SiO_2-Supported $CeCl_3$•$7H_2O$−NaI Lewis Acid Promoter: Investigation into the Garcia Gonzalez Reaction in Solvent-Free Conditions[⊥]

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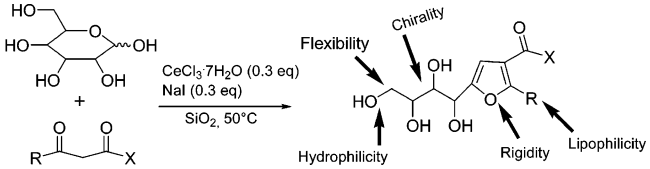

The Knoevenagel condensation of aldose sugars with β-dicarbonyl compounds produces furan derivatives having polyhydroxyalkylated alkyl side chains; this reaction is known as the Garcia Gonzalez reaction. Despite the fact that these polyhydroxyalkyl furans are interesting scaffolds for synthetic chemists to utilize in the synthesis of a variety of biologically interesting molecules, the reported approach suffers from harsh conditions. The development of a general and more efficient protocol is of considerable importance, and in this manuscript, we wish to explore the role of the NaI in enhancing the activity of $CeCl_3$•$7H_2O$ as a useful water-tolerant Lewis acid promoter for the Garcia Gonzalez reaction. The procedure proceeds with good yields at 50 °C using our system supported on SiO_2 in solvent-free conditions and represents a simple and convenient methodology for the preparation of densely functionalized molecules. Furthermore, the first qualitative results obtained on mechanistic investigation on the role of iodide on this our heterogeneous reaction may be of value for optimization of existing organic transformations and for the development of new ones.

1. Introduction

Trivalent rare earth compounds[1] such as Ce(III) salts exhibit characteristic acid properties, and they activate Lewis base functionalities to promote useful organic transformations. For this reason, we have frequently employed cerium(III) compounds as highly efficient reagents or catalysts in modern organic synthesis. $CeCl_3$, the most common source of cerium(III) commercially available, has recently become an attractive candidate for use as a Lewis acid in chemistry due to its relative nontoxicity and ready availability at a low cost. In fact, after the pioneering works by Luche[2] and Imamoto,[3] numerous reactions and methodologies employing cerium(III) derivatives as key components have been developed.[4] In particular, major attention has focused on the use of inexpensive $CeCl_3$•$7H_2O$, which exhibits excellent properties; e.g., it is water tolerant,

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[⊥] Dedicated to Prof. Achille Umani-Ronchi on his 70th birthday.

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nontoxic, easy to handle, and suitable for use without further purification.[5] The fact that this water-tolerant Lewis acid promoter is optimal with regard to economic and ecological considerations has allowed its application in important organic transformations. However, the main limitation is that a stoichiometric amount of $CeCl_3 \cdot 7H_2O$ is required, and long reaction times are observed. Therefore, the development of a catalytic version of a cerium(III) salt promoted reaction remains as a major objective of modern organic chemistry. Recent studies by us and by others have shown that the activity of $CeCl_3 \cdot 7H_2O$ increases dramatically in the presence of an iodide source such as NaI.[6] Further to the methodologies involving the $CeCl_3 \cdot 7H_2O$−NaI system to facilitate the cleavage of carbon−oxygen and silicon−oxygen bonds under neutral conditions,[7] new reactions for nitrogen−carbon[8] and oxygen−carbon[9] bond formation promoted by the $CeCl_3 \cdot 7H_2O$−NaI system have also been developed. Differences between the activity of $CeCl_3 \cdot 7H_2O$ and that of the $CeCl_3 \cdot 7H_2O$−NaI combination are especially apparent in the context of carbon−carbon bond-forming reactions.[10] The presence of NaI is crucial in these reactions, resulting in shorter reaction times, diminished byproduct formation, and improved yields and purity of the products. A pertinent example is found in work by Spinelli et al.[11] on the 1,4-addition of Fischer bases to nitroenamines. All of these results have established that the interaction between $CeCl_3 \cdot 7H_2O$ and an inorganic iodide[10c] gives a complex which exhibits a stronger Lewis acid character. $CeCl_3$, being a hard Lewis acid,[12] is suitable to form a weak and labile iodide ion−Lewis acid complex,[13] and then the nucleophilic donor can enhance the electrophilicity of the lanthanide metal.[14] Although there is evidence for the formation of this complex, the nature of the species obtained by the interaction of $CeCl_3 \cdot 7H_2O$ with NaI is not known. For this, even if only very sensible conjectures about the role of NaI on the performance of $CeCl_3 \cdot 7H_2O$ as Lewis acid promoter in many organic reactions have been advanced, our $CeCl_3 \cdot 7H_2O$−NaI combination is very suitable from a synthetic standpoint.

