Phenylthio)acetamide.** NMR δ 8.3 (1 H, s), 7.2 (5 H, s), 2.2 (3 H, s). IR 3220 (N–H), 1660 (C=O) cm^{-1}. Anal. Calcd for

(1) Organic Sulfur Chemistry, 34; for part 33, see D. N. Harpp, D. K. Ash, and R. A. Smith, *J. Org. Chem.*, companion paper in this issue.

(2) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Am. Chem. Soc.*, **90**, 4181 (1968); D. N. Harpp and J. G. Gleason, *Tetrahedron Lett.*, 1447 (1969); D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3529 (1970); D. N. Harpp and D. K. Ash, *Chem. Commun.*, 811 (1970); D. N. Harpp and B. A. Orwig, *Tetrahedron Lett.*, 2691 (1970); D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 73 (1971); D. N. Harpp, J. G. Gleason, and D. K. Ash, *ibid.*, **36**, 322 (1971); D. N. Harpp and J. G. Gleason, *J. Am. Chem. Soc.*, **93**, 2437 (1971); D. N. Harpp and S. M. Vines, *J. Org. Chem.*, **39**, 647 (1974); D. N. Harpp, J. Adams, D. Mullins, J. G. Gleason, and K. Steliou, *Tetrahedron Lett.*, 3989 (1978); D. N. Harpp and R. A. Smith, *Org. Synth.*, **58**, 138 (1978). It should be noted that the title compounds (*N*-(thioalkyl)amides) fail to desulfurize with tris(diethylamino)phosphine even under forcing conditions.

(3) Only two *N*-(arylthio)amides have been reported (*m*- and *p*-nitrophenyl): M. Furukawa, Y. Fujino, Y. Kojima, M. Ong, and S. Hayashi, *Chem. Pharm. Bull.*, **20**, 2024 (1972).

(4) (a) D. N. Harpp, B. Friedlander, D. Mullins, and S. M. Vines, *Tetrahedron Lett.*, 963 (1977); (b) Y. Abe, T. Nakabayashi, and J. Tsurugi, *Bull. Chem. Soc. Jpn.*, **46**, 1898 (1973); (c) M. Behforouz and J. Kerwood, *J. Org. Chem.*, **34**, 51 (1969).

(5) (a) D. N. Harpp, K. Steliou, and T. H. Chan, *J. Am. Chem. Soc.*, **100**, 1222 (1978); (b) M. V. Kalnins, *Can. J. Chem.*, **44**, 2111 (1966).

(6) Presumably, the reaction of **1** with thiols could provide a general route to symmetric and unsymmetric disulfides: cf. D. N. Harpp, D. Ash, T. Back, J. G. Gleason, B. A. Orwig, W. E. VanHorn, and J. P. Snyder, *Tetrahedron Lett.*, 3351 (1970); A. B. Sullivan and K. Boustany, *ibid.*, 3547 (1970). When thiophenol is treated with *N*-(phenylthio)acetamide in acetone at 50 °C, diphenyl disulfide is formed in good yield.

(7) R. S. Glass, *J. Organomet. Chem.*, **61**, 83 (1973).

(8) Sulfenyl chlorides were prepared by the method of Abe, Nakabayashi, and Tsurugi[4b] or of D. N. Harpp, B. T. Friedlander, and R. A. Smith, *Synthesis*, 181 (1979).

(9) *N*-(Trimethylsilyl)acetamide was synthesized by method of L. Birkofer, A. Ritter, and H. Dickopp, *Chem. Ber.*, **96**, 1473 (1963). This compound is also available from Silar Laboratories Inc.

(10) D. N. Harpp and T. G. Back, *J. Org. Chem.*, **38**, 4328 (1973).

(11) ^1H NMR spectra of $CDCl_3$ or Me_2SO-d_6 solutions (Me_4Si, δ 0) were recorded on a Varian T-60 spectrometer. Infrared spectra were obtained as KBr pellets on a Perkin-Elmer 257 spectrophotometer calibrated on the 1602-cm^{-1} band of polystyrene. Melting points were obtained on a Gallenkamp block apparatus and are uncorrected. High-resolution mass spectra were obtained on a Model AEI-MS-902 spectrometer using a direct insertion probe with an ionization potential of 70 eV. Organic microanalyses were performed by Dr. C. Daesslé of Montreal and by Galbraith Laboratories, Inc., Knoxville, TN.

