Tetrahedron Letters 54 (2013) 703–706

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Manganese(II) salts as efficient catalysts for chemo selective transesterification of β-keto esters under non-conventional conditions

G. Krishnaiah [a], B. Sandeep [b], D. Kondhare [d], K. C. Rajanna [a,*], J. Narendar Reddy [b], Y. Rajeshwar Rao [c], P. K. Zhubaidha [d]

[a] Department of Chemistry, Osmania University, Hyderabad 500 007, AP, India
[b] Department of Chemistry, Govt. City College, Hyderabad 500 001, AP, India
[c] Department of Chemistry, Rajiv Gandhi University of Knowledge Technologies, IIIT Basara, AP, India
[d] School of Chemical Sciences, SRTM University, Nanded 431 606, MS, India

ARTICLE INFO

Article history:
Received 31 October 2012
Revised 7 December 2012
Accepted 8 December 2012
Available online 19 December 2012

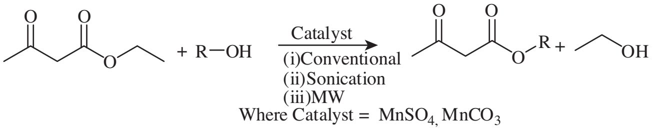
Keywords:
Transesterification
β-Ketoesters
Sonication
Microwave irradiation
Manganese carbonate
Manganese sulfate

ABSTRACT

Transesterification of β-ketoesters with various alcohols has been studied under conventional and non-conventional conditions using desktop chemicals such as Mn(II) salts as catalysts. These methods offered transesterification of β-ketoesters in good yields with dramatic rate accelerations and reduced reaction times. The developed protocols under nonconventional methods such as sonication and microwave irradiation are highly promising compared with the existing procedures.

Transesterification of β-ketoesters is an important class of synthetic procedures.[1] Transesterification is more advantageous than the ester synthesis from carboxylic acid and alcohol, due to poor solubility of some of the acids in organic solvents, whereas the esters are commonly soluble in most of the solvents.[2] Some esters, especially methyl and ethyl esters are commercially available and thus serve conveniently as starting materials in transesterification. A survey of literature shows that β-ketoesters are versatile organic intermediates that are extensively used in agrochemical, pharmaceutical, and dyestuff industries.[3] Apart from these β-ketoesters are also useful organic building blocks for the synthesis of complex natural products like thiolactomycin,[4] polyoxomimic acid,[5] prostaglandin,[6] and syncarpic acid.[7] In general, transesterification of β-ketoesters is a sluggish reaction,[8,9] which requires large excess of β-ketoester and high boiling alcohols. Over a period of time quite some attention is paid to effectively catalyze this reaction by using Bronsted acids, Lewis acids,[10] and basic catalysts.[11–14] But protic acid catalysts such as sulfuric acid and phosphoric acid are known to cause several environmental problems.[1] Therefore, lot of attention has been diverted to overcome this problem. Several heterogeneous catalysts such as sulfated tin oxide,[15] borated zirconia,[16] zeolites,[17] kaolinitic clay,[18] Mo–ZrO_2,[19] $FeSO_4$, and $CuSO_4$,[20] yettria-based strong Lewis acid,[21] DMAP,[22] Zinc,[23] montmorillonite K-10,[24] Mg–Al–O–*t*-Bu hydrotalcite,[25] and ionic liquid-regulated sulfamic acid[26] have been employed to minimize the problems associated with the homogeneous catalysts.

Although there are many reagents to catalyze the transesterification, they are either expensive, less selective, and require long reaction times. Therefore, practical and environmentally benign protocols are needed for laboratory and industrial scale preparations. Manganese (Mn) is a versatile element[27] with the electronic configuration [Ar] $4s^2$ $3d^5$. It is a required trace mineral for all known living organisms and essential for aerobic life because its compounds are not highly toxic. The most common oxidation states of manganese are +2, +3, +4, +6, and +7, though oxidation states from −3 to +7 are observed. Mn(II) often competes with Mg(II) in biological systems. Manganese(II) ions are known to function as cofactors for a large variety of enzymes with many



Scheme 1. Transesterification of β-ketoesters.

---

* Corresponding author.

