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An alternative approach towards the syntheses of thioethers and thioesters using CsF–Celite in acetonitrile[†]

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Abstract—It has been found that syntheses of thioethers and thioesters of aliphatic, aromatic and heterocyclic compounds, bearing thiol groups, can be accomplished with alkyl, acyl, benzyl or benzoyl halides in acetonitrile and cesium fluoride–Celite. In this manner, compounds like ethanethiol, 1-pentanethiol, thiophenol, 4-methoxythiophenol, 4-nitrothiophenol, and 2-mercaptobenzoxazole, 2-mercaptobenzothiazole, and 2-mercapto-2-thiazoline can be successfully alkylated, acylated, benzylated or benzoylated. This procedure is convenient, efficient and practical for the preparation of thioethers and thioesters. © 2002 Elsevier Science Ltd. All rights reserved.

Protection of thiol groups is important in many areas of organic research, particularly in peptide, protein and β-lactam synthesis.[1,2a] A free SH group can be protected as thioether, thioester or, after oxidation, as disulfide, from which it can be regenerated by reduction. Thioethers are, in general, formed by reaction of thiols or thiophenols under basic conditions with alkyl or benzyl halides. Thioesters are formed and cleaved in the same way as oxygen esters; they are more reactive against nucleophilic substitution[2b] and used as 'activated esters'.

The conversion of thiols to thioethers is usually achieved by reaction of thiolate with organic halides.[3] The yields and reaction conditions depend on the solvent, the basic catalyst and the acidity of thiol. These reactions require very long refluxing time and yields obtained were low.[4]

Several other methods were employed for preparing thioethers which include palladium(0)-mediated alkylation,[5] phase transfer catalysis,[6] platinum(II) complex with bis(diphenylphosphino)methane,[7] bis(diphenylstannyl)telluride,[8] tin sulfides with aryl halides,[9] ligand transfer reactions,[10] organometallic sulfides,[11] montmorillonite clay catalysis[12] and trifluoroacetic acid.[13] Recently, Yin and Pidgeon[14] reported a high yield method for the preparation of unsymmetrical sulfides by using very strong basic *n*-butyllithium.

In continuation of our interest in developing new organic synthetic methodologies,[15] we reported very recently the *N*-alkylation[16] of amines using CsF–Celite as a solid base. In extension of our work on the reactivity of CsF–Celite, we wish to report the utility of CsF–Celite for the synthesis of thioethers and thioesters in good yields (Scheme 1).

The CsF–Celite-assisted coupling of aliphatic and aromatic thiols with various alkyl, acyl, benzyl and benzoyl halides resulted in thioethers and thioesters (Tables 1 and 2).

In a typical reaction, to a mixture of thiol (1.0 mol) and CsF–Celite (1.5 mol) in 20 ml of acetonitrile, alkyl,

$$\mathrm{RSH + R'X \xrightarrow[CH_3CN,\ r.t.\ or\ Reflux]{CsF\text{-}Celite} RSR'}$$

R = Phenyl or Benzyl
X = Cl, Br or I
R'= Alkyl, Acyl, Benzyl or Benzoyl

Scheme 1.

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[†] Dedicated to Professor Atta-ur-Rahman on the occasion of his 60th birthday.

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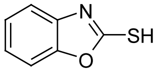
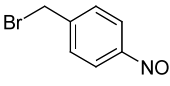
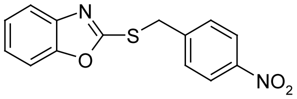
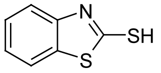
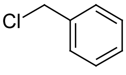
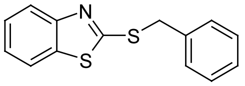
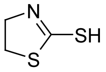
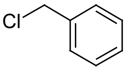
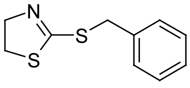
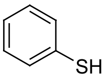
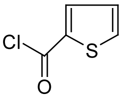
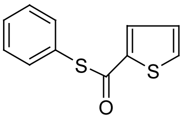
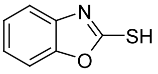
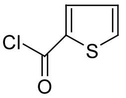
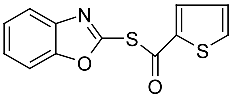
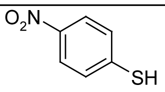
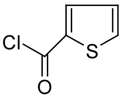
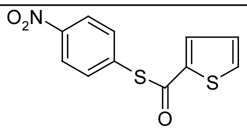
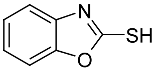
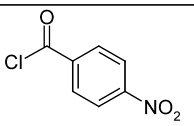
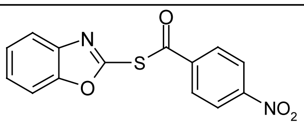
Table 1. Synthesis of thioethers using CsF–Celite

