Green Chemistry: Air-Triggered Catalyst- and Oxidant-Free Decarboxylative Oxysulfonylation of Arylpropionic Acids With Sodium Sulfinates

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Research Article

Keywords: Air, Catalyst-free, Oxidant-free, Decarboxylative oxysulfonylation, β -Keto sulfones, Green chemistry, Room temperature

Posted Date: December 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1091233/v1>

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Abstract

The exploration of novel green synthetic strategies to obtain useful organic molecules is one of the most important missions for sustainable development. Herein, an efficient and sustainable decarboxylative oxysulfonylation between arylpropionic acids and sodium sulfinates has been established, providing a broad scope of β -ketosulfones in excellent yields. The reactions proceed at room temperature employing air as the only oxidant and oxygen source without extra catalyst, oxidant, and additive. Additionally, the reaction is scalable, and the products have been easily isolated by simple recrystallization, avoiding the chromatographic purification. Mechanistic studies have also been conducted to reveal that the reaction proceed via a radical mechanism.

Introduction

Over the last few decades, decarboxylative-coupling reaction of carboxylic acids has become an important and robust instrument in the synthetic chemist's toolkit (Goossen et al. 2008; Sharma et al. 2021; Varenikov et al. 2021; Wei et al. 2017). Owing to the potential driving force in the breaking of C-COOH bond, such a synthetic strategy is easier to overcome the thermodynamic barriers compared with the direct C-H activation, offering an effective route to construct various valuable carbon-carbon and carbon-heteroatom bonds with fascinating chemo- and regio-selectivity (Nanjo et al. 2018; Nanjo et al. 2019). However, these reactions are dominated by C-C (Kaur et al. 2019; Liu et al. 2016; Rodriguez et al. 2011) and C-N bond-forming transformations (Arshadi et al. 2019; Majedi et al. 2019; Wang et al. 2020). The field of decarboxylative C-S bond-forming reactions remained relatively quiet. In 2009, Duan (Duan et al. 2009) reported the first direct decarboxylative coupling between ortho-substituted aryl carboxylic acids with thiols to produce aryl sulfides. Later, a number of processes have been devised in the C-S bond construction through decarboxylative strategy (Shen et al. 2015; Hosseinian et al. 2018). In this context, most of these cases could be summarized into two patterns (Fig. 1a): (i) The cross-coupling reactions of C-M species with various sulfurative reagents after transition-metal-mediated decarboxylation of carboxylic acids; (ii) The oxidants triggered radical coupling reactions of carbon radical with sulfur radicals through the decarboxylation of carboxyl radical. However, these methods always required expensive and toxic metal catalysts, photoredox catalysts, and external oxidants, which severely limited their application in pharmaceutical and industrial manufacturing. Hence, the catalyst- and oxidant-free decarboxylative C-S bond forming reactions are incontrovertibly in great demand but remain largely underdeveloped.

Organosulfones are important structural motifs widely distributed in natural products and bioactive agents (Dunbar et al. 2017; Scott et al. 2018; Zhao et al. 2019). These privileged moieties have also been employed as the subsequent intermediates for a range of useful organic transformations. Due to their significant applications, the preparation of organosulfones has attracted considerable attentions of synthetic and pharmaceutical chemists (Alba et al. 2010; Liu et al. 2015; Manolikakes et al. 2016; Shaaban et al. 2017). Classically, organosulfones were prepared through thioether oxidation and direct C-sulfonylation processes. Recently, radical involved sulfonylation of alkynes with different sulfonyl

precursors has emerged as an efficient solution to prepare β -keto sulfones because of its elegant atom-economy and step-economy (Lu et al. 2013; Handa et al. 2014; Ni et al. 2020; Pampana et al. 2021). However, these processes are concomitant with the highly reactive and unstable vinyl radical intermediates (Wille 2013), making it difficult to avoid of the unwanted vinyl sulfones by-products via atom transfer radical addition (ATRA) (An et al. 2021). Moreover, the use of terminal alkynes always accompanied with undesirable side reactions such as Glaser homocoupling (Su et al. 2016; Sindhu et al. 2014). To this end, alkynyl carboxylic acids, as a kind of promising surrogate for terminal alkynes, appear to be fitted building blocks because of their superior stability, easy handling and better regio- and chemo-selectivity. In 2017, Wu (Yu et al. 2017) disclosed a Cu (I)-catalyzed multicomponent reaction of aryldiazonium tetrafluoroborates, 3-arylpropionic acids, and sulfur dioxide to construct β -ketosulfones (Fig. 1b). Later, a manganese (III)-mediated decarboxylative oxysulfonylation of arylpropionic acids was explored by Lu (Xiong et al. 2018). Excess manganous (III) acetate were employed as catalyst and oxidant (Fig. 1c). As our unremitting effort in the antimalarial drug exploration from natural products and synthetic molecules under the guidance of Prof. Youyou Tu (Chen et al. 2020; Ma et al. 2019; Tu 2016), herein, we delivered an eco-friendly and convenient synthetic approach to β -ketosulfones for further bio-evaluation (Fig. 1d). Compared to the existing methods, this protocol exhibited notable features as following: (i) Simple and sustainable conditions without toxic metal catalysts, oxidants and additives; (ii) Air was used as the only oxidant and oxygen source; (iii) Excellent regio- and chemo-selectivity without tricky by-products (e.g., Glaser-Hay homocoupling products and vinyl sulfones); (iv) Facilitative products purification avoiding column chromatography; (v) Easily to scaled up; (vii) Application in the direct synthesis and late-stage modification of complex bioactive agents.

