

Ytterbium Triflate-Promoted Tandem One-Pot Oxidation–Cannizzaro Reaction of Aryl Methyl Ketones

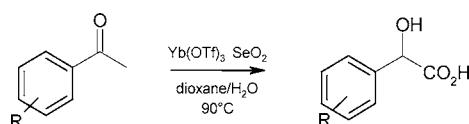
Massimo Curini,* Francesco Epifano, Salvatore Genovese,
M. Carla Marcotullio, and Ornelio Rosati

Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica,
Via del Liceo, 06123 Perugia, Italy

curmax@unipg.it

Received January 20, 2005

ABSTRACT



Ytterbium triflate was shown to be an effective catalyst in promoting the synthesis of either isopropyl esters or free α -hydroxy-arylacetic acids from substituted aromatic glyoxals and aryl methyl ketones, respectively. The reaction to provide acids starting from differently substituted ketones was carried out by an environmentally friendly method using an aqueous medium as a solvent and giving the adducts in 78–99% yield without any further purification after the usual workup.

The Cannizzaro reaction is one of the oldest processes described in synthetic organic chemistry.¹ It is conventionally promoted by strong bases such as stoichiometric amounts of alkali metal hydroxides at high temperatures. Moreover, requiring drastic conditions, the Cannizzaro reaction is of limited use and scope, except when performed as an intramolecular process. In particular, when carried out using aryl glyoxals as starting materials, the intramolecular Cannizzaro reaction becomes one of the most efficient routes for the synthesis of mandelic acid and other substituted α -hydroxy-arylacetic acids that are important synthons of many natural and semisynthetic biologically active compounds such as prostaglandins,² β -lactams,^{3,4} vanillic acid metabolites,⁵ and homatropine.⁶ Recently, new methods have been developed using Lewis acids as catalysts instead of

“traditional” Brønsted bases to promote the intramolecular Cannizzaro reaction for the synthesis of mandelic acid derivatives. The use of catalytic quantities of a Lewis acid would in fact decrease competitive side reactions that frequently occur when the process is carried out in a strong basic medium. Until now, only one method has been reported to efficiently promote the synthesis of α -hydroxy-arylacetic esters from the corresponding glyoxals: recently Morken and co-workers⁷ described the use of 10 mol % $\text{Cr}(\text{ClO}_4)_2$ hexahydrate as a catalyst in 2-propanol/dichloroethane as a solvent for 24 h at room temperature to obtain isopropyl α -hydroxy-aryl acetates in 40–84% yield. Notably, other Lewis acids such as $\text{Cu}(\text{II})$, $\text{Fe}(\text{III})$, Li^+ , Mg^{2+} , Al^{3+} , Y^{3+} and other transition metal salts gave no reaction or their catalyzed processes were limited by conditions requiring high temperature and more than 20% loading and by the occurrence of several side reactions.⁸ Although the one reported by Morken and co-workers represents an effective method for converting glyoxals into mandelate ester derivatives, the

(1) For a review, see: Geissman, T. A. *Org. React.* **1944**, 2, 94–113.

(2) Miersch, O.; Kramell, R.; Parthier, B.; Wasternack, C. *Phytochemistry* **1999**, 50, 353–361.

(3) Hoover, J. R. E.; Dunn, G. L.; Jakas, D. R.; Lam, L. L.; Taggart, J. J.; Guarini, J. R.; Phillips, L. J. *Med. Chem.* **1974**, 17, 34–41.

(4) Nishihata, T.; Takahagi, H.; Yamamoto, M.; Tomida, M.; Rytting, J. H.; Higuchi, T. *J. Pharm. Sci.* **1984**, 73, 109–113.

(5) Yoshioka, M.; Yoshida, A.; Ichihashi, Y.; Saito, H. *Chem. Pharm. Bull.* **1985**, 33, 2145–2148.

(6) El Nimr, A. E.; Salama, H. A.; Khalil, R. M.; Kassem, M. A. *Pharmazie* **1983**, 38, 728–730.

(7) Russell, A. E.; Miller, S. P.; Morken, J. P. *J. Org. Chem.* **2000**, 65, 8381–8383.

(8) (a) Maruyama, K.; Murakami, Y.; Yoda, K.; Mashino, T.; Nishinaga, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1617–1618. (b) Jin, S. J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, 55, 3011–3018. (c) Okuyama, T.; Kimura, K.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1982**, 55, 2285–2286.

use of toxic and hazardous Cr(III) and perchlorate salts,⁹ the use of toxic chlorinated solvents, the need for SiO₂ gel column chromatography for purification of adducts, and no recycling of the catalyst renders this method environmentally unsound, especially with regard to a potential application on large-scale synthesis. So, although different methods are available for the synthesis of the above cited compounds,¹⁰ development of another facile, high-yielding, nonpolluting preparation is still of great importance.

Table 1. Yb(OTf)₃-Catalyzed Cannizzaro Reaction of Aryl Glyoxals

Substrate	Product	Yield (%) ^a
		99
		80
		70
		84
		84

^a Yields of pure isolated products, characterized by IR, GC-MS, ¹H NMR, and ¹³C NMR.

Recently, we began a research program to explore the utility of lanthanide triflate-catalyzed processes in synthetic organic chemistry, and in particular we studied the use of Yb(OTf)₃ as a catalyst to promote new carbon–carbon and carbon–heteroatom bond formation.¹¹ Lanthanide triflates

are important as a novel class of Lewis acids because they are water-tolerant, nontoxic, reusable catalysts and their use in organic synthesis has been recently exhaustively reviewed.¹² Herein, we wish to report that the intramolecular Cannizzaro reaction can be effectively catalyzed by Yb(OTf)₃ in good yield using aromatic glyoxals as starting materials to give mandelate esters and more generally that Yb(OTf)₃ is capable of producing α-hydroxy-arylacetic acids directly from aryl methyl ketones.

