

Radical-mediated Carbonylation of Alkyl Iodides in Aqueous Media

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Radical-mediated single carbonylation of alkyl iodides furnishing carboxylic acids proceeded in water using phosphinic acid as a radical initiator in the presence of a surfactant (CTAB). On the other hand, formation of double carbonylation product (α -keto carboxylic acid) along with single carbonylation product was observed for the first time, when the reaction was carried out in aqueous ethanol without any surfactants.

Carbonylation of organic halides with carbon monoxide provides a versatile method for the preparation of various carbonyl compounds. While much attention has been paid to development of transition metal catalysts, free-radical carbonylation has become a practical alternative since the discovery of tin hydride-mediated radical formylation of alkyl halides by Ryu and Sonoda, et al. in 1990.^{1,2} Meanwhile, development of environmentally benign, efficient processes using less toxic agents under milder reaction conditions is a current issue. In this context, we have been interested in the possibility of radical carbonylation in water, since water is a clean, safe, and inexpensive solvent.^{3,4} In addition, we anticipated that acyl radical intermediates, which were formed via addition of alkyl radicals to carbon monoxide, could be stabilized in aqueous media due to the high polarity of water leading to enhancement of reactivity and unique reaction outcomes.⁵ Herein, we report the first example of radical carbonylation in aqueous media as well as the first observation of radical-mediated double carbonylation affording α -keto carbonyl compounds.

To realize radical carbonylation in water, we chose phosphinic acid as a radical mediator, because it is inexpensive and less toxic than tin reagents, and can be utilized in aqueous media.⁶ At first, carbonylation of 1-iododecane (**1a**) was investigated using 2,2'-azobisisobutyronitrile (AIBN) (0.3 equiv.), phosphinic acid (5 equiv.), sodium hydrogencarbonate (15 or 7 equiv.), and an additive (0.2 equiv.) in water under carbon monoxide (50 atm) at 70 °C (Table 1). In the absence of any additives, carbonylation did not proceed at all, and most of **1a** was recovered (Entry 1). However, it turned out that, in the presence of cetyltrimethylammonium bromide (CTAB), decyl undecanoate (**2a**) was formed in good yield (Entry 2). Interestingly, both an anionic surfactant, sodium dodecyl sulfate (SDS), and other ammonium salts possessing shorter alkyl groups were ineffective (Entries 3–5).⁷ Under the conditions with CTAB at slightly higher temperature (75 or 80 °C), the yield of **2a** was improved and a trace amount of undecanoic acid **3a** was observed (Entries 6 and 7).

Carbonylations of several other alkyl iodides were next investigated under the conditions shown in Entry 6 of Table 1 (Table 2). While 1-iodo-3-phenylpropane (**1b**) provided ester **2b** in high yield (80%), 1-iodobutane (**1d**) afforded pentanoic acid (**3d**) as a major carbonylated product. It is suggested that alkyl iodides with more hydrophobic alkyl groups tend to give

Table 1. Radical carbonylation of 1-iododecane (**1a**)

$\text{RI} + \text{CO} \xrightarrow[\text{H}_2\text{O, 70 } ^\circ\text{C, 15 h}]{\begin{array}{c} \text{AIBN (0.3 equiv.)} \\ \text{H}_3\text{PO}_2 \text{ (5 equiv.)} \\ \text{NaHCO}_3 \text{ (15 or 7 equiv.)} \\ \text{Additive (0.2 equiv.)} \end{array}} \text{R}-\text{C}(=\text{O})-\text{OR} + \text{R}-\text{C}(=\text{O})-\text{OH}$		Yield/% ^a		
Entry	Additive	2a	3a	Rec. 1a ^d
1 ^b	—	0	0	88 ^e
2 ^b	<i>n</i> -C ₁₆ H ₃₃ NMe ₃ Br (CTAB)	52	0	38
3 ^b	<i>n</i> -C ₁₂ H ₂₅ OSO ₃ Na (SDS)	0	0	95
4 ^b	<i>n</i> -Hex ₄ NBr	15	0	61
5 ^c	<i>n</i> -Bu ₄ NI (TBAI)	0	0	quant.
6 ^{c,f}	CTAB	74	1	11
7 ^{c,g}	CTAB	72	1	7

^aYields were determined by ¹H NMR analysis using naphthalene as an internal standard. ^bNaHCO₃ (15 equiv.). ^cNaHCO₃ (7 equiv.). ^dRecovered starting material. ^eIsolated yield. ^fAt 75 °C. ^gAt 80 °C.

Table 2. The effect of alkyl iodides

$\text{RI} + \text{CO} \xrightarrow[\text{H}_2\text{O, 75 } ^\circ\text{C, 15 h}]{\begin{array}{c} \text{AIBN (0.3 equiv.)} \\ \text{H}_3\text{PO}_2 \text{ (5 equiv.)} \\ \text{NaHCO}_3 \text{ (7 equiv.)} \\ \text{CTAB (0.2 equiv.)} \end{array}} \text{R}-\text{C}(=\text{O})-\text{OR} + \text{R}-\text{C}(=\text{O})-\text{OH}$		Yield/% ^a	
Entry	R (1)	2	3
1 ^b	<i>n</i> -C ₁₀ H ₂₁ (1a)	74 (2a)	1 (3a)
2	Ph(CH ₂) ₃ (1b)	80 (2b)	0 (3b)
3	<i>n</i> -C ₈ H ₁₇ (1c)	55 (2c)	0 (3c)
4	<i>n</i> -Bu (1d)	3 (2d)	15 (3d)
5	<i>c</i> -Hex (1e)	0 (2e)	70 (3e)
6	<i>s</i> -C ₈ H ₁₇ (1f)	8 (2f)	80 (3f)

^aYields were determined by ¹H NMR analysis using naphthalene as an internal standard. ^bSee Table 1, Entry 6.

esters in higher yields (Entries 1–4). On the other hand, secondary alkyl iodides, iodocyclohexane (**1e**) and 2-iodooctane (**1f**), gave the corresponding acids (**3e** and **3f**) in high yields (70% and 80%, respectively) (Entries 5 and 6).

