ORGANIC
LETTERS

2010
Vol. 12, No. 11
2653−2655

NHC Catalyzed Transformation of Aromatic Aldehydes to Acids by Carbon Dioxide: An Unexpected Reaction[†]

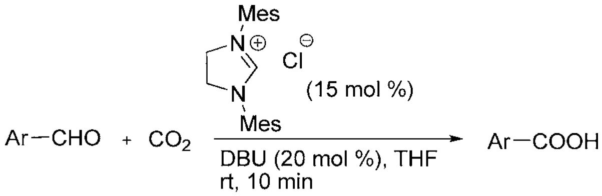
Vijay Nair,* Vimal Varghese, Rony Rajan Paul, Anu Jose, C. R. Sinu, and Rajeev S. Menon

Organic Chemistry Section, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum 695 019, India

vijaynair_2001@yahoo.com

Received April 19, 2010

ABSTRACT



A facile NHC-mediated reaction of aromatic aldehydes with carbon dioxide leading to carboxylic acids is described. The present protocol is mechanistically important, and it can serve as a tool for the sequestration of carbon dioxide.

In nature, decarboxylation of pyruvic acid to an acetal anion equivalent[1] is initiated by the coenzyme thiamine pyrophosphate (TPP), the modus operandi as elucidated by Breslow[2] involves the deprotonation of the thiazolium ring of TPP and addition of the resulting ylide to pyruvate to form a tetrahedral intermediate. The latter, by virtue of the thiazolium moiety serving as an "electron sink", undergoes isomerization to an enaminol. In his seminal work, Breslow has shown that a variety of azolium species afford the ylides which react with aldehydes to form the corresponding enaminols (Breslow intermediate), and the latter participate in benzoin condensation in a manner akin to the acetoin synthesis in nature. In recent years, the chemistry of azolium ylides, popularly known as nucleophilic heterocyclic carbenes (NHC),[3] has received considerable attention as ligands for transition metals,[4] building blocks in heterocyclic construction,[5] and catalysts in a number of synthetic transformations[6] especially in the area of homoenolate reactions.[7,8] During the course of our work involving NHCs, we were intrigued by the possibility of trapping the Breslow intermediate with CO_2 to afford aryl glyoxylic acids (Scheme 1). Notwithstanding the unfavorable thermodynamic factors, this seemingly simple idea was considered worthy of pursuit because of the known facile transformation of the latter to mandelic acids[9] and arylglycine derivatives which are building blocks for pharmaceuticals and other valuable materials.[10]

[†] Dedicated with best wishes to Professor Gilbert Stork.

(1) For a concise description of this process, see: Dugas, H. *Bioorganic Chemistry*; 2nd ed.; Springer-Verlag: New York, 1989; pp 563−570.

(2) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(3) For recent reviews of NHC chemistry, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Marion, N.; Diez Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (d) Nair, V.; Bindu, S.; Vellalath, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.

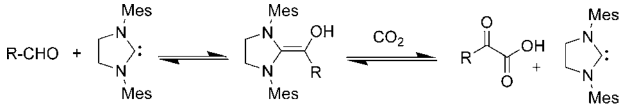
(4) (a) Wanzlick, H.-W. *Angew. Chem., Int. Ed.* **1962**, *1*, 75. (b) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648. (c) Hermann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (d) Hermann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162.

(5) (a) Enders, D.; Breuer, K.; Raabe, J.; Runsik, J.; Teles, J. H. *Liebigs Ann.* **1996**, 2019. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665. (c) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297. (d) Ma, C.; Yang, Y. *Org. Lett.* **2005**, *7*, 1343. (e) Ma, C.; Ding, H.; Zhang, Y.; Bian, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7793.

(6) (a) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639. (b) Suzuki, Y.; Toyota, T.; Imada, F.; Sato, M.; Miyashita, A. *Chem. Commun.* **2003**, 1314. (c) Liu, Q.; Rovis, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (d) Duong, H. A.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785. (e) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (f) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

10.1021/ol1008697

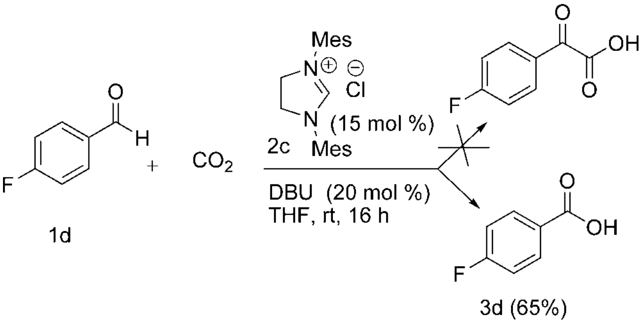
Scheme 1. Concept of Glyoxylic Acid Synthesis