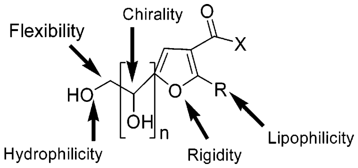

FIGURE 1. Useful properties of polyhydroxyalkyl furan moieties.

We have recently become interested in evaluating the $CeCl_3 \cdot 7H_2O$-NaI catalytic system in the so-called Garcia Gonzalez reaction:[15] the Knoevenagel condensation of a β-dicarbonyl compound[16] with an unprotected carbohydrate to give a polyhydroxyalkyl furan (Figure 1). Interestingly, more than 100 furans structurally similar to that of Figure 1 have been recently isolated from plants and microorganisms,[17] albeit in low yield. Substituted furans are also broadly represented among natural products and medicinal agents. Furthermore, they are useful building blocks in heterocyclic chemistry[18] and in the synthesis of carbohydrates.[19] The latter compounds, of course, are of enormous importance in chemical, biological, and medicinal science,[20] as well as being of great value in the preparation of polyfunctional heterocycles of interest in pharmaceutical and agrochemical practice.[21] There is clearly a need for efficient

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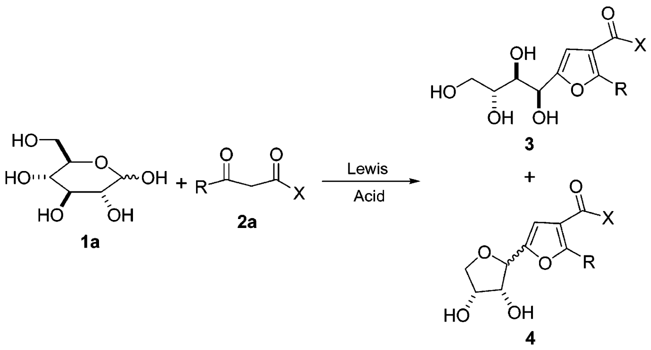
SCHEME 1. Garcia Gonzalez Reaction for the Preparation of Furan Derivatives

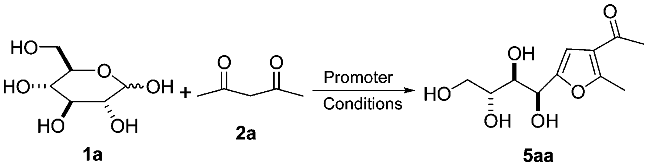


synthetic avenues to furans.[22] In this paper, we describe the application of our $CeCl_3{\cdot}7H_2O$−NaI system to the condensation of β-dicarbonyl compounds with unprotected carbohydrates under solvent-free conditions.[23]

2. Results and Discussion

Since the initial Garcia Gonzalez reaction (Scheme 1) using $ZnCl_2$ in alcohol[24] gives polyhydroxyalkylfuran in very low yield (about 30%), major attention has been focused on the application of various Lewis acid catalysts. Since trifluoromethanesulfonate salts promote acid-catalyzed reactions under mild conditions,[25] the Knoevenagel condensation of hexoses with 1,3-dione compounds has been recently carried out under aqueous conditions in the presence of $Yb(OTf)_3$ or $Sc(OTf)_3$.[26] In any case, the reaction produces the polyhydroalkyl furans **3** taken with relative further cyclized tetrahydrofuranylfuran derivatives **4**, which could with difficulty be separated by chromatography. Misra et al. have found that unprotected aldose sugars react with 1,3-diones and β-keto esters in the presence of $CeCl_3{\cdot}7H_2O$ in aqueous mixtures at 90 °C to produce furan derivatives in good yields.[27] Under the Misra conditions, pentose sugars produce furan derivatives having polyhydroxylated alkyl side chains. However, when an aldohexose **1** is treated with a β-dicarbonyl compound a single isolable product is obtained, but this is a hydroxytetrahydrofuranylfuran **4**. Under these harsh conditions, in fact, after the formation of **3**, it further rearranges to form a double cyclic derivative, which is a less important synthetic scaffold than polyhydroxyalkyl furans.[19b,28] It has also been reported that the condensation of an aldose with benzyl acetoacetate and $CeCl_3{\cdot}7H_2O$ (25%) provokes the total epimerization[29] at C-1′, in contradiction with Misra's results.

