ACS Catalysis

Letter

pubs.acs.org/acscatalysis

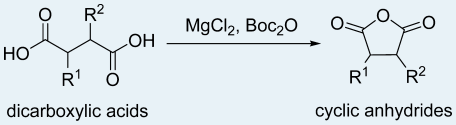
Facile and Efficient Synthesis of Cyclic Anhydrides from Dicarboxylic Acids

Carine Robert,[†] Frédéric de Montigny,[†] and Christophe M. Thomas*[,†]

[†]PSL Research University, CNRS - Chimie ParisTech, Institut de Recherche de Chimie Paris, 75005 Paris, France

Supporting Information

ABSTRACT: An efficient, high-yielding sustainable route to cyclic anhydrides from biorenewable and inexpensive dicarboxylic acids has been developed. Cyclic anhydrides were synthesized from dicarboxylic acids using a catalyst prepared in situ from $MgCl_2$ and dialkyl dicarbonates. This robust and cheap system operates under mild conditions to give cyclic anhydrides with high yield and selectivity.



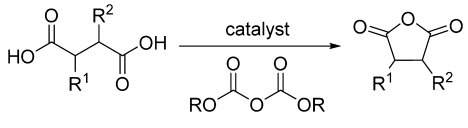
KEYWORDS: *dicarboxylic acid, cyclic anhydride, catalysis, magnesium, cyclization*

The vast majority of commodity chemicals are obtained from fossil fuels.[1] Because these resources are predicted to be exhausted within the next century at the current rate of consumption,[2−4] there is a growing effort to develop new chemical processes using biorenewable resources.[5,6] Biomass represents an abundant carbon-neutral renewable resource for the production of bioenergy and bulk chemicals, and its enhanced use would address several societal needs.[7−14] Therefore, a major step for the development of a sustainable, industrial society will be the shift from our dependence on petroleum to the use of renewable resources. Advances in genetics, biotechnology, process chemistry, and engineering are leading to a new manufacturing concept for converting renewable biomass to valuable fuels and products, generally referred to as the biorefinery. The implementation of such advanced biorefinery concepts requires the development of novel and versatile catalytic processes for the selective transformation of biomass-derived feedstocks to a broad range of valuable chemicals and materials. Molecular building blocks from renewable feedstocks are attractive as they are already highly functionalized: several steps are avoided for the synthesis of the final product and they are biodegradable, a point which has a real and strong ecological impact.[15]

Carboxylic acids are key building blocks as biobased alternatives for fossil-fuel-based applications: 8 out of 12 platform chemicals identified as top value-added chemical targets to produce from biomass are organic acids.[16] These derivatives are used in the production of polymers, pharmaceuticals, solvents, and food additives, projecting an important market volume of carboxylic acids.[16,17] Among them, dicarboxylic acids have been suggested as important renewable platform chemicals because they are available in a minimum number of steps from biorefinery carbohydrate streams.[18] Despite the established relevance of cyclic anhydrides in synthetic chemistry, development of new methods for their synthesis from dicarboxylic acids, whether catalytic and/or chemoselective, remains a considerable synthetic challenge.[19] Indeed their syntheses have been limited to a few methods, and these processes often rely on toxic reagents and/or drastic conditions, thus limiting their industrial applications. Among these methods, carboxylic anhydrides are generally prepared by dehydration of carboxylic acids with acylating or dehydrating agent such as acid chloride, phosgene, thionyl chloride, benzenesulfonyl chloride, ketene, or phosphorus pentoxide. Also, these methods are not always so effective for the acid-sensitive and/or unreactive carboxylic acids. Accordingly, there is a need for a process for the synthesis of cyclic anhydrides, which is fast and which produces cyclic anhydrides in high yield.

