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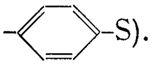
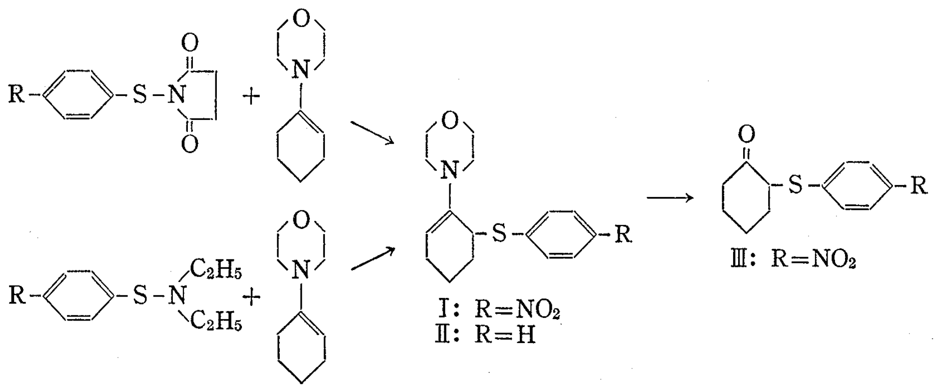
Sulfenylation of Morpholine Enamine of Cyclohexanone with Sulfenamides and Thiosulfonates

It has recently been demonstrated that alkyl and arylsulfenimides react with thiols,[1a] hydrodisulfides,[1b] alkoxides,[2] amines[3] and active methylene compounds[4] to give disulfides, trisulfides, alkyl sulfenates, sulfenamides and alkylthio derivatives of active methylene compounds. Alkyl thiosulfonates have also been known to act as an efficient reagent for thiols,[5] amines[5b,c,6] and active methylene compounds.[7] These reactions are believed to occur by the nucleophilic attack to the sulfur atoms of thioimides and thiosulfonates.

In the present studies, a novel sulfenylation of enamine with sulfenamides and thiosulfonates was attempted. When 4-nitrophenylsulfensuccinimide was stirred with two equivalent amounts of 1-morpholino-1-cyclohexene in dichloromethane at room temperature for 5 hours, 1-morpholino-6-*p*-nitrophenylthio-1-cyclohexene (I) melting at 138° was obtained in 50% yield. *Anal.* Calcd. for $C_{16}H_{20}O_3N_2S$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.01; H, 6.19; N, 9.01. IR ν_{max}^{KBr} cm^{-1}: 1331, 1513 (NO_2); 1119 (ether). NMR ($CDCl_3$) τ: 8.45—7.60 (6H, m, 3,4,5-protons); 7.50—6.75 (4H, m, $N\langle\begin{smallmatrix}CH_2)\\CH_2\end{smallmatrix}$); 6.23 (4H, t, J=5 Hz, $O\langle\begin{smallmatrix}CH_2)\\CH_2\end{smallmatrix}$; 5.75 (1H, broad s, 6-proton); 5.10—4.90 (1H, m, 2-proton) 2.75—2.40 (2H, m, aromatic proton); 1.95—1.70 (2H, m, aromatic proton). Mass Spectrum m/e: 319 (M^+), 165 (M^+-NO_2--S).



I: R=NO_2
II: R=H
III: R=NO_2

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1) *a*) K.S. Boustany and A.B. Sullivan, *Tetrahedron Letters*, **1970**, 3547; *b*) D.N. Harpp, D.K. Ash, T.G. Back, J.G. Greason, B.A. Orwig, W.F. VanHorn, and J.P. Snyder, *ibid.*, **1970**, 3551; *c*) D.N. Harpp and T.G. Back, *J. Org. Chem.*, **36**, 3828 (1971).

2) D.H.R. Barton, G. Page, and D.A. Widdowson, *Chem. Commun.*, **1970**, 1466.

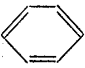
3) *a*) D.N. Harpp and T.G. Back, *Tetrahedron Letters*, **1971**, 4953; *b*) K.S. Boustany, *Chimia*, **1970**, 396.

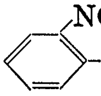
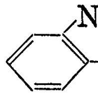
4) *a*) T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Letters*, **1970**, 5115; *b*) T. Mukaiyama and K. Saigo, *Bull. Chem. Soc. Japan*, **44**, 3077 (1971); *c*) T. Mukaiyama, S. Kobayashi, K. Kamio, and H. Takei, *Chemistry Letters*, **1972**, 237.

