The interconversion of functional groups is an essential exercise in the multistep synthesis and in any organic synthesis in general. An armament of methods are very rapidly being added to the literature[1] signifying the importance of the topic. In many a occasions the sulfur derived reagents are employed for such transformations[2]. The proper introduction and removal of protecting groups[3] is the most widely carried out transformation for organic synthesis of any length. In this context one frequently encounters with phenolic hydroxyl or carboxylic acid groups requiring selective masking and subsequent deprotection of these functional groups during the course of a multistep synthesis. Considering the ease of preparation and availability of starting materials phenolic hydroxyl and carboxilic acid groups are protected as their methyl ethers or esters as the case may be. Sulfur derived reagents are frequently employed for the deprotection of aryl alkyl ethers as well as esters[4]. However these reagents suffer from the disadvantage of being not compatible with substrates bearing functional groups susceptible to nucleophilic substition and reduction. Use of large excess of costly, difficult to handle thiols and the stringent reaction conditions (sealed tube heating at ~ 184^0C for prolonged period of time) and need to use defficult to handle hydride bases (for generation of the stoichiometric thiolate) make the applicabilty of these protocols less attractive. Realising the inevitable need for methods of deprotection of aryl alkyl ethers and esters and the potentiality of sulfur derived reagents in this regard the present investigations were undertaken.

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1. a) A. R. Katrizky, Ed. In Chief, "Comprehensive Organic Functional Group Transformations", **Vols. 1 - 6**, Pergamon (1995); (b) R. C. Larock, "Comprehensive Organic Transformations : A Guide to Functional Group Preparations", VCH, N. Y. (1989).
2. a) P. C. B. Page, Ed., "Organo-Sulfur Chemistry: Synthetic Aspects", Academic, London (1995); (b) P. Metzner and A. Thuiller, "Sulfur Reagents in Organic Synthesis", Academic, London (1994); (c) W. E. Truce, *Sulfur Reports*, **9**, 351 (1990).
3. a) T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., Wiley, N. Y. (1991); (b) P. J. Kociensky, "Protecting Groups", D. Ender, R. Noyori and B. M. Trost, Eds., George Thieme Verlag, Stuttgart (1994); (c) K. Jarowicky and P. J. Kociensky, *Contemp. Org. Synth.*, **2**, 315 (1995).

The results of these studies embodied in this thesis entitled "Sulfur Compounds in Organic Synthesis" have been presented in two sections.

Section I : This section deals with the review of the application of sulfur reagents in organic synthesis and has been divided into the following subsections :

i) Protection/Deprotection of Functional Groups - Protection/deprotection of carbonyl groups, deprotection of aryl alkyl ethers, epoxides, esters and amine have been discussed.

ii) Carbon - Carbon Bond Formations - use of sulfur derived compounds in carbon - carbon bond formation involving carbanionic, ylide and radical intermediates have been dealt with.

Section II : This section elaborates the works carried out under the present investigation in order to develop modified methods for deprotection of aryl alkyl ethers, aryl/alkyl esters and aryl actetates/benzoate.

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4. a) B. C. Ranu and S. Bhar, *Org. Prep. Proced. Int.*, **28**, 371 (1996); (b) M. Tiecco, *Synthesis*, 749 (1988); (c) A. Maercker, *Angew. Chem. Int. Ed. Engl.*, **26**, 972 (1987); (d) M. V. Bhatt and S. Kulkarni, *Synthesis*, 249 (1983); (e) K. Lal, S. Ghosh and R. G. Solomon, *J. Org. Chem.*, **52**, 1072 (1987); (f) J. W. Huffman, S. Yu, V. Showalter, M. E. Abood, J. L. Wiley, D. R. Compton, B. R. Martin, R. D. Branblett and P. H. Reggia, *J. Med. Chem.*, **39**, 3875 (1996); (g) J. R. Hwu and S. -C. Tsay, *J. Org. Chem.*, **55**, 5987 (1990); (h) M. J. Shiao, W. S. Ku and J. R. Hwu, *Heterocycles*, **36**, 323 (1993);(i) J. R. Hwu, F. F. Wong and M. -J. Shiao, *J. Org. Chem.*, **57**, 5254 (1992); (j) M. -J. Shiao, L. -L. Lai, W. -S. Ku, P.-Y. Lin and J. R. Hwu, *ibid*, **58**, 4742(1993); (k) T. Fukuyama, C. -K. Jow and M. Cheung, *Tetrahedron Lett*, **36**, 6373 (1995); (l) T. Fukuyama, M. Cheung, C. -K. Jow, Y. Hidai and T. Kan, *ibid*, **38**, (1997); (m) C. Kay, P. J. Murray, L. Sandow and A. B. Holmes, *ibid*, **38**, 6941 (1997); (n) L. Yang and K. Chiu, *ibid*, **38**, 7307 (1997); (o) C. J. Salomon, E. G. Mata and O. A. Mascaretti, *Tetrahedron*, **49**, 3691(1993); (p) A. Haslam, *ibid*, **36**, 2409 (1989); (q) J. E. McMurry, *Org. React.*, **24**, 187 (1976).

