# Remarkably Fast Direct Synthesis of Thiols from Alcohols under Mild Conditions

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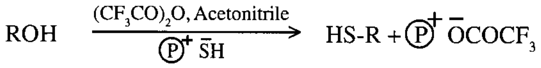
One pot rapid synthesis of thiols from alcohols via trifluoroacetates using polymer supported hydrosulfide in acetonitrile under mild conditions has been described.

Thiols are important not only for their use in the synthesis of organosulfur compounds but also for their roles in cell biochemistry.[1] Therefore, many synthetic methods have been developed.[2,3] Although direct preparations of thiols from alkyl halides and metal sulfides would be straightforward, direct methods give only a moderate yield of thiols accompanying a considerable amount of dialkyl sulfide.[2] Therefore, indirect methods involving thiourea,[2] xanthate[2] and thioacetate[2] are commonly utilized for the synthesis of thiols and other indirect methods have been reported.[4–9] These indirect methods usually give around 80% yield and no dialkyl sulfides or other undesired byproducts; however, intermediates have to be transformed to thiols by hydrolysis with base[5–9] or by reduction with lithium aluminium hydride.[10,11] Recently thiols have been prepared in quantitative yield from the corresponding thioacetates[2] and alkyl halides.[12]

We now report for the first time rapid and efficient method for direct synthesis of thiols from alcohols using trifluoroacetic anhydride and polymer supported hydrosulfide under mild condition (Scheme 1). It is worth commenting that this method produces thiols in excellent yields without any trace of dialkyl sulfide.



$$\mathrm{ROH} \xrightarrow[\text{Ⓟ}^{+}\ \bar{\mathrm{S}}\mathrm{H}]{(\mathrm{CF_3CO})_2\mathrm{O},\ \text{Acetonitrile}} \mathrm{HS\text{-}R} + \text{Ⓟ}^{+}\ \bar{\mathrm{O}}\mathrm{COCF_3}$$

**Scheme 1.**

The synthesis of thiols from alkyl halides and NaSH always results in the formation of dialkyl sulfide[13] because the alkyl thiols formed initially further react with excess of alkyl halide. Alcohols are cheap and easily available compared with alkyl halides. Attempts to prepare thiols from alcohols via the corresponding trifluoroacetates with NaSH required longer reaction time and resulted in poor yields. This is due to low solubility of NaSH in organic solvents. However alcohols via trifluoroacetates (which are not isolated as such) on treatment with polymer supported hydrosulfide under mild condition gave corresponding thiols in good yield in a very short time. This is because polymer supported hydrosulfide has more nucleophilic character than NaSH. The success of this transformation may also be attributed to the high nucleofugal character of the trifluoroacetate moiety in nucleophilic substitution,[14] which resembles that of triflates.[15]

Trifluoroacetylation was carried out in almost quantitative yield by treatment of the alcohol with an excess of trifluoroacetic anhydride. The reaction was complete in a few minutes at room temperature. The resulting trifluoroacetic acid and the excess of anhydride were evaporated off and the intermediate trifluoroacetate was treated in situ with polymer supported hydrosulfide in acetonitrile at 25 °C to give corresponding thiol in a very short time in essentially pure form and in good yield. The results are summarized in Table 1.

Various primary, secondary, tertiary, acyclic and cyclic alcohols, diols, benzylic alcohols are converted into corresponding thiols using trifluoroacetic anhydride and polymer supported hydrosulfide. Alcohols are selectively converted into thiols without interfering other functional groups such as carbonyl, methoxy, methylenedioxy, C=C, ester, THP ether, isopropylidenedioxy, boc, fmoc and phenolic OH. It is worth commenting that secondary alcohol in the presence of tertiary alcohol (entry 16), benzyl alcohol in the presence of primary alcohol (entry 17), benzyl alcohol in the presence of phenol (entry 18), and secondary alcohol in the presence of phenol (entry 19), is converted chemoselectively into corresponding thiol. In addition it is interesting to note that (+) optically active alcohol (entry 14) and (–) optically active alcohols (entries 4, 15, 17, 19) were converted into (–) optically active mercaptans and (+) optically active mercaptans respectively under these reaction conditions indicating that the reaction involves $S_N2$ mechanism. Optical rotation values of these alcohols and thiols are shown in Table 1.

Amberlite IRA- 400 ($Cl^-$) was procured from S. D. Fine Chemicals, Mumbai.

Procedure for preparation of polymer supported hydrosulfide: To a solution of NaSH (50 mmol) in distilled water (50 mL), Amberlite IRA 400 ($Cl^-$) (10 g) was added and mixture was shaken for 1 h. Then resin was filtered and washed with distilled water, ethanol, ether and then dried under vacuum at 50 °C for 2 h. The capacity of hydrosulfide exchange resin (by titration method) was found to be 1 mmol/g dry resin.

