Pergamon

Tetrahedron Letters 39 (1998) 4883–4886

TETRAHEDRON LETTERS

Chemoselective *O*-Methylation of Phenols under Non-aqueous Condition[!]

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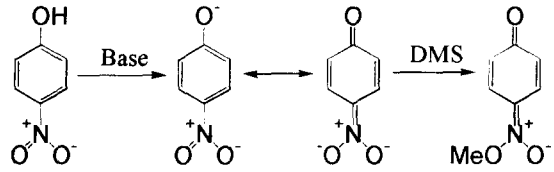
Received 21 January 1998; revised 27 February 1998; accepted 24 April 1998

Abstract *: Chemoselective O-methylation of substituted phenols takes place in dry tetrahydrofuran (THF) in the presence of $LiOH.H_2O$ and dimethylsulfate (DMS). Quantitative methyl transfer from DMS preserves the atom economy.*

Functional group interconversion is the inevitable operation for logic centred synthesis of target molecules. In this regard the masking of phenols is amongst the most frequently desirable transformation. Considering the ease of regeneration[1] it is convenient to protect phenols as methyl ethers. Aryl methyl ethers are conventionally prepared[2] by treating phenols with DMS in aqueous alkali at 70-100^{0}C. Other methods relevant to this coveted transformation include K_2CO_3-MeI in acetone under reflux,[3] KOH-MeI in DMSO,[4] K_2CO_3-Cl_3CCO_2Me-(18-C-6) at 150^{0}C,[5] KOH-H_2O-DMS in dioxane or triglyme at 40-60^{0}C,[6] Li_2CO_3-MeI in DMF at 55^{0}C,[7] Cs_2CO_3- R_2SO_4 in acetone under reflux,[8] MeCl in aqueous KOH-NaOH (7:3) at 110^{0}C under pressure,[9] NaOH-DMS-PTC,[10] Cs_2CO_3-MeI in MeCN at 80^{0}C,[11] and DMS in aqueous NaOH under microwave heating.[12] These methods suffer from the disadvantages of using costly reagents, requiring high temperature/pressure, involving longer reaction time and needing special equipment. The use of high boiling solvents like DMSO, DMF, NMP or triglyme make the solvent recovery (necessary for large scale reactions) a tidious process. The most serious drawback being the unwanted hydrolytic cleavage of DMS for reactions carried out in aqueous alkaline medium necessitating the use of a large excess of the toxic reagent. Protection in aqueous alkali is not feasible with substrates bearing alkali labile groups such as amide or ester. Moreover reactions carried out in highly polar solvents such as H_2O, DMSO etc. are not suitable for phenols bearing strong electron withdrawing groups (CN or NO_2) due to the additional problem of chemoselectivity (eq 1).[13]

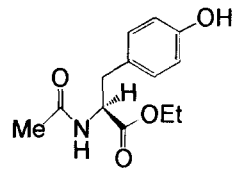
0040-4039/98/$19.00
PII: S0040-4039(98)00885-5



Eq. 1

We directed our focus towards the development of a non-aqueous method for methylation of phenols using DMS so as to avoid the unwanted hydrolytic loss of the reagent. From the view point of atom economy[14] we also kept our objective to utilise both the methyl groups of DMS for quantitative methyl transfer. Much to our delight, we found that the use of a stoichiometric amount of $LiOH.H_2O$ and 0.5 equivalent of DMS in dry THF afforded quantitative formation of methyl ether of phenols in most of the cases (table 1).[15]

The scope and limitations of this protocol may be realised in that no hydrolytic cleavage of ester or amide group takes place (entries 10-12,23,24). No competitive *N*-[4,16] or *O*-[17] alkylation of amide group is observed (entries 12,23,24). Efficient ether formation is achieved for substrates containing electron withdrawing groups (entries 8-22) although a stoichiometric amount of the alkylating agent is required for excellent results. Tyrosine derivatives **1** and **2** are methylated in excellent yields on treatment with 0.5 equivalent of DMS under this protocol without affecting the optical purity and ester/amide functionalities of the molecules implicating the mildness of the procedure.