The major problems of using the existing thiolate protocols for deprotection of aryl alkyl ethers are the need to use difficult to handle bases for the generation of the effective thiolate anion and the necessity to use these reagents in stoichiometric amount or more. Particularly the stoichiometric use of the thiolate reagent raises the problem of chemo-selectivity for multifunctional substrates as the aryloxide anion (bearing other functional groups), derived from the starting ether, has a chance to interact further with the thiolate present in the reaction medium. We planned to carry out the cleavage in presence of stiochiometric amount of thiol and catalytic quantities of suitable base. The initial reaction should be the proton exchange between the thiol and the base (used in catalytic amount) to liberate the corresponding thiolate anion which is expected to attack the alkoxy alkyl carbon of the ether giving rise to aryloxide anion. Proton exchange between the aryloxide anion, liberated after initial ether cleavage, and the thiol (present in the medium) should replenish the effective nucleophile (R^1S^-) and maintain the catalytic cycle (**Figure 1**). This 'demand based thiolate anion generation' protocol should be able to deprotect aryl alkyl ethers chemoselectively.

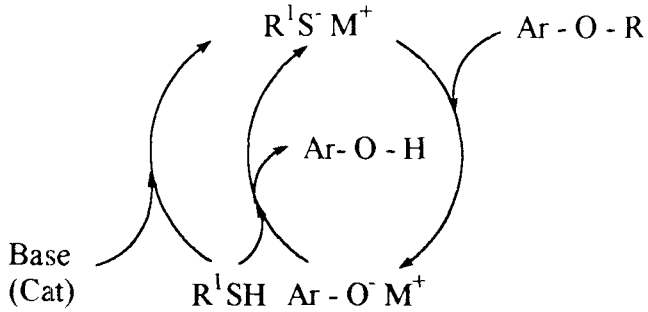
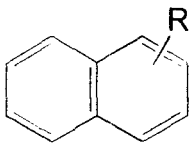


Figure 1

However the effectiveness of this catalytic procedure will depend on the effective proton exchange (i) between the thiol and the base and (ii) between the aryloxide and the thiol. We chose to use aromatic thiol (R^1 = Ph) considering its more acidic nature

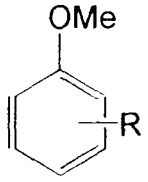
(compared to alkane thiols) so that the initial proton exchange with carbonate or hydroxide base easily takes place to trigger the reaction and more specifically the proton exchange with the liberated aryloxide anion becomes feasible (alkane thiols are not acidic enough for such purpose) apart from its easy handling (b.p. : PhSH 169^{0}C; EtSH 35^{0}C; ^{n}PrSH 68^{0}C; ^{i}PrSH 60^{0}C) and low cost (1996 - 1997 Aldrich Price in US $: PhSH 75.10 for 1 Kg.; 4-Me-C_6H_4SH 134.75 for 500 g.).

Ether cleavage reactions were carried out with different naphthyl alkyl ethers (**1a - f**) and phenyl methyl ethers [bearing Cl, NO_2, NH_2, CN, CHO, COMe, CH = CH (styryl), CH = CH - CO -, CO - COPh and CONHPh functionalities] (**2a - k**; **3 - 8**). The effects of base, solvent and reaction temperature were evaluated. The results obtained under the best operating system are summarised in **Table 1**.



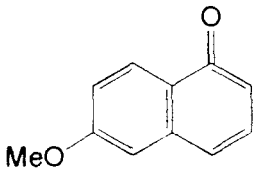
1

a : R = 2-OMe;
b : R = 2-OEt;
c : R = 2-OCH_2Ph;
d : R = 1-OMe;
e : R = 1-OEt;
f : R = 1-OCH_2Ph



2

a : R = 2-Cl; **b** : R = 2-NH_2;
c : R = 3-CHO; **d** : R = 4-Cl;
e : R = 4- NO_2; **f** : R = 4-CN;
g : R = 4-COMe; **h** : R = 4-CHO
i : R = 4-COCOPh;
j : R = 4-CONHPh;
k : R = 4-NHCOPh



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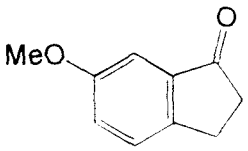