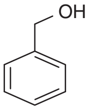
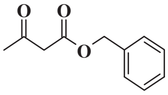
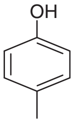
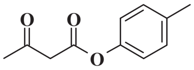
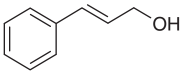
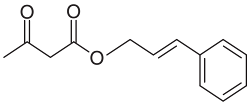
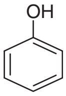
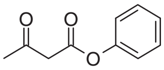
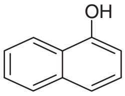
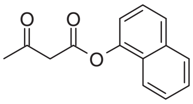
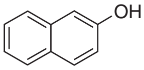
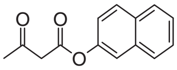
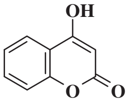
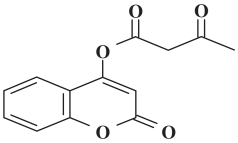
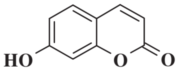
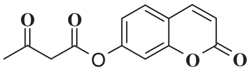
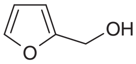
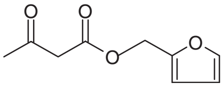
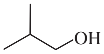
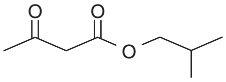
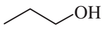
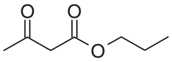
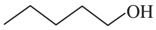
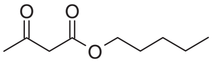
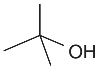
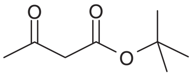
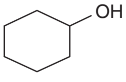
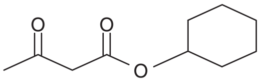
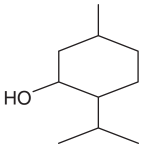
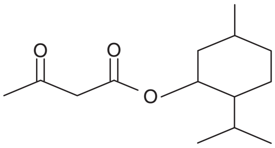
E-mail addresses: kcrajannaou@yahoo.com, kcrajannaou@rediffmail.com (K.C. Rajanna).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.030

functions. Manganese enzymes are particularly essential in the detoxification of superoxide free radicals in organisms that must deal with elemental oxygen. Manganese also functions in the oxygen-evolving complex of photosynthetic plants. Manganese carbonate is widely used as an additive to plant fertilizers to cure Mn deficient crops. Above all, Mn(II) is a well known readily available, easy to use, inexpensive compound. Probably because of these reasons Mn(II) has been used as a catalyst for rate enhancements in several chemical reactions performed under homogeneous and heterogeneous conditions.[28] Compounds such as β-ketoesters are multicoupling reagents having electrophilic carbonyl and nucleophilic carbon which make them a valuable tool for the synthesis of complex molecules. Toluene was chosen as a solvent since it forms an azeotropic mixture with ethanol content

Table 1

Ultrasonic and microwave assisted chemoselective transesterification of ethyl acetoacetate by certain hydroxy compounds in the presence of inexpensive Mn(II) carbonate and Mn(II) sulfate