Experimental

General Information

All the commercially available reagents were used as received. ^1H and ^{13}C NMR spectra were collected on BRUKER AV-600 (600 MHz) spectrometer using CDCl_3 as solvent. High Resolution Mass measurement was performed on Waters Xevo G2-XS QTOF mass spectrometer with electron spray ionization (ESI) as the ion source. All the experiments were monitored by thin-layer chromatography (TLC) on commercial silica gel plates (GF254) and visualized under ultraviolet (UV) lamp at 254 nm. Recrystallization was performed in ethyl acetate/petroleum ether (EA/PE).

General procedure for the synthesis of Arylpropionic Acids (1)

A 10 mL vessel was charged with caesium carbonate (6 mmol), silver (I) oxide (1 mol%) and dimethyl sulfoxide (DMSO) (5 mL). The reaction vessel was purged with carbon dioxide, and the alkyne (5 mmol) was added via syringe. The resulting mixture was stirred for 16 h at 50 °C at ambient CO_2 pressure. At the end of the reaction, the reaction mixture was cooled to room temperature and diluted with water. Then the aqueous layer was acidified with aqueous HCl and extracted with EA (3 $\times$ 30 mL). The combined organic

layers were washed with brine, dried over magnesium sulfate (MgSO_4), filtered and the volatiles were removed in vacuo to afford the corresponding arylpropionic acids **1**.

General procedure for the synthesis of sodium sulfinate substrates (2)

A 25 mL round bottom flask was charged with sodium sulfite (20 mmol), sodium bicarbonate (20 mmol) and deionized H_2O (10 mL). After stirring for 5 min, the sulfonyl chloride (10 mmol) was added portion-wise to the flask. The mixture was heated to 80 °C in an oil bath for 12 h. After cooling to room temperature, water was removed under vacuum, affording the crude sulfinate salt. Recrystallization of the residue in ethanol afforded the corresponding sodium sulfinate **2**.

General procedure for the synthesis of β -keto sulfones (3)

A mixture of aryl alkynes **1** (1 mmol), sulfinate **2** (10 mmol) and HFIP was stirred at 25 °C under air atmosphere for 6 h. Upon completion, the solvent was removed by rotary evaporation. The residue was extracted with EA (3 $\times$ 30 mL). The organic phase was washed with water and brine, respectively. The solvent was concentrated in vacuo and purified by recrystallization to give the desired β -keto sulfones **3**.

Results And Discussion

The research originated from the reaction of phenylpropionic acid **1a** with sodium benzenesulfinate **2a**. β -Ketosulfone product **3aa** was generated in 32% yield in hexafluoroisopropanol (HFIP) at room temperature for 10 hours. Motivated by this initial result, various conditions were screened to promote the isolated yield to 93% (Table 1, Supporting Information (SI)). We then set out to investigate the generality of this method. First, a vast array of alkynyl carboxylic acids were tested (Fig. 2). Methyl, methoxyl, and phenyl substituted substrates were well-tolerated to give corresponding products in 81%-91% yields. Product with bromo group (**3af**) was prepared in 90% yield. Electron-withdrawing groups such as cyano, trifluoromethyl, ester, and aldehyde groups were compatible with the conditions, and the corresponding products were synthesized in the yields of 73–86% (**3ae**, **3ag-3ai**). Thienyl and naphthyl propionic acids were also suitable substrates, and offering **3am** and **3an** in 88% and 90% yields, respectively. Next, the scope of sodium sulfinate was evaluated. Benzenesulfinate bearing electron-donating groups such as $t\text{-Bu}$, $-\text{OMe}$, and $-\text{NHAc}$ provided up to 90% yields (**3bb-3bd**). Sulfinate with moderate to strong electron-withdrawing groups (e.g., halogen, OCF_3 , CN , NO_2) remained suitable under the conditions (**3be-3bi**, 69%-85%). Naphthyl and thiophenyl-substituted counterparts took part in this transformation equally well, leading to **3bj** and **3bq** in the yields of 81% and 92%, respectively. Further efforts were made to evaluate the alkyl sulfinate. Pleasingly, both cyclic and acyclic alkyl sulfinate delivered products in nearly quantitative yields (**3bl-3bm**).

To demonstrate the synthetic utility of the developed chemistry, the reaction was carried out in 10 mmol scale, and the target product was synthesized without loss of efficiency. Following similar procedures, some representative biologically active molecules such as **3af** (anti-analgesic agents) (Abdel-Aziz et al.

