The Reaction of Benzonitrile Oxide and Diphenyl Nitrile Imine with β-Keto Sulfoxides. Synthesis of 4-Methylsulfinyl Isoxazoles and Pyrazoles.

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The synthetic utility of β-keto sulfoxides is documented by a number of papers by several authors (1a-e) dealing with their transformations into several classes of both sulphur-containing or sulphur-free compounds. Recently M. von Strandtmann and coworker (2) have also reported an interesting synthesis of some heterocyclic nuclei resulting from cyclization of particular *ortho*-substituted β-keto sulfoxides.

We wish to report here the transformation of β-keto sulfoxides into heterocycles through the addition of 1,3-dipolar compounds to β-keto sulfoxide anions. We have found that benzonitrile oxide reacts smoothly with the sodium salts of β-keto sulfoxides (IIa-c) in THF or in DMSO giving rise to the corresponding 4-methylsulfinyl isoxazoles (IVa-c) in fair yields. The reaction can be outlined as follows:

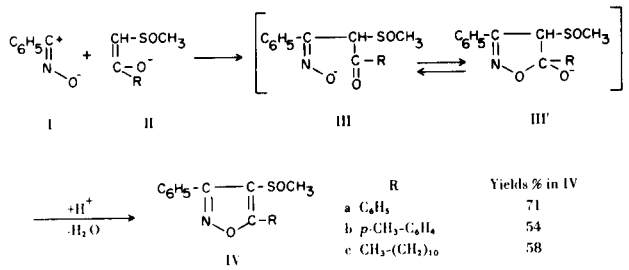

Figure 1

The intermediate III that can be formed by a nucleophilic attack of the anion on the nitrile oxide cyclizes to III', which, upon protonation loses a mole of water to give the isoxazole IV. Alternatively the direct formation of III' by a concerted cycloaddition (3) of the 1,3-dipolar compound into the double bond of the anion II is also possible. The reaction is related to the synthesis of isoxazole-4-ketones, -4-esters or -4-nitriles from nitrile oxides and β-diketone, β-ketoester or β-ketonitrile anions, respectively (4); and, as is reported to happen in that synthesis, produces isoxazoles directly. In no case could we isolate the intermediate-5-hydroxyisoxazoline.

The reaction can be performed also by adding benzalchlorooxime, instead of benzonitrile oxide, to the solution of the sodium salt of the β-keto sulfoxide obtained *in situ* from the corresponding ester and methylsulfinyl anion (5). This modification has been checked in the synthesis of IVb. In both ways the isoxazole is obtained in fair yields.

In a similar manner the diphenylnitrile imine, obtained *in situ* by dehydrohalogenation of the *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (V), upon reaction with the sodium salt of ω-methylsulfinyl-*p*-methylacetophenone gave the 1,3-diphenyl-4-methylsulfinyl-5-*p*-tolylpyrazole (VI) in 62% yield.

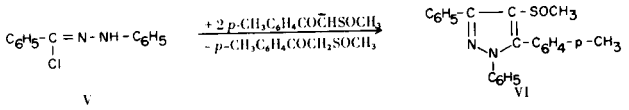

Figure 2

Attempts were made to remove the methylsulfinyl group from the cyclic products in order to obtain the parent sulphur-free heterocycles. This would be of interest since by this method 3,5-disubstituted isoxazoles and pyrazoles of unequivocal structure, whose synthesis normally requires acetylenic compounds (3), could be easily obtained from readily accessible starting materials. Unfortunately, the action of aluminum amalgam-water-THF (1a), Raney nickel-95% ethanol (6) or zinc dust and acetic acid (1b) in VI led only to the 4-methylthiopyrazole (VII).

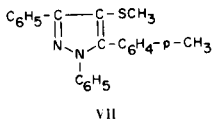

Figure 3

EXPERIMENTAL

Solvents were dried: DMSO over calcium hydride and THF over LAH. Sodium hydride was used as an 80% suspension in mineral oil. Melting points are uncorrected. Ir spectra were measured in Nujol with a Perkin-Elmer Model 137 Spectrometer. Only prominent peaks are reported (cm^{-1}). Nmr spectra were

recorded on a Varian A-60 instrument; chemical shifts (δ, ppm) were measured from TMS as internal reference. Mass spectra were taken on a Hitachi-Perkin-Elmer RMU 6D single focusing spectrometer at 70 eV. Column chromatographies were performed on silica gel 0.05-0.20 (Merck-Darmstadt).

