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Erbium(III) Chloride in Ethyl Lactate as a Smart Ecofriendly System for Efficient and Rapid Stereoselective Synthesis of *trans*-4,5-Diaminocyclopent-2-enones

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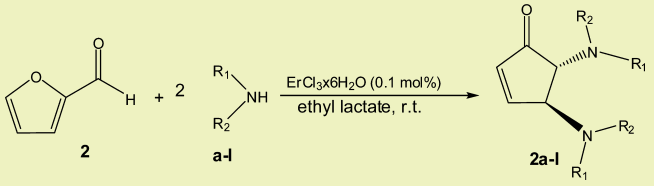
Supporting Information

ABSTRACT: Erbium(III) chloride in ethyl lactate is used as an environmentally very friendly system for the reaction of furfural and amines to yield diastereoselectively differently *N*,*N*-substituted *trans*-4,5-diaminocyclopent-2-enones as versatile synthetic intermediates to the formation of densely functionalized derivatives.



KEYWORDS: *Ethyl lactate, Erbium(III) chloride, Furfural, Diaminocyclopent-2-enones*

INTRODUCTION

1,2-Diaminocyclopentane is a structural motif widely present in numerous natural and synthetic bioactive compounds[1−9] and colored Maillard reaction products.[10] In particular, the *trans*-diaminocyclopentane moiety **1** (Figure 1) has recently attracted much attention because it could be employed as a very useful key intermediate in the retrosynthetic pathway of (-)-agelastatin A, an architectural unique cytotoxic tetracyclic alkaloid first isolated from the axinellid sponge *Agelas dendromorpha*.[11,12]

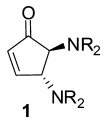


Figure 1. *trans*-Diaminocyclopentane moiety **1**.

Traditionally, **1** can be synthesized in low yield from the reaction of furan-2-carboxyaldehyde **2** and anilines[10,13−15] but only under harsh conditions (i.e., refluxing methanol in the presence of hydrochloric acid) or in high yield under very long reaction times (80 days) and with the concomitant production of the thermodynamically stable 2,4-diaminocyclopenten-2-enones in high yield.[10,13−18] The recent renewed interest for this transformation lead to the development of a new synthetic protocol for the exclusive formation of **1** using $Sc(OTf)_3$ and $Dy(OTf)_3$ in dry acetonitrile.[19] More recently, acidic ionic liquid 1-methylimidazolium tetrafluoroborate $[Hmim]^+[BF_4]^-$ was successfully employed in a dual role of reusable catalyst and reaction medium in the reaction of furfural and secondary amines to yield 4,5-diaminocyclopent-2-enones **1**.[20] The last proposed method is surely a consistent improvement in respect to previously used protocols, but it still suffers from some disadvantages such as the use of toxic organic solvents, long reaction times (16 h), strictly anhydrous conditions, and expensive reagents.

In an attempt to avoid these drawbacks, we herein describe the use of erbium(III) chloride in ethyl lactate as a smart ecofriendly system in a rapid and efficient method for the synthesis of **1**.

EXPERIMENTAL SECTION

The following general experimental guidelines apply for all experiments described in this paper. All reagents, unless otherwise stated, were used as received (Aldrich, Fischer Scientific Ltd. or Lancaster). ^1H and ^{13}C NMR spectra were recorded on a Bruker WM 300 instrument on samples dissolved in $CDCl_3$ or other specified solvents when necessary. Chemical shifts are given in parts per million (ppm) from tetramethylsilane as the internal standard for ^1H NMR spectra (0.0 ppm) and the central line of $CDCl_3$ for ^{13}C NMR spectra (77.0 ppm). Coupling constants (*J*) are given in Hertz. Flash column chromatography on silica gel (60 Å, 230−400 mesh, obtained from Silicycle, Inc.) was performed with petroleum ether/EtOAc. Analytical thin layer chromatography (TLC) was performed using silica plates 60-F_{264} on alumina, commercially available from Merck.

General Procedure for the $ErCl_3 \times 6H_2O$ Catalyzed Formation of *trans*-4,5-Diaminocyclopent-2-enones from 2-Furaldehyde and Secondary Amines. To a solution of furan-2-carboxyaldehyde **2** (1.00 mmol) and amine (2.00 mmol) in ethyl lactate (0.5 mL) was added $ErCl_3 \times 6H_2O$(0.001 mmol). The resulting reaction mixture was stirred for 20−30 min at room temperature. In the cases of solid products (**1a**, **1c**), H_2O (0.3 mL) was added to the reaction solution, and the mixture was cooled down

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at ice−water temperature. The precipitated product was collected from the solution in satisfactory pure form. In all other cases, solvent removal under reduced pressure gave the crude product, which was then purified by column chromatography with petroleum ether/EtOAc. With the exception of compound **1g**, all other products in this report are known. They were, however, characterized by standard techniques (^{1}H and ^{13}C NMR, GC/MS), and the data were compared with those reported in the literature[10,13,19,20] for identification (Supporting Information).

