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Water as efficient medium for mild decarbonylation of tertiary aldehydes

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1. Introduction

Despite being long known as a dangerous, toxic, and pollutant gas,¹ carbon monoxide (CO) has been found to have advantageous biological effects.² Since the discovery of the endogenous production of CO in stress situations³ a considerable research has been done in order to understand the biological mechanisms and the beneficial effects of CO in several disease models like: systemic and pulmonary hypertension, cardiac, renal and small bowel graft rejection, preservation of organs for transplantation.²

Due to its toxicity CO is rather unsafe to administer by inhalation requiring special equipment and stringent control procedures. In order to circumvent these difficulties CO releasing molecules (CORM's) have been developed to deliver CO at specific sites with a controllable appropriate rate.⁴ Among the CO releasing molecules, disclosed metal carbonyl complexes and dichloromethane, both of which release CO under mild and physiological conditions, have been shown to have therapeutic efficacy.⁵ More recently it was found that tertiary aldehydes are also CO releasing compounds under such conditions.⁶

A B S T R A C T

Decarbonylation of the tertiary aldehydes 4-ethyl-4-formyl-hexanenitrile (2) and 2-methyl-2-phenylpropanal (4) promoted by dioxygen occurs at room temperature only if suspended in water probably via the sequential acyl radical–CO liberation–tertiary radical that is promoted by an 'on water' process originating preferentially from the corresponding tertiary hydroperoxide.

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Aldehyde decarbonylation is a well known process that occurs under drastic conditions like UV irradiation,^{7,8} high temperatures,⁹ extremely acidic or basic conditions,^{10,11} radical, and metal catalyzed reactions.¹² Obviously, these conditions are incompatible with biological applications in physiological medium.

Recently, de Matos and Romão reported that tertiary aldehydes are able to release a significant amount of CO under mild oxidative conditions, compatible with physiological uses.⁶ They describe a group of aldehydes that have the general structure shown in Figure 1.

The ability of these compounds to liberate CO was evaluated in vitro, using oxidizing agents, such as *tert*-butyl hydroperoxide (TBHP) and hydrogen peroxide that are or mimic reactive oxygen species (ROS) present in inflamed physiological environments. The addition of a radical inhibitor (2,6-di-*tert*-butylphenol–BHT) reduces the amount of CO released indicating that this type of aldehydes liberates CO through a radical mechanism (Fig. 2). The proposed mechanism relies on aldehyde decarbonylation via formation of an acyl radical.

Acyl radicals have gained an increasing significance in synthetic chemistry.¹³ Lately some new methods for carbon–carbon bond formation involving acyl radicals have been successfully developed.¹⁴ One of the major problems encountered for these reactions is the decarbonylation of acyl radicals. This decarbonylation is dependent on the nature of the substituents. Substituents that stabilize the alkyl radical after CO liberation (tertiary alkyl and benzylic substituents) favor decarbonylation. Additionally,





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Figure 1. General structure of aldehydes that release CO under mild oxidative conditions, where $R^1 = R^2 = Me$ and $R^3 = Me$, allyl, hydroxymethyl, acetoxymethyl, *p*-methylbenzyl, phenyl or $R^1 = R^2 = Ethyl and R^3 = Me$, cyanoethyl.



Figure 2. Proposed mechanism of CO liberation from tertiary aldehydes.

coupling reactions with acyl radicals are favored by substituents, which stabilize the acyl radical like aryl, α -unsubstituted alkyl, and conjugated unsaturated alkyl substituents.¹⁵

