Reductive Acetylation of Nitro Compounds. III. Chemical Transformations in Three Thiophene Systems (1)

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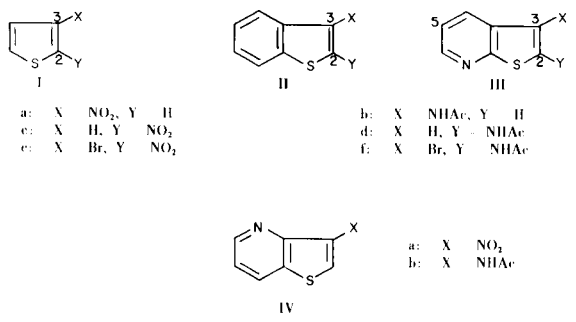
Received September 15, 1975

Nitro groups on thiophene ring systems are transformed directly into acetylamino functions in yields of 61-82% by means of a mixture of iron, acetic acid, and acetic anhydride at 50-105°. When a bromo substituent is also present on the ring partial hydrodebromination occurs during the reaction.

Because of the facility with which the thiophene ring can be nitrated, the chemical sequence TH → TNO_2 → TNH_2 → TNHAc (where T is a thienyl or condensed thienyl system) represents a logical, straightforward route for the synthesis of acetylamino-substituted thiophene compounds. As has been repeatedly noted, however, the intermediate amino-substituted thiophenes are unstable in air (3-5), while their *N*-acetyl derivatives can be stored on the shelf indefinitely. Thus, a convenient and general one-step procedure for reductive acetylation of nitro-substituted thiophenes to their acetylamino derivatives seems desirable.

Examination of the literature revealed three procedures which were employed to effect such reductive acetylation, but each suffers from serious limitations. Thus, Raney nickel and acetic anhydride converted two isomeric nitrothiophene-2-carboxylic acids into acetylamino compounds, but yields were widely different (10 and 61%) (6). Reduction of 3-nitrothieno[3,2-*b*]pyridine (IVa) with iron and glacial acetic acid gave a 25% yield of IVb, but the same method produced no acetylamino derivative from the isomeric 3-nitrothieno[2,3-*b*]pyridine (IIIa) (7). When the 5-ethyl homolog of IIIa was heated with a mixture of iron, glacial acetic acid, and acetic anhydride instead, there resulted a high yield of the corresponding acetylamino derivative (8). Unfortunately, processing of the basified reaction mixture was difficult because of persistent emulsions and tenacious films on the glassware. We now report extension of the iron-acetic acid-acetic anhydride reductive acetylation method to the substrates Ia, Ic, IIa, IIe, IIIa, and IIIe, plus a change in the processing procedure which avoids the previous mechanical difficulties.



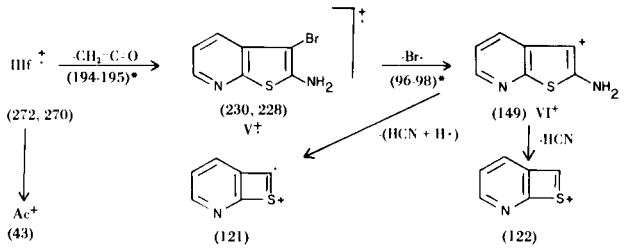
The nitro compound was heated and stirred with iron powder, acetic acid, and acetic anhydride at a constant temperature (in the range of 50-105°) for a period of 18-24 hours. This reaction temperature, which was lower than used previously (8), gave relatively little charring. Moreover, treating the reaction mixture with water, rather than with aqueous base, avoided emulsions. Yields of acetylamino products varied from 61-82%. For bromo-nitro substrates IIe and IIIe partial debromination occurred. This was small (8 mole% of total product) in the case of IIIe (run at 65 ± 5°), but appreciably larger (33 mole% of total product) in the case of IIe (run at 97 ± 7°). No investigation of the effect of changing reaction time or temperature on the extent of debromination was made.

It is suggested that the stoichiometry of the reductive acetylation reaction can be appropriately represented by the equation TNO_2 + 3 Fe + HOAc + 3 Ac_2O → TNHAc + 3 $Fe(OAc)_2$. It seems unlikely that the free amine TNH_2 or its salt is ever formed in the reaction mixture. Hence, we believe that the relative stability in air of the corresponding amine is incidental to the success of the method; in contrast to the two-step Steinkopf procedure (3), where the amine is acetylated *in situ* and overall yields for the transformation TNO_2 → TNHAc are

typically lower (40-60%).

