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# Catalyst-free decarboxylative alkylation: access to quaternary center

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# Abstract

The formation of  $C(sp^3)-C(sp^3)$  bonds has received continuous attention in organic synthesis, and the focus on versatile alkyl precursors remains constant. In our work, prevalent amines and carboxylic acids successfully serve as alkyl sources to construct  $C(sp^3)-C(sp^3)$  bonds via decarboxylative deamination. The catalyst-free decarboxylative alkylation reaction provides alternative access to the quaternary center. Primary mechanistic experiments suggest that it undergoes a polar mechanism.

Keywords: Amines, pyridinium salts, decarboxylation, deamination, polar reaction

## INTRODUCTION

The generation of new organic molecules relies on the formation of new bonds. Primary amines, as general and useful feedstocks, are generally used in constructing C–N bonds in organo-metallic chemistry and biochemistry [Scheme 1A]<sup>[1,2]</sup>. If primary aliphatic amino groups are converted into leaving groups, they will be considered versatile alkyl sources, expanding the synthetic value of amines. Alkyl ammonium salts and alkyl pyridinium salts, prepared from primary amines, have been treated as versatile alkyl precursors. Especially, there is significant progress in deaminative functionalization of pyridinium salts through polar and radical processes. Commonly, alkyl radicals are accessible via metal reduction, photoredox catalysis, electron donor-acceptor complex, Lewis base catalysis, and electrochemical reduction<sup>[3-6]</sup>. The generated carbon radical could participate in subsequent transformation, establishing secondary and tertiary centers.



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**Scheme 1.** (A) Amidation reaction between amines and carboxylic acids; (B) esterification reaction between carboxylic acids and amine-derived pyridinium salts; (C) this work: decarboxylative alkylation reaction. TPT: 2,4,6-triphenylpyrylium; DMSO: Dimethyl sulfoxide; RT: room temperature.

In 1979, Katritzky found that alkylpyridinium salts reacted with diverse nucleophiles to form C-hetero bonds<sup>[7]</sup>. Recently, McGrath *et al.* disclosed esterification reactions between carboxylic acids and aminederived Katritzky salts. In this work, second and tertiary alkyl carboxylic acids participated in the formation of C–O bonds [Scheme 1B]<sup>[8]</sup>. To the best of our knowledge, decarboxylative deamination has rarely been studied. In consideration of the significance of quaternary centers<sup>[9-11]</sup>, we report nucleophilic substitution reactions of alkyl pyridinium salts with alkyl carboxylic acids to form  $C(sp^3)-C(sp^3)$  bonds containing these specialized centers [Scheme 1C].

It is well known that alkyl carboxylic acids could undergo radical decarboxylation via single electron oxidation to generate alkyl radicals<sup>[12-14]</sup>. When treated with base, the nucleophilic  $C(sp^3)$  intermediates can be generated by ionic decarboxylation<sup>[15-20]</sup>. Based on the previous work, a plausible mechanistic pathway is proposed in Scheme 2. In the presence of a base, alkyl carboxylate is generated. After decarboxylation, carbon anion II attacks Katritzky salts I, giving the final target products. The key step is ionic decarboxylation, which could give relatively stable tertiary carbon anion II under mild conditions.

#### EXPERIMENTAL

To a mixture of pyridinium salt 1 (0.1 mmol), 2,2,2-triphenylacetic acid 2a (0.1 mmol), KHCO<sub>3</sub> (0.1 mmol) was added Dimethyl sulfoxide (DMSO) (0.5 mL) under N<sub>2</sub> atmosphere. Next, the reaction mixture was replaced Magnetic Stirrer at room temperature for 6 h. When the reaction finished, the mixture was purified by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 50/1).

