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C–H carboxylation of heteroarenes with ambient CO_2†

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The C–H carboxylation of heteroarenes was achieved under transition metal-free reaction conditions with naturally abundant CO_2 as the C1 source at relatively low temperature. The C–H carboxylation was mediated by KO*t*-Bu at atmospheric pressure of CO_2, and thereby provided atom- and step-economical access to various heteroaromatic carboxylic acid derivatives.

Introduction

Strategies for the fixation of carbon dioxide (CO_2) as an easily accessible, inexpensive, naturally abundant, and renewable C1 source towards valuable commodity chemicals[1,2] have attracted major topical interest.[3] While significant progress has been witnessed in the chemical use of CO_2 during the recent decade,[4–14] the vast majority of these procedures require pre-functionalized substrates, such as aryl halides or aryl boronic acids.[1] The synthesis of the prerequisite pre-oxidized arenes calls for a number of reaction steps, which contradicts the principles of green chemistry.[15] In contrast, the direct functionalization of otherwise inert C–H bonds represents a considerably more atom- and step-economical strategy,[16] with important advances in direct carboxylations[17,18] accomplished by Iwasawa,[19–21] Nolan,[22,23] Hou,[24] Hu,[25] Klankermayer/Leitner,[11] and Beller,[26,27] among others.[28] Within our program on catalytic C–H activation,[29,30] we became attracted by devising reaction conditions for sustainable C–H carboxylation with ambient CO_2 under mild conditions.[31] As a result of our efforts, we have developed a highly effective protocol for step-economical C–H carboxylations of heteroarenes with ambient CO_2 under transition metal-free reaction conditions, on which we now[31] wish to report herein. In contrast to previously reported methods,[22–24] our C–H carboxylation protocol is operative in the absence of transition metals at relatively low temperatures of only 80–100 °C.

Results and discussion

At the outset of our studies, we chose reaction conditions similar to the ones previously described for the carboxylations of organoboronic esters with CO_2 (Table 1).[32] Thus, when reacting benzo[*d*]oxazole (**1a**) in the presence of 10 mol% of the well-defined N-heterocyclic carbene copper(I) complex [Cu(IPr)Cl] in DMF at 80 °C under an atmosphere of CO_2, 82% isolated yield of methylbenzo[*d*]oxazole-2-carboxylate (**3a**) were obtained upon treatment with methyl iodide (**2a**) (Table 1, entry 1). In order to establish a more economical and user-friendly method, the reaction was conducted with simple CuCl as the catalyst under ligand-free reaction conditions, which provided product **3a** in a comparable yield (entry 2). Interestingly, when conducting a test reaction in the absence of a transition metal catalyst solely with the base KO*t*-Bu[33] in DMF at 100 °C,[34] the desired product **3a** was isolated in 80% yield (entry 3).‡ An elevated reaction temperature of 125 °C failed to afford an improvement (entry 4), whilst a reaction conducted at 80 °C proceeded efficiently (entries 4 and 5), clearly highlighting the beneficial features of KO*t*-Bu as compared to Cs_2CO_3 that required 125 °C (*vide infra*).[25] Polar solvents other than DMF, such as NMP, 1,4-dioxane, THF and DMSO,

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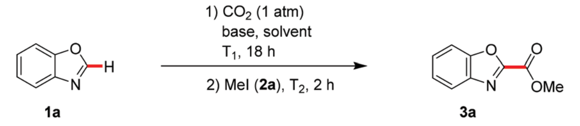
‡ Representative procedure for the C–H carboxylation using CO_2: synthesis of methylbenzo[*d*]oxazole-2-carboxylate (**3a**): a mixture of **1a** (118 mg, 0.99 mmol), KO*t*-Bu (135 mg, 1.20 mmol) and DMF (5.0 mL) was degassed in a Schlenk-tube. The Schlenk-tube was then flushed with CO_2 *via* a balloon and CO_2 was bubbled through the reaction mixture for 10–20 minutes. After removal of the balloon, the reaction mixture was heated to 100 °C for 18 h. After cooling to 65 °C, **2a** (3.00 equiv.) was added and the reaction mixture was stirred at 65 °C for 2 h. At ambient temperature, the reaction mixture was diluted with H_2O (25 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography (*n*-pentane/Et_2O = 20/1 → 10/1 → 7/1 → 5/1) yielded **3a** (141 mg, 80%) as a colorless solid.

