A Directed Metalation Route to the Selenium Analogue of Methimazole

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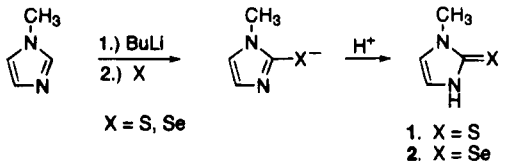
Despite the fact that thiocarbonyl compounds have often proved to be important therapeutic agents, the corresponding selenocarbonyl compounds have until recently been much less investigated. One such important thiocarbonyl agent is 1,3-dihydro-1-methyl-2H-imidazole-2-thione (**1**), commonly referred to as methimazole (MMI). This compound is one of a class of thiourylene drugs, useful as antithyroid agents.[1] For a number of years the mechanism of action of these drugs was presumed to involve inhibition of a key thyroid enzyme, 5'-iodothyronine deiodinase (ID-1), by formation of a mixed disulfide between a cysteine residue on the enzyme and the sulfur atom of the thiourylene.[2,3] Recently, the importance of selenium in thyroid metabolism has been recognized, culminating in the discovery that ID-1 is, in fact, a selenoenzyme containing a selenocysteine residue which is necessary for full biological activity.[4,5]



Because of our interest in the chemistry of both selenocarbonyl compounds[6,7] and anti-thyroid therapeutic agents,[8] we sought to prepare the selenium analogue **2** of methimazole, to see whether this compound could be a more effective inhibitor of ID-1, in particular because of the very mild conditions necessary for forming diselenide bonds. Remarkably, this compound, 1,3-dihydro-1-methyl-2*H*-imidazole-2-selone (**2**), has not been reported in the literature.

Initial attempts to prepare **2** by an alkylation–selenation sequence, commonly used to prepare acyclic selenoureas[6,7] failed to afford the desired selone derivative in this case. An alternative approach involving directed metalation of 1-methylimidazole was investigated. Metalation of 1-methylimidazole using *n*-butyllithium is known to lead to α-lithiation at the 2-position of the heterocycle.[9] The recent success of Silks and co-workers in direct selenation of metalated oxazolidines[10] also indicated the potential of this reaction to incorporate selenium into a heterocyclic system.

Treatment of 1-methylimidazole in THF at −78 °C with *n*-butyllithium (1.0 equiv) followed by treatment with elemental sulfur (1.0 equiv) at room temperature and aqueous workup afforded authentic **1** in 42% (unoptimized) yield.[11] When the reaction was repeated using elemental selenium, under identical conditions after trituration, crystalline **2** was obtained essentially pure in 43% yield. Use of 1.5 equiv of selenium increased the yield of **2** to 58%.

One additional point of interest dealt with the tautomeric behavior of **2**. Did this compound exist in the selone **2** or selenol **2'** form? MMI itself is often represented as existing in the thiol form—1-methyl-2-mercaptoimidazole (**1'**).[12] The selenol form **2'** would be expected to predominate even more than the thiol form **1'**. This should occur because of a poorer C—Se π overlap in the selenium analogue compared with the C—S π overlap in the thione form of MMI (**1**).[6,7] Comparison of the ^{13}C NMRs of both the sulfur and selenium compounds showed very close similarities. Careful examination of the $^{13}C-{}^{77}Se$ coupling constants in **2**, however, showed a value of ~220 Hz, typical of the values obtained for carbon–selenium double bonds (230–240 Hz) as opposed to the ~110–140 Hz values associated with sp^2-hybridized carbon–selenium single bonds that would be expected for the selenol tautomer.[10,13]

The successful introduction of a selenocarbonyl group into heterocycles using metalation procedures constitutes a new and potentially very convenient route to compounds previously available only by multistep procedures.

The proposal that 1,3-dihydro-1-methyl-2*H*-imidazole-2-selone (**2**) might be a more effective inhibitor of ID-1 appears to be correct. It was marginally more active than MMI in inhibiting ID-1 *in vitro*. Full biological studies on the comparisons of MMI with **2** will be published separately.[14]

Experimental Section

The general experimental conditions used are as those recently reported.[15]

1,3-Dihydro-1-methyl-2*H*-imidazole-2-thione (1). To a cooled (−78 °C) solution of 1-methylimidazole (0.485 mL, 6.09 mmol) in freshly distilled THF (50 mL) was added via syringe *n*-butyllithium (4.9 mL, 6.09 mmol, 1.24 M in hexanes). The

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resulting mixture was stirred with cooling for 30 min and then allowed to come to rt at which time elemental sulfur (0.195 g, 6.09 g atoms) was added. This mixture was heated at reflux overnight under nitrogen. After cooling, the reaction was quenched with water and neutralized with 1 N HCl. The aqueous mixture was extracted with $CHCl_3$ and the organic layer was washed with brine and dried over Na_2SO_4. Removal of solvent afforded MMI as a grey solid, 292 mg (42% crude yield). The spectroscopic properties of the crude product were identical to those of an authentic sample of methimazole. ^{13}C NMR ($CDCl_3$): δ 34.23, 34.24, 114.3, 119.2, 160.1.

1,3-Dihydro-1-methyl-2*H*-imidazole-2-selone (2). To a cooled (−78 °C) solution of 1-methylimidazole (0.485 mL, 6.09 mmol) in freshly distilled THF (50 mL) was added via syringe *n*-butyllithium (3.8 mL, 6.09 mmol, 1.6 M in hexanes). The mixture was stirred with cooling for 35 min and then allowed to come to rt at which time elemental selenium (0.721 g, 9.14 g atoms) was added. The resulting mixture was stirred at rt overnight under nitrogen. After cooling, the mixture was quenched with water and neutralized with 1 N HCl. The aqueous mixture was extracted with $CHCl_3$ and the organic layer washed with brine and dried over Na_2SO_4. Removal of solvent afforded an orange solid, 568 mg (58% yield), mp 130−133 °C. Recrystallization from ethyl acetate/hexanes afforded an analytically pure orange crystalline solid, mp 142 °C: IR (KBr) 3450, 3071, 2995, 2894, 1574, 1469, 1278 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 6.86 (d, 1H), 6.90 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 36.06, 36.13, 116.9, 120.8, 150.7. Anal. Calcd for $C_4H_6N_2Se$: C, 29.83; H, 3.76; N, 17.40. Found: C, 29.71; H, 3.71; N, 17.19.

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