Tetrahedron Letters 53 (2012) 1630-1633

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

p-Sulfonic acid calix[*n*]arenes as homogeneous and recyclable organocatalysts for esterification reactions

Sergio Antonio Fernandes *, Ricardo Natalino, Poliana Aparecida Rodrigues Gazolla, Márcio José da Silva, Gulab Newandram Jham

Grupo de Química Supramolecular e Biomimética (GQSB), Departamento de Química, CCE, Universidade Federal de Viçosa, Viçosa, MG, Brazil

ARTICLE INFO

Article history: Received 25 November 2011 Revised 18 January 2012 Accepted 19 January 2012 Available online 28 January 2012

Keywords: Esterification reaction p-Sulfonic acid calix[n]arene Organocatalyst Catalyst recovery

Introduction

After a decade of intensive research, organocatalysis have been established as a powerful method for chemical transformations, filling the gap between enzyme and metal-based catalysis.

This explosive growth can be ascribed to the fundamental advantages, such as, stability in water and air, non-toxic nature, and the ready accessibility of starting material from natural or synthetic sources. However, major drawbacks include high catalyst loadings and difficulties in catalyst separation and recycling.¹

Esterification is one of the most fundamental and important reactions in organic synthesis.² Esters are key intermediates in the synthesis of polymers, perfumes, and pharmaceutical intermediates, biodiesel or final products.³ The acid-catalyzed reaction under reflux is the most common procedure adopted for esterification.^{2a} Although several methods have been reported, the search for new environmentally friendly, atom-efficient methods, which avoid the use of large amounts of condensing reagents and activators has attracted increasing interest.⁴ Despite the fact that a wide variety of catalysts have been used in the esterification reactions, only a few organic catalysts have been described.⁵

Calix[n]arenes macrocycles are formed by the condensation of *para*-substituted phenols with formaldehyde in basic medium and have been widely used as ligands in organometallic catalysis.⁶ On the other hand, examples of the use of calix[n]arenes as organocatalysts are even less explored.⁷ For instance, few *p*-sulfonic acid

ABSTRACT

Esterification yields were significantly improved using calix[*n*]arenes catalysts under simple conditions. *p*-Sulfonic acid calix[4]arene and *p*-sulfonic acid calix[6]arene were powerful organocatalysts in several esterification reactions, which showed activity comparable or even superior to other well-established acids catalysts, such as, sulfuric acid, *p*-toluenesulfonic acid, and *p*-hydroxybezenesulfonic acid described in the literature.

© 2012 Elsevier Ltd. All rights reserved.

calix[*n*]arenes have been used as catalysts in organic reactions. Liu et al. described the catalytic use of sulfonic calix[*n*]arenes in the allylic alkylation reaction.⁸ Shoichi et al. reported the use of calix[*n*]arenes as catalysts in Mannich-type reactions.⁹ Recently, de Fátima and co-workers described the use of calix[*n*]arenes as organocatalysts in the Biginelli reaction.¹⁰ Conversely, the use of calix[*n*]arenes still remains little explored for esterification reactions.^{5c}

In this Letter, we report novel studies on esterification using calix[n]arene catalysts and demonstrate that *p*-sulfonic acid calix[4]arene and *p*-sulfonic acid calix[6]arene are efficient and reusable organocatalysts for the synthesis of carboxylic esters. To the best of our knowledge, this is the first application of *p*-sulfonic acid calix[n]arenes as organocatalysts for these esterification reactions.

Results and discussion

The esterification reactions of palmitic acid in deuterated methanol using five catalysts (Fig. 1) were evaluated via ¹H NMR



Figure 1. Molecular structures of the five catalysts: (1) *p*-sulfonic acid calix[4]arene; (2) *p*-sulfonic acid calix[6]arene; (3) sulfuric acid, (4) *p*-toluenesulfonic acid and (5) *p*-hydroxybenzenesulfonic acid.





