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Efficient synthesis of primary 2-aminothiols from 2-aminoalcohols and methyldithioacetate

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ABSTRACT

Various primary 2-aminothiols have been prepared by a general and efficient method, in three steps, starting from commercially available 2-aminoalcohols and methyldithioacetate as a convenient source of sulfur.

2-Aminothiols constitute an important class of compounds for medicinal and synthetic chemistry. Some of them (e.g., cysteine, homocysteine, cysteamine, and penicillamine) are naturally occurring and are involved in important biological processes. They are constituents of complex biomolecules such as peptides and coenzyme A. Their biological and physicochemical specificities are especially due to the properties of the thiol function (acidity, metal affinity). They found various applications as enzyme inhibitors,[1] radioprotective agents,[2] as intermediates for the synthesis of a number of biologically active compounds,[3] or in peptide synthesis (when attached through their thiol group on resins[4]). More recently, 2-aminothiols and their thioethers derivatives have been used as ligands for organometallic catalysis.[5]

Most of the methods reported for the preparation of 2-aminothiols start from 2-aminoalcohols. The main drawback of these methods is probably that a multi-step sequence is generally required, including addition of a sulfur nucleophile and protection/deprotection of amino and thiol groups.[6] A few other methods are limited by less accessible starting materials such as thiiranes,[7] aziridines,[8] or 2-thiazolidinones.[9] Thus, developing a convenient method for the synthesis of a wide range of 2-aminothiols remains a challenge for organic chemists.

This Letter describes an efficient and general method to prepare primary 2-aminothiols via thiazolines. Although the use of 2-aminothiols as precursors of thiazolines is well known in organic synthetic chemistry,[10] the opposite process, which consists of preparing a primary aminothiol via a thiazoline, was used only in a few cases[11] but, to our knowledge, was never described and developed as a general method for such purpose. The method uses simple starting materials: commercially available 2-aminoalcohols and a dithioester which are easy to access and handle.

Various enantiopure 2-amino alcohols **1a**–**h** (see Table 1) have been transformed into the corresponding aminothiols using methyldithioacetate ($MeCS_2Me$) as the sulfur source.[12] Thiazoline precursors **3** were prepared using a two-step sequence that was previously reported by some of us.[13] Thus, in a first step, thioacylation of the aminoalcohols using methyldithioacetate led to thioamides **2**, which were transformed in a second step by intramolecular cyclization via a mesylate into thiazolines **3** (Scheme 1). Yields obtained after each step are given in Table 1. The obtained thiazolines were hydrolyzed in acidic medium in a refluxing 5 M aqueous solution of HCl. After 12–72 h, the desired aminothiols **4a**,**c**–**f** were obtained and isolated as their hydrochloride derivatives in good yields (Scheme 1, Table 1). The hydrolysis of thiazoline **3b** was particularly slow; the reaction was stopped after 192 h at 70% conversion, which explains the lower yield (58% obtained for aminothiol **4b**).

In the case of thiazoline **3g** derived from L-serine methyl ester, the acidic hydrolysis also transformed the ester group into the carboxylic acid derivative, leading to product **4g′** (Scheme 1, Table 1). This product, which represents the L-cysteine hydrochloride, was compared with a commercial sample,[14] and the two compounds were found to be identical (same ^{1}H NMR spectra and $[\alpha]_D$). In

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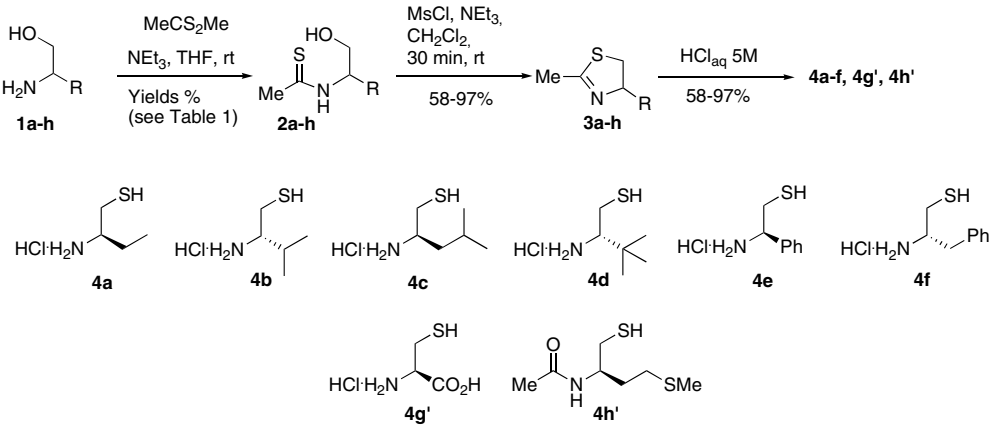
Table 1
Transformation of 2-aminoalcohols **1** into 2-aminothiols **4** (amino alcohol→thioamide→thiazoline→aminothiol)

