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S-2-Naphthylmethyl Thioacetimidate Hydrobromide: A New Odorless Reagent For The Mild Synthesis Of Substituted Acetamidines

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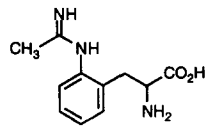
Abstract: *The development, synthesis and use of S-2-naphthylmethyl thioacetimidate hydrobromide* ***7*** *as a highly reactive reagent for the mild conversion of amines to substituted acetamidines in a nonodorous process is described.* Copyright © 1996 Elsevier Science Ltd

The synthesis of amidines has been known for over a century.[1] Pinner's landmark work in 1892 describing imidate chemistry still represents the most practical and useful method for preparing amidines.[2] During our course of investigations relating to the development of novel nitric oxide synthase inhibitors, we targeted the substituted acetamidine **1** for synthesis as a conformationally restricted analogue of the known inhibitor **L-NIO**. Our attempts to convert the aromatic amine **2** to the acetamidine intermediate **3**



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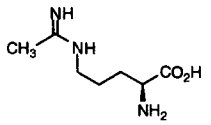
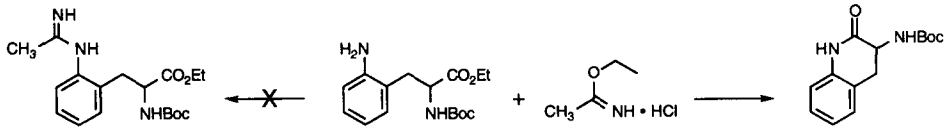


L-NIO

with O-ethylacetamidate failed completely. The bicyclic lactam **4** was the sole product detected. Hence, we required a reagent with sufficient reactivity to preclude intramolecular lactam formation.

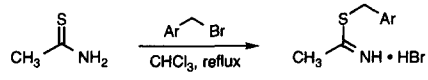


3 **2** **4**

The enhanced leaving group properties of thiols compared to alcohols suggested that a thioimidate derived reagent may prove adequetly reactive toward non-nucleophilic aromatic amines to successfully effect our desired amidine formation process. A major drawback to employing thioimidates is the strongly unpleasant odor resulting from the liberated thiol. As a result, synthetic strategies have not

exploited thioimidates as often as imidates. To our knowledge, a versatile thioimidate reagent to synthesize substituted acetamidines has not been reported.[3]

Our initial efforts focused on the use of S-benzyl thioacetimidate hydrobromide **6**. Examination of the literature reveals this thioimidate has been used to synthesize unsymmetrical sulfides from alkyl halides under phase transfer catalysis.[4] Additionally, fused heterocyclic s-triazolo[4,3-a]pyrazines have been constructed from 2-hydrazinopyrazines via condensation with S-benzyl thioacetimidate.[5] We found that treatment of amine **2** with thioimidate **6** in EtOH (0°C to room temperature, 18h) successfully afforded our desired acetamidine intermediate **3**, albeit in only 30% isolated yield. The competing intramolecular lactamization product **4** was also obtained. This result exemplifies the greater reactivity of thioimidates versus imidates and prompted us to explore the potential of this class of reagent for the general synthesis of amidines.



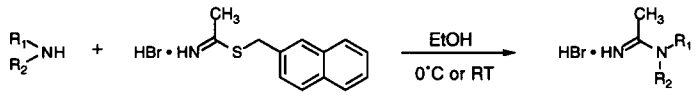
5

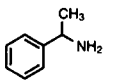
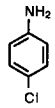
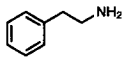
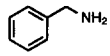
6 R = Ph (92%)
7 R = 2-Naphthyl (89%)

