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LITHIUM *tert*-BUTOXIDE-MEDIATED CARBOXYLATION REACTIONS OF UNPROTECTED INDOLES AND PYRROLES WITH CARBON DIOXIDE[#]

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[#] Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

Abstract – Unprotected indoles and pyrroles were found to undergo base-mediated carboxylation reactions under ambient pressure of carbon dioxide. It was found that this transition metal-free carboxylation reaction proceeded smoothly with the use of a large excess of LiO^{t}Bu.

INTRODUCTION

The chemical incorporation of carbon dioxide (CO_2) as a C1 source into organic compounds is desirable since CO_2 is non-toxic, non-flammable, and a readily available gas. In particular, the carboxylation reaction of carbon-based nucleophiles with CO_2 represents a facile method to access carboxylic acids and their derivatives. However, due to its thermodynamic and kinetic stability, most protocols relies on the use of reactive organometallic reagents and/or transition metal catalysts to facilitate the C-C bond forming reactions with CO_2.[1]

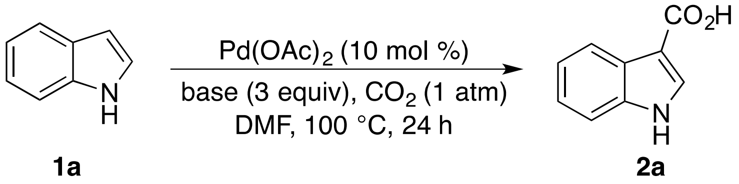
The direct carboxylation of the carbon-hydrogen (C-H) bonds of arenes and heteroaromatics is attractive since the use of C-H bonds has the potential to streamline synthesis by circumventing the need for pre-activation of the nucleophile prior to the coupling event.[2] The chemical fixation of CO_2 with C-H bonds have been reported through the use of transition metal catalysts,[3] Lewis acid-mediated Friedel-Crafts reactions,[4] and base-mediated carboxylation of aromatic heterocycles bearing acidic C-H bonds.[5]

Indole-3-carboxylic acids are ubiquitous in bioactive natural products and pharmaceuticals.[6] As such, there is interest in the development of new synthetic strategies to access these molecules efficiently and in a timely manner. Most synthetic protocols are either multi-step processes or relies on the use of pre-functionalized starting materials.[7] As such, the direct carboxylation reaction of indole derivatives with readily available CO_2 would represent a significant advance in this endeavour. Previously, Hattori and co-workers disclosed a dialkylaluminum chloride-mediated direct carboxylation reaction of indoles and pyrroles.[4f] However, the Friedel-Crafts carboxylation reaction suffered from narrow substrate scope, modest yields, and relatively high pressure of CO_2. In order to address these limitations, we recently reported a simple protocol for the preparation of indole-3-carboxylic acid through a lithium *tert*-butoxide-mediated carboxylation reaction of indole derivatives under atmospheric pressure of CO_2.[5b] In this paper, we will disclose a full account of the base-mediated carboxylation reaction.

RESULTS AND DISCUSSION

In order to develop an efficient synthetic protocol to access indole-3-carboxylic acids, we considered the use of electrophilic metal catalysts for the Friedel-Craft-type carboxylation reaction. Based on previous literature precedent on the use of $Pd(OAc)_2$ as a catalyst for C-H bond functionalization of indole derivatives,[8] we began our investigation by examining the carbonxylation reaction of indole under basic conditions with an atmospheric pressure of CO_2 (Table 1).

Table 1. Effect of bases for the direct carboxylation of indole (**1a**) with CO_2[a]



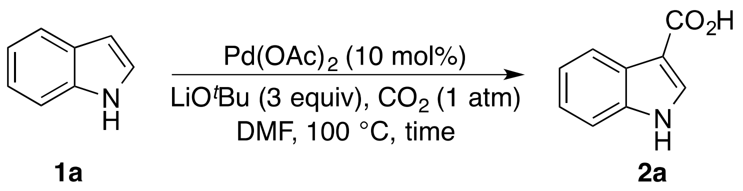
entry	base	yield (%)[b]
1	K_2CO_3	<5
2	K_3PO_4	N.D.
3	Cs_2CO_3	70
4	KOH	N.D.
5	CsOH	N.D.
6	KO*t*Bu	19
7	NaO*t*Bu	N.D.
8	LiO*t*Bu	91
9	DBU	<5
10	TMG	N.D.