Recently several research groups reported efficient protocols for the preparation of esters from the reaction of carboxylic acids with alcohols in the presence of dialkyl dicarbonates under weak Lewis acid catalysis.[20] The mechanism involved a double addition of the acid to the dicarbonate, affording a carboxylic anhydride and an alcohol. The final esters arose from the attack of the alcohols on the anhydrides. Inspired by these previous findings, we envisaged that Lewis acid catalysts might provide the basis for an efficient catalytic system that opens direct access to cyclic anhydrides with high selectivity and flexibility starting from dicarboxylic acids. Herein, we report the cyclization of dicarboxylic acids using a simple and robust catalyst system, which is prepared in situ from magnesium dichloride ($MgCl_2$), and di-*tert*-butyl dicarbonate (Boc_2O) (Scheme 1). This convenient route employs readily available reagents that afford cyclic anhydrides in good yields with high

Scheme 1. Synthesis of Cyclic Anhydrides from Dicarboxylic Acids



Received: August 21, 2014
Revised: September 7, 2014
Published: September 9, 2014

selectivity, without the need for time-consuming and expensive processes that are usually required.

We focused our initial efforts on succinic acid as a model substrate, which is a widely investigated chemical building block available from biochemical transformation of biorefinery sugars.[18] The performances of different catalytic systems were evaluated in THF in the presence of commercially available dialkyl dicarbonates (Scheme 1). Representative results are summarized in Figure 1. We first investigated the reaction of 50

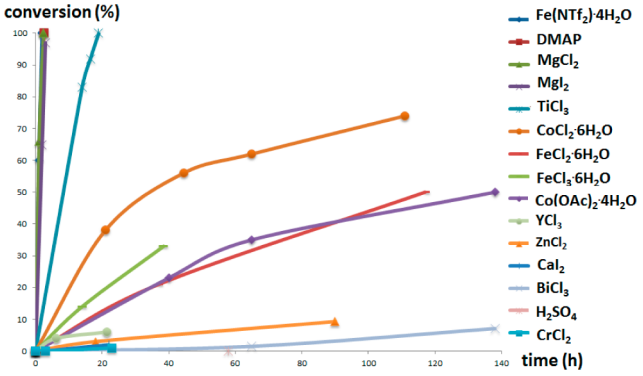


Figure 1. Cyclization reactions with different catalysts (Conditions: Complex (1 equiv), succinic acid (50 equiv), Boc_2O (50 equiv) are charged in THF and stirred at 40 °C. Conversion obtained by ^1H NMR spectroscopy).

equiv of succinic acid with 50 equiv of Boc_2O in the presence of a Brønsted acid at 40 °C. It is worth noting here that cyclization was unsuccessful in the presence of sulfuric acid. By contrast, Lewis acid derivatives showed catalytic activity in the cyclization of succinic acid. Among them, magnesium chloride, magnesium iodide and iron triflimidate ($Fe(NTf_2)_2·6H_2O$) were the most efficient Lewis acids. Both $FeCl_3·6H_2O$ and $FeCl_2·6H_2O$ complexes proved to be active under mild conditions. However, using these derivatives, complete conversions were not observed and traces of *tert*-butyl ester were formed. Under the same reaction conditions, a nucleophilic catalyst, such as DMAP, was as effective as $MgCl_2$.

Having demonstrated the potential of cheap and nontoxic $MgCl_2$ complex in the cyclization of succinic acid, we envisioned to optimize this system by varying the reaction conditions (i.e., temperature and catalyst loading) for the cyclization of succinic acid (Table 1). As a control experiment, the reaction was performed using a complex in the absence of

Table 1. Cyclization of Succinic Acid with $MgCl_2$[a]

entry	catalyst	[acid] /[cat.]	T (°C)	t (h)	yield[b] (%)
1	$MgCl_2$	50	40	1.5	100
2	$MgCl_2·6H_2O$	50	40	5	100
3[c]	$MgCl_2$	50	40	0.5	80[d]
4	$MgCl_2$	100	40	22	100
5	$MgCl_2$	100	40	1.5	45
6	$MgCl_2$	100	20	1.5	5
7	$MgCl_2$	100	60	1.5	95
8	$MgCl_2$	500	40	12	100
9	$MgCl_2$	1000	40	24	97

[a]All reactions performed in THF at 40 °C with [dicarbonate] = [succinic acid]. [b]As determined by the integration of ^1H NMR. [c]Reaction carried out with Moc_2O. [d]20% of ester.