Entry	Substrate	Reagent	Product	Compound	% Yield	Mp (lit.)
1	CH_3CH_2SH	$CH_3O_2CCH_2CH_2Br$	$CH_3O_2CCH_2CH_2SCH_2CH_3$	1	60^b	Liquid[20]
2	$CH_3(CH_2)_4SH$	$C_6H_5CH_2Cl$	$CH_3(CH_2)_4SCH_2C_6H_5$	2	81^b	Liquid[21]
3	C_6H_5SH	$C_6H_5CH_2Br$	$C_6H_5SCH_2C_6H_5$	3	85^b	42-43, (43-44)[22]
4	C_6H_5SH	CH_3CHICH_3	$C_6H_5SCH(CH_3)_2$	4	78^b	Liquid[23]
5	4-$CH_3OC_6H_4SH$	$C_6H_5CH_2Br$	4-$CH_3OC_6H_4SCH_2C_6H_5$	5	81^b	48-50, (48-49)[24]
6	4-$NO_2C_6H_4SH$	CH_3CHICH_3	4-$NO_2C_6H_4SCH(CH_3)_2$	6	61^b	46-47, (46-47)[25]
7	4-$NO_2C_6H_4SH$	$CH_2{=}CHCH_2Br$	4-$NO_2C_6H_4SCH_2CH{=}CH_2$	7	75^b	39-41, (38-39)[26]
8	4-$NO_2C_6H_4SH$	CH_3CH_2I	4-$NO_2C_6H_4SCH_2CH_3$	8	60^b	41-42, (42-43)[17]
9	4-$NO_2C_6H_4SH$	$C_6H_5CH_2Cl$	4-$NO_2C_6H_4SCH_2C_6H_5$	9	77^b	128-129, (128-129)[24]
10	4-$CH_3OC_6H_4SH$	4-$CH_3OC_6H_4CH_2Cl$	4-$CH_3OC_6H_4SCH_2C_6H_4OCH_3$-4	10	86^b	90-91, (90)[27]
11				11	90^b	112-114, (114-115)[28]
12				12	74^a	38-40, (39-40)[29]
13				13	81^a	47-48, (48)[30]

a = room temp. for 1 to 8h, b = reflux at 82 °C for 2 to 48h.

Table 2. Synthesis of thioesters using CsF–Celite

Entry	Substrate	Reagent	Product	Compound	% Yield	Mp (lit.)
1	C_6H_5SH	C_6H_5COCl	$C_6H_5SOCC_6H_5$	14	88^a	55-56, (55-57)[31]
2	C_6H_5SH	CH_3COCl	$C_6H_5SOCCH_3$	15	85^a	Liquid[32,33]
3	4-$CH_3OC_6H_4SH$	$CH_3O_2CCH_2CH_2COCl$	4-$CH_3OC_6H_4SOCCH_2CH_2CO_2CH_3$	16	89^b	Liquid
4	4-$CH_3OC_6H_4SH$	CH_3COCl	4-$CH_3OC_6H_4SCO_2CH_3$	17	88^b	Liquid[34]
5	4-$CH_3OC_6H_4SH$	4-$CH_3OC_6H_5COCl$	4-$CH_3OC_6H_4SOCC_6H_5$-4-OCH_3	18	81^b	134-137, (134-136)[31]
6	4-$CH_3OC_6H_4SH$	C_6H_5COCl	4-$CH_3OC_6H_4SOCC_6H_5$	19	71^b	96-98, (97.5-99.5)[31]
7	4-$NO_2C_6H_4SH$	C_6H_5COCl	4-$NO_2C_6H_4SOCC_6H_5$	20	49^b	125-127, (126-127)[31]
8				21	83^b	60-62, (59-60)[35]
9				22	79^b	110-112
10				23	75^b	139-141
11				24	80^b	Liquid

a = room temp. for 1 to 8h, b = reflux at 82 °C for 2 to 48 h.

acyl, benzyl, or benzoyl halides (2.0 mol) were added. Then, the mixture was stirred at room temperature or refluxed up to completion of the reaction, indicated by TLC monitoring. The reaction mixture was filtered and the solvent evaporated. The product was purified, whenever necessary, by column chromatography on silicagel using appropriate solvent systems like dichloromethane and petroleum ether etc. as eluents, to afford pure thioether or thioester products. The physical properties and NMR spectra of compounds agreed with those reported in the literature[17–35] and were furthermore identified by comparing the data with those of authentic samples. The unknown compounds were characterized by different spectroscopic techniques and their elemental analyses.

In conclusion, CsF–Celite-assisted reactions provide an easy access to thioethers as well as thioesters in good yields. As this methodology has several advantages, it is a valuable addition to existing methods. In short this is an efficient, convenient, inexpensive, non-corrosive and practical method for preparing thioethers and thioesters.

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