Reactions of some 5-Substituted Imidazo[2,1-*b*]-1,3,4-thiadiazoles

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The conversion of the 5-bromoimidazo[2,1-*b*]-1,3,4-thiadiazole Ib to the 5-cyano derivative Ic is firstly described. The 5-nitroimidazo[2,1-*b*]-1,3,4-thiadiazole Id is smoothly reduced by aluminium amalgam to the 5-imino-5,6-dihydroimidazo[2,1-*b*]-1,3,4-thiadiazole II. However, reaction of Id with sodium dithionite unexpectedly gives 1,3,4-thiadiazoles III and V depending upon conditions.

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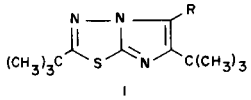
Numerous reports [1] have appeared on the reactivity of the imidazole ring in bicyclic fused imidazoles. The reactions of substituent groups in the imidazole ring of imidazo[2,1-*b*]thiazoles have been investigated [2]. Studies [3,4] on imidazo[2,1-*b*]-1,3,4-thiadiazoles have so far dealt with electrophilic substitution in the 5-position. This paper reports the synthesis of some 5-bromo- and 5-nitroimidazo-[2,1-*b*]-1,3,4-thiadiazoles and describes attempts to convert them to other 5-substituted derivatives.

The compounds chosen for this study were the 5-bromo and 5-nitro derivatives Ib and Id, respectively, and were prepared from the 2,6-di-*t*-butyl analogue Ia by methods similar to those previously reported [3,4].

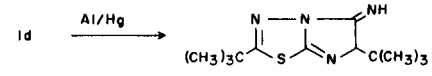
5-Bromoimidazo[2,1-*b*]-1,3,4-thiadiazoles were regarded as possible precursors for the hitherto unknown 5-amino derivatives *via* reaction with ammonia. However, as might be expected [5], simple nucleophilic displacement of the bromine atom was not possible and the only displacement which occurred involved introduction of cyanide using copper(I) cyanide in DMF at elevated temperature, providing the nitrile Ic.



I

a R = H
b R = Br
c R = CN
d R = NO_2
e R = $NHCOCH_3$
f R = NH_2

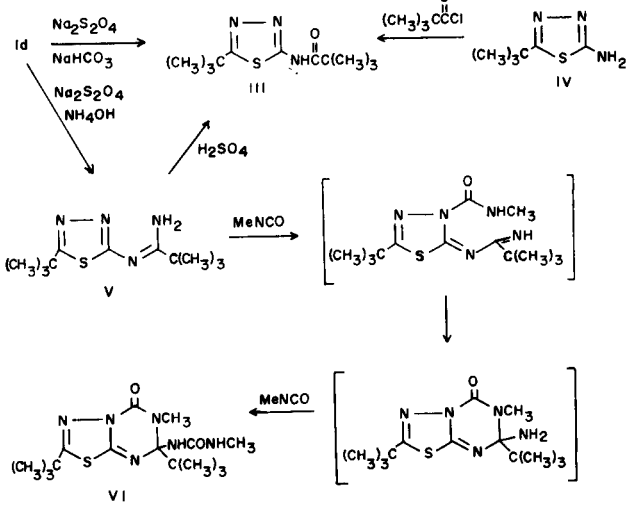
As an alternative approach to 5-amino compounds, reduction of a 5-nitro group was explored. Previous work [2] on imidazo[2,1-*b*]thiazoles suggested that catalytic hydrogenation would be successful if conducted in the presence of acetic anhydride to produce the corresponding amide. However, the reduction of the nitro compound Id in acetic anhydride/acetic acid with palladium/-charcoal gave only intractable material with none of the expected amide Ie. The reduction of Id was accomplished with aluminium amalgam in a low yielding reaction (36%) which produced the tautomeric imine II of the required amine If.



II

Attempts to improve the yield of II by reducing Id with sodium dithionite resulted in the unexpected cleavage of the imidazole ring. In an aqueous ethanolic bicarbonate solution, the thiadiazolyl amide III was obtained and identified by an alternative preparation from the 2-aminothiadiazole IV and pivaloyl chloride [6]. Using ammonia instead of bicarbonate with dithionite converted Id to the amidine V, acid hydrolysis of which gave III, whilst reaction of V with two equivalents of methyl isocyanate yielded the thiadiazolo[3,2-*a*]-1,3,5-triazinone system VI.