TABLE 1. Reaction between D-Glucose (1a) and 2,4-Pentandione (2a) under Different Experimental Conditions[a]



entry	$CeCl_3{\cdot}7H_2O$ (equiv)	NaI (equiv)	conditions/time (h)	T (°C)	yield[b] (%)
1	0.25		H_2O/7	60	20
2	0.25		H_2O/7	80	8
3	1.0		H_2O/15	60	25
4	1.2		H_2O/15	60	31
5	1.0		CH_3CN/25	60	18.5
6	1.0	0.30	CH_3CN/25	60	54
7	1.0	0.3	SiO_2/25	rt	60
8	0.30	0.3	SiO_2/22	50	95

[a] All reactions were carried out by stirring mixtures of **1a** (10 mmol), 1,3-dione **2a** (13 mmol), and catalyst for the selected reaction times. [b] All yields of product isolated by column chromatography.

We decided to explore the role of the NaI in enhancing the activity of $CeCl_3{\cdot}7H_2O$, and we discovered important advances in the Garcia Gonzalez reaction. Our initial efforts focused on achieving the optimum conditions for increasing the yields of **3** with D-glucose (**1a**) as a model aldohexose, in the presence of cerium trichloride as the Lewis acid. The results are summarized in Table 1. By screening the various conditions, we have observed that the use of acetonitrile as solvent in this reaction gives a poor yield (18.5%) in a slow reaction (25 h) (Table 1, entry 5), probably owing to incomplete solution of carbohydrate **1a**. With catalytic amounts of NaI the corresponding product **5aa** is realized in moderate yield (Table 1, entry 6). About the same yield of the corresponding polyhydroxyalkyl furan is obtained under solvent-free conditions and in the presence of an inorganic support such as silica gel (SiO_2) (Table 1, entry 7). The reaction proceeds with good yield at 50 °C using the $CeCl_3{\cdot}7H_2O$−NaI system supported on SiO_2 in solvent-free conditions. After further attempts to increase the yield by changing relative amounts of the reactants, we have found that a mixture of D-glucose (1.0 mmol), 2,4-pentandione (**2a**, 1.30 mmol),[30] $CeCl_3{\cdot}7H_2O$ (0.3 mmol), and NaI (0.3 mmol) mechanically stirred at an external temperature of 50 °C for 22 h gave an excellent yield (95%) of product **5aa** (Table 1, entry 8).

The first clear result is that the use of SiO_2 support facilitates the workup of the reaction mixture[31] with better yields of product, even though the reaction has also been observed in its absence. Furthermore, the use of inorganic support allows the reaction to proceed without solvent to adopt the best experimental conditions to reduce the large amounts of organic

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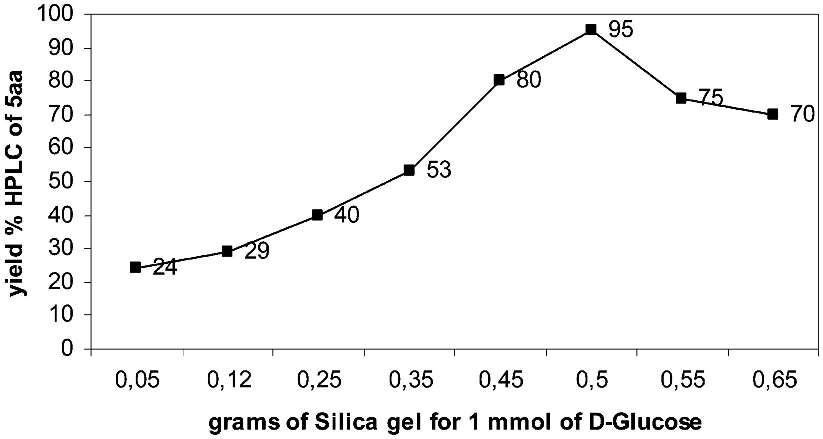

FIGURE 2. Amount of SiO_2 influences the efficiency of the reaction.

