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Oxidative decarboxylation of arylacetic acids in water: One-pot transition-metal-free synthesis of aldehydes and ketones

Trimbak B. Mete, Tushar M. Khopade, Ramakrishna G. Bhat*

Department of Chemistry, Indian Institute of Science Education & Research (IISER), Pune 411008, Maharashtra, India

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Introduction

Aldehydes and ketones are very important class of compounds and they have been used extensively in wide areas of chemical synthesis.¹ Evidently, the effort towards the quick and short synthesis of aldehydes and ketones always has been desirable. Traditional synthesis of aldehydes and ketones rely on activating the carboxylic acid into a Weinreb amide² or into an acyl halide³ with subsequent nucleophilic attack with hydrides or organometallic species. One-step synthesis of ketones starting from carboxylic acids can be achieved using excess of organolithium reagents; however formation of tertiary alcohols is unavoidable.⁴ These harsh conditions can lead to the erosion of stereochemical purity thus leading to partial racemization.⁵ Nevertheless, efforts have been made to improvise the existing methods. Cyanocuprates have been explored to convert the carboxylic acids directly into ketones.⁶ Quick and efficient cleavage of carbon-carbon bond is one of the most important challenges in organic synthesis.⁷ The selective cleavage of C–C σ bond has greatly attracted the attention of researchers in the recent times due to its inert nature. Undoubtedly, development of an efficient protocol for the selective cleavage of C–C σ bond is a great challenge and still much to be explored. Transition metal catalyzed decarboxylation via C--C bond cleavage has been gaining a great importance due its significant role in decaboxylative reactions.⁸ Elegant and valuable protocols are developed in this area for making carbon-carbon and

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ABSTRACT

One-pot transition-metal-free synthesis of aromatic aldehydes and ketones via oxidative decarboxylation of arylacetic acids in water is developed. Protocol relies on the direct decarboxylation of sp³-hybridized carbon in water without any over oxidation into carboxylic acids with minimal waste. Reaction mechanism is investigated and application of this protocol is demonstrated on a gram scale.

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carbon-heteroatom bonds starting from carboxylic acids and by cleaving the C–C bond to carboxylate group.⁹ Also, decarboxylation reaction procedures are usually done at neutral reaction conditions and importantly carbon dioxide liberated as a sole nontoxic by-product. Transition metal catalyzed decarboxylation at sp²-hybridized carbon is mostly explored in the literature and more strikingly, decarboxylation at sp³⁻hybridized carbon to introduce a functional group is relatively rare and challenging.¹⁰ Transition metal catalyzed synthesis of aldehydes, ketones and amides via oxidative decarboxylation has been explored very recently.^{11,12} Reactivity of cuprous salt was explored for the novel synthesis of aldehydes from methyl ketones in presence of oxygen.¹³ Recently, Song and co-workers demonstrated the ability of cupric salts for the aerobic oxidative decarboxylation at sp³⁻hybridized carbon to afford aldehydes, ketones¹¹ and amides¹² at high temperatures. Decarboxylative non-aerobic oxidation of phenyl acetic acid to benzaldehyde was described by using cupric salts at high temperature and pressure thus mimicking the geochemically relevant conditions.¹⁴ All of these protocols rely on transition metal, viz. copper for catalyzing the transformation.¹⁵ However, there are only countable protocols for the oxidative decarboxylation of aryl carboxylic acids under transition-metal-free conditions. Earlier, decarboxylation of carboxylic acids to aldehydes and ketones were achieved by using tetrabutylammonium periodate in 1,4-dioxane under refluxing condition, combination of iron(III)/manganese(III) tetraphenylprorphyrins and tetrabutylammonium periodate, and (diacetoxyiodo)benzene/NaN3.16,17 Thus development of more easier, practical and non-hazardous protocol for the synthesis of aldehydes and ketones via oxidative decarboxylation under





^{*} Corresponding author. *E-mail address:* rgb@iiserpune.ac.in (R.G. Bhat).

transition-metal-free conditions is highly desirable. There are ambiguities in defining a true 'green method'. However, some of the most accepted guiding principles such as minimal waste, higher mass productivity lower E-factor, non-toxicity etc define the greener methods. Practical, efficient and highly selective transition-metal-free transformations using environmentally benign, less expensive and readily available reagents are gaining a great importance for the last few years.¹⁸ As a part of our ongoing efforts to develop transition metal free protocols,¹⁹ we herein, report an oxidative decarboxylative strategy for the direct and clean synthesis of aldehydes and ketones without over oxidation into carboxylic acids in water with a minimal waste and lower E-factor. This simple protocol uses potassium persulfate as a reagent and makes the novel use of it for the synthesis of aldehydes and ketones starting from arylacetic acids.

