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Cyclic *Anti*-Azacarboxylation of 2-Alkynylanilines with Carbon Dioxide

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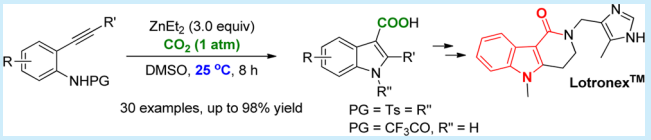
Supporting Information

ABSTRACT: Direct *anti*-azacarboxylation of 2-alkynylanilines with CO_2 mediated by $ZnEt_2$ was observed to afford indole-3-carboxylic acids, a class of important compounds for the synthesis of many biologically active compounds, efficiently under 1 atm of CO_2. The readily available nature of the different starting materials and tolerance of various functional groups provide vast opportunities for the efficient construction of diversified libraries for bioactive compounds listed in Figure 1. As an example, this methodology has been applied to the synthesis of Lotronex, a drug molecule used for the treatment of irritable bowel syndrome.



Indole-3-carboxylic acids and the derivatives are important fragments that exist in various alkaloids and drug molecules[1] that have attracted attention from organic chemists and medicinal chemists due to their unique structures and bioactivities (Figure 1).[2−4]

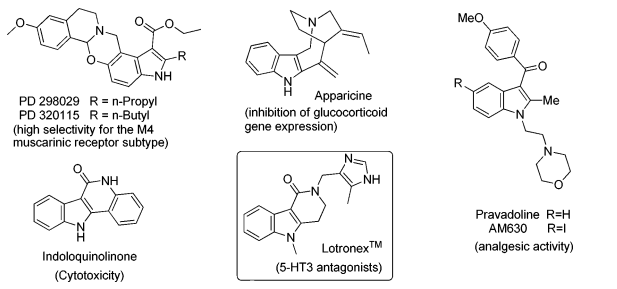
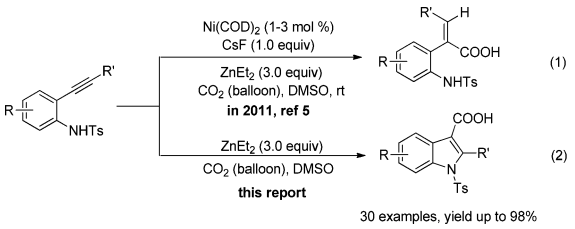


Figure 1. Bioactive indole-3-carboxylic derivatives.

In 2011, we reported a highly regioselective $Ni(COD)_2$-catalyzed *syn*-hydrocarboxylation of 2-alkynylanilines with a CO_2 balloon to afford (*E*)-2-aryl-2-alkenyl acids **A**, in which the tosylamine acted as a directing group for the control of regioselectivity (Scheme 1, eq 1) (Table 1, entry 1).[5] Rather unexpectedly, we found that by reducing the loading of $Ni(COD)_2$ to 1 mol % we started to observe the formation of an unexpected new product, which was identified as indole-3-carboxylic acid **2a**, in 10% yield together with the normal product **A** (Table 1, entry 2). This minor product must be formed via cyclic *anti*-azazincation followed by reaction with CO_2. As we know, the reaction of zinc reagents with CO_2 usually requires transition-metal catalysis,[5−7] however, in very limited cases, zinc reagents may also directly react with carbon dioxide.[8] This made

Scheme 1. Our Previous Report and New Observation on the Carboxylation of 2-Alkynylanilines via CO_2 Activation



us check the role of $Ni(COD)_2$ in this type of reaction.[5,9] Surprisingly, in the absence of $Ni(COD)_2$, the reaction exclusively afforded indole-3-carboxylic acid **2a** in 93% yield (Table 1, entry 3). The addition of 1.0 equiv of CsF did not affect the yield (Table 1, entry 4), and the carboxylation reaction did not occur in the absence of $ZnEt_2$ (Table 1, entry 5). It should be mentioned that Nakamura and Zhao reported the treatment of the in situ generated indolyl zinc intermediates with active electrophiles including H^+, allylic bromides, acyl chlorides, or α,β-unsaturated ketones in some cases with the help of 1.0 equiv of CuCN·2LiCl.[12] Herein we report the efficient azacarboxylation with CO_2 for facile synthesis of indole-3-carboxylic acids, which are important precursors for bioactive compounds listed in Figure 1. Its application in the synthesis of Lotronex has been demonstrated as an example.