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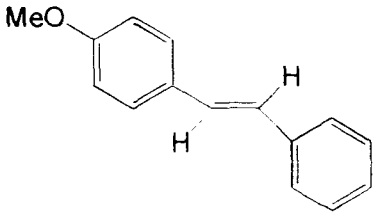

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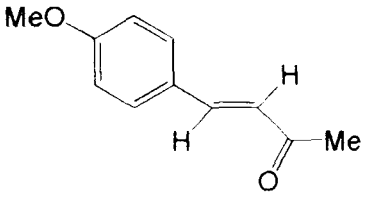

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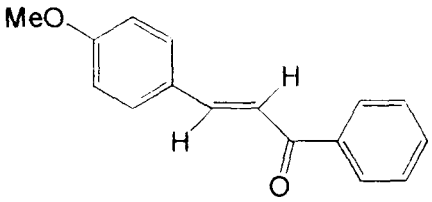
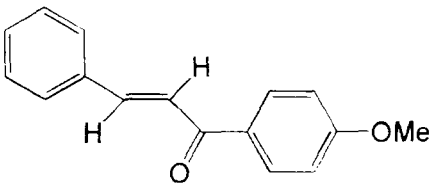


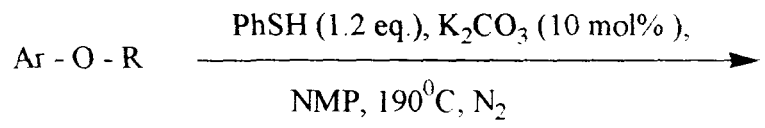
7



8

[The work involving the chemoselective cleavage of aryl alkyl ether forms a communication entitled " Chemoselective Aryl Alkyl Ether Cleavage by Thiophenolate Anion Through its *In Situ* Generation in Catalytic Amount", by Mrinal K. Nayak and Asit K. Chakraborti*, *Tetrahedron Lett.*, In Press.]

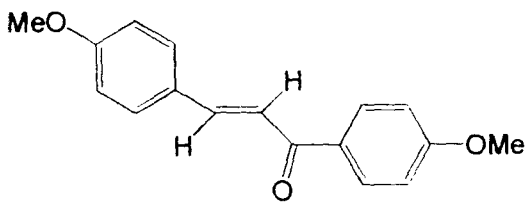
Table 1. Chemoselective Cleavage of Aryl Alkyl Ethers *via in situ* Generation of PhS^- in a 'Demand Based Fashion'.



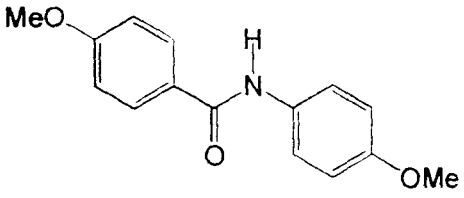
Entry	Ar - O - R	Reaction Time (min)	Yield (%)
1	**1a**	30	97
2	**1b**	30	60
3	**1c**	30	76
4	**1d**	30	97
5	**1e**	30	58
6	**1f**	30	80
7	**2a**	30	65
8	**2b**	60	75
9	**2c**	30	85
10	**2d**	30	70
11	**2e**	10	68
12	**2f**	10	60
13	**2g**	10	85
14	**2h**	10	90
15	**2i**	10	85

16	**2j**	30	53
		120	94
17	**2k**	120	32
18	**2l**	60	40
19	**2m**	60	25
20	**3**	30	90
21	**4**	30	75
22	**5**	30	80
23	**6**	30	73
24	**7**	30	90
25	**8**	10	83

Reactions were carried out to judge the selectivity of the protocol in various intermolecular competitions and to evaluate the influence of steric and electronic factors in the course of the reaction. Different dimethoxy compounds (**9** - **13**) were subjected to ether cleavage reaction for evaluation of regioselectivity of the process and the results are summarised in **Schemes I - VII**.



9



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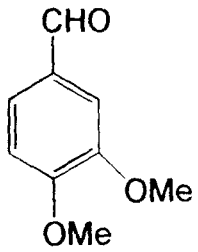

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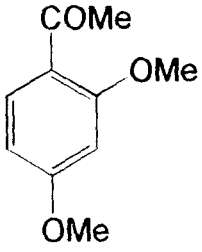

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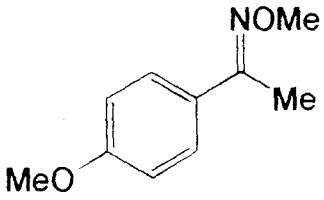
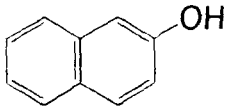


