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Simple, solvent free syntheses of unsymmetrical sulfides from thiols and alkyl halides using hydrotalcite clays

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Abstract

A wide range of unsymmetrical sulfides have been synthesized in good yield from thiols and alkyl halides using synthetic hydrotalcite clays as basic catalysts.

Keywords: Hydrotalcite; Alkylation of thiols; Unsymmetrical sulfides; Solvent free synthesis

1. Introduction

Chemistry of organosulfur compounds [1], particularly sulfides, assume significance due to their relevance in many biological processes [2] and pharmaceutical applications. Well known examples of such organosulfur compounds are dapsone (leprosy drug), feldene (arthritis drug), glutathione (scavenger for oxidizing agents), cysteine and sulfur containing penicillin family of drugs. Sulfides are useful synthetic intermediates and many syntheses have been reported for their preparation. Commonly employed methods are the alkylation of thiols [1–4], the reaction of alkyl halide with sodium sulfide [5], addition of hydrogen sulfide to alkene [6], reduction of disulfide with copper in the presence of halide [7], reduction of sulfoxides with titanium(II) chloride [8], deoxygenation of sulfoxide with triphenylphosphine iodide–sodium iodide [9] and the synthesis of alkyl sulfides via allyl dialkyl telluronium salts [10]. In this context, it is relevant to note that symmetrical sulfides can be synthesized more conveniently [1,11].

Methods for the formation of aryl–sulfur bonds are indispensable tools in synthetic chemistry [12]. Traditional methods for the synthesis of aryl–sulfur bonds often require harsh reaction conditions. For example coupling of copper thiolates with aryl halides requires polar solvents such as HMPA and temperatures around 200 °C. Reduction of aryl sulfones or aryl sulfoxides requires strong reducing agents such as diisobutylaluminium hydride or $LiAlH_4$ [13]. In the presence of catalytic amount of tetrakis(triphenylphosphine)-palladium, thiolate anion reacts with aryl halides, to yield the corresponding aryl sulfides [14].

Kosugi et al. [15] have reported preparation of aryl sulfides in good yields from the palladium catalyzed reaction of stannyl sulfides with aryl bromide. Bates et al. [16] have reported a general method for the formation of aryl–sulfur bonds using CuI and neocuproine as catalysts with sodium *tert*-butoxide as the base. Jaisinghani and Khadilkar [17] have employed alumina-supported potassium carbonate for the S-alkylation of thiols with alkyl halides under solvent free conditions using microwaves. Allyl sulfides and selenides are also synthesized by the reactions of allyl bromide with disulfides/diselenides by the Sm–$BiCl_3$ system in aqueous media [18]. In a novel approach, allyl sulfides are synthesized from alkyl thiosulfate using organosamarium reagents as catalysts involving organosamarium(II) and organosamarium(III) intermediates [19].

Hydrotalcites (HT) are one of the most promising synthetic solid basic catalysts [20] employed in organic reactions. They are homogeneous, basic, mixed hydroxycarbonates of magnesium and aluminum with a layered structure [21] having the general formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}A_{x/n}{}^{n-}] \cdot mH_2O$, where A is the anion. This basic nature of the hydrotalcite is due

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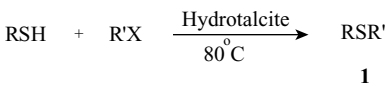
to the presence of the surface hydroxyl groups. Several base-catalyzed reactions like aldol condensation [22], Baeyer–Villiger oxidation [23], aldol and Knoevenagel condensations [24], N-oxidation of pyridine [25], epoxidations [26,27], Michael addition [28], and Henry reaction [29] have been promoted over HT. Recently, we have reported [30,31] the synthesis of benzyl sulfide of formula $ArCH_2SR$ by the reaction between benzyl chloride and thiols in the presence of a modified montmorillonite clay containing 3-aminopropyl-triethoxysilane (3-APTES). Though HT has been widely used in catalytic C–C bond formation reactions, to the best of our knowledge, there is no report dealing with the formation of C–S bond using HT as a catalyst. This has prompted us to study the synthesis of sulfides by alkylation of thiols with the corresponding halides, in the presence of HT clays.

