A Method for Nitration of Thiazoles

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Nitrations of some sensitive thiazole derivatives with trifluoromethanesulfonic acid-trifluoromethanesulfonic anhydride:potassium nitrate in 1,2-dichloroethane gave significantly higher yields of the nitro compounds in comparison with nitrations in sulfuric acid-nitric acid mixtures.

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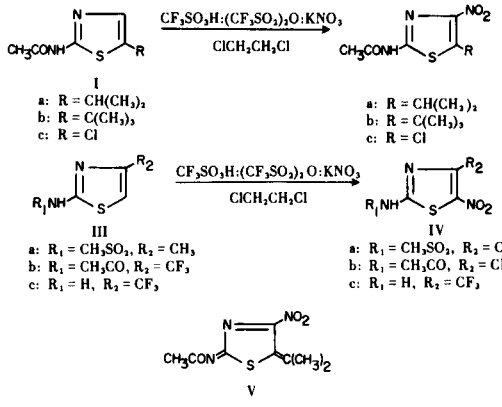
In a synthetic study of certain thiazolylthiourea derivatives one of the crucial steps was the nitration of 2-acetylamino-5-alkylthiazoles I. Earlier investigations (1,2) showed that thiazoles easily can be nitrated with sulfuric acid-nitric acid mixtures in the 5-position even when they are substituted in the 4-position with the bulky *t*-butyl group. However, 5-substituted thiazole derivatives are more resistant to nitration in the 4-position (3,4). The presence of a bulky or an oxidation-susceptible group in the 5-position further reduces the yield of the 4-nitro compound, probably due to undesirable oxidation of the substrate (5). A striking exception seems to be the nitration of 2-acetylamino-5-thiocyanatothiazole with sulfuric acid-nitric acid, which reaction is said to give the 4-nitro derivative (no yield or spectral data given) (6). In the case of Ia, nitration with sulfuric acid-nitric acid only gave traces of IIa together with dark tars, and Ib behaved similarly. Attempted nitrations of Ia in trifluoroacetic acid-sodium nitrate (7) and trifluoroacetic anhydride-nitric acid (8) failed (only starting material was recovered). The use of oleum-potassium nitrate (9) in the nitration of Ic raised the yield of IIc compared to that using sulfuric acid-nitric acid.



However, it has now been found that the use of trifluoromethanesulfonic acid (triflic acid)-triflic anhydride-potassium nitrate in dry 1,2-dichloroethane gives significantly increased yields compared to sulfuric acid-nitric acid with four different thiazoles: Ia, Ic, IIIa and IIIb. (With Ib however, only minor amounts of the desired 4-nitro compound were obtained). The higher yields are probably due to the lower oxidative power of triflic acid, previously used in the nitration of aromatic compounds (10,11). The addition of triflic anhydride with exclusion of oxygen and moisture from the reaction mixture seems to favourably influence the yield. More severe conditions however, (higher temperature and prolonged reaction times) increase the formation of side products. Although homogeneous nitrations of the 4-position in the thiazole nucleus have been achieved in nitromethane (12,13), treatment of Ia with triflic anhydride and ethyl nitrate in nitromethane only afforded the starting materials.

Substance IIa is unstable in solution and decomposes on standing to Ia and a yellow compound which is rapidly destroyed in contact with air. This substance is also present in the crude nitration mixture and from its mass spectrum a possible structure V could be suggested. The nitration product IIb could not be obtained pure even after repeated chromatography. This is probably due to its spontaneous conversion to Ib during the workup. The mass spectrum of IIb was very similar to the mass spectrum of 2-acetylamino-4-*t*-butyl-5-nitrothiazole.

The nitration of IIIb gives, after workup, IVc as the sole product. This compound, previously obtained from IIIc using sulfuric acid-nitric acid (2), could be acetylated by standard methods. The acetyl derivative IVb is readily hydrolysed in water and IVc is recovered.

Attempted reduction of IIc with activated aluminium in moist ether (14) to the corresponding amine only afforded a complex mixture from which Ic could be recovered. Treatment of IIa with the same reducing agent caused disruption of the thiazole ring.