Table 1 Optimization of C–H carboxylation with CO_2 [a]



Entry	Base	Solvent	T_1 [°C]	T_2 [°C]	**3a** [%]
1	KO*t*-Bu	DMF	80	65	82[b]
2	KO*t*-Bu	DMF	100	65	76[c]
3	KO*t*-Bu	DMF	100	65	80
4	KO*t*-Bu	DMF	125	65	80
5	KO*t*-Bu	DMF	80	65	71
6	KO*t*-Bu	DMF	40	40	(10)
7	KO*t*-Bu	NMP	100	65	69
8	KO*t*-Bu	1,4-Dioxane	100	65	—
9	KO*t*-Bu	THF	65	65	(4)
10	KO*t*-Bu	DMSO	100	65	52
11	KO*t*-Bu	PhMe	100	65	(11)
12	KO*t*-Bu	DMA	100	65	77
13	Cs_2CO_3	DMF	100	65	69
14	Rb_2CO_3	DMF	100	65	8
15	Cs_2CO_3	DMF	80	65	23

[a] Reaction conditions: **1a** (1.0 mmol), base (1.2 mmol), solvent (5.0 mL), CO_2 (1 atm), T_1, 18 h; **2a** (3.0 mmol), T_2, 2 h; yields of isolated products; GC-conversion in parentheses. [b] With [Cu(IPr)Cl] (10 mol%). [c] With CuCl (10 mol%).

provided less satisfactory results (entries 7–10), as did apolar toluene (entry 11). However, the encouraging result obtained with NMP as the solvent (entry 7) indicates the potential of our strategy for the use of greener solvents, such as 1-butylpyrrolidinone or Cyrene.[35] On the contrary, the C–H functionalization performed in DMA furnished carboxylic acid ester **3a** with a high efficacy (entry 12). Interestingly, bases other than KO*t*-Bu, including Cs_2CO_3 or Rb_2CO_3, proved to be considerably less effective under otherwise identical reaction conditions (entries 13 and 14), illustrating the unique power of KO*t*-Bu as the base, particularly at a reaction temperature of 80 °C (entry 15 *versus* 5).

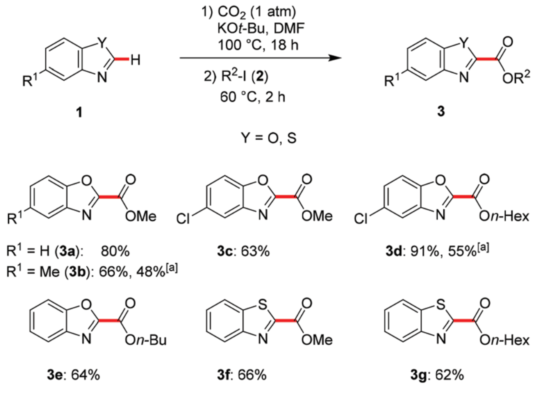
With the optimized reaction conditions in hand, the scope of the C–H carboxylation was explored next (Scheme 1).[36] A series of representative heteroarenes **1** was successfully converted into the desired carboxylic acid esters **3** under transition metal-free reaction conditions with atmospheric CO_2.

