Pergamon

Tetrahedron Letters 40 (1999) 1843–1846

TETRAHEDRON LETTERS

Cesium Promoted *O*-Alkylation of Alcohols for the Efficient Ether Synthesis

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Received 18 November 1998; revised 5 January 1999; accepted 7 January 1999

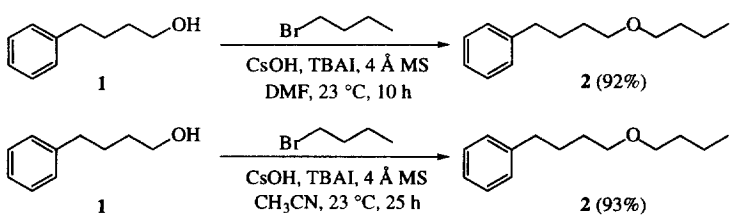
Abstract

Efficient Williamson type *O*-alkylation of alcohols was developed using cesium bases in the presence of tetrabutylammonium iodide (TBAI) and molecular sieves. Various substrates including unreactive primary and secondary alcohols were converted smoothly to the corresponding ethers. Electrophiles used herein encompass primary bromides and reactive halides such as benzyl bromide and MPMCl.

Keywords: Cesium carbonate and cesium hydroxide; TBAI; molecular sieves; *O*-alkylation of alcohols; hydroxyl protection

The ether linkage[1] is found prevalently in a variety of synthetic targets including oligonucleotides and carbohydrates,[2] and it is also recognized as a crucial element in hydroxyl protection.[3] Among the numerous conditions developed for ether formation, the Williamson type synthesis seems to provide the best generality for the preparation of both symmetric and unsymmetric ethers.[4] The aforementioned methodologies utilize either pre-formed or *in situ* generated alkoxides, of which reactivities are typically augmented by exploiting crown ethers, metal salts, or phase transfer catalysts.[5] Pursuing a universal method, we sought a complementary protocol employing cesium bases for *O*-alkylation of aliphatic alcohols.

Scheme A



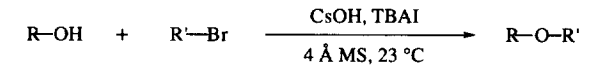
Cesium bases have demonstrated several merits in alkylation, highlighted by comparatively high solubilities, appropriate basicities and good stabilities.[6] Taking advantage of these properties, C-O bond formation between aliphatic alcohols and alkyl bromides was probed carefully,[7] and it was found that the employment of cesium hydroxide in the presence

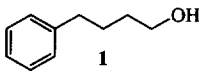
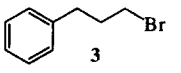
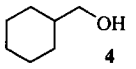
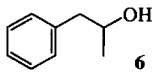
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00083-0

of both tetrabutylammonium iodide (TBAI) and powdered molecular sieves gave the most satisfactory results for the ether synthesis (Scheme A). When the alcohol **1** was subjected to the standard conditions in either *N,N*-dimethylformamide or acetonitrile, the desired ether **2** was produced exclusively in excellent yields.

Due to weak solvation (*i.e.*, "naked anions"), the *in situ* generated cesium alkoxides are considered to be more nucleophilic than the corresponding alkoxides conjugated with other alkali metals, facilitating the S_N2 type replacement.[8] In addition, TBAI and molecular sieves accelerated the conversion and improved the yield significantly. Contribution from TBAI stemmed presumably from a Finkelstein type reaction and phase transfer catalysis,[5e] while powdered 4 Å molecular sieves removed water, securing the alkoxides from protonation and driving reactions to completion.

Scheme B



Entry	Alcohol (ROH)	Bromide (R'Br)	Solvent	Time	Yield
1	 **1**	 **3**	DMF	11 h	97%
2	 **4**	**3**	DMF	13 h	93%
3	**1**	$BrCH_2CO_2{}^tBu$	CH_3CN	25 h	89%
4	Dihydrocholesterol (**5**)	*n*-BuBr	DMF	24 h	86%
5	Dihydrocholesterol (**5**)	*n*-BuBr	CH_3CN	36 h	82%
6	 **6**	*n*-BuBr	DMF	22 h	78%

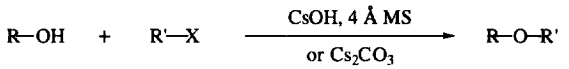
As delineated in Scheme B, the developed technology was evaluated for benefits and limitations. Unreactive aliphatic alcohols and bromides were coupled to give the corresponding ethers in remarkable yields. Both primary (**1** and **4**) and secondary alcohols (**5** and **6**) reacted smoothly with primary halides, providing the desired products exclusively under standard conditions, whereas secondary bromides were resistant to the intended transformation. When 3-phenyl-1-bromopropane **3** was utilized as an electrophile (entry 1 and 2), the desired ethers were prepared in high yields with trace dehydrobromination products.[9] When *tert*-butyl bromoacetate, vulnerable to transesterification, was employed in CH_3CN (entry 3), the etherification proceeded smoothly without complications.

