Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2705–2708
Tetrahedron Letters

Niobium(V) oxide: a new and efficient catalyst for the transesterification of β-keto esters

Mirela Inês de Sairre, Érika Soares Bronze-Uhle and Paulo Marcos Donate*

Universidade de São Paulo, Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Avenida Bandeirantes 3900, 14040-901 Ribeirão Preto, SP, Brazil

Received 7 December 2004; revised 28 January 2005; accepted 28 January 2005

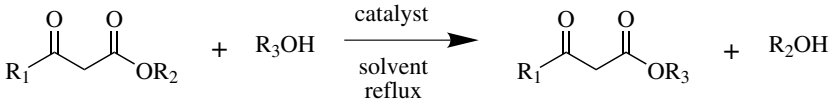
Abstract—Niobium(V) oxide is an efficient catalyst for the transesterification of β-keto esters with several kinds of alcohols, leading to good conversions. Moderate to good isolated product yields have been obtained at faster rates than those recently reported for various catalysts.

β-Keto esters are among the most important intermediates in organic synthesis, since they can be transformed into useful building blocks and serve as a valuable tool for chain extension reactions used in the synthesis of various complex compounds.[1] In the literature, there are various alternative routes for the obtention of β-keto esters,[1,2] but the transesterification of these compounds has been recognized as a very important and useful process because it allows the preparation of more complex products from more easily accessible synthons.[3]

The transesterification of β-keto esters (Scheme 1) is an equilibrium process[3] that can be catalyzed by many kinds of catalysts, such as Brønsted base,[4] DMAP,[5] distanoxanes,[6] solid superacids,[7] zeolites,[8] titanium(IV) alkoxides,[9] indium triiodide,[10] natural clays,[2f,11] transition metal complexes,[12] Mo–ZrO_2,[13] nonionic superbase,[14] yttria–zirconia Lewis acid,[15] Mg–Al–O–*t*-butyl hydrotalcite,[16] diphenylammonium triflate,[17] montmorillonite,[18] zinc dust,[19] basic silica,[20] amberlyst-15,[21] sodium perborate,[22] lithium perchlorate,[23] and NBS.[24]

In connection with our interest in the synthesis of biologically active compounds, in this work we aimed at the transesterification of β-keto esters **1** to obtain **3** (Scheme 1), in toluene reflux, by using allylic alcohol or glycidol (**2**), and several types of catalysts described in the literature.[7,8,11,18,21] However, to our surprise, we were unable to find any pertinent examples of transesterification reactions with epoxy alcohols in the literature. Moreover, it was found that a number of the catalysts reported in the literature extensively degraded the reaction products. Some of the tested modified clays (laponite RD, laponite RDS, and montmorillonite K-10)[11,18] only furnished low yields (29–48%) of the desired β-keto ester **3** ($R_1 = CH_3$, $R_2 = CH_2CH_3$, R_3OH = allylic alcohol or glycidol), even after a long reaction time (12–24 h). The SnO_2 catalyst[7] used under the same conditions afforded β-keto ester **3** in better yields (60–65%), after a shorter reaction time (8–12 h).

Therefore, these poor results prompted us to test a new catalyst that might be more suitable for the satisfactory



1 **2** **3**

Scheme 1. General transesterification process for β-keto esters.

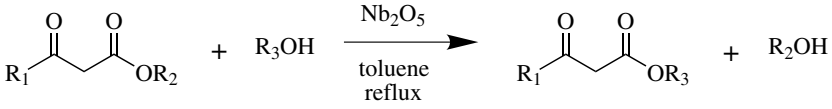
Keywords: Transesterification; β-Keto esters; Alcohols; Niobium oxide; Niobium catalyst.
* Corresponding author. Tel.: +55 16 602 3696; fax: +55 16 633 8151; e-mail: pmdonate@usp.br

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.158

interconversion of a β-keto ester through its transesterification with allylic or epoxy alcohols, which generally is not a trivial process.