^{*} Corresponding author. Tel.: +55 31 3899 3071; fax: +55 31 3899 3065. *E-mail addresses*: sefernandes@gmail.com, santonio@ufv.br (S.A. Fernandes).

^{0040-4039/\$ -} see front matter \odot 2012 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2012.01.078



2.40 2.39 2.38 2.37 2.36 2.35 2.34 2.33 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.24 2.23 2.22 2.21 2.20 2.19 2.18 2.17

Figure 2. Representative ¹H NMR spectra (300.069 MHz, CD₃OD, δ_{CHD2OD} = 3.30, 323 K). (a) (*) RCH₂CO₂H (palmitic acid); (b) mixture of palmitic acid and deuterated methyl palmitate; and **c**) (•) RCH₂CO₂CD₃ (deuterated methyl palmitate).

spectroscopy in situ (Fig. 2). NMR spectroscopy showed to be an efficient monitoring method and allowed the accurate analysis of the five catalysts assessed.¹¹ No unknown products were detected during the reaction, indicating the absence of side reactions in the experimental conditions used herein. Reaction progress was monitored by analysis of the resonance signals (triplet) of the methylene group hydrogen atoms next to the carbonyl group of both the ester and fatty acid (highlighted in Fig. 2). A typical spectrum containing resonance signals of the methylene groups of both deuterated methyl palmitate and palmitic acid obtained in the *p*-sulfonic acid calix[4]arene-catalyzed esterification reaction is presented in Figure 2.

All catalysts were used at the same hydrogenionic concentration (molar ratio of carboxylic acid:H⁺; 800:1). The two catalysts more commonly used in fatty acid esterification reactions (i.e. sulfuric acid and *p*-toluenesulfonic acid) and *p*-hydroxybenzenesulfonic acid monomer of the calix[*n*]arene catalysts (**1** and **2**) were selected for comparison and used in concentrations equal to 0.25, 0.50 and 0.50 mol %, respectively (Fig. 3). Literature reports that the catalytic activity in esterification reactions is strongly dependent on the acid



Figure 3. Effect of catalyst in the esterification reaction with deuterated methanol, monitored by ¹H NMR spectroscopy^a. ^aReaction conditions: palmitic acid (0.08 mmols); catalysts (0.0001 mmols); deuterated methanol (14.80 mmols); temperature (323 K).

catalyst strength.¹² Although when in aqueous solution there is a levelling effect on the acid strength of these catalysts, in ethanol solutions the same does not occur, especially for *p*-toluenesulfonic acid and *p*-hydroxybenzenesulfonic acid, which are less active. This later showed a very poor activity comparatively to two proposed organocatalysts in the reaction herein assessed: while in the *p*-toluenesulfonic acid and *p*-hydroxybenzenesulfonic acid-catalyzed reaction a conversion of only 20% and 31%, respectively was reached after 300 min (Fig. 3), conversion rates greater than 88% were obtained in *p*-sulfonic acid calix[*n*]arene-catalyzed reactions.

p-Sulfonic acid calix[*n*]arene can be considered as a cluster of *p*-hydroxybenzenesulfonic acids linked by a methylene spacer, which provides hydrophobic cavity. For comparison, *p*-toluenesulfonic acid (**4**) and *p*-hydroxybenzenesulfonic acid (**5**) were used under the same reaction conditions. Based on the above experimental results, it was suggested that the higher catalytic activity of (**1** and **2**) comparatively to (**4**) and (**5**) may be originated from the formation of the inclusion complex of *p*-sulfonic acid calix[-*n*]arene (**1** or **2**) with organic acid.^{7a,13}

Noticeably, best results were obtained in presence of the two organocatalysts proposed: *p*-sulfonic acid calix[4]arene (0.125 mol %) and *p*-sulfonic acid calix[6]arene (0.080 mol %), which were revealed to be as active as the sulfuric acid catalyst (Fig. 3). They promoted palmitic acid conversion into deuterated methyl palmitate at the same initial rates, achieving an 85% conversion after 160 min reaction. Moreover, a very close conversion was reached after 240 min of reaction (ca. 88–90%). Although the final conversion obtained in the sulfuric acid-catalyzed reaction was slightly higher than that obtained in *p*-sulfonic acid calix[*n*]arene-catalyzed reactions, these latter catalysts have a remarkable advantage: are easily recyclable.