We commenced our initial work with 4-methyl phenylacetic acid **1a** with K₂S₂O₈ as a model reaction (Table 1). Attempted reaction of **1a** with K₂S₂O₈ (2 equiv.) in CH₃CN/H₂O (1:1) at room temperature (both in air and inert condition) did not work even after prolonged reaction condition (entry 1, Table 1). Interestingly, when the reaction was carried at elevated temperature (80 °C), to our delight, the desired product, 4-methylbenzaldehyde 2a was formed in 75% isolated yield (Table 1, entry 2) in 12 h. With this result in hand, further the reaction was screened in different solvent conditions. However, the reaction was sluggish in CH₃CN and DCE (entries 4, 6) and afforded only trace amount of desired product 2a. However, the reaction in DCE/H₂O at 80 °C afforded the desired product in 60% yield (entry 7). Interestingly, the model reaction worked efficiently only in water at 80 °C affording the desired product 4-methyl benzaldehyde 2a in 75% yield (entry 8). Gratifyingly, with the elevated temperature (90 °C) under aerial condition reaction afforded the compound 2a in excellent yield of 85% (entry 9). PIDA, PIFA and Oxone were found to be ineffective reagents for the desired transformation (entries 10–12). Attempts to lower the reaction temperature resulted in lower yield with

Table 1

Optimization of the reaction conditions.^a

incomplete conversion of the starting material (entry 13). Reactions under oxygen or open air atmosphere did not change the course of the reaction and also did not have any significant effect on yield or reaction time (entries 9, 14). Reaction did not work in the absence of potassium persulfate (entry 15). After extensive screening of solvents and temperature optimum reaction condition was emerged as 4-methylphenyl acetic acid **1a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 90 °C in water under aerial atmosphere (entry 9, Table 1) in 12 h. It is also important to note that persulfates are very popular for their ability to oxidize variety of contaminants in ground water via 'in situ chemical oxidation' (ISCO).²⁰ Persulfates are known to be benign, eco-friendly or green and low cost reagent.²¹

Encouraged by the initial success and with an optimized reaction condition in hand; we explored the substrate scope of the method. Under optimal reaction conditions arylacetic acids (1a-**10**) possessing the electron-donating group as well as electron withdrawing groups reacted smoothly by affording the corresponding aldehydes (2a-2o) in moderate to good yields (Scheme 1). 1-Naphthylacetic acid 1p reacted smoothly and gave the corresponding naphthaldehyde **2p** in 80% yield. Similarly, the heteroaromatic acid such as 2-thienyl acetic acid 1q under reaction conditions afforded the 2-thienyl carboxylaldehyde (2q). α -Substituted phenyl acetic acids (1r-1w) under optimal reaction conditions afforded the corresponding ketones (2r-2w) in excellent yields (86-92%). The anti-inflammatory drug, ibuprofen 1u afforded the corresponding ketone²² **2u** in excellent yield as well. Interestingly, the amino acid phenyl glycine 1x afforded benzaldehyde 2d instead of anticipated amide. Probably, imine might have formed during the course of reaction, which upon hydrolysis resulted in 2d. The position of the substituents on the ring had no significant and noticeable effect on reaction rate and yields. Functional group such as hydroxyl, chloro, bromo, methoxy and nitro were well tolerated. However, unfortunately, attempted reac-



| Entry | Reagent | Solvent | Temp (°C) | Atm | Yield ^b (%) |
|-------|-------------|---|-----------------|----------------|------------------------|
| 1 | $K_2S_2O_8$ | CH ₃ CN/H ₂ O (1:1) | rt | Air | NR |
| 2 | $K_2S_2O_8$ | CH ₃ CN/H ₂ O (1:1) | 80 | Air | 75 |
| 3 | $K_2S_2O_8$ | CH ₃ CN | Reflux | Air | Trace |
| 4 | $K_2S_2O_8$ | CH ₃ CN | Reflux | O ₂ | 12 |
| 5 | $K_2S_2O_8$ | MeOH | Reflux | Air | NR |
| 6 | $K_2S_2O_8$ | DCE | 90 | 02 | Trace |
| 7 | $K_2S_2O_8$ | DCE/ H ₂ O (1:1) | 80 | Air | 60 |
| 8 | $K_2S_2O_8$ | H ₂ O | 80 | Air | 75 |
| 9 | $K_2S_2O_8$ | H ₂ O | 90 | Air | 85 |
| 10 | PIDA | H ₂ O | 90 ^c | Air | 27 |
| 11 | PIFA | H ₂ O | 90 ^c | Air | 21 |
| 12 | Oxone | H ₂ O | 90 ^c | Air | 15 |
| 13 | $K_2S_2O_8$ | H ₂ O | 50 | Air | 20 |
| 14 | $K_2S_2O_8$ | H ₂ O | 90 | 02 | 83 |
| 15 | - | H ₂ O | 90 | Air | - |

Bold values correspond to the optimum reaction conditions.