13

Scheme I



100 %

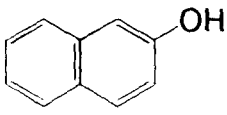
+

1a + **1b**

40 % 60 %

1a + **1b** —PhSH (2.5 mmol), K_2CO_3 (10 mol%), NMP, 190^{0}C, 30 min, N_2→

2.5 mmol 2.5 mmol



100 %

+

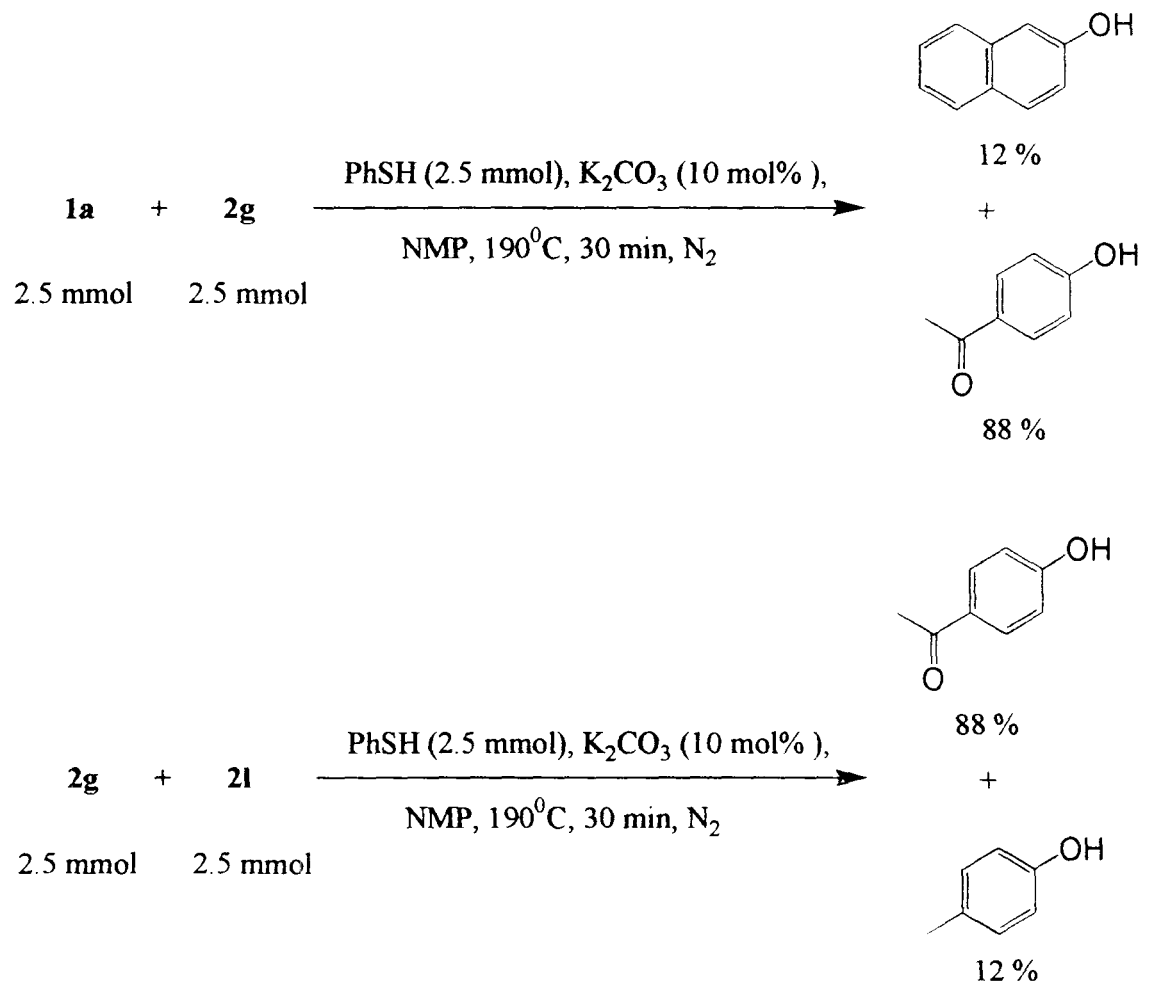
1b + **1c**

61 % 39 %

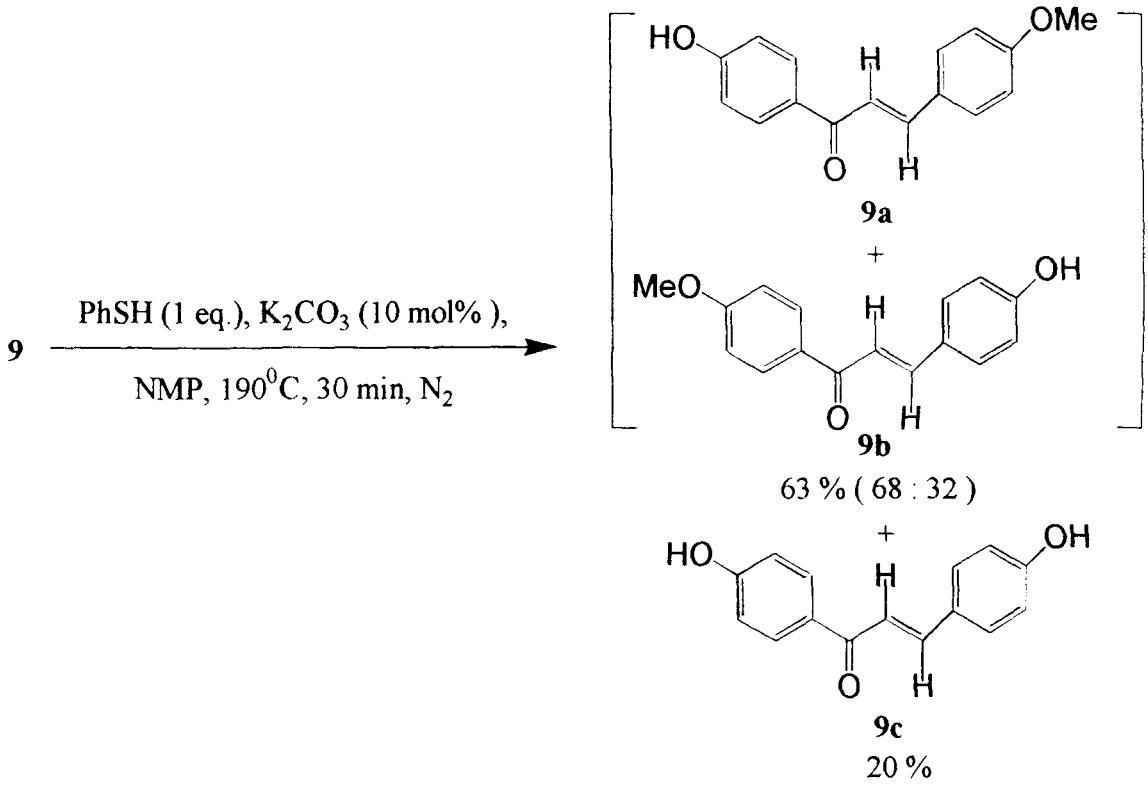
1b + **1c** —PhSH (2.5 mmol), K_2CO_3 (10 mol%), NMP, 190^{0}C, 30 min, N_2→