EXPERIMENTAL

All melting points are uncorrected. Tlc analyses and preparative chromatography were performed on Merck's precoated uv-sensitive silica gel plates. All solvents used were analytical grade or redistilled and the R_f values given refer to toluene-acetonitrile 1:1 (A) or chloroform-acetic acid 7:2 (B), freshly prepared mixtures, (chamber saturation). All compounds described were chromatographically pure unless otherwise stated. All glassware used in the nitrations was thorougly dried (150°, 15 hours). The triflic acid and anhydride were distilled with exclusion of

moisture and kept cool in sealed glass vessels. The 1,2-dichloroethane was carefully purified and dried over molecular sieves. The nmr spectra were recorded on a JEOL FX 60 or a JEOL FX 100 in acetone-d_6 (~ 2% solution) with TMS as internal standard. An LKB 9000 gc-mass spectrometer was employed for determination of the low resolution 70 eV mass spectra using the direct inlet system. The more important peaks for each compound are given in the text (the relative abundances as percent of the base peak in parentheses) and some probable fragmentations are indicated.

2-Acetylamino-5-isopropylthiazole (Ia).

Thiourea and crude α-bromo-isovaleraldehyde were condensed in aqueous dioxane according to a previously described method (15) and the resulting crude 2-amino-5-isopropylthiazole was acetylated in acetic anhydride-pyridine as usual. Crystallisation from ethanol-water 1:1 (15 ml./g.) using decolourizing carbon gave white needles. The overall yield based on isovaleraldehyde is 14%; R_f (A) = 0.12, m.p. 149-150°; nmr: δ = 1.30 (d, 2H, J = 7 Hz, $CH(CH_3)_2$), δ = 2.21 (s, 3H, CH_3CO), δ = 3.15 (m, 1H, $CH(CH_3)_2$), δ = 7.08 (d, 1H, J = 1Hz, C_4-H) mass spectrum m/e: 184(20%; $[M]^+$), 169(3%; $[M-CH_3]^+$), 142(61%; $[M-CH_2CO]^+$), 127 (100%; $[M-CH_2CO-CH_3]^+$, 100 (8%), 85 (5%), 43 (31%; $[CH_3CO]^+$).

Anal. Calcd. for $C_8H_{12}N_2OS$: C, 52.15; H, 6.52; N, 15.21. Found: C, 52.20; H, 6.54; N, 15.17.

2-Acetylamino-5-*t*-butylthiazole (Ib).

In analogy with Ia this compound was prepared from thiourea and 2-bromo-3,3-dimethylbutanal (16). Recrystallisation from ethanol-water 1:1 (10 ml./g.) and hexane:dichloromethane 10:1 (25 ml./g.) using decolourizing carbon gave white short needles. The overall yield from 3,3-dimethylbutanal is about 3%; R_f (A) = 0.12, m.p. 170-172°; nmr: δ = 1.36 (s, 9H, $C(CH_3)_3$), δ = 2.22 (s, 3H, CH_3CO); δ = 7.10 (s, 1H, C_4-H); mass spectrum m/e: 198 (16%; $[M]^+$), 183 (8%; $[M-CH_3]^+$), 156 (39%; $[M-CH_2CO]^+$), 141 (100%, $[M-CH_2CO-CH_3]^+$), 114 (4%), 99 (3%), 43 (23%; $[CH_3CO]^+$).

Anal. Calcd. for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 54.70; H, 7.11; N, 14.04.

2-Acetylamino-5-chlorothiazole (Ic).

Compound Ic was prepared from 2-acetylaminothiazole and sulfurylchloride in dry carbon disulphide (17); R_f (B): 0.83, m.p. 209-210° (litt. 208°); nmr: δ = 2.25 (s, 3H, CH_3CO), δ = 7.32 (s, 1H, C_4-H); mass spectrum m/e: ⟦178 (8%)/176 (21%); $[M^+]$⟧, ⟦136 (35%)/134 (100%; $[M-CH_2CO]^+$⟧, 98 (16%), 43 (90%; $[CH_3CO]^+$).

2-Methanesulfonylamino-4-methylthiazole (IIIa).

Compound IIIa was prepared from 2-amino-4-methylthiazole (18) and methanesulfonyl chloride in pyridine as described for 2-methanesulfonylaminothiazole (19). One crystallisation from ethanol (10 ml./g. decolourizing carbon) yielded 57%; R_f (B) = 0.52, m.p. 208-209°; nmr: δ = 2.23 (d, 3H, J = 1 Hz, CH_3), δ = 2.84 (s, 3H, (CH_3SO_2), δ = 6.27 (q, 1H, J = 1 Hz, C_5-H); mass spectrum m/e: 192 (52%; $[M]^+$), 177 (9%; $[M-CH_3]^+$), 114 (34%), 113 (100%; $[M-CH_3SO_2]^+$), 86 (10%), 79 (5%); $[CH_3SO_2]^+$), 71 (31%), 69 (45%).

