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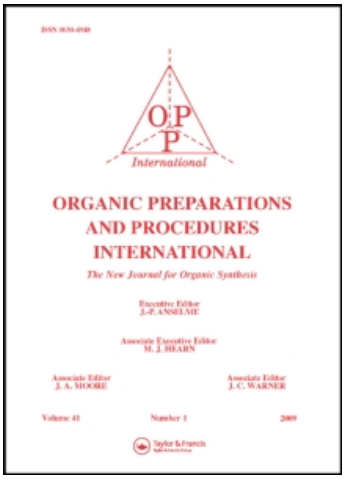

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FACILE PREPARATION OF TERMINALLY FUNCTIONALIZED THIOLS FROM 6-BROMOHEXANENITRILE

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OPPI BRIEFS

FACILE PREPARATION OF TERMINALLY FUNCTIONALIZED THIOLS FROM 6-BROMOHEXANENITRILE

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(5/19/06)

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Functionalized thiols have found utility in numerous applications ranging from DNA/RNA sequencing[1] to the detection of chemical agents and biological pathogens.[2] The demand for this class of compound is also attributed to recent expansion within the self-assembly arena.[3-5] Although there are a variety of reported transformations that result in thiol formation, many are limited in scope or functionality. While many of these transformations are successful, oxidation to the disulfide frequently occurs during subsequent isolation and purification steps. In addition, the transformations do not occur in the presence of sensitive functionalities to afford substrates suitable for subsequent self-assembly schemes, as desired by our laboratory.

Because of the extreme versatility and responsiveness of multi-functional thiols in which the thiol is separated from other functional groups by six methylene groups, we attempted to synthesize such thiols possessing the nitrile, amide, and imidoximine functionalities for investigation in a series of evaluative experiments to determine utility in chemical detection environments. The separation by six carbons is important in that it prevents auto-cyclization of the molecule and affords a densely-packed molecule which does not allow folding to occur. Furthermore, it was necessary to incorporate other functionalities into the thiol molecule in an attempt to increase sensitivity and reactivity toward target vapors. Because of their unique chemical properties and potential application in self-assembly synthetic schemes, we have developed synthetic approaches which involve the incorporation of functionalities such as imidoximines, nitriles, and amides, all of which have shown previous success in similar applications.[6]

A common method for conversion of an alkyl halide into the corresponding thiol makes use of thiourea.[7] This effective multi-step reaction sequence displaces the halide *via* nucleophilic substitution with thiourea, followed by hydrolysis employing sodium hydroxide to afford the sodium salt of the thiol, which upon subsequent acidification affords the corresponding thiol. This method is quite effective on a variety of substrates; however, cannot be employed on those that possess pH-sensitive functionalities.

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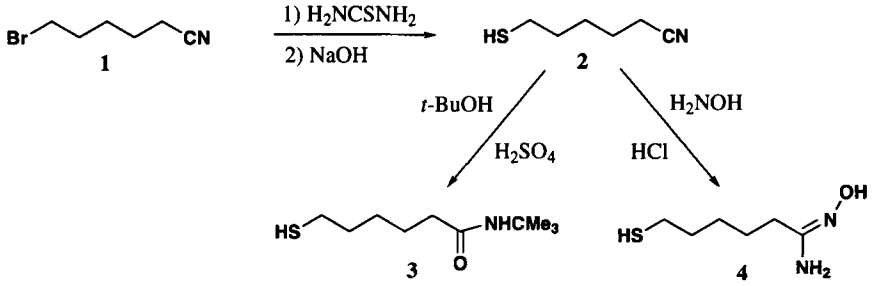
In our reported sequence, 6-bromohexanenitrile (**1**) was converted to the corresponding thiol (**2**) employing thiourea followed by hydrolysis employing sodium hydroxide and subsequent protonation. We were pleased to learn that conversion of the alkyl bromide into the corresponding thiol was achieved without degradation of the nitrile. These conditions are aggressive enough for high conversion, yet mild enough to avoid decomposition of the nitrile functionality present in the molecule. In our laboratory, compound **2** is, in itself, of utility; however, it may also be subjected to subsequent reaction conditions to afford two additional terminally functionalized thiols. When **2** was treated under modified Ritter conditions[8], the nitrile was easily transformed into the corresponding amide (**3**) in a single step in an 82% yield. Likewise, making use of the same starting material, conversion of the nitrile (**2**) into the amidoxime (**4**) is easily accomplished upon treatment with hydroxylamine hydrochloride in a 78% yield.



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EXPERIMENTAL SECTION

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were taken on a Bruker 300 MHz spectrometer. FTIR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. The elemental analyses were performed by Atlantic Microlab, Norcross, GA 30071. Diethyl ether and THF were both distilled from sodium/benzophenone under nitrogen before use.