Table 2. Yb(OTf)₃-Catalyzed Synthesis of Mandelic Acid Derivatives

Substrate	Product	Yield (%) ^a
		90
		97
		84
		99
		78
		78
		99
		85

^a Yields of pure isolated products, characterized by IR, GC-MS, ¹H NMR, and ¹³C NMR.

As a preliminary test reaction we studied the conversion of commercially available phenyl glyoxal hydrate (**1**) to isopropyl mandelate (**2**) in the presence of Yb(OTf)₃. The reaction was optimized by carrying it out in 2-propanol at 80 °C for 18 h with 10 mol % catalyst; under these conditions, **2** was obtained in 80% yield after purification by SiO₂ gel column chromatography.⁷ Other aryl glyoxals,

(9) Perchlorate salts pose an explosion hazard. See: *Prudent Practices for Handling Hazardous Chemicals in Laboratories*; National Academy Press: Washington, DC, 1981; p 65.

(10) Chung, Y. M.; Gong, J. H.; Kim, J. N. *Bull. Kor. Chem. Soc.* **2002**, 23, 1363–1364 and references therein.

(11) (a) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, 42, 3193–3195. (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Eur. J. Org. Chem.* **2002**, 1562–1565. (c) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Tetrahedron Lett.* **2002**, 43, 4895–4897. (d) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552–554. (e) Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M. C. *Eur. J. Org. Chem.* **2003**, 1631–1634. (f) Curini, M.; Epifano, F.; Montanari, F.; Rosati, O.; Taccone, S. *Synlett* **2004**, 1832–1834.

used as model compounds, were synthesized from the corresponding methyl ketone by SeO₂ oxidation as described in the literature,¹³ and the results of their conversion into isopropyl α -hydroxy esters, under the same reaction conditions, are reported in Table 1.

Although yields of this reaction are very good, the low yields (5–26%) obtained in the synthesis of aryl glyoxals dramatically decrease the overall yield of the “ketone to mandelate ester” process, and this inconvenience prompted us to search for an alternative method to carry out this transformation.

It is well known that, among lanthanide elements, Yb³⁺ is the “hardest” and thus most oxophilic, due to its smaller ionic radius.¹⁴ So, coordination of an oxygen atom of a carbonyl to Yb³⁺ would result in a great enhancement of the reactivity of this functional group, as witnessed by several high-yielding transformations of ketones and aldehydes catalyzed by Yb(OTf)₃.⁶ Because glyoxal formation and Cannizzaro reactions involve carbonyl functions, it is conceivable that Yb(OTf)₃ could be an ideal catalyst for both efficiently promoting the methyl oxidation to aldehyde by SeO₂ (thus increasing yields of this step) and subsequent rearrangement of glyoxal to the α -hydroxy acid, and these two reactions could be carried out in the same reaction vessel.

The possibility of employing Yb(OTf)₃ as an efficient catalyst in aqueous media suggested the use of H₂O as a solvent. Thus, when acetophenone was treated with a 2-fold excess of SeO₂ and 0.1 mmol of Yb(OTf)₃ in a 3:1 dioxane/H₂O mixture at 90 °C for 18 h, mandelic acid (**13**) was obtained in 90% yield without any further purification after standard workup. The same protocol was applied to differently substituted acetophenones and to heteroaromatic and condensed aromatic methyl ketones, affording in each case very good yields, ranging from 78 to 99%, as reported in Table 2.

After each reaction, Yb³⁺ was recovered from the mother liquors simply by precipitation as the hydroxide at pH 12

and filtration, and this was transformed again into the triflate salt.¹⁵ Excess SeO₂ and other selenium-containing byproducts were removed by adsorption on Celite. The process reported herein is selective in yielding α -hydroxy-arylacetic acids as the only reaction products, and no side products such as intermediate glyoxals or those deriving, for example, from aldol-type condensations or further oxidation of the intermediate aldehyde function to α -ketoacids were detected.

To propose a rational reaction mechanism, we hypothesize that coordination of the carbonyl oxygen to Yb³⁺ greatly enhanced the susceptibility of the methyl to be oxidized by SeO₂, not only by electronic effects but also because the oxidation would provide a stable chelate between the metal center and the hydrate form of glyoxal, from which an internal 1,2-hydride shift would furnish the hydroxy acid, in a mechanistic way similar to that described by Morken and co-workers.⁷

In conclusion, we disclosed an easy and environmentally sound method for the synthesis of α -hydroxy-arylacetic acids directly from substituted aryl methyl ketones under the catalysis of Yb(OTf)₃. The simple workup procedure, mild reaction conditions, and high yields (78–99%) make our methodology a valid contribution to the existing processes in the field of mandelic acid derivative synthesis. Moreover, the reaction described herein represents, to the best of our knowledge, the first example of a direct one-pot transformation of aryl methyl ketones into α -hydroxyacetic acids.

Acknowledgment. Financial support from MIUR National Project “Sviluppo di processi sintetici ecocompatibili nella sintesi organica”, COFIN 2004, and from University of Perugia is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data, including spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL050125E

(12) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L. *Chem. Rev.* **2002**, *6*, 2227–2302.

(13) Fuson, R. C.; Emerson, W. S.; Gray, H. W. *J. Am. Chem. Soc.* **1939**, *61*, 480–482.

(14) Pitzer, K. S. *Acc. Chem. Res.* **1974**, *12*, 271–276.

(15) Fieser, M. *Reagents for Organic Synthesis*; Wiley-Interscience: New York; Vol. 14, p 188.