[a] Reaction conditions: indole **1a** (0.4 mmol), base (3 equiv.), and $Pd(OAc)_2$ (10 mol%) in DMF at 100 °C under CO_2 (1 atm).
[b] Yield based on **1a** and determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

When various bases were examined for the palladium-catalyzed C-3 carboxylation of indole (**1a**), we found that a weak carbonate base, such as K_2CO_3, provided the desired carboxylic acid **2a** in trace amounts (entry 1). After screening several weak inorganic bases, we found that Cs_2CO_3 furnished **2a** in a relatively good yield (entry 3). When strong bases were examined, LiO*ᵗ*Bu was revealed to be an excellent base that facilitated the CO_2 incorporating reaction in a high yield (entry 8). In addition, we investigated strong organic bases and found that these were not suitable additives (entries 9-10).

Although the optimization studies revealed the best reaction conditions for the direct carboxylation of indole (**1a**) under an atmospheric pressure of CO_2, we found that these results were not reproducible. In order to understand this phenomenon, we profiled the carboxylation reaction and found that the yield of the desired indole-3-carboxylic acid (**2a**) decreased after a prolonged time period (Table 2, entries 1-6).

Table 2. Time profile for the direct carboxylation of indole (**1a**) with CO_2[a]



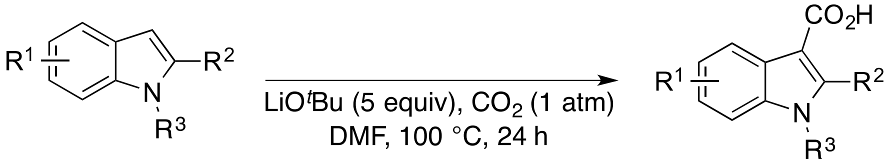
entry	time (h)	yield (%)[b]
1	4	55
2	8	71
3	9	75
4	10	80
5	15	88
6	24	66
7[c]	24	>95
8[c,d]	24	>95

[a] Reaction conditions: indole **1a** (0.4 mmol), base (3 equiv.), and $Pd(OAc)_2$ (10 mol%) in DMF at 100 °C under CO_2 (1 atm). [b] Yield based on **1a** and determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Using 5 equivalents of LiO*ᵗ*Bu. [d] In the absence of $Pd(OAc)_2$.

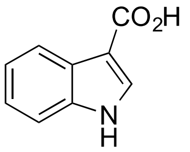
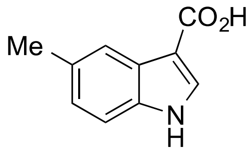
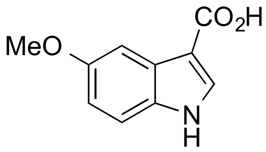
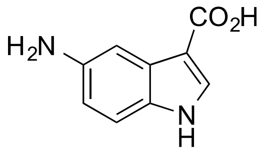
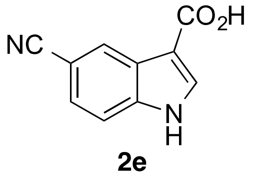
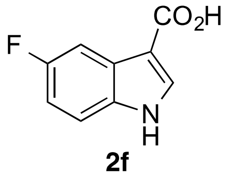
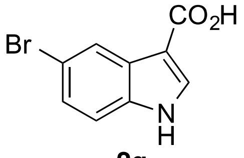
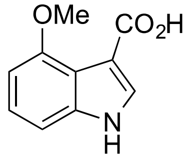
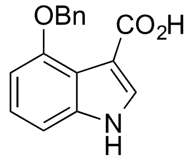
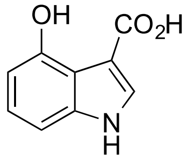
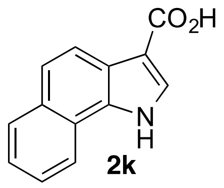
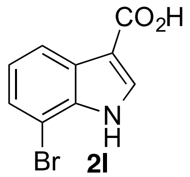
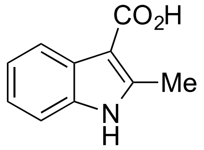
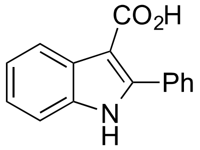
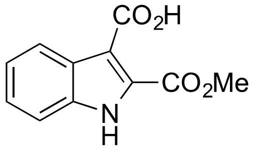
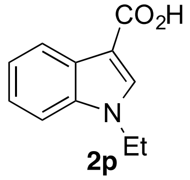
Based on these results, we hypothesized that 3-carboxylated indole **2a** underwent a competing decarboxylative side reaction,[9] and that the origin of the reproducibility problem might have been derived from this process. When we increased the amount of the base, the decarboxylation process was effectively suppressed and the carboxylated product **2a** could be reliably obtained in excellent yields (entry 7). Finally, control studies revealed that $Pd(OAc)_2$ was not necessary, and that the direct C-H carboxylation of indole (**1a**) found in this study was a base-mediated process.

