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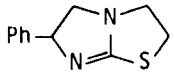
7-Alkyl-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazolium salts behave as ambident electrophiles, which give ring-opened products on reaction with a variety of nucleophiles. The results are rationalised in terms of thermodynamic or kinetic control.

J. Heterocyclic Chem., 14, 603 (1977).

The discovery of 2,3,5,6-tetrahydro-6-phenylimidazo-[2,1-*b*]thiazole (**1**) as a broad-spectrum anthelmintic (2), and the diverse biological activity of a large number of related compounds (3) has led to a growing interest in imidazo[2,1-*b*]thiazoles. Little work on the basic chemistry of the ring system has, however, been reported although, by analogy with other *iso*thioureas, imidazo[2,1-*b*]thiazoles might be expected to undergo a variety of addition-elimination and dipolar cycloaddition reactions. As part of a continuing study we now report the behavior of 7-alkyl-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazolium salts with nucleophiles.



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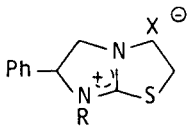
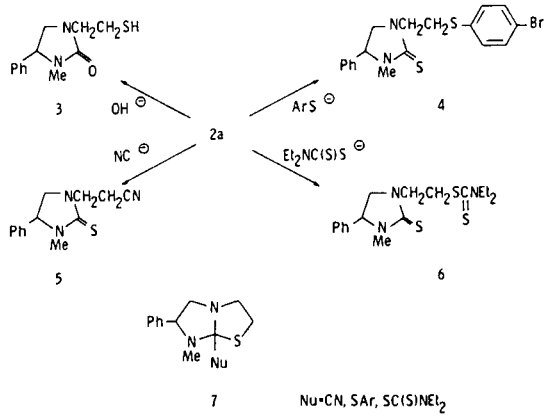


2a, R=Me, X=I
b, R=CH_2Ph, X=Br

Alkylation of the imidazo[2,1-*b*]thiazole **1** with iodomethane or benzyl bromide readily gave **2a** and **2b** in good yield. The compounds had satisfactory microanalyses and the pmr spectra were consistent with the expected products but, surprisingly, the mass spectra of both compounds showed weak parent ions which included the halide counterion. Analysis of **2a** for ionic iodine, however, indicated no incorporation of halide at room temperature. The benzyl derivative **2b** proved to be somewhat hygroscopic, hence the majority of reactions reported below were carried out on the methiodide **2a**. Scheme I indicates the nucleophiles examined, and the products obtained.

Scheme 1



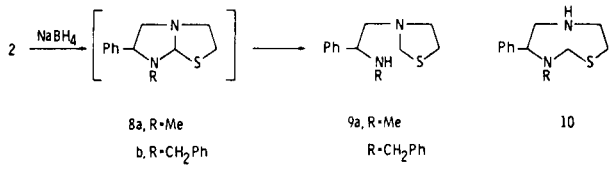
The results show, as might be expected, that the tetrahydroimidazo[2,1-*b*]thiazolium ion behaves as an ambident electrophile. Thus with hydroxide ions the observed product is that derived from attack at the 7a carbon atom, while with the other nucleophiles examined the products obtained are those derived from attack at the 2-position.

The structure of compound **3** was readily assigned from the mass spectrum, the presence of thiol and carbonly absorptions in the infrared region (2600 and 1680 cm^{-1}), and a characteristic thiol triplet in the pmr spectrum (1.4 δ). Furthermore, an analogous hydrolysis of 7-aryl-imidazo[2,1-*b*]thiazolium salts has been reported by Dorn (4). Structure assignment for products **4-6** was more difficult because of the absence of strong characteristic absorptions in the infrared region, and because of the complex second-order pmr spectra (5). In particular, it was necessary to distinguish between the open-chain structures written above, and the bicyclic adducts **7**, in view of the work of Nakai *et al.*, (6). It is evident from the pmr spectra that the three products have a similar structure, since both the benzylic and methyl hydrogens resonate at very similar fields in all the compounds, as shown in Table I. The chemical shifts are more consistent with an imidazolidinethione rather than structure **7** but few data are available on compounds containing carbon atoms attached to four heteroatoms. The carbon-13 nmr (cmr) spectra of the compounds confirmed the similarity of structure for the three compounds, and clearly showed a signal at *ca.* 183 ppm consistent with an NC(S)N linkage (7).