dicarbonate or using a dicarbonate without a complex, and no reaction product could be isolated after an even longer period of time. As previously described, we first used anhydrous $MgCl_2$, and a quantitative conversion of succinic anhydride was obtained in 1.5 h (entry 1). As a comparison, at 40 °C, the conversion was 100% in 5 h using $MgCl_2·6H_2O$ (entry 2). We then sought to determine whether the use of other dialkyldicarbonates could improve the activity of our system. Dimethyldicarbonate (Moc_2O) was previously reported for the synthesis of methyl esters, but it has not been used for the formation of anhydrides. Under the conditions described with Boc_2O, the conversion of succinic acid with Moc_2O was much faster but simultaneous formation of succinic anhydride and monomethyl ester was detected (entry 3). We observed that the activity decreases by lowering the catalyst loading or the reaction temperature (entries 4−6). However, the reaction can also be performed at higher temperatures within shorter reaction times without a loss of selectivity (entry 7). Finally, magnesium chloride exhibited interesting productivity and efficiency, in the presence of 500 or 1000 equiv of succinic acid (entries 8 and 9). Interestingly, purification of the products is particularly easy because most byproducts are volatile. Therefore, final cyclic anhydrides are quantitatively separated from $MgCl_2$ by sublimation.

Based on previous observations,[19−21] the plausible mechanism for the formation of carboxylic anhydrides involves the initial activation of the dicarbonate by the Lewis acid. Electrophilic activation of carbonyl groups with Lewis acids is a well-established method for enhancing their reactivity and selectivity toward nucleophilic addition.[22] Then, the activated dicarbonate reacts with the dicarboxylic acid to afford a mixed anhydride−carbonate intermediate. The byproducts are one equivalent of carbon dioxide and one equivalent of the alcohol corresponding to the selected dicarbonate. This mixed anhydride reacts rapidly to give the cyclic anhydride. Finally, if the alcohol is nucleophilic enough, ester formation might occur from attack of alcohol to the anhydride. Therefore, in order to avoid alcoholysis of the anhydride, the reaction has to be stopped before the formation of ester from the corresponding anhydride or Boc_2O (instead of Moc_2O) has to be used, owing to the much lower nucleophility of *tert*-butanol. As to determine if the final ester arose from the attack of the alcohol on the anhydride, the succinic anhydride was reacted in the presence of an equimolar amount of *tert*-butanol and $MgCl_2$ for 28 h at 40 °C. This reaction did not undergo nucleophilic attack of the alcohol in THF or in *tert*-butanol. By contrast, in the presence of methanol and after 14 h, ester formation was detected due to the increased nucleophilicity of methanol.

We then sought to test the generality of the presented methodology (Table 2). Under the same reaction conditions, a range of cyclic anhydrides was accessed in quantitative yield starting from dicarboxylic acids (Figure 2). In addition, all isolated yields were greater than 90% after sublimation. For instance, we were able to synthesize adipic, pimelic, methylsuccinic, itaconic, diphenic, camphoric, and phenylsuccinic anhydrides (entries 3−9). Also, we observed that 6-membered rings such as glutaric anhydride are less favored in the presence of anhydrous $MgCl_2$ (entry 2). Satisfyingly, the presence of double bonds did not appear to affect the efficiency of the system, as maleic and phtalic acids afforded the corresponding cyclic anhydrides in high yields (entries 10 and 11). By contrast, the reaction does not tolerate functional

dx.doi.org/10.1021/cs501237p | ACS Catal. 2014, 4, 3586−3589

Table 2. Cyclization of Various Dicarboxylic Acids with $MgCl_2$[a]

entry	acids	[acid] (mol L^{-1})	[acid] /[cat.]	t (h)	yield[b] (%)
1	succinic	1	50	1.5	100
2	glutaric	0.75	50	9	100
3	adipic	1	50	1	100
4	pimelic	1	50	1	100
5	methylsuccinic	1	50	1.5	100
6	itaconic	1	50	2.5	100
7	diphenic	1.5	50	3	100
8	camphoric	1	50	3	100
9	phenylsuccinic	1	50	2.5	100
10	maleic	1	100	12	100
11	phtalic	1	50	6.5	100

[a]All reactions performed in THF at 40 °C with [Boc_2O] = [acid]. [b]As determined by the integration of ^1H NMR.

