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$ZrCl_4$ dispersed on dry silica gel provides a useful reagent for S-alkylation of thiols with alcohols under solvent-free conditions

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Abstract—$ZrCl_4$ which is commercially available and not a costly compound, is a relatively safe chemical [LD_{50} [$ZrCl_4$, oral rat] = 1688 mg Kg]. In this report we describe the use of $ZrCl_4$ dispersed on dry silica gel as an efficient reagent for the efficient preparation of thioethers from thiols with alcohols under solvent-free conditions.

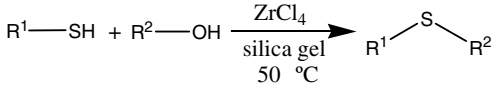
Versatile synthetic uses of thioethers in both bioorganic and organic chemistry have ensured many studies of their preparation by different methods. The thioether linkage has been used to prepare cyclic analogues of acyclic polypeptides to restrict their conformational mobility and thus to increase their biological activity and stability against biodegradation.[1–4] They are also useful heteroatomic functional groups in organic synthesis, for example, by oxidation of thioethers, chiral sulfoxides can be generated which can be used as auxiliaries in asymmetric synthesis.[5–8] Moreover, sulfones have been employed for stabilizing α-radicals[9] and α-anions,[10] can act as cationic synthons,[11] and also for the formation of C–C bonds.[12]

A variety of methods is available for the preparation of thioethers, such as, deoxygenation of sulfoxides,[13,14] displacement of leaving groups with sulfur nucleophiles,[15,16] addition of thiols to carbonyl compounds followed by in situ reduction of the generated intermediate thionium ion,[17] anti-Markovnikov addition of arene- and alkane–thiols to alkenes,[18,19] Mitsunobu-type reactions,[20–24] metal-mediated cross-coupling processes,[25–27] and metal catalyzed hydrothiolation of alkynes.[28] These reported methods have been recently reviewed.[29,30]

However, in the majority of cases reported, the thioethers have been prepared using expensive and commercially unavailable materials,[23,26] hazardous and corrosive compounds such as, alkylating agents,[24] strong reducing agents,[17] harsh reaction conditions and involve tedious work-up procedures.[29,30] Additionally, some of the reported methods cannot be used for the preparation of different structurally and electronically diverse thioethers. For example, by applying modified Mitsunobu conditions using liquid trimethylphosphine combined with 1,1′-(azodicarbonyl)dipiperidine (a hazardous material) in the presence of imidazole, aliphatic thiols react only with primary alcohols to give thioethers. Other types of thiols and alcohols did not react.[20]

In continuation of our interest in exploring new applications of $ZrCl_4$ in organic synthesis,[31–34] we report that $ZrCl_4$ dispersed on dry silica gel allows the efficient preparation of thioethers by the reaction of thiols with alcohols under solvent-free conditions (Scheme 1).

In order to optimize the reaction conditions, condensation of benzyl alcohol with 4-methylthiophenol was studied as a model reaction in the presence of $ZrCl_4$. We observed that a sticky reaction mixture was obtained



Scheme 1.

Keywords: Zirconium tetrachloride; Alcohols; Thiols; Silica gel; Thioether; Solvent free.
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Table 1. S-Alkylation of thiols with alcohols using $ZrCl_4$ dispersed on dry silica gel under solvent-free conditions[a]