The reduction of **2a** with sodium borohydride or sodium bis(2-methoxyethoxy)aluminium hydride gave the thiazolidine **9a** [ir: 3250 cm^{-1} (NH); mass spectrum: m/e 221 (m-1); pmr: 4.05 δ (AB, NCH_2S)], presumably *via* reduction to **8** followed by reductive cleavage of a C-N bond.

The alternative structure **10** is less likely in view of a strong peak at m/e 120 ($PhCHNHCH_3$) in the mass

spectrum. Furthermore, reaction of the product with phenyl isocyanate led to a urea **11** in which the AB signal at 4.05 δ remained essentially unchanged, but the benzylic hydrogen signal was shifted from 3.55 to 5.6 δ, thus eliminating structure **10**. Reduction of **9a** with sodium cyanoborohydride, under acidic conditions, gave the open-chain disulphide **12**.

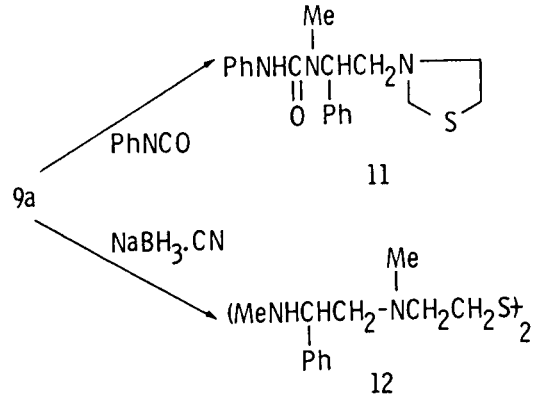


8a, R=Me
b, R=CH_2Ph

9a, R=Me
R=CH_2Ph

10

The *N*-benzyl compound **2b** was similarly reduced by sodium borohydride to **9b**. Attempts to isolate the intermediate **8** by reduction of compound **2** at *ca.* 0° were unsuccessful, only compound **9** being isolated. The formation of **9** is consistent with the reported cleavage of imidazolium iodides by sodium borohydride (8), and the relative stability of thiazolidines to this reagent (9).



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12

Nakai, Okawara, and co-workers in investigations of the electrophilic behaviour of cyclic dithiocarbamidium ions demonstrated their ambident behaviour with a variety of nucleophiles (6,10), and rationalised their results in terms

Scheme II

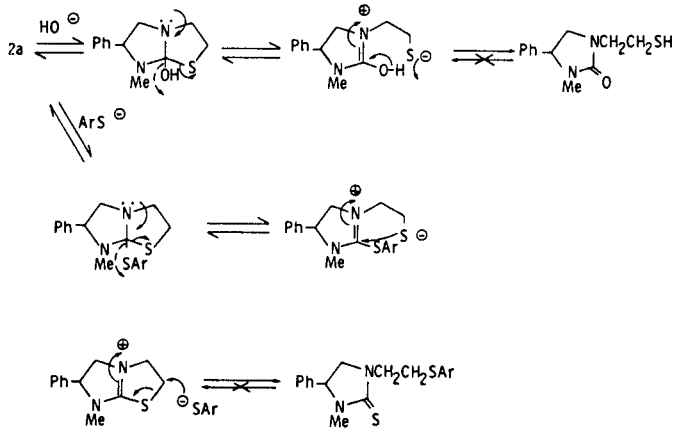


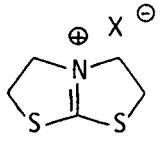
TABLE I

Nmr data for Compounds **4**, **5**, **6**

Compound	pmr (δ) NCH_3	pmr (δ) PhCH	cmr (ppm) NCH_3	cmr (ppm) PhCH	cmr (ppm) NC(S)N
4	2.85	4.64	32.9	63.7	182.6
5	2.90	4.68	32.9	63.9	182.8
6	2.95	4.68	32.9	63.8	182.6

