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Mustard Carbonate Analogues as Sustainable Reagents for the Aminoalkylation of Phenols

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N,N-dialkyl ethylamine moiety can be found in numerous scaffolds of macromolecules, catalysts, and especially pharmaceuticals. Common synthetic procedures for its incorporation in a substrate relies on the use of a nitrogen mustard gas or on multistep syntheses featuring chlorine hazardous/toxic chemistry. Reported herein is a one-pot synthetic approach for the easy introduction of aminoalkyl chain into different phenolic substrates through dialkyl carbonate (β-aminocarbonate) chemistry. This new direct alcohol substitution avoids the use of chlorine chemistry, and it is efficient on numerous pharmacophore scaffolds with good to quantitative yield. The cytotoxicity via MTT of the β-aminocarbonate, key intermediate of this synthetic approach, was also evaluated and compared with its alcohol precursor.

Nitrogen and sulfur mustards (Figure 1; **1**–**4**), also called yperites, occupy a peculiar place in chemistry history; from battlefields to the first cancer treatment, their story covers almost 200 years. Bis(2-chloroethyl)sulfide **1**, discovered in 1822,[1] was described as a malodorous, high boiling compound able to aggressively attack the hydrated parts of the body, like eyes and lungs, leading, in case of prolonged exposure, to death.[2–3]

In 1942 Goodman and Gilman, demonstrated that nitrogen mustards, as ß-chloroethylamine **2**, were effective as cytotoxic agents. Their studies led to clinical investigations of nitrogen mustards to treat a non-Hodgkin's lymphoma, paving the way for anticancer chemotherapy.[4] Despite their well-known toxicity and undesired adverse effects, some nitrogen mustard drugs are still considered first-line therapy for certain types of cancer.

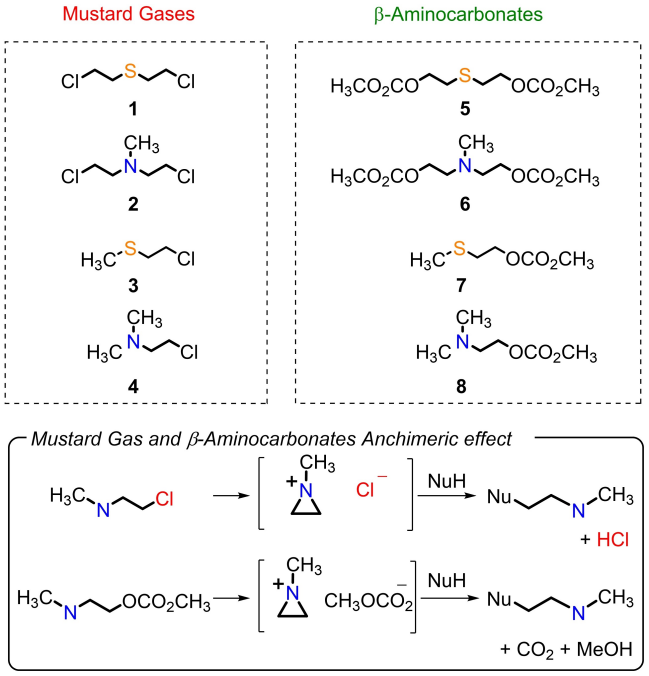

Figure 1. Structure and reactivity of mustard gas versus ß-aminocarbonates.

Nitrogen yperites have been also investigated as versatile electrophiles in the preparation of catalysts,[5] macromolecules,[6] and numerous pharmaceuticals. Such great interest in these molecules is grounded on their exceptional electrophile behavior enhanced by the nitrogen anchimeric assistance (Neighboring Group Participation, NGP) (Figure 1).[7] In fact, mustard gases can undergo fast intramolecular nucleophilic substitution to form an aziridinium ring that acts as electrophilic trap leading to effective alkylation of chemical building blocks or biological macromolecules (Figure 1).