## **RESULTS AND DISCUSSION**

To verify our proposal presented in Scheme 2, 1-benzyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate and 2,2,2-triphenylacetic acid were selected as the model substrate [Table 1]. In the presence of KHCO<sub>3</sub>, the reaction proceeded smoothly in MeCN, giving the desired product in 43% yield, without esterification

Ph BF <sub>4</sub> Ph N Ph	+ Ph Ph base (1 solvent	$\begin{array}{c} 0 \text{ equiv} \\ \hline RT, N_2 \end{array} Ph + Ph $		
Bn 1a	2a	3a		
Entry	Solvent	Base	Yield (%) <sup>b</sup>	
1	CH <sub>3</sub> CN	KHCO <sub>3</sub>	43	
2	Toluene	KHCO <sub>3</sub>	0	
3	CHCl <sub>3</sub>	KHCO <sub>3</sub>	29	
4	Acetone	KHCO <sub>3</sub>	79	
5	DMSO	KHCO <sub>3</sub>	95	
<b>6</b> <sup>c</sup>	DMSO	KHCO <sub>3</sub>	91 (84)	
7 <sup>c</sup>	DMSO	K <sub>2</sub> HPO <sub>4</sub>	82	
8 <sup>c</sup>	DMSO	KH <sub>2</sub> PO <sub>4</sub>	13	
9 <sup>c</sup>	DMSO	2,4,6-Collidine	18	
10 <sup><i>c,d</i></sup>	DMSO	KHCO <sub>3</sub>	21	
11 <sup>c,e</sup>	DMSO	KHCO3	20	
12 <sup>c</sup>	DMSO	-	17	
13 <sup>c,f</sup>	DMSO	KHCO <sub>3</sub>	92	

#### Table 1. The optimization of reaction<sup>a</sup>

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), base (0.1 mmol, 1.0 equiv), DMSO (2.0 mL), room temperature, 6 h; <sup>b</sup>Determined by GCMS using biphenyl as the internal standard. The number in parentheses is the isolated yield; <sup>c</sup>DMSO (0.5 mL); <sup>d</sup>KHCO<sub>3</sub> (0.02 mmol, 0.2 equiv); <sup>c</sup>Air; <sup>f</sup>Dark conditions. DMSO: Dimethyl sulfoxide; GCMS: gas chromatography mass spectrum.



Scheme 2. The proposed mechanism. TPT: 2,4,6-triphenylpyrylium.

product (entry 1). The screening of solvents showed that DMSO resulted in the best yield (entries 1-5). These results suggested that aprotic solvent was beneficial to decarboxylation for the carboxylate. When inducing the amount of DMSO (0.5 mL), a similar yield was obtained (84% isolated yield, entry 6). Inorganic base performed better than organic base (entries 6-9). When using 20% equiv of KHCO<sub>3</sub>, a lower yield was given (21%, entry 10). Exposure to air adversely affects the polar reaction (entry 11). The carbon anion intermediate may be oxidized by O<sub>2</sub>, delivering triphenylmethanol, detected by gas chromatography mass spectrum (GCMS). Hence, 1.0 equiv of KHCO<sub>3</sub> and inert gas atmosphere were crucial for this decarboxylative alkylation reaction (entries 10-12). The possibility of formation of electron donor-acceptor (EDA) could be excluded (entry 13).

With the optimal reaction conditions in hand, we evaluated the scope of the reaction, as summarized in Scheme 3. Generally, the reaction occurred in good to excellent yield with benzylic pyridinium salts. Benzylic amines with donating groups on the phenyl ring at para-position performed well in this



**Scheme 3.** The scope of pyridinium salts. <sup>a</sup>Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), KHCO<sub>3</sub> (0.1 mmol, 1.0 equiv), DMSO (0.5 mL), room temperature, 6 h; <sup>b</sup>24 h; <sup>c</sup>**1x** (0.2 mmol, 2.0 equiv), DMSO (2.0 mL), 48 h. DMSO: Dimethyl sulfoxide; RT: room temperature.

decarboxylative alkylation (3b-3c, 70%-80%). Moreover, strong electron-deficient (CN, CF<sub>3</sub>, OCF<sub>3</sub>) benzylic pyridinium salts were tolerated and isolated in acceptable yields (3e-3g, 51%-55%), while (4-chlorophenyl)methanamine gave a better result (3d, 80%). The substituent groups at ortho-position and meta-position were both compatible (3h-3l). Under the reaction conditions, substrates could bear bis-



Scheme 4. Gram-scale reaction. DMSO: Dimethyl sulfoxide; RT: room temperature.



