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Silver catalyzed decarboxylative direct C2-alkylation of benzothiazoles with carboxylic acids†

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A novel and efficient silver catalyzed decarboxylative direct C2-alkylation of benzothiazoles with carboxylic acids for the synthesis of 2-alkyl benzothiazoles was developed.

In recent years, transition-metal-catalyzed[1] and photo-catalyzed[2] decarboxylative cross-coupling reactions using simple carboxylic acids as coupling partners have been widely studied in organic synthesis as novel methods for formation of various carbon–carbon[3] and carbon–heteroatom[4] bonds. Since carboxylic acids and their derivatives as cross-coupling components are non-toxic, low cost, stable and structurally diverse, extensive studies have been accomplished in this area, particularly since Ag-catalyzed decarboxylative alkylation of pyridines and quinolines was reported by F. Minisci in the 1970s.[5] Afterward, Pd-catalyzed decarboxylative Heck-type reactions of benzoic acids with alkenes and Pd-catalyzed decarboxylative coupling of benzoic acids or heteroaromatic carboxylic acids with aryl halides, *etc.* were developed by Myers,[6] Goossen,[3b,7] Forgione[8] and others,[3a,c–e,9] respectively. Recently, Greaney[10] reported that in the presence of $K_2S_2O_8$, aroylbenzoic acids can undergo intramolecular radical decarboxylation coupling reactions to form fluorenones. In addition, α-oxo-,[3j,11] alkenyl[3g,12] and alkynyl[3h,i,13] carboxylic acids (or their salts) can also be employed as coupling partners. Despite the significant advances, the reactions reported in the literature were mainly focused on decarboxylative cross-coupling reactions involving the breaking of C_{sp}–COOH or C_{sp^2}–COOH bonds. Only recently, Liu,[14] Li,[15] and others[16] examined transition metal catalyzed decarboxylative coupling reactions involving the breaking of C_{sp^3}–COOH bonds. Such reactions are synthetically useful for making aliphatic compounds but still have been less studied. In particular, the alkylation of benzothiazoles and benzoxazoles using saturated aliphatic carboxylic acids as alkylating reagents is rarely reported despite the fact that benzothiazoles, benzoxazoles and their derivatives exhibit a lot of biological activities such as being anti-inflammatory, *etc.*[17] According to the literature most of the successful direct C–H alkylation of benzothiazoles and benzoxazoles were performed using transition metals as catalysts and alkyl halides,[18] Grignard reagents,[19] *N*-tosylhydrazones[20] and potassium alkyltrifluoroborates[21] as alkylating reagents under very harsh reaction conditions. A metal free DTBP catalyzed direct sp^2C–H bond alkylation of heteroaromatics with cycloalkanes, which has very recently been reported by Guo and co-workers, appears to be an environmentally friendly method, however, these processes are limited to cyclic alkanes as alkylating reagents.[22] Therefore, further developments for more general alkylation methodologies are strongly desired. Herein, we report silver catalyzed alkylation of benzothiazoles with carboxylic acids through direct decarboxylative cross-coupling reaction, in which a wide range of carboxylic acids including secondary or tertiary α-substituted, cyclic and acyclic carboxylic acids were employed as the alkylation reagents.

We began our studies with the commercially available benzothiazole (**1a**) and pivalic acid (**2a**). When 1 equiv. of **2a** was reacted with **1a** in the presence of 10 mol% of $AgNO_3$ and 2 equiv. of $K_2S_2O_8$ in CH_2Cl_2–H_2O (v/v = 1/1) at room temperature, we were delighted to know that our desired product, 2-(*tert*-butyl)benzothiazole (**3a**), was indeed formed in 52% yield (Table 1, entry 1). The control experiment showed that a silver catalyst was necessary for the reaction to proceed (entry 2). With this intriguing result in hand, we investigated other silver catalysts. The use of $AgSbF_6$ was worse (entry 6), while Ag_2CO_3, AgOAc and Ag_2O catalyzed the reaction with moderate efficiency (entries 3–5). But Cu cannot catalyze this reaction although Cu and Ag are in the same group in the periodic table (entry 7). Subsequently, the effect of other different oxidants such as $Na_2S_2O_8$, H_2O_2, TBHP and DTBP was also screened, and unfortunately, only $Na_2S_2O_8$ can catalyze this reaction with a moderate yield (51%) (entries 8–11). Then, the effect of the amount of carboxylic acid, $AgNO_3$ and $K_2S_2O_8$ was examined, and the results showed that an increase in the amount of carboxylic acid, $AgNO_3$ and $K_2S_2O_8$ led to higher conversion of **1a** (entries 12 and 13). When we used 2 equiv. of **2a**, 20 mol% $AgNO_3$ and 4 equiv. of $K_2S_2O_8$, a full conversion was

