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LETTERS

Cs_2CO_3 Promoted *O*-Alkylation of Alcohols for the Preparation of Mixed Alkyl Carbonates

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Abstract

The presence of cesium carbonate and tetrabutylammonium iodide (TBAI) facilitated efficient *O*-alkylation of alcohols with alkyl halides, giving rise to the exclusive formation of mixed alkyl carbonates. The cesium effect was also examined comparatively with other alkali carbonates.

Keywords: Cesium carbonate; TBAI; *O*-alkylation of alcohols; mixed alkyl carbonates

Organic carbonates exhibit unique physical and chemical properties, accommodating a variety of applications.[1] In numerous organic syntheses, carbonates have been useful intermediates for functional group manipulations,[2] while also being utilized in everyday applications (*e.g.*, dyes, fuel additives, and lubricating oils).[3] Regarding polymerization, organic carbonates have been used in industry[4] as well as in biological and medicinal fields.[5] Recent studies have demonstrated promise in medical applications of aliphatic carbonates,[6] necessitating efficient carbonate synthesis.

Common methods leading to carbonates are categorized into alcoholysis of phosgene or its derivatives,[7] organic carbonate exchange,[8] carbon dioxide alkylation,[9] and inorganic carbonate alkylation.[10] Nonetheless, these methods lack in generality for the synthesis of mixed alkyl carbonates, prompting us to embark on carbonate synthesis by cesium promoted *O*-alkylation. In the presence of TBAI, 4-phenyl-1-butanol **1** was ligated to 1-bromobutane through a CO_2 bridge derived from Cs_2CO_3, resulting in the exclusive formation of carbonate **2** in excellent yield (Scheme A). Advantages of this methodology and its mechanistic insights are discussed in this report.

Scheme A

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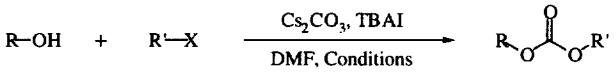
Under the explored standard conditions,[11] both primary and secondary alcohols reacted readily with primary halides, where various alkyl halides such as *t*-butyl bromoacetate were suitable to prepare exclusively unsymmetrical alkyl carbonates (entry 1, Scheme B). When active halides were employed, electrophiles appeared to decompose in the presence of TBAI, complicating the reaction results, whereas *O*-alkylations of primary alcohol **1** took place smoothly in the absence of TBAI to provide benzyl carbonates (entry 2 and 3). With secondary alcohols, similar trends were observed, delivering various mixed alkyl carbonates in reliable yields (entry 4 – 7). Relatively reactive alcohols encompassing benzyl alcohol were also converted to their corresponding carbonates by coupling with unreactive secondary bromides such as 2-bromobutane (*i.e.*, entry 8).

Scheme B

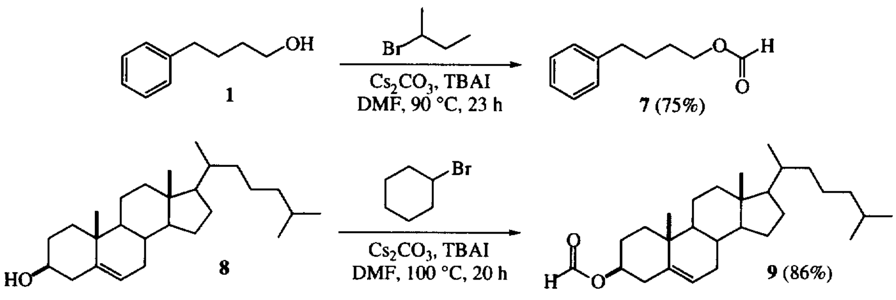


Entry	Alcohol (ROH)	Halide (R'X)	Temperature	Time	Yield
1	**1**	$BrCH_2CO_2{}^tBu$	100 °C	18 h	71%
2	**1**	BnCl*	95 °C	36 h	97%
3	**1**	MPMCl*	60 °C	20 h	59%
4	1-Phenyl-2-propanol (**3**)	$BrCH_2CO_2{}^tBu$	100 °C	18 h	72%
5	Menthol (**4**)	*n*-BuBr	100 °C	32 h	68%
6	Menthol (**4**)	$BrCH_2CO_2{}^tBu$	100 °C	25 h	55%
7	Ethyl lactate (**5**)	BnBr*	70 °C	5 h	44%
8	Benzyl alcohol (**6**)	2-Bromobutane	85 °C	20 h	76%

* When active halides were used, the reactions were run without TBAI to give satisfactory results.

