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Ph_2S_2–CaH_2 in *N*-methyl-2-pyrrolidone as an efficient protocol for chemoselective cleavage of aryl alkyl ethers

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Dedicated to Professor Srinivasan Chandrasekaran on his 60th birth anniversary.

Abstract—CaH_2 was been found, for the first time, as a mild reducing agent to generate thiophenolate anion from Ph_2S_2 in *N*-methyl-2-pyrrolidone (NMP) for deprotection of aryl alkyl ethers. Excellent chemoselctivity was observed for substrates having chloro and nitro groups without displacement of the chlorine atom and the nitro group. Selective ether cleavage took place in the presence of α,β-unsaturated carbonyl and nitro groups without reduction and conjugate addition (to the α,β-unsaturated carbonyl group).

1. Introduction

The phenolic moiety constitutes an important pharmacophore due to the wide spread biological activity of compounds containing phenolic hydroxyl group. Thus, the cleavage of aryl alkyl ethers is a versatile organic reaction keeping in view the ease of the generation of aryl alkyl ethers.[1] Although various methods such as nucleophilic,[2] reductive,[3] and photo/electrochemical cleavage[4] of aryl alkyl ethers are available, alkaline thiolates have been the commonly employed reagents for this purpose.[5] However, due to their obnoxious smell and radical generation ability, handling of thiols become difficult. The requirement of stoichiometric amount of bases such as NaH or MeLi to generate the thiolate anions do not make these procedures attractive. Moreover, the propensity of the thiolate anion to undergo oxidation to form the corresponding disulfides also necessitates special attention in using alkaline thiolates. Recently, Me_3SiSNa has been introduced for aryl alkyl ether cleavage.[6] However, the use of Me_3SiSNa requires stringent reaction conditions such as heating in sealed tube in DMEU/DMPU and is not compatible with functional groups (e.g., NO_2) that are susceptible to reduction. Recently, we have demonstrated Ph_2S_2 and Na in NMP as an efficient protocol for in situ generation of thiophenolate anion for selective deprotection of aryl alkyl ethers.[7] Although excellent results were obtained using this method, we felt that the use of highly moisture sensitive sodium metal still demands milder reagent for reductive generation of the thiophenolate anion from Ph_2S_2. This led us to develop a better reducing agent for in situ generation of thiophenolate anion from Ph_2S_2 and we report herein, for the first time, CaH_2 as a mild reducing agent to generate thiophenolate anion from Ph_2S_2 in NMP for chemoselective cleavage of aryl alkyl ethers.[8]

In the pursuit for a suitable reducing agent, we came across the use of potassium triisopropoxyborohydride[9] and lithium tri-*tert*-butoxyaluminiumhydride[10] for generation of thiolate anions from the corresponding disulfides and subsequent reaction with various alkyl halides. However, these reducing agents are not suitable for substrates bearing reducible functionalities such as carbonyl and nitro groups. Recently lanthanoid metals,[11] transition metal complex and salt such as benzyltriethylammonium tetrathiomolybdate[12] and indium(I) chloride[13] have been used for generation of thiolate anions from the corresponding disulfides. However, the high cost of these reagents does not make them attractive for routine applications. Other methods involve the treatment with Cu_2O-bpy (10 mol%) and Mg (0.6 equiv) in DMF at 110 °C for 18–72 h[14] and $NiBr_2$-bpy (10 mol%) and zinc (200 mol%) in DMF at 110 °C for 48 h.[15] In all of these reports the thiolate anion has been used either for conjugate addition to α,β-unsaturated carbonyl compounds[11,12,13b] or aryl sulfide formation by reaction with aromatic halides.[13a,14,15]

Keywords: Ether cleavage; Diphenyl disulfide; Calcium hydride; Chemoselective; Thiophenolate anion.
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2. Results and discussion

To find out the best reducing agent(s), 2-methoxynaphthalene (**1**) was treated with Ph_2S_2 in NMP in the presence of various metals such as Mg, Fe and In under varied experimental conditions such as the amount of Ph_2S_2 and the reducing agent, reaction temperature and time. The reactions conditions providing the optimum results in each case are provided in Table 1. In each occasion, the progress of the reaction was monitored by GCMS and HPLC. Moderate result was obtained in using Fe affording 2-hydroxynaphthalene (**2**) in 38% yield. The use of Mg and In were proved to be ineffective as evidenced by the formation of **2** in 2 and 1% yields, respectively (GCMS and HPLC). As calcium metal (Ca) has been reported to be a milder reducing agent compared to the alkali metals,[16] we planned to use Ca as the reducing agent. However, the use of Ca afforded 46% conversion to **2**. We next choose NaH and CaH_2 as alkali metal hydrides were known to possess reducing property[17] and generated alkali selenoates from diorganodiselenides.[18] We were delighted to observe that 95 and 90% conversion (HPLC) to **2** took place in the presence of NaH and CaH_2, respectively. The best result was obtained by the treatment of **1** (1 equiv) with Ph_2S_2 (0.6 equiv) and MH (1.6 equiv) in NMP by heating under reflux for 30 min.