solvents needed.[32] Although SiO_2 was originally introduced as only a support, kinetic studies have revealed that it not only acts as a carrier to increase the surface area as intended but also enhances the rate constant[33] for the Garcia Gonzalez reaction. It is known that the silanol groups on the silica surface might affect the activity of the immobilized catalyst,[34,35] and in fact, the $CeCl_3{\cdot}7H_2O-NaI$ system supported on SiO_2 gives a better yield of the adduct than in an unsupported system. This is possibly due to the interaction between the cerium(III) site of the catalyst with the silanol groups of the uncapped silica surface changing the environment of the catalyst active site. The $CeCl_3{\cdot}7H_2O-NaI$ system is also more well-dispersed throughout the porous support and better separated from each other.[36] This shows that SiO_2 functions as an activator for $CeCl_3{\cdot}7H_2O-NaI$ Lewis acid system as well as support. Whereas its high performance as a support has been well documented, the fact that SiO_2 works as a good activator for our $CeCl_3{\cdot}7H_2O-NaI$ system has often been overlooked. We have argued that the function of SiO_2 as an activator stems from a very probable electronic interaction between a catalytically active cerium(III) species and hydroxyl or even oxide groups at surface of SiO_2. Then, the treatment of $CeCl_3{\cdot}7H_2O-NaI$ system with SiO_2 might lead to the formation of a supported cerium(III) salt in which the cerium atom is grafted to the surface via one covalent bond ($\equiv$SIO$-$Ce)[37] and mass balance analysis is in progress in our laboratories to investigate this possibility. Consequently, this interaction may reduce the LUMO energy of cerium(III)/SiO_2, and this one is lower in energy than the LUMO of cerium(III). Given that the strength of a Lewis acid is related to the energy of its LUMO in such as way that the lower the LUMO energy, the easier its interaction with a base molecule, we believe that the Lewis acidity of cerium(III) salt is considerably increased by incorporation of the lanthanide in the framework of SiO_2. In its absence, the reaction of Garcia Gonzalez affords low yields of adduct **5aa** with longer reaction times, which do not improve the conversion, because the competitive decomposition of dicarbonyl compound begins to be important. Even the amount of SiO_2 is decisive for completion of this type of Garcia Gonzalez reaction (Figure 2). The results indicate that 0.5 g/mmol of carbohydrate is the most appropriate ratio, and the use of an excessive amount of silica gel (more than 0.5 g/mmol) causes a significantly lower yield of furan derivative **5aa**. Analogously, a decrease in the amount of SiO_2 leads to the partial recovery of the starting material even when the reaction time is prolonged.

The fact that our methodology is clean and the adduct **5aa** has been obtained in high yield without formation of any side products normally observed under the influence of strong acids does not exclude the existence in the solid promoter of a distribution of sites that may contain simultaneously Brönsted and Lewis sites.[38] In fact, according to Spencer's study,[39] investigations aimed at confirming the effective catalyst do not preclude the existence of a Brönsted acid-catalyzed pathway in our procedure. The presence of the weak base 2,6-di-*tert*-butyl-4-methylpyridine, which only binds to protons and is unable to coordinate to metal cerium, due to the bulky *tert*-butyl groups,[40] significantly retards the Garcia Gonzalez reaction. Certainly, the catalytic activity of the $CeCl_3{\cdot}7H_2O-NaI$ Lewis acid is indispensable for promoting new bond-forming reactions and is related to its ability to form acid$-$base adducts with either the nucleophile or the electrophile reagent enhancing its reactivity.

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[32] The $CeCl_3{\cdot}7H_2O$-NaI system dispersed on chromatography silica gel (Baker analyzed reagent with particle size distribution 30$-$60 μm) was prepared by simply mixing both reagents in acetonitrile followed by complete removal of the solvent; see: Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594$-$4597.

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Extending this procedure to reactions of a variety of aldohexoses with different β-dicarbonyl compounds, good to excellent yields of the corresponding polyhydroxyalkyl furan derivatives have been realized (Table 2, entries 1–10). The success of the reaction is independent of the type of hexoses used with the results that are comparable to those of pentoses reported in the literature.[28] Workup is very easy, the hydroxyl groups did not require prior protection,[41] and the avoidance of harsh conditions for deprotection permits compatibility with a wide range of functional groups. However, the column chromatography cannot be avoided because we always observe the formation of traces of unwanted hydroxytetrahydrofuranyl furan (type **4**) as byproduct. The reaction works well with 1,3-dione and β-keto esters, and by screening a range of 1,3-dicarbonyl compounds in the reaction with D-glucose, we have observed that with α-benzoil carbonyl compound the Garcia Gonzalez adduct is obtained in very modest yield (Table 2, entry 6). In fact, for steric and electronic reasons the formation of the product **5ag** is not observed at 50 °C after 36 h, so we have increased the temperature of the reaction to 75 °C obtaining a very low yield (25%). Under these conditions, a competitive decomposition of dicarbonyl compound begins to be important. To avoid the necessity of using too elevated temperatures, we attempted to favor the homogenization of the reagents by adding the carbohydrate and the dicarbonyl compound to the $CeCl_3$•$7H_2O$–NaI mixture in acetonitrile, allowing it to stir for 0.5 h, and then removing the solvent. In this way, we have succeeded in getting an increase of the yield to 40%, and this indicates a limitation of the methodology. Furthermore, while ethyl β-keto esters (Table 2, entries 2, 4, 7, and 9) work well as substrates, in the case of the *tert*-butyl analogue (Table 2, entry 5), a significantly different result occurs during the course of the reaction. We have, in fact, purified the desired product in moderate yield. By analysis of the reaction mixture, besides the presence of polyhydroxyalkyl furan **5ae** and traces of double-cyclized byproduct, we observe the formation of a β-C-glycosidic ketone **8** that accounted for 36% of the reaction. This result prompted us to propose the mechanism in Scheme 2. Initially, the *tert*-butyl β-keto ester **2e** adds to the aldehyde moiety of the D-glucose, and the $CeCl_3$•$7H_2O$–NaI system in this case acts as a Lewis acid promoter of a Knoevenagel condensation.[10a] Under the reaction conditions, deprotection of *tert*-butyl ester **5** is promoted by our system[7a,42] for providing keto acid derivative **6**. Then, a decarboxylation occurs spontaneously during the reaction, and finally, an intramolecular Michael reaction promoted by our $CeCl_3$•$7H_2O$–NaI system[43] would give the β-C-glycoside target.[44] Given that these β-C-glycosides are useful building blocks for the synthesis of various type of natural products and as potential enzyme inhibitors, the possibility to obtain β-C-glycosidic ketones with better yields in one step directly from the unprotected sugar is currently under investigation in our laboratories.