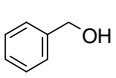
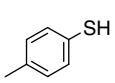
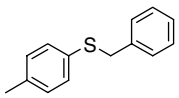
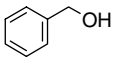
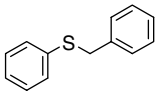
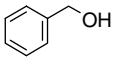
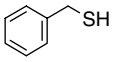
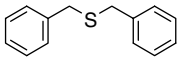
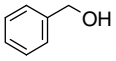
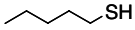
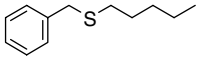
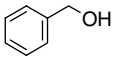
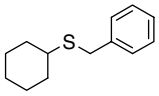
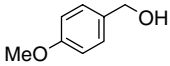
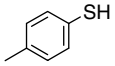
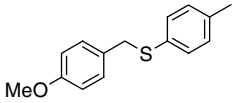
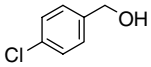
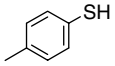
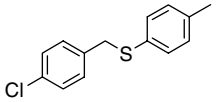
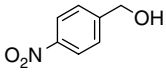
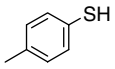
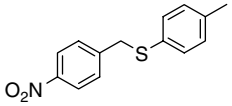
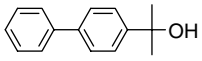
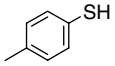
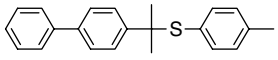
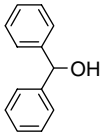
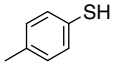
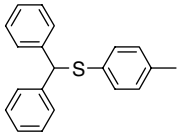
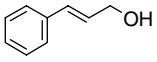
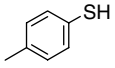
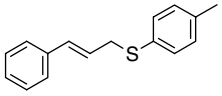
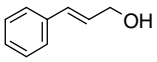
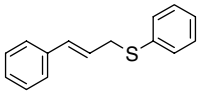
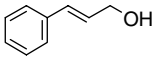
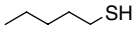
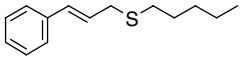
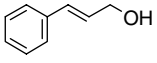
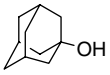
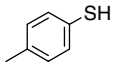
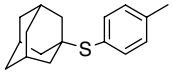
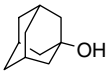
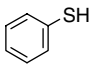
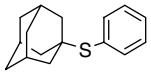
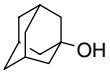
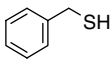
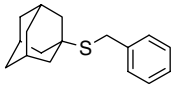
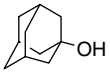
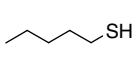
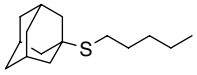
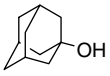
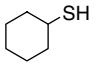
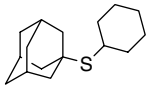
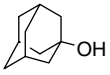
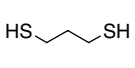
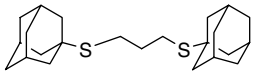
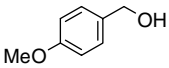
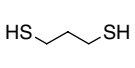
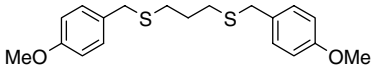
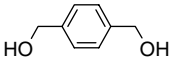
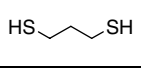
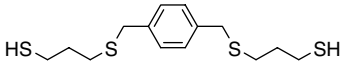
Entry	Alcohol	Thiol	Product[b]	Time (min)	Conversion	Isolated yield (%)
1				5	100	94
2				15	95	90
3				40	60	53
4				25	80	75
5				20	93	87
6				2	100	94
7				25	100	94
8				60	56	50
9				4	100	95
10				3	100	95
11				5	100	95
12				15	96	92
13				10	93	88
14				8	96	90
15				180	20	—
16				180	15	—
17				10	100	80

Table 1 (*continued*)

Entry	Alcohol	Thiol	Product[b]	Time (min)	Conversion	Isolated yield (%)
18				7	100	94
19				10	100	96
20				30	100	95
21				15	100	94
22				15	100	95
23[c]				20	100	95
24[c]				10	100	96
25[d]				20	100	94

[a] The reactions were run at 50 °C and the molar ratio of alcohol/thiol/$ZrCl_4$ was 1:1.1:0.5.
[b] All products were identified by their ^1H NMR, ^{13}C NMR and MS spectral data and elemental analysis.
[c] The molar ratio of alcohol/thiol/$ZrCl_4$ was 2:1.1:1.
[d] The molar ratio of alcohol/thiol/$ZrCl_4$ was 1:2.1:1.

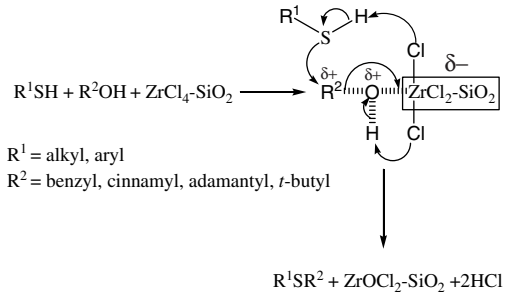
with the formation of the corresponding thioether in around 50–60% yield. Increasing the reaction time did not affect the yield of the product. We found that, using benzyl alcohol (1 mmol), 4-methylthiophenol (1.1 mmol) and $ZrCl_4$ (0.5 mmol) dispersed on 0.3 g of molecular sieves, alumina, or silica gel, in the absence of solvent, the reaction proceeded very cleanly at 50 °C and the corresponding thioether was isolated in 94% yield. We also tried a similar reaction in the presence of molecular sieves, alumina or silica gel *without* using $ZrCl_4$. The reaction was not successful and the starting materials remained intact. $ZrCl_4$ dispersed on dry silica gel was used for the remainder of this study for the preparation of other thioethers.