The chemistry that underlies mustard gases has been extensively used to insert basic amine-containing side chains into pharmacophore scaffolds. This moiety, incorporated in several class of compounds such as Tamoxifen, Raloxifene, Amiodarone, Phenyltoloxamine, Trifenagrel, Trimethobenzamide, etc. (Figure 2), engages crucial interactions with target macromolecules and, as expected, subtle variations in the aminoalkyl chain structural features greatly influence the pharmacodynamic and/or pharmacokinetic profile of the compound. Therefore, in a hit-to-lead and lead-to-drug candidate

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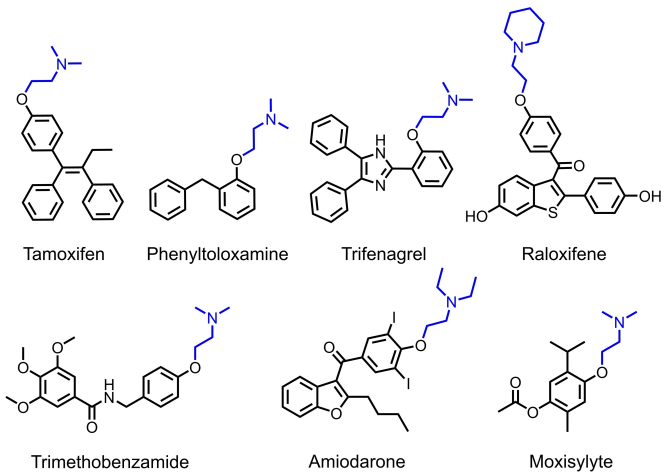


Figure 2. Pharmaceuticals incorporating *N,N*-dialkyl ethylamine moiety in their backbone structures.

optimization process,[8] several compounds should be synthesized to optimize this fragment.

If we consider phenolic moieties, which are preferred precursors of numerous pharmacophore scaffolds (Figure 1),[9] there are three main synthetic approaches for the introduction of the aminoalkyl chain in the molecular backbone, besides the anchimerically driven nucleophilic substitution via *N*-(2-chloroethyl)dialkylamine:

- Nucleophilic aromatic substitution between a (2-hydroxyethyl)dialkylamine and an aryl halide;[10]
- Mitsunobu reaction of (2-hydroxyethyl)dialkylamine with a (substituted) phenol; this synthesis mainly employs diethyl azodicarboxylate (DEAD) a well-known toxic and potentially explosive reagent;[11]
- Nucleophilic aliphatic substitution, i.e., reaction of dialkylamine and a (2-halide)ethoxyaryl substrate.[12]

These synthetic procedures are in general multistep and have as common features the use of hazardous/toxic chlorine chemistry and the necessity for time-consuming purification of the products.

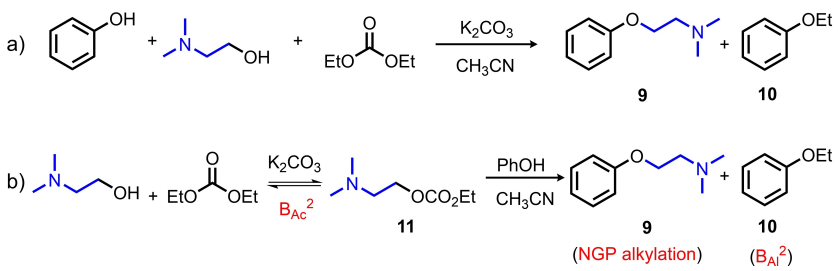
Over the years, it has been demonstrated that the replacement of a halogen atom by a carbonate moiety via dialkyl carbonate (DAC) chemistry has led to safer and greener syntheses.[13] In this context, we have recently reported a new class of organic carbonates, i.e. ß-aminocarbonates **5**–**8** (Figure 1), as green homologues of mustard gas.[14] Their syntheses and related reactivity have been investigated employing different reaction conditions (Scheme 1b);[15] data collected confirmed that ß-aminocarbonates retain the anchimeric effect of their mustard gas analogues, without showing evidence for toxic properties.

Herein, we described for the first time a one-pot procedure (Scheme 1a) for the high yielding introduction of the *N,N*-dialkyl ethylamine moiety by reaction of its alcohol precursor with a nucleophile (phenol) in the presence of a dialkyl carbonate (DAC). The latter is used for the *in-situ* formation, via the B_{Ac}^2 mechanism, of ß-aminocarbonate **11** that acts as an alkylating agent via nitrogen NGP (Scheme 1a). Different substrates have been investigated including precursors of commercially available drugs. This one-pot alkylation approach is a striking example of chlorine-free direct substitution of an alcohol, indicated as one of the key Green Chemistry research areas for pharmaceuticals manufacturers.[16] Furthermore, an *in vitro* toxicity study has been conducted on ß-aminocarbonate **11** and its alcohol precursor, giving an insight into the cytotoxicity values of the reagents for the synthetic procedure proposed.