With this new finding of important advances in the Garcia Gonzalez reaction promoted by the $CeCl_3$•$7H_2O$–NaI system, we decided to explore the mechanistic role of NaI in enhancing the Lewis acid activity of cerium trichloride. In contrast to Brönsted acidity, it is very difficult to define and quantify Lewis acidity.[37] The trivalent cerium shows a strong affinity toward hard bases.[6] The formation of an adduct implies that an electron density transfer from the donor to the Lewis acid acceptor occurs which is directly proportional to the energy difference and degree of overlap between the occupied orbitals of the base and the empty orbitals of the acid. In this process of Lewis acid activity, modification of electronic levels of the metal by adsorption of a molecule on the metal center should be taken into account. Consequently, the Lewis acid activity of $CeCl_3$•$7H_2O$ depends not only on the properties of the isolated acid site but also on the changes caused by its interaction with an iodide source additive, such as NaI. The central question concerning the mechanism is whether our optimized Garcia Gonzalez reaction occurs through a heterogeneous or homogeneous promoting pathway. In a heterogeneous manner, the reaction takes place predominantly on the cerium salt surface and not in the solution phase; therefore, the reaction would occur inside the pores of the silica gel. This mechanism would lead to a complete recovery of our system because leading into the solution phase would not occur. Under homogeneous conditions with a heterogeneous promoter, the reaction takes place in the solution phase with cerium species that are leaded from the solid. In order to determine if the $CeCl_3$•$7H_2O$–NaI system is acting in a heterogeneous or homogeneous form, we have performed this interesting experiment. We have stopped the reaction of D-glucose (1.0 equiv) with β-dicarbonyl compound **2a** (1.3 equiv) in the presence of $CeCl_3$•$7H_2O$ (0.3 equiv), NaI (0.3 equiv) supported on SiO_2 after the formation of approximately 50% of the product **5aa**. Then, after filtration of the heterogeneous materials using acetonitrile as solvent, we have allowed the reaction to continue in the filtrate under the same reaction conditions (Table 1, entry 6). We later found that the reaction is completely stopped. This observation led us to conclude that the reaction takes place via a heterogeneous pathway because no active-promoting cerium species have been present in solution.

Having established what appeared to be the promoting pathway of the solid $CeCl_3$•$7H_2O$–NaI system, we switched our attention to the water of crystallization in the cerium(III) salt. It seemed appropriate to investigate if the amount of water present in the reaction mixture might vary the yield of Garcia Gonzalez adduct.[45] Therefore, we carried out a systematic study on the influence of the amount of water on the reaction rate by drying $CeCl_3$•$7H_2O$[46] before using it supported on dry silica gel[47] and then adding water in known amounts to the reaction mixture (Scheme 3). We analyzed the conversion of **1a** in polyhydroxyalkyl furan **5aa** in the presence of increasing amounts of added water.

With <1 equiv of water, decreased activity was observed, and the rate dropped dramatically. On the other hand, with 4 equiv of water, essentially identical results were obtained as

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(41) *O*-Benzyl protection is a standard strategy in syntheses of carbohydrate derivatives; see: Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11–109.

(42) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 4430–4432. (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Massaccesi, M.; Marcantoni; E.; Petrini, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553–4559.

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(45) In some reactions promoted by the $CeCl_3$•$7H_2O$–NaI system, the presence of water in the reaction mixture is essential; for instance, see: Bartoli, G.; Giovannini, R.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Eur. J. Org. Chem.* **2006**, 1476–1482 and references cited therein.