The solvent, base, and additive effects were attempted at room temperature with a CO_2 balloon. Amide solvents such as DMF

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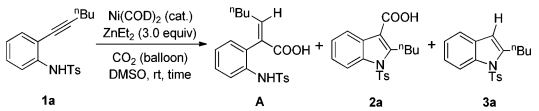
Table 1. Optimization of the Reaction Conditions[a]

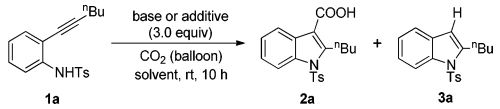


entry	$Ni(COD)_2$ (mol %)	CsF (equiv)	time (h)	yield of **A** (%)[c]	yield of **2a** (%)[c]	yield of **3a** (%)[d]
1[b]	3	1	3	95[5]	–	–
2	1	0	8	80	10	–
3	0	0	10	–	93	trace
4	0	1	10	–	92	6
5[e]	0	1	10	–	–	20[f]

[a]The reaction was conducted on 1.0 mmol of **1a**, $Ni(COD)_2$ (1 mol %) (if any), 1.0 equiv of CsF (if any), and 3.0 equiv of $ZnEt_2$ (1.5 M in toluene) in 6 mL of anhydrous DMSO with a CO_2 balloon. [b]The reaction was conducted on 0.5 mmol of **1a**, $Ni(COD)_2$ (3 mol %), 1.0 equiv of CsF, and 3.0 equiv of $ZnEt_2$ (1.5 M in toluene) in 3 mL of anhydrous DMSO with a CO_2 balloon. [c]Isolated yields. [d]NMR yields. [e]Without $ZnEt_2$. [f]70% recovery of **1a**.

and NMP gave much lower yields of **2a**, while other solvents including THF, toluene, and *n*-hexane only led to a high proportion recovery of **1a** (Table 2, entries 2–6). The yield of **2a** sharply dropped to 44% when the amount of $ZnEt_2$ was reduced to 2.0 equiv (Table 2, entry 7). Replacing $ZnEt_2$ with $ZnMe_2$ caused a diminished yield (Table 2, entry 8), and the addition of

Table 2. Investigation on the Solvent, Base, and Additive Effects[a]



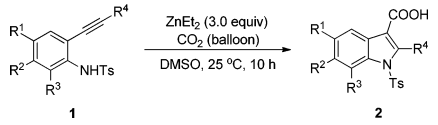
entry	solvent	additive	yield of **2a**[b] (%)	yield of **3a**[b] (%)	recovery of **1a**[b] (%)
1	DMSO	$ZnEt_2$	93	trace	–
2	DMF	$ZnEt_2$	41	44	14
3	NMP	$ZnEt_2$	47	39	4
4	THF	$ZnEt_2$	–	4	86
5	toluene	$ZnEt_2$	–	–	97
6	hexane	$ZnEt_2$	–	–	95
7[c]	DMSO	$ZnEt_2$	44	37	–
8	DMSO	$ZnMe_2$	70	23	–
9	DMSO	$ZnBr_2$	–	63	–
10	DMSO	ZnI_2	–	17	83
11	DMSO	$AlEt_3$	–	10	81
12	DMSO	BEt_3	–	–	75
13	DMSO	EtMgCl	–	2	86
14	DMSO	EtMgBr	–	4	82
15[d]	DMSO	EtMgBr	–	5	74
16[d,e]	DMSO	nBuLi	–	6	77
17[d,f]	DMSO	nBuLi	–	16	45
18	DMSO	K_2CO_3	4	2	93
19	DMSO	KOH	1	13	85
20	DMSO	NaO^{t}Bu	6	9	84
21	DMSO	Et_3N	–	>99	–
22	DMSO	pyridine	–	11	84

[a]The reaction was conducted with 1.0 mmol of **1a** and 3.0 mmol of base (or additive) in 6 mL of anhydrous solvent under 25 °C with a CO_2 balloon. [b]NMR yields. [c]2.0 equiv of $ZnEt_2$. [d]The reaction of **1a** with base in DMSO for 10 h followed by quenching with a CO_2 balloon. [e]1.0 mmol of BuLi were used. [f]2.0 mmol of BuLi were used.