Given the increasing importance of these types of reactions several techniques to produce acyl radicals were discovered and improved.^{13,14} Acyl radicals can be formed by RCO-X homolytic cleavage where X can be: -H, -Cl, -OH, -SR, -SeR, -TeR, -CoLn, -P(=O)Ar₂ and metal carbene complexes. Acyl radicals are also produced from the cleavage of CO–C bonds of ketones, α -keto acids or α -acvlalkoxy, and from carbonylation¹⁶ of alkyl, aryl, and vinyl radicals. Aldehydes give acyl radicals by hydrogen abstraction using radical initiators, UV light, γ -irradiation, or transition metal ions.¹³ Besides these, there are also some reported examples of hydrogen abstraction by the less reactive molecular oxygen¹⁷ which can act as efficient source for new C-C bond formation^{17c,d} or to green oxidation of aldehydes to carboxylic acids and the further use of the involved intermediate as co-oxidant.^{17e,f} As described before, the aldehydes in Table 1⁶ release CO without strong oxidants, only under air and in aqueous solvents.

The intriguing release of CO⁶ prompted us to perform a detailed study on the ease formation of acyl radicals from tertiary aldehydes under mild conditions. A screening study of the behavior of aldehydes showed that the molecules presented in Table 2 liberated CO in water. From these preliminary data, aldehydes 2 and 4 were selected and studied in detail, namely the influence of oxygen, light, presence of antioxidant, concentration, and solvent.

Aldehyde decarbonylation was found to be light independent, some experiments followed by GC-TCD performed in the dark and under light did not show large CO release differences (see Table 3 and Fig. 3). Nevertheless, the presence of molecular oxygen is

Table 1					
% of CO	released	in	aq	ueous	n

% of CO released in aqueous media ⁶				
Entry	Aldehyde	Buffer (pH=2)	RPMI ¹⁸	
1	©H	8.5%, 16 h	3.2%, 16 h	
2	NC	21.2%, 23.5 h	20.7%, 24 h	
3	о Н	16.6%, 23 h	15.5%, 19 h	
4	O H	34.9%, 25 h	_	

Table 2

Aldehydes	CO release	in water (0	0.1 M) after 24 h

Compound	Aldehyde	% CO released
1	©H	6.4
2	NC	28.4
3	ОН	35.1 ^a
4	O	34.2 ^a

^a Less accurate value lying outside the range of the calibration curve.

necessary. Experiments performed under nitrogen as well as in the presence of an antioxidant showed almost no CO liberation (Table 3 and Fig. 3). In fact, the decarbonylation of these aldehydes was followed by NMR. No evolution of the reaction was observed under nitrogen, while complete decarbonylation was achieved under air (see Supporting information). The aldehyde signal of 4 is almost undetectable after 22 h of reaction in water under air. However, under nitrogen none of the aldehyde signals disappeared within 24 h.

Similar results were obtained with aldehyde 2. After 17 days of reaction under nitrogen no decarbonylation was observed by NMR. On the contrary, a rapid evolution of reaction was observed after 24 h under air and after 7 days the signal of aldehyde had practically disappeared. GC-TCD results are in accordance with these observations (Table 3 and Fig. 3).

Table 3

% CO released from aldehvdes 2 and 4 within 24 h under different conditions

Entry	Conditions	% CO	
		2	4
1	Water, air, light	28.4	101.5
2	Water, air, dark	24.4	91.9
3	Water, N ₂ , light	5.9	11.1
4	Water, air, BHT	0.0	0.0



Figure 3. % CO release of aldehydes 2 and 4 under different conditions. These assays were repeated up to 4 times.

During the studies with **4** was found that the reaction rate is also concentration dependent. NMR studies of **4** performed in deuterated water with two different concentrations showed that the reaction is faster at high concentrations (Fig. 4). Two concentrations were studied by NMR: 13 mM and 3.3 mM. At 3.3 mM the reaction rate is very slow the signal of aldehyde being still present after 4 days. At 13 mM the signals of aldehyde almost disappeared after 22 h. Surprisingly, we found that at high concentrations two signals in the aldehyde region were detected whereas at low concentrations only one signal was observed. The explanation for the two signals observed was that they are due to the solubility of aldehyde: at 3.3 mM the aldehyde is completely dissolved in water and at 13 mM the aldehyde is partially emulsified. This leads to the conclusion that the signal at $\delta = 9.5$ ppm was due to dissolved aldehyde and the signal at δ = 9.0 ppm was due to aldehyde in emulsion form.

