



Carboxylation of indoles and pyrroles with CO₂ in the presence of dialkylaluminum halides

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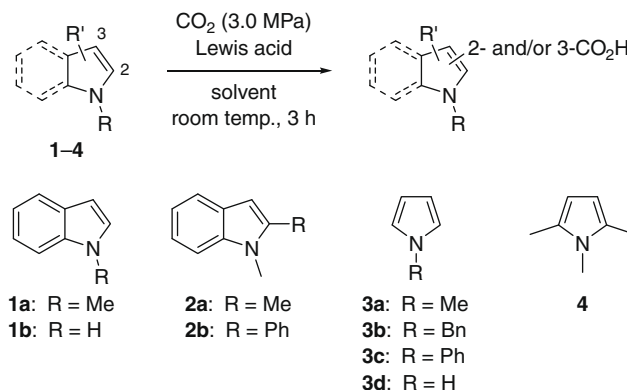
ABSTRACT

The Lewis acid-mediated carboxylation of arenes with CO₂ has been successfully applied to 1-substituted indoles and pyrroles by using dialkylaluminum chlorides instead of aluminum trihalides. Thus, the carboxylation of 1-methylindoles, 1-benzyl-, and 1-phenylpyrroles proceeds regioselectively with the aid of an equimolar amount of Me₂AlCl under CO₂ pressure (3.0 MPa) at room temperature to afford the corresponding indole-3-carboxylic acids and pyrrole-2-carboxylic acids in 61–85% yields, while the same treatment of 1,2,5-trimethylpyrrole affords the 3-carboxylic acid in 52% yield.

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Indole-3-carboxylic acid and pyrrole-2-carboxylic acid are important structural motifs found in various artificial drugs, as well as biologically active natural products, such as a drug for the prophylaxis and treatment of acute respiratory infections, Arbidol,¹ a serotonin 5-hydroxytryptamine type-3 receptor antagonist used as an antiemetic, Tropisetron,² and a potent calcium channel modulator, Ryanodine.³ Although a number of synthetic approaches have been reported for the construction of these structures via cyclization reactions, such as the Fischer,⁴ Saegusa–Ito,⁵ Hantzsch,⁶ and Knorr syntheses,⁷ the Friedel–Crafts acylation,⁸ the carbonation of arylmetal species,⁹ and so on,¹⁰ they require a multi-step reaction sequence and/or prefunctionalization of starting materials and, therefore, a more straightforward method is desired. It has been known that arenes are directly carboxylated with CO₂ with the aid of Lewis acids to give arylcarboxylic acids, though generally in poor yields.¹¹ The reaction is believed to be an electrophilic aromatic substitution; an aromatic nucleus is attacked by Lewis acid-activated CO₂ to give an arenium intermediate, which eliminates a proton to give a carboxylic acid after aqueous workup (the S_EAr mechanism).^{11b} In our continuing efforts to extend the scope and utility of this reaction,¹² we have found that 1-substituted indoles and pyrroles can be efficiently carboxylated under CO₂ pressure in the presence of dialkylaluminum halides, although the S_EAr mechanism may not or not always operate in the carboxylation of these heteroaromatic compounds. Herein, we report preliminary results of the carboxylation of indoles and pyrroles **1–4** under the Friedel–Crafts conditions (Scheme 1).

First, the carboxylation of 1-methylindole (**1a**) was tested with varying aluminum-based Lewis acids (1.0 mol equiv) under CO₂ pressure (3 MPa) at room temperature (Table 1, entries 1–10).¹³ The reaction was carried out in benzene or toluene, depending on the acidity of the Lewis acid employed, so as not to contaminate desired carboxylic acid(s) with undesired one(s) formed by the carboxylation of the solvent; under the reaction conditions, toluene was slightly carboxylated with the aid of aluminum trihalides while benzene was not, and both the solvents were not carboxylated with weaker Lewis acids. Alkylaluminums were employed as hexane solutions and, therefore, an amount of incidental hexane was included into the reaction mixture in runs carried out by using alkylaluminums. The reaction proceeded regioselectively to give



Scheme 1.

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Table 1
Carboxylation of indoles and pyrroles^a