The principal mass spectral fragmentation pathways for IIIf are presented in Scheme 1. As expected, the acetylamino group readily ejects both ketene and the acetylium ion. The cation radical of the unknown 2-amino-3-bromothieno[2,3-*b*]pyridine (V) (most abundant

Scheme 1

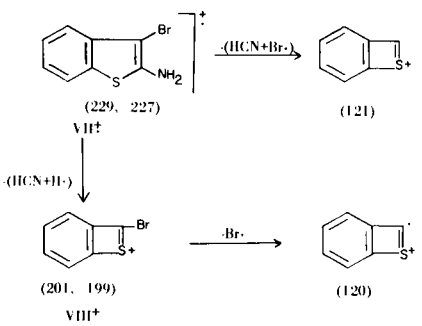


*Peaks for metastable ions.

peaks) is postulated as an intermediate (8,9). Consistent with the intermediacy of $V^{+\cdot}$ are the losses of a bromine atom [*cf.* mass spectrum of 3-bromothieno[2,3-*b*]pyridine (10)], of hydrogen cyanide, and of a hydrogen atom [*cf.* mass spectrum of aniline (11)].

The mass spectrum of 2-acetylamino-3-bromobenzo-[*b*]thiophene (IIf) shows major similarities to that of IIIf, though no peaks for metastable ions were discerned. The proposed intermediate cation radical of 2-amino-3-bromobenzo[*b*]thiophene (VII) (most abundant peaks) appears to fragment in a modified manner (Scheme 2). The intensity of the 148 peak (analogous to VI^+) is only 3%. Instead, a doublet (9% for each peak), ascribed to VIII^+, is observed. Significant additional peaks are also found at m/e 119 and 117 (doublet?), 45 (CHS^+), 44, and 40.

Scheme 2



EXPERIMENTAL (12)

Starting Materials and Reference Compounds.

2-Nitrothiophene (Ic) (13), 3-nitrothiophene (Ia) (13), 3-nitrobenzo[*b*]thiophene (IIa) (14), 3-nitrothieno[2,3-*b*]pyridine (IIIa) (7), 2-nitro-3-bromothieno[2,3-*b*]pyridine (IIIe) (10), 2-acetylaminobenzo[*b*]thiophene (IId) (15), 2-acetylaminothieno-[2,3-*b*]pyridine (IIId) (7), and 3-acetylaminothieno[2,3-*b*]pyridine (IIIb) (7) were prepared by reported methods. 2-Acetylamino-thiophene (Id) was obtained from bis(2-thienyl) hexachloro-stannate (IV) (13) by the *in situ* acetylation method of Steinkopf (3). 2-Nitro-3-bromobenzo[*b*]thiophene (IIe) resulted from successive steps of bromination (16) and nitration (17) of benzo-[*b*]thiophene.

Reductive Acetylation.

A magnetically stirred mixture of 2-4 g. of nitro compound, 75 ml. of glacial acetic acid, 10 ml. of acetic anhydride, and 4.5 g. of reduced iron powder was gradually heated (oil bath) until onset of reaction (evidenced by bubbling and attainment of a creamy texture in the mixture) was apparent. The temperature was then raised 10-20° higher where it was maintained constant (± 7°) for a period of 18-24 hours. The cooled mixture was poured into 300 ml. of ice-water and filtered (glass frit). For nitro compounds Ia, Ic, and IIIa (products soluble in the aqueous mixture) the filtrate was concentrated *in vacuo* and extracted with ether. Evaporation of the ether layer gave crude acetylamino solid, which was washed with a little cold water. For nitro compounds IIa, IIe, and IIIe (insoluble products) the resultant crude solid was washed well with cold water. Further details for each particular case are presented in the following paragraphs.

2-Acetylaminothiophene (Id).