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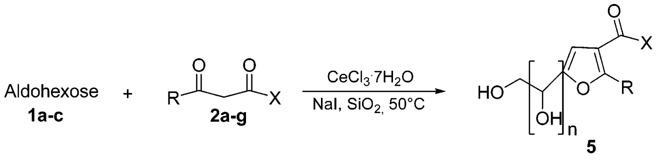
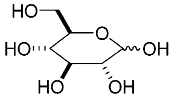
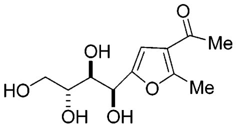
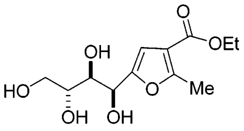
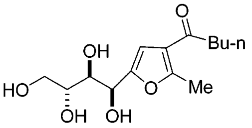
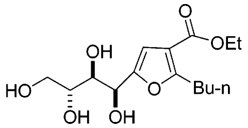
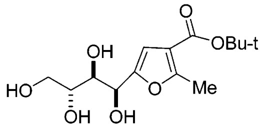
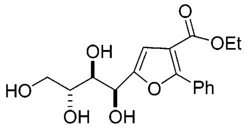
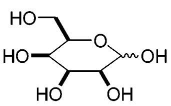
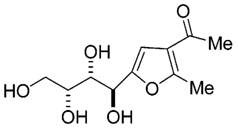
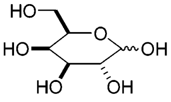
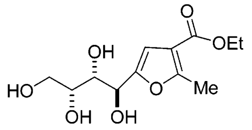
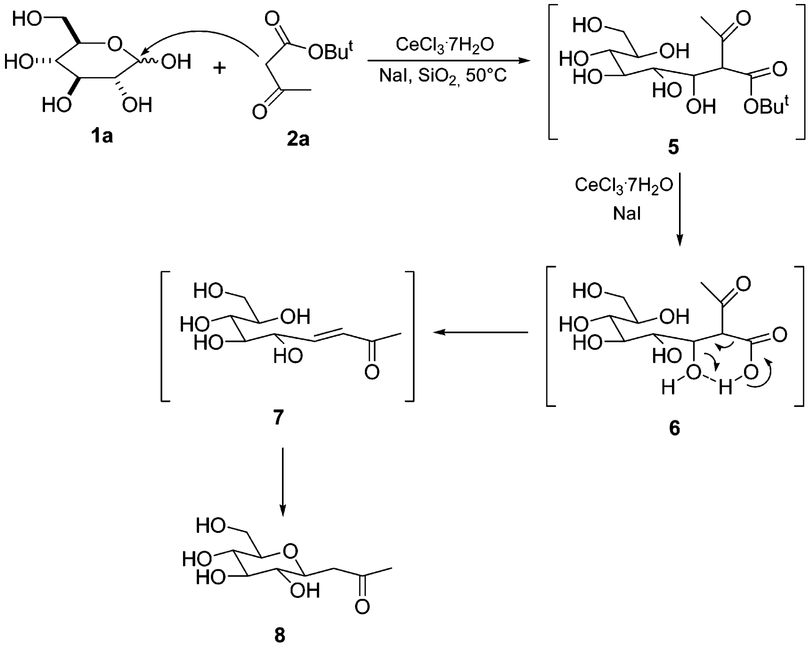
TABLE 2. Reaction of Aldohexoses (3) with β-Dicarbonyl Compounds (2) Promoted by $CeCl_3{\cdot}7H_2O-NaI$ System on SiO_2 Under Solvent-Free Conditions



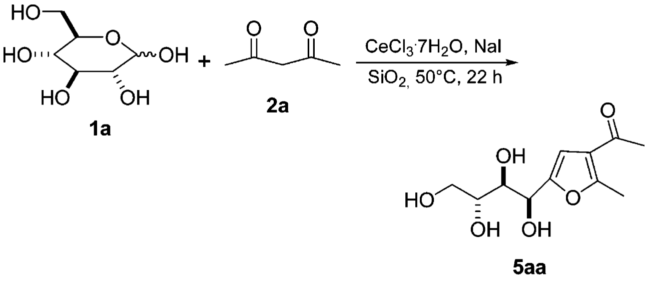
Entry	Aldohexose	Dicarbonyl Compound		Product[a]	Yield (%)[b]
		R	X		Time/h
1	 **1a**	Me **2a**	Me	 **5aa**	95 22
2	**1a**	Me **2b**	OEt	 **5ab**	85 30
3	**1a**	Me **2c**	n-Bu	 **5ac**	45[c] 30
4	**1a**	n-Bu **2d**	OEt	 **5ad**	83 30
5	**1a**	Me **2e**	OBu-t	 **5ae**	55[d] 48
6	**1a**	Ph **2f**	OEt	 **5af**	40 72
7	 **1b**	Me **2a**	Me	 **5ba**	97 18
8	 **1c**	Me **2b**	OEt	 **5cb**	95 18
9	**1c**	Me **2a**	Me	**5ba**	89 24

