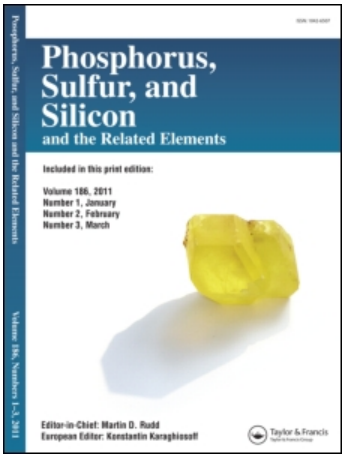

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REACTION OF 2-PHENYL-4-(ETHOXYMETHYLENE)-5(4H)-OXAZOLONE WITH 3,4-DITHIO-TOLUENE IN THE PRESENCE OF LEWIS BASE

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A convenient procedure for the synthesis of thiocoumarin by the condensation of 2-phenyl-4-(ethoxymethylene)-5-(4H)-oxazolone with 3,4-dithio-toluene in the presence of triethylamine is reported. Here, both thio groups are able to react with the carbonyl group to produce a mixture of isomeric products at ambient temperature. Only one of the isomers upon heating gives a new coumarin product.

Keywords: 3,4-Dithio-toluene; 5(4H)-oxazolone; electrophoresis; NMR spectroscopy; thiocoumarin

5(4H)-Oxazolones have emerged as an important class of synthons. 2-Phenyl-4-(ethyoxymethylene)-5(4H)-oxazolone is one of the 5(4H)-oxazolone derivatives with biological activity.[1] It has been reported that an ethoxy group attached to the ring can be displaced by various nucleophilie reagents. Thus, this compound can be utilized as a synthone to synthesize other derivatives which contain sulfur, and nitrogen.[2–4]

We now report new reactions of 2-phenyl-4-(ethoxymethylene)-5(4H)-oxazolone, which are not nucleophilic substitution reactions and where the ethoxy group is not displaced. It also should be noted that after a short period some Fungi was observed on the crude compounds.

When 2-phenyl-4-(ethoxymethylene)-5(4H)-oxazolone is mixed with 3,4-dithio-toluene in the presence of triethylamine at room temperature, the carbonyl group of the oxazolone ring is attacked and the ring is cleaved. Both thio groups (meta and para) are able to attack the carbonyl group, and therefore we have isomeric products but the group of para is more reactive than the meta group.

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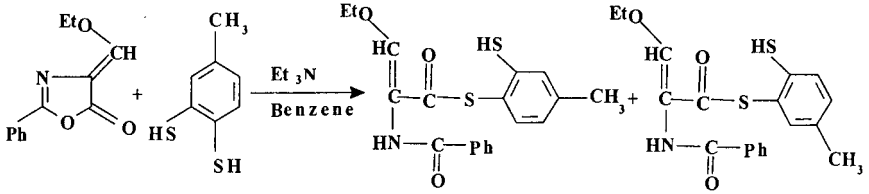
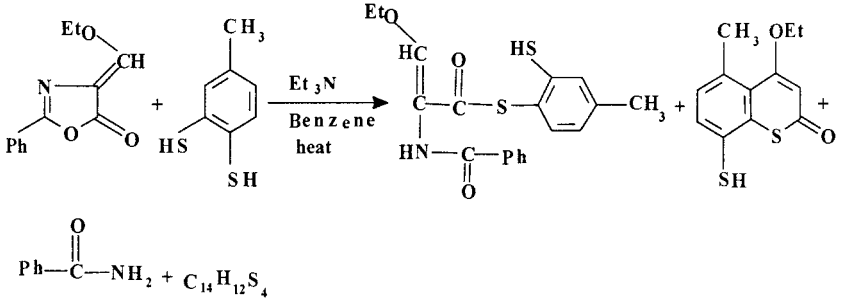


SCHEME 1

These isomeric products could not be separated with ordinary methods. Therefore the isomeric products were determined with capillary electrophoresis technique.

Solution of isomeric pairs were prepared by dissolving the crystaline powder at 10^{-4} M carrier electrolyte. Cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) is a powerful separation technique for the resolution of enantiomeric mixtrures as well as isomeric paris (1, 2).[5,6] In this technique inclusion complexation of CDs with different stability constants can be utilized for enantioseparation and resolution of isomeric pairs. To look for another evidence for the formation of isomeric pairs of 1 and 2 in the reaction of 2-phenyl-4(ethoxymethylene)-5(4H)-oxazolone with 3,4-dithio-toluene a mixture of reaction products was injected into the CD-MEKC system in the presence and absence of α-CD in the carrier electrolyte and the results were compared. When α-CD was not included in the carrier electrolyte, electropherogram A in Figure 1 was obtained which shows the disability of MEKC for the separation of isomeric paris. Then 10 Mm α-CD was added to the carrier electrolyte, and the obtained electropherogam B is also shown in Figure 1. Two distinct differences can be seen between electropherogams A and B. First the reduction of migration time in the presence of α-CD due to isomeric complexation with α-CD and consequent increase of their apparent mobilities which caused their faster elution. This phenomenon is common and was reported before.[7] Second the resolution of isomeric pairs is achieved which is a consequence of different stabilities of complexes formed between α-CD and isomers. The first peak was tentatively identified as isomer 2 and second one as isomer 1. The percent of 2 and 1 isomers was calculated using the area of each peak and found to be 71.82% and 28.18% respectively. These relative amounts are in good agreement with the results obtained by ^{1}HNMR studies.

