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FACILE REDOX FORMATION OF A 3-SUBSTITUTED MALEIMIDE FROM A 3-SUBSTITUTED N-HYDROXYSUCCINIMIDE

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ABSTRACT: Treatment of 3-(Phenylthio)-N-hydroxysuccinimide **1** with methanesulfonyl chloride and pyridine in dry toluene resulted in the formation of 3-(Phenylthio)maleimide **3a**.

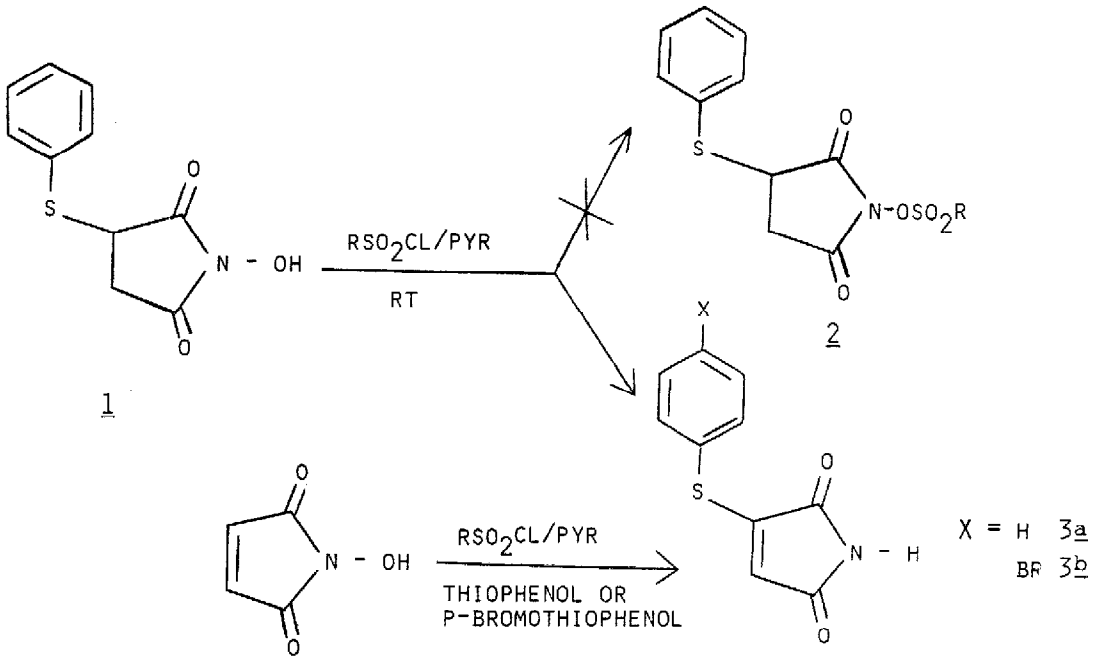
Several lines of evidence strongly support the hypothesis that pulmonary emphysema results from an imbalance between proteinases, primarily elastase, released by phagocytic cells and their naturally-occurring inhibitors[1]. The plasma glycoprotein alpha-1-proteinase inhibitor functions as a highly effective inhibitor of elastase. Inadequate modulation of the activity of elastase due to depressed levels of alpha-1-proteinase inhibitor leads to the degradation of lung connective tissue by elastase[2,3]. Oxidants in cigarette smoke and/or endogenous oxidants produced by leukocytes are also known to inactivate alpha-1-proteinase inhibitor via the oxidation of a critical methionine residue (Met-358) that is present at the reactive center of the inhibitor. Re-establishing a proteinase/antiproteinase balance via the development of compounds, such as **2**, that have **both** inhibitory activity toward elastase, as well as antioxidant properties, has been a major goal of our investigations in this area[4-7].

We have observed that the attempted sulfonylation of **1** to yield **2**, followed an unanticipated course and produced compound **3a** (X = H) instead (Scheme I). The structure of **3a** was established on the basis of the following data: the high resolution mass spectrum of compound **3a** was determined to be 205.01975, corresponding to the molecular formula $C_{10}H_7NSO_2$. The infrared spectrum of **3a** in chloroform showed a sharp absorption at 3400 cm^{-1} and a broad absorption at 3260 cm^{-1} (NH free and hydrogen-bonded, respectively) and two strong carbonyl absorptions at 1770 and 1720 cm^{-1} (asymmetric and symmetric CO stretch). The greater intensity of the symmetric CO stretch suggested the presence of a cyclic 1,3-dicarbonyl compound. The uv spectrum of **3a** in dimethyl sulfoxide showed maxima at 346.0 and 260.0 nm, indicating the presence of a conjugated system. The ^1H nmr spectrum of **3a** (300 MHz, dimethylsulfoxide-d_6) showed three resonances at 5.7 (s,1H), 7.6 (m,5H) and 11.1 (s,1H) ppm. The resonance at 11.1 ppm was broad and its chemical shift was solvent and concentration-dependent. Furthermore, addition of deuterium oxide to a deuteriochloroform solution of the compound caused the resonance at 11.1 ppm to disappear.

