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Base-Mediated Carboxylation of Unprotected Indole Derivatives with Carbon Dioxide

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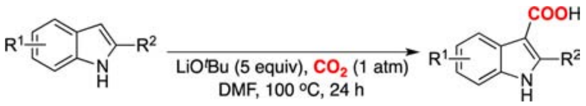
ABSTRACT



A simple and straightforward method for the preparation of indole-3-carboxylic acids was discovered through the direct carboxylation of indoles with atmospheric pressure of carbon dioxide (CO_2) under basic conditions. The key for the reaction was found to be the use of a large excess of LiO^{t}Bu as a base to suppress the undesired decarboxylation side reaction.

The use of CO_2 as a C1 building block is attractive since it is an inexpensive, nontoxic, and nonflammable gas that is readily available and is a potentially promising renewable resource. Despite these advantages, the chemical transformation of CO_2 is challenging as it represents the most oxidized state of carbon, and the relatively low energy molecule possesses high thermodynamic stability and low reactivity.[1] However, the carbon atom of CO_2 is electron-deficient and CO_2 has a strong affinity toward nucleophiles such as water, alkoxides, amines, organometallic nucleophiles, etc.

The direct carboxylation of the carbon–hydrogen (C–H) bonds of arenes and heteroaromatics represents an important and useful synthetic method to access carboxylic acids that may serve as precursors for the preparation of biologically active compounds.[2] The most common strategy toward the chemical fixation of CO_2 with C–H bonds is through transition-metal catalysis,[3] through Lewis-acid-mediated Friedel–Crafts reactions,[4] or by base-mediated carboxylation of aromatic heterocycles.[5] Recently, Hattori successfully employed dialkylaluminum chloride as a Lewis acid mediator for the direct carboxylation of indoles and pyrroles with CO_2.[4f] However, the narrow substrate scope, modest chemical yields, and relatively high pressure of CO_2 (3.0 MPa) required for the Friedel–Crafts carboxylation limited the synthetic utility of this reaction. In this communication, we report a novel and general method for the synthesis of 3-carboxylated indole derivatives derived from free (NH) indoles under an atmospheric pressure of CO_2.

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(1) For representative reviews on the use CO_2 for chemical transformations, see: (a) Min, M.; Shen, Y.-M. *Curr. Org. Chem.* **2003**, *7*, 737. (b) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (c) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (d) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435. (e) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kuehn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510.

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(3) (a) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858. (b) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674. (c) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (d) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251. (e) Inomata, H.; Ogata, K.; Fukuzawa, S.-I.; Hou, Z. *Org. Lett.* **2012**, *14*, 3986.

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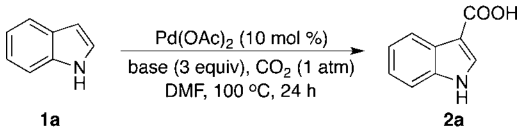
(5) Vechorkin, O.; Hirt, N.; Hu, X. *Org. Lett.* **2010**, *12*, 3567.

10.1021/ol3025082

To develop a general method toward the carboxylation of indole derivatives with CO_2, we hypothesized that the direct functionalization of the indolyl core at the C-3 position catalyzed by transition metals would provide the means to access indole-3-carboxylates. Thus, we focused our attention to the use of palladium acetate, a well-known catalyst for the C–H bond functionalization of indoles,[6] as a catalyst and examined a variety of bases under an atmospheric pressure of CO_2 (Table 1).

Table 1. Screening of Bases for the Direct Carboxylation of Indole **1a** with CO_2[a]



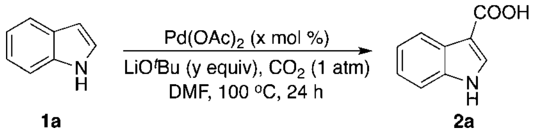
entry	base	yield (%)[b]
1	K_2CO_3	<5
2	K_3PO_4	NR
3	Cs_2CO_3	70
4	KOH	NR
5	KO^{t}Bu	19
6	NaO^{t}Bu	NR
7	LiO^{t}Bu	91
8	DBU	<5

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

When we examined the palladium-catalyzed direct carboxylation of indole **1a** with a weak base such as K_2CO_3 in DMF at 100 °C under a balloon pressure of CO_2, we were able to obtain a trace amount of the desired carboxylated product **2a** (entry 1). Encouraged by these initial results, we examined several weak inorganic bases and found that Cs_2CO_3 provided 70% of indole carboxylate **2a** (entry 3). We also examined stronger inorganic bases and found that the use of LiO^{t}Bu as a base lead to the formation of **2a** in an excellent yield (entry 7).