When a mixture of 2-phenyl-4-(ethoxymethylene)-5(4H)-oxazolone and 3,4-dithio-toluene in the presence of triethylamin was heated in



SCHEME 2

dry benzene the products were found to be isomer 2 and (5-methyl-8-thio-benzo)-4-ethoxy-thiopyrene-2-one (thiocoumarin) (Scheme 2).

Isomer 1 reacts intramolecularly and looses a bezoamido group. However, heat may cause 3,4-dithio-toluene dimerization.

If a mixture of isomeric pairs (1, 2) in the presence of triethylamin was heated in dry n-hexan, isomer 2 does not react but isomer 1 reacts

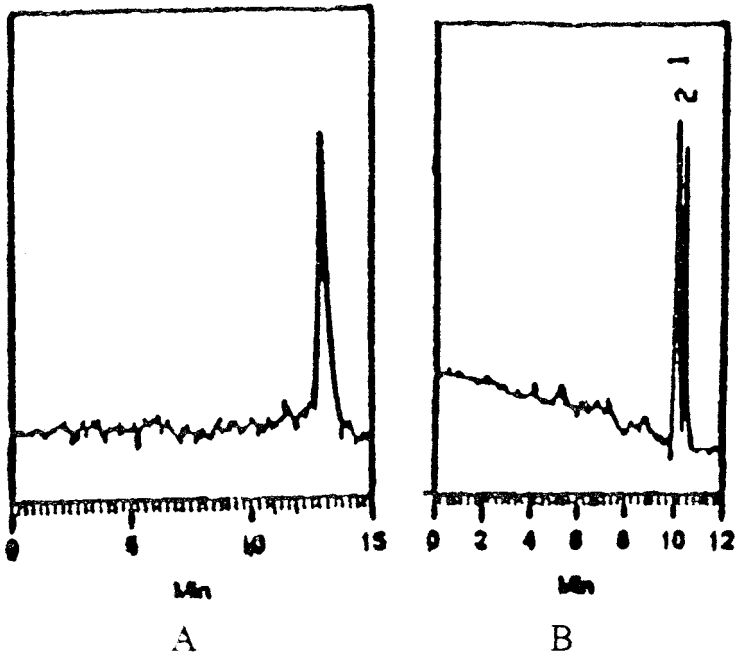
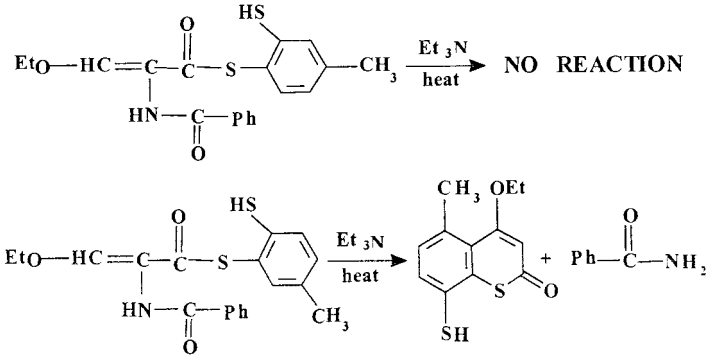


FIGURE 1 Effect of ∝-CD complexation on peak resolution of isomeric pairs. (A) without ∝-CD; (B) with ∝-CD peak 1: isomer 2 and peak 2: isomer 1.

intramolecularly and produces (5-methyl-8-thio-benzo)-4-ethoxy-thio-pyrene-2-one (thiocoumarin) (Scheme 3).



SCHEME 3

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained on a Shimadzu QP1100 EX mass spectrometer, and IR spectra were recorded with a Matson 1000 FT-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-500 Avance spectrometer using tetramethylsilane as an internal standard.

A Jasco model CE-800 capillary electrophoresis system (Jasco/Tokyo/Japan, consists of Jasco 890-CE high voltage power supply and a Jasco 875-CE intelligent UV-Vis detector) was used in this study.

Electropherograms were processed and recorded on a chromatopac model CR3A instrument (Shimadzu/Japan).

Separation was performed at 20 KV which produced a current of 17 μA. The detection of the separated peaks, was performed at 254 nm. Separation was done using a fused-silica capillary tube (60 cm long. $\times$ 50 μm I.D. and 375 μm O.D.) 48 cm to the detector.

Capillaries were obtained from GL scinces (Tokyo/Japan).