Methylsulfinyl *n*-Undecyl Ketone (IIc).

Compound IIc (12 g., 92% yield) was prepared according to the Corey procedure (1a) from methylsulfinyl carbanion (0.1 mole) and methyl laurate (10.5 g., 0.05 mole); m.p. 89° from methanol-hexane; ir: 1690, 1020 cm^{-1}; mass spectrum: 260 (M^+); 197 (M^+-MeSO) m/e.

Anal. Calcd. for $C_{14}H_{28}O_2S$: C, 64.58; H, 10.84. Found: C, 64.31; H, 10.90.

3,5-Diphenyl-4(methylsulfinyl)isoxazole (IVa).

ω-(Methylsulfinyl)acetophenone (1a) (1.82 g., 1 mmole) was converted to its sodium salt by the action of 1 equivalent of sodium hydride in 40 ml. of THF. A solution of benzonitrile oxide, obtained from benzalchlorooxime (1.55 g., 1 mmole) and a few drops of triethylamine in 40 ml. of THF at -5°, was added dropwise. The mixture was allowed to warm to room temperature under stirring and diluted with water; the *p*H was adjusted to 5 with hydrochloride acid. Extraction with ether yielded a yellow oil after drying (sodium sulfate) and solvent removal. The oil was chromatographed on a silica gel column. The 3,5-diphenyl-4-methylsulfinylisoxazole (2.0 g., 71% yield) was eluted with hexane-ether (60/40) and was identified by comparison (ir spectra) with an authentic sample (7).

3-Phenyl-4-methylsulfinyl-5-*p*-tolylisoxazole (IVb).

A solution of methylsulfinyl carbanion was prepared according to Corey (1a) from sodium hydride (1.2 g., 0.04 mole) in DMSO (100 ml.). To the solution diluted with THF (30 ml.) and cooled to -5°, methyl-*p*-toluate (6.0 g., 0.04 mole) was added and the solution was stirred four hours at room temperature then cooled again to -5°. A solution of benzalchlorooxime (3.1 g., 0.02 mole) in THF (20 ml.) was added. The mixture was stirred overnight and decomposed with water. After acidification with hydrochloric acid, the mother liquor was extracted with ether. The extracts, dried over sodium sulfate and evaporated under vacuum, gave a solid residue from which upon chromatography on silica gel (hexane ether 70/30) 3-phenyl-4-(methylsulfinyl)-5-*p*-tolylisoxazole (3.2 g., 54% yields calculated on chlorooxime) was obtained; m.p. 133° from benzene-heptane; ir: 1495, 1370, 1060, 835, 777, 737, 700 cm^{-1}; nmr (deuteriochloroform): 2.46 (3H, s); 2.70 (3H, s); 7.25-8.10 ppm (9H, aromatics); mass spectrum: 297 (M^+), 282 (M^+ - Me), 119 base peak ($MeC_6H_4CO^+$), 103 m/e ($C_6H_5CN^+$).

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.67; H, 5.08; N, 4.71; S, 10.76. Found: C, 68.83; H, 5.18; N, 4.75; S, 10.88.

3-Phenyl-4-methylsulfinyl-5-*n*-undecylisoxazole (IVc).

Methylsulfinyl *n*-undecyl ketone (2.4 g., 0.01 mole) was converted to its sodium salt by the reaction of 1 equivalent of sodium hydride in DMSO (30 ml.) and THF (30 ml.). A solution of benzonitrile oxide, obtained from benzalchlorooxime (1.15 g., 0.01 mole) and triethylamine in THF (40 ml.) at -5°, was added and the mixture was allowed to warm to room temperature with stirring. The mixture was poured into water, and the *p*H was adjusted to 5 with hydrochloric acid. The residue obtained upon evaporation of the ether extracts was chromatographed over silica gel (hexane-ether 60/40) to give IVc (2.1 g., 58% yields) as a viscous oil that crystallized on standing; m.p. 40-41° from hexane; ir: 1585, 1460, 1380, 1070, 1050, 975, 770, 730, 700 cm^{-1}; nmr (deuteriochloroform): 0.8-1.5 (21 H, m; $CH_3(CH_2)_9$); 2.7 (3H, s; CH_3S); 2.85-3.20 (2H, m; CH_2-CH_2-C=); 7.10-8.20 (5H, m; aromatics).