The crude product from Ic (reaction temperature, 75°) was crystallized from hot water to yield a purplish solid, m.p. 156-161° (72%); converted to white leaflets, m.p. 161-162° after sublimation at 95-110° (0.4 mm.) and recrystallization; ir (chloroform): 3410 (NH), 1680, 1560, and 1490 (amide bands), 930 and 850 cm^{-1} (18,19); pmr (deuteriochloroform): δ 2.16 (s, 3, Ac), 6.6-6.7 (m, 1, H-5), 6.8-7.0 (m, 2, H-3 and H-4), 7.6-8.2 ppm (broad s, 1, NH); identified by direct comparison (m.p. mixture m.p., spectra) with an authentic sample prepared by the Steinkopf procedure (3) (20).

3-Acetylaminothiophene (Ib).

The crude solid from Ia (reaction temperature 60°) was purified in the manner used for amide Id. The once-crystallized brown solid (69%) melted at 136-141°, changed to white leaflets (m.p. 144-146°) on further purification; ir (chloroform): 3440 (NH), 1670-1690, 1530 cm^{-1} (amide bands); pmr (deuterio-chloroform): (21) δ 2.16 (s, 3, Ac), 6.98 (dd, 1, $J_{4,5}$ = 5 Hz, $J_{2,x} \simeq 1.5$ Hz, H-5 or H-4), 7.21 (dd, 1, $J_{2,y} < 2$Hz, H-4 or H-5), 7.53 ppm (modified dd, 2, H-2 signal superimposed on 7.25-7.8 broad singlet for NH); reported, m.p. 145-148° (3) (20,22a).

3-Acetylaminobenzo[*b*]thiophene (IIb).

The crude product from IIa (reaction temperature 55°) was sublimed at 110-140° (0.4 mm.) to give a white solid (80%), m.p. 157-160°, converted to needles (m.p. 168-170°) on further sublimation plus recrystallization from ethanol; ir (chloroform): 3440 (NH), 1690, 1525 cm^{-1} (amide bands); pmr (hexadeuterio-acetone): δ 2.21 (s, 3, Ac), 7.2-7.5 (m, 2, H-5 and H-6), 7.7-8.2 (m, including a sharp singlet at 8.06, 3 total, H-2, H-4, and H-7),

9.38 ppm (broad s, 1, NH); reported, m.p. 169-171° (5), ir (22b).

3-Acetylaminothieno[2,3-*b*]pyridine (IIIb).

The crude product from IIIa (reaction temperature 55°) was purified in the manner used for amide Id. The once-crystallized purplish solid (m.p. 133-147°, 82%) was converted to white platelets, m.p. 156-157°; ir (chloroform): 3440 (NH), 1695 and 1520 cm^{-1} (amide bands); pmr (hexadeuterioacetone): (23) δ 2.18 (s, 3, Ac), 7.39 (dd, 1, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 4 Hz, H-5), 8.07 (s, 1, H-2), 8.36 (dd, 1, $J_{4,6}$ ≃ 1.5 Hz, H-4), 8.57 (dd, 1, H-6), 9.48 ppm (broad s, 1, NH); identified by direct comparison with an authentic sample (7).

Reductive Acetylation of IIe.

The crude, white solid from IIe (reaction temperature 97°) was evaporatively distilled (130-150°, 0.4 mm.) to yield crystals (m.p. 147-155°, 79% combined), which consisted of a 2:1 molar ratio of 2-acetylamino-3-bromobenzo[*b*]thiophene (IIf) and 2-acetylaminobenzo[*b*]thiophene (IId), as indicated by pmr analysis. Thin layer chromatography with silica gel and carbon tetrachloride-ethyl acetate (1:1 by volume) showed two spots, R_f values 0.43 and 0.67. Column chromatography (299 mg. of mixed product, 35 g. of Baker 60-200 mesh silica gel, aforementioned eluent) showed two fluorescent bands in ultraviolet light (24). From the lower band (purple fluorescence) was obtained 203 mg. of IIf and from the upper band (pale green fluorescence) was obtained 53 mg. of IId.

The foregoing IIf was recrystallized from ethyl acetate and sublimed at 0.5 mm. pressure to give cream-colored prisms, m.p. 152-153°, positive Beilstein test; ir (chloroform): 3880 (NH), 1695, 1680, and 1570 cm^{-1} (amide bands); pmr (hexadeuterioacetone): δ 2.29 (s, 3, Ac), 7.2-8.0 (m, 4, H-4 to H-7), 9.76 ppm (very broad signal, 1, NH); mass spectrum, m/e (relative abundance) (25): 271 (30, M^{+}), 269 (30, M^{+}), 229 (100), 227 (100), 191 (12), 121 (32), 120 (22), 119 (15), 117 (14), 93 (12), 45 (16), 44 (25), 43 (74), 40 (42); reported, m.p. 153-154° (26).