^a Reaction conditions: 4-methylphenyl acetic acid **1a** (1 equiv.), potassium persulfate (2 equiv.), solvent (2 mL) under corresponding atmosphere for 12 h.

^b Isolated yield after purification by column chromatography.

^c Reactions did not work at rt.

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Scheme 1. Oxidative decarboxylation of arylacetic acids to aldehydes and ketones. ^aReaction conditions: arylacetic acid 1 (1 equiv.), potassium persulfate (2 equiv.), water (2 mL) open atmosphere; reaction was monitored by TLC. ^bIsolated yield after purification by column chromatography.

tions of aliphatic acids such as 3-butenoic acid, *tert*-butyl acetic acid and valeric acid did not afford the desired products.

To make the protocol more general and for the wider applicability we demonstrated the synthesis of benzaldehyde **2d** (83%) and benzophenone **2r** (93%) on a gram scale starting from the corresponding arylacetic acids **1d** and **1r** respectively under optimum conditions. During the optimization we observed that reaction worked efficiently in water under atmosphere of air as well as oxygen. Effective minimization of reagents in this protocol led to a minimal waste (free from halogen and transition metal), thus producing only 3.5 g of waste for every 1 g of the product formed. It is also gratifying to note that this one pot reaction with E (environmental) factor of 3.49^{23} and mass productivity of 23% (mass intensity 4.5)²³ satisfies the defined metrics²⁴ for the cleaner and greener chemical processes.

In order to investigate and elucidate the reaction mechanism few control experiments were carried out. Compound **1a** when treated with $K_2S_2O_8$ (2 equiv.) in water under inert conditions afforded the corresponding aldehyde **2a** in good yield (80%). This



Scheme 2. Control experiments for understanding the mechanism.



Scheme 3. Plausible mechanism for the formation of aldehyde and ketones.

experiment indicates that oxygen did not have any role in the reaction mechanism. Interestingly, reaction did not work in the absence of water. To validate the role of water in the reaction, compound **1r** was treated with $K_2S_2O_8$ (2 equiv.) in labeled water (H₂¹⁸O, 97%) under inert condition for 12 h. To our delight we isolated the corresponding **2r**' in excellent yield (81%, eq. i, Scheme 2). Presence of ¹⁸O was confirmed by the HRMS and GC-mass spectrometry (¹⁸O content 96.3%, see ESI). It is very significant to note that this protocol gives a direct access to prepare ¹⁸O-labeled aldehydes and ketones quantitatively without resorting to an exchange experiment. Later, to gain further insight into the mechanism, diphenyl acetic acid 1r was treated with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard optimal conditions. The result showed that reaction did not proceed even after prolonged reaction time indicating that TEMPO inhibited the radical pathway (eq. ii, Scheme 2).

Based on our investigations and previous literature²⁵ we propose that sulfate radical anion (SO_4^-) (produced by the decomposition of potassium persulfate) upon reaction with phenyl acetic acid **1d** generates benzyl radical **I** by extrusion of carbon dioxide. SO_4^- further oxidizes the benzyl radical to the corresponding benzyl carbocation **II** via one electron oxidation. This reactive species reacts with water to form the corresponding benzyl alcohol **III**. Persulfate further oxidizes benzyl alcohol to the corresponding intermediates **IV** and **V**. Ultimately, the loss of proton from **V** would afford the desired product, benzaldehyde **2d** by the loss of hydrogen radical (Scheme 3).

Conclusions

In conclusion, we have demonstrated a one-pot protocol for the direct and clean transformation of arylacetic acids to aldehydes and ketones in water with minimal waste. Protocol employs envi4

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ronmentally friendly and less expensive $K_2S_2O_8$ as reagent, and commercially available arylacetic acids without any over oxidation. Method also demonstrated the direct access to ¹⁸O-labeled aldehydes and ketones without relying on exchange experiment. Experimental conditions are simple and above all reaction is carried out only in water and it has been demonstrated on a gram scale for wider application.

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A. Supplementary data

Supplementary data (experimental details and ¹H, ¹³C NMR spectra of compounds **2a–2w**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2017.06.013.

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