***trans*-4,5-Bis(diisobutylamino)cyclopent-2-enone (1g).** Isolated as a viscous, bright yellow oil (0.0721 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (1H, d, J = 6.5 Hz), 6.16 (1H, d, J = 6.5 Hz), 4.37−4.20 (2H, m), 3.36−2.95 (8H, m), 3.23−3.10 (4H, m), 1.32−0.95 (24H, m); ^{13}C NMR (300 MHz, CDCl3) δ 203.1, 165.4, 132.9, 83.4, 65.1 (4 peaks), 58.8, 26.8 (4 peaks), 20.2 (8 peaks); $C_{21}H_{40}N_2O$. Elemental Analysis: C, 74.94; H, 11.98; N, 8.32. Found: C, 74.85; H, 11.79; N, 8.26.

RESULTS AND DISCUSSION

On the basis of our previous experience in developing new protocols in nonconventional media and efficient nontoxic catalysts,[21−27] we tested the catalytic activity of Er(III) in the reaction pictured in Scheme 1. Starting from the study reported by R. A. Batey et al.[6], we focused our attention upon the formation of **1a** from furan-2-carboxyaldehyde **2** and morpholine **a** in the presence of 10 mol % of $Er(OTf)_3$ in CH_3CN. Total conversion to **1a** was registered after only 5 min at room temperature without employing strictly dry conditions (Table 1, entry 1). The product **1a** is exclusively formed as *trans*-diastereomers, consistent with a thermal conrotatory π4a electrocyclization reminiscent of the Nazarov cyclization.[19,28] The formation of *trans* diastereomer was enstablished from the coupling constant between H-4 and H-5 in ^{1}H NMR spectrum.[19,20,28] Surprisingly, the same fulfilling result was observed when the reaction was performed using only 1 mol % of catalyst (Table 1, entry 2), whereas no reaction was registered when the same reaction pictured in Scheme 1 was performed in absence of any catalyst (Table 1, entry 3).

Scheme 1. Synthesis of *trans*-4,5-Di(morpholin-4-yl)-cyclopent-2-enone (1a) Catalyzed by Er(III) at Room Temperature

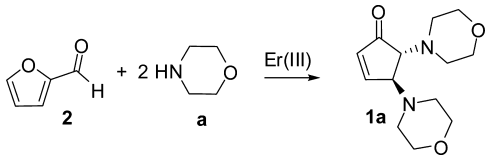

Table 1. Er(III) Catalyzed Reaction of Furan-2-carboxyaldehyde (2) and Morpholine (a) in Various Experimental Conditions

entry	catalyst (% mol)	solvent	time (min)	yield (%)[a]
1	$Er(OTf)_3$ (10)	CH_3CN	5	>99
2	$Er(OTf)_3$ (1)	CH_3CN	5	>99
3	–	CH_3CN	60	–
4	$Er(OTf)_3$ (1)	ethyl lactate	60	>99
5	$Er(OTf)_3$ (0.5)	ethyl lactate	20	>99
6	$Er(OTf)_3$ (0.1)	ethyl lactate	30	>99
7	$ErCl_3$ (1)	ethyl lactate	5	>99
8	$ErCl_3 \times 6H_2O$ (1)	ethyl lactate	5	>99
9	$ErCl_3 \times 6H_2O$ (0.1)	ethyl lactate	30	>99

[a]Isolated yield.

These experimented reaction conditions are very advantageous from an environmental point of view except for the use of an organic solvent like acetonitrile. As a matter of fact, solvents make a large contribution to the environmental impact of manufacturing processes of active pharmaceutical ingredients and fine chemicals. Indeed, the great challenge of designing and implementing completely green processes requires that the use of alternative solvents should be considered. In spite of the promising characteristics of the most popular green solvents (supercritical carbon dioxide, water, and ionic liquids), their adoption in large scale processes is very scarce nowadays,[29] especially for ionic liquids that from the currently available data are clearly very far from the image of green chemicals that are often cited in the literature.[30−32] Hence, other alternative organic solvents, with characteristics more similar to the traditional ones, may be considered if their properties are adequate both from technological and environmental point of view. Among these alternative organic solvents, ethyl lactate is one of the most promising ones.[29,33] Ethyl lactate complies with at least eight of the "Twelve Principles of Green Chemistry"[34] because it can be obtained by carbohydrate feedstocks at very low and competitive prices, and it is nontoxic and biodegradable.[35] Because of these reasons, the FDA approved it as a food additive;[36] moreover, ethyl lactate owns good properties to be applied as a green solvent in several synthetic and industrial applications. Thus, when the reaction depicted in Scheme 1 was performed at room temperature using 1 mol % of $Er(OTf)_3$ in ethyl lactate, we collected again quantitative yield of product **1a** in only 5 min (Table 1, entry 4). Looking for the best experimental conditions, the reaction was performed in the presence of a lower amount of catalyst (Table 1, entries 5 and 6), and only 0.1 mol % of catalyst was sufficient to furnishing quantitative conversion to product **1a** in 30 min.