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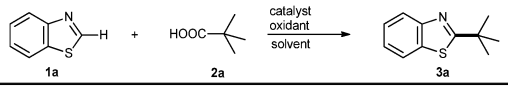
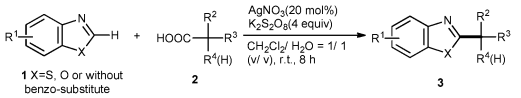
Table 1 Optimization of reaction conditions[a]

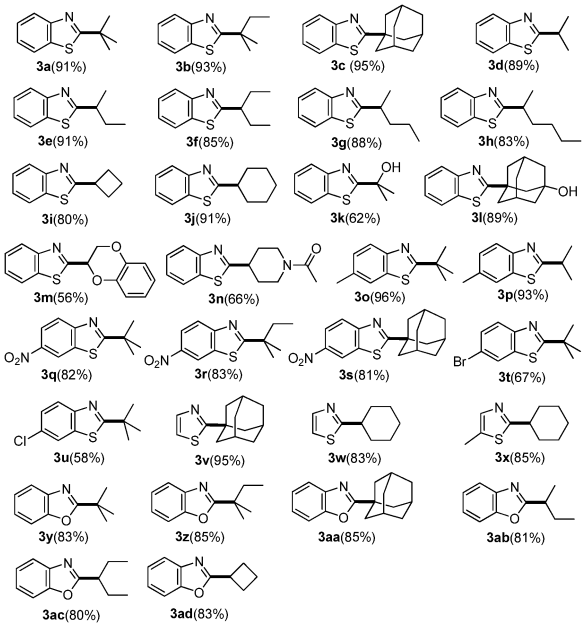


Entry	Catalyst (equiv.)	Oxidant (equiv.)	Mixed solvent	Yield[b] (%)
1	$AgNO_3$(10%)	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	52(45)
2[c]		$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	0
3	Ag_2CO_3(10%)	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	49
4	AgOAc(10%)	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	51
5	Ag_2O(10%)	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	47
6	$AgSbF_6$(10%)	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	40
7[d]	Cu salts	$K_2S_2O_8$(2)	CH_2Cl_2–H_2O	0
8	$AgNO_3$(10%)	$Na_2S_2O_8$(2)	CH_2Cl_2–H_2O	51
9	$AgNO_3$(10%)	H_2O_2(2)	CH_2Cl_2–H_2O	0
10	$AgNO_3$(10%)	TBHP(2)	CH_2Cl_2–H_2O	0
11	$AgNO_3$(10%)	DTBP(2)	CH_2Cl_2–H_2O	0
12[e]	$AgNO_3$(15%)	$K_2S_2O_8$(3)	CH_2Cl_2–H_2O	73
13[f]	**$AgNO_3$(20%)**	**$K_2S_2O_8$(4)**	**CH_2Cl_2–H_2O**	**96(91)**
14[f]	$AgNO_3$(10%)	$K_2S_2O_8$(4)	CH_2Cl_2–H_2O	78
15[f]	$AgNO_3$(20%)	$K_2S_2O_8$(4)	CH_3CN–H_2O	Trace
16[f]	$AgNO_3$(20%)	$K_2S_2O_8$(4)	DMF–H_2O	Trace
17[f]	$AgNO_3$(20%)	$K_2S_2O_8$(4)	Acetone–H_2O	Trace
18[f]	$AgNO_3$(20%)	$K_2S_2O_8$(4)	$CHCl_3$–H_2O	63

[a] Reaction conditions: 0.2 mmol of **1a**, 1 equiv. of **2a**, catalyst, oxidant and 2 mL of mixed solvent (v/v = 1/1) in a 25 mL round-bottom flask at room temperature for 8 h. [b] Yield determined by GC analysis. Yield of isolated products given in parentheses. [c] No $AgNO_3$ added. [d] CuI, CuBr and CuCl were tested. [e] 1.5 equiv. of **2a** added. [f] 2 equiv. of **2a** added.

Table 2 Scope of decarboxylative alkylation[a]





[a] Reaction conditions: 0.5 mmol of **1**, 2 equiv. of **2**, 20 mol% of $AgNO_3$, 4 equiv. of $K_2S_2O_8$ and 5 mL of CH_2Cl_2–H_2O (v/v = 1/1) in a 25 mL round-bottom flask at room temperature for 8 h.

obtained and the isolated yield of **3a** reached 91% (entry 13). Disappointedly, when we reduced the amount of the silver catalyst to 10 mol%, a lower conversion of **1a** was obtained (entry 14). Solvents were crucial for this reaction, as well. Using CH_3CN–H_2O, DMF–H_2O, or acetone–H_2O as solvent led to a trace amount of **3a**, while $CHCl_3$–H_2O led only to a moderate yield (entries 15–18). Further screening of reaction time showed that 8 h was the best choice. Therefore, optimal reaction conditions involved 2 equiv. of carboxylic acid, $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (4 equiv.) in the mixed solvent of CH_2Cl_2–H_2O (v/v = 1/1) at room temperature for 8 h.