To determine the possible intermediacy of the imine II in the dithionite reduction of Id, its stability to refluxing aqueous ethanolic ammonia was investigated. No reaction occurred. Under the same conditions the nitro compound Id was unchanged, thus indicating that sodium dithionite is essential in the conversion to V. Further work is under cosideration to investigate the scope of the degradation and the mechanism involved.



EXPERIMENTAL

Melting points are uncorrected. The ir spectra were determined on a Pye Unicam SP 1100 spectrophotometer using potassium chloride discs.

The ^1H nmr spectra were determined on a Perkin-Elmer R-32 and ^{13}C spectra on a Bruker WP-80 instrument. Chemical shifts are reported on the δ scale using TMS as an internal standard. Mass spectra were obtained on AEI MS-30 and Varian MAT 44 spectrometers. Elemental analyses were performed on a Carlo Erba Elemental Analyser Model 1102.

2,6-Di-*t*-butylimidazo[2,1-*b*]-1,3,4-thiadiazole (Ia).

A mixture of 15.7 g (0.1 mole) of 2-amino-5-*t*-butyl-1,3,4-thiadiazole, 17.9 g (0.1 mole) of bromopinacolone and 80 ml of ethanol was refluxed on a heating mantle for 2 hours. The solution was concentrated under vacuum to approximately 30 ml. The resulting white precipitate was triturated with ether and filtered. After drying in a vacuum dessicator the solid weighed 18.0 g. A solution of 11.5 g of the solid and 40 ml of water was refluxed for 30 minutes. The solution was cooled to room temperature and basified with sodium carbonate to afford a white precipitate which was filtered, washed with water and dried. Recrystallisation from 40-60 petroleum ether gave 8.0 g (53%) of colourless crystals, mp 98-99°; ^1H nmr (deuteriochloroform): δ 1.32 (s, 9H), 1.42 (s, 9H), 7.37 (s, 1H).

Anal. Calcd. for $C_{12}H_{19}N_3S$: C, 60.72; H, 8.07; N, 17.71. Found: C, 61.0; H, 8.5; N, 17.3.

5-Bromo-2,6-di-*t*-butylimidazo[2,1-*b*]-1,3,4-thiadiazole (Ib).

To 4.10 g (0.017 mole) of Ia, 2.85 g (0.035 mole) of sodium acetate and 30 ml of acetic acid stirred together at room temperature was added dropwise 2.91 g (0.018 mole) of bromine. After the addition, stirring was continued for 10 minutes. The mixture was poured into 400 ml of water from which a solid separated. The solid was collected, washed with water and dried. Recrystallisation from acetonitrile gave 4.3 g (80%) of white flakes, mp 81°; ^1H nmr (DMSO-d_6): δ 1.35 (s, 9H), 1.4 (s, 9H).

Anal. Calcd. for $C_{12}H_{18}BrN_3S$: C, 45.57; H, 5.74; Br, 25.27; N, 13.29. Found: C, 45.28; H, 5.84; Br, 25.02; N, 12.94.

2,6-Di-*t*-butyl-5-cyanoimidazo[2,1-*b*]-1,3,4-thiadiazole (Ic).

A mixture of 9.5 g (0.03 mole) of Ib, 2.9 g (0.033 mole) of copper(I) cyanide and 200 ml of dimethylformamide was stirred at 150-160° for 6 hours. The reaction mixture was allowed to cool to room temperature and was then poured into 600 ml of water giving a precipitate which was filtered and washed with water. The precipitate was stirred in a solution of 10 g of sodium cyanide and 100 ml of water. After a few minutes the aqueous solution was extracted with ether and the extracts washed with water and dried. After removing the ether by distillation there remained a white solid which recrystallised as needles from 60-80 petroleum ether, yield 4.6 g (58%), mp 134-137°; ir: ν CN 2230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.39 (s, 9H), 1.45 (s, 9H).

Anal. Calcd. for $C_{13}H_{18}N_4S$: C, 59.51; H, 6.92; N, 21.35. Found: C, 59.14; H, 7.03; N, 21.72.

