A NEW SYNTHESIS OF METATHIAZANONE DERIVATIVES VIA INTRAMOLECULAR PUMMERER REARRANGEMENTS

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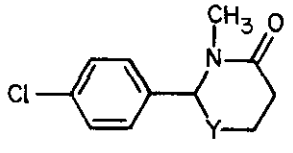
A new synthesis of metathiazanone derivatives is described. The synthesis involves a novel, intramolecular Pummerer rearrangement.

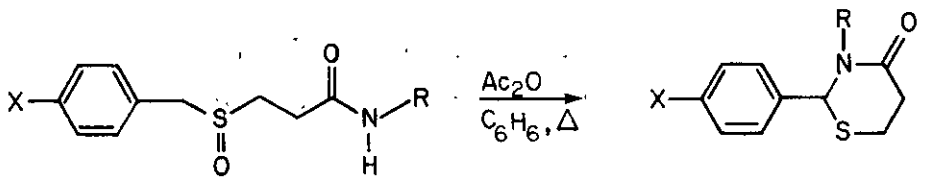
The compound 2-(p-chlorophenyl)-3-methyl-4-metathiazanone (I)[1-4] is an important synthetic precursor for the corresponding sulfoxide (II)[2,5] and sulfone (III)[2,6], both known muscle relaxants. Up to the present time, compound I has been synthesized by: (a) reaction of p-chlorobenzaldehyde



I Y = S
II Y = SO
III Y = SO_2

with 3-mercapto-N-methylpropionamide or with 3-mercaptopropionic acid-methylamine,[1,2] (b) reaction of N-(p-chlorobenzylidene)methylamine with 3-mercaptopropionic acid[1], or (c) reaction of p-chlorobenzal chloride with 3-mercapto-N-methylpropionamide[4] We here report a novel method for the synthesis of metathiazanone derivatives. The overall equation is illustrated

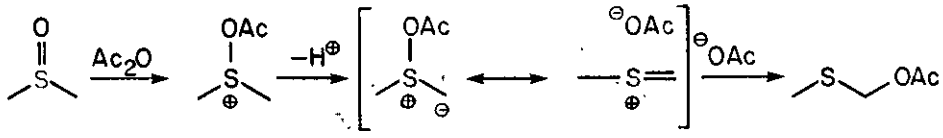
in Scheme 1.[7,8]



IV	X = Cl, R = CH_3	I	X = Cl, R = CH_3
V	X = H, R = CH_3	VIII	X = H, R = CH_3
VI	X = Cl, R = CH_2CH_3	IX	X = Cl, R = CH_2CH_3
VII	X = Cl, R = $CH_2C_6H_5$	X	X = Cl, R = $CH_2C_6H_5$

SCHEME 1

It is well known that the reaction of a dialkyl sulfoxide with acetic anhydride affords the corresponding α-acetoxy sulfide. This reaction, known as the Pummerer rearrangement,[10,11] has been shown to take place via the pathway outlined in Scheme 2. On basis of this mechanism, it seemed reasonable to propose that rearrangement of a sulfoxide with an



SCHEME 2

internal nucleophilic center suitably placed could result in intramolecular neutralization of the intermediate cation. To test this hypothesis, sulfoxide IV was heated with an excess of acetic anhydride in benzene for 1 h. During this time, the initial heterogeneous mixture became homogeneous. Purification

of the product by column chromatography (silica gel, 3:1 benzene-ethyl acetate) afforded, in 82% yield, 2-(p-chlorophenyl)-3-methyl-4-metathiazanone (I), m.p. 49-50°; i.r. (KBr), ν_{max} 1656, 1390 cm^{-1}; n.m.r. ($CDCl_3$) δ 2.80 (m, 4H), 2.96 (s, 3H), 5.48 (s, 1H), 7.2-7.7 (m, 4H).

Oxidation of compound I with peracetic acid (1 equiv.) or with potassium permanganate (2 equiv.) yielded compounds II or III, respectively.[1,2]

The synthetic method was extended to include the sulfoxides V - VII. In each case, the corresponding metathiazanone derivative (VIII - X, respectively) was formed in reasonably good yield. The results are summarized in Table 1.