$ZnBr_2$ or ZnI_2 only afforded indole **3a** (Table 2, entries 9 and 10). Interestingly, when $AlEt_3$, BEt_3, or even nBuLi and Grignard reagents were used instead of $ZnEt_2$, the *anti*-azacarboxylation did not occur (Table 2, entries 11–17)! Moreover, other common bases gave only trace amounts of acid products (Table 2, entries 18–22), which indicates that the $ZnEt_2$ may not act only as a base but also helped in both cyclization of 2-alkynylaniline **1** and the following carboxylation process.

On the basis of the standard reaction conditions shown in entry 1 of Table 2, the scope of the reaction has been extensively explored. Various substituents such as halogen (Table 3, entries

Table 3. Synthesis of Indole-3-carboxylic Acid Analogues from 2-Alkynylanilines[a]



	1				
entry	R^1	R^2	R^3	R^4	yield of **2**[b] (%)
1	H	H	H	nBu (**1a**)	93 (**2a**)
2	F	H	H	nBu (**1b**)	94 (**2b**)
3	Cl	H	H	nBu (**1c**)	98 (**2c**)
4	Br	H	H	nBu (**1d**)	91 (**2d**)
5	CF_3	H	H	nBu (**1e**)	91 (**2e**)
6	CO_2Me	H	H	nBu (**1f**)	79 (**2f**)
7	CN	H	H	nBu (**1g**)	68 (**2g**)
8	NO_2	H	H	nBu (**1h**)	60 (**2h**)
9[c]	OMe	H	H	nBu (**1i**)	87 (**2i**)
10[c]	Me	H	H	nBu (**1j**)	96 (**2j**)
11	Cl	H	F	nBu (**1k**)	80 (**2k**)
12[d]	F	H	Cl	nBu (**1l**)	80 (**2l**)
13[d]	Me	H	Me	nBu (**1m**)	55 (**2m**)
14	H	H	H	$^nC_6H_{13}$ (**1n**)	88 (**2n**)
15	H	H	H	$^nC_8H_{17}$ (**1o**)	83 (**2o**)
16	H	H	H	CH_2CH_2Ph (**1p**)	96 (**2p**)
17	H	H	H	$(CH_2)_3Cl$ (**1q**)	93 (**2q**)
18	H	Cl	H	$(CH_2)_3CN$ (**1r**)	80 (**2r**)
19	H	H	H	CH_2CH_2Ac (**1s**)	67 (**2s**)
20[e]	H	H	H	CH_2CH_2OH (**1t**)	94 (**2t**)
21[c]	H	H	H	cyclopropyl (**1u**)	70 (**2u**
22[c]	Cl	H	H	cyclohexenyl (**1v**)	65 (**2v**)
23[c]	H	H	H	Ph (**1w**)	45 (**2w**)
24[c]	H	H	H	*p*-$MeOC_6H_4$ (**1x**)	52 (**2x**)
25	H	H	H	CH_2OBn (**1y**)	57 (**2y**)
26[d]	H	H	H	H (**1z**)	60 (**2z**)
27	H	Me	H	$(CH_2)_3Cl$ (**1A**)	75 (**2A**)

[a]The reaction was conducted with 1.0 mmol of **1** and 3.0 mmol of $ZnEt_2$ in 6 mL of DMSO under 25 °C with a CO_2 balloon. [b]Isolated yield. [c]The reaction was conducted at 80 °C. [d]The reaction was conducted at 100 °C. [e]4.0 equiv of $ZnEt_2$ was used.

2–4, 11–12, 18, 22), CF_3– (Table 3, entry 5), ester (Table 3, entry 6), and cyano and nitro (Table 3, entries 7 and 8) on different positions of the aromatic ring were tolerated to afford the targeted acids in very high yields. Substrates with electron-donating groups underwent the reaction smoothly, regardless of whether they were in the R^1, R^2, or R^3 positions (Table 3, entries 9–10, 13, and 27). 2-Alkynylanilines bearing alkyl- (Table 3, entries 14–20), alkenyl- (Table 3, entry 22), cycloalkyl- (Table 3, entries 21–22), and aryl groups (Table 3, entries 23–24) on the