Entry	Substrate	Lewis acid	Solvent	Yield (%) (2-:3- ratio) ^b
1	1a	AlCl ₃	Benzene	36 (–:1)
2	1a	AlBr ₃	Benzene	32 (–:1)
3	1a	AlBr ₃ ^c	Benzene	32 (–:1)
4	1a	AlBr ₃ ^d	Benzene	32 (–:1)
5	1a	AlI ₃	Benzene	5 (–:1)
6	1a	MeAlCl ₂	Toluene–hexane	21 (–:1)
7	1a	Me ₂ AlCl	Benzene–hexane	62 (–:1)
8	1a	Me ₂ AlCl	Toluene–hexane	85 (–:1)
9	1a	Et ₂ AlCl	Toluene–hexane	69 (–:1)
10	1a	Me ₃ Al	Toluene–hexane	6 (–:1)
11	1a	Me ₂ AlCl	Hexane	48 (–:1)
12	1a	Me ₂ AlCl	CS ₂ –hexane	65 (–:1)
13	1a	Me ₂ AlCl	CH ₂ Cl ₂ –hexane	59 (–:1)
14	1a	Me ₂ AlCl	THF–hexane	0 (–:1)
15	1b	Me ₂ AlCl	Toluene–hexane	28 (–:1)
16	1b	Me ₂ AlCl ^e	Toluene–hexane	21 (–:1)
17	2a	Me ₂ AlCl	Toluene–hexane	73 (–:1)
18	2b	Me ₂ AlCl	Toluene–hexane	61 (–:1)
19	3a	AlCl ₃	Benzene	2 (–:1)
20	3a	MeAlCl ₂	Toluene–hexane	7 (–:1)
21	3a	Me ₂ AlCl	Toluene–hexane	25 (7:1)
22	3a	Me ₃ Al	Toluene–hexane	3 (50:1)
23	3b	Me ₂ AlCl	Toluene–hexane	80 (1:–)
24	3c	Me ₂ AlCl	Toluene–hexane	79 (1:–)
25	3d	Me ₂ AlCl	Toluene–hexane	6 (10:1)
26	3d	Me ₂ AlCl ^e	Toluene–hexane	6 (8:1)
27	4	Me ₂ AlCl	Toluene–hexane	52 (–:1)

^a Reaction conditions: substrate (1.00 mmol), Lewis acid (1.0 mol equiv), solvent (1.0–2.2 cm³), CO₂ (3.0 MPa), room temp., 3 h.

^b Determined by ¹H NMR analysis.

^c Me₃SiCl (1.0 mol equiv) was added.

^d Ph₃SiCl (1.0 mol equiv) was added.

^e Lewis acid (2.0 mol equiv) was employed.

1-methylindole-3-carboxylic acid but the yield varied depending on the Lewis acid employed; Me₂AlCl and Et₂AlCl exhibited better performances than stronger Lewis acids, AlCl₃ and AlBr₃, which are indispensable for the carboxylation of arenes.^{12a,b} Although the carboxylation of arenes is promoted by the addition of trialkyl- or triarylhalosilanes,^{12c} such a beneficial effect could not be observed for **1a** (entries 3 and 4, as compared with entry 2). The employment of solvents other than benzene and toluene did not improve the yield of the carboxylic acid (entries 11–14). We then prescribed Me₂AlCl and toluene as a standard Lewis acid and solvent, respectively. The reaction of 2-substituted 1-methylindoles **2a** and **2b** afforded the corresponding 3-carboxylic acids in good yields, while the reaction of indole (**1b**) was sluggish even by using 2.0 mol equiv of Me₂AlCl (entries 15–18). A similar exploration of reaction conditions for 1-methylpyrrole (**3a**) again revealed that the combination use of Me₂AlCl and toluene was most suitable for the carboxylation to take place, giving 1-methylpyrrole-2-carboxylic acid with good regioselectivity over the 3-carboxy isomer (entries 19–22). Under the conditions, 1-benzyl and 1-phenyl derivatives **3b** and **3c** were exclusively converted into the corresponding 2-carboxylic acids in high yields, while pyrrole (**3d**) hardly gave the expected 2-carboxylic acid (entries 23–26). On the other hand, the reaction of 1,2,5-trisubstituted pyrrole **4** took place at the 3-position (entry 27).

In order to shed light on the reaction mechanisms, the susceptibility of compounds **1–3** toward metallation was tested. Each compound was treated with an equimolar amount of Me₂AlCl (1.0 M solution in hexane) under nitrogen at room temperature for 3 h. After quenched with D₂O, the reaction mixture was extracted with CDCl₃ and the extract was dried over MgSO₄ and was analyzed by ¹H NMR spectroscopy. It was revealed that **1a** was deuterated at the 3-position; the percentage of deuterated **1a** in the recovered one was 81%. Other 1-substituted indoles **2a**

