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Efficient synthesis in water of mixed carbonates of cyanohydrins from aromatic aldehydes

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Introduction

Cyanohydrins are important intermediates in the synthesis of various biological active compounds [1]. Because of their instability, cyanohydrins have been O-protected and the ethoxycarbonyl protective group has attracted much interest due to the great stability exhibited by mixed carbonates of cyanohydrins [2]. In addition, anions of cyanohydrin ethyl carbonates of aromatic aldehydes have been employed as synthetic equivalents of acyl carbanions in Michael addition / Claisen condensation tandem reaction type [3]. For the preparation of cyanohydrin ethyl carbonates, ethyl cyanoformate in the presence of catalyst is frequently used as a cyanide and simultaneously as the protective hydroxy group source. Various catalysts, such as salen Ti(IV) complexes [4,5] and V(V) complexes [6,7], allowed the preparation of asymmetric cyanohydrin carbonates. On the other hand, 4-dimethylaminopyridine (DMAP) [8], trimethylamine [9], and dimetylsulfoxide (DMSO) [10] have been shown to be effective activators in the synthesis of racemic cyanohydrin carbonates. Sodium cyanide has also been used as a cyanide source in combination with ethyl chlorocarbonate in phase transfer reaction conditions in the presence of tetrabutylammonium bromide [11]. All these methods afford high yields of cyanohydrin carbonates. However, the use of halogenated solvents in most cases presents unsatisfactory reactions conditions from an environmental point of view. Recently, organic reactions in aqueous media have emerged as a powerful and eco-friendly

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ABSTRACT

An efficient preparation of cyanohydrin ethyl carbonates via cyanocarbonation of aromatic and heteroaromatic aldehydes with sodium cyanide and ethyl chlorocarbonate using commercial surfactants (5 mol %) in aqueous media at low temperature afforded almost quantitative isolated yields (\geq 94%) in 30 min. Aromatic aldehydes bearing electron-donating as well as electron-withdrawing groups have been successfully employed without any significant changes. Centrifugation of the reaction mixture allows accessible purification without the need of solvent extraction. Reaction conditions can be readily upscaled to multigrams.

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alternative to substitute organic solvents in organic reactions [12]. In this media the issues linked with the low solubility of organic reacting species and products have been partially solved by the action of surfactants and several well-known reactions have already been reported in the literature. Some recent examples include olefin cross metathesis [13], Sonogashira couplings [14], Suzuki-Miraura cross couplings [15], Prins reaction [16], Diels-Alder cycloadditions [17], Morita-Baylis-Hillman reaction [18], and Mannich-type reactions [19]. In the context of the preparation of carbonated cyanohydrins, due to the solubility of NaCN in water, we considered that aqueous reaction condition could be used for the preparation of such compounds using NaCN as a cyanide source in the presence of ethyl chlorocarbonate, the aldehyde and a surfactant. A previous synthesis of ethyl carbonates of cyanohydrins in water from aromatic aldehydes using KCN, ethyl chlorocarbonate and excess of MgSO₄ has been described in 1950 [20]. However, detailed role of MgSO₄ was not explained. The present article describes our results when NaCN as a cyanide source was used in the presence of ethyl chlorocarbonate, the aldehyde and a surfactant in aqueous reaction conditions. Additionally, centrifugation of the final reaction mixture allows to skip the extraction step, permitting the immediate chromatographic purification of the cyanocarbonates.

Results and discussion

Initially, in order to assess the reactivity of the method, 4methylbenzaldehyde, a deactivated aldehyde towards nucleophilic additions, was considered as a convenient model compound.

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Reactions were carried out by the addition of NaCN aqueous solution (1.2 eq.) to a stirred mixture of the aldehyde (1 eq.), ethyl chlorocarbonate (1.2 eq.), water and the surfactant at $4 \, {}^{0}C.[21]$ Several surfactants, both cationic and anionic (Fig. 1), were tested under different conditions of temperature and concentration. Results are summarized in Table 1.

Initially, the reaction was performed without the presence of any surfactant and cyanocarbonate **3b** was obtained in only 23% yield (Table 1, entry 1). With dodecyltrimethylammonium chloride (DTMAC) as surfactant, in 10 mol% and 30 min at 4 °C, cyanocarbonate **3b** was obtained in 99% yield (Table 1, entry 2). Lowering the concentration of DTMAC to 5 mol% did not affect the yield (entry 3). However, when the reaction time decreased to 15 min, the yield dropped to 89% (entry 4). When the substrates were mixed at room temperature, the reaction temperature immediately rose to 35 °C, the mixture darkened and **3b** was obtained in 57%, along with large amounts of unreacted aldehyde (Table 1, entry

Table 1

Optimization of the reaction conditions.