2,6-Di-*t*-butyl-5-nitroimidazo[2,1-*b*]-1,3,4-thiadiazole (Id).

A solution of 5.0 g (0.021 mole) of Ia in 50 ml of concentrated sulphuric acid was stirred in ice-water and treated dropwise with 2.5 ml of concentrated nitric acid (d = 1.42). Stirring was continued for 15 minutes after the addition. The reaction mixture was poured into ice-water in which a thick precipitate formed. The precipitate was filtered, washed with water, dried and crystallised as pale yellow needles from 2-propanol, yield 5.1 g (86%), mp 132-135°; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H), 1.51 (s, 9H).

Anal. Calcd. for $C_{12}H_{18}N_4O_2S$: C, 51.04; H, 6.43; N, 19.84. Found: C, 50.79; H, 6.20; N, 20.04.

2,6-Di-*t*-butyl-5-imino-5,6-dihydroimidazo[2,1-*b*]-1,3,4-thiadiazole (II).

Aluminium amalgam was prepared as follows: a saturated aqueous solution of mercuric chloride was added to 4.0 g of aluminium turnings. After a few minutes the aqueous solution was decanted and replaced with another portion of the aqueous mercuric chloride solution which was itself decanted after a few minutes. The amalgam was washed with water and then stirred with a solution of 16.0 g (0.057 mole) of Id in 200 ml of tetrahydrofuran. An exothermic reaction ensued and caused refluxing. After 2 hours, the reaction mixture was filtered and the insoluble material washed with ether. The filtrate and washings were combined, dried and distilled. The residual material was taken up in ether and the solution washed with water, dried and distilled. The residual solid crystallised from 2-propanol/60-80 petroleum ether affording 8.0 g of a mixture of the product II and starting material Id (^1H nmr). This mixture was taken up in 80 ml of tetrahydrofuran and mixed with a further quantity of aluminium amalgam prepared from 8.0 g of aluminium turnings. After 3 hours, the reaction mixture was worked up as before giving 5.1 g (36%) of product as white needles from 2-propanol/60-80 petroleum ether with mp 199-202°; ir: ν NH 3200-3350 cm^{-1}; ms: m/e 252 (M^+); ^1H nmr (deuteriochloroform): δ 1.12 (s, 9H), 1.36 (s, 9H), 4.65 (s, 1H), 6.50 (b, 1H, exchanged with deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 26.0 (q), 30.8 (q), 35.4 (s), 36.3 (s), 56.5 (d), 118.4 (s), 168.1 (s), 172.1 (s).

Anal. Calcd. for $C_{12}H_{20}N_4S$: C, 57.11; H, 7.99; N, 22.20. Found: C, 57.40; H, 7.64; N, 22.60.

N-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)pivalamide (III).

(a) A suspension of 2.5 g (8.86 mmoles) of Id and 4.46 g (53.16 mmoles) of sodium bicarbonate in 70 ml of ethanol and 35 ml of water was stirred at 50° and treated in one portion with 5.58 g (26.6 mmoles) of sodium dithionite. After the initial effervescence had ceased the mixture was refluxed for 1 hour. The mixture was then cooled and filtered. The filtrate was concentrated under vacuum to a small volume. The residual solid was dissolved in dichloromethane and the solution washed with water and dried. The solvent was evaporated under vacuum and the residue crystallised from acetonitrile to afford 0.9 g (42%) of III, mp 184-186°; ir: ν NH 3100-3200, C=O 1695 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (s, 9H), 1.42 (s, 9H), 10.55 (b, 1H, exchanged with deuterium oxide); ms: m/e 241 (M^+).

Anal. Calcd. for $C_{11}H_{19}N_3OS$: C, 54.74; H, 7.92; N, 17.41. Found: C, 54.48; H, 8.33; N, 17.45.

(b) A mixture of 3.14 g (0.002 mole) of 2-amino-5-*t*-butyl-1,3,4-thiadiazole and 50 ml of ethyl acetate was treated dropwise with 1.2 g (0.001 mole) of pivaloyl chloride. The reaction mixture was refluxed for 10 minutes and then evaporated to dryness under vacuum. The residue was stirred with 2*N* hydrochloric acid and filtered. The solid crystallised from acetonitrile affording III, mp 184-186° [6], identical in all respects to the compound prepared by méthod (a).