Buffer electrolyte consisted of disodium hydrogen phosphate adjusted to pH = 10, 50 mM sodium dodecyl sulfate (SDS), and 10 mM α-cyclodextrin ($\propto$-CD).

Hydrodynamic injection was performed by raising the anodic end of the capillary 5 cm higher than the level of cathodic vial for 15 s.

2-Phenyl-4-(ethoxymethylene)-5(4H)-oxazolone

A mixture of hippuric acid (18 g, 0.1 mmol), triethylorthoformate (14 g, 0.094 mmol) and acetic anhydride (20 ml, 0.21 mmol) was heated at

140°C for 1 h. The solvents removed in vacuo, the residue dissolved in 25 ml of alcohol, cooled, filtered, and the residue washed with cold petroleum ether to give 70% of product, m.p. 100–101°C, IR(KBr); 2980 (w, aliphatic), 1783 (s, C=O), 1672 (s, N=C) cm^{-1}. Anal. Calcd $C_{12}H_{11}NO_3C$, 66.35%; H, 5.06% N, 6. 45%; Found C, 66.17%; H, 5.10%; N, 6.43%.

^1H NMR ($CDCl_3$), δ_H: 8.2 (m, 2H, ortho ArH), 7.5 (m, 3H, meta and par a ArH), 7.35 (s, 1H, vinyl H), 4.5 (q, 2H, CH_2O), 1.5 (t, 3H, CH_3).

(2-Mercapto-4-methyl-phenyl)-2-benzamido-3-ethoxy-thiopropenoate and (2-Mercapto-5-methyl-phenyl)-2-benzamido-3-ethoxy-thiopropenoate

To a solution of 0.434 g (2 mmol) of 2-phenyl-4-(ethoxymethylene)-5(4H)-oxazolone in 50 ml of dry benzene was added 0.312 g (2 mmol) of 3,4-dithio-toluene and 0.2 ml of triethylamine. The mixture was stirred for 3 h at room temperature, then filtered and washed with dry benzene. The residue was recrystallized from ethanol 96%, giving 0.47 g of white crystals (yield 64%), m.p. 210°C.

IR (KBr) ν_{max}: 1638 (CO), 1689 (CO), 3336 (NH) cm^{-1}. Anal. Calcd $C_{19}H_{19}NO_3S_2$ C, 61.12%; H, 5.09%; N, 3.60%; Found C, 60.89%; H, 5.08%; N, 3.66%. ^1H NMR ($CDCl_3$) δ_H H 1.2 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.5 (q, 2H, CH_2), 3.9 (m, 1H, SHpara), 4.8 (m, 1H, NH) 5.2 (m, 1H, SH mata), 6.9 (s, 1H, C=CH), 7.2–7.7 (m, 8H, ArH) ppm. ^{13}C NMR: ($CDCl_3$): 14.6, 21, 1, 59.4, 59.6, 64, 89.4, 127–141, 166.6, 1983 ppm.

(5-Methyl-8-thio-benzo)-4-ethoxy-thiopyrene-2-one (Thiocoumarin)

To a solution of 0.434 g (2 mmol) of 2-phenyl-4-(ethoxy methylene)-5(4H)-oxazolone in 50 ml of dry benzene was added 0.468 g (3 mmol) of 3,4-dithio-toluene and 0.5 ml of triethylamine.

The mixture was stirred and heated for 12 h. Then the precipitate was filtered. The crude product was dissolved in hot ethanol and filtered while it was hot, and kept at room temperature; it got pinkish and fungi grew on the compound. The product decomposed at 160–165°C.

IR (KBr) ν_{max}: 1688 (C=O), 2962 (C=C–H) cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 1.2 (t, 3H, CH_3), 2.1–2.4 (brs, 4H, CH_3, SH), 3.7 (q, 2H, CH_2), 6.9 (s, 1H, Hvinyl), 7.3 (m, 2H, ArH) ppm. Anal Calcd. Calcd $C_{12}H_{12}O_2S_2$ C, 57.14%; H, 4.76%; S, 25.39%; Found C, 57.00%, H, 5.20%; S, 25.50%. ^{13}C NMR ($CDCl_3$): 18.37, 21.2, 58.3, 127.2–139.3 ppm. m/z 252 (M^+, 37%), 122 (20%), 154 (30%), 105 (100%).

Dimer of 3,4-Dithio-toluene

When 3,4-dithio-toluene is taken in excess in of the conditions given above, some of it dimers m.p. 50–51°C, were obtained. ^{1}H NMR ($CDCl_3$) δ_H: 2.2 (s, 6H, CH_3), 7.2–7.4 (m, 6H, Arh) ppm. ^{13}C NMR ($CDCl_3$): 2.10, 127.2–139.3 ppm. m/z 308 (M^+, 40%), 154 (100%), 122 (67%). Anal. Calcd $C_{14}H_{12}S_4$ C, 54.54%; H, 3.89%; N, 0.0%. Found: C, 53.82%; H, 4.01%; N, 0.0%.

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