**Scheme 5.** Mechanistic studies. DMSO: Dimethyl sulfoxide; RT: room temperature; TEMPO: 2,2,6,6-tetramethylpiperidinyloxy; BHT: 2,6-di-tert-butyl-4-methylphenol; PBN: N-tert-Butyl-α-phenylnitrone.

substituted methyl, methoxy groups, and halogen (3m-3q). Heteroaromatic rings, given their importance in numerous pharmaceuticals, were next examined. To our delight, the pyridinium salts, such as those containing functionalized thiophenes, pyridines, pyrimidines, and pyrazines, were successfully treated as alkyl sources to construct quaternary centers (3r-3u). Generally, secondary pyridinium salts show larger steric hindrance than primary pyridinium salts. As expected, 1x resulted in a low yield, even extended to 48 h. Surprisingly, allylic carbon cations may be more stable and suitable for this type of nucleophilic substitution, leading to the desired product in an excellent yield (3w, 85%). Unfortunately, other carboxylic acids are incompatible with the reaction [Supplementary Materials].

To clarify the practice of this method, a gram-scale reaction between 1-(but-3-en-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1w) and 2,2,2-triphenylacetic acid (2a) was performed [Scheme 4]. The desired coupling product (3w), a kind of terminal olefine with a quaternary carbon center, was afforded as a white solid in 61% yield.

When monitoring the reaction, it was shown that most of the reactants transferred into 3a in a short time (59% in 0.5 h), and the reaction rate decreased as time increased due to a decrease in reactant concentration [Scheme 5A]. To further clarify the possible reaction mechanism, radical inhibiting experiments were first conducted [Scheme 5B]. Under the standard condition, three kinds of radical inhibitors were added. It is clear that reductive inhibitors, such as 2,6-di-tert-butyl-4-methylphenol (BHT) and N-tert-Butyl- $\alpha$ phenylnitrone (PBN), make no difference. When adding 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), the reaction was inhibited, probably due to its strong oxidation. These results suggest that the present decarboxylative alkylation may be a polar reaction. We assume that pyridinium salts might act as electrophiles, and 2,2,2-triphenylacetic acid undergoes ionic decarboxylation to give nucleophilic alkyl carbon anion intermediates. In the presence of D<sub>2</sub>O<sub>2</sub>, we found that the prepared potassium 2,2,2triphenylacetate directly proceeded with decarboxylation and gave D-triphenylmethane in 98% yield [Scheme 5C]. Next, anhydrous DMSO was used as the solvent. The desired decarboxylative alkylation product was afforded in a compatible yield (88%), accompanying a trace amount of triphenylmethane. As shown in Scheme 2, in the presence of KHCO, tertiary carboxylate was formed. When finishing decarboxylation, the generated carbon anion (II) acted as a nucleophile. Followed by the cleavage of C-N bonds, the desired product 3 was delivered.

# CONCLUSIONS

In conclusion, a catalyst-free decarboxylative alkylation has been developed. Versatile pyridinium salts, prepared from primary amines, acted as an effective electrophile and reacted with tertiary carboxylic acids to afford quaternary centers under mild conditions without excess reagents. Radical-inhibiting and deuteration-labeled experiments suggest that the reaction may proceed via a polar mechanism.

# DECLARATIONS

## Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Xu W Synthesizing the substrates and performing the experiments: Cai L, Li F, Wang S

## Availability of data and materials

Detailed experimental procedures and spectroscopic data are published as Supplementary Materials in the journal, and the data supporting the findings of this study are available within its Supplementary Materials.

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## Conflicts of interest

Xu W and Cai L declare a competing interest, stating that one patent has been registered (202311376023.8).

**Ethical approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

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