2. Experimental

Hydrotalcite (5:1) was prepared [21] by mixing an aqueous solution (100 ml) of $Mg(NO_3)_2{\cdot}6H_2O$ (0.5 M) and $Al(NO_3)_3$ (0.1 M) with NaOH (3.5 M), and Na_2CO_3 (60 ml of 1 M solution) under vigorous stirring. The mixture was heated to 65 °C and kept at this temperature for 18 h. Then the precipitate was cooled, filtered, washed with deionised water and dried at 110 °C for over night. Dried hydrotalcite was crushed into powder and used as such. It was characterized by TGA-DTA analysis (NETZSCH STA 409PC instrument), which showed two endothermic transitions. The first transition at lower temperature (149 °C) was due to the loss of interlayer water and the second one at high temperature (413 °C) to the loss of hydroxyl groups and carbonates as reported earlier [21].

In a typical experiment for the synthesis of sulfide, thiol (0.025 M) and alkyl bromide (0.025 M) were mixed with 250 mg of powdered hydrotalcite in a 25 ml round bottom flask. Then it was sealed and heated on a oil bath at 80 °C. After 2 h, the products were extracted with dichloromethane, filtered, concentrated, and analyzed in on a gas chromatograph (Shimadzu GC-17A, SE-30 10% capillary column and FID as detector). Sulfides are also actually isolated and are characterized by their ^{1}H NMR spectra.[1]



1

R = C_6H_5, *p*-Cl-C_6H_4, *p*-CH_3-C_6H_4, n-butyl, n-hexyl or n-octyl
R' = allyl, n-propyl, isopropyl, n-butyl or benzyl
X = Br, Cl or I

Scheme 1.

3. Results and discussion

The results of alkylation of thiophenols using HT as a catalyst are given in Table 1. From the data, it is obvious that the reaction proceeds very smoothly in a simple, clean and easier protocol with very good yield. The method is very general and a wide range of aliphatic and aromatic thiols react readily with alkyl halide (Scheme 1). Also formation of disulfide, a common side reaction in thiol chemistry, is very much suppressed.

We have also studied the effect of substituents in the *para*-position of thiophenol. Thiophenol having electron-withdrawing groups, like chlorine in the *para*-position undergoes faster alkylation than the thiophenol containing electron-releasing groups (Table 1, entries 19 and 20), indicating that the formation of thiolate anion is easier with the former.

It is also observed that the reaction is selective as evident in the case of allyl bromide as the alkylating agent. Allyl phenyl sulfide is formed selectively and the olefinic group is unaffected (Table 1, entry 1). It is also interesting to note that no elimination reaction is observed, which is expected to occur because of the higher acidity of the SH bond. We have extended the work to aliphatic thiols also and higher yield of alkylated product (Table 1, entries 13–15) is obtained. Facile alkylation of aliphatic thiols is also observed with non-benzylic/non-allylic alkyl halides (Table 1, entries 16–19).

The catalyst is recovered at least three times and HT is found to be still very active (Table 1, entries 25–27) with only a marginal decrease in its efficiency. In another approach, the recovered catalyst is activated (first by washing with Na_2CO_3 solution followed by heating to 100 °C) and the catalytic efficiency is found to be almost intact after the