Best results were obtained in the presence of the three catalysts p-sulfonic acid calix[4]arene (91%), p-sulfonic acid calix[6]arene (90%) and sulfuric acid (94%) (Fig. 3). Poor conversion (less than 20% and 31%, respectively even after 300 min reaction) was obtained with the widely used p-toluenesulfonic acid or and p-hydroxybenzenesulfonic acid (Fig. 3).

With the objective of potential application in biofuel production processes, the reusability of *p*-sulfonic acid calix[4]arene (1) and *p*-sulfonic acid calix[6]arene (2) catalysts was examined for the synthesis of several fatty esters (**6f-j**) (Table 1). After each catalytic run, the calix[*n*]arenes catalysts (1) and (2) were recovered from the reaction medium by liquid-liquid extraction with water. After drying, the calix[*n*]arene catalysts were weighed and used again in successive reactions. Both *p*-sulfonic acid calix[4]arene (1) and *p*-sulfonic acid calix[6]arene (2) catalysts remained active after multiple cycles of recovery and reuse (Fig. 4). Even after recycling the organocatalysts five times, the yields obtained were practically identical to those observed with fresh catalyst. The inevitable loss of catalyst during recovery process was less than 10%.

The feasibility and applicability of the calix[*n*]arene catalysts in esterification reactions were extended to organic acids **6a–p** (Table 1). For this study, all reaction conditions remained constant as described above and only the nature of the organic acids was altered.

According to the data in Table 1, high conversions were obtained in the esterification reactions of linear and saturated carboxylic acids in the presence of catalysts (1), (2) and (3). Straight-chain organic acids (compounds 1–10, Table 1) were converted into esters in yields ranging from 53–99% with the catalysts (1–3). Catalysts (4) and (5) were not efficient for esterification of 15 carboxylic acids studied (Table 1). None of the catalysts studied were suitable for esterification of aromatic organic acids (compounds 11–14). It is well known that carboxyl group reactivity of the benzoic acid and their derivates is strongly influenced by conjugation with the aromatic ring and distorted by the substituent attached to the ring.

Table 1

Esters yields obtained in esterification reactions catalyzed by *p*-sulfonic acid calix[4]arene (1), *p*-sulfonic acid calix[6]arene (2), sulfuric acid (3), *p*-toluenesulfonic acid (4), and *p*-hydroxybenzenesulfonic acid (5)^a

$$\begin{array}{c} O \\ R \\ \hline OH \\ \hline OH \\ \hline EtOH, Reflux, 4 h \\ \hline \mathbf{(5a-p)} \\ \end{array} \begin{array}{c} O \\ R \\ \hline OEt \\ \hline H_2O \\ \hline OEt \\ \hline H_2O \\ \hline \mathbf{(5a-p)} \\ \hline \end{array}$$