The one-pot alkylation reaction was initially investigated by reaction of phenol, 2-dimethylaminoethanol and diethylcarbonate (DEC) in 1.0:1.5:1.5 mol ratio in the presence of potassium carbonate as a base (Table 1). DEC was preferred to dimethyl carbonate (DMC) due to its higher boiling point that renders it more suitable for this synthetic approach.

Preliminary tests were conducted by controlling the reaction temperature; the autoclave was at first heated at 140 °C (4 hours) to maximize the formation of 2-(dimethylamino)ethyl ethylcarbonate **11**. The temperature was then increased to 180 °C (20 hours) to promote the anchimerically driven alkylation (#1; Table 1). In these conditions phenol was quantitatively converted with 92% selectivity toward the alkylated product *N,N*-dimethyl-2-phenoxyethanamine **9**. The pure compound was recovered by rapid extraction in a separating funnel to remove potassium carbonate, the excess of DEC and alcohol. Ethoxybenzene **10**, formed in small amounts as a by-product, was distilled off whilst evaporating the excess solvent.

The reaction was repeated, now increasing the temperature of the alkylation to 200 °C and reducing the reaction time to a total of 8 hours (#2; Table 1). Despite observing a similar phenol conversion and product selectivity, the isolated yield of compound **9** was markedly lower.



Scheme 1. a) One-pot alkylation approach via ß-aminocarbonates formed in-situ versus b) two steps alkylation approach.

Table 1. One-pot alkylation: optimization of the reaction conditions.[a]

#	K_2CO_3 Eq. [mol].	CH_3CN [mL]	Temp. [°C]	Time [h]	Selectivity[%][b] **9**	**10**	Yield [%][c]
1	1.00	50	140 to 180	24	92	8	92
2	1.00	50	140 to 200	8	96	4	75
3[d]	1.00	50	180	8	90	10	74
4	1.00	50	200	8	98	2	98
5	1.00	50	200	6	92	8	85
6	1.00	30	200	8	90	10	92
7	1.00	100	200	8	92	8	80
8	–	50	200	8	12	88	–
9	0.25	50	200	8	93	7	86
10	0.50	50	200	8	93	7	81

[a] Reaction conditions: Phenol: 2-dimethylaminoethanol: DEC : K_2CO_3 1.0:1.5:1.5:1.0 mol ratio; Reactions were conducted in autoclave, Conversion was always quantitative unless differently specified; [b] Calculated via GC-MS and ^{1}H NMR; [c] Isolated yield; [d] Conversion of phenol was 90%.

On the other hand, the anchimerically driven alkylation was very efficient when carried out without varying the temperature (#3–4; Table 1) reaching 98% isolated yield of **9**.

Further experiments included: i) reducing the reaction time (#5; Table 1); ii) investigating the effect of the regent concentration (#6–7; Table 1); iii) decreasing the amount of potassium carbonate (#8–10; Table 1).

In all these trials *N*,*N*-dimethyl-2-phenoxyethanamine **9** was the main reaction product with isolated yields ranging from 80 to 92%. Interestingly if the reaction is conducted without base, ethoxybenzene **10** formed in high yield, while the alkylated product **9** was present only in trace amounts (#8; Table 1); this result confirms the importance of a base in promoting the formation of ß-aminocarbonate **11**, that is the key reaction intermediate.

It is noteworthy that in this one-pot alkylation approach, DAC chemistry is exploited at its full potential; in fact, DEC acts as *in-situ* ethoxycarbonylating agent *via* the BAc^2 mechanism, leading to an unsymmetrical carbonate able to selectively alkylate the phenol via nitrogen NGP; formation of the ethoxy derivatives **10** via concurrent $B_{Al}2$ mechanism is negligible (see Scheme 1b).