Having established the splendid performance of $Er(OTf)_3$ in promoting the reaction between furan-2-carboxyaldehyde (**2**) and morpholine (**a**), we tested the much less expensive and toxic $ErCl_3$ in the same reaction.[37] Interestingly, 1 mol % of $ErCl_3$ in ethyl lactate showed the same catalytic activity of its triflate analogous (Table 1, entry 7), and surprisingly, quantitative yield was also obtained when the reaction was performed using 1 mol % of $ErCl_3 \times 6H_2O$ under the same experimental conditions (Table 1, entry 8). Finally, we experienced the employment of only 0.1 mol % of $ErCl_3 \times 6H_2O$ in ethyl lactate as the best protocol to obtain quantitative yield of product **1a** in 30 min (Table 1, entry 9).

Application of the protocol described in Table 1, entry 9, using various other secondary amines and anilines resulted in the formation of the desired 4,5-diaminocyclopenten-2-enones **1a−j** in quantitative yields in only 20−30 min (Table 2, entries 1−8).

However, primary aniline **k** gave only very poor yields of product **1k**, also after prolonged reaction time at 50 °C (Table 2, entry 9). Traces of the corresponding *N*-substituted 2,4-diaminocyclopenten-2-one were also observed. Finally, primary aliphatic amines, like benzylamine **l**, did not give any product, and the corresponding imine was the only product detected also after very long reaction time at 50 °C.

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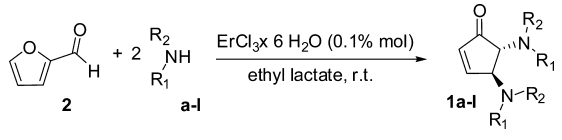
Table 2. $ErCl_3$-Catalyzed Reaction of Furan-2-carboxyaldehyde (2) with Amines (a–l) in Ethyl Lactate

entry	R_1R_2NH	time (min)	yield (%)[a]
1	morpholine (**a**)	30[b]	>99
2	$PhNHCH_3$ (**b**)	30[c]	>99
3	Bn_2NH (**c**)	40[c]	>99
4	piperidine (**d**)	20[b]	>99
5	pyrrolidine (**e**)	20[b]	>99
6	AllylNPh (**f**)	30[c]	>99
7	$^iBu_2NH$ (**g**)	20[b]	88
8	$(allyl)_2NH$ (**h**)	20[b]	>99
9	Indoline (**i**)	20	>99
10	1,2,3,4-tetrahydroquinoline (**j**)	30	>99
11	$PhNH_2$ (**k**)	60[d]	25
12	$BnNH_2$ (**l**)	60[e]	-

[a]Isolated yield, all products were characterized by ^1H and ^{13}C NMR. [b]The reaction was monitored by GC-MS. [c]The reaction was monitored by TLC. [d]Traces of the corresponding *N*-substituted 2,4-diaminocyclopenten-2-enone were observed even at 50 °C. [e]The corresponding imine was the only product observed.

Scheme 2. $ErCl_3$-Catalyzed Reaction of Furan-2-carboxyaldehyde (2) with Amines (a–l) in Ethyl Lactate



CONCLUSIONS

We have reported a new environmental friendly protocol for the synthesis of various substituted 4,5-diaminocyclopent-2-enones **1a–k** using only a very small catalytic amount of Er(III) chloride hexahydrate in ethyl lactate and avoiding strictly dry experimental conditions. Taking into account that $ErCl_3 \times 6H_2O$ can be considered even less toxic than table salt[16] and the "greenness" of ethyl lactate as a solvent, we propose $ErCl_3$/ethyl lactate as a cheap, efficient, and environmentally sustainable system for the synthesis of *N*,*N*-substituted 4,5-diaminocyclopent-2-enones.

ASSOCIATED CONTENT

Supporting Information

Structures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(37) $ErCl_3$ is less toxic than table salt: Oral mouse LD_{50} for $ErCl_3$ and NaCl from Sigma−Aldrich security sheets are 4417 and 4000 mg kg^{-1}. Prices for $ErCl_3$ and $Er(OTf)_3$ are 79.10 and 219,50 € (for 25 g), respectively.