Anal. Calcd. for $C_{21}H_{31}NO_2S$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.53; H, 8.45; N, 3.76.

1,3-Diphenyl-3-methylsulfinyl-5-*p*-tolylpyrazole (VI).

ω-(Methylsulfinyl)-*p*-methylacetophenone (1b) (2.12 g., 0.01 mole) was converted to its sodium salt by the reaction of 1 equivalent of sodium hydride in DMSO (30 ml.). A solution of *N*-(α-chlorobenzylidene-*N'*-phenylhydrazine (1.15 g., 0.005 mole) in THF (20 ml.) was added and the mixture was allowed to warm to room temperature with stirring. After decomposition with water, adjustment of the *p*H to 4 with hydrochloric acid, extraction with ether and evaporation of the extracts, a crude residue was obtained. Upon silica gel chromatography (hexane-ether 50/50) VI (1.15 g., 62% yields) was obtained; m.p. 175-176° from aqueous ethanol; ir: 1500, 1485, 1090, 1070, 970, 828, 764, 740, 700 cm^{-1}; nmr (deuteriochloroform): 2.17 (3H, s); 2.31 (3H, s); 7.05-8.12 (14 H, aromatics); mass spectrum: 372, (M^+); 357, base peak (M^+ - Me); 342 m/e (M^+ - 2 Me).

Anal. Calcd. for $C_{23}H_{20}N_2OS$: C, 74.17; H, 5.41; N, 7.52; S, 8.59. Found: C, 74.20; H, 5.47; N, 7.50; S, 8.31.

1,3-Diphenyl-4-methylthio-5-*p*-tolylpyrazole (VII).

A mixture of VI (126 mg., 0.3 mmole) and aluminum amalgam (1a) (80 mg.) in THF (20 ml.) and water (2 ml.) was stirred two hours at room temperature and four hours at reflux. The solution was filtered from inorganic material, dried over sodium sulfate and evaporated to dryness. The residue was purified by tlc (hexane-ether, 70/30) and VII (60 mg. 57% yield) was obtained as a white crystalline solid; m.p. 166° from aqueous ethanol; ir: 1495, 1450, 965, 822, 770, 695 cm^{-1}; mass spectrum: 356, base peak (M^+); 341 (M^+-Me); 309 [(M^+-Me)-S], 308 m/e [(M^+-Me)-SH]; nmr (deuteriochloroform): 2.10 (3H, s); 2.38 (3H, s); 7.10-8.20 (14H, aromatics).

Anal. Calcd. for $C_{23}H_{20}N_2S$: N, 7.8. Found: N, 7.7.

Compound VII (100 mg., 93% yield) was also obtained when VI (126 mg., 0.3 mmole) and zinc dust (98 mg.) in absolute ethanol (10 ml.) and galcial acetic acid (10 ml.) were refluxed for twenty hours.

Compound VII (60 mg., 56% yield) was also obtained when VI (126 mg., 0.3 mmole) was refluxed 72 hours in 95% ethanol (25 ml.) with Raney nickel (2.5 g.).

REFERENCES

(1a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965); (b) G. A. Russell and G. J. Mikol, *ibid.*, **88**, 5498 (1966); (c) G. A. Russell, E. Sabourin and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966); (d) T. L. Moore, *ibid.*, **32**, 2786 (1967); (e) G. A. Russell and G. Hamprecht, *ibid.*, **35**, 3007 (1970).

(2) M. von Strandtmann, S. Klutchko, M. P. Cohen and J. Shavel, *J. Heterocyclic Chem.*, **9**, 171 (1972); *ibid.*, **9**, 173 (1972); *ibid.*, **9**, 175 (1972).

(3) R. Huisgen, *Angew. Chem. Intern. Edit. Engl.*, **2**, 565 (1963).

(4) A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **76**, 148 (1946).

(5) Two moles of the sodium salt per mole of chlorooxime are required: one as a base to dehydrohalogenate the chlorooxime to the nitrile oxide, the second one to react as a nucleophile.

(6) G. R. Petitt and E. E. van Tamelen, *Organic Reactions*, **12**, 356-529 (1962).

(7) P. Bravo, G. Gaudiano and A. Umani-Ronchi, *Gazz. Chim. Ital.*, **97**, 1664 (1967).