With the optimized conditions in hand, we examined the substrate scope for the LiO*ᵗ*Bu-mediated carboxylation of indole derivatives **1a-p** under an atmospheric pressure of CO_2 (Table 3).

Table 3. Substrate scope and limitations of the LiO^{t}Bu-mediated direct carboxylation of indole derivatives **1a-p** under atmospheric pressure of CO_2[a]



1a-p **2a-p**

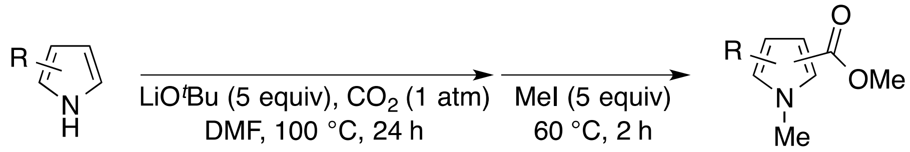
 **2a** 95%[b]	 **2b** 97% (90%)[c]	 **2c** 92%[b]	 **2d** N.D.
 **2e** 90%[b]	 **2f** 94%[b]	 **2g** 96%[b]	 **2h** 30%[b]
 **2i** 19%[b]	 **2j** 83%[b]	 **2k** 65% (51%)[c]	 **2l** 88%[b]
 **2m** 80%[b]	 **2n** 31%[b]	 **2o** N.D.	 **2p** N.D.

[a] Reaction conditions: indole **1** (0.4 mmol) and LiO^{t}Bu (5 equiv) in DMF (2 mL) at 100 °C under CO_2 (1 atm). [b] Yield based on **1** and determined by weight of the isolated products **2**. [c] Yield based on **1b** or **1k** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The isolated yield was determined after derivativation of **2b** or **2k** to the methyl ester and are given in parentheses.