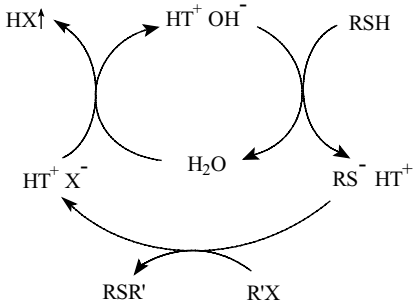
[1] ^{1}H NMR data of isolated sulfides: (1) $C_6H_5SCH_2CH{=}CH_2$: δ 7–7.5 (m, 5H), 5.7–6 (m, 1H), 5–5.3 (dd, 2H), 3.5 (d, 2H); (2) $C_6H_5SCH_2CH_2CH_3$: δ 7.1–7.4 (m, 5H), 2.8–3 (t, 2H), 1.5–1.7 (m, 2H), 1.0 (t, 3H); (3) $C_6H_5SCH(CH_3)_2$: δ 7.1–7.3 (m, 5H), 3.1–3.3 (m, 1H), 1.1–1.2 (d, 6H); (4) *p*-CH_3–$C_6H_5S(CH_2)_3CH_3$: δ 7.2–7.4 (m, 5H), 2.8–3 (t, 2H), 2.4 (s, 3H), 1.3–1.5 (m, 2H), 0.8–1 (t, 3H); (5) *p*-Cl–$C_6H_4SCH_2CH{=}CH_2$: δ 7.1–7.4 (m, 4H), 5.7–6 (m, 1H), 5–5.3 (dd, 2H), 3.5 (d, 2H); (6) *p*-Cl–$C_6H_4SCH_2CH_2CH_3$: δ 7.1–7.4 (m, 4H), 2.8–3 (t, 2H), 1.5–1.7 (m, 2H), 1.0 (t, 3H); (7) *p*-Cl–$C_6H_4SCH(CH_3)_2$: δ 7.1–7.3 (m, 4H), 3.1–3.3 (m, 1H), 1.1–1.2 (d, 6H); (8) *p*-Cl–$C_6H_5S(CH_2)_3CH_3$: δ 7.2–7.4 (m, 5H), 2.7–2.8 (t, 2H), 1.4–1.6 (m, 2H), 1.2–1.4 (m, 2H), 0.7–0.9 (t, 3H); (9) *p*-CH_3–$C_6H_4SCH_2CH{=}CH_2$: δ 7.1–7.4 (m, 4H), 5.7–6 (m, 1H), 5–5.3 (dd, 2H), 3.5 (d, 2H), 2.3 (s, 3H); (10) *p*-CH_3–$C_6H_4SCH_2CH_2CH_3$: δ 7.1–7.4 (m, 4H), 2.8–3 (t, 2H), 2.3 (s, 3H), 1.5–1.7 (m, 2H), 1.0 (t, 2H); (11) *p*-CH_3–$C_6H_4SCH(CH_3)_2$: δ 7.1–7.4 (m, 4H), 3.1–3.3 (m, 1H), 2.3 (s, 3H), 1.1–1.2 (d, 6H); (12) $C_6H_5S(CH_2)_3CH_3$: δ 7.2–7.4 (m, 5H), 2.8–3 (t, 2H), 1.5–1.7 (m, 2H), 1.3–1.5 (m, 2H), 0.5–0.1 (t, 3H); (13) $C_6H_5CH_2SCH_2(CH_2)_2CH_3$: δ 7.3 (5H, m), 3.7 (2H, s), 2.3–2.4 (2H, t), 1.4–1.5 (4H, m), 0.8–0.9 (3H, t); (14) $C_6H_5CH_2SCH_2(CH_2)_4CH_3$: δ 7.2–7.3 (5H, m), 3.7 (2H, s), 2.3–2.4 (2H, t), 1.2–1.4 (8H, m), 0.8–0.9 (3H, t); (15) $C_6H_5CH_2SCH_2(CH_2)_6CH_3$: δ 7.2–7.3 (5H, m), 3.6 (2H, s), 2.3–2.4 (2H, t), 1.1–1.3 (12H, m), 0.8–0.9 (3H, t); (16) $(CH_3CH_2CH_2CH_2)_2SCH_2$: δ 2.3–2.4 (4H, t), 1.3–1.5 (8H, m) 0.8–1.0 (6H, t); (17) $CH_3CH_2CH_2CH_2SCH_2CH_2CH_3$: δ 2.3–2.5 (4H, t), 1.5–1.7 (2H, m), 1.3–1.5 (4H, m), 0.8–1.0 (6H, t); (18) $CH_3(CH_2)_4CH_2SCH_2(CH_2)_2CH_3$: δ 2.3–2.5 (4H, t), 1.2–1.4 (12H, m), 0.8–1.0 (6H, t); (19) $CH_3(CH_2)_4CH_2SCH_2CH_2CH_3$: δ 2.3–2.5 (4H, t), 1.5–1.7 (2H, m), 1.3–1.5 (8H, m), 0.8–1.0 (6H, t).