and **2b**, and 1-substituted pyrroles **3a–c** were remained almost intact after the treatment. On the other hand, 1-unsubstituted compounds **1b** and **3d** were completely deuterated at the 1-position. Therefore, the carboxylation of **1a** is suggested to proceed rather via the metallation of **1a** with Me₂AlCl, followed by the carbonation of the resulting indole-3-ylaluminum species than via the S_EAr mechanism. This is supported by the fact that an organoaluminum species, which was prepared beforehand by the treatment of **1a** with an equimolar amount of Me₂AlCl in toluene–hexane under nitrogen, was exposed to 3.0 MPa CO₂ for 3 h to give the 3-carboxylic acid in 65% yield. The organoaluminum species is expected to be methyl(1-methylindole-3-yl)aluminum chloride because methane was detected from the gas phase by GC analysis when the metallation was carried out in a sealed vessel. The relatively low yields of 1-unsubstituted carboxylic acids as compared to those of 1-substituted ones are attributed to the N-metallation of **1b** and **3d**;¹⁵ the resulting aluminum amide will be in situ carbonated to an aluminum carbamate, which resists further carboxylation and is decomposed to recover the substrate by aqueous workup. Close scrutiny of the literature revealed that in 2000, Okauchi et al. reported the acylation of indoles with the aid of dialkylaluminum chlorides.¹⁶ They found that 1-substituted and 1-unsubstituted indoles were efficiently acylated at the 3-position with various acyl chlorides in the presence of Me₂AlCl or Et₂AlCl, while the use of a conventional Friedel–Crafts catalyst, AlCl₃, for the reaction of indole (**1b**) resulted in the decomposition and oligomerization of **1b**. The successful use of dialkylaluminum chlorides was attributed to their mild Lewis acidities and abilities to scavenge HCl liberated by the acylation. Later on, Huffman et al. pointed out the intermediary of an indole-3-ylaluminum species in the acylation, based on the observation that the treatment of 1-pentylindole with Me₂AlCl, after quenching the mixture with D₂O, afforded 3-deuterio-1-pentylindole.¹⁷ Therefore, the present observation is not the first example of the aluminium of 1-substituted indoles with dialkylaluminum chlorides. However, it is important to have shown the possibility that **1a** is metallated under CO₂ atmosphere and in situ carbonated to give a carboxylic acid. One may suspect that Me₂AlCl is carbonated with CO₂ under the reaction conditions. However, the treatment of Me₂AlCl with 3.0 MPa CO₂ in hexane at room temperature for 3 h gave, after acidic workup, no acetic acid. In addition, by using the CO₂-pretreated Me₂AlCl, **1a** could be carboxylated in 61% yield under the conditions employed in entry 8 (Table 1). Therefore, the carbonation of Me₂AlCl is negligible. Quite recently, Huffman et al. examined the acylation of 1-(*p*-toluenesulfonyl)pyrrole with acyl halides in the presence of aluminum-based Lewis acids.¹⁸ They concluded that when AlCl₃ is used as a Lewis acid, the acylation proceeds via a pyrrolylaluminum intermediate, while the reaction using weaker Lewis acids, such as EtAlCl₂ and Et₂AlCl, proceeds via the S_EAr mechanism. However, in order to fully elucidate the reaction mechanisms of the present carboxylation of heteroaromatic compounds, further experiments have to be done to know how much acidity is required for a Lewis acid to activate CO₂ to the extent that the Lewis acid–CO₂ complex can react with aromatic nuclei by the S_EAr mechanism.

Until recently, there have been only a few reports on the direct metallation of indoles and pyrroles,¹⁹ other than lithiation.⁹ It has been a hot and fascinating topic that the alkali metal-mediated magnesiation,²⁰ zincation,^{20,21} aluminium,²² cupration,²³ and cadmium²⁴ of aromatic compounds, including indoles and pyrroles, have been achieved by using ate bases^{20–24} or a neutral base.^{21b} It should be noted that Me₂AlCl metallated 1-methylindole (**1a**) at the 3-position (vide supra), while an ate base, *i*-Bu₃Al(TM-P)Li, metalates 1-(Boc)indole at the 2-position.²² Iwao and co-workers reported that 1-(2,2-diethylbutanoyl)indole was lithiated at the most acidic 2-position with a sterically undemanding super

base, *sec*-BuLi–*tert*-BuOK, while it was lithiated at the 3-position with bulky *sec*-BuLi–*N,N,N',N',N''*-pentamethyldiethylenetriamide (PMDTA).^{9a} It should also be noted that 1-phenylpyrrole (**3c**) was selectively carboxylated at the 2-position, as regiocontrol in the metallation of 1-arylpyrroles with organolithiums or ate bases has been a troublesome problem.^{9b,21a}

In conclusion, we have shown here that 1-substituted indoles and pyrroles are directly carboxylated with CO₂ in the presence of dialkylaluminum chlorides, which provides an easy access to 1-substituted indole-3-carboxylic acids and pyrrole-2-carboxylic acids. Further studies on the reaction mechanisms are underway.

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- Typical procedure for the carboxylation (Table 1, entry 8): In a 50 cm³ autoclave equipped with a glass inner tube and a magnetic stirring bar were charged compound **1a** (131 mg, 1.00 mmol), toluene (1.0 cm³), and Me₂AlCl (1.0 M solution in hexane; 1.0 cm³) under nitrogen and the apparatus was purged with CO₂ by repeated pressurization and subsequent expansion, the final pressure being adjusted to 3.0 MPa. After stirring the mixture at room temperature for 3 h, the reactor was depressurized and the mixture was quenched with 2 M HCl and extracted with chloroform. The organic layer was extracted with 0.5 M Na₂CO₃ and the extract was acidified with conc. HCl to liberate the free acid, which was extracted with chloroform. The extract was dried over MgSO₄ and evaporated to leave a residue, which was purified by TLC (silica gel) with diethyl ether–hexane (1:1) as a developer to give 1-methylindole-3-carboxylic acid¹⁴ (149 mg, 85%). The exclusive formation of the 3-carboxylic acid was confirmed by the ¹H NMR analysis of the residue left by the evaporation of the chloroform extract.
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