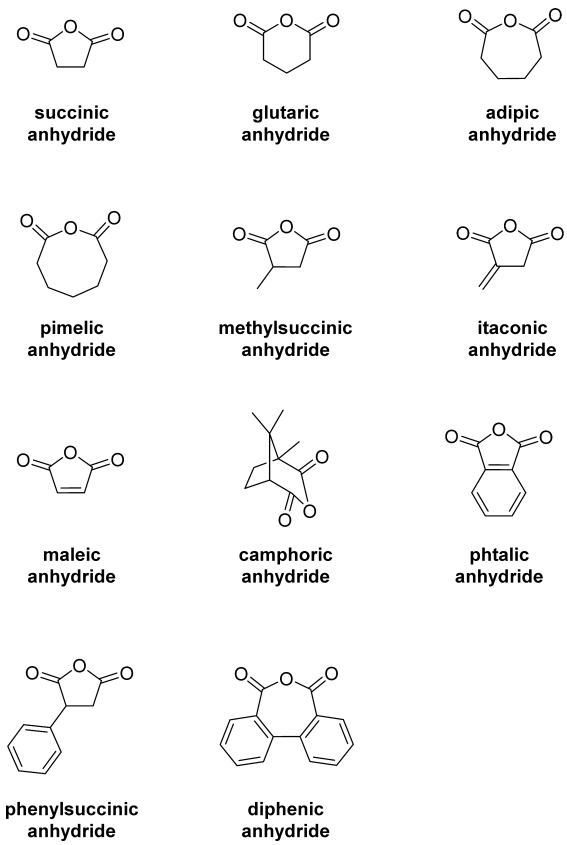


Figure 2. Cyclic anhydrides synthesized.

groups, such as ether, acid and alcohol, as functionalized anhydrides (or any side products) such as malic, diglycolic, and tartaric anhydrides could not be synthesized by this method.

Finally, we were interested to perform the reaction in greener solvents such as dimethyl carbonate (DMC), cyclopentylmethyl ether[23] (CPME), and methyltetrahydrofuran[24] (MeTHF). Dicarboxylic acids are only sparingly soluble in DMC and CPME, and no reaction occurs in this solvent within 24 h. MeTHF is more convenient, and cyclization proceeds efficiently, albeit slightly slower than in THF because dicarboxylic acids are generally less soluble in MeTHF. However, a similar or better activity has been observed in MeTHF for succinic, diphenic, camphoric, methylsuccinic, and glutaric acids.

In summary, cyclic anhydrides were prepared from dicarboxylic acids using a catalyst prepared in situ from $MgCl_2$ and dialkyl dicarbonates. This robust system operates under mild conditions to give cyclic anhydrides with high yield and selectivity. This method, using commercially available and cheap $MgCl_2$, is rapid and convenient.[25] The release of volatile byproducts renders the reaction very attractive for synthetic chemistry. We are hopeful that the ready access to these important building blocks through a convenient and easy experimental protocol will be useful for the chemical community. Efforts to elucidate the structure of the catalyst and obtain more mechanistic informations are underway.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all new compounds are included in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: christophe.thomas@chimie-paristech.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

ENSCP, CNRS, and Région Île-de-France are thanked for financial support. C.M.T. is grateful to the Institut Universitaire de France.