In a typical procedure, to a solution of (–)-menthol (5 mmol) in dichloromethane (10 mL) was added trifluoroacetic anhydride (6 mmol). The reaction mixture was stirred for 15 min at room temperature. The trifluoroacetic acid formed, along with the solvent is then evaporated off and the residue was diluted with acetonitrile (10 mL) which was treated with hydrosulfide supported resin (6 g, 6 mmol). The reaction mixture was stirred for 5 min at 25 °C. After completion of the reaction, the resin was filtered off and washed with dichloromethane (2 × 10 mL). Then, removal of the solvent under reduced pressure gave (+)-menthyl mercaptan in almost pure form. Yield = 88%; IR: 2565 $cm^{-1}$ (SH); $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 0.82 (d, 3H, $CH_3$), 0.90 (d, 3H, $CH_3$), 0.93 (d, 3H, $CH_3$), 1.52–2.6 (m, 10H), 3.12 (m, 1H); MS (70 eV): $m/z$ (%) = 172.27 (37) [$M^+$]; $C_{10}H_{20}S$ (172). Anal. Calcd for : C, 69.66; H, 11.61; S, 18.58%. Found: C, 69.71; H, 11.58; S, 18.61%.

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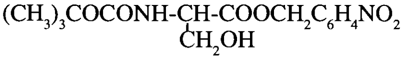
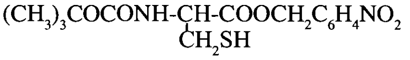
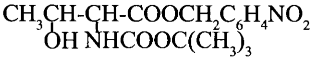
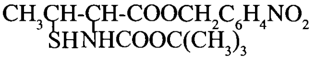
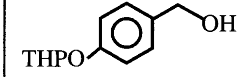
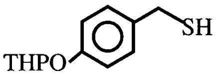
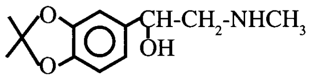
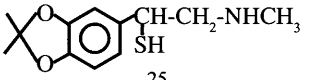
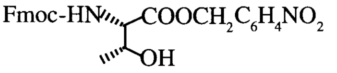
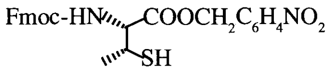
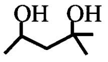
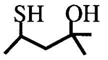
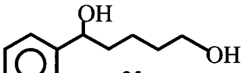
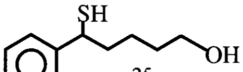
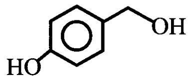
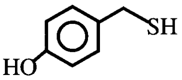
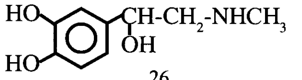
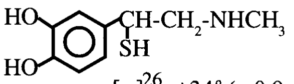
**Table 1**. Direct synthesis of thiols from alcohols

| Entry | Alcohol | Product | Yield/%[a,b] |
|---|---|---|---|
| 1. | Octadecanol | Octadecanethiol | 85 |
| 2. | 1,8-Octanediol | 1,8-Octanedithiol | 88 |
| 3. | Benzoin | Benzoin mercaptan | 78 |
| 4. | (–)-Menthol $[\alpha]_D^{20}$ -50° (c 10, $C_2H_5OH$) 99%ee | (+)-Menthyl mercaptan $[\alpha]_D^{23}$ +38° (c 10, $C_2H_5OH$)98.8%ee | 88 |
| 5. | Choresterol | Cholestryl mercaptan | 73 |
| 6. | t-Butyl alcohol | t-Butyl mercaptan | 75 |
| 7. | 4-Bromobenzyl alcohol | 4-Bromobenzyl mercaptan | 78 |
| 8. | 4-Methoxy benzyl alcohol | 4-Methoxy benzyl mercaptan | 83 |
| 9. | 3,4-Methylenedioxy benzyl alcohol | 3,4-Methylenedioxy benzyl mercaptan | 68 |
| 10. | Cinnamyl alcohol | Cinnamyl mercaptan | 70 |
| 11. |  $(CH_3)_3COCONH\text{-}\underset{CH_2OH}{CH}\text{-}COOCH_2C_6H_4NO_2$ |  $(CH_3)_3COCONH\text{-}\underset{CH_2SH}{CH}\text{-}COOCH_2C_6H_4NO_2$ | 85 |
| 12. |  $CH_3\underset{OH}{CH}\text{-}\underset{NHCOOC(CH_3)_3}{CH}\text{-}COOCH_2C_6H_4NO_2$ |  $CH_3\underset{SH}{CH}\text{-}\underset{NHCOOC(CH_3)_3}{CH}\text{-}COOCH_2C_6H_4NO_2$ | 81 |
| 13. |  |  | 87 |
| 14. |  $[\alpha]^{25}D$ -37° (c 1.1, $CH_3OH$) 99.4% ee |  $[\alpha]_D^{25}$ +27° (c 1.3, $CH_3OH$) 99.1% ee | 88 |
| 15. |  $[\alpha]_D^{25}$ -38° (c 1.5, $CHCl_3$)99.5% ee |  $[\alpha]_D^{25}$ +43° (c 1.5, $CHCl_3$) 99.4% ee | 87 |
| 16. |  |  | 84 |
| 17. |  $[\alpha]_D^{25}$ -38.5° (c 1.2, $CH_3OH$) 88%ee |  $[\alpha]_D^{25}$ +17° (c 1.2, $CH_3OH$) 87.5% ee | 86 |
| 18. |  |  | 87 |
| 19. |  $[\alpha]_D^{26}$ -41.5° (c 0.9, $CH_3OH$) 94% ee |  $[\alpha]_D^{26}$ +34° (c 0.9, $CH_3OH$) 93.2 % ee | 81 |

[a] Yields are of pure isolated products. [b] Products are characterized by their physical constants[15], IR, $^1H$ NMR and comparison with authentic samples.

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