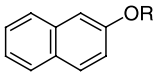
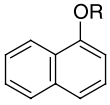
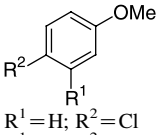
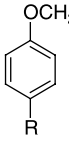
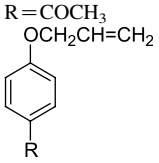
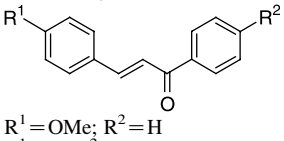
Table 1. Reaction of **1** with Ph_2S_2 in NMP in the presence of various reducing agents[a]

Entry	Reducing agent	Time (min)	Yield (%)[b]
1	Mg	30	2
2	Fe	30	38
3	In	30	1
4	Ca	30	48
5	NaH	30	96
6	CaH_2	30	90
7	CaH_2	15	64

[a] **1** (1 mmol) was treated with Ph_2S_2 (0.6 equiv) and the reducing agent (1.6 equiv) by heating under reflux in NMP (~220 °C).
[b] GCMS and HPLC yields of **2**.

To establish the generality, various aryl alkyl ethers were subjected to the treatment with Ph_2S_2 and CaH_2 in NMP (Table 2). Although the use of NaH afforded marginally better result than that of CaH_2 (compare the results of entries 5 and 6, Table 1), we planned to carry out the remaining reactions with CaH_2 as NaH is highly moisture sensitive and its strong basic property may induce sulfenylation as major side reaction with substrates bearing enolisable proton. Excellent results were obtained with methyl, ethyl and benzyl ethers. However, allyl and propargyl ethers afforded moderate yields (Table 2: entries 3, 4 and 7). In each occasion, the isolated (after aqueous work up) product was pure (GCMS, NMR) and the reaction temperature had no detrimental effect on purity of the product. The rate of ether cleavage was affected by the steric and electronic factors of the alkyl group. Inferior yield was obtained during the cleavage of ethyl ether compared to that of methyl ether under identical reaction conditions (compare entries 1 and 2, Table 2). The cleavage of benzyl ether was more facile compared to that of methyl ether (compare the results of entry 1 with that of 5 and the result of entry 6 with that of 8, Table 2). The presence of an electron withdrawing group made the ether cleavage facile as evidenced by the excellent

Table 2. Chemoselective deprotection of aryl alkyl ethers[a]

Entry	Ether	Yield (%)[b,c]
		
1	R=Me	80
2	R=Et	69
3	R=CH_2–CH=CH_2	42
4	R=CH_2–C≡CH	35
5	R=CH_2-Ph	100
		
6	R=Me	76
7	R=CH_2–CH=CH_2	47
8	R=CH_2-Ph	95
		
9	R^1=H; R^2=Cl	99
10	R^1=H; R^2=COMe	88
11	R^1=$COCH_3$; R^2=H	83
12	R^1=H; R^2=CHO	98
13	R^1=H; R^2=CN	100
14	R^1=H; R^2=NO_2	100
		
15	R=CN	100
16	R=$COCH_3$	88
		
17	R=CN	100
18	R=$COCH_3$	100
		
19	R^1=OMe; R^2=H	100
20	R^1=H; R^2=OMe	100

[a] The ether (1 mmol) was treated with Ph_2S_2 (0.6 equiv) and CaH_2 (1.6 equiv) by heating under reflux in NMP (~220 °C) for 30 min.
[b] Isolated yields of the corresponding phenol.
[c] The products were characterized by GCMS and NMR.