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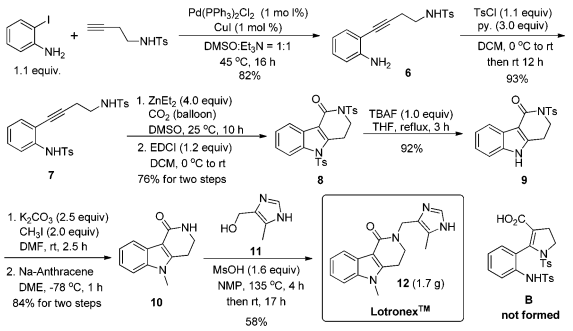
R^4 positions generated the corresponding acids in decent yields. Even an sp C−H bond did not affect the yield (Table 2, entry 26). Various sensitive functional groups at the terminal position of the alkyne moiety were also tested: 2-alkynylanilines with halogen (Table 3, entries 17 and 27), cyano (Table 3, entry 18), ketal carbonyl (Table 3, entry 19), and even a hydroxyl group (Table 3, entry 20) on R^4 produced excellent yields of the corresponding indole-3-carboxylic acids. Substrate bearing a removable benzyl ether segment **1y** is also compatible, although the yield is lower (Table 3, entry 25).

Even an additional −NHTs group did not affect the selectivity of the targeted cyclization reaction (Scheme 2) as demonstrated in the synthesis of Lotronex **12**, a 5-HT3 antagonist originated by GlaxoSmithKline plc., used for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) with women.[10] The Sonogashira coupling between 2-iodoaniline and *N*-Ts-protected homopropargyl amine afforded **6**. Following the protection of the free amino group, the key tricyclic framework **8** was constructed via aza-metalation−carboxylation of alkyne **7** with two different *N*-tosylamine units. The formation of the alternative alkylamine-based *anti*-azacarboxylation product **B** was not observed. The *N*-tosyl group on the indole ring of **8** was then removed highly selectively by treatment with TBAF in refluxing THF to afford **9**. After methylation on the nitrogen atom of the indole in **9**, the *N*-tosyl group on the lactam was deprotected by its treatment with a sodium anthracene solution under −78 °C in DME.[11] The reaction of intermediate **10** with imidazole **11** yielded Lotronex **12** (Scheme 2). Based on this, we reasoned that this method may be applied to the synthesis of the compounds and their derivatives listed in Figure 1 for further biological study.

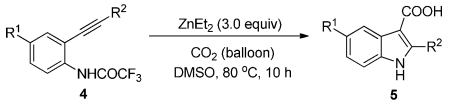
Scheme 2. Synthesis of Lotronex



Interestingly, indole-3-carboxylic acids **5a−c** with no protecting group on the N atom were afforded directly when starting from *N*-trifluoroacetyl-protected 2-alkynylanilines bearing functional groups such as cyano and halogen in moderate to good yields (Table 4).

In order to unveil the mechanism, the reaction of **1a** with $ZnEt_2$ in DMSO in the absence of CO_2 for 10 h followed by quenching with DOAc yielded **3a** in 85% yield with a D incorporation of 81%, which indicated the formation of the zinc intermediate **Int 1** (Scheme 3, eq 1). Subsequent reaction of such an in situ formed intermediate with CO_2 followed by quenching with a 3 M aqueous solution of HCl afforded carboxylic acid **2a** in 74% yield together with 23% of **3a** (Scheme 3, eq 2). If such a reaction was quenched with DOAc after reaction with CO_2, the D incorporation at C3-position of **3a** is less than 5%, indicating that **3a** was formed by abstracting H^+ from the reaction environment.

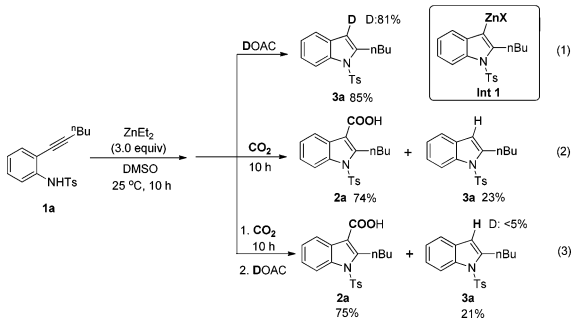
Table 4. Synthesis of Indole-3-carboxylic Acid Analogues from *N*-(Trifluoroacetyl)-2-alkynylanilines[a]



entry	R^1	R^2	yield of 5[b] (%)
1	H	^{n}Bu (**4a**)	62 (**5a**)
2	CN	CH_2CH_2Ph (**4b**)	81 (**5b**)
3	Cl	$^nC_{10}H_{21}$ (**4c**)	80 (**5c**)