■ REFERENCES

(1) Okada, M. *Prog. Polym. Sci.* **2002**, *27*, 87−133.
(2) Rass-Hansen, J.; Falsig, H.; Jorgensen, B.; Christensen, C. H. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 329−333.
(3) Weisz, P. B. *Phys. Today* **2004**, *57*, 47−52.
(4) Williams, C. K.; Hillmyer, M. A. *Polym. Rev.* **2008**, *48*, 1−10.
(5) Zaldivar, J.; Nielsen, J.; Olsson, L. *Appl. Microbiol. Biotechnol.* **2001**, *56*, 17−34.
(6) (a) Gerngross, T. U.; Slater, S. C. *Sci. Am.* **2000**, *283*, 36−41. (b) Gross, R. A.; Kalra, B. *Science* **2002**, *297*, 803−807. (c) Danner, H.; Braun, R. *Chem. Soc. Rev.* **1999**, *28*, 395−405.
(7) (a) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; pp 11−30. (b) Vennestrøm, P. N. R.; Osmundsen, C. M.; Christensen, C. H.; Taarning, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10502−10509. (c) Azadi, P.; Carrasquillo-Flores, R.; Pagán-Torres, Y. J.; Gürbüz, E. I.; Farnood, R.; Dumesic, J. A. *Green Chem.* **2012**, *14*, 1573−1576. (d) Gallezot, P. *Chem. Soc. Rev.* **2012**, *41*, 1538−1558. (e) Deuss, P. J.; Barta, K.; de Vries, J. G. *Catal. Sci. Technol.* **2014**, *4*, 1174−1196. (f) Perego, C.; Riccia, M. *Catal. Sci. Technol.* **2012**, *2*, 1776−1786.
(8) Poliakoff, M.; Licence, P. *Nature* **2007**, *450*, 810−812.
(9) Ragauskas, A. J.; Williams, C. K.; Davison, B. H.; Britovsek, G.; Cairney, J.; Eckert, C. A.; Frederick, W. J., Jr.; Hallett, J. P.; Leak, D. J.; Liotta, C. L.; Mielenz, J. R.; Murphy, R.; Templer, R.; Tschaplinski, T. *Science* **2006**, *311*, 484−489.
(10) Güner, F. S.; Yagci, Y.; Erciyes, A. T. *Prog. Polym. Sci.* **2006**, *31*, 633−670.
(11) Jenck, J. F.; Agterberg, F.; Droescher, M. J. *Green Chem.* **2004**, *6*, 544−556.
(12) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411−2502.

(13) Biermann, U.; Friedt, W.; Lang, S.; Lühs, W.; Machmüller, G.; Metzger, J. O.; Rüsch Gen Klaas, M.; Schäfer, H. J.; Schneider, M. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2206−2224.
(14) Lucia, L. A.; Argyropoulos, D. S.; Adamopoulos, L.; Gaspar, A. R. *Can. J. Chem.* **2006**, *84*, 960−970.
(15) Selected reviews: (a) Tschan, M. J. L.; Brule, E.; Haquette, P.; Thomas, C. M. *Polym. Chem.* **2012**, *3*, 836−851. (b) Coates, G. W.; Hillmyer, M. A. *Macromolecules* **2009**, *42*, 7987−7989. (c) Gandini, A. *Macromolecules* **2008**, *41*, 9491−9504. (d) Meier, M. A. R.; Metzger, J. O.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1788−1802.
(16) Huber, G. W.; Iborra, S.; Corma, A. *Chem. Rev.* **2006**, *106*, 4044−4098.
(17) Sauer, M.; Porro, D.; Mattanovich, D.; Branduardi, P. *Trends Biotechnol.* **2008**, *26*, 100−108.
(18) Their overall production cost still remains to be reduced in order to be competitive with petrochemical-derived chemicals: Bechthold, I.; Bretz, K.; Kabasci, S.; Kopitzky, R.; Springer, A. *Chem. Eng. Technol.* **2008**, *31*, 647−654.
(19) Robert, C.; de Montigny, F.; Thomas, C. M. *Nat. Commun.* **2011**, DOI: 10.1038 / ncomms1596.
(20) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Mercantoni, E.; Melchiorre, P.; Sembri, L. *Synthesis* **2007**, *22*, 3489−3496.
(21) Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, *10*, 1063−1066.
(22) (a) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798−13799. (b) Coulembier, O.; Sanders, D. P.; Nelson, A.; Hollenbeck, A. N.; Horn, A. W.; Rice, J. E.; Fujiwara, M.; Dubois, P.; Hedrick, J. L. *Angew. Chem.* **2009**, *121*, 5272−5275.
(23) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process. Res. Dev.* **2007**, *11*, 251−258.
(24) Aycock, D. *Org. Process. Res. Dev.* **2007**, *11*, 156−159.
(25) (a) Mestres, R.; Palomo, C. *Synthesis* **1981**, 218−220. (b) Balasubramaniya, V.; Bhatia, V. G.; Wagh, S. B. *Tetrahedron* **1983**, *39*, 1475−1485.