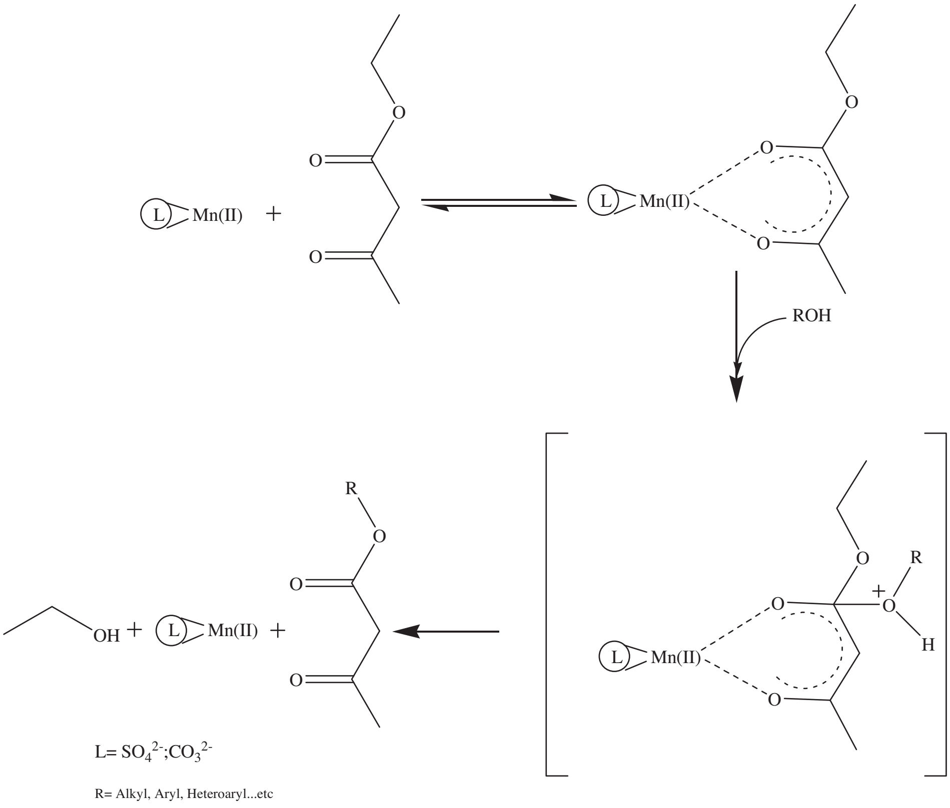
Entry	Hydroxy compound	Product	Mn(II) catalyst	Conventional synthesis		USAS		MWAS	
				Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1			$MnSO_4$ $MnCO_3$	18.0 18.0	72 75	2.00 2.15	73 74	0.75 0.75	72 74
2			$MnSO_4$ $MnCO_3$	24.0 24.0	76 73	3.50 3.50	74 75	0.83 0.83	73 75
3			$MnSO_4$ $MnCO_3$	24.0 24.0	76 72	3.15 3.15	73 71	0.83 0.83	72 75
4			$MnSO_4$ $MnCO_3$	24.0 24.0	68 69	3.50 3.15	67 71	0.75 0.75	70 69
5			$MnSO_4$ $MnCO_3$	24.0 24.0	62 60	3.50 3.40	60 63	0.75 0.75	65 65
6			$MnSO_4$ $MnCO_3$	24.0 24.0	58 63	3.30 3.30	61 64	0.91 0.91	64 67
7			$MnSO_4$ $MnCO_3$	24.0 24.0	57 52	2.50 2.50	59 55	0.66 0.66	65 69
8			$MnSO_4$ $MnCO_3$	24.0 24.0	58 53	2.30 2.40	59 61	0.58 0.58	68 65
9			$MnSO_4$ $MnCO_3$	18.0 18.0	60 60	2.15 2.15	69 65	0.63 0.66	68 65
10			$MnSO_4$ $MnCO_3$	15.0 15.5	68 69	3.00 3.15	73 72	0.75 0.70	72 70
11			$MnSO_4$ $MnCO_3$	16.0 16.0	71 71	3.00 3.00	75 79	0.91 0.90	75 75
12			$MnSO_4$ $MnCO_3$	16.0 16.0	63 64	3.15 3.00	67 66	0.83 0.83	70 70
13			$MnSO_4$ $MnCO_3$	19.0 19.0	58 60	2.15 2.15	60 60	0.66 0.66	57 58
14			$MnSO_4$ $MnCO_3$	16.0 16.0	67 65	2.15 2.30	72 75	0.70 0.70	68 70
15			$MnSO_4$ $MnCO_3$	18.0 18.0	57 54	2.15 2.15	69 70	0.66 0.66	70 75

of 70%, owing to which the effectiveness of ethanol removal increases. In this present work, we report that Mn(II) serves as an efficient catalyst for the selective transesterification of β-ketoesters with a variety of alcohols and ethyl acetoacetate (Scheme 1).