2.5 mmol 2.5 mmol

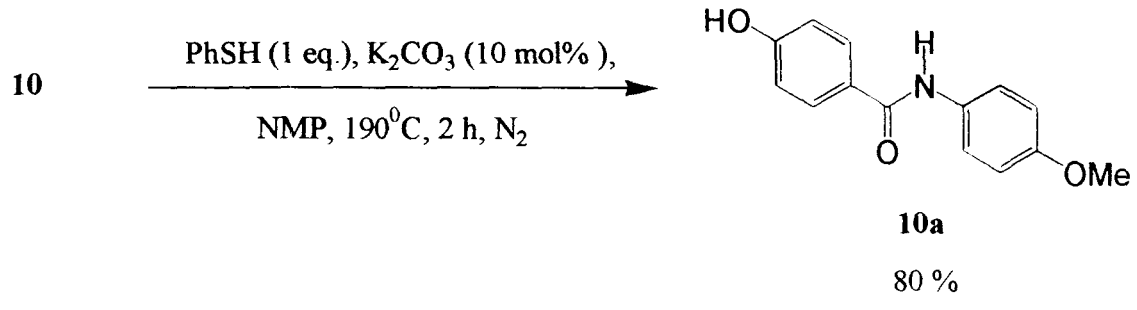
Scheme II


OH
12 %
1a + 2g
PhSH (2.5 mmol), K2CO3 (10 mol%),
NMP, 190°C, 30 min, N2
+
2.5 mmol 2.5 mmol
OH
O
88 %
OH
O
88 %
2g + 2l
PhSH (2.5 mmol), K2CO3 (10 mol%),
NMP, 190°C, 30 min, N2
+
2.5 mmol 2.5 mmol
OH
12 %
2c + 2h
PhSH (2.5 mmol), K2CO3 (10 mol%),
NMP, 190°C, 30 min, N2
2c + OH CHO
2.5 mmol 2.5 mmol
100 % 100 %