These observations are also supported by the behavior noticed during the GC studies under air. At the beginning of the assay was observed an emulsion that became more opaque within 4 h and changed to a colorless and completely transparent solution after 24 h.

These results led us to conclude that due to partial dissolution of the aldehyde in water an equilibrium between dissolved and suspended aldehyde was formed, while the aldehyde suspended at the surface reacts with oxygen to give carbon monoxide and water soluble products, the aldehyde dissolved in water remains unchanged. These results are in accordance with the 'on-water' reaction phenomena.¹⁹ In fact, no CO liberation was found when



Figure 4. Reaction of 2-methyl-2-phenylpropanal (4) in D₂O under air along the time, followed by NMR using 3.3 mM (top) and 13 mM (bottom) concentration.

Table 4

% CO released from **2** and **4** within 24 h in different solvent media

Aldehyde	Conditions	% CO
2	Dichloromethane, air	0.0
4	Dichloromethane, air	0
2	Methanol, air	0.0
2	Hexane/water 50:50, air	0.3
2	Ethanol/water 50:50, air	0.0
4	Methanol/water 50:50, air	0
2	Water, air	28.4
4	Water, air	101.5

the reaction was carried out in methanol, hexane, or dichloromethane instead of water. Moreover, the addition of methanol or hexane completely inhibited the reaction (Table 4 and Fig. 5). Note that those aldehydes are completely soluble in these organic solvents but only partially soluble in water. In conclusion decarbonylation of aldehyde does not occur in organic solvents or is very slow in water as a solution (diluted in water). A similar solvent effect has already been recently described for oxidation of aldehydes, but no CO release was observed in that case since the aldehydes studied were not tertiary.^{17e}

Those reactions were scaled up in order to isolate and characterize the products formed. Compound **2** gave a complex mixture of products that were separated by preparative chromatography. One of the products was collected pure and identified as being the corresponding alcohol 4-ethyl-4-hydroxyhexanenitrile (**5**). Compound **4** gave, after CO release,²⁰ two products which could



Figure 5. % CO release of compound 2 (top) and compound 4 (bottom) in different media.

not be separated but were identified by NMR in the mixture by comparison with spectra of authentic samples as the corresponding alcohol 2-phenyl-2-propanol (**6**) and the peroxide cumene hydroperoxide (**7**)–with a total isolated yield between 39% and 44%.



2. Conclusions

Tertiary aldehydes are molecules that easily undergo decarbonylation 'on water'¹⁹ in the presence of molecular oxygen by a radical mechanism, probably via acyl radical (Fig. 2). It was verified that aldehyde solubility is an important factor in reaction rate since there is no CO released when aldehydes are dissolved in organic solvents or when their concentration in water is very low. Oxygen also plays an important role in decarbonylation of tertiary aldehydes. In the presence of antioxidants (BHT) or in the absence of oxygen no CO release was observed. The unique observed reactivity of this type of molecules under very mild conditions may provide a new tool for further functionalization of the formed tertiary radical.

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Supplementary data

Supplementary data (Electronic Supplementary Information (ESI) available: Experimental procedures, UV, FT-IR, ¹H and ¹³C NMR data is provided.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.012.

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- 20. Reaction of 2-methyl-2-phenylpropanal (4)in water: A mixture of 4 (1.05 g, 0.007 mol) in 10 mL of water was stirred at room temperature and under air. After 31 days the organics were extracted with diethyl ether, dried with MgSO₄, and the solvent was removed under vacuum to yield a yellow oil (crude). The obtained crude was properly characterized (NMR) and identified as being a mixture of 2-phenyl-2-propanol 6 and cumene hydroperoxide 7 (0.42 g, 39–44%) by comparison with authentic samples.