## Synthesis of 3-Carboxylated Indoles through a Tandem Process Involving Cyclization of 2-Ethynylanilines Followed by CO<sub>2</sub> Fixation in the Absence of Transition Metal Catalysts

2012 Vol. 14, No. 10 2622–2625

ORGANIC LETTERS

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## Received April 13, 2012



In this study, a facile synthesis of 3-carboxylated indoles involving a tandem-type cyclization of 2-ethynylanilines and subsequent  $CO_2$  fixation at the 3-position of the indole ring is realized. The reaction proceeds efficiently at 65 °C under 10 atm of  $CO_2$ , giving rise to variously substituted 3-carboxylated indoles, generally in high yields. An inorganic base, such as  $K_2CO_3$ , is the only reagent required, and the addition of transition metal catalysts is not necessary. The method provides a novel, simple, and promising strategy for  $CO_2$  fixation in the research field of heterocyclic chemistry.

The fixation of  $CO_2$  into certain molecules has recently attracted considerable attention because  $CO_2$  is inexpensive, easy-to-handle, and nontoxic; thus it can be considered as an ideal, renewable C1 unit in organic synthesis.<sup>1</sup> As a carbon nucleophile, highly reactive organometallic reagents such as organolithiums and Grignard reagents have been employed with relatively less reactive  $CO_2$  for the synthesis of carboxylic acids and their derivatives; however, the low functional group compatibility of these methods limits their practical use in organic synthesis. In 2006, Iwasawa's group reported a method for the carboxylation of aryl and alkenylboronic esters using  $CO_2$  in the presence of a rhodium catalyst.<sup>2b</sup> It was later found that copper-based catalytic systems also participate in a similar carboxylation of boronic esters.<sup>2d,e</sup> Moreover, Oshima and Yorimitsu,<sup>2c</sup> and Dong<sup>2f</sup> independently reported the Niand Pd-catalyzed coupling of organozinc reagents with CO<sub>2</sub>. Recently, Pd-catalyzed direct transformation of aryl bromides to the corresponding aryl carboxylic acids in the presence of 1 atm of CO<sub>2</sub> was realized.<sup>2h</sup> Although these catalytic processes<sup>2</sup> provide novel, efficient routes to aryl and alkylcarboxylic acids under much milder conditions, the need for the use of a stoichiometric amount of

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Table 1. Screening of Reaction Parameters<sup>a</sup>

	Ph NHTs CC te	base solvent D <sub>2</sub> ( <b>x</b> atm) mp., 24 h	2a	CO <sub>2</sub> H Ph Ts	) ;	H N Ts	-Ph
					yield <sup><math>b</math></sup> (%)		
entry	base (equiv)	solvent	<b>x</b> (atm)	$temp(^{\circ}C)$	2a	3a	1a
$1^c$	$K_2CO_3(10)$	DMF	1	50	29	30	36
2	$K_2CO_3(10)$	DMF	1	50	14	0	85
3	$K_2 CO_3 (10)$	DMF	3	50	25	0	75
4	$K_2 CO_3 (10)$	DMF	6	50	24	0	75
5	$K_2 CO_3 (10)$	DMF	10	50	20	0	75
6	$K_{2}CO_{3}(10)$	DMF	10	65	93	7	0
7	$K_{2}CO_{3}(10)$	DMF	10	80	92	8	0
8	$K_{2}CO_{3}(6)$	DMF	10	65	75	0	22
9	none	DMF	10	65	0	0	>99
10	$K_{2}CO_{3}\left(10 ight)$	1,4-dioxane	10	65	0	0	>99
11	$K_{2}CO_{3}\left(10 ight)$	toluene	10	65	0	16	84
12	$K_{2}CO_{3}\left(10 ight)$	MeCN	10	65	0	5	90
13	$K_{2}CO_{3}\left(10 ight)$	$Et_3N$	10	65	0	4	96
14	$K_3PO_4(10)$	DMF	10	65	67	$\overline{7}$	26
15	$NaO^{t}Bu\left(10 ight)$	DMF	10	65	40	19	39
16	$Cs_{2}CO_{3}\left( 10\right)$	DMF	10	65	87	$\overline{7}$	3
17	KH (10)	DMF	10	65	86	8	5