of hard acid-soft base interactions, which necessitated definition of hydride ions as hard nucleophiles (9a). In our case we suggest that the products obtained by nucleophilic attack on the cation **2** can reasonably be explained in terms of kinetic or thermodynamic control. Thus we consider that, in the absence of overwhelming steric effects, the nucleophile initially attacks at the bridgehead carbon, and where this reaction is irreversible (*e.g.* attack by hydride), or where further reaction of the adduct to a stable product occurs, as illustrated for hydroxide ions in Scheme II, then the observed product is that derived from attack at the 7a-position. Where, however, the initial attack is reversible and no stabilising reaction pathway is available to the intermediate, then the thermodynamically-controlled product is observed, *i.e.* that derived by attack at C-2, as illustrated in Scheme II for attack by thiophenoxide ion,

It is noteworthy that the reactions of thiophenoxide and cyanide ions with the 2,3,5,6-tetrahydrothiazolo-[2,3-*b*]thiazolium ion **13** lead to stable bicyclic adducts **14** (6), whereas with the 2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazolium ion **2a** open-chain compounds **4** and **5** result.



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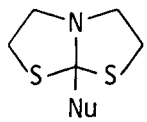

14, Nu=RS, CN

We suggest that the observed difference in products between the two series can be rationalised in terms of the greater +E effect of nitrogen, relative to sulphur, in destabilising the initial adduct.

EXPERIMENTAL

General.

Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 157 spectrometer using sodium chloride plates. Pmr spectra were recorded at 100 MHz using a Varian HA 100 D spectrometer. The chemical shift values are expressed in δ values relative to a tetramethylsilane internal standard. Carbon-13 magnetic resonance spectra (cmr) were determined

using a Bruker HX 90E spectrometer with chloroform or tetramethylsilane as an internal standard. The mass spectra were determined on an AEI-MS902 instrument. Microanalyses were carried out on a Carlo Erba Elemental Analyser Model 1104. Column chromatography was performed using silica gel (60-120 mesh) from B.D.H. Ltd., or Woelm neutral alumina (activity 3).

2,3,5,6-Tetrahydro-7-methyl-6-phenylimidazo[2,1-*b*]thiazolium Iodide (**2a**).

Iodomethane (14.2 g., 0.1 mole) was added to a solution of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (**1**) (10.2 g., 0.05 mole) in acetone (150 ml.) and the reaction mixture stirred at room temperature for 18 hours. Filtration gave 15.2 g. (88%) of **2a**; m.p. 189-191°. Concentration of the filtrate gave a further 1.3 g. (7.5%), m.p. 189-191°. Recrystallisation from ethanol/light petroleum (b.p. 60-80°) raised the m.p. to 191-192°; pmr (DMSO-d_6 + deuteriochloroform): 2.9 δ (s, 3H, NCH_3), 3.7-4.6 (m, 6H), 5.74 (t, 1H, PhCH), 7.5 (s, 5H, ArH); mass spectrum: m/e 346 (M^+), 219 (M-I).

Anal. Calcd. for $C_{12}H_{15}IN_2S$: C, 41.6; H, 4.37; N, 8.09; S, 9.26; I, 36.7. Found: C, 41.6; H, 4.4; N, 8.2; S, 9.4: I (ionic), 37.1.

7-Benzyl-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazolium Bromide (**2b**).

Benzyl bromide (2 g., 8.5 mmoles) was added to a solution of **1** (1.6 g., 8 mmoles) in toluene and the reaction mixture stirred at room temperature. Filtration after 48 hours gave 1.7 g. (58%) of **2b**, m.p. 112-116°. Recrystallisation from ethanol/light petroleum (b.p. 60-80°) gave **2b** as the monohydrate m.p. 114-115°; pmr (DMSO-d_6 + deuteriochloroform): 3.3 δ (s, 2H, NCH_2Ph), 3.8-4.6 (m, 6H), 5.67 (t, 1H, PhCH), 7.1-7.75 (m, 10H, ArH); mass spectrum: m/e 376, 374 (M^+), 295 (M-Br).

