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Synthesis of 3-Carboxylated Indoles through a Tandem Process Involving Cyclization of 2-Ethynylanilines Followed by CO_2 Fixation in the Absence of Transition Metal Catalysts

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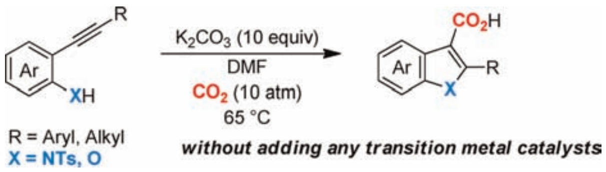
ABSTRACT



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.[1] 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.[2b] It was later found that copper-based catalytic systems also participate in a similar carboxylation of boronic esters.[2d,e] Moreover, Oshima and Yorimitsu,[2c] and Dong[2f] independently reported the Ni- and Pd-catalyzed coupling of organozinc reagents with CO_2. Recently, Pd-catalyzed direct transformation of aryl bromides to the corresponding aryl carboxylic acids in the presence of 1 atm of CO_2 was realized.[2h] Although these catalytic processes[2] 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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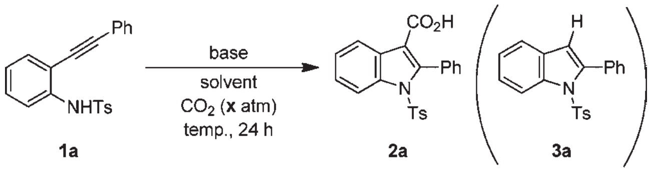
(1) For selected recent reviews on the use of CO_2 in organic synthesis, see: (a) Louie, J. *Curr. Org. Chem.* **2005**, *9*, 605. (b) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (c) Darensboug, D. J. *Chem. Rev.* **2007**, *107*, 2388. (d) Correa, A.; Martín, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (e) Aresta, M.; Dibenedetto, A. *Dalton Trans.* **2010**, *39*, 3347. (f) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (g) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842. (h) Zhang, Y.; Riduan, S. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6210w. (i) Boogaerts, I. I. F.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 3021.

(2) For selected recent examples of the CO_2 fixation in the presence of a transition metal catalyst, see: (a) Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, *126*, 5956. (b) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706. (c) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 2681. (d) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697. (e) Ohishi, T.; Nishimura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (f) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 7826. (g) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254. (h) Correa, A.; Martín, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974. (i) Dang, L.; Lin, Z. *Organometallics* **2010**, *29*, 917.

10.1021/ol300958c

Table 1. Screening of Reaction Parameters[a]



					yield[b] (%)		
entry	base (equiv)	solvent	**x** (atm)	temp (°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_2CO_3 (10)	DMF	3	50	25	0	75
4	K_2CO_3 (10)	DMF	6	50	24	0	75
5	K_2CO_3 (10)	DMF	10	50	20	0	75
6	K_2CO_3 (10)	DMF	10	65	93	7	0
7	K_2CO_3 (10)	DMF	10	80	92	8	0
8	K_2CO_3 (6)	DMF	10	65	75	0	22
9	none	DMF	10	65	0	0	>99
10	K_2CO_3 (10)	1,4-dioxane	10	65	0	0	>99
11	K_2CO_3 (10)	toluene	10	65	0	16	84
12	K_2CO_3 (10)	MeCN	10	65	0	5	90
13	K_2CO_3 (10)	Et_3N	10	65	0	4	96
14	K_3PO_4 (10)	DMF	10	65	67	7	26
15	NaO^{t}Bu (10)	DMF	10	65	40	19	39
16	Cs_2CO_3 (10)	DMF	10	65	87	7	3
17	KH (10)	DMF	10	65	86	8	5

[a] Reaction conditions: **1a** (0.25 mmol), a base, and a solvent (3 mL) under a CO_2 atmosphere. [b] Isolated yield. [c] 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.[3a] 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_2. Subsequent reports indicated that a copper version of the catalyst also participates in a similar C−H carboxylation in the presence of CO_2 (1 or 1.5 bar).[3b,c] Recently, the chelating-group-directed carboxylation of unactivated aryl C−H bonds was accomplished in the presence of a Rh catalyst.[3d]

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.[4] 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.[5]

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.[6]

During the course of our studies on CO_2 fixation employing transition metal catalysts,[7] it was found that the reaction of ethynylaniline **1a** in the presence of a catalytic amount of CuI and 10 equiv of K_2CO_3 under a CO_2 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_2CO_3 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).[8] Moreover, although the use of K_3PO_4 or NaO^{t}Bu as a base gave lower conversions (entries 14 and 15), the reactions in the presence of other

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(3) (a) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858. (b) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (c) 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. (d) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251.