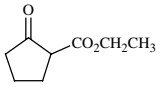
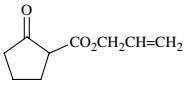
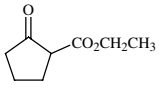
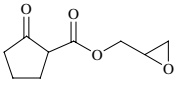
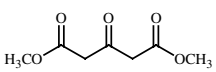
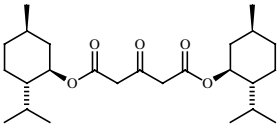
Niobium chemistry is not widely known, despite the increasing interest in the use of niobium compounds in many fields. In the area of heterogeneous catalysis, for instance, they are used as catalyst components.[25] Hydrated niobium(V) oxide ($Nb_2O_5{\cdot}nH_2O$) is a white, air-stable and water-insoluble solid, with unknown water content.[26] Among the various solid acid catalysts currently in use, niobium(V) oxide is particularly interesting for esterification and transesterification reactions,[27] since it presents high acid strength associated with both Lewis and Brønsted acid sites.[26] Moreover, this compound is resistant to water vapor when hydrated, which makes it an effective catalyst for reactions where water molecules participate or are released.[27,28] There are few examples of esterification reactions in the presence of niobium compounds reported in the literature.[25] Niobium(V) oxide exhibited high catalytic activity and 100% selectivity for the esterification of acetic acid with ethyl alcohol,[27a] and also for the esterification of acrylic acid with methanol,[27b] where good stability of the catalyst was observed. However, to the best of our knowledge, there is no report on the use of this compound in the transesterification process. Therefore, we decided to investigate the use of niobium(V) oxide as a new catalyst for the transesterification of β-keto esters **1** with several kinds of alcohols (Scheme 2). The transesterification results obtained by us are presented in Table 1.

With this new catalyst, the transesterification of the β-keto esters **1** with a variety of alcohols led to moderate to good isolated yields, after reduced reaction times (5–8 h).[29] Ethyl cyclopentanone-2-carboxylate, a sterically hindered substrate, was quite rapidly converted into the desired product, in moderate isolated yields (57–63%, Table 1, entries 3 and 6). Even the double transesterification of dimethyl acetone-1,3-dicarboxylate with enantiopure (−)-menthol gave the product with a relatively good isolated yield (61%, Table 1, entry



Scheme 2. Transesterification process for β-keto esters with the catalyst niobium(V) oxide.

Table 1. Transesterification reaction of β-keto esters **1** with the catalyst niobium(V) oxide, via Scheme 2[a]

Entry	β-Keto ester **1**	Alcohol **2**	Product **3**	Reaction time (h)	Conversion[b] of **1** (%)	Isolated yield[c] of **3** (%)
1	$R_1 = CH_3$, $R_2 = CH_2CH_3$	Allylic alcohol	$R_1 = CH_3$, $R_3 = CH_2CH{=}CH_2$	6	65	52
2	$R_1 = CH_3$, $R_2 = CH_3$	Allylic alcohol	$R_1 = CH_3$, $R_3 = CH_2CH{=}CH_2$	6.5	70	58
3		Allylic alcohol		8	85	57
4	$R_1 = CH_3$, $R_2 = CH_2CH_3$	Glycidol	$R_1 = CH_3$, 	5	75	58
5	$R_1 = CH_3$, $R_2 = CH_3$	Glycidol	$R_1 = CH_3$, 	5.5	80	76
6		Glycidol		8	70	63
7	$R_1 = CH_3$, $R_2 = CH_3$	*n*-Butyl alcohol	$R_1 = CH_3$, $R_3 = CH_2CH_2CH_2CH_3$	5.5–7[d]	100 (100, 100)[d]	98 (93, 87)[d]
8	$R_1 = CH_3$, $R_2 = CH_3$	*t*-Butyl alcohol	$R_1 = CH_3$, $R_3 = C(CH_3)_3$	8	93	60
9	$R_1 = CH_3$, $R_2 = CH_3$	2-Propanol	$R_1 = CH_3$, $R_3 = CH(CH_3)_2$	8	81	63
10	$R_1 = CH_3$, $R_2 = CH_3$	Benzyl alcohol	$R_1 = CH_3$, $R_3 = CH_2C_6H_5$	12	50	33
11		(−)-Menthol		8	65	61

[a] All the reactions were carried out with niobium(V) oxide in toluene reflux, with distillation of the formed alcohol.[29]
[b] Conversion determined by gas chromatography (GLC) of the crude reaction mixture.
[c] Isolated yield of β-keto ester **3** after purification by silica gel column chromatography.
[d] Catalyst was recovered and reused three times without appreciable activity loss.