Anal. Calcd. for $C_{18}H_{19}BrN_2S.1H_20$: C, 55.0; H, 5.3; N, 7.1. Found: C, 55.2 H, 5.3; N, 7.0.

1-(2-Mercaptoethyl)-3-methyl-4-phenyl-2-imidazolidone (**3**).

A suspension of the methiodide **2a** (6.9 g., 0.02 mole) in aqueous sodium hydroxide (50 ml. of 2*N*) was heated on a steam-bath for 18 hours. The yellow solution was diluted with water (200 ml.), acidified with acetic acid, and extracted with ether. Evaporation of the dried (magnesium sulfate) extract left 3.5 g. of an oil which was purified by column chromatography on silica gel. Elution with ethyl acetate/methanol (1/1) gave 3.0 g. (63%) of **3** as a clear oil; ir (film): 2600 (SH), 1680 cm^{-1} (C=O); mass spectrum: m/e 236 (M^+); pmr (deuteriochloroform): 1.4 δ (t, 1H, SH), 2.6 (s, 3H, CH_3), 2.4-2.9 (m, 2H, CH_2S), 3.1-3.8 (m, 4H, $CH_2NC(O)$), 4.4 (t, 1H, PhCH), 7.3 (s, 5H, ArH).

Anal. Calcd. for $C_{12}H_{16}N_2OS$: C, 61.0; H, 6.82; N, 11.8. Found: C, 60.6; H, 7.0; N, 11.4.

1-[2-(4-Bromophenylthio)ethyl]-3-methyl-4-phenyl-2-imidazolidinethione (**4**).

Compound **2a** (6.9 g., 0.02 mole) was added to a solution of sodium 4-bromothiophenoxide (0.02 mole) in ethanol (25 ml.) and the mixture heated on a steambath for 12 hours. The reaction mixture was cooled and filtered to give 4.9 g. (60%) of **4** as a crystalline white solid m.p. 141-143°; pmr (DMSO-d_6 + deuteriochloroform): 2.85 δ (s, 3H, CH_3), 3.2 (t, 2H, CH_2S), 3.48 + 4.0 (q + t, 2H, NCH_2CPh), 3.84 (t, 2H, $C(S)NCH_2C$-S), 4.64 (q [AMX], 1H, PhCH), 7.35 (s, 5H, ArH); mass spectrum: m/e 408, 406 (M^+), 218 ($M-SC_6H_4Br$), 205; cmr (deuteriochloroform): 30.6 ppm (CH_2S), 32.9 (CH_3N), 63.7 (PhC), 182.6 (NC(S)N).

Anal. Calcd. for $C_{18}H_{19}BrN_2S_2$: C, 53.1; H, 4.70; N, 6.88; S, 15.7. Found: C, 53.0; H, 4.6; N, 6.7; S, 15.4.

1-(2-Cyanoethyl)-3-methyl-4-phenyl-2-imidazolidinethione (**5**).

A solution of **2a** (6.9 g., 0.02 mole) and potassium cyanide (3.9 g., 0.06 mole) in acetonitrile (70 ml.) was heated on a steam-bath for 42 hours. The solvent was evaporated and the residual solid extracted with chloroform. The extracts were concentrated and added to a column of silica gel (400 g.). Elution with ethyl acetate/chloroform (9/1) gave 1.0 g. (20%) of **5** as an oil; pmr (deuteriochloroform): 2.78 δ (t, 2H, $CH_2C{\equiv}N$), 2.9 (s, 3H, CH_3), 3.56 + 4.13 (q + t, 2H, NCH_2CPh), 3.6-4.1 (m, 2H, $NC(S)NCH_2$), 4.68 (q [AMX], 1H, PhCH), 7.35 (s, 5H, ArH); mass spectrum: m/e 245 (M^+), 205 ($M-CH_2CN$), 192, 149; cmr ($CHCl_3$): 16.3 ppm *C*-CN), 32.9 (NCH_3), 63.9 (C-Ph), 119.6 (C≡N), 182.8 (NC(S)N).