0022-3263/79/1944-4196$01.00/0

C_8H_9NOS: C, 57.46; H, 5.42; N, 8.38; S, 19.17. Found: C, 57.20; H, 5.35, N, 8.10; S, 18.98.

***N*-[[(Carboethoxy)methyl]thio]acetamide.** NMR δ 8.2 (1 H, s), 4.2 (2 H, q), 3.5 (2 H, s), 2.2 (3 H, s), 1.3 (3 H, t). IR 3150 (N-H), 1730 (-C(O)O-), 1670 (C=O) cm^{-1}. Exact mass: calcd for $C_6H_{11}NO_3S$, 177.0460; found, 177.0459.

***N*-(Benzylthio)acetamide.** NMR δ 7.2 (5 H, s), 3.85 (2 H, s), 1.9 (3 H, s). IR 3240 (N-H), 1660 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.78; H, 6.33; N, 7.59.

***N*-(*p*-Tolylthio)acetamide.** NMR δ 7.1 (4 H, s), 2.35 (3 H, s), 2.1 (3 H, s). IR 3195 (N-H), 1675 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.76; H, 6.39; N, 7.54.

***N*-[(*o*-Nitrophenyl)thio]acetamide.** NMR δ 7.1-8 (4 H, m), 2.1 (3 H, s). IR 3200 (N-H), 1665 (C=O), 1330 (NO_2) cm^{-1}. Anal. Calcd for $C_8H_8NO_3S$: C, 45.27; H, 3.80; N, 13.20. Found: C, 45.42; H, 3.91; N, 13.07.

***N*-Sulfinylacetamide.** To a solution of the *N*-(thio)acetamide (20 mmol) in 100 mL of $CHCl_3$ at 0 °C was added dropwise over 1 h a solution of *m*-chloroperbenzoic acid (20 mmol) in 40 mL of $CHCl_3$. The reaction was stirred for a further 0.5 h and then evaporated. Addition of ether to dissolve *m*-chlorobenzoic acid followed by filtration afforded the *N*-sulfinylacetamide in 80% yield.

***N*-(Phenylsulfinyl)acetamide.** NMR δ 7.6 (5 H, s), 2.0 (3 H, s). IR 3000 (N-H), 1670 (C=O), 1050 (S=O) cm^{-1}. Exact mass: calcd for $C_8H_9NO_2S$, 183.0354; found, 183.0374. Yield 82%; mp 105-108 °C.

***N*-[[(Carboethoxy)methyl]sulfinyl]acetamide.** NMR δ 4.3 (2 H, q), 4.0 (2 H, s), 2.2 (3 H, s), 1.3 (3 H, t). IR 3200 (N-H), 1720 (-C(O)O-), 1680 (C=O), 1070 (S=O) cm^{-1}. Exact mass: calcd for $C_6H_{11}NO_4S$, 193.0409; found, 193.0414. Yield 73%; mp 66-68 °C.

Preparation of *N*-Bis(*p*-tolylthio)acetamide (4). To *N*-(trimethylsilyl)acetamide (31.5 mmol) in 30 mL of hexane was added *p*-tolylsulfenyl chloride in 10 mL of hexane over 1 h. Further stirring for 1 h afforded 5.4 g of a white solid. This was dissolved in CH_2Cl_2, extracted with H_2O (dried with $MgSO_4$), and evaporated (precipitation with hexane) to afford 4.43 g of a white solid which was separated by chromatography on silica gel (CH_2Cl_2). Two fractions were obtained: **1c** (47%) followed by **4** [34%; mp 64-67 °C; NMR δ 7.0 (8 H, $A_2'B_2'$), 2.4 (3 H, s), 2.3 (6 H, s); IR 1700 (C=O) cm^{-1}]. A molecular peak at 303 is observed for **4**.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and the Department of Education of Quebec for financial support.