(4) For recent reviews, see: (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469.

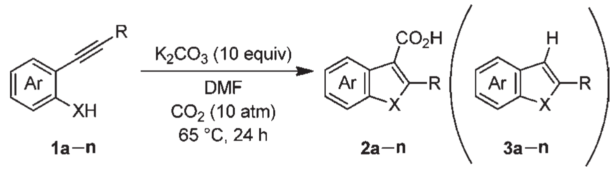
(5) For selected examples, see: (a) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799. (b) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803. (c) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355. (d) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (e) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (f) Boyer, A.; Isono, N.; Lackner, S.; Leutens, M. *Tetrahedron* **2010**, *66*, 6468. (g) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (h) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 8770. (i) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 3336.

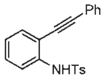
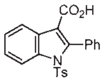
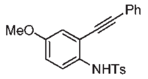
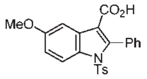
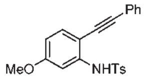
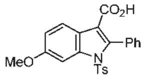
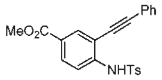
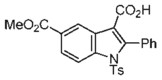
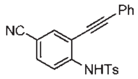
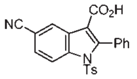
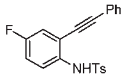
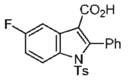
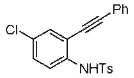
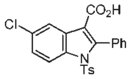
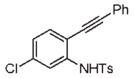
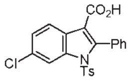
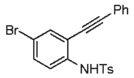
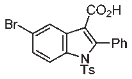
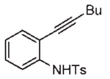
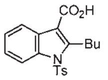
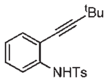
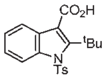
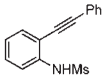
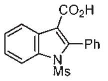
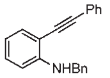
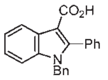
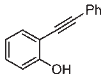
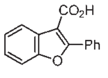
(6) (a) Base-mediated carboxylation of relatively acidic C−H bonds of azoles using CO_2 has recently been reported; see: Vechorkin, O.; Hirt, N.; Hu, X. *Org. Lett.* **2010**, *12*, 3567. (b) For transition-metal-free carboxylation of organozinc reagents using CO_2, see: Kobayashi, K.; Kondo, Y. *Org.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

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

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

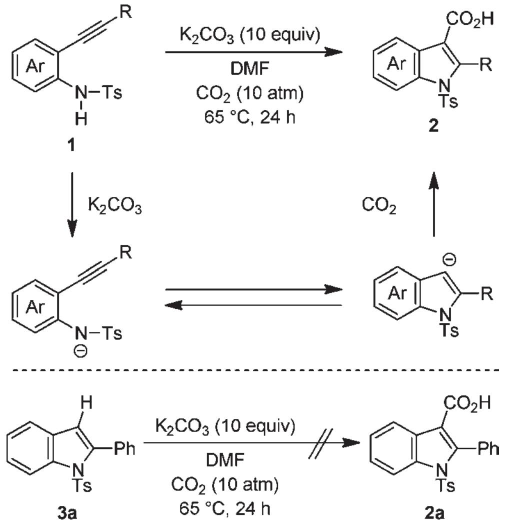
Table 2. Substrate Scope of the Process[a]



entry	substrate	1	product	yield[b,c] (%)
1		1a		93 (7)
2[d]		1b		93 (0)
3[d]		1c		62 (15)
4[d,e]		1d		78 (15)
5		1e		58 (18)
6		1f		95 (0)
7		1g		96 (0)
8		1h		93 (6)
9		1i		96 (0)
10		1j		58 (32)
11[d]		1k		0 (11)
12[d]		1l		0 (0)
13[d]		1m		0 (0)
14		1n		>99 (0)

[a] Reaction conditions: **1** (0.25 mmol), K_2CO_3 (2.5 mmol), and DMF (3 mL) under a CO_2 atmosphere. [b] Isolated yield. [c] Yield of **3** in parentheses. [d] MS 4 Å was added. [e] 48 h of reaction time.

Scheme 1. Plausible Reaction Mechanism



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, affording the corresponding indoles.[5] 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.[9]

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 yield (entry 10), whereas the introduction of a −^{t}Bu group completely inhibited the process (entry 11). Although *N*-mesyl and *N*-benzylethynylanilines (**1l** 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

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(9) 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 3-carboxylated 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_2 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.

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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.