Anal. Calcd. for $C_{13}H_{15}N_3S$: C, 63.6; H, 6.16; N, 17.2. Found: C, 63.5; H, 6.3; N, 16.8.

2-(3-Methyl-4-phenyl-2-thioxo-1-imidazolidinyl)ethyl *N,N*-diethyldithiocarbamate (**6**).

A solution of **2a** (6.9 g., 0.02 mole) and sodium *N,N*-diethyldithiocarbamate (4.5 g., 0.02 mole) in DMF (30 ml.) was heated overnight at 60°. The reaction mixture was poured into water and extracted with chloroform. The extracts were washed with water, dried (magnesium sulfate), and evaporated to give an oil which solidified on standing. Recrystallisation of the cream-coloured solid from ethanol gave 5.2 g. (70%) of **6** as white crystals m.p. 79-81°; pmr (deuteriochloroform): 1.25 δ (t, 6H, CH_2CH_3), 2.95 (s, 3H, NCH_3), 3.5-4.3 (m, 10H), 4.68 (q [AMX], 1H, PhCH), 7.35 (s, 5H, ArH); mass spectrum: m/e 367 (M^+), 251, 219; cmr (chloroform): 11.3, 12.2 ppm ($C-CH_3$), 32.9 (NCH_3), 46.2, 46.6 ($N-C-CH_3$), 63.8 (Ph-C), 182.6 (NC(S)N), 194.5 (SC(S)N).

Anal. Calcd. for $C_{17}H_{25}N_3S_3$: C, 55.5; H, 6.85; N, 11.4. Found: C, 55.3; H, 6.9; N, 11.3.

Reduction of **2a**. A. Sodium Borohydride at Room Temperature.

A suspension of sodium borohydride (2.7 g., 0.07 mole) and **2a** (12.15 g., 0.035 mole) in ethanol (200 ml.) was stirred at room temperature for 2 hours. The reaction mixture was acidified with acetic acid, concentrated, diluted with water, and extracted with chloroform. The dried (magnesium sulfate) extracts were evaporated to give an oil which was purified by chromatography on a column of alumina (400 g.). Elution with ethyl acetate gave 5.7 g. (73%) of *N*-methyl-1-phenyl-2-(3-thiazolidinyl)ethylamine (**9a**) as a clear oil; ir (film): 3250 cm^{-1} (NH); pmr (deuteriochloroform): 2.3 δ (s, 3H, NCH_3), 2.1-3.1 (m, 7H [1 exchangeable]) 3.55 (q, 1H, PhCH), 4.05 (q [AB], 2H, NCH_2S), 7.3 (s, 5H, ArH); mass spectrum: m/e 221 (M-1), 120 ($PhCHNHCH_3$).

Anal. Calcd. for $C_{12}H_{18}N_2S$: C, 64.8; H, 8.16; N, 12.6. Found: C, 65.2; H, 8.4; N, 12.7.

B. Sodium Borohydride at 0°.

The methiodide **2a** (6.9 g., 0.02 mole) was added in portions to a suspension of sodium borohydride (0.76 g., 0.04 mole) in ethanol (100 ml.) keeping the temperature below 0°. The reaction mixture was maintained below 0° for a further 4 hours. Work up, as described for the preceeding reaction, gave 2.65 g. (60%) of **9a**, whose ir and pmr spectra were identical to those of the previously obtained material.

