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Copper-Catalyzed Oxidative Decarboxylative Arylation of Benzothiazoles with Phenylacetic Acids and α-Hydroxyphenylacetic Acids with O_2 as the Sole Oxidant

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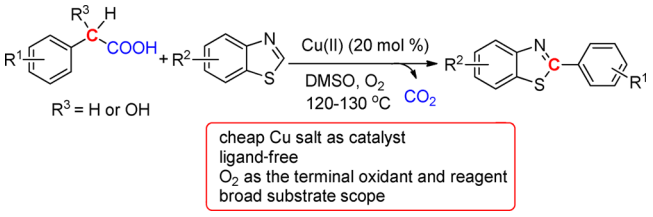
ABSTRACT



A Cu(II)-catalyzed oxidative decarboxylative synthesis of 2-aryl benzothiazole from phenylacetic acids and α-hydroxyphenylacetic acids has been developed. This reaction proceeds via Cu(II)-catalyzed decarboxylation, C−H bond oxidation, ring-opening, and condensation steps in a one-pot protocol with dioxygen as the sole terminal oxidant. Various functional groups were tolerated under standard conditions, and isolated yields were as high as 95%.

The use of decarboxylation[1] to activate reactions has attracted great attention due to the ready access of starting materials, the use of neutral conditions, and the relative cleanliness of a pathway with CO_2 as the only byproduct. Since the pioneering work of Myers[2] and Goossen,[3] catalytic decarboxylation of C(sp^2) (aromatic[4] and alkenyl[5]) and C(sp) (alkynyl[6]) acids has been extensively studied, yet decarboxylation at an sp^3-hybridized carbon for functional introduction is relatively rare[7] and remains a significant challenge. The most common decarboxylation of an sp^3-hybridized carbon is the Pd-catalyzed decarboxylative allylation reaction,[8] yet the decarboxylative allylation reaction required presynthesis of allylic carboxylates from sp^3-hybridized carboxylic acids. In 2009, Li reported a novel Cu(I)- and $FeSO_4$-catalyzed decarboxylative coupling of the sp^3-hybridized carbon of α-amino acids,[9] but

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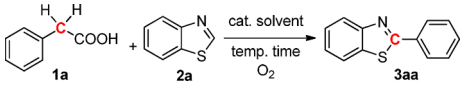
the reactions work well chiefly with prolines and require excess peroxides as oxidants under an inert atmosphere. Recently, Liu et al. developed Pd-catalyzed decarboxylation of aliphatic carboxylate salts;[7b,c,e,10] these are the first examples of intermolecular decarboxylative coupling of various types of aliphatic carboxylates, but these reactions require carboxylate salts, not free carboxylic acids. Thus the direct oxidative decarboxylation of sp^3-hybridized carboxylic acids with the formation of new C−C or C−heteroatom bonds remains a challenge, especially with O_2 as the terminal oxidant.

2-Substituted benzothiazoles are important heterocyclic scaffolds in pharmaceuticals, organic electronic materials, and biologically active natural products. Conventional methods for the synthesis of 2-substituted benzothiazoles typically involve the condensation of 2-amino thiophenols and aldehydes.[11] Very recently condensations between benzothiazoles and aldehydes were also developed.[12] Direct C−H activation by transition metal catalyzed cross-coupling of benzothiazoles and aryl halides[13] or aromatic boronic acids[14] was another attractive method. In term of decarboxylative coupling, Tan et al. reported elegant work on the synthesis of 2-arylbenzothiazole from coupling benzothiazole with benzoic acid.[15] Yet this reaction used an expensive Pd salt as the catalyst, phosphine ligands and silver salts were necessary for the success of the reactions, and benzoic acids were only limited to ortho-substituted ones, thus limiting the substrate scope.

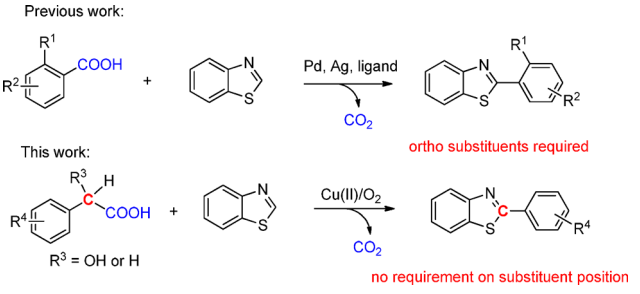
Very recently, the Cu-catalyzed decarboxylative coupling reaction has attracted much attention[1b,16] due to the readily availability, low cost, and low toxicity of copper salts. To the best of our knowledge, there is no oxidative decarboxylation of an sp^3-hybridized carbon using Cu(II) salts as the catalyst without added ligands and using dioxygen as the terminal oxidant. Herein we report the first Cu(II)-catalyzed oxidative decarboxylative synthesis of 2-aryl benzothiazole from phenylacetic acids and α-hydroxyphenylacetic acids. This reaction proceeds via Cu(II)-catalyzed decarboxylation, dioxygen activation, C−H bond functionalization, ring-opening, and condensation steps in a one-pot reaction in DMSO with dioxygen as the sole terminal oxidant. This transformation represents a novel protocol for preparation of 2-aryl benzothiazoles. Furthermore, the easy availability of phenylacetic acids, α-hydroxyphenylacetic acids, and copper(II) salts makes this reaction highly practical and broad in scope.