Conceivably, the carboxylation envisioned above would provide a simple route for the synthesis of value-added products and in turn open up a potentially useful approach to the sequestration of CO_2,[11,12] culpable for the green house effect and global warming. In this context, it is noteworthy that the reaction of NHCs and imidazoles with CO_2 resulting in the carboxylates is known in the literature,[13] and the latter have been proposed as carriers of NHCs as well as CO_2. NHC-catalyzed reaction of CO_2 with propargylic alcohols and epoxides leading to carbonates is also known.[14] Recently, Zhang and coworkers have reported the NHC-catalyzed reduction CO_2 to methanol.[15] Subsequently, while this work was under completion, the same group reported the NHC-catalyzed reaction of CO_2 with aldehydes leading to carboxylic acids.[16]

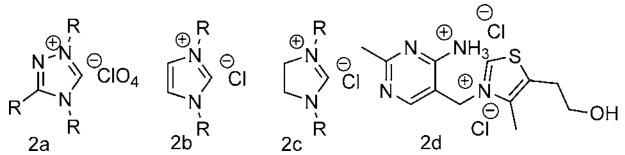
In a prototype experiment designed to test the validity of the concept outlined above (Scheme 1), *p*-fluorobenzaldehyde (1 equiv) and 1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium (SIMes) chloride (0.15 equiv) were taken in THF. After the addition of DBU (0.2 equiv), the solution was stirred in a CO_2 atmosphere (balloon). After 16 h, the reaction mixture was quenched with hydrochloric acid (1 N, 5 mL) and extracted with DCM. The organic layer on usual processing and chromatography afforded a colorless crystalline solid that to our surprise was found to be *p*-fluorobenzoic acid (mp 182−184 °C). Interestingly, not even a trace of *p*-fluorophenylglyoxylic acid was obtained from the reaction mixture (Scheme 2). Although the conceptualization of a novel synthesis of phenyl glyoxylic acid did not materialize, the preparative value of this transformation proceeding under mild conditions and its mechanistic importance prompted us to pursue the reaction in some detail.

Scheme 2



Subsequent to the preliminary experiments, it was found that the reaction worked more efficiently when a slow stream of CO_2 was passed through the solution of the aldehyde and the catalyst for 10 min; the product was obtained in 72% yield. A number of commonly used NHC catalysts were screened for assessing their utility in optimizing this reaction, and the results are summarized in Table 1.

Table 1. Catalyst Screening



2a 2b 2c 2d

entry	catalyst	condition	yield[a] (%)
1	**2a**	THF, rt, 10 min	0
2	**2b**	THF, rt, 10 min	61
3	**2c**	THF, rt, 10 min	72
4	**2d**	THF, rt, 10 min	5

[a] Isolated yield. **2a**: R = phenyl. **2b**: R = 2,4,6-trimethylphenyl. **2c**: R = 2,4,6-trimethylphenyl.

The reaction was extended to a number of aldehydes, and the products were characterized by conventional spectroscopic methods and by comparison to the data available in the literature.[17,18] The results are presented in Table 2. From our studies, it was found that in general best results were obtained when THF was used as the solvent, the exception being benzaldehyde and 3,4-dimethoxybenzaldehyde which gave better results in acetonitrile.

---

(7) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (c) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (d) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (e) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (f) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (g) Philips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *130*, 2416. (h) Nair, V.; Sreekumar, V.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (i) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem.* **2006**, *71*, 8964.

(8) For a recent review, see: Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

(9) (a) Harada, K.; Munegumi, T. In *Comprehensive Organic Synthesis*; Fleming, I., Ed.; Pergamon Press: New York, 1991; Vol. 8, pp 144−145. (b) Arterburn, J. B.; Pannala, M.; Gonzalaz, A. M.; Chamberlin, R. M. *Tetrahedron Lett.* **2000**, *41*, 7847. (c) Kamochi, Y.; Kudo, T.; Masuda, T.; Takadate, A. *Chem. Pharm. Bull.* **2005**, *53*, 1017. (d) Wang, Z.; La, B.; Fortunak, J. M.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1998**, *39*, 5501.

(10) (a) Taylor, M. B. *Cosmet. Dermatol.* **1999**, 26. (b) Green, B. A.; Yu, R. J.; Van Scott, E. J. *Clin. Dermatol.* **2009**, *27*, 495.

(11) For a recent review on biocatalytic carboxylation, see: Glueck, S. M.; Guemues, S.; Fabian, W. M. F.; Faber, K. *Chem. Soc. Rev.* **2010**, *39*, 313.

(12) (a) Kayaki, Y.; Yamamoto, M.; Ikariya, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4194. (b) Koinuma, H. *React. Funct. Polym.* **2007**, *67*, 1129. (c) Correa, A.; Martin, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201.

(13) (a) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 12834. (b) Holbery, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem. Commun.* **2003**, 28. (c) Tommasi, I.; Sorrentino, F. *Tetrahedron Lett.* **2005**, *46*, 2141.

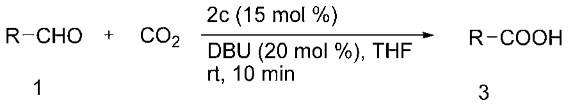
(14) Zhou, H.; Zhang, W. Z.; Liu, C. H.; Qu, J. P.; Lu, X. B. *J. Org. Chem.* **2008**, *73*, 8039.

