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Carbon Dioxide as the C1 Source for Direct C−H Functionalization of Aromatic Heterocycles

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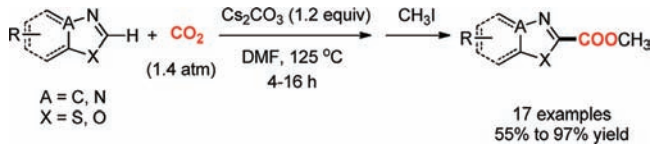
ABSTRACT



A simple and straightforward method has been developed for the direct carboxylation of aromatic heterocylces such as oxazoles, thiazoles, and oxadiazoles using CO_2 as the C1 source. The reactions require no metal catalyst and only Cs_2CO_3 as the base. A good functional group tolerance is achieved.

Carbon dioxide (CO_2) is a cheap, abundant, and readily available C1 source.[1−5] Carboxylation of carbon nucleophiles with CO_2 to form new C−C bonds therefore represents an attractive method for the synthesis of carboxylic acids and derivatives, which are in turn valuable organic products. However, because of the high thermodynamic and kinetic stability of CO_2, the carbon nucleophiles have been mostly limited to certain metal-activated unsaturated hydrocarbons[6−8] and reactive organometallic reagents such as Grignard and organolithium compounds.[1,9] Metal-catalyzed or -assisted coupling of CO_2 with less nucleophilic and more functional group tolerant organometallic reagents such as allylstannanes,[10] aryl- and alkynyl organoboronic esters,[11−13] and organozinc compounds[14,15] has been reported only recently. In addition, several groups have shown that catalytic carboxylation of allenes,[16,17] styrenes,[18] and aryl halides[19] is possible using CO_2 and a reducing agent such as $AlEt_3$ and Et_2Zn. Although these newly developed methods improve significantly the scope and group tolerance of carboxylation reactions, stoichiometric amounts of organometallic reagents are still required. Some of these reagents are reactive (e.g., organozincs, $AlEt_3$) and need to be stored and

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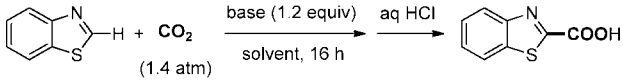
handled under inert atmosphere; others (e.g., boronic esters) are costly and require multiple-step synthesis. A desirable alternative is to directly couple CO_2 with a C−H bond of the organic substrates,[1,4,20] with the best example being the synthesis of salicyclic acid by direct carboxylation of phenol.[1,4] Here we report the direct carboxylation of aromatic heterocycles following a similar strategy.

We chose benzothiazole as the initial substrate following our work on direct alkylation of similar heterocycles.[21] Furthermore, direct C−H functionalization of these heterocycles with carbon (sp^2 and sp) nucleophiles is now ubiquitous.[22−32] The C(2)-H is slightly acidic (pK_a = 27 in DMSO)[33] and might form carbon anion in the presence of a base such as *tert*-butoxide, phosphate, or carbonate. We hypothesized that coupling of this carbon anion with CO_2 is possible under appropriate reaction conditions and with an active catalyst. As Cu is active in many C−H functionalization reactions of heterocycles[22,23,25,29−31,34] and in carboxylation of boronic esters,[11,15] we initially tried CuI as a catalyst. Indeed, using LiOBu^t as the base, carboxylation of benzothiazole proceeded well at 125 °C in DMF and gave full conversion (entry 1, Table 1). 2-Benzothiazolecarboxylic acid was identified as the only detectable product by NMR. To our surprise, control experiment showed that the same reaction occurred even without CuI under otherwise identical conditions (entry 2, Table 1). Thus, the carboxylation does not require a catalyst. Consistent results were obtained with a 400 mBar over pressure of CO_2. Both 97% (Sigma-Aldrich) and 99.9% LiOBu^t (Alfa Aesar) worked. Other bases were then tested. NaOMe, NaOH, and KOH were ineffective (entries 3, Table 1). The use of K_2CO_3 and K_3PO_4 resulted in low conversions (10−20%, entries 4 and 5, Table 1). Cs_2CO_3 (purity from 98−99.995%) could be used and gave reproducible results (entry 6).[35] Since Cs_2CO_3 is less basic than LiOBu^t, it is used for further reactions.[36] Further experiments showed that no reaction occurred in other solvents (entries 7 and 8, Table 1). Without CO_2, the reaction did not proceed (entry 9, Table 1), suggesting that the COO moiety in the product does not originate from Cs_2CO_3. The pure product, 2-benzothiazolecarboxylic acid, can be isolated as a white solid in 98% yield from a preparative reaction. The compound decarboxylates slowly in solution (20% decomposition in 5 h). The acid can be converted to a stable ester by reacting with an alkyl halide.[37]

Table 1. Optimization of Conditions for Direct Carboxylation of Benzothiazole[a]



entry	conditions	conversion (%)
1	DMF, 125 °C, 5 mol % CuI, LiOBu^t	100
2	DMF, 125 °C, LiOBu^t	100
3	DMF, 125 °C, NaOMe or NaOH or KOH	0
4	DMF, 125 °C, K_2CO_3	10
5	DMF, 125 °C, K_3PO_4	20
6	DMF, 125 °C, Cs_2CO_3	100 (95[b])
7	dioxane or toluene, 125 °C, Cs_2CO_3	0
8	THF or CH_3CN, 90 °C, Cs_2CO_3	0
9	DMF, 125 °C, Cs_2CO_3, no CO_2	0

[a] Reaction scale: benzothiazole (1 mmol), base (1.2 mmol), and solvent (2 mL). [b] Isolated yield.