Entry	Product	(1)	(2)	(3)	(4)	(5)
	R	Yield (%)				
1	СН ₃ ба	94	83	97	<5	<5
2	C ₂ H ₅ 6b	99	90	99	28	<5
3	C ₃ H ₇ 6c	91	85	98	42	<5
4	C ₅ H ₁₁ 6d	89	86	99	<5	<5
5	C ₇ H ₁₅ 6e	91	82	99	<5	<5
6	C ₁₁ H ₂₃ 6f	74	53	80	35	42
7	C ₁₃ H ₂₇ 6g	66	55	94	16	53
8	C ₁₅ H ₃₁ 6h	91	91	95	<5	65
9	C ₁₇ H ₃₅ 6i	91	89	92	14	44
10	C ₁₇ H ₃₃ 6j	88	76	90	<5	48
11	C ₆ H ₅ 61	<5	<5	<5	<5	<5
12	2-C ₅ H ₄ N 6m	<5	<5	11	<5	<5
13	3-NH ₂ C ₆ H ₄ 6n	<5	<5	<5	<5	<5
14	3,5-NO ₂ C ₆ H ₃ 60	<5	<5	<5	<5	<5
15	4-NO ₂ C ₆ H ₄ CH ₂ 6p	46	34	36	10	<5

^a Reaction conditions: palmitic acid (0.40 mmols); catalysts (0.0005 mmols); ethanol (352.17 mmols).



Figure 4. Conversion rates obtained in the calix[*n*]arene-catalyzed esterification reactions of palmitic acid with methanol after successive cycles of catalyst recovery/reuse.

Conclusion

In this study, a novel and efficient process based on *p*-sulfonic acid calix[*n*]arenes as homogeneous and recyclable organocatalysts was developed for the synthesis of esters. The calix[*n*]arene catalysts were able to efficiently promote the esterification of a broad variety of organic acids with ethanol in high yields and under mild reaction conditions. Furthermore, it was also demonstrated that the catalytic activity of calixarene catalysts remained unaltered even after several recovery/reutilization cycles. Moreover, this environmentally friendly methodology avoids the use of metal-based catalyst. The noticeable advantages of these organocatalysts compared to traditional acid homogeneous catalysts used in

esterification reactions may make this process an interesting and very useful alternative for the synthesis of straight-chain carboxylic esters, especially for biodiesel synthesis.

Experimental section

General procedures

All chemicals were obtained from commercially available sources and used without further purification. Reactions did not require anhydrous conditions. GC–MS analyses were carried out on a Shimadzu GC 17A gas chromatograph coupled with a MS-QP 5000 Shimadzu mass spectrometer (Tokyo, Japan), with a DB5 capillary column (30 m length, 0.25 mm id, 0.25 mm film thickness). The ¹H and ¹³C-NMR spectra were recorded on a Varian Mercury spectrometry at 300 MHz and 75 MHz respectively, in CD₃OD.

General procedure for the synthesis of calix[n]arenes

The *p*-sulfonic acid calix[4,6]arenes were synthesized in our laboratory following the literature procedures. First, *p*-tert-butyl-calix[4,6]arene was prepared by the Gutsche and Iqbal method.¹⁴ Secondly, the *p*-tert-butylcalix[4,6]arene was dealkylated by treatment with aluminium chloride in the presence of toluene and phenol according to the method described by Ungaro and co-works.¹⁵

Preparation of the *p*-sulfonic acid calix[4,6]arene was carried out with the treatment of calix[4,6]arene with concentrated sulfuric acid (98% wt) added to (Shinkai, et al.).¹⁶ The reaction mixture was shaken under nitrogen; the temperature was maintained at 353 K.

The reaction was monitored by removing small aliquots followed by the addition of a minimum quantity of water. Complete solubility indicated complete sulfonation. At this stage the reaction was stopped. This took about 4 h.

General procedure for the synthesis of esters

General procedure for the synthesis of compounds (**6a–p**); organic acid (0.40 mmol.), and catalyst (0.0005 mmol.) was combined with 20 mL ethanol in a 50 mL round bottomed flask equipped with a stir bar. Reaction was allowed to stir at reflux temperature for the appropriate amount of time (4 h). After completion of reaction, the reaction mixture was concentrated in vacuum to give a crude product which was analyzed by ¹H NMR and GC–MS.

Acknowledgments

This work was funded by FAPEMIG, CAPES, FUNARBE, and CNPq.