[a] All products were identified by their IR, NMR, MS, and elemental analysis. [b] All yields refer to pure isolated compounds. [c] No selectivity was obtained, and a mixture other the furan trisubstitute regioisomer was isolated. [d] Formation of the corresponding β-C-glycosidic ketone has been observed in 36% yield.

SCHEME 2. Proposed Mechanism for Formation of β-C-Glycosidic Ketone of Type 8



SCHEME 3. Yield Effect of Water on the Garcia Gonzalez Reaction Promoted by $CeCl_3$•$7H_2O$−NaI−SiO_2



with the cerium salt heptahydrate. The same reaction rate was obtained with 7 and 10 equiv of water. It is worth noting that not only does our Lewis acid perform best in the presence of water,[48] but also its promoting activity is amplified by the water. This effect is taken as a proof-of-principle that substrate interaction cerium(III) Lewis acid species and water are not mutually exclusive.[49] To obtain further evidence for this effect, we have carried out the reaction by adding D_2O instead of H_2O,[50] given that D_2O has a higher viscosity that makes mixing more difficult and reduces the hydrophobic effect.[51] The first results indicate a decrease in the reaction rate, but this isotopic effect can be only speculative because the transformation is performed on SiO_2, which naturally contains a lot of water as well as Si−OH functions. Therefore, the D_2O could become a trace amount highly diluted with H_2O; other kinetic experiments in support of this are in progress. However, the remarkable observed ability of water to generate more active species[52] can find explanation in its coordination, which simplifies the disaggregation of the crystal lattice of cerium salt and might lead to a notable increase in the Lewis acidity of the cerium available at the particle surface.[53]

The results have established that the choice of hydrated cerium(III) salt plays a crucial role in the ability of the $CeCl_3$•$7H_2O$−NaI system supported on SiO_2 to promote the Garcia Gonzalez reaction. We have attempted a similar reaction in the presence of silica gel and NaI without using $CeCl_3$•$7H_2O$. The reaction was not successful, and the starting materials remained intact. We have also noted that in the absence of NaI the procedure with $CeCl_3$•$7H_2O$ on SiO_2 does not afford the adduct **5** in the typical reaction conditions. Undoubtedly, the presence of NaI is also essential for allowing the efficient preparation of polyhydroxyalkyl furan derivatives **5** by reaction of aldohexoses with β-dicarbonyl compounds. These findings suggest that the $CeCl_3$•$7H_2O$−NaI combination leads to a more powerful Lewis acid. We therefore set about identifying the nature of the Lewis acid generated from a 1:1 mixture of $CeCl_3$•$7H_2O$ and NaI by NMR spectroscopy. For this we tried to study the complexation of substrate **1a** with $CeCl_3$•$7H_2O$ and with a $CeCl_3$•$7H_2O$−NaI combination. Unfortunately, no identifiable species could be discerned from the ^1H NMR and ^{13}C NMR, due, very probably, to the presence of paramagnetic Ce(III) species.[54]

The acceleration effect caused by addition of NaI to $CeCl_3$•$7H_2O$ might be rationalized by an halogen exchange reaction[55] that leads to more strong Lewis acid (eq 1). But hydrated CeI_3

$$\mathrm{CeCl_3 + n\,NaI \xrightarrow[n=1-3]{} CeCl_{(3-n)}I_n + n\,NaCl} \qquad (1)$$

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[48] Catalysis in water depends on the ability of the catalysts to tolerate water on one hand and to remain active on the other hand; see: (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209−217. (b) Bosnich, B. *Aldrichim. Acta* **1998**, *31*, 76−83.

[49] This hydrophobic amplification concept is marvelously rationalized in: Narayau, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279.