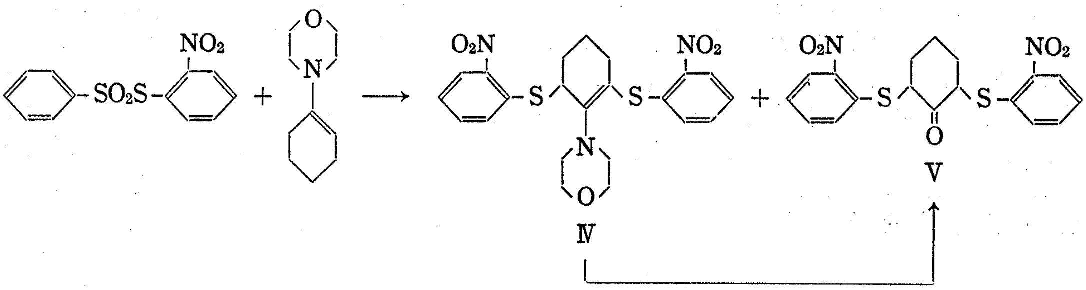
5) *a*) T.F. Parsons, J.D. Buckman, D.E. Person, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965); *b*) S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 954 (1969); *c*) J.P. Weidner and S.S. Block, *J. Med. Chem.*, **10**, 1167 (1967).

6) *a*) B.G. Boldyrev and S.A. Kolenikova, *C. A.*, **62**, 13076e (1965); *b*) J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, **31**, 2842 (1965); *idem*, *Tetrahedron Letters*, **1965**, 4291.

7) *a*) S. Hayashi, M. Furukawa, J. Yamamoto, and K. Niigata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1188 (1967); *b*) S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *ibid.*, **17**, 419 (1969).

Further evidence for the structure I was obtained by hydrolysis of I with 10 % hydrochloric acid to give 2-p-nitrophenylthiocyclohexanone (III), melting at 99—100°, which exhibited infrared (IR) absorptions assignable to the carbonyl group at 1707 cm^{-1} and due to the nitro group at 1331 cm^{-1} and 1508 cm^{-1}. Phenylsulfensuccinimide also reacted with 1-morpholino-1-cyclohexene to give 1-morpholino-6-phenylthio-1-cyclohexene (II) melting at 83—85° in 23% yield. *Anal.* Calcd. for $C_{16}H_{21}ONS$: C, 69.78; H, 7.69; N, 5.09; S, 11.66. Found: C, 69.93; H, 7.59; N, 5.03; S, 11.82. NMR ($CDCl_3$) τ: 8.70—7.75 (6H, m, 3,4,5-protons); 7.50—6.80 (4H, m, $N\langle^{CH_2}_{CH_2}$); 6.32 (4H, t, J=5 Hz, $O\langle^{CH_2}_{CH_2}$); 6.05 (1H, broad s, 6-proton); 5.30—5.10 (1H, m, 2-proton); 3.00—2.40 (5H, m, aromatic proton). Mass Spectrum *m/e*: 275 (M^+), 166 (M^+--S). Treatment of the equimolecular amounts of phenylsulfen-N,N-diethylamide and 1-morpholino-1-cyclohexene in benzene under the similar conditions also gave 1-morpholino-6-phenylthio-1-cyclohexene (II) in 4.5% yield, which was identified with the authentic sample obtained by the reaction described above.

On the other hand, heating of *o*-nitrophenylthiobenzenesulfonate with two equivalent amounts of 1-morpholino-1-cyclohexene in benzene for 13 hours under reflux afforded a 38% yield of 1-morpholino-2,6-bis-*o*-nitrophenylthio-1-cyclohexene (IV) melting at 171—173° and a small amount of 2,6-bis(*o*-nitrophenylthio)-cyclohexanone (V) melting at 109—111°. *Anal.* Calcd. for $C_{22}H_{23}O_5N_3S_2$: C, 55.81; H, 4.90; N, 8.88. Found: C, 55.48; H, 4.83; N, 9.09. IR ν_{max}^{KBr} cm^{-1}: 1335, 1507 (NO_2); 1117 (ether). NMR ($CDCl_3$) τ: 8.45—7.55 (6H, m 3,4,5-protons); 7.10—6.75 (4H, m, $N\langle^{CH_2}_{CH_2}$); 6.34 (4H, t, J=5 Hz, $O\langle^{CH_2}_{CH_2}$); 5.55 (1H, broad s, 6-proton); 2.80—2.25 (6H, m, aromatic proton); 1.90—1.70 (2H, m, aromatic proton). Mass Spectrum *m/e*: 473 (M^+), 319 (M^+ - -S), 155 (M^+- 2 -S). Facile hydrolysis of IV gave V which exhibited IR absorptions assignable to the carbonyl group at 1705cm^{-1} and due to the nitro group at 1345 cm^{-1} and 1512 cm^{-1}.



Further studies and the details will be reported in the near future.

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