Registry No. 1 (R = C_6H_5), 71032-76-3; 1 (R = $C_6H_5CH_2$), 71032-77-4; 1 (R = *p*-$CH_3C_6H_4$), 69189-02-2; 1 (R = *o*-$NO_2C_6H_4$), 70413-90-0; 1 (R = $EtOCOCH_2$), 71032-78-5; **3** (R = C_6H_5), 71050-18-5; **3** (R = $EtOCOCH_2$), 71032-79-6; **4**, 71032-80-9; *N*-(trimethylsilyl)acetamide, 13435-12-6; phenylsulfenyl chloride, 931-59-9; benzylsulfenyl chloride, 26826-81-3; *p*-tolylsulfenyl chloride, 933-00-6; *o*-nitrophenylsulfenyl chloride, 7669-54-7; carboethoxymethylsulfenyl chloride, 71032-81-0.

Action of Potassium Amide in Ammonia on Some Benzophenone Derivatives. Evidence That *o*-Bromophenyl Anions Partition between Aryne Formation and Protonation to Aryl Bromides[1]

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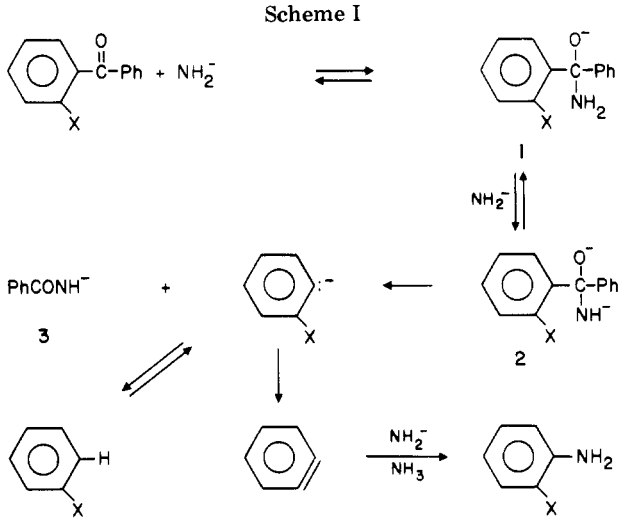
Received June 25, 1979

This research had two different but related objectives. One was to extend knowledge of the effects of substituents on the cleavage of benzophenones by KNH_2 in ammonia. Bunnett and Hrutfiord[3] observed that *o*-fluorobenzophenone is cleaved to form fluorobenzene, benzamide, and benzoic acid, that *o*-chlorobenzophenone furnishes aniline, benzamide, and benzoic acid, that *m*- and *p*-chlorobenzophenones furnish products in which the benzophenone framework remains intact with little or no cleavage, and that benzophenone itself is not cleaved. The mechanism of Scheme I was suggested for these reactions.[3] The initial work left unclear what effects other substituents would have on the occurrence of cleavage.

Scheme I



The second question was whether *o*-bromophenyl anions in ammonia solution are foreordained to lose bromide ion and form benzyne or whether they may at least in part take protons from the solvent to form bromobenzene molecules. In the pioneering work of Roberts and co-workers[4] on the aryne mechanism, it was found that the primary isotope effect, k_H/k_D, with respect to hydrogen in the 2-position of bromobenzene is 5.5 "which is close to the 6-7 range expected for a concerted E2 dehydrobromination".[4] Their conclusion that benzyne formation is concerted implies that *o*-bromophenyl anions formed in ammonia would react exclusively by bromide ion loss without being protonated at all by the solvent.

Results

Several substituted benzophenones were found to resist cleavage by KNH_2 in ammonia. They were the *m*-fluoro, *p*-fluoro, *o*-methoxy, and *p*-methoxy derivatives, as well as the anion of *o*-benzoylbenzoic acid. Probably these compounds did add amide ion, to form an adduct of the type shown on the first line of Scheme I, but such an adduct would decompose to regenerate the original benzophenone derivative during the conditions of workup employed.

o-Bromobenzophenone was cleaved to form benzamide (62%), benzoic acid (12%), and aniline (51%). That such cleavage would occur was implied by previous work[3] but not actually observed before.

2-Chloro-4-methylbenzophenone was cleaved by KNH_2 in ammonia to form benzamide (31%), benzoic acid (36%), and a mixture of isomeric toluidines (42%). The mixture of toluidines was acetylated, and the resulting acet-

(1) Based on the Sc.B. theses of D. S. Connor (1960) and K. J. O'Reilly (1962).
(2) University of California, Santa Cruz, CA 95064.
(3) Bunnett, J. F.; Hrutfiord, B. F. *J. Org. Chem.* **1962**, *27*, 4152.
(4) Roberts, J. D.; Semenow, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601.

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