Amino alcohol	R	Configuration	Thioamide **2** (yield %)	Thiazoline **3** (yield %)	Aminothiol **4** (yield %)
2-Aminobutanol **1a**	Et	*R*	**2a** (89)	**3a** (52)	**4a** (84)
L-Valinol **1b**	*i*-Pr	*S*	**2b** (78)	**3b** (63)	**4b** (58)[a]
L-Leucinol **1c**	*i*-Bu	*S*	**2c** (93)	**3c** (86)	**4c** (97)[a]
L-*tert*-Leucinol **1d**	*t*-Bu	*S*	**2d** (43)	**3d** (71)	**4d** (82)[a]
2-Phenylglycinol **1e**	Ph	*R*	**2e** (89)	**3e** (58)	**4e** (94)[a]
L-Phenylalaninol **1f**	Bn	*S*	**2f** (65)	**3f** (60)	**4f** (81)[a]
L-Serine methyl ester **1g**	CO_2Me	*S*	**2g** (90)	**3g** (71)	**4g′** (94)[a,b]
L-Methioninol **1h**	CH_2CH_2SMe	*R*	**2h** (97)	**3h** (73)	**4h′** (87)[c]

[a] Isolated as the hydrochloride salt.
[b] The carboxylic acid derivative **4g′** was obtained under acidic hydrolysis conditions from **3g** (transformation of R = CO_2Me into CO_2H).
[c] The *N*-acetyl aminothiol **4h′** was obtained from **3h** instead of the N-deprotected derivative.



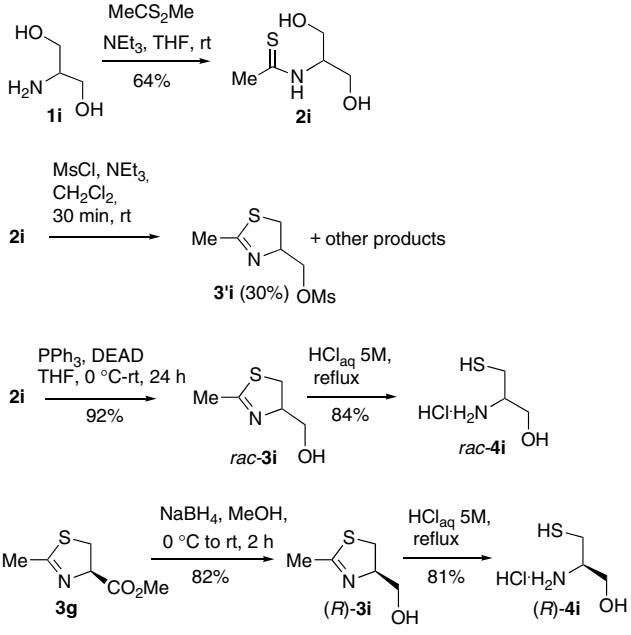
Scheme 1.

the case of thiazoline **3h** derived from L-methioninol, the acidic hydrolysis at reflux led to a complex mixture of products. Performing the reaction at room temperature for 16 h afforded *N*-acetyl aminothiol **4h′**, which was the expected product resulting from the thiazoline ring-opening without deprotection of the amino group (Scheme 1, Table 1).