<sup>*a*</sup> Reaction conditions: **1a** (0.25 mmol), a base, and a solvent (3 mL) under a  $CO_2$  atmosphere. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> With addition of CuI (6 mol %).

organometallic species or prefunctionalized substrates (aryl halides) remains a disadvantage. The direct carboxylation of C–H bonds of azoles and electron-deficient arenes was first achieved by Nolan using a catalytic amount of a Au(I)–NHC complex.<sup>3a</sup> The process efficiently proceeds at room temperature in the presence of a stoichiometric amount of KOH base under 1.5 bar (~1.5 atm) of CO<sub>2</sub>. Subsequent reports indicated that a copper version of the catalyst also participates in a similar C–H carboxylation in the presence of CO<sub>2</sub> (1 or 1.5 bar).<sup>3b,c</sup> Recently, the chelating-group-directed carboxylation of unactivated aryl C–H bonds was accomplished in the presence of a Rh catalyst.<sup>3d</sup>

In contrast, the indole scaffold frequently occurs in a range of biologically active compounds, including natural products and designed medicinal agents. Therefore, the development of more practical and efficient procedures for synthesizing indoles still remains an area of intensive research. Among a variety of methods, the ring closing reactions of 2-ethynylaniline derivatives have become a versatile and efficient tool for constructing the indole nucleus. A wide range of reagents, including various metal complexes and bases, have so far been reported to mediate or catalyze the cyclization process.<sup>4</sup> These methods generally afford 3-unsubstituted indoles; in some cases, however, subsequent functionalization of the 3-position, including carbonylation, allylation, alkenylation, and arylation, can be performed in a one-pot manner, particularly in the presence of transition metal catalysts.<sup>5</sup>

Herein we report a novel approach for synthesizing indole 3-carboxylic acids from the corresponding 2-ethynylaniline derivatives. The process involves a tandem-type, cyclization–carboxylation sequence and proceeds efficiently under 10 atm of  $CO_2$  without the addition of any transition metal catalyst. An inorganic base such as  $K_2CO_3$  is the only reagent required. The method represents the first example of the synthesis of carboxylated heterocyclic compounds involving both cyclization and subsequent  $CO_2$  fixation processes and provides a novel, convenient, and highly practical route to 3-carboxylated indoles.<sup>6</sup>

During the course of our studies on CO<sub>2</sub> fixation employing transition metal catalysts,<sup>7</sup> it was found that the reaction of ethynylaniline 1a in the presence of a catalytic amount of CuI and 10 equiv of K<sub>2</sub>CO<sub>3</sub> under a CO<sub>2</sub> atmosphere at 50 °C afforded 3-carboxylated indole 2a (Table 1, entry 1). Interestingly, the process proceeded to some extent even in the *absence* of a copper catalyst (entry 2). Intrigued by this unexpected metal-free process, further examination of the reaction parameters was performed. While increasing the pressure of  $CO_2$  to 10 atm had little effect on the reaction efficiency (entries 3-5), raising the reaction temperature from 50 to 65 °C resulted in a drastic improvement in the yield; in this case, the desired product 2a was obtained in 93% yield (entry 6). Use of a decreased amount of K<sub>2</sub>CO<sub>3</sub> led to a lower yield (entry 8), and essentially, no product was obtained from the reaction in the absence of  $K_2CO_3$  (entry 9). Among a variety of solvents tested, DMF was found to be the best (entry 6 vs entries 10-13).<sup>8</sup> Moreover, although the use of K<sub>3</sub>PO<sub>4</sub> or NaO<sup>t</sup>Bu as a base gave lower conversions (entries 14 and 15), the reactions in the presence of other

(8) DMF is also an efficient solvent in the previously reported our transition-metal-free carboxylation of organozinc reagents, see ref 6b.