References and notes

- (a) Dalko, P. I.; Moisan, L. Angew. Chem. 2004, 43, 5138; (b) Amarante, G. W.; Coelho, F. Quim. Nova 2009, 32, 469.
- (a) Larock, R. C. Comprehensive Organic Transformations; New York, NY: VCH, 1989. p. 966; (b) Otera, J. Esterification: Methods; Reactions and Applications; Wiley: New York, NY, 2003.
- (a) Carmo, A. C.; de Souza, L. K. C.; de Costa, C. E. F.; Longo, E.; Zamian, J. R.; Rocha Filha da, G. N. Fuel 2009, 88, 461; (b) Ansari, H. R.; Curtis, A. J. J. Soc. Cosmet. Chem. 1974, 25, 203; (c) Nishikubo, T.; Kameyama, A.; Yamada, Y.; Yoshida, Y. J. Polym. Sci., Part:A, Polymer Chem. 1996, 34, 3531.
- (a) Ishihara, K.; Ohara, S.; Yamamoto, H. Science 2000, 290, 1140; (b) Corma, A.; Nemeth, L. T.; Renz, M.; Valencia, S. Nature 2001, 412, 423; (c) Hoydonckx, H. E.; de Vos, D. E.; Chavan, S.; Jacobs, P. A. Top. Catal. 2004, 27, 83; (d) Chen, C.-T.; Munot, Y. S. J. Org. Chem. 2005, 70, 8625; (e) Yang, C.-G.; He, C. J. Am. Chem. Soc. 2005, 127, 6966; (f) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R.; Hedrick, M. J. L. Org. Lett. 2002, 4, 3587.
- (a) Iwahana, S.; Iida, H.; Yashima, E. *Chem. Eur. J.* **2011**, *17*, 8009; (b) Molina, M. T.; Navarro, C.; Csaky, A. G. J. Org. *Chem.* **2009**, *74*, 9573; (c) Akceylan, E.; Yilmaz, M. *Tetrahedron* **2011**, *67*, 6240.

- 6. Homden, D. M.; Redshaw, C. Chem. Rev. 2008, 108, 5086.
- 7. (a) Santos, L. S.; Fernandes, S. A.; Pilli, R. A.; Marsaioli, A. J. *Tetrahedron: Asymmetry* **2003**, *13*, 2515; (b) Li, Z.-Y.; Chen, J.-W.; Liu, Y.; Xia, W.; Wang, L. Curr. Org. Chem. **2011**, *15*, 39. Liu, L; Wang, Y. L.; Han, Y. C.; Chen, Y. J. Green Chem. **2008**, *10*, 635.
- 8.
- 9. Shimizu, S.; Shimada, N.; Sasaki, Y. Green Chem. 2006, 8, 608.
- 10. da Silva, D. L.; Fernandes, S. A.; Sabino, A. A.; de Fátima, A. Tetrahedron Lett. 2011, 52, 6328.
- 11. Fernandes, S. A.; Cardoso, A. L.; da Silva, M. J. Fuel Proc. Technol. in press.
- 12. Abiney, A. L.; Augusti, R.; da Silva, M. J. *J. Am. Oil. Chem. Soc.* **2008**, *85*, 555. 13. (a) Goto, K.; Murakami, Y.; Ueoka, R. *J. Mol. Catalysis B* **2001**, *11*, 985; (b) Goto, K.; Yano, Y.; Okada, E.; Liu, C. W.; Yamamoto, K.; Ueoka, R. J. Org. Chem. 2003, 68, 865.
- 14. Gutsche, C. D.; Iqbal, M. Org. Synth. 1989, 68, 234.
- 15. Casnati, A.; Ca, N. D.; Sansone, F.; Ugozzoli, F.; Ungaro, R. Tetrahedron 2004, 60, 7869.
- 16. Shinkai, S.; Araki, K.; Tsubaki, T.; Some, T.; Manabe, O. J. Chem. Soc. Perkin Trans. **1987**, 2297.