(83–100%) yields of the phenolic products for substrates bearing electron withdrawing groups such as Cl, COMe, CHO, CN, NO_2, and α,β-unsaturated carbonyl (Table 2: entries 9–20). Excellent chemoselectivity was observed with substrates that are susceptible to undergo competitive aromatic nucleophilic substitution, conjugate addition and reduction. Exclusive ether cleavage took place for 4-chloro anisole (Table 2: entry 9) and 4-nitro anisole (Table 2: entry 14) without displacement of the chlorine atom[19] and the nitro group.[20] No reduction of the nitro group (Table 2: entry 14)[6b,c] and α,β-unsaturated double bond (Table 2: entries 19 and 20)[16,21] was observed although thiolate anions have reducing properties.[22] The reactions with the 1,3-diaryl-2-propenones (Table 2: entries 19 and 20) further

demonstrated chemoselectivity of ether cleavage without any competitive conjugate addition.[23,24]

3. Conclusion

In conclusions, we have described Ph_2S_2–CaH_2 in NMP as a highly efficient protocol for in situ generation of thiophenolate anion for chemoselective deprotection of aryl alkyl ethers. We have demonstrated, for the first time, the use of CaH_2 as a reducing agent to generate thiolate anion from disulfides. The mildness of CaH_2 should find its application in various other organic transformations.

4. Experimental

4.1. General

The ^1H and ^{13}C spectra were recorded on Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. The IR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid and neat for liquid samples. Mass spectra were recorded on QCP 5000 (Shimadzu) GCMS. The reactions were monitored by TLC (Merck). Evaporation of solvents were performed under reduced pressure using a Büchi rotary evaporator. Indium and calcium metals, 2-methoxynaphthalene, 4-methoxyacetophenone, 3-methoxyacetophenone, 4-methoxybenzaldehyde were purchased from Aldrich, India. Magnesium and iron metals, NaH, CaH_2 and *N*-methyl 2-pyrrolidone were from S-D Fine Chemicals, India. 4-Methoxychlorobenzene,[25] 4-methoxynitrobenzene,[25] 4-methoxybenzonitrile,[25] 2-ethoxynaphthalene,[25] 2-benzyloxynaphthalene,[26] 1-benzyloxynaphthalene,[27] 2-allyloxynaphthalene,[28] 1-allyloxynaphthalene,[29] 2-propynyloxynaphthalene,[30] 4-benzyloxyacetophenone,[31] 4-allyloxyacetophenone,[32] 4-allyloxybenzonitrile,[33] 1-phenyl-3-(4-methoxyphenyl)-2-propenone[34] and 1-(4-methoxyphenyl)-3-phenyl-2-propenone[34] were prepared following reported procedures.

4.1.1. Representative experimental procedure. 2-Methoxynaphthalene (**1**) (158 mg, 1 mmol) in NMP (0.4 mL) was added to a magnetically stirred mixture of Ph_2S_2 (130 mg, 0.6 mmol) and CaH_2 (70 mg, 1.6 mmol) in NMP (0.6 mL) under N_2 and the mixture was heated under reflux for 30 min. The cooled reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3×10 mL) to separate any neutral component. The combined ethereal extracts were washed with 5% aqueous NaOH (10 mL) and the alkaline washing was added to the aqueous portion. The aqueous part was acidified in the cold (ice bath) with 6 N HCl and extracted with Et_2O (3×15 mL). The combined ethereal extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under vacuum to afford the crude product which on crystallization (MeOH) afforded 2-hydroxynaphthalene (**2**) (115 mg, 80%). Mp 121 °C; IR (KBr) cm^{-1}: 3300,1630, 1601; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.1 (dd, 1H, J=2.5, 8.8 Hz), 7.18 (d, 1H, J=2.5 Hz), 7.36 (ddd, 1H, J=1.24, 6.88, 6.96 Hz), 7.46 (ddd, 1H, J=1.2, 6.88, 6.92 Hz), 7.71 (d, 1H, J=8.28 Hz), 7.77–7.81 (m, 2H); MS (EI): m/z=144 (M^+), 115 (M^+-29); identical with an authentic sample.[5g,35] The remaining reactions were carried out following this general procedure and the isolated product was purified either by crystallization (MeOH) or passing through a column of silica gel and eluting with eluting with hexane–EtOAc (9/1). The physical data (mp, IR, NMR and MS) of 1-hydroxynaphthalene,[35] 4-chlorophenol,[35] 4-hydroxyacetophenone,[35] 3-hydroxyacetophenone,[35] 4-hydroxybenzaldehyde,[35] 4-cyanophenol,[35] 4-nitrophenol,[35] 1-phenyl-3-(4-hydroxyphenyl)-2-propenone[5f] and 1-(4-hydroxyphenyl)-3-phenyl-2-propenone[5f] were in complete agreement with those of authentic samples.

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