Preliminary studies with Mn(II) sulfate and Mn(II) carbonate as catalysts for transesterification of ethylacetoacetate (EAA) with hydroxy compounds indicated that the reactions are too sluggish even at reflux temperatures. These observations necessitated us to carry out the reactions under non-conventional conditions such as sonication and microwave irradiation because in recent past ultrasonically assisted (USA)[29–32] and microwave assisted (MWA)[33,34] protocols provided important tools to accelerate chemical reactions by providing eco-friendly and green environment.[35]

Control experiments[36] were performed with a mixture of ethyl acetoacetate (5 mmol), phenol (5 mmol), and varied amounts of catalyst in the range of 0.2–3.0 mmol (separately Mn(II) sulfate and Mn(II) carbonate) in toluene (20 mL) stirred at 100–110 °C in a round bottom flask provided with a distillation condenser to remove ethanol and the progress of the reaction monitored by thin layer chromatography (TLC). Reactions afforded very good yield of product only when 1.0 mmol catalyst was used. Below 1.0 mmol reactions were too slow even after 24 h and under reflux conditions, and above 1.0 mmol reaction times and yield of the product did not differ much. In view of this we have performed the reaction under ultrasonic and microwave assisted (USA and MWA) conditions.[37] Experimental results obtained for the transesterification reaction with a variety of alcohols under different conditions are summarized in Table 1, which indicated that even though the reaction times in Mn(II) sulfate and Mn(II) carbonate mediated reactions are too long, very good yields of products are obtained. The +2 oxidation state of Mn is the most used state in living organisms for essential functions while other states are toxic for the human body. The +2 oxidation state of Mn results from the removal of two 4s electrons, leaving a 'high spin' ion in which all five of the 3d orbitals contain a single electron. Mn(II) is a hard acid with sufficient number of vacant orbitals that can easily form adducts with ethyl acetoacetate and hydroxy compounds. According to Pearson's HSAB theory,[38] 'Hard acids (HA) prefer to bind to hard bases (HB) and soft acids (SA) prefer to bind to soft bases (SB)'. Ethyl acetoacetate being a harder base than hydroxy compound interaction between hard acid Mn(II) and hard base ethyl acetoacetate through two carbonyl oxygen atoms to form a cyclic intermediate is more likely. Further support for the formation of cyclic intermediate during the complexation of Lewis acid with 1,3 dicarbonyl systems can be obtained from the recent work of Dario Pasini et al. on supramolecular systems.[39] The cyclic intermediate thus formed then probably reacts with hydroxy compound and affords the product with the elimination of ethyl alcohol and Mn(II) catalyst. Reaction sequence of the proposed mechanism is shown in Scheme 2. Further, it is interesting to note that the catalyst could be recycled without any problem.

Comparison of the results obtained under three procedures made it possible to draw some general conclusions regarding the effect of sonication and MW irradiation on the transesterification. Data presented in Table 1 clearly indicate that even though the yields of end products are by and large similar with very good percentage, there is a remarkable change in the rates/reaction times from the conventional method to sonication and/or microwave irradiation. Reaction times reduced by almost ten times from conventional to USA conditions. This remarkable rate acceleration could be attributed to the 'Cavitation phenomenon', which is generated during ultra-sonication. A large amount of energy and pressure are released from the collapse of cavitation bubbles during sonication of the reaction,[29–32] which may cause an increase in



SCHEME-2

Scheme 2. Mn(II) catalyzed transesterification mechanism (proposed).

the fraction of activated molecules compared with normal reactions resulting in higher rates of the reaction. MW irradiation generates volumetric nature of power dissipation in dielectric, which causes direct heating inside the sample.[33–35] This in situ mode of energy conversion leads to a fast heating rate with minimized thermal gradients. This leads to the reduction of the reaction times rapidly as observed in the present study from several hours (16–24 h) in the conventional reaction to a few minutes (45 min) in the MWA reaction.

In conclusion, we have demonstrated that Mn(II) salts such as sulfate and carbonate could be used as efficient and selective catalysts for the transesterification of β-ketoesters under mild reaction conditions. These catalysts are not only inexpensive but also available as desktop chemicals in any undergraduate laboratory. These reagents are operationally simple and environmentally safe and thus have an advantage over many literature reports. The new method allows rapid access to diverse esters (–OR) without using large excess of the corresponding alcohol (often as a solvent). Ultrasonically assisted methodology reduced reaction times from 16–24 h (under reflux conditions) to about 2.5 h; while microwave assisted reactions could complete the transesterification within 45 min. We hope that the protocols developed in this part of the work would become good contribution under non-conventional conditions. These approaches are environmental friendly in terms of energy saving and time saving requirements.