(15) Riduan, S. N.; Zhang, Y.; Ying, J. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3322.

(16) Gu, L.; Zhang, Y. *J. Am. Chem. Soc.* **2010**, *132*, 914.

(17) All of the compounds reported here in are known in the literature; most of them are commercially available.

Table 2. Substrate Scope



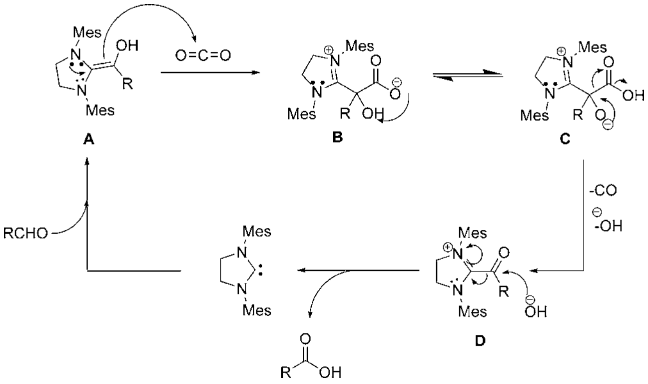
$$\underset{1}{R{-}CHO} + CO_2 \xrightarrow[\text{DBU (20 mol \%), THF, rt, 10 min}]{\text{2c (15 mol \%)}} \underset{3}{R{-}COOH}$$

entry	R-	product	yield[a,b] (%)
1	3,4-dichlorophenyl	**3a**	92 (95)
2	4-trifluoromethylphenyl	**3b**	90 (94)
3	phenyl	**3c**	86[c] (88)
4	4-fluorophenyl	**3d**	72 (84)
5	4-nitrophenyl	**3e**	76 (85)
6	2-thienyl	**3f**	72 (78)
7	4-bromophenyl	**3g**	71 (79)
8	4-chlorophenyl	**3h**	70 (85)
9	2-furyl	**3i**	65 (72)
10	4-methylphenyl	**3j**	62 (71)
11	3,4-dimethoxyphenyl	**3k**	60[c] (69)
12	2-bromophenyl	**3l**	56 (70)
13	4-methoxyphenyl	**3m**	36 (57)

[a] Isolated yield. [b] Yield based on recovered aldehyde. [c] CH_3CN (80 °C, 30 min).

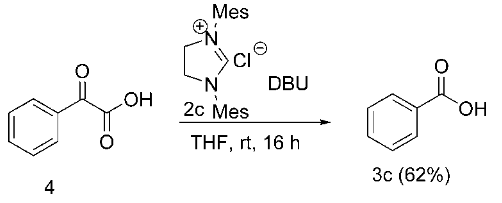
In the absence of any oxidant or source of oxygen in the reaction mixture, it was surmised that carbon dioxide is undergoing reduction to CO and in the process the aldehyde is getting oxidized to acid. Mechanistically, the reaction may be viewed as occurring via the addition of carbon dioxide to the readily formed Breslow intermediate A to afford the hydroxycarboxylate B and the tautomer C. Conceivably, the latter can lose CO and hydroxide (cf. decomposition of formate) to afford the benzoic acid (Scheme 3). Support for this hypothesis was obtained by the detection of CO in the reaction mixture.[19]

Scheme 3. Proposed Mechanistic Pathway



It may be mentioned that species D is generally invoked as an intermediate in the oxidative esterification of aldehydes. Gratifyingly, indirect evidence for the mechanistic postulate outlined above was accrued by the formation of benzoic acid when phenylglyoxylic acid was exposed to NHC under the same experimental conditions in which benzaldehyde was transformed to benzoic acid (Scheme 4).

Scheme 4



It is noteworthy that Gu and Zhang also have identified CO in the effluent gases, and a mechanistic scheme for the reduction of CO_2 has been presented.[16] However, it is unlikely that their postulate is correct, since a preformed NHC-carboxylate depicted as intermediate in their work failed to react with aldehyde to afford the acid.

In conclusion, we have encountered a facile NHC-mediated reaction of carbon dioxide and aldehyde leading to carboxylic acid under simple, mild, experimental conditions. In addition to the preparative utility of the present protocol, its potential value in the sequestration of CO_2 cannot be underestimated, especially in the current era of global warming.

Acknowledgment. V.N. thanks the Department of Science and Technology (DST), New Delhi, for the Raja Ramanna Fellowship. We also thank CSIR, New Delhi, for financial assistance.

Supporting Information Available: Experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1008697

---

(18) (a) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (b) Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2007**, *72*, 7030. (c) Dodd, R. H.; Le Hyaric, M. *Synthesis* **1993**, 295. (d) Mortier, J.; Moyroud, J. *J. Org. Chem.* **1994**, *59*, 4042.

(19) CO in the reaction mixture was detected by reduction of $PdCl_2$ in solution to palladium metal (see the Supporting Information).