11).[5d] Substrate conversion reached a fairly good value (65–100%) with most of the β-keto esters and alcohols employed, but did not exceed 50% when benzyl alcohol was used (Table 1, entry 10), probably due to the easy dehydration of this compound to form benzyl ether in the reaction conditions. As volatile alcohols can also be removed by distillation during the transesterification process, gradual addition of new portions of alcohol significantly increased substrate conversion. The transesterification of methyl acetoacetate with allylic alcohol and glycidol produced better results than the corresponding ethyl derivative (Table 1, entries 1, 2, 4, and 5). The nature of the R_3 group in the alcohols had a significant effect on the transesterification reactions. Considering both conversion and isolated yields, primary alcohols afforded much superior results to those obtained with secondary and tertiary alcohols (Table 1, entries 7–9). Allylic alcohol reacted with different β-keto esters (Table 1, entries 1–3), leading to good conversions (65–85%) and moderate isolated yields (52–58%). These latter results show this process is very useful, since the transesterification of allylic alcohols is rather difficult due to successive decarboxylation and rearrangement.[8] Good results were also obtained with glycidol (Table 1, entries 4–6). In the case of niobium(V) oxide, catalyst lifetime could be maximized due to its easy recovery. In fact, niobium(V) oxide was recovered and reused at least three times in our experiments, without appreciable activity loss, as indicated in the transesterification of *n*-butyl alcohol (Table 1, entry 7).

In summary, we have demonstrated that niobium(V) oxide serves as an efficient catalyst for the transesterification of β-keto esters with several kinds of alcohols, leading to good conversion and moderate to good isolated product yields. Therefore, it is expected that this catalyst will find general application for the preparation of these important compounds in the future.

Acknowledgements

The authors wish to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support. The generous gift of niobium oxide samples by CBMM–Companhia Brasileira de Metalurgia e Mineração is also gratefully acknowledged.