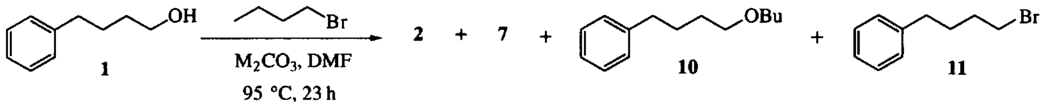
Despite limited success, most secondary bromides failed to promote the carbonate synthesis, favoring exclusively the competing process, formylation. As delineated in Scheme C, *O*-alkylations of primary alcohol **1** and cholesterol **8** yielded only the corresponding formates **7** and **9**, respectively. Because of clean conversion and high yield, these techniques would constitute an alternative to the existing methods in the preparation of formates.[12]

Scheme C



Subsequently, the roles of cesium carbonate were investigated by comparing alkali carbonates (Scheme D).[13] Since TBAI influenced the results,[14] all the reactions were carried out without TBAI for the same duration, then the products and the starting alcohol **1** were isolated. It is noteworthy that the use of Cs_2CO_3 culminated in the predominat formation of carbonate **2** while other alkali carbonates led to a complicated mixture of formate **7**, ether **10**, and bromide **11** in greater abundance than carbonate **2**. Apparently, cesium carbonate addresses a pronounced effect on alkyl carbonate synthesis.

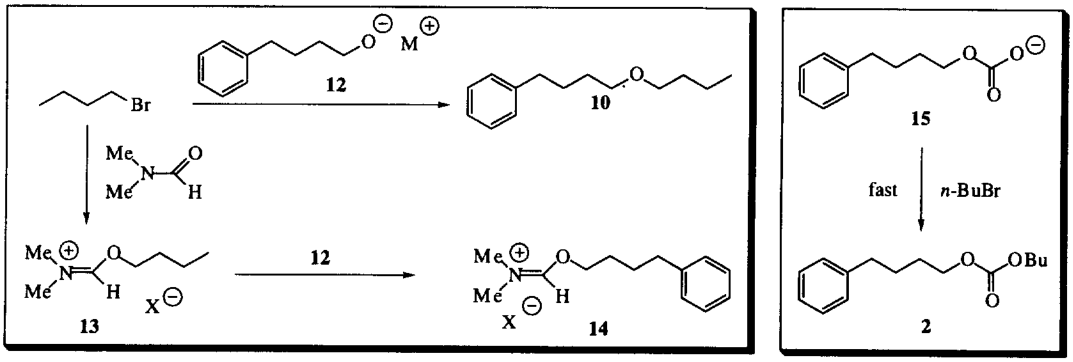
Scheme D



M_2CO_3	1 (recovered)	Carbonate (2)	Formate (7)	Ether (10)	Bromide (11)
Li_2CO_3	17%	Not observed	18%	31%	29%
Na_2CO_3	17%	Not observed	26%	32%	15%
K_2CO_3	15%	3%	21%	44%	11%
Rb_2CO_3	11%	18%	34%	20%	12%
Cs_2CO_3	18%	73%	3%	3%	Not observed

In Scheme E, plausible reaction pathways are proposed for the various products formed. The incipient alkoxide **12** would undergo etherification to deliver **10** or be incorporated into the Vilsmeier-Haack salt **14**,[12] forming bromide **11** or formate **7**.[15] On the other hand, Cs_2CO_3 liberates CO_2 and/or HCO_3^- which, in turn, react with the formed alkoxide **12**, and the resultant carbonic acid **15** would be *O*-alkylated to synthesize mixed carbonate **2**.[10b] Cesium bases and alkoxides are distinguished from those paired with other alkali metals in terms of "nakedness", weak conjugaton or solvation,[13] thus demonstrating the extraordinary effect on the carbonate formation under our conditions.

Scheme E



In summary, we have developed an efficient protocol for the synthesis of unsymmetric alkyl carbonates utilizing cesium carbonate as both a base and a carbon dioxide source. In this reported *O*-alkylation, primary and secondary alcohols were reacted with various primary alkyl bromides. This methodology is strongly believed to offer a general synthetic method of mixed carbonates for a variety of applications.

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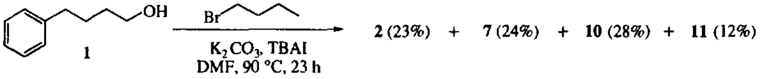
14. The carbonate formation was enhanced by the use of TBAI as demonstrated in the scheme below (*cf.* Scheme D).



15. The intermediate **13**, derived from the alkyl halide, was believed to be responsible for the formate formation because the reaction did not occur without alkyl halides. Moreover, non-volatile halides such as 3-phenyl-1-bromopropane and benzyl bromide produced the corresponding formates from these halides under the similar conditions in moderate yields.