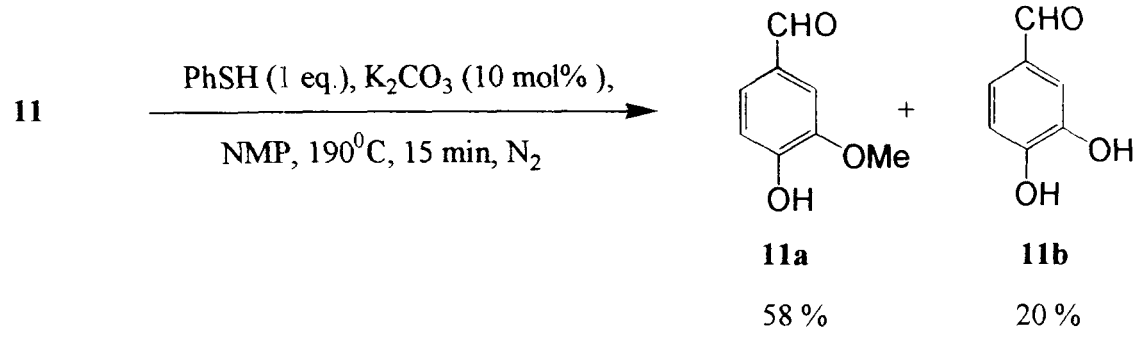
Scheme III



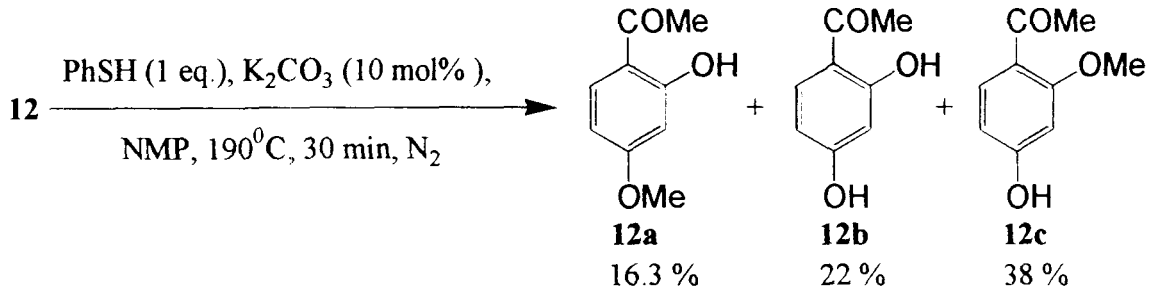
Scheme IV



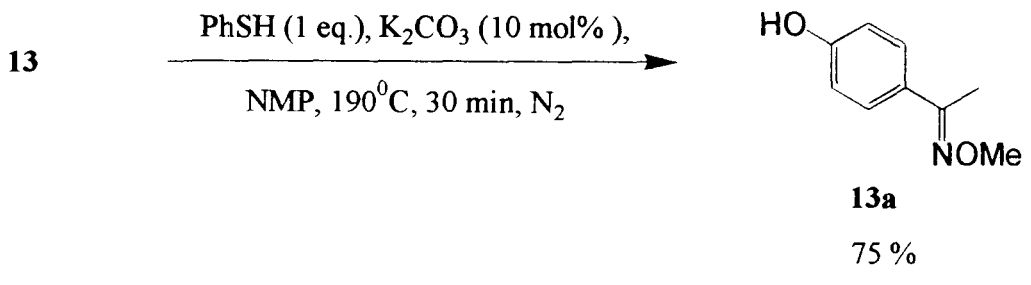
Scheme V



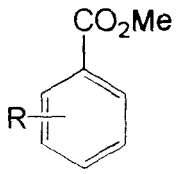
Scheme VI



Scheme VII

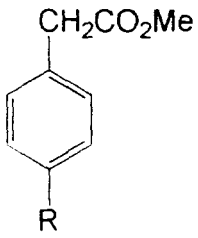


The efficacy of this 'demand based generation of the thiophenolate anion' for non-hydrolytic deprotection of methyl esters was evaluated using various substrates (**14a - h, 15a,b**; **16**, **17a,b**; **18a,b**; **19a,b**). The catalytic effect of alkali metal salts MX (M = Na, K; X = F, Cl, Br, I) in the non-hydrolytic ester O - Me cleavage *via in situ* generation of the thiophenolate anion was also evaluated. The results obtained through these protocols are summarised in **Tables 2** and **3**.