With the optimized reaction conditions in hand (#4; Table 1), the scope and limitations of this procedure were next investigated employing differently substituted phenols or amino alcohols (Figure 3, see also supporting information).

p-Methoxy- and *p*-chlorophenol were converted to the corresponding alkylated compounds **12**–**13** in excellent yield. Phenols *p*-substituted with electron-withdrawing groups (–NO_2 and –CN) have also been tested. As expected, the enhanced phenolic acidity of these substrates affects the selectivity towards the NGP driven alkylation leading to moderate yields of the wanted products **14** and **17**.

Similar results were observed when the nitro group was positioned in *ortho* or *meta* to the phenolic hydroxy moiety. Sterically hindered o-nitrophenol showed modest conversion (40%) and selectivity toward the alkylated product **15** (60%).

N,*N*-dimethyl-2-(2-naphthoxy)ethanamine **18** was obtained from β-naphthol in only moderate yield; a quite unexpected result in consideration of its similar nucleophilic behavior with phenol.

2-*tert*-Butylphenol and 2,6-di-*tert*-butylphenol were selected as sterically hindered substrates. The alkylated product **19** formed readily in good yield. On the other hand, di-*tert*-butylphenol, resulted in only partially conversion (67%) although the selectivity toward the wanted alkylated product was quantitative.

A range of different *N*,*N*-dialkyl aminoalcohols were next investigated. Reaction of 2-(diethylamino)ethanol with phenol and DEC led to the related *N*,*N*-diethyl-2-phenoxyethanamine **21** in high yield. 1-(2-Hydroxyethyl)pyrrolidine, 1-piperidinylethanol and 4-(2-hydroxyethyl)morpholine, incorporating 5- and 6-membered cyclic structures, gave the alkylated products **22**–**24** in excellent yields despite the more sterically hindered nature of their related aziridinium ring.

It is noteworthy that morpholine-containing side chains are incorporated in numerous pharmacophore scaffolds exhibiting optimum anti-malarial[17] and antitumor[18] activity, as well as having great potential in the treatment of Alzheimer's disease.[19]

N,*N*-dimethyl-2-phenoxypropanamine **25** was obtained in 78% yield from 3-(diethylamino)propanol; in this case a strained four-member 1,1-dimethylazetidinium[20] is the key intermediate leading to the alkylated product.

The aromatic diols hydroquinone and bisphenol-A were also investigated as substrates for the one-pot double alkylation reaction, resulting in the formation of bis(*N*,*N*-dimethyl ethylamine) derivatives **26** and **27** in almost quantitative yield. The high yielding alkylation observed on bifunctional substrates raises the possibility of applying this procedure in the synthesis of macromolecules such as macrocycles or polymers.

To further explore the value of this approach in drug discovery, we also tested different nucleophiles commonly used in the development of bioactive small molecules. For these compounds (**28**–**33**), in consideration of their more complex structure, we compared the one-pot alkylation procedure (Scheme 1a) with the previously reported methodology where 2-(dimethylamino)ethyl ethylcarbonate **11** was used as reagent (Scheme 1b). In the latter synthetic approach, experiments were conducted in the absence of a base.

Phenyltoloxamine **28**, used as an enhancing agent for analgesics and antitussives, was obtained in high yield from its