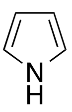
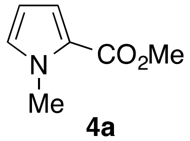
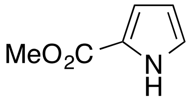
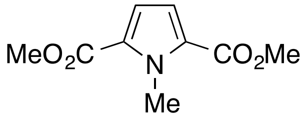
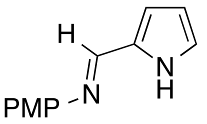
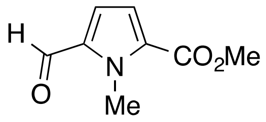
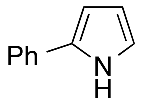
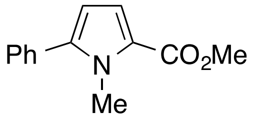
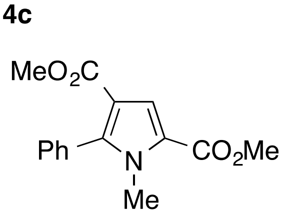
When 5-substituted indoles **1a-g** were subjected to our optimized reaction conditions, both electron-rich and -poor groups were tolerated, with the exception of an amino group (**1d**), to provide the desired carboxylated product in excellent yields. With 4-substituted indoles **1h-i** were utilized, the CO_2 fixation hardly proceeded and low chemical yields were obtained. Interestingly, when these 4-substitued ethers were replaced with a hydroxyl group, the carboxylation occurred smoothly to provide indole-3-carboxylic acid **2j** in a good yield. Indoles with substitution on the 7-position (**1k-1l**) were also found to be amenable for the direct carboxylation reaction to furnish carboxylic acids **2k-l** in good yields. Although 2-methyl indole **1m** could undergo carboxylation in a good yield, electron-withdrawing substituents diminished the nucleophilic addition of indoles **1n-o** to CO_2. Finally, when an *N*-substituted indole **1p** was utilized as a substrate, the desired product was not obtained. This result suggests that the free NH is essential, and that the initial deprotonation of the NH bond by LiO^tBu is an important step for the carboxylation reaction.

With the discovery of a successful CO_2 fixation reaction of indole derivatives using LiO^tBu as a base, we examined the possibility of extending these conditions to induce the direct carboxylation of pyrroles **3a-d** (Table 4).

Table 4. Substrate scope and limitations of the LiO^tBu-mediated direct carboxylation of pyrrole derivatives **3a-d** under atmospheric pressure of CO_2[a]



3a-d **4a-e**

entry	pyrrole	product	yield (%)[b]
1	 **3a**	 **4a**	N.D.
2	 **3b**	 **4b**	20
3	 **3c**	 **4c**	50
4	 **3d**	 **4d**  **4e**	83 (1:1.2)

[a] Reaction conditions: pyrrole **3** (0.2 mmol) and LiO^tBu (5 equiv) in DMF (2 mL) at 100 °C under CO_2 (1 atm) for 24 h. MeI (5 equiv) at 60 °C. [b] Yield based on **3** and determined by weight of isolated products **4**.

Initially, when we subjected pyrrole (**3a**) to our previously optimized reaction conditions for the carboxylation reaction with indoles, the desired carboxylated product **4a** was not detected (entry 1). This was due to the fact that under these conditions, pyrrole decomposed. However, when an electron-withdrawing substituent, such as a methyl ester, was introduced to the pyrrole core, the desired 2-carboxylated product **4b** was obtained in a low yield (entry 2). Similarly, pyrrole **3c**, bearing an imine, underwent carboxylation to provide **4c** in a moderate yield (entry 3). When 2-phenylpyrrole (**3d**) was utilized as a substrate, a mixture of mono- and di-carboxylated products was obtained in a good yield (entry 4).

In summary, we developed a base-mediated carboxylation protocol for the efficient carboxylation of indole and pyrrole derivatives with broad substrate scope under an atmospheric pressure of CO_2. It was found that the key for this CO_2 fixation relies on the use of a large excess of base to prevent the reversible decarboxylation process. The direct carboxylations of other heteroaromatic C-H bonds are currently under investigation in our laboratory.

EXPERIMENTAL

General information: ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-500 and a JEOL ECX-600 in $CDCl_3$. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane using the solvent resonance as the internal standard. IR spectra were measured on a JASCO FT/IR-610 spectrometer. High-resolution mass spectrometry was carried out using a JEOL JMS-T100TD (DART). Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F from Wako Pure Chemical Industries, Ltd.

Reagents: Unless stated otherwise, commercial reagents were used as received. All organic solvents were purified by distillation under dry argon atmosphere. 7-Bromoindole (**1g**),[10] 4-benzyloxy-1*H*-indole (**1i**),[11] 1*H*-benzo[*g*]indole (**1k**),[11] 2-imino pyrrole **3c**,[12] and 2-phenylpyrrole (**3d**)[13] were prepared according to literature procedures.