Anal. Calcd. for $C_5H_8N_2O_2S_2$: C, 31.24; H, 4.19; N, 14.57. Found: C, 31.21; H, 4.20; N, 14.54.

2-Acetylamino-4-trifluoromethylthiazole (IIIb).

The crude amine IIIc (2) was treated with excess boiling acetic anhydride for 30 minutes and the mixture was left overnight and quenched in water, yield 64% after one recrystallisation from toluene (10 ml./g.). The product contained some acetic acid of solvation which could be removed by repeated crystallisation; R_f (B) = 0.81, m.p. 185-186°; nmr: δ = 2.30 (s, 3H, CH_3CO), δ = 7.72 (q, 1H, J = 1 Hz, C_5-H); mass spectrum m/e: 210 (16%; $[M]^+$), 191 (5%; $[M-F]^+$), 168 (78%; $[M-CH_2CO]^+$), 148 (4%), 141 (6%), 126 (8%), 73 (8%), 69 (4%), 45 (14%), 43 (100%; $[CH_3CO]^+$).

Anal. Calcd. for C H F N OS: C, 34.28; H, 2.40; N, 13.33. Found: C, 34.28; H, 2.33; N, 13.27.

2-Acetylamino-4-nitro-5-isopropylthiazole (IIa).

Triflic acid (3 ml.) was added dropwise with vigorous stirring to a slurry of Ia (1.84 g., 10 mmoles dried) and potassium nitrate (1.0 g., 10 mmoles dried) in dichloroethane (60 ml.).

The bright yellow slurry was stirred at 20° (1 hour) and at 50° (2 hours). After cooling, potassium nitrate (0.3 g., 3 mmoles) and triflic anhydride (3.0 g., 11 mmoles) were introduced under dry nitrogen. The temperature was raised to 50° during 2 hours and the brownish suspension was then stirred overnight at room temperature. The reaction was monitored by tlc, (small samples of the mixture were quenched in ice-water and the products extracted with dichloromethane); if larger amounts of starting material remained, more nitrating agent was added.

The contents were poured onto ice-water and the product was extracted with dichloroethane (3 x 100 ml.). The extract was washed with aqueous sodium bicarbonate and brine and dried (magnesium sulfate). The orange solution was evaporated under reduced pressure to give 1.0 g. of an orange-yellow solid residue which contained approximately 70% of the desired compound (nmr).

Purification by column chromatography (25 x 7 cm) on silica gel with toluene-acetonitrile gave 0.66 g. (29%) of a yellow powder. Further purification with tlc gave a pale yellow substance; R_f (A) = 0.19, m.p. = 220-222° dec.; nmr: δ = 1.38 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), δ = 2.29 (s, 3H, CH_3CO), δ = 3.95 (m, 1H, $CH(CH_3)_2$), δ = 11.25 (s broad, 1H, NH); mass spectrum: m/e: 229 (14%; $[M^+]$), 214 (3%; $[M-CH_3]^+$), 212 (4%; $[M-OH]^+$), 187 (41%; $[M-CH_2CO]^+$), 172 (15%; $[M-CH_2CO-CH_3]^+$), 170 (11%), 169 (15%), 142 (8%), 140 (18%), 111 (9%), 100 (7%), 99 (8%), 43 (100%; $[CH_3CO]^+$).

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.90; H, 4.80; N, 18.05.

Continued elution of the column gave small amounts of a bright yellow compound considered to be V, which, after preparative tlc (R_f)A) = 0.15), gave the mass spectrum m/e: 227 (12%; $[M]^+$), 185 (12%; $[M-CH_2CO]^+$), 142 (22%), 139 (5%), 114 (19%), 111 (21%), 97 (17%), 43 (100%; $[CH_3CO]^+$).

The 227 → 185 fragmentation was confirmed by a metastable peak at m/e: 150.8 present in the 12 eV mass spectrum.

2-Acetylamino-5-*t*-butyl-4-nitrothiazole (IIb).

Compound Ib was nitrated according to the method described for Ia using one tenth of the amount. After workup, the resulting complex mixture was subjected to repeated preparative tlc and the spot with R_f (A) = 0.23 was eluted. The yellow unstable solid containing some minor contaminants gave the mass spectrum (12 eV) m/e 243 (64%; $[M]^+$), 228 (10%; $[M-CH_3]^+$), 201 (100%; $[M-CH_2CO]^+$), 186 (15%; $[M-CH_2CO-CH_3]^+$). The transitions 243 → 201 and 201 → 186 were ascertained by the appearance of metastable peaks at m/e 166.3 and m/e 172.2.