Table 1
Alkylation of thiols with alkyl halides using hydrotalcite (HT)

Entry	R	R′X	% conversion[a]	% of products	
				1	Disulfide
1	C_6H_5	Allyl bromide	100	95.5	4.50
2	C_6H_5	*n*-Propyl bromide	100	94.9	5.10
3	C_6H_5	iso-Propyl bromide	100	65.5	34.5
4	C_6H_5	*n*-Butyl bromide	100	100	–
5	*p*-Cl–C_6H_4	Allyl bromide	100	100	–
6	*p*-Cl–C_6H_4	*n*-Propyl bromide	100	91.9	8.10
7	*p*-Cl–C_6H_4	iso-Propyl bromide	100	78.7	21.3
8	*p*-Cl–C_6H_4	*n*-Butyl bromide	100	91.6	8.40
9	*p*-CH_3–C_6H_4	Allyl bromide	100	100	–
10	*p*-CH_3–C_6H_4	*n*-Propyl bromide	100	86.0	14.0
11	*p*-CH_3–C_6H_4	iso-Propyl bromide	100	94.3	5.70
12	*p*-CH_3–C_6H_4	*n*-Butyl bromide	100	95.5	4.50
13	*n*-Butyl	Benzyl chloride	100	90.8	9.20
14	*n*-Hexyl	Benzyl chloride	100	88.4	11.6
15	*n*-Octyl	Benzyl chloride	100	93.0	7.00
16	*n*-Butyl	*n*-Butyl bromide	100	98.9	1.10
17	*n*-Butyl	*n*-Propyl bromide	97.0	99.3	0.70
18	*n*-Hexyl	*n*-Butyl bromide	100	82.8	17.2
19	*n*-Hexyl	*n*-Propyl bromide	98.0	87.0	13.0
20	C_6H_5[b]	*n*-Butyl chloride	73.0	92.0	8.00
21	C_6H_5[b]	*n*-Butyl bromide	94.5	96.0	4.00
22	C_6H_5[b]	*n*-Butyl iodide	100	100	–
23	*p*-Cl–C_6H_4[b]	*n*-Butyl bromide	100	100	–
24	*p*-CH_3–C_6H_4[b]	*n*-Butyl bromide	75.7	94.0	6.00
25	C_6H_5[c]	*n*-Butyl bromide	100	95.0	5.00
26	C_6H_5[d]	*n*-Butyl bromide	96.2	89.0	11.0
27	C_6H_5[e]	*n*-Butyl bromide	91.0	87.6	12.4
28	C_6H_5[f]	*n*-Butyl bromide	100	98.9	1.10

[a] Analyzed by GC; error limit ±2%.
[b] Heated in oil bath for 1 h.
[c] Reused hydrotalcite.
[d] HT reused for the second time.
[e] HT reused for third time.
[f] Activated (first by Na_2CO_3 wash and then heated to 100 °C) HT reused for the third time.

third use (Table 1, entry 28). Control experiments show that aliphatic thiols, when subjected to the present experimental conditions (in the absence of HT), have produced the corresponding disulfides as the major product. Among the halides, the order of reactivity is found to be chloride < bromide < iodide, reflecting the strength and electron deficiency on the carbon atom of the C–X bond.



Scheme 2. A plausible mechanism for the syntheses of unsymmetrical sulfides from thiols and alkyl halides using hydrotalcite clays.

The observed catalytic efficiency of HTs in the alkylation of thiols with alkyl halides has prompted us to propose the following mechanism (Scheme 2). Proton abstraction from thiol by HT generates the thiolates anion, which subsequently attacks the alkyl halide yielding the sulfide. The other product HT^+X^- removes a proton from water, regenerating HT. The byproduct hydrogen halide subsequently vaporizes under our experimental conditions.

4. Conclusions

Hydrotalcites are found to be efficient catalysts for the alkylation of various alkyl/arene thiols with alkyl halides under milder reaction conditions. This unique catalysis is due to the basic sites present on the surface of the hydrotalcite. Apart from its basic character, hydrotalcites also have advantages like reusability (Table 1, entry 25), easy separation of catalyst by simple filtration, use of non-toxic, inexpensive materials and ecofriendliness. They also suppress disulfide formation which is a common side reaction associated with chemistry of thiols [32].

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