Table 1. Investigation of the Reaction Parameters[a]



entry	catalyst		solvent	temp (°C)	time (h)	yield (%)[b]
1	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	120	24	66[c]
2	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	100	24	18
3	$Cu(OAc)_2$ (20 mol %)	O_2	DMSO	100	26	45
4	$Cu(OAc)_2$ (20 mol %)	O_2	DMSO	130	26	77[c]
5	$Cu(OAc)_2$ (20 mol %)	O_2	DMF	130	26	52
6	$Cu(OTf)_2$ (20 mol %)	O_2	DMSO	130	24	40
7	$Cu(TFA)_2$ (20 mol %)	O_2	DMSO	130	24	32
8	$CuBr_2$ (20 mol %)	O_2	DMSO	130	24	trace
9	$CuSO_4$ (20 mol %)	O_2	DMSO	130	24	36
10	$Cu(OAc)_2$ (20 mol %)	air	DMSO	130	24	20
11	$Cu(OAc)_2$ (20 mol %)	N_2	DMSO	130	24	6
12	$Cu(OAc)_2$ (20 mol %)	O_2	DMSO	130	24	0[d]

[a] Reaction conditions: phenyl acetic acid (1.0 mmol), benzothiazole (0.5 mmol), cat. in solvent (0.75 mL) in a sealed tube under corresponding atomsphere. [b] GC yield. [c] Isolated yield. [d] 2 equiv of TEMPO was added.



We commenced our study with phenylacetic acid (**1a**) and benzothiazole (**2a**) under $Cu(OAc)_2/O_2$ as a model reaction (Table 1). To our delight, the desired product was formed in 66% isolated yield (Table 1, entry 1) with 10 mol % $Cu(OAc)_2$ at 120 °C under 1 atm of O_2. Further catalysts, solvents, and temperatures were all extensively screened, and eventually, the optimal reaction conditions emerged as phenylacetic acid (**1a**) (1.0 mmol), benzothiazole (**2a**) (0.5 mmol), and $Cu(OAc)_2$ (20 mol %) at 130 °C in DMSO (0.75 mL) under an O_2 atomosphere (Table 1, entry 4).

With these optimized conditions in hand, the substrate scope was investigated (Scheme 1). Phenylacetic acids possessing electron-donating groups on the aromatic rings gave the desired products in moderate to good yields