C. Sodium bis(2-Methoxyethoxy)aluminium Hydride (SMEAH).

SMEAH (14.2 ml. of 70% solution in benzene, 0.05 mole) was added, with cooling and stirring, to a suspension of the methiodide **2a** (8.65 g., 0.025 mole) in toluene (125 ml.). The reaction mixture was stirred for 18 hours at room temperature, poured

onto crushed ice and extracted with chloroform. A chromatographic purification, carried out as described above, gave 3.8 g. (44%) of **9a**, whose spectroscopic properties were identical to those of the previously obtained samples.

N-Benzyl-1-phenyl-2-(3-thiazolidinyl)ethylamine (**9b**).

Compound **2b** (2.55 g., 6.8 mmoles) was reduced with sodium borohydride in ethanol at room temperature, as described for compound **2a**, to give 1.3 g. (64%) of **9b** as an oil; pmr (deuteriochloroform): 2.2-3.9 δ (m, 10H), 4.0 (q, 2H, NCH_2S), 7.1-7.6 (s, 10H, ArH); mass spectrum: m/e 297 (M-1), 196 (PhCH-$NHCH_2Ph$).

Anal. Calcd. for $C_{18}H_{22}N_2S$: C, 72.4; H, 7.43; N, 9.39. Found: C, 72.0; H, 7.3; N, 9.2.

N-Methyl-*N*-[1-phenyl-2-(3-thiazolidinyl)]ethyl-*N*-phenylurea (**11**).

A solution of **9a** (2.2 g., 0.01 mole) and phenyl isocyanate (1.2 g., 0.01 mole) in ether (35 ml.) was stirred at room temperature for 5 hours. Filtration gave 2.4 g. (71%) of **11** as a white solid m.p. 146-148° (unchanged by recrystallisation from ethanol/light petroleum); ir (nujol): 3280 (NH), 1670 cm^{-1} (C=O); pmr (deuteriochloroform): 2.67 δ (s, 3H, NCH_3), 2.82-3.0 (m, 4H), 3.1-3.25 (m, 2H), 4.13 (q [AB], 2H, NCH_2S), 5.6 (q [AMX], 1H, PhCH), 6.9-7.6 (m, 10H, ArH); mass spectrum: m/e 341 (M^+), 239, 102.

Anal. Calcd. for $C_{19}H_{23}N_3OS$: C, 66.9; H, 6.7; N, 12.3. Found: C, 66.8; H, 7.1; N, 12.2.

Bis[2-(2-methylamino-2-phenyl)ethylaminoethyl]disulphide (**12**).

A solution of **9a** (2.2 g., 0.01 mole) in methanol (50 ml.) was adjusted to *p*H 6 by the addition of concentrated hydrochloric acid and treated with sodium cyanoborohydride (0.63 g., 0.01 mole). The reaction mixture was stirred at room temperature, maintaining the *p*H at 5-6 by the occasional addition of hydrochloric acid. After 48 hours the reaction mixture was acidified to $pH < 2$ with concentrated hydrochloric acid and left for 1 hour. The solvent was evaporated and the residue taken up in water, basified with sodium hydroxide, and extracted with ether. The extracts were dried (magnesium sulfate) and evaporated to give 2.1 g. (95%) of **12** as a yellow oil; ir (film): 3250 cm^{-1} (NH); pmr (deuteriochloroform): 2.25 δ (s, 6H, NCH_3), 2.3 (s, 6H, NCH_3), 2.0-3.0 (m, 14H), 3.55 (q [AMX], 2H, PhCH), 7.25 (s, 10H, ArH); mass spectrum: m/e 446 (M^+), 326 (M-$PhCHNHCH_3$), 223 (M/2), 120 ($PhCHNHCH_3$).

Anal. Calcd. for $C_{24}H_{38}N_4S_2$: C, 64.5; H, 8.57; N, 12.5. Found: C, 64.4; H, 8.9; N, 12.7.

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(5) The pmr spectrum of compound **6** was particularly complex due to restricted rotation of the side-chain. The cmr spectrum showed doublets for the carbon atoms in different conformations, and the pmr spectrum in DMSO-d_6 at 40° and 100° confirmed that the degree of complexity of the spectra was temperature dependent.

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