Various alkyl carboxylates **3** were obtained upon subsequent esterification with different alkyl iodides **2** under rather mild reaction conditions. Methyl- as well as chloro-substituted benzo[*d*]oxazoles **1b** and **1c** were site-selectively functionalized, affording the 2-substituted carboxylic acid esters **3b–d** in high yields after treatment with the corresponding alkyl iodide **2**. Notably, the use of Cs_2CO_3 as the base under otherwise identical reaction conditions resulted in an inferior yield of only 48% for product **3b**. Likewise, it is noteworthy that chloro-substituted azole **1c** provided the corresponding product **3d** in an excellent yield of 91%, whereas Cs_2CO_3 delivered only 55% of the desired ester **3d**. As showcased in a representative set of C–H functionalizations, our sustainable approach was not restricted to the use of methyl iodide as the electrophile, but also allowed esterification with a variety of alkyl iodides **2**. Moreover, our protocol set the stage for the C–H carboxylation of benzothiazole in a step-economical fashion. Indeed, the corresponding methyl ester **3f** and hexyl ester **3g** were isolated in 66% and 62% yield, respectively.

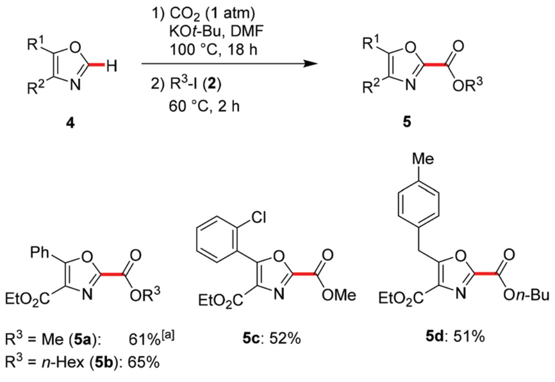
Furthermore, oxazoles **4** served as viable substrates for the C–H carboxylation, delivering the corresponding carboxylic acid derivatives **5a–d** in a step- and atom-economical manner (Scheme 2).[37] Intriguingly, valuable chlorine substituents on the heteroarenes were well tolerated under the optimized reaction conditions, which should prove instrumental for further late-stage diversification by *inter alia* cross-coupling technology.

Finally, we were pleased to observe that 1,3,4-oxadiazoles **6** proved to be viable substrates for the C–H carboxylation under an ambient CO_2 atmosphere as well, providing the desired carboxylic acid esters **7a–c** with high levels of selectivity control (Scheme 3).

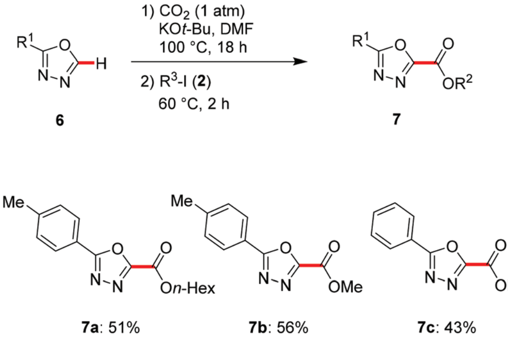
Based on the literature precedents,[25,38] we propose the reaction to proceed by initial reversible C–H cleavage (Scheme 4), along with subsequent C–C formation by the action of ambient CO_2.



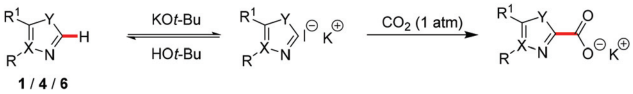
Scheme 1 C–H carboxylation with ambient CO_2. [a] Cs_2CO_3 as the base.



Scheme 2 C–H carboxylation of oxazoles **4**. [a] GC-conversion.



Scheme 3 C–H carboxylation of oxadiazoles **6**.



Scheme 4 Proposed mechanism for the C–H carboxylation.

Conclusions

In summary, we have reported on the use of CO_2 as an easily accessible, inexpensive, and renewable C1 source for green C–H carboxylations under transition metal-free reaction conditions. Hence, KO*t*-Bu enabled efficient C–H functionalizations on heteroarenes with an ample substrate scope under mild[39] reaction conditions, namely at a rather low reaction temperature and ambient pressure of CO_2.

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