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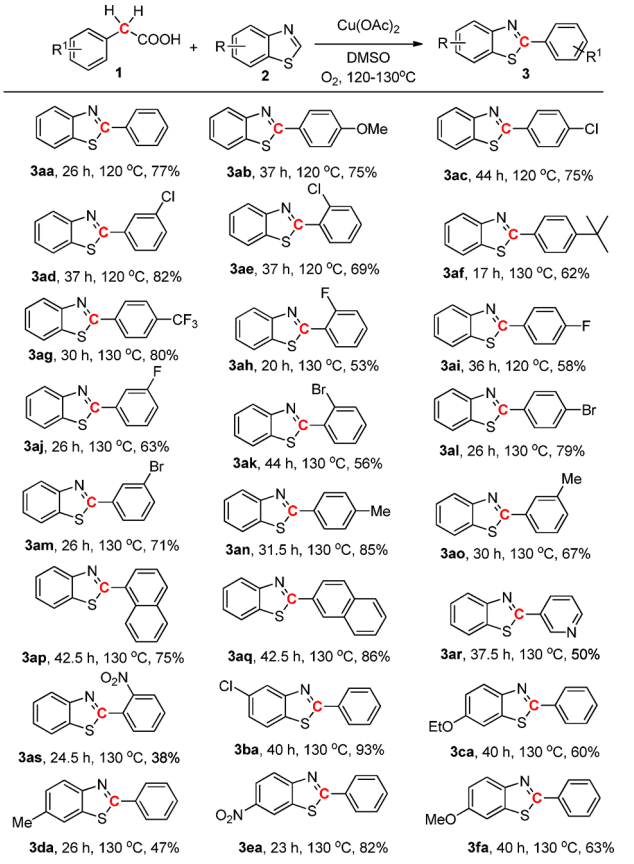
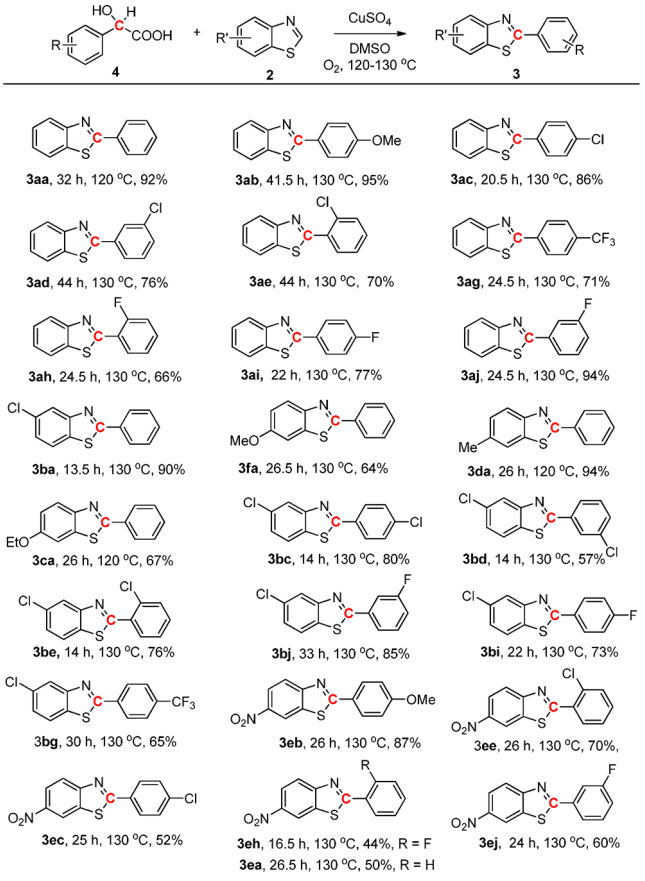
Scheme 1. Copper-Catalyzed Aerobic Oxidative Decarboxylative Arylation of Benzothiazoles with Phenylacetic Acid[a]



[a] Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (20 mol %), DMSO (0.75 mL), O_2; reaction was monitored by TLC plate. [b] All the yields are isolated yields.

Scheme 2. Copper-Catalyzed Aerobic Oxidative Decarboxylative Arylation of Benzothiazoles with α-Hydroxyphenylacetic Acid[a]



[a] Reaction conditions: **4** (1 mmol), **2** (0.5 mmol), $CuSO_4$ (20 mol %), O_2; reaction were monitored by TLC plate. [b] All the yields are isolated yields.

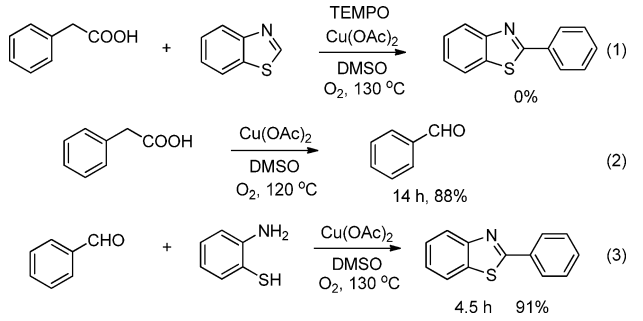
(**3ab**, **3af**, **3an**–**3ao** in Scheme 1). Phenylacetic acids bearing electron-withdrawing groups on the aromatic ring were better, with the desired 2-arylbenzothiazoles obtained in good to excellent yields (Scheme 1, **3ac**–**3ae**, **3ag**–**3am**). It was noteworthy that halo-substituted phenylacetic acid survived well, leading to halo-substituted benzothiazole derivatives, which could be used for further transformation. The position of the substituents on aromatic rings of phenylacetic acids had little effect (Scheme 1, **3ac**–**3ae**, **3ah**–**3aj**, **3ak**–**3am**, **3an**–**3ao**), with only *o*-substitution giving slightly inferior yields to *m*- and *p*-substitution, probably as a result of steric hindrance. Both 1- and 2-naphthylacetic acid reacted well and gave the corresponding benzothiazole derivatives in 75% and 86% yields (Scheme 1, **3ap** and **3aq**). Heteroaromatic acetic acid, 3-pyridylacetic acid, also worked well under standard conditions to give a moderate isolated yield (Scheme 1, **3ar**). Benzothiazoles bearing substituents with diverse electronic properties on the benzo group were also explored for the reactions. Both electron-withdrawing groups (such as chloro and nitro groups) and electron-donating groups (such as methyl, methoxy, and ethoxy groups) reacted smoothly with phenyacetic acid to afford the desired products in up to 93% isolated yields (Scheme 1, **3ba**–**3fa**). All in all, fluoro, chloro, bromo, methoxy, ethoxyl, methyl, *tert*-butyl, nitro, and trifluoromethyl groups were well tolerated.