The optimized conditions can be applied for the carboxylation of other heterocycles (Table 2). Because of the limited stability of the heterocyclic carboxylic acids, the products of carboxylation, the carboxylates, were directly converted to stable esters in a one-pot procedure.[37] Substituted benzothiazoles can be carboxylated, including those containing sensitive nitrile and keto groups (entries 1−3, Table 2). Benzoxazoles are suitable substrates, and aryl ester and Cl groups are tolerated (entries 4−7, Table 2). Naphtho[1,2-*d*]oxazole can be coupled (entry 8, Table 2), 5-phenyloxazoles are carboxylated at the C(2) position (entries 9−11, Table 2), and 2-aryl-1,3,4-oxadiazoles can be successfully carboxylated as well (entries 12−16, Table 2). The reactions are compatible with aryl-Cl, Br, CF_3, and OMe groups. Unfortunately, imidazole and thiophene derivatives cannot be coupled, probably because of the low acidity of their C(2)−H bonds. 2-Aryl-1,3,4-thiadiazoles gave ring-opened products under the carboxylation conditions.

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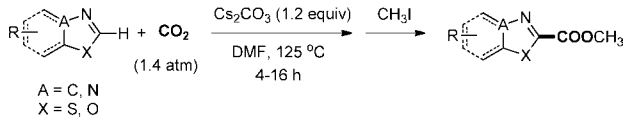
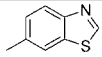
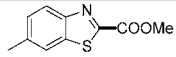
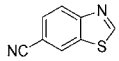
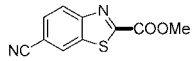
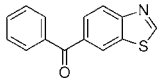
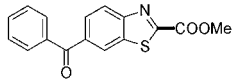
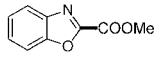
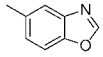
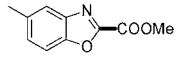
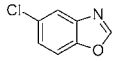
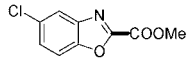
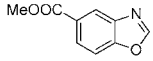
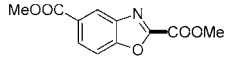
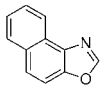
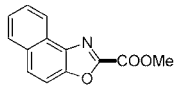
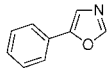
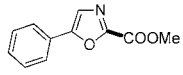
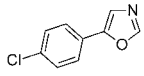
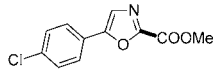
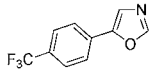
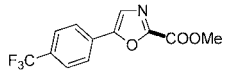
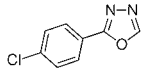
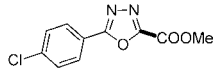
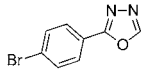
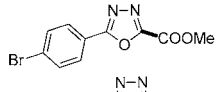
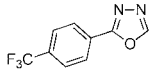
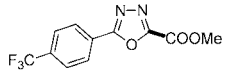
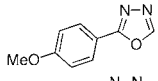
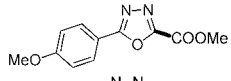
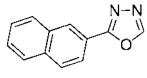
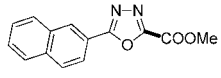
Table 2. Carboxylation of Aromatic Heterocycles[a]

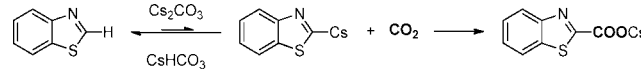


entry	substrate	product	yield (%)[b]
1			91
2			90
3			68
4			91
5			83
6			92
7			92
8			97
9			65
10			55
11			61
12			88
13			83
14			71
15			96
16			64

[a] Reaction scale: heterocycle (2 mmol), base (2.4 mmol), and DMF (3 mL). [b] Isolated yield.

To probe the mechanism of the reactions, the carboxylation of benzothiazole was followed by NMR.[37] At partial conversion, only benzothiazole and 2-benzothiazolecarboxylate were detected and not 2-benzothiazolyl anion. In the absence of CO_2, benzothioazole was not deprotonated by Cs_2CO_3 to a detectable degree. Therefore, we propose that the carboxylation proceeds first via an uphill C−H cleavage at the C(2) position, followed by C−C bond formation with CO_2 (Scheme 1).

Scheme 1



In summary, we describe here a simple and straightforward carboxylation method of aromatic heterocycles using CO_2 as the C1 source.[38] The resulting heteroaryl carboxylic acids and esters are significant compounds for medicinal and materials sciences. Remarkably, direct C−H functionalization is possible without a metal catalyst and with only Cs_2CO_3 as the base. Compared to other carboxylation procedures, the method is more atom- and step-economic and is practical for industrial use. The use of a mild base results in a high tolerance toward reactive and unsaturated functional groups.

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Supporting Information Available: Experimental details, additional entries, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) During the prepartion of this manuscript, a gold-catalyzed direct carboxylation of heterocycles was reported: Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859.