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A novel method for the syntheses of symmetrical disulfides using CsF–Celite as a solid base

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Dedicated to Professor Atta-ur-Rahman on the occasion of his 60th birthday

Abstract—The oxidative coupling of aliphatic, aromatic and heteroaromatic thiols to disulfides using cesium fluoride–Celite is described. CsF–Celite provides an efficient, convenient and practical method for the syntheses of symmetrical disulfides.

Disulfides are useful reagents in organic synthesis.[1,2] Disulfides are also used in sulphenylation of enolates and other anions,[3] and they are essential moieties of biologically active compounds for peptide and protein stabilization.[4] As disulfides are relatively more stable to organic reactions such as oxidation, alkylation and acylation compared to the corresponding free thiols, the thiol group can conveniently be protected as a disulfide. The desired thiol can be generated from the disulfide either by reduction or by other sulfur–sulfur bond cleavage reactions such as CN^-, OH^- or hydrazines.[5] Various reagents for oxidative coupling of thiols to disulfides are described, e.g. iodine/hydrogen iodide,[6] neat bromine,[7] $FeCl_3$/NaI,[8] $KMnO_4$/$CuSO_4$[9] and hydrogen peroxide in tetrafluoroethanol.[10] Furthermore, some of the non-metallic reagents like Br_2,[11] DMSO[12] also accomplish thiol coupling, but they encounter the difficulty of product handling and isolation. Enzymatic[13] and electrochemical[14] methods are also known to perform this oxidative transformation. However, there is still an interest in developing a clean, mild and efficient method to synthesize aliphatic, aromatic and heteroaromatic disulfides.

In connection with our current studies on the synthesis of ethers, esters, thioethers and thioesters[15] using cesium fluoride–Celite as a solid base, we further explored its utility by preparing disulfides using similar reaction conditions. Moreover, importance of the fluoride ion as a catalyst for the promotion of various types of base-catalyzed reactions in organic synthesis has been previously recognized.[16] In particular the work of Clark and Miller revealed that the fluoride ion has an effect on coupling reactions because of its high capability of hydrogen bond formation.[17] As reagents for generating the fluoride ion in these reactions, potassium, cesium and tetraalkylammonium fluorides were generally used so far. However, it is not easy to handle these hygroscopic reagents and the reproducibility of these reactions are invariably poor. Previously, poorly hygroscopic reagents generating fluoride ions were designed by allowing cesium fluoride to be absorbed on Celite.[18] The effect of cesium fluoride–Celite might be twofold: (a) activation of thiol groups by the fluoride ion, whose ionic character is increased owing to the low charge/surface area ratio of the cesium cation and (b) activation of the alkyl group by a Lewis acid type effect.[19]

The present method (Scheme 1) is equally applicable for the oxidative coupling of alkyl, aryl and heterocyclic thiols, and the efficiency of the procedure is also

$$\mathrm{RSH} \xrightarrow[\mathrm{CH_3CN,\ r.t.\ or\ Reflux}]{\mathrm{CsF\text{-}Celite,\ O_2}} \mathrm{RSSR}$$

Scheme 1.

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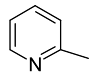
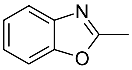
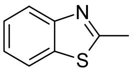
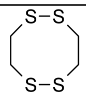
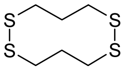
Table 1. Synthesis of disulfides using CsF–Celite

Entry	R	Compound	% Yield	Mp °C (lit.)
1	$CH_3(CH_2)_4$-	1	81[a]	Liquid[9]
2	$CH_3(CH_2)_7$-	2	81[a]	Liquid[20]
3	$CH_3(CH_2)_{11}$-	3	81[a]	30-31, (30-31)[20]
4	C_6H_5-	4	78[a]	59-61, (61)[21]
5	$HOCH_2CH_2$-	5	85[a]	Liquid[21]
6	HOC_6H_4-	6	75[b]	149-151, (149-150)[22]
7	4-$CH_3OC_6H_4$-	7	81[a]	40-42, (42-44)[13]
8	4-$NO_2C_6H_4$-	8	92[a]	177-178, (177-178)[9]
9		9	90[b]	57-58, (57)[21]
10		10	74[b]	110-111, (110)[23]
11		11	81[a]	183-184, (182.5-183.5)[24]

a = room temp. for 1 to 24h, b = reflux at 82 °C for 2 to 12h.

Table 2. Synthesis of cyclic tetrasulfides using CsF–Celite

Entry	Product	Compound	% Yield	Mp °C (lit.)
1		12	79[a]	100-101, (100)[25]
2		13	84[a]	53-54, (53-54)[26]

a = room temp. for 1 to 24h.

demonstrated by coupling of long chain thiols (entries 1–3). We have noticed that the coupling of dithiol compounds resulted in the formation of cyclic tetrasulfide products (compounds **12** and **13**).

The reactions catalyzed by cesium fluoride–Celite are usually carried out under mild conditions with good yields and simple workup: Only filtration is required to remove the catalyst and often evaporation of the filtrate afforded pure products. We explored the utility of the CsF–Celite system as an efficient, inexpensive and non-corrosive reagent for the synthesis of disulfides and cyclic tetrasulfides, depending upon the substrate used. Several examples of CsF–Celite-assisted couplings of aliphatic, aromatic and heteroaromatic thiols into disulfides are presented in Tables 1 and 2.

In a typical reaction, a mixture of thiol (1.0 mol), CsF–Celite (1.5 mol) in acetonitrile is stirred at room temperature or under reflux and access to atmospheric/oxygen. The completion of reaction is monitored by TLC. After completion of the reaction, the reaction mixture is filtered and the filtrate evaporated to afford the pure product. The physical properties and NMR spectra of compounds agreed with those reported in the literature[9,13,20–26] 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 for the syntheses of disulfides 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 symmetrical disulfides.

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