Intrigued by the above results, we applied the same conditions to α-hydroxyphenylacetic acids (Supporting Information (SI), Table S1). To our delight, under the above-mentioned standard conditions, 2-phenyl benzothiazole (**3aa**) was obtained in 72% isolated yield from α-hydroxyphenylacetic acid (**4a**) and benzothiazole (**2a**) (SI, Table S1, entry 1). Solvents, catalysts, catalysts loadings, and temperatures were all investigated, and after condition screening, it appeared that 20 mol % of $CuSO_4$ showed the highest efficiency for this transformation with a 92% isolated yield (SI, Table S1, entry 10).

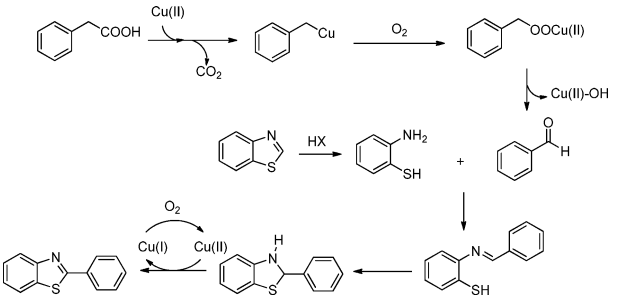
Under the optimized conditions, various α-hydroxyphenylacetic acids and benzothiazoles were explored to check the tolerance of the reaction. As shown in Scheme 2, the reaction worked very well with diverse benzothiazoles and various α-hydroxyphenylacetic acids to give 2-arylbenzothiazoles in 44–95% isolated yields.

In order to elucidate the reaction mechanism, several control experiments were carried out (Schemes 3 and S1).

Scheme 3. Control Experiments



Scheme 4. Plausible Reaction Mechanism



Since the reaction involves oxygen, radical trapping experiments were conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) with phenylacetic acid and benzothiazole under standard conditions. The result showed that the reactions were inhibited by TEMPO (Table 1, entry 12, Scheme 3, eq 1). The reaction of benzyl alcohol with both benzothiazole and 2-aminothiophenol gave just a trace of desired products, showing that benzyl alcohol is not an intermediate for this reaction (SI, Scheme S1, eqs S1 and S2). Toluene was also treated under standard conditions, and no desired product was formed (SI, Scheme S1, eq S3). Interestingly, if only phenylacetic acid was applied under the standard conditions, 88% of benzaldehyde was obtained (Scheme 3, eq 2). When benzaldehyde reacted with benzothiazole and 2-aminothiophenol respectively, only the latter gave the desired product in 91% yield (Scheme 3, eq 3); the former gave no product (SI, Scheme S1, eq S4), suggesting that 2-aminothiophenol is a key intermediate. This result demonstrated that a ring-opening pathway was taken in the reaction. However, if only benzothiazole was treated under the standard conditions, no ring-opened product, 2-aminothiophenol, was detected (SI, Scheme S1, eq S5). Significantly, when 2-oxo-2-phenylacetic acid was treated under the standard conditions, only 13% of the desired product was obtained along with 37% benzaldehyde (SI, Scheme S1, eq S6). At this point point, even though the exact reaction mechanism is not clear for 2-substituted benzothiazole formation, we may give a plausible reaction mechanism (Scheme 4): Phenylacetic acid is decarboxylated and oxidized to the aldehyde, and at the same time the benzothiazole ring is opened in the presence of acid. The resulting 2-aminothiophenol reacts with the aldehyde, and after oxidative condensation, the desired 2-substituted benzothiazole is obtained (Scheme 4).

In the case of the reaction between benzothiazoles and α-hydroxyphenylacetic acid, control experiments were performed and a proposed mechanism is given in the SI (Schemes S2 and S3).

In summary, Cu(II)/O_2 systems that catalyzed the oxidative decarboxylative synthesis of 2-aryl benzothiazole from phenylacetic acids and α-hydroxyphenylacetic acids has been developed. These reactions are the first decarboxylations of an sp^3-hybridized carbon catalyzed by Cu(II) followed by oxidation of the α-methylene group with dioxygen as the oxidant and reagent, thus expanding the utility of decarboxylation in organic synthesis and also providing a sustainable synthesis for 2-aryl benzothiazole derivatives. Further studies on the scope, mechanistic elucidation, and synthetic application of this reaction are in progress in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.