

College of Chemistry and Physics, North Dakota State University and
Union Carbide Corporation, Chemicals Division, Research and Development Department

2-(4-Morpholino)-5-phenylthiophene, a 2-*t*-Aminothiophene Derivative (I)

Carl D. Slater (2) and Donald L. Heywood

The reaction of 4-phenyl-3-buten-2-one, sulfur, and morpholine produces 2-(4-morpholino)-5-phenylthiophene (Ia). The structure of Ia has been assigned on the basis of elemental analysis, molecular weight, infrared, ultraviolet, and nuclear magnetic resonance spectra, and on the basis of its acid-catalyzed hydrolysis product. Similarly, 4-(4-chlorophenyl)-3-buten-2-one, sulfur, and morpholine form 2-(4-morpholino)-5-(4-chlorophenyl)thiophene (Ib).

Nightingale and Carpenter (3) explored the reaction of 4-phenyl-3-buten-2-one, sulfur, and refluxing morpholine as a possible pathway to the desired 4-(4-phenyl-3-thiobutenoyl)morpholine (II). However, hydrolysis of the reaction product did not give the expected 4-phenyl-3-butenic acid (*vide infra*). Although these authors isolated Ia in 35% yield by direct crystallization from ethanol, it has been found that greater purity, ease of handling, and reproducibility result from an isolation procedure that utilizes the basicity of the compound. When such a procedure was employed, however, the yield was characteristically in the range of 10-15%. It was shown that 90% of the substance can be recovered by the method used, which indicates that hydrolysis during work-up is not a serious consideration. Despite the poor yields of this reaction, the previous inaccessibility (4, 5) of 2-*t*-aminothiophenes imparts synthetic interest to it.

The infrared spectra of Ia and Ib, respectively, show strong absorptions at 773 and 768 cm^{-1} , attributable to carbon-hydrogen out-of-plane deformations. Schulte, Kreuzberger, and Bohn (6) have examined the spectra of a series of 2,5-disubstituted thiophenes, and give the region of $800 \pm 15 \text{ cm}^{-1}$ as characteristic of this absorption. In addition to these easily recognizable absorptions, the spectra of Ia and Ib contain bands in the other expected regions (6), but detailed interpretation is not possible in the present case because of the large number of bands exhibited.

The ultraviolet spectra of Ia and Ib have maxima at 334 $\text{m}\mu$ ($\log \epsilon = 4.28$) and 340 $\text{m}\mu$ ($\log \epsilon = 4.27$), respectively. Although an extensive series of model compounds is not available for spectral comparison, these values seem reasonable. Bruzzi, Degani, and Tundo (7) have found that 2-(4-dimethylaminophenyl)-thiophene shows a maximum at 318 $\text{m}\mu$ ($\log \epsilon = 4.33$).

The n.m.r. spectra of Ia and Ib permit definitive structural assignments. The spectrum of Ia has the morpholine multiplets centered at 3.56 and 3.85

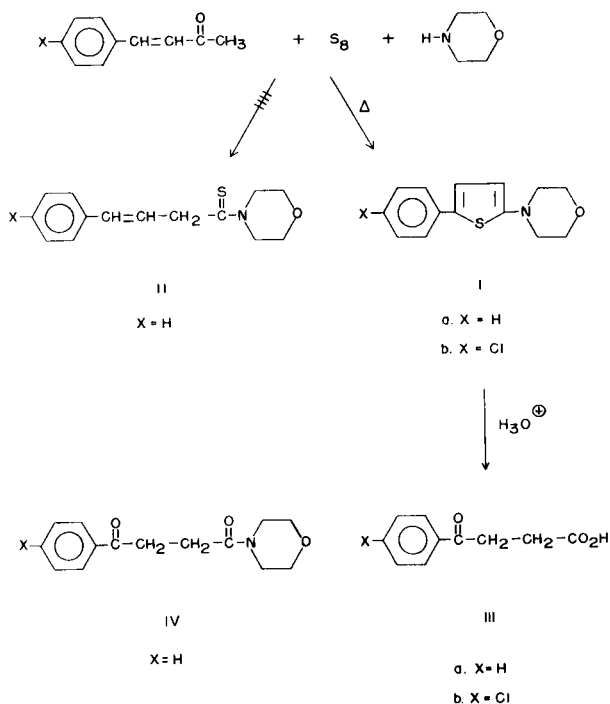
p.p.m., and the aromatic proton multiplets at 7.10 and 7.50 p.p.m. The thiophene protons appear as doublets, $J_{34} = 4 \text{ c.p.s.}$, at 5.89 and 6.95 p.p.m. The assignments can be made by using as a model the spectrum of 2,5-dimethylthiophene, which has thiophene proton peaks at 6.39 p.p.m. (8). The absorption at 5.89 p.p.m. can be attributed to the proton in the 3-position. The increased shielding of this proton could possibly arise from electron donation into the thiophene ring by the nitrogen atom attached at the 2-position. The decreased shielding of the proton in the 4-position (6.95 p.p.m.) could result from its location in the plane of the adjacent benzene nucleus (9). The observed coupling of 4 c.p.s. agrees with that found by Hoffman and Gronowitz (10) for protons at the 3- and 4-positions of the thiophene nucleus. The corresponding absorptions of Ib appear as doublets, $J_{34} = 4 \text{ c.p.s.}$, at 5.82 and 6.78 p.p.m.