We found that this method was applicable for the preparation of thioethers from the reaction of cinnamyl alcohol, adamantanol and structurally and electronically diverse benzyl alcohols with aromatic or aliphatic thiols and also with dithiols.[35,36] We noted that electronic factors play a role in these reactions. Aromatic alcohols substituted with electron-donating groups reacted faster than those substituted with electron-withdrawing groups and also provided the thioethers in higher yields (Table 1, entries 6–9). This method is also useful for the high yielding preparation of dithioethers using dithiols (Table 1, entries 23 and 24). We have also used this method for the efficient preparation of dithioethers,[37] (Table 1, entry 25) which could be used as precursors for the preparation of macrocyclic or polymeric sulfur-containing compounds.

Primary and secondary aliphatic alcohols do not react with thiols in the presence of this reagent and remain mostly intact after the typical reaction times (Table 1, entries 15 and 16).

Generation of a classical carbocation is improbable in these reactions. Adamantanol, because of its structure, does not allow the generation of a classical carbocation (Table 1, entry 18). In addition, the reaction of 2-(4-biphenyl-4-yl)-2-propanol (Table 1, entry 9) was not accompanied by the production of its corresponding olefin as an elimination by-product. The low yield and the rather slow rate of the reaction involving 4-nitrobenzyl alcohol is an indication of the generation of an unstable *partially* positively charged intermediate (Table 1, entry 8). By considering these facts, we may suggest the following mechanism for the reaction (Scheme 2).

In conclusion, we have described a new application of $ZrCl_4$ dispersed on dry silica gel for the easy and efficient synthesis of different thioethers by the reaction of aliphatic and aromatic thiols with cinnamyl alcohol, adamantanol and structurally and electronically diverse benzyl alcohols under solvent-free conditions. The method is not suitable for the preparation of thioethers from saturated primary and secondary alcohols.



Scheme 2.

Dithiols have also been used successfully for the preparation of their corresponding dithioethers using structurally different alcohols in excellent yields. We believe that this procedure provides a valuable addition to current methodologies.