The preceding IId was recrystallized and sublimed in the manner used with IIf to give prisms, m.p. 220-222°; ir (chloroform): 3420 (NH), 1690-1700, 1570, and 1510-1550 (amide bands), 930 and 810 cm^{-1} (18); pmr (hexadeuterioacetone): δ 2.16 (s, 3, Ac), 6.94 (s, 1, H-3), 7.0-7.4 (m, 2, H-5 and H-6), 7.4-7.9 (m, 2, H-4 and H-7), *ca.* 10.4 ppm (very broad signal, NH); identified by direct comparison with an authentic sample prepared by the method of Abramenko and Zhiryakov (15); reported m.p. 224-226° (27).

Reductive Acetylation of IIIe.

The pale green solid from IIIe (reaction temperature 65°) was sublimed at 130-160° (0.4 mm.) to yield white crystals (m.p. 168-178°, 61% conbined), which consisted of a 11.5:1 molar ratio of 2-acetylamino-3-bromothieno[2,3-*b*]pyridine (IIIf) and 2-acetylaminothieno[2,3-*b*]pyridine (IIId), as indicated by pmr analysis. Thin layer chromatography, as in the preceding example, showed two spots, R_f values 0.22 and 0.45. Column chromatography (301 mg. of mixed product, 36 g. of silica gel, carbon tetrachloride-ethyl acetate [2.3:1 by volume]) gave a yellow (in ordinary light) lower band and a greenish fluorescent (in ultraviolet light) (24) upper band. From the lower band was obtained 292 mg. of IIIf (186-187°), purified further by recrystallizations from ethyl acetate and from ethanol, m.p. 186.5-187.5°, positive Beilstein test; ir (chloroform): 3380 (NH), 1700, 1685, 1580, 1560, 1540 cm^{-1} (amide bands); pmr (hexadeuterioacetone) (23): δ 2.31 (s, 3, Ac), 7.46 (dd, 1, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 4.6 Hz, H-5), 7.95 (dd, 1, $J_{4,6}$ = 1.5 Hz, H-4), 8.51 (dd, 1, H-6), 9.8 ppm (broad s, 1, NH); mass spectrum, m/e (relative abundance) (28): 272 (31, M^{+}), 270 (30, M^{+}), 231 (9), 230 (100), 229 (9), 228 (98), 149 (18), 148 (6), 122 (15), 121 (11), 43 (40).

Anal. Calcd. for $C_9H_7BrN_2OS$: C, 39.9; H, 2.6; N, 10.3; S, 11.8. Found: C, 39.9; H, 2.9; N, 10.2; S, 11.8.

Pure IIId was not isolated in this experiment, but its presence in effluent from the upper chromatographic band was indicated by direct tlc comparison (R_f value and fluorescence) with an authentic sample of the compound (7).

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(9) It should be noted that an approximation to the mass spectrum of an unstable amine may be derived from the mass spectrum of its *N*-acetyl derivative. It is proposed to elaborate on this thesis in a later publication.

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(12) Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan. Melting points were determined by means of a Mel-Temp apparatus. Infrared spectra were obtained by means of a Beckman IR-7 or IR-10 spectrophotometer; pmr spectra, by means of a Varian Associates T-60 or XL-100 spectrometer with (unless otherwise noted) tetramethylsilane as internal reference; and mass spectra, at 70 eV by means of a CEC model 21-110 instrument.

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(20) R. A. Hoffman and S. Gronowitz [*Arkiv Kemi*, **16**, 515 (1960)] measured the pmr spectrum in dimethyl sulfoxide, but they reported only limited data therefrom.

(21) Based on a reference signal at δ 7.25 for chloroform.

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(23) Based on a reference signal of δ 2.05 (for the central peak) for pentadeuterioacetone.

(24) Long wavelength light with maximum intensity at *ca.* 366 nm.

(25) For all peaks of relative abundance ≥ 12%.

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(28) For all peaks of relative abundance ≥ 5%.