With the optimized reaction conditions established, the scope of this transformation was subsequently investigated. We evaluated the reactivity of benzothiazole toward different tertiary and secondary α-substituted carboxylic acids (Table 2). 2-*tert*-Butyl benzothiazole and 2-*tert*-pentyl benzothiazole were obtained with 91% (**3a**) and 93% (**3b**) yield, respectively. Notably, the silver catalysis could also be applied to cyclic carboxylic acids. 2-Adamantan-1-yl-benzothiazole **3c** was synthesized from 1-adamantanecarboxylic acid in an excellent yield (95%). The cyclic and acyclic secondary alkylation was also achieved, affording the corresponding products **3d–j** in good to excellent yields. Comparatively, the cyclopropyl benzothiazole cannot be obtained from the corresponding coupling reaction perhaps owing to ring-opening of the cyclopropyl radical formed after decarboxylation of cyclopropane carboxylic acid.[23] The tolerance of functional groups in aliphatic carboxylic acids and benzothiazoles during this transformation were further investigated. Carboxylic acids that contain hydroxyl, ether and amide groups, respectively, afforded the corresponding products in moderate to good yields (**3k–n**). It is worth noticing that halogen-containing saturated aliphatic carboxylic acids cannot result in the formation of the corresponding products, testified by our purposely designed experimental reaction of 2-bromo-isobutyric acid with benzothiazole, in which an immediate AgBr precipitate was observed. The reactivity of different substituted benzothiazoles toward secondary and tertiary α-substituted carboxylic acids was subsequently examined. The alkylated benzothiazoles (**3o–u**) were obtained with moderate to excellent yields. It was noteworthy that the electronic effect had an obvious influence on the decarboxylative coupling reactions. Benzothiazole with an electron-donating methyl group underwent the secondary and tertiary alkylation smoothly under standard conditions (**3o–p**), while the electron-withdrawing nitro-, bromo- and chloro-substituents only participated in the alkylation with tertiary α-substituted carboxylic acid, forming the corresponding alkylated benzothiazole derivatives with relatively low yields (**3q–u**). It is worth mentioning that the coupling reaction was also suitable for the direct alkylation of thiazoles (not limited to benzo-substituted). Thiazole and methylthiazole underwent the secondary and tertiary alkylation smoothly under standard conditions with good yields (**3v–x**). We next attempted to apply the reaction to other 1,3-azoles and immediately found that the abovementioned silver catalysis was also suitable for the direct alkylation of benzoxazoles. Both secondary and tertiary α-substituted carboxylic acids gave rise to corresponding products **3y–ad** in satisfactory yields.

A plausible mechanism for this novel decarboxylative coupling reaction is proposed. If tetramethylpiperidinyloxy (TEMPO),

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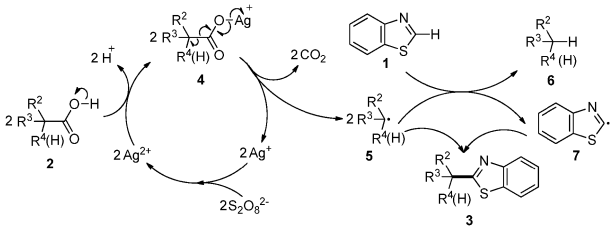

Scheme 1 Plausible mechanism.

a widely used radical scavenger, was added into the reaction system, decarboxylative cross-coupling reactions of both pivalic acid **2a** and isobutyric acid **2d** with benzothiazole **1a** were quenched. The results suggest that the reactions may undergo a radical mechanism. The plausible mechanism of the decarboxylative cross-coupling reaction may be as follows (Scheme 1). Initially, an Ag(I) cation is oxidized to an Ag(II) cation by peroxodisulfate. Then, carboxylic acid **2** reacts with the Ag(II) cation to form cation salt **4** by losing a proton. **4** further loses one molecule of CO_2 and the Ag(I) cation to form alkyl radical **5**. The obtained free radical **5** subsequently underwent hydrogen atom abstraction from the C2 of benzothiazole forming the corresponding benzothiazole radical **7**. Subsequently, another alkyl radical **5** couples with benzothiazole radical **7**, forming the coupling product **3**. The ease of carboxylic acid decarboxylation seems to be closely related to the stability of the *in situ* formed alkyl radical, as the reactivity appears to increase on going from secondary to tertiary radicals. This may explain the slightly lower yields of **3d–j** obtained.

In conclusion a novel and efficient silver catalyzed decarboxylative direct C2-alkylation of benzothiazoles, thiazoles and benzoxazoles was developed. To the best of our knowledge, this reaction is the first example that uses carboxylic acids as coupling partners to perform direct C2-alkylation of benzothiazoles, thiazoles as well as benzoxazoles. In comparison with Minisci reaction, our decarboxylative alkylation of heterocycles was carried out at room temperature and under acid-free conditions. The approach has advantages in terms of experimental simplicity, mild reaction conditions and easy work-up. Further expansion of this novel method to a more broader spectrum of substrates is underway.

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