Selected spectral data of thioethers: (Table 1, entry 1): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 2.28 (s, 3H), 4.05 (s, 2H), 7.10–7.68 (m, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 21.08, 39.23, 128.55, 129.71, 130.15, 131.79, 132.822, 136.49, 136.94; MS (m/e) = 214 $[M]^+$. Anal. Calcd for ($C_{14}H_{14}S$): C, 78.46; H, 6.58. Found: C, 78.48; H, 6.61. (Table 1, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 0.82 (m, 6H), 1.33 (m, 4H), 1.55 (m, 1H), 4.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 24.9, 27.6, 33.7, 36.5, 38.9, 127.9, 128.8, 129.1, 139.4; MS (m/e) = 206 $[M]^+$. Anal. Calcd for ($C_{13}H_{18}S$): C, 75.67; H, 8.79. Found: C, 75.63; H, 8.82. (Table 1, entry 9): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 1.69 (s, 6H), 2.29 (s, 3H) 6.97–7.69 (m, 13H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 21.08, 30.8, 48.6, 127.5, 127.7, 128.1, 128.3, 130.2, 130.4, 133.02, 134.8, 135.2, 148.6; MS (m/e) = 318 $[M]^+$. Anal. Calcd for ($C_{22}H_{22}S$): C, 82.97; H, 6.96. Found: C, 82.95; H, 6.99. (Table 1, entry 10): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 2.23 (s, 3H), 5.46 (s, 1H), 7.10–7.46 (m, 14H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 21.1, 52.2, 127, 127.6, 129.4, 130.1, 131.1, 133.3, 135.4, 145.3; MS (m/e) = 290 $[M]^+$. Anal. Calcd for ($C_{20}H_{18}S$): C, 82.71; H, 6.25. Found: C, 82.74; H, 6.27. (Table 1, entry 18): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 1.47–1.99 (m, 15H), 2.35 (s, 3H), 7.06 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 21.0, 26.2, 28.3, 37.4, 37.9, 44.2, 128.5, 129.78, 129.88, 132.85, 137.7; MS (m/e) = 258 $[M]^+$. Anal. Calcd for ($C_{17}H_{22}S$): C, 79.01; H, 8.58. Found: C, 79.04; H, 8.60. (Table 1, entry 24): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 1.71 (m, 2H), 2.45 (t, J = 7.3 Hz, 4H), 3.57 (s, 4H), 3.79 (s, 6H), 6.85 (d, J = 6.65 Hz, 4H), 7.17(d, J = 6.65 Hz, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 29.7, 32.2, 36.9, 55.5, 113.3, 127.9, 131.6, 158.7; MS (m/e) = 348 $[M]^+$; Anal. Calcd for ($C_{19}H_{24}O_2S_2$): C, 65.48; H, 6.94. Found: C, 65.50; H, 6.97. (Table 1, entry 25): ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 1.30 (t, J = 6.2 Hz, 2H), 1.86 (m, 4H), 2.40–2.63 (m, 8H), 3.68 (s, 4H), 7.26 (s, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 24.7, 32.4, 36.7, 39.2, 128.6, 137.4; MS (m/e) = 318 $[M]^+$. Anal. Calcd for ($C_{14}H_{22}S_4$): C, 52.78; H, 6.96. Found: C, 52.80; H, 6.95.

Acknowledgments

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35. *General procedure for the S-alkylation of thiols by alcohols*: To a mixture of $ZrCl_4$ (0.116 g, 0.5 mmol) and dry silica gel [0.3 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h] at 50 °C, thiol (1.1 mmol) was added and the resulting mixture was stirred for a few minutes. Then, the alcohol (1 mmol) was added and the mixture was stirred at 50 °C for the appropriate reaction time (monitored by TLC and GC) (Table 1). Then, the reaction mixture was washed with an aqueous solution of NaOH (10%, 10 ml) and extracted with Et_2O (2×10 ml). The organic layer was separated and dried over anhydrous $CaCl_2$ and filtered. Evaporation of the solvent afforded the desired product. Further purification was achieved by preparative plate silica chromatography eluting with *n*-hexane. Structural assignments of the products are based on their ^1H NMR, ^{13}C NMR and MS spectra and elemental analysis.
36. *General procedure for the double S-alkylation of dithiols using alcohols*: To a mixture of $ZrCl_4$ (0.233 g, 1 mmol) and dry silica gel [0.3 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h] at 50 °C, dithiol (1.1 mmol) was added and the mixture stirred for a few minutes. Then, alcohol (2 mmol) was added and the mixture was stirred at 50 °C for the appropriate reaction time (monitored by TLC and GC), (Table 1, entries 23 and 24). Then, the reaction mixture was washed with an aqueous solution of NaOH (10%, 10 ml) and extracted with Et_2O (2×10 ml). The organic layer was separated and dried over anhydrous $CaCl_2$ and filtered. Evaporation of the solvent afforded the desired product. Further purification was achieved by preparative plate silica chromatography eluting with *n*-hexane. Structural assignments of the products are based on their ^1H NMR, ^{13}C NMR and MS spectra and elemental analysis.
37. *Typical procedure for the double S-alkylation of 1,3-propanedithiol using 1,4-benzenedimethanol (entry 24)*: To a mixture of $ZrCl_4$ (0.233 g, 1 mmol) and dry silica gel [0.3 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h] at 50 °C, 1,3-propanedithiol (2.1 mmol) was added and the mixture stirred for a few minutes. Then, 1,4-benzenedimethanol (1 mmol) was added and the resulting mixture was stirred at 50 °C for 20 min (monitored by TLC). The product was extracted by the addition of acetone followed by filtration. The filtrate was evaporated under vacuum to afford the desired product. Further purification was achieved by preparative plate silica chromatography eluting with *n*-hexane. Structural assignment of the product was based on its ^1H NMR, ^{13}C NMR and MS spectra and elemental analysis.