Reaction of equivalent amounts of N-hydroxymaleimide, methanesulfonyl chloride and thiophenol in the presence of a five-fold excess pyridine in dry toluene under the same conditions lead to the isolation of **3a** (19% yield). When p-bromothiophenol was used, compound **3b** isolated. The structure of **3b** was conclusively elucidated by X-ray crystallography (Figure 1).

Further insight into the mechanism of the reaction was provided by the observation that the formation of **3a** and **3b** is invariant to the structure of the alkyl or aryl sulfonyl chloride used (unpublished observations). N-hydroxyimides with an **alkyl** thioether side chain at C-3 form the expected sulfonylated products. A plausi-

SCHEME I



1 2

ble mechanism that is consistent with these observations is shown in Scheme II, where sulfonylation is followed by base-induced ketene-acyl nitrene formation. Subsequent intramolecular trapping of the acyl nitrene leads to **3a-b**. To our knowledge this is the first example of a direct, one-step conversion of a 3-substituted N-hydroxysuccinimide to a 3-substituted maleimide.

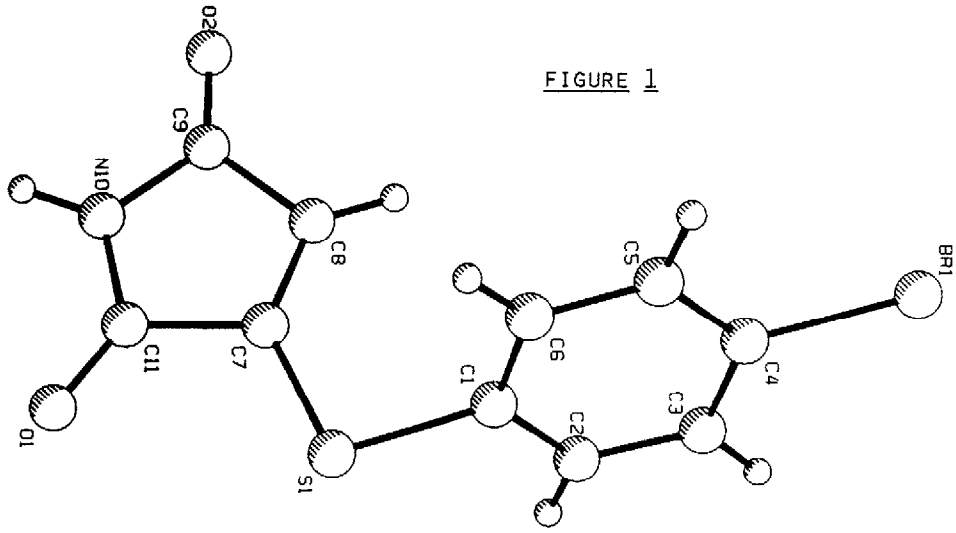
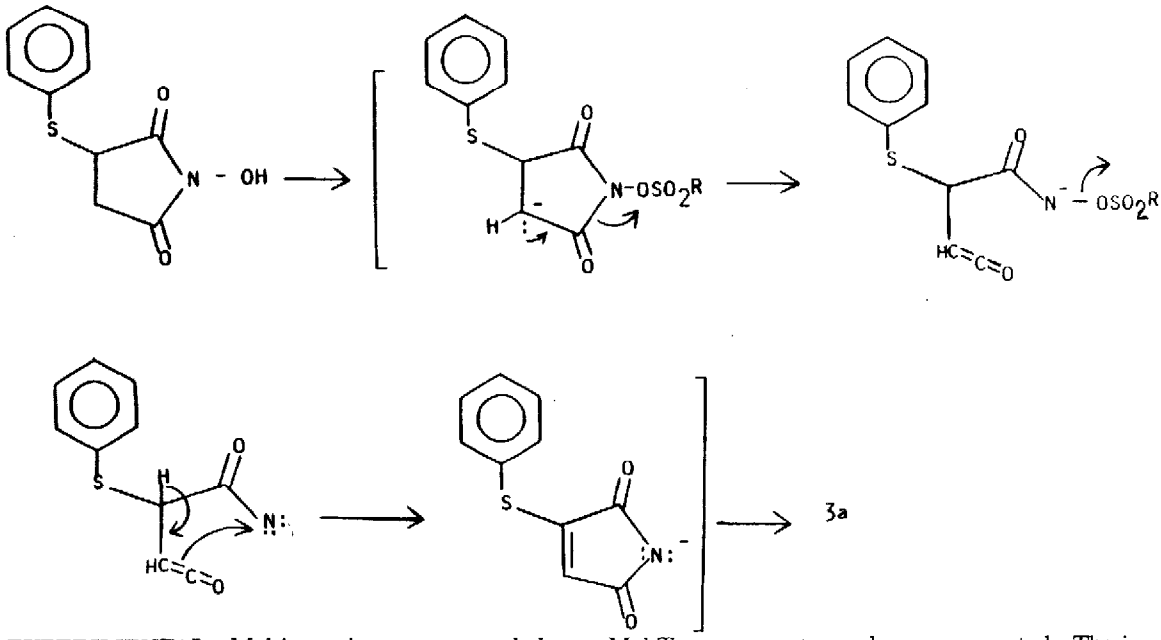