A possible reaction mechanism of this unique carbonylation of alkyl iodides is depicted in Figure 1. In this mechanism, CTAB possibly acts as a phase transfer catalyst as well as a surfactant. The phosphinate radical, generated from phosphinate and AIBN, abstracts the iodine atom from an alkyl iodide. Then, the generated alkyl radical reacts with carbon monoxide to give an acyl radical, followed by formation of an acid iodide via the

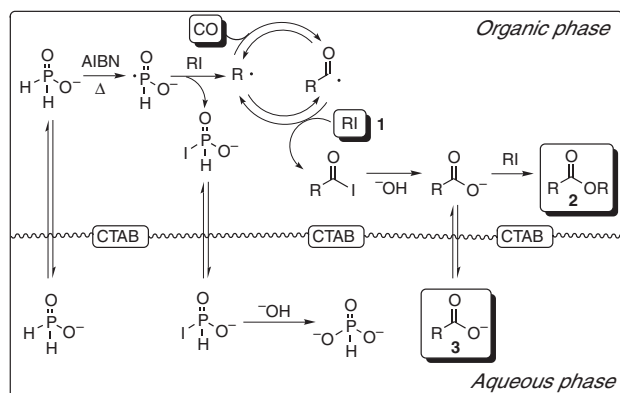


Figure 1.

iodine atom transfer from the alkyl iodide.² The acid iodide readily hydrolyzes to a carboxylate that can provide a carboxylic acid or an ester via attack to the alkyl iodide. This mechanism explains our observation shown in Table 2 that alkyl iodides with less hydrophobic or bulkier alkyl groups tend to give acids rather than esters. High hydrophobicity of carboxylates would suppress their transfer to the aqueous phase leading to esters, while the bulkiness of alkyl iodides would prevent the attack by carboxylates.

According to the proposed mechanism, phosphinic acid and AIBN act as radical initiators, meaning that both may be reduced to catalytic amounts in principle. Thus, further optimization of the reaction conditions was pursued using iodocyclohexane (**1e**) as a substrate (Table 3). Indeed, reduction of the amounts of phosphinic acid, NaHCO₃, and AIBN was attained (Entries 1–4), and acid **3e** was obtained in high yield (82%) under the conditions shown in Entry 4. Control experiments without using phosphinic acid (Entry 5) or AIBN (Entry 6) clearly showed that the combination of both reagents was essential for the radical initiation. On the other hand, reduction of the amount of CTAB or CO pressure resulted in significant decrease of the yield of **3e** (Entries 7 and 8). Carbonylation of 1-iododecane (**1a**) under the optimized conditions for **1e** gave

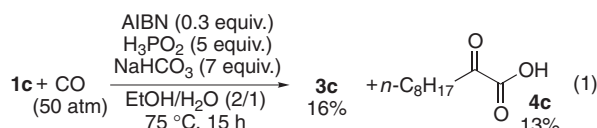
Table 3. Further optimization of carbonylation of **1e**

Entry	Reagents/equiv.				Yield/% ^a	
	H ₃ PO ₂	NaHCO ₃	AIBN	CTAB	3e	Rec. 1e ^d
1 ^b	5	7	0.3	0.2	70	0
2	1	3	0.3	0.2	63	0
3	0.5	2.5	0.3	0.2	76	0
4	0.5	2.5	0.1	0.2	82	0
5	—	2.5	0.1	0.2	0	59
6	0.5	2.5	—	0.2	0	26
7	0.5	2.5	0.1	0.1	30	39
8 ^c	0.5	2.5	0.1	0.2	59	20

^aYields were determined by ¹H NMR analysis using naphthalene as an internal standard. ^bSee Table 2, Entry 5. ^cUnder CO (30 atm). ^dRecovered starting material.

ester **2a** in low yield (11%) with recovery of **1a** (82%).

Finally, we investigated the radical carbonylation of 1-iodooctane (**1c**) in an ethanol/water system in the absence of any surfactants (Eq 1), since it was reported that radical-mediated, reductive cyclization of organic halides with phosphinic acid proceeded well in this mixed solvent.^{4,6} It was unexpectedly found that α -keto carboxylic acid **4c** was formed via double carbonylation along with the formation of singly carbonylated product **3c**. Although the yield was still low and the precise mechanism is unclear, this is, to the best of our knowledge, the first observation of radical-mediated double carbonylation.⁸ Stabilization of radical intermediates by the highly polar solvent system might give rise to this unprecedented reaction. Further optimization of the reaction conditions as well as theoretical and mechanistic studies of this novel double carbonylation are now under investigation.



In summary, we have demonstrated the first example of radical carbonylation of alkyl iodides in aqueous media. Single carbonylation of alkyl iodides was found to proceed smoothly using phosphinic acid as a radical initiator in the presence of a surfactant in water as the sole solvent. Furthermore, radical-mediated double carbonylation was observed for the first time by performing the reactions in an ethanol/water system. It should be noted that these novel results have been obtained not in standard organic solvents but in aqueous media.

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