Acid-catalyzed hydrolysis of Ia produces, in addition to an intractable material, 3-benzoylpropionic acid, IIIa. Similarly, Ib gives 3-(4-chlorobenzoyl)-propionic acid, IIIb. The hydrolytic process could possibly proceed *via* initial protonation at C-3 of the thiophene nucleus. The presence of the electron pair on the nitrogen atom attached at C-2 could be expected to facilitate this electrophilic attack. Activation by the nitrogen atom at C-2 could thus be the cause of the high reactivity (compared to thiophene, which is inert to hydrolysis) of 2-aminothiophenes (4). Such a hydrolysis mechanism suggests, however, that amide IV could be an intermediate. The infrared spectrum of the neutral fraction obtained by stopping the hydrolysis at 20% completion failed to reveal the presence of this amide. Carbonyl absorption in the region expected for an amide (11) was absent.

EXPERIMENTAL (12)

2-(4-Morpholino)-5-phenylthiophene (Ia).

In a round bottom flask was placed 73.7 g. (0.504 mole) of 4-phenyl-3-buten-2-one, 48 g. (0.55 mole) of morpholine, and 40.1 g. (1.25 moles) of sulfur. The suspension was warmed gently on the steam bath for 15 minutes, during which time the sulfur dissolved. The black solution was refluxed for 4.5 hours, cooled, and taken up in 750 ml. of benzene. The benzene solution was washed four times



with 200-ml. portions of 12 *N* hydrochloric acid. The combined acidic extracts were extracted with 100 ml. of benzene. The acidic solution was diluted with 3 liters of water. The oily solid was collected and crystallized from isopropyl alcohol to give 16.5 g. (0.067 moles, 14%) of colorless plates, m.p. 128.5–132.0°. A sublimed sample had m.p. 131.5–133.5° (lit. (3) 133–134°); ν max (KBr) 3042, 3013, 1593, 1498, 1444, 1270, 773, 703 cm^{-1} ; λ max (CHCl_3) 334 μ (19,200).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{NOS}$: C, 68.53; H, 6.16; N, 5.71; S, 13.07; MW, 245. Found: C, 68.36; H, 6.32; N, 5.63; S, 12.76; MW(ebul.) 253 \pm 3%.

Recovery of Ia.

A solution of 1.00 g. of Ia in 100 ml. of benzene was extracted three times with 20-ml. portions of 12 *N* hydrochloric acid. The combined acidic extract was diluted to 400 ml. with ice water, and the precipitated solid was collected and dried. There was obtained 0.90 g. (90%) of Ia, m.p. 131–132°.

2-(4-Morpholino)-5-(4-chlorophenyl)thiophene (Ib).

The procedure employed was identical to that for Ia. Use of 56.0 g. (0.311 mole) of 4-(4-chlorophenyl)-3-buten-2-one, 39.2 g. (0.45 mole) of morpholine, and 24.0 g. (0.75 mole) of sulfur gave 8.2 g. (0.029 mole, 9%) of pale yellow plates, m.p. 159.5–160.6°. A sublimed sample had m.p. 160–162°; ν max (KBr) 3068, 3054, 1591, 1492, 1446, 1280, 767, 698 cm^{-1} ; λ max (CHCl_3) 340 μ (18,800).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{ClNOS}$: C, 60.09; H, 5.40; N, 5.01. Found: C, 60.07; H, 4.93; N, 4.85.

Hydrolysis of Ia.

To a mixture of 25 ml. of glacial acetic acid and 20 ml. of concentrated hydrochloric acid was added 2.21 g. (9.02 mmoles) of Ia,

and the solution was refluxed for 17 hours. The cooled solution was diluted with 100 ml. of ice water and was extracted four times with 50-ml. portions of ether. The combined ether extract was washed six times with 25-ml. portions of 3% sodium hydroxide solution. The combined basic extract was acidified with hydrochloric acid and was shaken five times with 50-ml. portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate, filtered, and evaporated. The oily residue was crystallized from water to give 0.76 g. (4.26 mmoles, 47%) of 3-benzoylpropionic acid, m.p. 115.5–117° (lit. (13) 116°). The identification of this substance was further substantiated by comparison of its infrared and ultraviolet spectra with those obtained from an authentic sample (14).

In another experiment with 1.43 g. (5.82 mmoles) of Ia, 15 ml. of glacial acetic acid, and 10 ml. of concentrated hydrochloric acid, reflux was stopped after 3.5 hours. Isolation of the acidic fraction as above gave 0.20 g. (1.13 mmoles, 19%) of 3-benzoylpropionic acid, m.p. 115.0–116.5°. The ether solution containing the neutral fraction was dried over anhydrous potassium carbonate, filtered and evaporated to leave 0.27 g. (1.10 mmoles, 19%) of unchanged starting material. The infrared spectrum of this substance (CHCl_3 solution) showed no carbonyl absorption in the amide region.

Hydrolysis of Ib.

In a mixture of 10 ml. of glacial acetic acid and 10 ml. of 12 *N* hydrochloric acid was placed 0.50 g. (1.79 mmoles) of 2-(4-morpholino)-5-(4-chlorophenyl)thiophene. The solution was refluxed for 2 hours. Work up for an acid fraction provided a residue which was crystallized from water-methanol to give 0.20 g. (0.94 mmole, 53%) of 3-(4-chlorobenzoyl)propionic acid as white needles, m.p. 129–131° (lit. (15) 131°); ν max (KBr) 2673 (bonded acid OH), 2591 (bonded acid OH), 1692 (acid C=O), 1678 (aryl ketone C=O), 820 (1,4-disubstituted benzene) cm^{-1} .

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Fargo, North Dakota 58103