2-Acetylamino-5-chloro-4-nitrothiazole (IIc).

A mixture of triflic acid (3.0 g.), triflic anhydride (1.0 g.,

3.5 mmoles) and potassium nitrate (0.40 g., 4.0 mmoles) was stirred for 1 hour at 20° under nitrogen. Dichloroethane (10 ml.) was added followed by Ic (0.53 g., 3.0 mmoles) in small portions. The yellow reaction mixture was stirred for 1 hour at 50° and 2 hours at 70°. After cooling the contents were poured into ice-water and the slurry was extracted with ether (5 x 70 ml.). The extract was washed with water, dried (magnesium sulfate) and evaporated to give 0.47 g. (71%) of a yellow powder, which was crystallized from chloroform (40 ml./g. decolourizing carbon); R_f (B) = 0.79, m.p. 262-264° dec.; nmr: δ = 2.34 (s, CH_3CO); mass spectrum m/e: [[223 (3%)/221 (9%); $[M]^+$], [[181 (13%)/-179 (37%); $[M\text{-}CH_2Cl]^+$], 79 (8%), 70 (8%), 43 (100%; $[CH_3CO]^+$).

Anal. Calcd. for $C_5H_4ClN_3O_3S$: C, 27.10; H, 1.82; N, 18.97. Found: C, 27.05; H, 2.03; N, 19.00.

2-Methanesulfonylamino-4-methyl-5-nitrothiazole (IVa).

This was prepared from IIIa as described for Ic; yield 53%. Crystallisation from dichloroethane (100 ml./g. decolourizing carbon) gave pale yellow crystals R_f (B) = 0.39, m.p. 232-233°; nmr: δ = 2.77 (s, 3H, CH_3), δ = 2.99 (s, 3H, CH_3SO_2); mass spectrum m/e: 237 (17%; $[M]^+$), 206 (6%), 192 (19%), 159 (17%), 137 (19%), 113 (38%), 112 (32%), 95 (17%), 80 (46%), 79 (100%; $[CH_3SO_2]^+$). The fragmentation 237 → 159 is confirmed by a metastable peak at m/e: 106.7.

Anal. Calcd. for $C_5H_7N_3O_4S_2$: C, 25.31; H, 2.97; N, 17.71. Found: C, 25.57; H, 3.11; N, 17.61.

2-Amino-5-nitro-4-trifluoromethylthiazole (IVc).

2-Acetamido-4-trifluoromethylthiazole was nitrated as described for Ic to give 59% of the crude product. The latter was crystallized from hexane-dichloroethane 1:1 (100 ml./g., decolourizing carbon) and gave bright yellow crystals R_f (B) = 0.55, m.p. 197-198°, litt. (2) 188-190°; mass spectrum m/e: 213 (100%; $[M]^+$), 197 (5%), 183 (9%; $[M\text{-}NO]^+$), 167 (85%; $[M\text{-}NO_2]^+$), 147 (91%; $[M\text{-}NO_2\text{-}HF]^+$), 139 (10%), 125 (63%), 123 (19%), 106 (24%), 87 (11%), 75 (19%), 69 (26%; $[CF_3]^+$. The transitions 213 → 183, 213 → 167 and 167 → 147 were confirmed by metastable peaks at m/e = 157.2, 130.9 and 129.4, respectively.

2-Acetylamino-5-nitro-4-trifluoromethylthiazole (IVb).

Compound IVc was heated with excess acetic anhydride-pyridine 1:1 (100°, 15 minutes) and the mixture was left overnight. After quenching in ice-water, the pale yellow solid was rapidly filtered, rinsed with ice-water and dried in vacuum over Granusic. The yield was about 80%. Crystallisation from hexane-chloroform 6:1 (dry solvents 200 ml./g. decolourizing carbon) gave straw-coloured lustrous flakes which contained some pyridine of solvation. Preparative tlc afforded the pure product R_f (B) = 0.71, m.p. 194-196°; nmr: δ = 2.40 (s, CH_3CO^+), mass spectrum m/e: 255 (7%; $[M]^+$), 213 (19% $[M\text{-}CH_2CO]^+$), 197 (3%), 194 (2%), 167 (5%), 166 (2%), 147 (3%), 125 (1%), 106 (1%), 70 (6%), 69 (2%), 43 (100% $[CH_3CO]^+$).

Anal. Calcd. for $C_6H_4F_3N_3O_3S$: C, 28.24; H, 1.58; N, 16.47. Found: C, 28.40; H, 1.57; H, 16.23.

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