5). When shifting the surfactant to OLSULP (sodium alpha-olefindodecyltrimethyl sulfonate) under the conditions of entry 3, the yield slightly decreased to 96% (entry 6), while QUAB18 (octadecyltrimethylammonium ethylsulfate) and TBAB (tetrabutylammonium bromide) provided **3b** in 92% and 73% yields respectively (**Table 1**, entries 7 and 8). From the above data, the reactions conditions of entry 3 (5 mol% DTMAC, 30 min at 4 °C) were selected to study the scope of the reactions with several aromatic aldehydes. After the reaction time, the mixture was allowed to reach room temperature and the resulting emulsion was centrifugated. The organic layer was separated from water and the product purified by column chromatography (Silica-Gel, Hexane - EtOAc: 9-1).[22]

The results are summarized in Table 2. It is worth noting that almost quantitative isolated yields (\geq 94%) of cyanocarbonates **3a-3n** were obtained both from substituted aromatic aldehydes with electron-donating groups (**3b**, **3c**, **3g**, **3h** and **3l**) and from electron-withdrawing groups (**3d**, **3e**, **3f**, **3i**, **3j** and **3k**) regardless



Entry	Surfactant	Concentration surfactant (mol%)	Reaction time (min)	Temp. (°C)	Yield ^a (%)
1			30	4	23
2	DTMAC	10	30	4	99
3	DTMAC	5	30	4	99
4	DTMAC	5	15	4	89
5	DTMAC	5	30	23	57
6	OLSULP	5	30	4	96
7	QUATB18	5	30	4	92
8	TBAB	5	30	4	73

^a Determined by NMR analysis from the crude mixture. Reaction conditions: 4-methylbenzaldehyde (360 mg, 3.0 mmol), ethyl chloroformate (390 mg, 3.6 mmol), and surfactant in H₂O (1 mL) were stirred at 4 °C and NaCN (176 mg, 3.6 mmol) in H₂O (1 mL) were added to the reaction mixture.



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^aThe aldehyde was dissolved in 3 mL of THF.

Table 2



of the substituted position. Similar results were obtained from thiophene-2-carboxyaldehyde (**3m**) and furan-2-carboxyaldehyde (**3n**). Additionally, no change in the yields and purity of the cyanohydrins occurred when the reaction was scaled to multigrams (30 mmol). To rationalize these data, one may assume that in the high concentrated ambient of reacting species, when the addition of the cyanide to the aldehyde takes place, the formed intermediate **A** is rapidly captured by ethyl chlorocarbonate, shifting the equilibrium to the right and consequently affording high yields of the product (Scheme 1). The use of a cationic surfactant facilitates the introduction of the cyanide anion into the organic phase.

Conclusion

In summary, a facile and efficient preparation of cyanohydrin ethyl carbonates starting from NaCN, ClCO₂Et and a range of electron-donating and electron-withdrawing substituted aldehydes has been developed. The use of an ammonium salt as a surfactant allowed to run the reaction in water. The availability of the substrates, use of aqueous media, mild reaction conditions, short reaction time, operational simplicity and separation procedure, upscaling ease and quantitative yields make this method a particularly convenient route for the cyanocarbonation of aldehydes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151414. These data include general synthetic procedures, characterization of the compounds, ¹H- and ¹³C NMR spectra.

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- [22] Typical procedure for cyanocarbonation of 4-methylbenzaldehyde. A solution of NaCN (176 mg, 3.6 mmol) in H₂O (1 mL) was added to a stirred mixture of DMAC (0.09 mL, 0.15 mmol, 46% wt. aqueous solution), 4-methylbenzaldehyde (360 mg, 3.0 mmol) and ClCO₂Et (390 mg, 3.6 mmol) in H₂O (1 mL) at 4 °C (ice/water bath). The reaction mixture was stirred for 30 minutes and then centrifugated for 1 minute. The organic phase was separated, and the crude material was purified by column chromatography

(silica-Gel, Hexane-EtOAc: 9-1) to afford 651 mg (2.97 mmol, 99%) of **3b** as a colorless oil. 1 H NMR (300.53 MHz, CDCl₃), δ (ppm): 7.50 (d, *J* = 8.2, 2H, CH_{Ar}), 7.34 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 6.32 (s, 1H, CH), 4.27 (m, 2H, CH₂), 2.4 (s, 3H, CArCH₃), 1.30 (t, *J* = 7.2 Hz, 3H, CH₃); 13 C NMR (75.5 MHz, CDCl₃) δ (ppm): 151.3 (CO₃), 141.5, 130.4, 129.4, 128.1, 117.9 (CN), 66.7, 65.9, 20.8 (C_{Ar}CH₃), 14.12 (CH₃). Anal. Calcd. for C₁₂H₁₃NO₃: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.89; H, 6.02; N 6.56.