While our initial optimization studies yielded excellent reaction conditions for the direct carboxylation of **1a** with CO_2, we found that these results were not reliable and reproducibility problems were encountered (Table 2, entry 1).

Table 2. Optimization of the Reaction Conditions for the Direct Carboxylation of Indole **1a** with CO_2[a]



entry	$Pd(OAc)_2$ (mol %)	LiO^{t}Bu (equiv)	yield (%)[b]
1	10	3	60
2	10	4	60
3	10	5	>95
4	0	5	>95

[a] Reaction conditions: indole **1a** (0.4 mmol), LiO^{t}Bu (y equiv), and $Pd(OAc)_2$ (x mol %) in DMF (2 mL) at 100 °C under a balloon pressure of CO_2. [b] Yield based on **1a** and determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Careful examination of the reaction conditions led to the discovery of a competing decarboxylative side reaction.[7,8] Gratifyingly, the decarboxylation of **2a** was suppressed by the addition of 5 equiv of the base, and total conversion of **1a** to the desired carboxylate **2a** was achieved (entry 3). Interestingly, we found that the carboxylation process also occurred in the absence of the palladium catalyst (entry 4).[9,10] Additional optimization to lower the reaction temperature or to change the solvent system resulted in lower yields of carboxylic acid **2a**.

With the optimized conditions in hand, we turned our attention to the scope of the LiO^{t}Bu-mediated carboxylation of free (NH) substituted indoles **1a**–**m** (Table 3).

With indoles **1a**–**f** substituted at the 5-position, both electron-rich and -poor substituents were tolerated, and excellent yields of the desired carboxylic acids **2a**–**f** were obtained (entries 1–6). When 4-substituted indoles **1g**–**h** were utilized, the carboxylation reaction proceeded sluggishly (entries 7–8). However, when these 4-substituted ethers were replaced with a hydroxyl group, the CO_2 fixation occurred readily to furnish the indole-3-carboyxlate **2i** in a good yield (entry 9). Indoles with substitution on the 7-position were also examined, and modest to excellent yields were obtained (entries 10–11). Finally, we examined 2-substitued indoles and found that while the methyl substituted indole **1l** was an excellent substrate for the direct carboxylation

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(6) For palladium-catalyzed direct C3 functionalization of indole derivatives under basic conditions, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. (d) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (e) Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499. (f) Gu, Y.; Wang, X.-M. *Tetrahedron Lett.* **2009**, *50*, 763. (g) Ackermann, L.; Barfusser, S. *Synlett* **2009**, 808. (h) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (i) Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80. (j) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365. (k) Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett.* **2011**, *40*, 555.

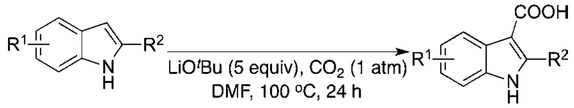
(7) The decarboxylation of **2a** was determined by monitoring the progress of the reaction with **1a**, $Pd(OAc)_2$ (10 mol %), and LiO^{t}Bu (3 equiv) in DMF (2 mL) at 100 °C under an atmosphere of CO_2. The details and results of the monitoring studies can be found in the Supporting Information.

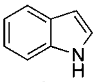
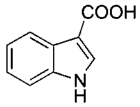
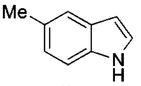
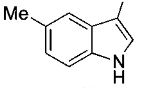
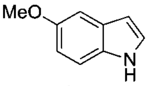
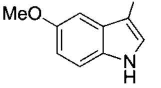
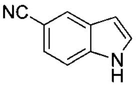
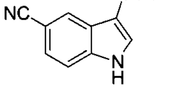
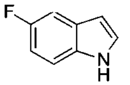
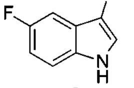
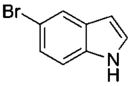
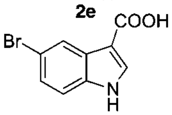
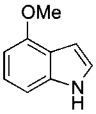
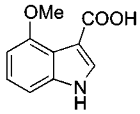
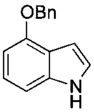
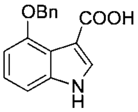
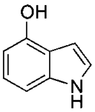
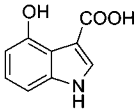
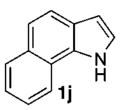
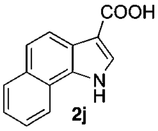
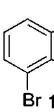
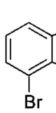
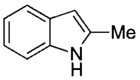
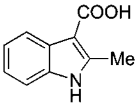
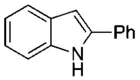
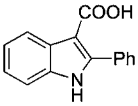
(8) For representative examples of decarboxylation of indole carboxylic acids, see: (a) Piers, E.; Brown, R. K. *Can. J. Chem.* **1962**, *40*, 559. (b) Jones, G. B.; Chapman, B. J. *J. Org. Chem.* **1993**, *58*, 5558. (c) Rudzki, M.; Alcald-Aragonés, A.; Dzik, W. I.; Rodríguez, N.; Goossen, L. J. *Synthesis* **2012**, *44*, 184. (d) Vandersteen, A. A.; Mundle, S. O. C.; Kluger, R. *J. Org. Chem.* **2012**, *77*, 6505.