The conversion of amines to acetamidines with thioimidate **6** proceeds efficiently. However, the obnoxious odor generated by the liberated benzyl mercaptan is quite unappealing. Alternatively, 2-naphthylmethyl replacement of the benzyl group provides the equally proficient reagent **7** for the synthesis of acetamidines from amines but advantageously generates an odorless thiol by-product which is easily separated from the reaction mixture upon work up. S-2-Naphthylmethyl thioacetimidate hydrobromide **7** is a stable white solid readily synthesized in high yield by alkylation of thioacetamide **5** with 2-bromomethylnaphthalene in refluxing chloroform. Treatment of amines with one equivalent of naphthylmethyl thioimidate **7** in EtOH cleanly affords substituted acetamidines in excellent yields. The reactions are simplistically worked up by concentrating at reduced pressure and partitioning the resulting residue between water and Et_2O. The aqueous layer is separated and lyophilized to afford the targeted acetamidine as it's hydrogen bromide salt. In most cases, the product is isolated from this process in analytically pure form.

The reaction of thioimidate **7** with representative primary, secondary, benzylic and aromatic amines was examined. The results of this survey are described in Table 1. Most reactions proceed at 0°C, but the rate of reaction is dependent upon the nucleophilicity of the reacting amine. For example, the conversion of benzylamine to N-benzylacetamidine is complete within 10 minutes at 0°C. Even the poorly nucleophilic aromatic amine aniline is completely converted to N-phenylacetamidine in only 10 minutes at 0°C displaying the high reactivity of this reagent. Comparatively, the less nucleophilic 4-chloroaniline

Table 1. Synthesis of substitutued acetamidines from amines.



Amine	Conditions	Yield[a]	Amine	Conditions	Yield[a]
	0°C , 10 min	98%		0°C to rt, 1.5 h	98%
	0°C , 8 h	98%		0°C , 10 min	99%
	0°C to rt, 4 h	69%		0°C to rt, 1.5 h	99%
	0°C , 10 min	95%		0°C to rt, 1.5 h	98%

[a] All compounds gave satisfactory ^{1}H NMR, mass spectrometry, capillary electrophoresis, and combustion analyses.

requires longer reaction time for complete conversion. Thioimidate **7** failed to react with the non-nucleophilic amine 4-nitroaniline even at room temperature.

We have developed a highly reactive thioimidate reagent allowing the efficient conversion of amines to acetamidines in a nonodorous procedure. The very mild reaction conditions and simplistic product isolation process provide easy access to substituted acetamidines. S-2-Naphthylmethyl thioacetimidate hydrobromide **7** should prove to be a versatile reagent applicable to the synthetic design of acetamidines.

Synthesis of S-2-Naphthylmethyl Thioacetimidate Hydrobromide 7. To a stirred solution of thioacetamide (32.6 g, 434 mmol) in $CHCl_3$ (1 L) was added 2-bromomethylnaphthalene (100 g, 434 mmol). The mixture was heated to reflux for 1.5 h, cooled to room temperature and placed in an ice

bath. The resulting solid was collected and dried in vacuo to afford **7** (115.5 g, 89%) as a white solid. mp=220-221°C. 200 MHz ^{1}H NMR (DMSO-d_6) δ 2.69 (3H, s), 4.81 (2H, s), 7.58 (3H, m), 7.99 (4H, m), 11.93 (1H, bs). Anal. Calcd. for $C_{13}H_{14}NSBr$: C, 52.71; H, 4.76; N, 4.73; S, 10.82; Br, 26.97. Found: C, 52.73; H, 4.84; N, 4.63; S, 10.73; Br, 27.03.

General Synthesis of Substituted Acetamidines. To a stirred, cooled (0°C) solution of amine (10.0 mmol) in EtOH (30 mL) was added S-2-naphthylmethyl thioacetimidate hydrobromide **7** (10.0 mmol). The resulting suspension eventually becomes homogeneous. Thin layer chromatography was used to monitor the progress of the reaction. Reactions are warmed to room temperature to facilitate complete conversion when necessary. Upon complete reaction, the mixture was concentrated at reduced pressure and partitioned between water and Et_2O. The aqueous layer was separated, washed with Et_2O and lyophilized to afford the desired acetamidine hydrobromide.

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