N'-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)pivalamidine (V).

A suspension of 2.5 g (8.86 mmoles) of Id in 70 ml of ethanol, 35 ml of water and 6 ml of concentrated ammonium hydroxide was stirred at 50° and treated in two portions with 5.58 g (26.6 mmoles) of sodium dithionite. The mixture was refluxed for 1 hour, allowed to cool to room temperature and then filtered. The filtrate was distilled under reduced pressure. The residual solid was dissolved in dichloromethane and the solution washed with water. After drying, the solvent was evaporated under vacuum and the residue crystallised as pale yellow prisms from acetonitrile, yield 1.30 g (61%), mp 170-171.5°; ir: ν NH 3180, 3350 (b) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (s, 9H), 1.41 (s, 9H), 5.5-6.5 (b, 2H, exchanged with deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 28.5 (s), 30.9 (s), 36.2 (s), 38.0 (s), 171.6 (s), 174.9 (s), 176.8 (s); ms: m/e 240 (M^+).

Anal. Calcd. for $C_{11}H_{20}N_4S$: C, 54.96; H, 8.39; N, 23.31. Found: C, 55.07; H, 8.47; N, 23.38.

Hydrolysis of V to III.

A solution of the amidine V in 4*N* sulphuric acid was refluxed for a few minutes. The reaction mixture was allowed to cool and then filtered from the precipitated solid. The solid was washed with water, dried and recrystallised from acetonitrile affording the amide III, mp 184-186°.

2,7-Di-*t*-butyl-6,7-dihydro-6-methyl-7-(3-methylureido)-5*H*-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazin-5-one (VI).

A mixture of 4.80 g (0.02 mole) of the amidine (V), 2.85 g (0.05 mole) of

methyl isocyanate and 15 ml of ethyl acetate was refluxed for 5 hours. The reaction mixture was cooled and the solid filtered, washed with ethyl acetate and crystallised from acetonitrile affording 3.9 g (55%) of colourless prisms, mp 195-196° (d); ir: ν NH 3400 (b), 3150-3250 (b), C=O 1720, 1675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (s, 9H), 1.25 (s, 9H), 2.76 (d, 3H, collapses to a singlet on addition of deuterium oxide), 2.90 (s, 3H), 5.90 (q, exchanges with deuterium oxide), 9.48 (b, 1H, exchanges with deuterium oxide); ms: m/e 354 (M^+).

Anal. Calcd. for $C_{15}H_{26}N_6O_2S$: C, 50.82; H, 7.39; N, 23.71. Found: C, 50.42; H, 7.01; N, 23.37.

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REFERENCES AND NOTES

[1] For examples see L. Pentimalli and L. Greci, *Gazz. Chim. Ital.*, **98**, 1360 (1968); L. Pentimalli and V. Passalacqua, *ibid.*, **100**, 110 (1970); L. Pentimalli and G. Milani, *ibid.*, **97**, 488 (1967); L. Pentimalli and A. M. Guerra, *ibid.*, **97**, 1286 (1967).

[2] J. P. Paolini, L. J. Lendvay, *J. Med. Chem.*, **12**, 1031 (1969).

[3] L. Pentimalli, G. Milani and F. Biavati, *Gazz. Chim. Ital.*, **105**, 777 (1975); S. Kano, *Yakugaku Zasshi*, **92**, 935 (1972); *Chem. Abstr.*, **77**, 126492v (1972).

[4] A ring-opening reaction involving cleavage of the 1,3,4-thiadiazolyl moiety is reported by T. Pyl, F. Waschk and H. Beyer, *Ann. Chem.*, **663**, 113 (1963).

[5] If an imidazo[2,1-*b*]-1,3,4-thiadiazole is regarded as the fusion of a 2-imino(3*H*)-1,3,4-thiadiazole with an olefin (similar to the way in which an imidazole ring is compared to an amidine fused to an olefin by C. Rev-Acha and L. A. Cohen, *J. Org. Chem.*, **46**, 4717 (1981), halogens in the 5- or 6-positions would be vinylic and unreactive.

[6] Synthesis of III from pivaloyl chloride and IV is reported by D. Leppard and H. Sauter, *J. Heterocyclic Chem.*, **17**, 1469 (1980), but no melting point is given.