Supplementary data

All chemicals used in the experiments were purchased either from SD fine Chemicals (India), Ranbaxy (India) or Aldrich Chemicals. Pure, ash colored, crystalline manganese carbonate was purchased from Chemical Corporation (Mumbai, India).

Acknowledgements

The authors thank the authorities of Osmania University, Hyderabad, Govt. City College, Hyderabad, Rajiv Gandhi University of Knowledge Technologies, IIIT Basara, and SRTM University, Nanded for constant encouragement. One of the authors (G. Krishnaiah) thanks CSIR, New Delhi, for support in the form of the CSIR, JRF fellowship.

References and notes

1. Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470.
2. Benetti, S.; Ramgnoli, R.; De Risi, C.; Giampiera, S.; Vinicio, Z. *Chem. Rev.* **1995**, *95*, 1065–1114.
3. Lakshmi Kantam, M.; Neeraja, V.; Bharathi, B.; Venkat Reddy, Ch. *Catal. Lett.* **1999**, *62*, 67–69.
4. Wang, C. L. J.; Salvino, J. M. *Tetrahedron Lett.* **1984**, *25*, 5243–5246.
5. Emmer, G. *Tetrahedron* **1992**, *48*, 7165–7172.
6. Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460–1461.
7. Benbakkar, M.; Baltas, M.; Gorrichon, L.; Gorrishon, J. P. *Synth. Commun.* **1989**, *19*, 3241–3247.
8. (a) Bader, A. R.; Cumming, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195–4197; (b) Mottet, C.; Hamelin, O.; Garavel, G.; Depres, J.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380–1382; (c) Gianotti, M.; Martelli, G.; Spunta, G.; Campana, E.; Panunzio, M.; Mendozza, M. *Synth. Commun.* **2000**, *30*, 1725–1730.
9. Witzeman, J. S.; Notingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713–1718.
10. Yazawa, H.; Tanaka, K.; Kariyane, K. *Tetrahedron Lett.* **1974**, *15*, 3995–3996.
11. Blossey, E. C.; Turner, L. M.; Neckers, D. C. *Tetrahedron Lett.* **1973**, *14*, 1823–1826.
12. Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618–3619.
13. Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 110–116.
14. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, D.; Weidmann, B.; Zűgger, M. *Synthesis* **1982**, 138–141.
15. Chavan, S. P.; Zubaidha, P. K.; Dantale, S. W.; Keshavaraja, A.; Ramaswamy, A. V.; Ravindranathan, T. *Tetrahedron Lett.* **1996**, *37*, 233–236.
16. Madje, B. R.; Patil, P. T.; Shindalkar, S. S.; Benjamin, S. B.; Shingare, M. S.; Dongare, M. K. *Catal. Commun.* **2004**, *5*, 353–357.
17. (a) Balaji, B. S.; Sasidharan, M.; Kumar, R.; Chanda, M. *Chem. Commun.* **1996**, 707–708; (b) Balaji, B. S.; Chanda, M. *Tetrahedron* **1998**, *54*, 13237–13252.
18. Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org. Chem.* **1998**, *63*, 1058–1063.
19. Reddy, B. M.; Reddy, V. R.; Manohar, B. *Synth. Commun.* **1999**, *29*, 1235–1239.
20. Bandgar, B. P. Uppalla, L..; Sadavarte, V.S *Green Chem.* **2001**, *3*, 39–41.
21. Kumar, P.; Pandey, R. K. *Synlett* **2000**, 251–253.
22. Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.
23. Chavan, S. P.; Shivasankar, K.; Shivappa, R.; Kale, R. *Tetrahedron Lett.* **2002**, *43*, 8583–8586.
24. Jin, T.; Zhang, S.; Li, T. *Green Chem.* **2002**, *4*, 32–34.
25. Choudary, B. M.; Kantam, M. L.; Reddy, C. V.; Aranganathan, S.; Santhi, P. L.; Figueras, F. *J. Mol. Catal.* **2000**, *159*, 411416.
26. Bo, Wang; Ming, Yang Li; Shuan, Suo Ji *Tetrahedron Lett.* **2003**, *44*, 5037–5039.
27. Reidies, A. H. Manganese Compounds. In *Ullmann's Encyclopedia of Chemical Technology*; John Wiley: New York, 2007.