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alone shows an activity only slightly superior to that of $CeCl_3 \cdot 7H_2O$ and significatively lower than that the $CeCl_3 \cdot 7H_2O-NaI$ system.[56] Moreover, the system $CeCl_3 \cdot 7H_2O-3NaI$ is less efficient than a 1:1 combination, so that the iodide ion is not active as a promoter whereas cerium is. Certainly, this 1:1 combination of $CeCl_3 \cdot 7H_2O$ and NaI might give $CeCl_2I \cdot 7H_2O$, which might be a more powerful Lewis acid than $CeCl_3 \cdot 7H_2O$ parent. All of the efforts into structural characterization of this complex $CeCl_{3-n}I_n$ have been unsuccessful. For understanding the mechanistic role of NaI we have analyzed the interaction between $CeCl_3 \cdot 7H_2O$ with NaI on SiO_2 by X-ray photoelectron spectroscopy. This provides a valuable technique to quantify the chemical surroundings of the probed atom by means of the analysis of the chemical shift in the core level binding energies.[58] Fundamental reasons for this are the inherent element specificity of the element specific core level binding energies. Another reason is the sensitivity both to the amount of the element present and its localization at the surface, the latter characteristic caused by the short mean free path of low energy (30−1000 eV) photoelectrons in the solids. Insulating rare-earth trihalides like $CeCl_3$ are wide gap in the trivalent state.[59] Such systems show interesting double peak structures in the 3d core-level spectra with the two peaks showing dramatic changes depending on the halide element. This is a final state because in the two different screenings a shoulder at lower binding energy is observed.[60] We have started from a belief that $CeCl_3$ is a rare-earth trihalide whose initial state is f^1 ($Ce = [Xe]4f^15d^16s^2$), as no promotion of f electron is required for a trivalent bonding with chlorine. Nevertheless, in the final state the charge-transfer energy defined as the energy required to take an electron from the ligand p level to the unoccupied 4f level (about 9.7 eV)[61] ($f^2\upsilon$) is less than the value of the 4f-core hole Coulomb attraction (12.2 eV). This led to an $f^2\upsilon$ satellite (where υ is the hole in the valence) at about 3.4 eV lower binding energy. The intensity and energy of this satellite are sensitive to the degree of hybridization of the f states with the conduction states.[62] Even if the XPS spectra[63] were unable to determine the coordination environment of the Ce(III) ion because we do not observe a variation within few percent in the intensity of the f^2 satellite, the results suggest that there is no direct interaction between the cerium(III) site and the iodide ion. The activity of the $CeCl_3 \cdot 7H_2O-NaI$ system is mainly exerted in the heterogeneous phase, and above all, we believe that a chloro-bridged oligomeric structure[64] of $CeCl_3 \cdot 7H_2O$ is easily broken by donor species such as the iodide ion. The resulting monomeric $CeCl_3 \cdot 7H_2O-NaI$ complex is a more active Lewis acid promoter.

3. Conclusion

In conclusion, our procedure represents another example of how the $CeCl_3 \cdot 7H_2O-NaI$ system promotes new bond-forming reactions in solvent-free conditions, such as the popularly known Garcia Gonzalez reaction, which provide a simple and convenient methodology for the synthesis of densely functionalized molecules. At the end of these investigations it is clear that incorporation of NaI in the most common starting material for cerium complexes as such as $CeCl_3 \cdot 7H_2O$ results in remarkable improvements of key Lewis acid activity. Moreover, the study provides the first experimental evidence that the origin of the enhanced activity of the $CeCl_3 \cdot 7H_2O-NaI$ system is not due to a halogen exchange reaction, as it has been observed with other metal ions.[65] Further work is in progress in our laboratories to study other nucleophiles that may enhance the electrophilicity of Lewis acidic promoter by disaggregation of oligomeric structures. Moreover, we are currently expanding our procedure to cover other synthetically useful organic chemistry processes which are Lewis acid catalyzed because the use of catalytic promoters to minimize waste has become a demanding challenge for chemists when atom economy and green chemistry are considered.

4. Experimental Section[66]

General Procedure for the Garcia Gonzalez Reaction (5aa). Silica gel (0.5 g) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.113 g, 0.3 mmol) and NaI (13.4 mg, 0.3 mmol) in acetonitrile (7 mL), and the mixture was stirred overnight at room temperature. D-Glucose (**1a**) (0.18 g, 1.0 mmol) was added, and the reaction mixture was then stirred at room temperature for 1 h. The acetonitrile was removed by rotary evaporation and to the resulting powder was added 2,4-pentandione (**2a**) (0.17 mL, 1.3 mmol). Then, the mixture was mechanically stirred at an external temperature of 50 °C until the disappearance of the starting aldehexose (22 h, checked by TLC analysis). After addition of methanol (15 mL), the mixture was passed through a short pad of Celite and the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography on a silica gel column (eluent, dichloromethane−ethyl acetate, 90:10) to give 0.26 g (95% yield) of the corresponding Garcia Gonzalez adduct **5aa**.

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Supporting Information Available: Complete experimental procedures and data on new compounds, copies of NMR on structures determined, and XPS measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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