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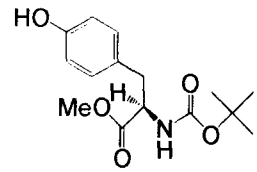


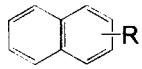
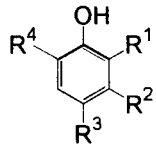
2

Use of other alkali or alkaline earth metal hydroxides or carbonates (including Li_2CO_3) provided only poor to moderate yields. Other solvents of comparable polarity such as Et_2O, dioxane, DME and THP were found to be inferior. The importance of the Li^+ counter ion was realised by the fact that preformed sodium 4-nitrophenolate provided an inferior result on treatment with an equivalent amount of DMS in THF. The coordinating capability of Li^+ seems to be the driving force for this quantitative methylation/ethylation procedure.[18]

This modified protocol is the only method that effectively exploits both the alkyl groups of dialkylsulfates. The two step[19] quantitative methyl transfer method finds its limitation in using aqueous medium at elevated temperature (94-98^{0}C) and a longer reaction time (4h).

We have described herein an efficient chemoselective methylation/ethylation of phenols in a non-aqueous medium enabling quantitative alkyl group transfer from dialkylsulfates. Further studies are in progress to evaluate the versatility of the procedure for inter and intramolecular competitions.

Table 1. Chemoselective Alkyl Ether Formation of Phenols with Dialkylsulfates

Entry	Phenol	Temp (°C)	Time (h)	Yield (%)
				
1	R = 1-OH	RT	1	100 (85)
2	2-OH	RT	1	100 (90)
				
3	R^1 = Cl; R^2 = R^3 = R^4 = H	RT	1	100 (85)
4	R^1 = R^2 = R^4 = H; R^3 = Cl	RT	1	100 (90)
5	R^1 = R^4 = H; R^2 = Me; R^3 = Cl	RT	1	100 (80)
6	R^1 = OMe; R^2 = R^4 = H; R^3 = Me	RT	1	100
7	R^1 = OMe; R^2 = R^4 = H; R^3 = $CH_2CH{:}CH_2$	RT	1	95
8	R^1 = CN; R^2 = R^3 = R^4 = H	70	0.5	90
9	R^1 = R^2 = R^4 = H; R^3 = CN	70	0.5	100
10	R^1 = CO_2Me ; R^2 = R^3 = R^4 = H	70	0.5	72
11	R^1 = R^2 = R^4 = H; R^3 = CO_2Me	70	0.5	80
12	R^1 = $CONH_2$; R^2 = R^3 = R^4 = H	70	0.5	70
13	R^1 = COMe ; R^2 = R^3 = R^4 = H	70	1.5	75
14	R^1 = R^2 = R^4 = H; R^3 = COMe	70	1.5	90
15	R^1 = NO_2 ; R^2 = R^3 = R^4 = H	70	0.5	95 (85)
16	R^1 = R^3 = R^4 = H; R^2 = NO_2	70	0.5	100 (100)
17	R^1 = R^2 = R^4 = H; R^3 = NO_2	70	0.5	100 (85)
18	R^1 = R^3 = NO_2; R^2 = R^4 = H	70	0.5	100 (94)
19	R^1 = NO_2 ; R^2 = R^4 = H; R^3 = Cl	70	0.5	80
20	R^1 = Cl; R^2 = R^4 = H; R^3 = NO_2	70	0.5	94
21	R^1 = NO_2 ; R^2 = R^4 = H; R^3 = COMe	70	1.5	72
22	R^1 = H; R^2 = Me; R^3 = Cl; R^4 = NO_2	70	1.5	72
23	**1**	RT	1	100
24	**2**	RT	1	90

[a]Figures under parentheses represent reaction with dialkylsulfate.

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! NIPER Communication No.9

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15. Phenol (5 mmol) was treated with $LiOH.H_2O$ (5 mmol) in dry THF (5 mL) at room temperature (0-5^{0}C for nitrophenols) for 10 min. Dialkylsulfate (2.5 mmol; 5 mmol in the case of activated phenols) was added and the mixture stirred for 1h at room temperature (or as mentioned in table 1). The solvent was distilled off, the residue treated with 5% aq. NaOH (20 mL) and extracted with Et_2O to afford the product, needing no further purification in most of the cases. Unreacted phenol, wherever applicable, was recovered and recycled raising the yields to virtually quantitative.
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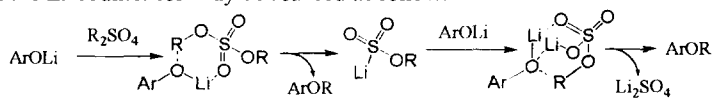
18. The role of the Li^+ counter ion may be realised as follow:



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