Tetrahedron Letters 50 (2009) 4512–4514

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Carboxylation of indoles and pyrroles with CO_2 in the presence of dialkylaluminum halides

Koji Nemoto, Satoru Onozawa, Naoki Egusa, Naoya Morohashi, Tetsutaro Hattori *

Department of Environmental Studies, Graduate School of Environmental Studies, Tohoku University, 6-6-11 Aramaki-Aoba, Aoba-ku, Sendai 980-8579, Japan

ARTICLE INFO

Article history:
Received 11 May 2009
Accepted 21 May 2009
Available online 25 May 2009

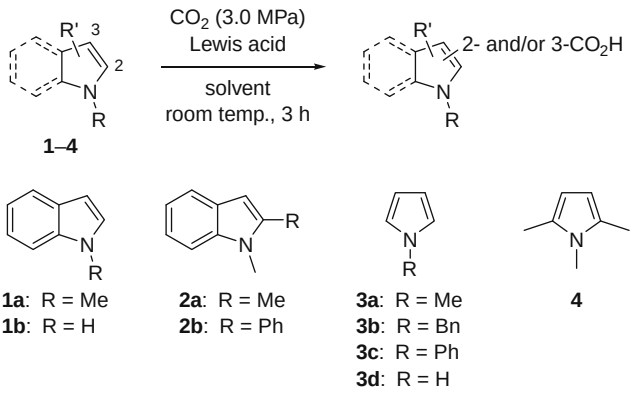
Keywords:
Carboxylation
Alumination
Indolecarboxylic acid
Pyrrolecarboxylic acid

ABSTRACT

The Lewis acid-mediated carboxylation of arenes with CO_2 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 Me_2AlCl under CO_2 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.

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 CO_2 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 CO_2 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 CO_2 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 CO_2 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.

* Corresponding author. Tel.: +81 22 795 7262; fax: +81 22 795 7293.
E-mail address: hattori@orgsynth.che.tohoku.ac.jp (T. Hattori).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.076

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_2AlCl	Benzene–hexane	62 (–:1)
8	**1a**	Me_2AlCl	Toluene–hexane	85 (–:1)
9	**1a**	Et_2AlCl	Toluene–hexane	69 (–:1)
10	**1a**	Me_3Al	Toluene–hexane	6 (–:1)
11	**1a**	Me_2AlCl	Hexane	48 (–:1)
12	**1a**	Me_2AlCl	CS_2–hexane	65 (–:1)
13	**1a**	Me_2AlCl	CH_2Cl_2–hexane	59 (–:1)
14	**1a**	Me_2AlCl	THF–hexane	0 (–:1)
15	**1b**	Me_2AlCl	Toluene–hexane	28 (–:1)
16	**1b**	Me_2AlCl[e]	Toluene–hexane	21 (–:1)
17	**2a**	Me_2AlCl	Toluene–hexane	73 (–:1)
18	**2b**	Me_2AlCl	Toluene–hexane	61 (–:1)
19	**3a**	$AlCl_3$	Benzene	2 (–:1)
20	**3a**	$MeAlCl_2$	Toluene–hexane	7 (–:1)
21	**3a**	Me_2AlCl	Toluene–hexane	25 (7:1)
22	**3a**	Me_3Al	Toluene–hexane	3 (50:1)
23	**3b**	Me_2AlCl	Toluene–hexane	80 (1:–)
24	**3c**	Me_2AlCl	Toluene–hexane	79 (1:–)
25	**3d**	Me_2AlCl	Toluene–hexane	6 (10:1)
26	**3d**	Me_2AlCl[e]	Toluene–hexane	6 (8:1)
27	**4**	Me_2AlCl	Toluene–hexane	52 (–:1)

[a] Reaction conditions: substrate (1.00 mmol), Lewis acid (1.0 mol equiv), solvent (1.0–2.2 cm^3), CO_2 (3.0 MPa), room temp., 3 h.
[b] Determined by ^1H NMR analysis.
[c] Me_3SiCl (1.0 mol equiv) was added.
[d] Ph_3SiCl (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; Me_2AlCl and Et_2AlCl exhibited better performances than stronger Lewis acids, $AlCl_3$ and $AlBr_3$, 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 Me_2AlCl 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 Me_2AlCl (entries 15–18). A similar exploration of reaction conditions for 1-methylpyrrole (**3a**) again revealed that the combination use of Me_2AlCl 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 Me_2AlCl (1.0 M solution in hexane) under nitrogen at room temperature for 3 h. After quenched with D_2O, the reaction mixture was extracted with $CDCl_3$ and the extract was dried over $MgSO_4$ 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 Me_2AlCl, 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 Me_2AlCl in toluene–hexane under nitrogen, was exposed to 3.0 MPa CO_2 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 Me_2AlCl or Et_2AlCl, while the use of a conventional Friedel–Crafts catalyst, $AlCl_3$, 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 Me_2AlCl, after quenching the mixture with D_2O, afforded 3-deuterio-1-pentylindole.[17] Therefore, the present observation is not the first example of the alumination of 1-substituted indoles with dialkylaluminum chlorides. However, it is important to have shown the possibility that **1a** is metallated under CO_2 atmosphere and in situ carbonated to give a carboxylic acid. One may suspect that Me_2AlCl is carbonated with CO_2 under the reaction conditions. However, the treatment of Me_2AlCl with 3.0 MPa CO_2 in hexane at room temperature for 3 h gave, after acidic workup, no acetic acid. In addition, by using the CO_2-pretreated Me_2AlCl, **1a** could be carboxylated in 61% yield under the conditions employed in entry 8 (Table 1). Therefore, the carbonation of Me_2AlCl 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 $AlCl_3$ is used as a Lewis acid, the acylation proceeds via a pyrrolylaluminum intermediate, while the reaction using weaker Lewis acids, such as $EtAlCl_2$ and Et_2AlCl, 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 CO_2 to the extent that the Lewis acid-CO_2 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] alumination,[22] cupration,[23] and cadmation[24] 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 Me_2AlCl metalated 1-methylindole (**1a**) at the 3-position (vide supra), while an ate base, i-Bu_3Al(TMP)Li, metalates 1-(Boc)indole at the 2-position.[22] Iwao and coworkers 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 CO_2 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.