(9) Quantitative elemental analysis of LiO^{t}Bu was conducted by ICP-AES (inductively coupled plasma–atomic emission spectroscopy) analysis, and the most abundant exogenous elements were Os (2.1 ppm), K (2.0 ppm), and Na (1.2 ppm). Although transition metal catalyzed carboxylation of indoles remains a distinct possibility, such catalysis would occur at parts per billion concentrations.

(10) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495.

Table 3. Substrate Scope of the LiO^{t}Bu-Mediated Direct Carboxylation of Indoles **1a**−**k**[a]



entry	substrate	product	yield (%)[b]
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	97 (90)[c]
3	 **1c**	 **2c**	92
4	 **1d**	 **2d**	90
5	 **1e**	 **2e**	94
6	 **1f**	 **2f**	96
7	 **1g**	 **2g**	30
8	 **1h**	 **2h**	19
9	 **1i**	 **2i**	83
10	 **1j**	 **2j**	65 (51)[c]
11	 **1k**	 **2k**	88
12	 **1l**	 **2l**	80
13	 **1m**	 **2m**	31

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

reaction, the phenyl counterpart provided the expected carboxylate **2m** in a disappointing amount (entries 12−13).

Although the precise mechanism for the LiO^{t}Bu-mediated carboxylation of indole derivatives has not been elucidated, a tentative mechanism is proposed (Scheme 1).

The initial deprotonation of **1a** by the lithium base most likely occurred on the most acidic N−H proton to generate lithiated anion **3**, and this was subsequently trapped by CO_2 to form N-centered carboxylate **5**. Such an intermediate is plausible given that the *in situ* formation of **5** through the deprotonation of **1a** with ^{n}BuLi and bubbled CO_2 at low temperature (−70 °C) has been reported.[10,11] Although nucleophilic addition of lithiated indoles should favor the N-1 substitution, the reversibility of the carboxylation at elevated reaction temperatures could be used to rationalize the formation of the C-3 carboxylate **6**.[12] While the direct nucleophilic addition of indole **1a** to CO_2 is possible, we found that the free NH plays an important role and the more nucleophilic 1-methylindole did not undergo the base-mediated carboxylation reaction under our optimized reaction conditions.[13]

In conclusion, an efficient protocol for the direct carboxylation of indole derivatives under an atmospheric pressure of CO_2 was developed. The relatively large excess and the careful choice of the base was key in achieving the carboxylation of indoles in excellent yields. Further studies

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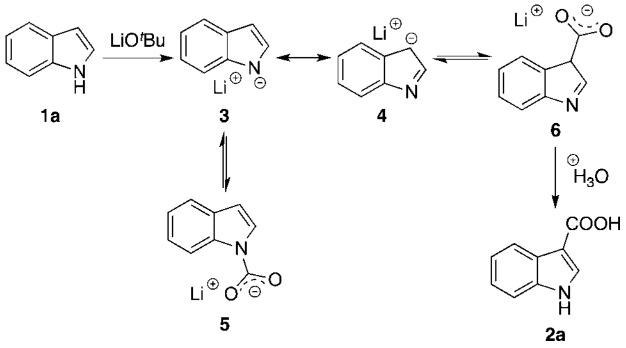
(11) Under our optimized reaction conditions at room temperature, we obtained the *N*-carboxylated product after derivatization to the methyl ester. The experimental details can be found in the Supporting Information.

(12) The carboxylation of metalated indole derivatives at the C-3 position has been posulated as an intermediate for the sequential intramolecular cyclization−carboxylation of 2-ethynylaniline derivatives under basic conditions. See: Inamoto, K.; Asano, N.; Nakamura, Y.; Yonemoto, M.; Kondo, Y. *Org. Lett.* **2012**, *14*, 2622.

(13) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088.

Scheme 1. Proposed Mechanism for the Direct Carboxylation of Indole **1a** Mediated by LiO^{t}Bu



concerning the mechanism, role of base, and the effect of metal catalysts are currently under investigation.

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Note Added after ASAP Publication. Reference 3d was incorrect in the version published ASAP October 4, 2012; the correct version reposted October 19, 2012.

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

The authors declare no competing financial interest.