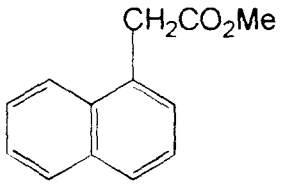
14

a : R = H; **b** : R = 2-Cl;
c : R = 2-NO_2; **d** : R = 2-OH;
e : R = 3-NO_2; **f** : R = 4-Cl;
g : R = 4-NO_2; **h** : R = 4-OH

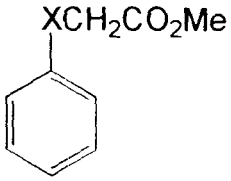


15

a : R = H;
b : R = OMe

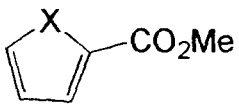


16



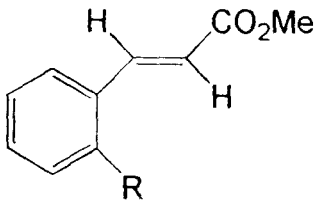
17

a : X = O;
b : X = S



18

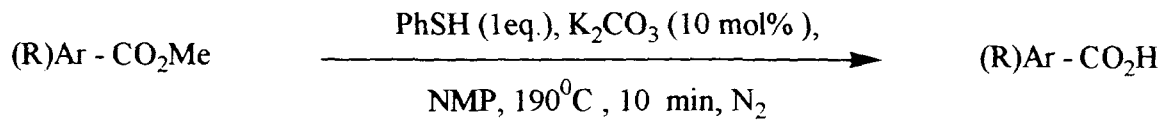
a : X = O;
b : X = S



19

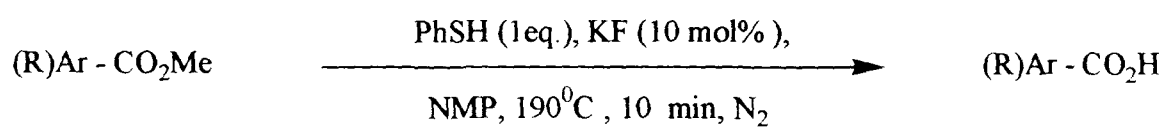
a : R = H
b : R = NO_2

Table 2. Chemoselective Non-hydrolytic Deprotection of Methyl Esters.



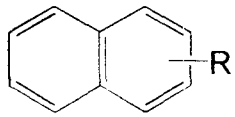
Entry	Substrate	Yield (%)
1	**14a**	100
2	**14b**	75
3	**14c**	65
4	**14d**	83
5	**14e**	70
6	**14f**	75
7	**14g**	60
8	**14h**	55
9	**15a**	95
10	**15b**	76
11	**16**	90
12	**17a**	80
13	**17b**	72
14	**18a**	100
15	**18b**	75
16	**19a**	86

Table 3. Chemoselective Non-hydrolytic Deprotection of Methyl Esters Under Neutral Condition



Entry	Substrate	Yield (%)
1	**14a**	90
2	**14b**	80
3	**14c**	60
4	**14d**	86
5	**14e**	70
6	**14f**	80
7	**14g**	70
8	**14h**	55
9	**15a**	85
10	**16**	80
11	**17a**	90
12	**17b**	75
13	**18a**	90
14	**19a**	70
15	**19b**	72

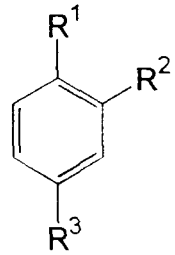
Chemoselective deprotection of aryl acetates and aryl benzoates were studied with the following substrates (**20a,b**; **21a - h**; **22a,b** and **23**) and the results are mentioned in **Table 4**.



20

a : R = 2-OCOMe;

b : R = 2-OCOPh



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a : R^1 = OCOMe, R^2 = H, R^3 = Cl;

b : R^1 = OCOMe, R^2 = H, R^3 = NO_2;

c : R^1 = OCOMe, R^2 = H, R^3 = COMe;

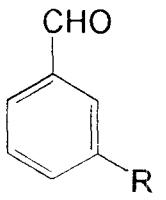
d : R^1 = OCOMe, R^2 = R^3 = Cl;

e : R^1 = OCOPh, R^2 = H, R^3 = Cl;

f : R^1 = OCOPh, R^2 = H, R^3 = NO_2;

g : R^1 = OCOPh, R^2 = H, R^3 = COMe;

h : R^1 = OCOPh, R^2 = R^3 = Cl;



22

a : R = OCOMe;

b : R = OCOPh

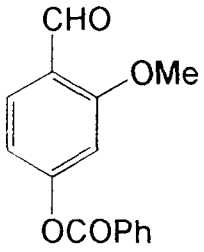


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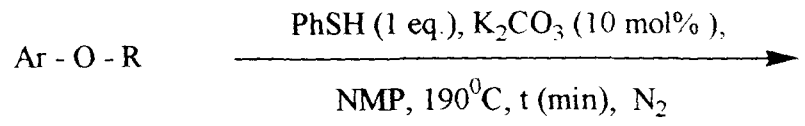
Table 4. Chemoselective Deprotection of Aryl Acetates and Aryl Benzoates.