Representative procedure for the direct C-H carboxylation of indole derivatives 1a-p: In a dried two-necked test tube was charged with LiO^{t}Bu (160 mg, 2.00 mmol) and indole **1a** (23.4 mg, 0.4 mmol). The reaction vessel was evacuated under high vacuum and the atmosphere was replace with a balloon of CO_2. Then DMF (2 mL) was added and the mixture was stirred for 24 h at 100 °C. Then the result mixture was cooled and carefully quenched with a solution of HCl (2 N) and extracted with EtOAc (5x). The combined organic layers were washed with water (2x), brine (1x) and dry over $MgSO_4$. The dried organics were concentrated under reduce pressure and the residue was purified by preparative TLC (hexane:acetone = 1:1) to afford the desired product **2a** (153.0 mg, 95%) as a white solid.

Indole-3-carboxylic acid (2a). ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 11.87 (bs, 1H), 11.7 (bs, 1H), 7.99-7.92 (m, 2H), 7.43-7.38 (m, 1H), 7.18-7.06 (m, 2H).

The spectra data of carboxylated indoles **2a-n** obtained in this study were in accordance with reported data.[5b]

For the derivativation of indole-3-carboxylic acids 2b and 2k: Following the above procedure, the crude reaction mixture was diluted with MeOH and cooled to 0 °C. Then $SOCl_2$ (36 μL, 0.5 mmol) was added and stirred for 3 h at room temperature. Additional MeOH was added and the reaction mixture was heated to reflux for 6 h. The resulting mixture was quenched with H_2O and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by preparative TLC (hexane:EtOAc = 7:3) to afford the desired products **5a-b**.

Methyl 5-methylindole-3-carboxylate (5a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.68 (bs, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.20 (d, 1H, *J* = 6.4 Hz), 6.99 (d, 1H, *J* = 8.2 Hz), 3.84 (s, 3H), 2.40 (s, 3H).

Methyl benzo[*g*]indole-3-carboxylate (5b). ^{1}H NMR ($(CD_3)_2CO$, 500 MHz): δ 11.8 (bs, 1H), 8.36 (d, 1H, *J* = 9.7 Hz), 8.25 (d, 1H, *J* = 9.2 Hz), 8.05 (d, 1H, *J* = 2.3 Hz), 7.97 (d, 1H, *J* = 8.05), 7.66 (d, 1H, *J* = 6.4 Hz) 7.56 (t, 1H, *J* = 6.9 Hz), 7.46 (t, 1H, *J* = 7.4 Hz), 3.90 (s, 3H).

The spectra data of derivatized carboxylated indoles **5a-b** obtained in this study were in accordance with reported data.[5b]

Representative procedure for the direct C-H carboxylation of pyrrole derivatives 3a-d: In a dried two-necked test tube was charged with LiO^{t}Bu (80.0 mg, 1.00 mmol) and 2-phenylpyrrole **3d** (28.6 mg, 0.2 mmol). The reaction vessel was evacuated under high vacuum and the atmosphere was replace with a balloon of CO_2. Then DMF (1 mL) was added and the mixture was stirred for 24 h at 100 °C. Next, the reaction mixture was cooled to room temperature, charged with iodomethane (60 μL, 1.0 mmol), and was stirred for 2 h at 60 °C. Then the result mixture was cooled and carefully quenched a solution of HCl (2 N) and extracted with EtOAc (5x). The combined organic layers were washed with water (2x), brine (1x) and dry over $MgSO_4$. The dried organics were concentrated under reduce pressure and the residue was purified by preparative TLC (hexane:EtOAc = 7:3) to afford the desired products **4d** (16.0 mg, 37%) and **4e** (25.0 mg, 46%) as yellow oils.

Methyl 1-methyl-5-phenyl-1*H*-pyrrole-2-carboxylate (4d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.43 (m, 5H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.17 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H).

Dimethyl 1-methyl-5-phenyl-1*H*-pyrrole-2,4-dicarboxylate (4e). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29-7.39 (m, 5H), 6.46 (d, *J* = 1.7 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H).

The spectra data of carboxylated pyrroles **4b-d** obtained in this study were in accordance with reported data.[14,15]

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