References and notes

1. (a) Witzemann, J. S.; Nottingham, W. D. *J. Org. Chem.* **1989**, *54*, 2815; (b) Otera, J. *Chem. Rev.* **1993**, *93*, 1449; (c) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425; (d) He, X. C.; Wang, B.; Yu, G. L.; Bai, D. L. *Tetrahedron: Asymmetry* **2001**, *12*, 3213; (e) Sugimura, T.; Nakagawa, S.; Tai, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 355; (f) Franco, D.; Riahi, A.; Henin, F.; Muzart, J.; Dunach, E. *Eur. J. Org. Chem.* **2002**, 2257; (g) Nishiwaki, N.; Nishida, D.; Ohnishi, T.; Hidaka, F.; Shimizu, S.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *J. Org. Chem.* **2003**, *68*, 8650; (h) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837; (i) Fraga, C. A. M.; Teixeira, L. H. P.; Menezes, C. M. S.; Sant'Anna, C. M. R.; Ramos, M. C. K. V.; Aquino Neto, F. R.; Barreiro, E. J. *Tetrahedron* **2004**, *60*, 2745.
2. (a) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1–203; (b) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241; (c) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917; (d) Park, H. S.; Lee, I. S.; Kim, Y. H. *Tetrahedron Lett.* **1995**, *36*, 1673; (e) Peçanha, E. P.; Barreiro, E. J.; Fraga, C. A. M. *Quím. Nova.* **1997**, *20*, 435; (f) Bandgar, B. P.; Uppalla, L. S.; Sadavarte, V. S. *Green Chem.* **2001**, *3*, 39; (g) Charonnet, E.; Filippini, M. H.; Rodriguez, J. *Synthesis* **2001**, 788; (h) Cordova, A.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 1906; (i) Habib-Zahmani, H.; Hacini, S.; Charonnet, E.; Rodriguez, J. *Synlett* **2002**, 1827; (j) Shimada, Y.; Matsuoka, Y.; Irie, R.; Katsuki, T. *Synlett* **2004**, 57; (k) Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2004**, *45*, 7027.
3. (a) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065; (b) Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J. P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380.
4. Shimomura, A.; Cohen, J. B. *J. Chem. Soc.* **1922**, *121*, 883.
5. (a) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618; (b) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1988**, *53*, 449; (c) Decicco, C. P.; Cano, F. H. *J. Org. Chem.* **1992**, *57*, 1005; (d) Christoffers, J.; Önal, N. *Eur. J. Org. Chem.* **2000**, 1633.
6. (a) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383; (b) Otera, J.; Dan-Oh, N.; Nozaki, J. *J. Org. Chem.* **1991**, *56*, 5307; (c) Xiang, J. N.; Toyoshima, S.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3670.
7. Chavan, S. P.; Zubaidha, P. K.; Dantale, S. W.; Keshavaraja, A.; Ramaswamy, A. V.; Ravindranathan, T. *Tetrahedron Lett.* **1996**, *37*, 233.
8. (a) Balaji, B. S.; Sasidharam, M.; Kumar, R.; Chanda, B. *Chem. Commun.* **1996**, 707; (b) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*, 13237; (c) Sasidharan, M.; Kumar, R. *J. Mol. Catal. A: Chem.* **2004**, *210*, 93.
9. Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096.
10. Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 6027.
11. (a) Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org. Chem.* **1998**, *63*, 1058; (b) Da Silva, F. C.; Ferreira, V. F.; Rianelli, R. S.; Perreira, W. C. *Tetrahedron Lett.* **2002**, *43*, 1165.
12. Kantham, M. L.; Neeraja, V.; Bharathi, B.; Reddy, C. V. *Catal. Lett.* **1999**, *62*, 67.
13. Reddy, B. M.; Redy, V. R.; Manohar, B. *Synth. Commun.* **1999**, *29*, 1235.
14. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.
15. (a) Kumar, P.; Pandey, R. K. *Synlett* **2000**, 251; (b) Pandey, R. K.; Deshmukh, A. N.; Kumar, P. *Synth. Commun.* **2004**, *34*, 1117.
16. Choudary, B. M.; Kantam, M. L.; Reddy, C. V.; Aranganathan, S.; Santhi, P. L.; Figueras, F. *J. Mol. Catal. A: Chem.* **2000**, *159*, 411.
17. Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249.
18. (a) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. *Tetrahedron* **2000**, *56*, 7291; (b) Bandgar, B. P.; Pandit, S. S.; Sadavarte, V. S. *Green Chem.* **2001**, *3*, 247; (c) Jin, T. S.; Zhang, S. L.; Li, T. S. *Green Chem.* **2002**, *4*, 32.
19. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *J. Chem. Res. (S)* **2001**, 16.

20. Kantham, M. L.; Sreekanth, P. *Catal. Lett.* **2001**, *77*, 241.
21. Chavan, S. P.; Subbarao, Y. T.; Dantale, S. W.; Sivappa, R. *Synth. Commun.* **2001**, *31*, 289.
22. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Chem. Lett.* **2001**, 894.
23. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Synlett* **2001**, 1338.
24. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Synlett* **2001**, 1715.
25. (a) Nowak, I.; Ziolek, M. *Chem. Rev.* **1999**, *99*, 3603; (b) Tanabe, K. *Catal. Today* **2003**, *78*, 65.
26. Iizuka, T.; Ogasawara, K.; Tanabe, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2927.
27. (a) Chen, Z. H.; Iizuka, T.; Tanabe, K. *Chem. Lett.* **1984**, 1085; (b) Iizuka, T.; Fujie, S.; Ushikubo, T.; Chen, Z. H.; Tanabe, K. *Appl. Catal.* **1986**, *28*, 1.
28. Moraes, M.; Pinto, W. S. F.; Gonzales, W. A.; Carmo, L. M. P. M.; Pastura, N. M. R.; Lachter, E. R. *Appl. Catal. A* **1996**, *138*, L7.
29. *General procedure for transesterification*: A mixture of β-ketoester **1** (1 equiv), alcohol **2** (2 equiv) and the catalyst (10% weight of β-ketoester) in toluene (about 20 mL) was refluxed in a system provided with a distillation condenser to remove the alcohol formed. The reaction was monitored by gas chromatography (GLC). After the consumption of β-ketoester was ceased, the catalyst was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel column, eluted with a mixture of *n*-hexane–ethyl acetate in different proportions, to afford the pure β-ketoester **3**. Isolated yields are indicated in Table 1. All products were analyzed by NMR, IR, and GC/MS, and the spectra were consistent with the structure of the desired products.