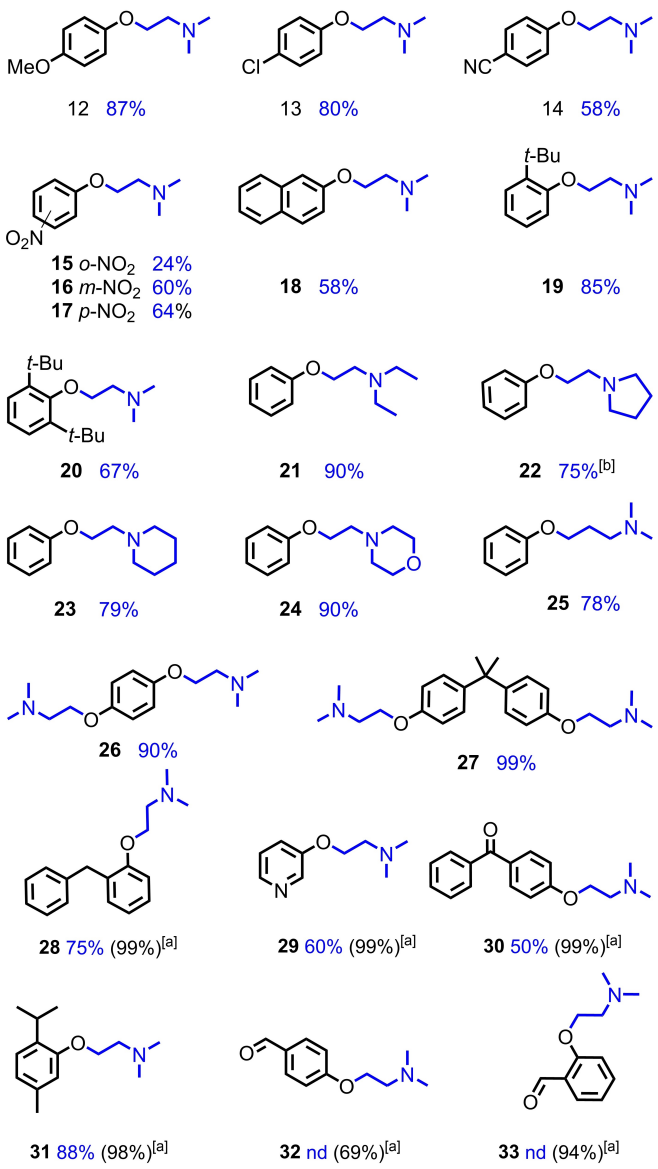


Figure 3. One-pot alkylation conditions (Scheme 1a): ArOH:aminoalcohol:DEC:K_2CO_3 1.0:1.5:1.5:1.0 mol ratio at 200 °C for 8 hour. For compounds **26**–**27** the molar ratio used were HOArOH:2-dimethylaminoethanol:DEC:K_2CO_3 1.0:3.0:3.0:2.0 mol ratio. Yields were calculated via ^{1}H NMR and GC-MS analysis. [a] Alkylations employing ß-aminocarbonate **11** (Scheme 1b); ArOH:ß-aminocarbonate **11** 1.00: 1.50 mol ratio at 200 °C for 8 hours.

precursor 2-benzylphenol via the one-pot synthetic approach. Introduction of the N,N-dimethyl ethylamine moiety employing previously synthetized ß-aminocarbonate **11** was even more effective, as the alkylated product was achieved in quantitative yield. The higher yield of the second methodology was to some extent expected as it was previously demonstrated that the use of a base, indispensable for the one pot procedure (see #8; Table 1), decreases the selectivity towards the anchimerically driven alkylation due to the formation of more nucleophilic phenoxide anions.[14]

Similar results were achieved in the preparation of 3-[(*N*,*N*-dimethyl)2-amminoethoxy]pyridine **29**, a building block used for Structure-Activity Relationship (SAR) studies for nicotinic acetylcholine (nACh) receptor ligands,[21] and 4-(dimethylaminoethoxy)benzophenone **30**, the building block for the synthesis of several estrogen receptor modulators related to Tamoxifene and Toremifene.[22] The one-pot alkylation reaction afforded 60% and 50% yields respectively, and quantitative yields were obtained when the reactions were performed employing directly with the ß-aminocarbonate **11**.

Moxisylite precursor **31** was achieved in excellent yield in both the investigated procedures.

More challenging substrates, i.e. hydroxybenzaldehydes that incorporate two reactive moieties were then investigated. The related O-aminoalkylated derivatives **32**–**33** are important building blocks used extensively in pharmaceutical preparation (trimethoxy benzamide and Trifenagrel), and in drug development for the synthesis of different heterocyclic compounds such as imidazole containing heterocycles,[23] as well as for decoration of pharmacophore scaffolds (e.g. generation of appendage diversity on the rhodanine core, a privileged scaffold in medicinal chemistry).[24]

Anchimerically driven alkylation of 4-hydroxybenzaldehyde and 2-hydroxybenzaldehyde was not efficient as – due to the presence of the aldehyde moiety – concurrent reactions took place leading to numerous by-products. It was thus decided to protect the aldehyde moiety of the two precursors via acetylation with ethylene glycol under acidic condition (see supporting information). However, one-pot alkylation (according to Scheme 1a) of the resulting 4- and 2-(1,3-dioxolan-2-yl) phenol was not successful: most probably the basic conditions led to the deprotection of the substrates that then underwent concurrent reactions. Conversely, when the protected 4-hydroxybenzaldehyde and 2-hydroxybenzaldehyde were reacted with 2-(dimethylamino)ethyl ethylcarbonate **11** in the absence of a base, the N,N-dimethyl ethylamine derivatives **33**–**34** were recovered in good to almost quantitative yield. It is noteworthy that deprotection of the aldehyde group in both products was conducted directly on the reaction mixture by addition of trifluoroacetic acid, evaporation of the exceeding solvent and rapid extraction (see supporting information).