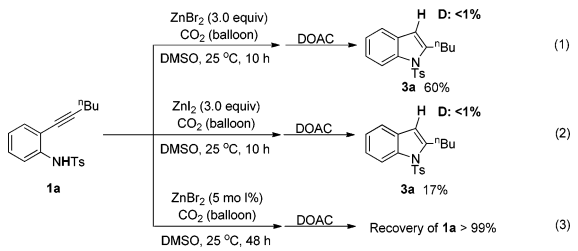
[a]The reaction was conducted with 1.0 mmol of **4** and 3.0 mmol of $ZnEt_2$ in 6 mL of DMSO under 80 °C with a CO_2 balloon. [b]Isolated yields.

Scheme 3. Deuterium-Labeling Experiments of 1a



Interestingly, the reaction of **1a** with 3.0 equiv of $ZnBr_2$ in DMSO with a CO_2 balloon for 10 h followed by quenching with DOAc yielded only **3a** in 60% yield with a D incorporation less than 1% (Scheme 4, eq 1). A similar result was observed in ZnI_2-mediated reaction (Scheme 4, eq 2). Again, we reasoned that **3a** was formed by abstracting H^+ from the substrate or reaction environment and the indolyl zinc intermediate formed in Scheme 4 was NOT able to reach CO_2. In addition, the addition of a catalytic amount of $ZnBr_2$ only led to a quantitative recovery of **1a** after 48 h (Scheme 4, eq 3).

Scheme 4. Deuterium-Labeling Experiments on ZnX_2-Mediation Reactions



Furthermore, as a comparison, when CO_2 was applied as an E^+ under the protocol developed by Nakamura and Zhao et al.,[12] the carboxylation failed (Scheme 5), indicating a much higher reactivity of zinc intermediates toward carbon dioxide generated in the current study.

Based on the experimental facts above, we propose that the reaction may occur via a zinc-mediated cyclization reaction to form **Int 1**.[12] $ZnEt_2$ acted not only as a base but also as a Lewis acid. The final indole-3-carboxylic acid **2** was afforded upon protonation (Scheme 6).

In summary, we have presented here a very mild and convenient methodology for the efficient construction of

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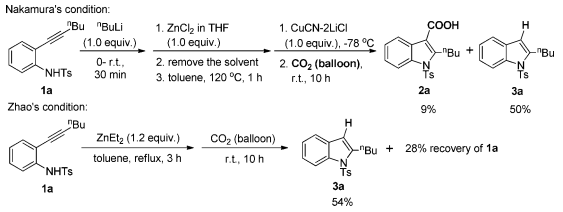
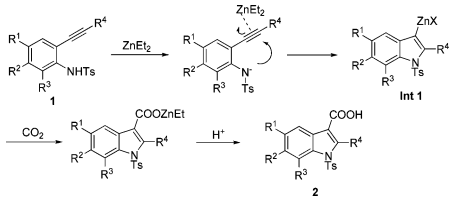
Scheme 5. Control Experiments



Scheme 6. Rational Hypothesis of the Cyclic *Anti*-Azacarboxylation Reaction



different indole-3-carboxylic acids. The reaction was conducted with $ZnEt_2$ under a balloon atmosphere of carbon dioxide and no transition metal catalyst is necessary. Functional groups including ester, cyano, nitro, acetyl, −OH, −NHTs, trifluoromethyl, etc. were smoothly tolerated, and the potential has been demonstrated by applying it to the synthesis of Lotronex. This protocol should be easily applicable to the synthesis of the targets listed in Figure 1. Thus, such a mild carbon dioxide reaction may provide an efficient entry to the library of bioactive compounds due to the easily available and diversified nature of the starting compounds. Such syntheses, including those of pravadoline, AM630, PD molecules, and their derivatives, by using this CO_2-based carboxylation reaction are being actively pursued by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00884.

Experimental procedures, analytical data, and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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