Table 1. Synthesis of Metathiazanone Derivatives (Scheme 1)

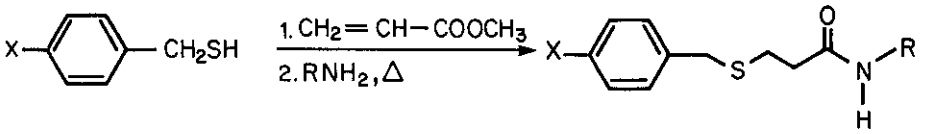
Reactant	Product	M.p.(°C)[a]	Yield (%)[b]
IV	I	49-50[c]	82
V	VIII	95-97[d]	50
VI	IX	103-110[e]	71
VII	X	oil	42

[a]Melting points are uncorrected. [b]Isolated yield.

[c]lit.[1] oil, b.p. 172-175° at 0.2 torr. [d]lit.[1] m.p. 95.2-96.2°

[e]lit.[1] m.p. 106-107.7°.

The starting materials (sulfoxides IV-VII) for the above-mentioned conversions were prepared as follows (see Scheme 3). Reaction of



XI X = H
XII X = Cl

XIII X = Cl, R = CH_3
XIV X = H, R = CH_3
XV X = Cl, R = CH_2CH_3
XVI X = Cl, R = $CH_2C_6H_5$

SCHEME 3

H_2O_2, CH_3OH

IV – VII

the appropriate benzylmercaptan[12] (XI, XII) with methyl acrylate in aqueous methanol in the presence of sodium hydroxide, followed by reaction of the resultant esters with the required primary amine, gave the sulfides XIII - XVI. Oxidation of these compounds with 1 equiv. of hydrogen peroxide in aqueous methanol yielded the corresponding sulfoxides IV-VII, respectively. The pertinent data is summarized in Table 2.

Table 2. Synthesis of Compounds XIII - XVI and IV - VII (Scheme 3)

Product	M.p. (°C)[a]	Yield (%)[b]
XIII	72-73	91
XIV	Oil	90
XV	88-90	47
XVI	78-80	31
IV	159-165	95
V	138-140	80
VI	173-176	49
VII	160-164	40

[a]Melting points are uncorrected. [b]Isolated yield.

References and Footnotes

1. A. R. Surrey, W. G. Webb and R. M. Gesler, J. Amer. Chem. Soc., 1958, 80, 3469.

2. A. R. Surrey, U.S. 3,082,209 (C.A., 1963, 59, 10074a).

3. K. Takamura, T. Asada, and T. Kanno, Japan 70-26,495 (C.A., 1971, 74, 88010q).

4. M. Hirata and M. Kaneo, Japan 73-33,752 (C.A., 1974, 80, 120969w).

5. A. R. Surrey, Brit. 866,761 (C.A., 1962, 56, 3487d).

6. R. M. Gesler and R. A. Surrey, J. Pharmacol. Exptl. Therap., 1958, 122, 517

7. I. Nagakura and H. Oka, Japan Kokai 74-35,389 (C.A., 1974, 81, 120655m).

8. Recently, Oae et. al., have reported a similar transformation involving the production of N-alkyldihydrobenzothiazine derivatives from the reaction of o-carbamoylphenylsulfoxides with acetic anhydride.[9]

9. S. Oae and T. Numata, Tetrahedron, 1974, 30, 2641.

10. (a) R. Pummerer, Ber., 1909, 42, 2282; (b) G. A. Russell and G. L. Mikol, "Mechanism of Molecular Migrations," Vol. 1, by B. S. Thyagarajan, J. Wiley & Sons, New York, 1968, p. 157.

11. M. Kise and S. Oae, Bull. Chem. Soc. Japan, 1970, 43, 1421, 1426.

12. (a) C. D. Hurd and L. L. Gershbein, J. Amer. Chem. Soc., 1947, 69, 2328; (b) J. L. Szabo and E. T. Steller, J. Amer, Chem. Soc., 1948, 70, 3667.

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