O-Alkylation of secondary carbinols also proved efficient, giving the substitution products exclusively (entry 4, 5, and 6). As observed in the above cases, the ether formation in DMF was more efficient than in acetonitrile (entry 4 and 5). These conditions are expected to constitute a general synthetic method for alkyl ethers from unreactive coupling partners.

Regarding hydroxyl protection, investigation was directed towards etherification with active electrophiles (Scheme C). Under the optimal conditions, unreactive alcohols were smoothly alkylated using CsOH in the presence of molecular sieves.[10] For instance, primary

and secondary alcohols were masked as benzyl and 4-methoxyphenylmethyl (MPM) ethers, affording high yields (entry 1, 2, and 3). However, these conditions were harsh to α-carbonyl alcohols, prompting us to search milder conditions for the etherification of such functionalities.

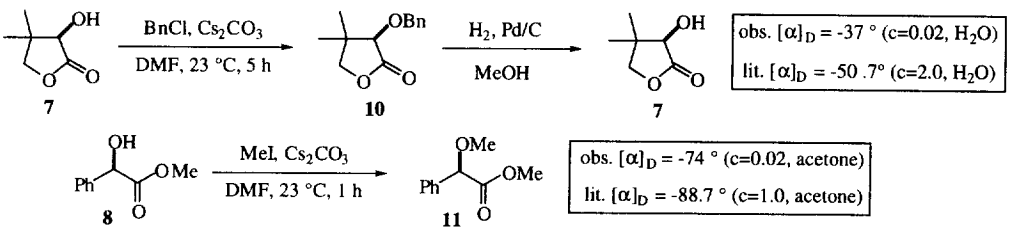
Scheme C



Entry	Alcohol (ROH)	Halide (R'X)	Conditions	Time	Yield
1	**1**	BnBr	CsOH, 4 Å MS, DMF, 23 °C	3 h	97%
2	**1**	MPMCl	CsOH, 4 Å MS, DMF, 23 °C	2.5 h	89%
3	**6**	MPMCl	CsOH, 4 Å MS, DMF, 23 °C	3 h	90%
4	Pantolactone (**7**)	BnCl	Cs_2CO_3, DMF, 23 °C	5 h	93%
5	Pantolactone (**7**)	MPMCl	Cs_2CO_3, DMF, 23 °C	3 h	84%
6	Pantolactone (**7**)	Allyl bromide	Cs_2CO_3, DMF, 23 °C	3 h	90%
7	Methyl mandelate (**8**)	MeI	Cs_2CO_3, DMF, 23 °C	1 h	88%
8	Pantolactone (**7**)	BnCl	Cs_2CO_3, CH_2Cl_2, reflux	11 h	96%
9	Ethyl lactate (**9**)	BnBr	Cs_2CO_3, CH_2Cl_2, reflux	5 h	73%

With α-hydroxy esters and lactones, Cs_2CO_3 was the base of choice and the use of 4 Å MS was not necessary. For instance, pantolactone **7** was converted to its corresponding ethers in high yields, using various halides (benzyl chloride, MPMCl, and allyl bromide), which was not possible with other known methods[11] (entry 4, 5, and 6). Hydroxyesters such as methyl mandelate **8** were also efficiently alkylated, giving satisfactory results (entry 7). Under milder conditions, hydroxyl protection was also feasible in dichloromethane, for example, pantolactone **7** was benzylated smoothly to provide an excellent yield (entry 8). These conditions were compatible with the substrates sensitive to hydrolysis or decomposition. While lactate **9** was marginally converted to the desired benzyl ether in DMF, benzylation carried out in methylene chloride was successful, delivering the ether cleanly (entry 9).

Scheme D



To our disappointment, racemization occurred to some degree when chiral α-carbonyl alcohols susceptible to enolization were employed (Scheme D). For instance, chiral pantolactone **7** was protected as its benzyl ether **10** (entry 4), causing about 27% racemization, while methylation of mandelate **8** suffered from 17% loss in optical purity.

Enantiomeric purities of ethers **10** and **11** were determined by comparing the optical rotation values of scalemic **7** and **11** with reported values.[12]

As a modification of Williamson's ether synthesis, our newly explored methods exhibit great substrate generality, mild conditions, and experimental conveniences. In summary, the protocol involving the use of CsOH, TBAI and 4Å MS in DMF or CH_3CN would be useful in the coupling of unreactive alcohol and bromide counterparts. Active halides such as BnBr seem compatible with the conditions without TBAI, and reactive substrates such as α-hydroxy carbonyl compounds require milder conditions using Cs_2CO_3. These unprecedented synthetic protocols developed in our laboratories are believed to offer general methods for the formation of various carbon-oxygen bonds essential to numerous organic syntheses.

Acknowledgments: Financial support from the USF Research Council is gratefully acknowledged, as is support from the H. Lee Moffitt Cancer Center & Research Institute.

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9. With alkyl iodides, alkylation reactions furnished moderate yields due to the rapid dehydrohalogenation of iodides.
10. The addition of TBAI accelerated the decomposition of active halides, disturbing the desired process.
11. Under the known conditions (*cf.* refernce 3 and 5), pantolactone was resistant to protection as alkyl ethers. The intended reactions were incomplete even after prolonged durations, offering extremely low yields of desired products if any.
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