28. (a) Burke, A.P., Hydrogen peroxide disproportionation and organic compound oxidation by peroxycarbonate catalyzed by manganese(II): Kinetics and mechanism, Ph.D., University of Florida, Florida 2005. AAT 319235628.; (b) Das, A. K. *Coord. Chem. Rev.* **2001**, *213*, 307–325; (c) Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1996**, *37*, 2623–2624; (d) Savanur, A.; Nandibewoor, S.; Chimatadar, S. *Trans. Met. Chem.* **2009**, *34*, 711–718; (e) Ram Reddy, M. K.; Rajanna, K. C.; Saiprakash, P. K. *J. Chem. Sci.* **1987**, *98*, 333–339; (f) Sanjeeva Reddy, Ch.; Manjari, P. S. *Indian J. Chem.* **2011**, *50A*, 979–990; (g) Ember, E.; Rothbart, S.; Puchta, R.; Van Eldik, R. *New J. Chem.* **2009**, *33*, 34–49.
29. (a) Suslick, K. S. *Ultrasound: Its Chemical, Physical and Biological Effects*; VCH: New York, 1988; (b) Mason, T. J. *Chemistry with Ultrasound*; Elsevier Science Publishers: London, 1990.
30. (a) Singh, V.; Kaur, K. P.; Khurana, A.; Kad, G. L. *Resonance* **1998**, *3*, 56–60; (b) Mason, T. J.; Peters, D. *Practical Sonochemistry: Power Ultrasound Uses and Applications*, 2nd Ed.; Harwood Publishing: Chichester, 2003.
31. (a) Bremner, H. *Ultrason. Sonochem.* **1994**, *1*, 119–124; (b) Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180–196.
32. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
33. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
34. (a) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; (b) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161–166.
35. (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; (b) Anastas, P. T.; Williamson, T. C. *Green Chemistry: Designing Chemistry for the Environment*; American Chemical Society: Washington, DC, 1996; (c) Anastas, P. T.; Heine, L. G. *Green Chemical Synthesis and Processes*; American Chemical Society: Washington, DC, 2000.
36. *General procedure for transesterification under conventional method:* A mixture of β-ketoesters (5 mmol), alcohol (5 mmol), and catalyst (1 mmol) in toluene (20 mL) was stirred at 100–110 °C in a round bottom flask provided with a distillation condenser to remove ethanol and the progress of the reaction was monitored by thin layer chromatography (TLC). Then the reaction mixture was filtered and the filtrate was concentrated to get crude product, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to afford the ester as a viscous colorless liquid in good to excellent yields.
37. (a) *General procedure for ultrasonic assisted transesterification:* For ultrasonically assisted transesterification, a flask containing a mixture of β-ketoesters (5 mmol), alcohol (5 mmol), and catalyst (1 mmol) in toluene (20 mL) was placed in a Sonicator bath at room temperature and the progress of the reaction was monitored by TLC. Then the reaction mixture was filtered and the filtrate was concentrated to get the crude product which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, ratio?) to afford the ester as a viscous colorless liquid in excellent yields.
    (b) *General procedure for microwave assisted transesterification:* The synthesis in the MW oven was performed with a radiation source consisting of a magnetron tube operating at 2.45 GHz with power output ranging from 0 to 300 W. The flask containing a mixture of β-ketoesters (5 mmol), alcohol (5 mmol), and catalyst (1 mmol) in toluene (20 mL) was placed in MW oven. The solutions were stirred by a magnetic stir bar to ensure high homogeneity. To prevent thermal gradients the reactions were carried out in 5 mL tubes and the progress of the reaction was monitored by TLC. Final product was obtained by using the above mentioned work up.
38. (a) Pearson, R. G. *Chemical Hardness*; John Wiley-VCH: Weinheim, 1997; (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539; (c) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581–586
39. (a) Pasini, D.; Righetti, P. P.; Rossi, V. *Org. Lett.* **2002**, *4*, 23–26; (b) Garlaschelli, L.; Messina, I.; Pasini, D.; Righetti, P. P. *Eur. J. Org. Chem.* **2002**, 3385–3392.