2014), **3ag** (11 β -hydroxysteroid dehydrogenase type I inhibitors) (Xiang et al. 2007), and **3an** (carboxylesterase 1) (Han et al. 2018) were also obtained in gram scale from the corresponding arylpropionic acids (Fig.3a). It is noteworthy that, the estrone unit, which broadly exist in drugs and bioactive molecules, could be efficiently assembled into **5** in over 90% yield (Fig.3b). This outcome highlighted the applicability and versatility of the present protocol.

Next, some experiments were carried out to probe the possible mechanism. The addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the reaction mixture gave no desired products (Fig. 1a., SI), which indicated that the reaction might be involved in a radical pathway. Then, in the presence of diphenylethene, a sulfonylative adduct **6** was detected by HRMS (Fig. 1b., SI), inferring the generation of sulfonyl radical. Moreover, when butylated hydroxytoluene (BHT) was added to this reaction system, the desired reaction was diminished dramatically and the capture of the superoxide radical anion ($O_2^{\cdot-}$) was observed by HRMS (BHT-OOH, **7**) (Fig. 1c., SI). On the other hand, the oxo-sulfonylation did not occur under nitrogen atmosphere (Fig. 1d., SI). When we studied the reaction under $^{18}O_2$ (97%) atmosphere, the ^{18}O -labeled ratio of the ketone **3aa** was 68% (Fig. 1e., SI). Furthermore, performing the reaction in the presence of $H_2^{18}O$ (10 equiv.) under the optimal conditions, only 6% **3aa** was labeled with ^{18}O (Fig. 1f., SI). These results indicated that the molecular oxygen was the oxidant as well as the O-source of the products.

Based on the aforementioned results and previous works (Chen et al. 2020; Lu et al. 2013; Lu et al. 2015), a tentative reaction pathway is depicted in Fig. 4. Initially, sodium sulfinate was activated by oxygen via autoxidation with formation of oxygen radical **A**, resonating with sulfonyl radical **B**, while producing superoxide radical anion $O_2^{\cdot-}$. Subsequently, the addition of **B** to alkynyl acids **1** offered vinyl radical **C**, which could be further trapped by dioxygen to form the peroxy radical **D**. Afterwards, intermediate **D** undergoes a single electron transfer (SET) to generate peroxide anion intermediate **E**. Besides, the capture of $O_2^{\cdot-}$ by the intermediate **C** may also generated the intermediate **E**, which further went through intramolecular proton transfer (PT) to render the hydroperoxide intermediate **F**. Finally, the reduction of intermediate **F** furnished species **G**, followed by isomerization to give the desired β -keto sulfone **3**.

Conclusion

In summary, we have developed a practical and green decarboxylative oxysulfonylation between arylpropionic acids and sodium sulfinates that allows the rapid synthesis of diversely functionalized β -ketosulfones. This reaction features mild and sustainable conditions, simple operation, good functional group tolerance, and broad substrate scope. Moreover, this is the first solely dioxygen triggered decarboxylative oxysulfonylation reaction of arylpropionic acids, which enriches the repertoire of the molecular oxygen in the decarboxylative coupling reactions toward sustainable synthesis of various valuable compounds.

Abbreviations

HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
NMR	Nuclear magnetic resonance
Q-TOF	Quadrupole time-of-flight
UV	Ultraviolet
PE	Petroleum ether
CDCl ₃	Chloroform- <i>d</i>
equiv.	Equivalent
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
SET	Single electron transfer
DMSO	Dimethyl sulfoxide
ATRA	Atom transfer radical addition
MHz	Megahertz
ESI	Electrospray ionization
TLC	Thin-layer chromatography
EA	Ethyl acetate
mmol	Millimole
HCl	Hydrochloric acid
BHT	Butylated hydroxytoluene
PT	Proton transfer

Declarations

Supporting Information

General information, general experimental procedure, mechanism studies, characterization data for compounds and NMR spectra of compounds (PDF)

Notes

The authors declare no competing financial interest.

Acknowledgment

The author thanks the generous financial support from the Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences CI2021A05102, the National Natural Science

Foundation of China (21702235, 81841001), the Fundamental Research Funds for the Central Public Welfare Research Institutes (ZZ13-YQ-098, ZZ14-FL-010, ZZ15-ND-10).

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Figures

a) The recent C-S bond-forming process via decarboxylative-coupling transformations.

Previous work: decarboxylative oxysulfonylation of arylpropionic acids

d) This work:

- Transition-metal-free
- External oxidant-free
- Air as oxidant and oxygen source
- Mild conditions
- Broad scope
- simplified work-up procedure

Figure 1

The recent C-S bond-forming process via decarboxylative-coupling transformations and strategies for the β -keto sulfone synthesis.

Figure 2

Scope of the reaction.

(a) Pictures of the corresponding products via recrystallization:

Figure 3

Gram-scale reaction and late-stage oxy-sulfonylation of bioactive molecules.

Figure 4

Plausible mechanism.

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