FIGURE 1

SCHEME II



EXPERIMENTAL. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. The infrared and ^1H nmr spectra were recorded on a Perkin-Elmer 1330 infrared spectrophotometer and a Varian XL-300 nmr spectrometer, respectively. The mass spectrometric analyses were performed at the mass spectrometry laboratory of the University of Kansas. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

3-(Phenylthio)-N-hydroxysuccinimide (1). A solution of hydroxylamine hydrochloride (3.5 g; 50 mmol) in 50 ml water was treated with anhydrous sodium carbonate (2.65 g; 25 mmol) with stirring. 3-(Phenylthio)succinic anhyride (10.4 g; 50 mmol)[8] was then added and the mixture was refluxed for 1 hour. The solution was acidified with concentrated hydrochloric acid while hot, cooled to room temperature and then extracted with ethyl acetate (2 x 50 ml). The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 8.2 g (74%) of 1. NMR (deutriochloroform): 9.72 (br,1H), 7.5 (m,2H), 7.32 (m,3H), 3.95 (dd,1H), 2.95 (dd,1H), 2.62 (dd,1H). IR (neat): 3460, 1770 and 1680 (C=O) cm^{-1}.

3-(Phenylthio)maleimide (3a). Compound **1** (2.0 g; 9 mmol) in 10 ml dry toluene was treated with dry pyridine (3.7 ml; 45 mmol), followed by the dropwise addition of methanesulfonyl chloride (1.03 g; 9 mmol). A mild exotherm and precipitation of a brown solid accompanied the addition. Stirring was continued overnight. Ethyl acetate (50 ml) and water (30 ml) were added. The layers were separated and the organic layer was washed with 5% sodium bicarbonate (20 ml), 5% hydrochloric acid (20 ml) and water (20 ml). Removal of the solvent left a yellow oil which was purified by flash chromatography (340 mg; 18%). ^1H nmr (dimethylsulfoxide-d_6): 11.1 (br,1H), 7.7 (m,2H), 7.6 (m,3H), 5.7 (s,1H). Anal. Calcd for $C_{10}H_7NSO_2.1/3\ H_2O$: C, 56.87; H, 3.32; N, 6.43; S, 15.15. Found: C, 56.87; H, 3.53; N, 6.43; S, 14.80.

Formation of (3b) from N-hydroxymaleimide. Using the same procedure as above and p-bromothiophenol, there was obtained 40 mg of compound **3b**. Crystals suitable for crystallographic analysis were grown from a solution of ethyl acetate and petroleum ether, mp 168-9°C. ^{1}H nmr (deuteriochloroform): 7.65 (d,2H), 7.45 (d,2H), 7.35 (br,1H), 5.7 (s,1H). IR (potassium bromide): 3400, 1635 cm^{-1}. Anal. Calcd for $C_{10}H_6NSO_2Br$: C, 42.25; H, 2.11; N, 4.93. Found: C, 42.02; H, 2.23; N, 4.77.

X-ray Crystal Analysis. Compound **3b** crystallized in the orthorhombic space group $P2_12_12_1$ with a = 11.966 A, b = 15.966, c = 5.408 and V = 1033.3 A. For Z = 4 and M_r = 284.13, the calculated density is 1.826 g/cm^3. The data were collected at a temperature of 25 ± 1°C using the ω-2 scan technique to a maximum 2θ value of 112.6°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.35°, with a take-off angle of 6.0°. A total of 842 reflections was collected. The linear absorption coefficient for Cu K_α is 71.6 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.69 to 1.00. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 807 observed reflections ($I > 3.00\sigma(I)$) and converged to a final discrepancy factor of 0.045 (R_w = 0.078).

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