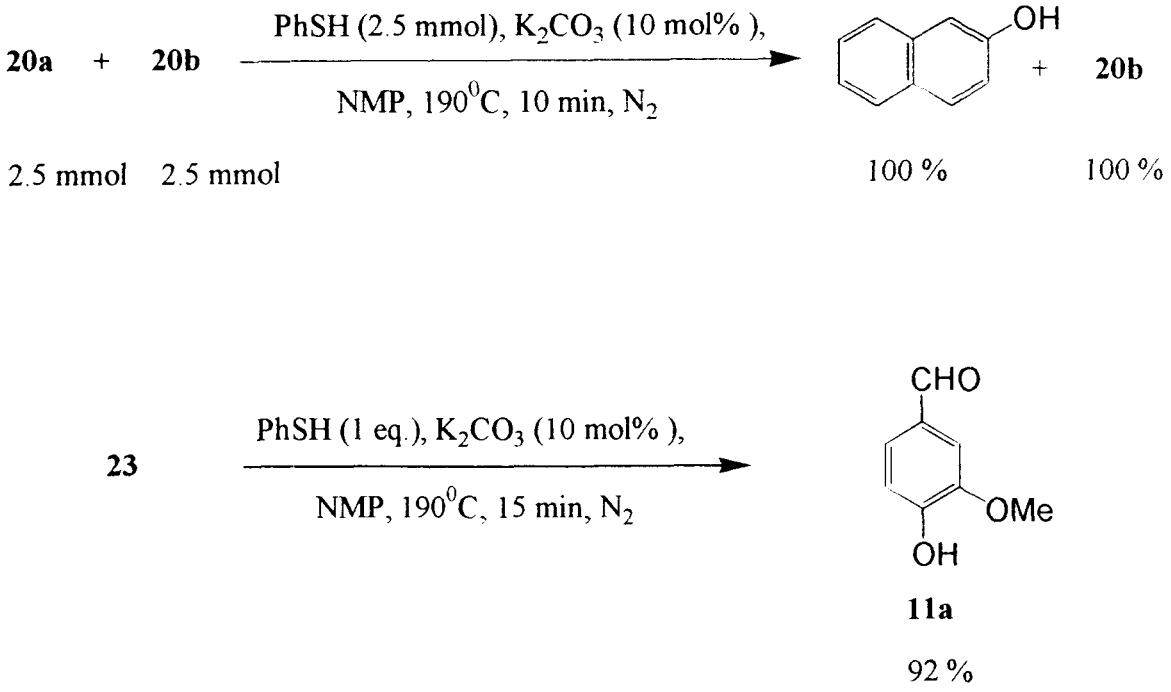
R = COMe, COPh

Entry	Substrate	Reaction Time (min)	Yield (%)
1	**20a**	5	91
2	**20b**	15	90
3	**21a**	5	92
4	**21b**	5	88
5	**21c**	5	90
6	**21d**	5	92
7	**21e**	15	74
8	**21f**	15	85
9	**21g**	15	85
10	**21h**	15	74
11	**22a**	5	90
12	**22b**	15	90
13	**20b**	60	00*

* Reaction was carried out in absence of PhSH.

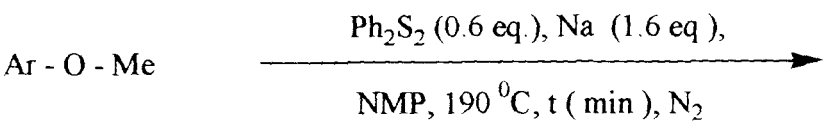
The selectivity of this protocol for inter- and intramolecular competition is demonstrated in **Schemes VIII**.

Scheme VIII



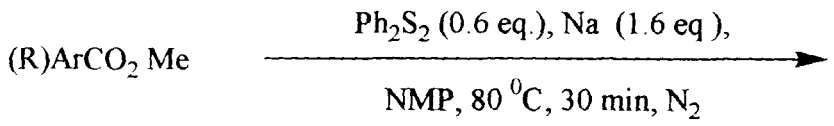
Nucleophilic O- Me cleavage was studied by reductive *in situ* generation of thiolate anion and the ethers (**1a**; **2g,h,i** and **7**) and esters (**14a - c**; **17b** and **18b**) were the substrates chosen for this investigation. The results of these studies are summarised in **Tables 5** and **6**.

Table 5. Chemoselective Aryl Methyl Ether Cleavage through *In Situ* Reductive Generation of PhS^- from PhSSPh.



Entry No.	Substrate	Time (min)	Yield (%)
1	**1a**	30	93
2	**2g**	15	90
3	**2h**	15	92
4	**2i**	15	97
5	**7**	30	65

Table 6. Chemoselective Ester O - Me Cleavage through *In Situ* Reductive Generation of PhS^- from PhSSPh.



Entry No.	Substrate	Yield (%)
1	**14a**	84
2	**14b**	100
3	**14c**	50
4	**17b**	97
5	**18b**	100