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<sup>(6) (</sup>a) Base-mediated carboxylation of relatively acidic C–H bonds of azoles using  $CO_2$  has recently been reported; see: Vechorkin, O.; Hirt, N.; Hu, X. *Org. Lett.* **2010**, *12*, 3567. (b) For transition-metal-free carboxylation of organozinc reagents using  $CO_2$ , see: Kobayashi, K.; Kondo, Y. *Org. Lett.* **2009**, *11*, 2035.

<sup>(7)</sup> Inamoto, K.; Asano, N.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. Org. Biomol. Chem. 2012, 10, 1514.

**Table 2.** Substrate Scope of the Process<sup>a</sup>



<sup>*a*</sup> Reaction conditions: **1** (0.25 mmol), K<sub>2</sub>CO<sub>3</sub> (2.5 mmol), and DMF (3 mL) under a CO<sub>2</sub> atmosphere. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Yield of **3** in parentheses. <sup>*d*</sup> MS 4 Å was added. <sup>*e*</sup> 48 h of reaction time.

bases such as  $Cs_2CO_3$  and KH provided a yield similar to that obtained with  $K_2CO_3$  (entries 16 and 17).

Transition metals such as Pd and Cu have been known to catalyze the cyclization of 2-ethynylaniline derivatives, Scheme 1. Plausible Reaction Mechanism



affording the corresponding indoles.<sup>5</sup> Considering the possibility that such trace amounts of metals in the reaction mixture were catalyzing our process, quantitative elemental analyses of 1a,  $K_2CO_3$ , and DMF were performed via inductively coupled plasma-mass spectrometry (ICP-MS). Fe was found to be the most abundant element in 1a, although in significantly low concentration (48.92 ppb). Furthermore, the concentration of other metals such as Pd and Cu was also found to be extremely low (below 5 ppb). Although the possible involvement of transition metals cannot be completely eliminated, such a catalytic process is unlikely to be operating in this reaction.<sup>9</sup>

To prove the generality of the method, the process was examined using variously substituted 2-ethynylanilines 1b-m (Table 2). Substrates possessing an electron-donating (-OMe) or an electron-withdrawing group  $(-CO_2Me)$ , -CN) at the *para*- or *meta*-position were suitable for the process, providing the corresponding indoles 2b-e, generally in good to high yields (entries 2-5). Halogen atoms such as -F, -Cl, and -Br on the benzene ring were also tolerated during the reaction (entries 6-9). In addition, substrate 1j, which has a terminal -Bu group on the alkyne (R in Table 2), provided the desired product 2j in moderate vield (entry 10), whereas the introduction of a  $-^{t}$ Bu group completely inhibited the process (entry 11). Although *N*-mesyl and *N*-benzylethynylanilines (11 and 1m) were completely inactive (entries 12 and 13), the reaction of 2-ethynylphenol 1n provided benzofuran 2n efficiently and in quantitative yield (entry 14).

Although the precise reaction mechanism remains to be elucidated, it seems reasonable to assume that the process occurs via the pathway shown in Scheme 1, which involves a base-promoted deprotonation of 1 and subsequent aminative cyclization, followed by  $CO_2$  fixation at the 3-position

<sup>(9)</sup> For detailed results of ICP-MS as well as the effect of the addition of transition metals, see Supporting Information.

of the indole nucleus. On the other hand, it was found that the reaction of independently prepared indole **3a** did not furnish carboxylated product **2a** at all under the optimized reaction conditions.

In summary, a novel method for the synthesis of 3carboxylated indoles from the corresponding 2-ethynylaniline derivatives through a tandem-type, cyclization – carboxylation sequence has been developed.  $K_2CO_3$  is the only reagent required to mediate the process, and the reaction proceeds efficiently under 10 atm of CO<sub>2</sub> without the addition of any transition metal catalyst. The yields are generally high, and good functional group compatibility is observed, thus providing a facile, efficient, and convenient route to 3-carboxylated indoles. Further studies to unveil the precise reaction mechanism of the process, as well as to apply this approach to the construction of other carboxylated heterocycles, are underway. Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 23390002), a Grant-in-Aid for Challenging Exploratory Research (No. 23659001), a Grant-in-Aid for Young Scientists (B) (No. 23790002) from Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 23390002) from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Detailed experimental procedures and spectroscopic and analytical data for compounds 1-3. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.