Acknowledgments

This study was supported in part by a Grant-in-Aid for Scientific Research on a Priority Area 'Advanced Molecular Transformations of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. Boriskin, Y. S.; Leneva, I. A.; Pécheur, E.-I.; Polyak, S. J. *Curr. Med. Chem.* **2008**, *15*, 997.
2. Yang, Z.; Ney, A.; Cromer, B. A.; Ng, H.-L.; Parker, M. W.; Lynch, J. W. *J. Neurochem.* **2007**, *100*, 758.
3. (a) Rogers, E. F.; Koniuszy, F. R.; Shavel, J., Jr.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3086; (b) Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett.* **2009**, *50*, 1035.
4. Fisher, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241.
5. Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 3532.
6. Hantzsch, A. *Ber.* **1890**, *23*, 1474.
7. Knorr, L. *Ber.* **1884**, *17*, 1635.
8. Park, C. M.; Kim, S. Y.; Park, W. K.; Park, N. S.; Seong, C. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3844.
9. (a) Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975, and references cited therein; (b) Fogassy, K.; Kovács, K.; Keserű, G. M.; Tőke, L.; Faigl, F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1039, and references cited therein.
10. Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1.
11. (a) Friedel, C.; Crafts, J. M. *Compt. Rend.* **1878**, *86*, 1368; (b) Olah, G. A.; Török, B.; Joschek, J. P.; Bucsi, I.; Esteves, P. M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2002**, *124*, 11379, and references cited therein; (c) Munshi, P.; Beckman, E. J. *Ind. Eng. Chem. Res.* **2009**, *48*, 1059.
12. (a) Suzuki, Y.; Hattori, T.; Okuzawa, T.; Miyano, S. *Chem. Lett.* **2002**, 102; (b) Hattori, T.; Suzuki, Y.; Miyano, S. *Chem. Lett.* **2003**, *32*, 454; (c) Nemoto, K.; Yoshida, H.; Suzuki, Y.; Morohashi, N.; Hattori, T. *Chem. Lett.* **2006**, *35*, 820.
13. *Typical procedure for the carboxylation* (Table 1, entry 8): In a 50 cm^3 autoclave equipped with a glass inner tube and a magnetic stirring bar were charged compound **1a** (131 mg, 1.00 mmol), toluene (1.0 cm^3), and Me_2AlCl (1.0 M solution in hexane; 1.0 cm^3) under nitrogen and the apparatus was purged with CO_2 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 Na_2CO_3 and the extract was acidified with conc. HCl to liberate the free acid, which was extracted with chloroform. The extract was dried over $MgSO_4$ 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 acid[14] (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.
14. Baiocchi, L.; Giannangeli, M. *J. Heterocycl. Chem.* **1988**, *25*, 1905.
15. Konishi, K.; Aida, T.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 816.
16. Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485.
17. Huffman, J. W.; Szklennik, P. V.; Almond, A.; Bushell, K.; Selley, D. E.; He, H.; Cassidy, M. P.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4110.
18. Huffman, J. W.; Smith, V. J.; Padgett, L. W. *Tetrahedron* **2008**, *64*, 2104.
19. (a) Mingoia, Q. *Gazz. Chim. Ital.* **1930**, *60*, 509; (b) Boev, V. I.; Denisov, S. P.; Moskalenko, A. I.; Stamova, L. G.; Gulin, A. V. *Russ. J. Gen. Chem.* **2000**, *70*, 1812.
20. Conway, B.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E. *Chem. Commun.* **2007**, 2864.
21. (a) Seggio, A.; Lannou, M.-I.; Chevallier, F.; Nobuto, D.; Uchiyama, M.; Golhen, S.; Roisnel, T.; Mongin, F. *Chem. Eur. J.* **2007**, *13*, 9982; (b) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685.
22. Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921.
23. Usui, S.; Hashimoto, Y.; Morey, J. M.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102.
24. L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Commun.* **2008**, 5375.