Finally, in order to obtain an insight into the toxicity of the ß-aminocarbonate **11** employed in the experiments reported here, either added as a reagent or formed in situ, its cytotoxicity was evaluated using the MTT assay and compared to its alcohol precursor 2-dimethylaminoethanol. The MTT assay is a colorimetric test commonly used for the nonradioactive quantification of cellular viability and cytotoxicity.[25] As shown in Figure 4, compounds reduced the cell viability in a dose dependent manner only at high concentrations. The trend of the reduction of cell viability was comparable for both compounds at 24 and 48 hours post treatment. In particular, the alcohol and ß-aminocarbonate **11** cytotoxic concentration capable of reducing the cell viability by 50% (CC_{50}) were 16.85 vs 14.67 mM and 9.15 vs 10.92 mM, respectively. These values indicate that the tested compounds are safer than many commercially available pharmaceuticals.[26]

In conclusion, in this work we have reported the first one-pot approach to facile incorporation of basic amine-containing

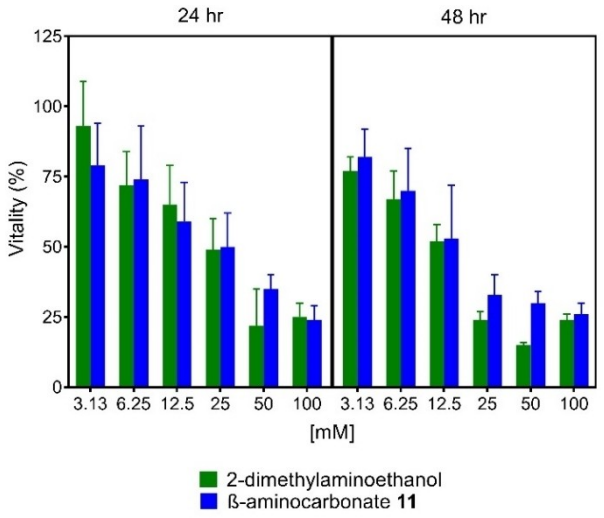


Figure 4. Effect of compounds on cell viability analyzed by MTT assay. Data (mean ± SD, N = 3 experiments in quadruplicate) are percentages of cell vitality, no treated set as 100%.

side chains in phenolic scaffolds. This synthetic procedure is not dependent on chlorine chemistry, and the so-formed alkylated products are obtained in good to excellent yields. All compounds were isolated as pure and fully characterized.

In this synthetic approach, DAC chemistry is at its full potential; DEC leads to in-situ formation of ß-aminocarbonate **11** (BAc^2 mechanism) that sequentially alkylates the substrate via the nitrogen NGP.

The DAC-mediated NGP alkylation has been applied to numerous substrates and proven in the preparation of several pharmaceutical compounds or related intermediates. In only two cases – compounds **32**–**33** – was the one-pot alkylation reaction not effective, although the target products could still be obtained in high yield by employing directly the ß-aminocarbonate **11**.

Cytotoxicity evaluation via the MTT assay demonstrated that 2-(dimethylamino)ethyl ethylcarbonate, **11** and its alcohol precursor have very limited toxicity.

It should be mentioned that the mutagenicity of compound **11** might still be an issue since the aziridinium ion is the key intermediate for the alkylation reaction promoted by β-aminocarbonates, as well as mustard gases. However, the main difference is the higher temperature required for the herein proposed procedure, which is typical of DAC-promoted alkylation[13] and it is an additional indication of the lower toxicity of ß-aminocarbonates compared to their chlorine homologues.

Future work on this novel, one-pot, anchimerically driven alkylation reaction include investigations on other carbonate homologues of mustard gases, as well as potential applications for the synthesis and functionalization of macromolecules.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chlorine-free · Dialkyl carbonate · Direct alcohol substitution · Green chemistry · Neighboring group participation

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