6-Mercaptohexanenitrile (2).- Into a Schlenk tube equipped with magnetic stir bar and a positive flow of nitrogen was placed 6-bromohexanenitrile (5.00 g, 28.40 mmol), thiourea (2.37 g, 31.23 mmol) and 17 mL absolute ethanol. The combined solution was heated at 97°C for 3 hr. After slowly cooling to rt, H_2O (0.50 g) and NaOH (1.60 g) was added and once again the reaction mixture was allowed to reflux for an additional 3 hr. A yellow precipitate began to form upon the addition of the base. The workup consisted of dilution with an additional 17 mL H_2O followed by acidification to pH 5 with 1M HCl. The resulting mixture was then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were then washed with H_2O (25 mL) and organic layer dried over $MgSO_4$ prior to concentration under reduced pressure. Distillation employing a short still head at 67-69°C (1 torr) afforded the desired product (2.61-2.86 g, 71-78%). FTIR: 2934, 2862, 2573, 2244, 1459, 1427, 1356, 1285, 1249 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (q, J = 6, 2H), 2.37 (t, J = 6, 2H), 1.74-1.51 (m, 6H), 1.37 (t, J = 4, 1SH); ^{13}C NMR

($CDCl_3$): δ 119.4, 32.9, 27.1, 24.7, 24.0, 16.9; MS *m/Z* = 129; see ref.[9] for an explanation of nitrile analysis using mass spectroscopy. Spectroscopic data correlates with that previously reported.[10]

6-Mercaptohexanoic acid *tert*-butylamide (3).- Into a 50 mL round bottomed flask were placed 6-mercaptohexanenitrile (1.00 g, 7.74 mmol), *tert*-butanol (1.14 g, 15.48 mmol), HOAc (7.75 mL) and conc. H_2SO_4 (1.55 g). The reaction mixture was allowed to stir for 12 hr at rt over which time a bright pink color developed. Workup consisted of dilution with 25 mL H_2O and neutralization with potassium carbonate. The neutral mixture was extracted with CH_2Cl_2 (3 x 30 mL) and washed with H_2O (2 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Final traces of solvent were removed upon storage for 2 hr under vacuum to afford the product as a colorless viscous oil (1.29 g, 82%). FTIR: 3310, 3072, 2958, 2921, 2858, 2597, 1645, 1546, 1455, 1391, 1368, 1225, 1165, 936 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.37 (bs, 1-NH), 2.53 (t, *J* = 7, 2H), 2.08 (t, *J* = 7, 2H), 1.65-1.56 (m, 4H), 1.43-1.31 (m, 2H), 1.33 (d, *J* = 8, 9H); ^{13}C NMR ($CDCl_3$): δ 172.2, 50.9, 41.7, 37.3, 30.9, 29.5, 28.1, 25.3.

Anal. Calcd for $C_{10}H_{21}NOS$: C, 59.07; H, 10.41; N, 6.89. Found: C, 59.31; H, 10.69; N, 6.62.

***N*-Hydroxy-6-mercaptohexanamidine (4).**- A freshly cut piece of sodium metal (0.117 g, 5.11 mmol) was combined with 1-butanol (6 mL) and allowed to stir at room temperature for 1 hr until all of the sodium metal had dissolved. To the reaction mixture was added hydroxylamine hydrochloride (0.332 g, 4.64 mmol). The resulting reaction mixture was allowed to stir at rt for 1 hr followed by the addition of 6-mercapto-hexanenitrile (0.90 g, 6.96 mmol). The reaction mixture was allowed to stir at room temperature for 12 hr and then diluted with 30 mL Et_2O. The organic layer was washed with deionized H_2O (3 x 15 mL) and the organic layer was concentrated under reduced pressure. The resulting white semi-solid product was placed under vacuum for an additional 4 hr to remove traces of residual alcohol. Upon drying, the product was treated with 5 mL of Et_2O at rt and stirred gently. The insoluble white precipitate (mp 119-123°C) was collected as pure product (0.59 g, 78%). FTIR: 3326, 2930, 2854, 2517, 2462, 2394, 1633, 1526, 1455, 1412, 956 cm^{-1}; ^1H NMR (CD_3OD): δ 2.73-2.67 (m, 3H), 2.45 (t, *J* = 7, 2H), 2.20 (t, *J* = 7, 2H), 1.76-1.54 (m, 6H), 1.43 (t, *J* = 6, 1-SH); ^{13}C NMR (CD_3OD): δ 178.6, 38.4, 34.2, 26.3, 23.6, 18.7.

Anal. Calcd for $C_6H_{14}N_2OS$: C, 44.41; H, 8.70; N, 17.27. Found: C, 44.58; H, 8.52; N, 16.99.

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A PRACTICAL METHOD FOR PHOSPHORYLATION OF COMBRETASTATIN A-4 WITH PHOSPHORUS OXYCHLORIDE

Submitted by (06/02/06)

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Isolated from the South African tree *Combretum caffrum*, combretastatin A-4 **1** (**CA-4**)[1] is one of the most promising experimental anticancer drugs, targeting tumor vasculature.[2] The combretastatin A-4 disodium phosphate prodrug **3** (**CA-4P**) has emerged as the most useful form of this compound in preclinical *in vivo* models, as well as in clinical trials,[2a] due to the limited solubility of the parent molecule in water.[3]

The synthetic methods reported for **3** (**CA-4P**) (*Scheme 1*) involve the two step reaction of the phenolic group of **CA-4** with *in situ* generated dibenzyl chlorophosphite[3,5,6] or dibenzyl bromophosphite[4] followed by cleavage of the benzyl esters with iodotrimethylsilane[3,5,6] or bromotrimethylsilane.[4] In an alternative procedure, dibenzyl halophosphite is replaced by *bis*