With achiral 2-amino-1,3-propanediol **1i**, thioamide **2i** was easily prepared by thioacylation of **1i** with methyldithioacetate (Scheme 2). When the intramolecular cyclization was performed via a mesylate, a mixture of products was obtained, from which only the O-mesylated thiazoline **3i′** was isolated in low yield (30%) and characterized. By using Mitsunobu reaction conditions, the racemic thiazoline **3i** bearing unprotected hydroxy group was obtained in excellent yield (92%). Acidic hydrolysis at reflux of this thiazoline led to the expected aminothiol hydrochloride *rac*-**4i** in good yield (84%). To access this aminothiol in enantiopure form, the carboxylic ester function of thiazoline **3g** was first reduced with $NaBH_4$ into alcohol to give the corresponding enantiopure thiazoline (*R*)-**3i**, which was then hydrolyzed under acidic conditions to afford the desired aminothiol **4i** as its *R*-enantiomer.

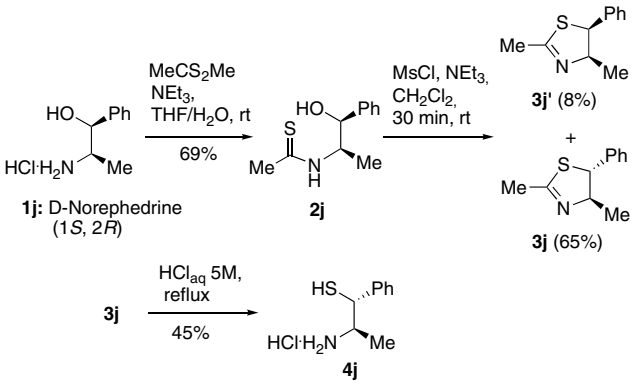
Finally, the methodology was tested on one example of 1,2-disubstituted aminoalcohol, the D-norephedrine. The thioacylation led to thioamide **2j** in 69% yield. The intramolecular cyclization via a mesylate led to the expected thiazoline **3j** (with inversion of configuration at the carbon bearing the hydroxy group) as the major product, together with its diastereomer **3j′**, which results from a partial epimerisation at the benzylic position under the conditions used (Scheme 3). The two diastereomers were separated by chromatography on silica gel to give pure **3j** (65%) and **3j′** (8%).

In conclusion, we have succeeded in preparing various primary 2-aminothiols, most of them in an enantiopure form, by a general and efficient method, starting from commercially available



Scheme 2.

2-aminoalcohols and methyldithioacetate as a convenient source of sulfur.[15] Compared to other methods starting from an aminoalcohol, our method reduces the reaction sequence to three steps, by combining the introduction of the sulfur atom and the protection of the amino group in the thioacylation step, the deprotection of both amino and thiol functions through thiazoline formation



Scheme 3.

and the acidic hydrolysis of the thiazoline. The extension of the method to access secondary aminothiols is currently under investigation in our laboratory.

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Supplementary data

Supplementary data (spectral data of compounds **2a–j**, **3a–j**, **4a–g**, **4i**, and **4j**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.014.

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14. The sample was purchased from Sigma–Aldrich.
15. *Typical procedure to transform 2-aminoalcohol* **1** *into the corresponding 2-aminothiol* **4**, *in three steps*:
(i) *Thioacylation*: A mixture of 2-aminoalcohol (47 mmol), methyldithioacetate (5 g, 47 mmol, 1 equiv), and triethylamine (6.6 mL, 47 mmol, 1 equiv) in THF (7 mL) was stirred at room temperature for 15 h. Then, the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford thioamide **2**.
(ii) *Cyclization*: Under nitrogen atmosphere, to a stirred mixture of thioamide **2** (15 mmol) and mesylchloride (1.7 mL, 22.5 mmol, 1.5 equiv) in dichloromethane (25 mL) was added dropwise triethylamine (6.3 mL, 45 mmol, 3 equiv) at 0 °C. Stirring was maintained at room temperature for 30 min, then Et_2O (15 mL) was added to precipitate the triethyl ammonium salt. After filtration, solvents were evaporated and the residual oil was purified by flash chromatography on silica gel affording thiazoline **3**.
(iii) *Hydrolysis*: Thiazoline **3** (2 mmol) was placed in a degazed aqueous solution of HCl 5 N (10 mL), under nitrogen atmosphere. The mixture was heated under reflux for 24–192 h. After cooling to room temperature, the aqueous layer was washed with ether (3 × 5 mL), then with dichloromethane (3 × 5 mL). After removal of the water under vacuum, the residue was triturated with acetone, filtered, and dried to give the corresponding aminothiol hydrochloride **4**.