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TRANSESTERIFICATION OF KETOESTERS USING AMBERLYST-15

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TRANSESTERIFICATION OF KETOESTERS USING AMBERLYST-15

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ABSTRACT

A facile one-to-one transesterification of ketoesters by Amberlyst-15 is described.

Ketoesters are multi-coupling reagents with electrophilic and nucleophilic sites and are proven to be valuable tools in a wide variety of molecular systems. Especially, the transesterification of β-ketoesters has received a great deal of attention and various catalysts (1–8) have been investigated in the attempt to effect this interconversion. These β-ketoesters are important by virtue of their facile bond formation at all four carbon atoms that feature in their structural unit and also due to their ease of transformation to chiral building blocks and use in chain extension reactions.

Although well-known using conventional acidic and basic catalysts, a need for new catalysts has arisen in order to meet the requirement for this transesterification to be highly efficient and chemo- and regioselective.

Heterogeneous catalysts have in some cases replaced conventional reagents due to their practical utility. We have reported (9) one such catalyst, *viz.*, sulfated tin

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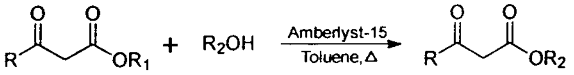
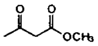
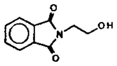
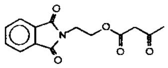
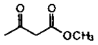
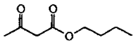
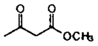
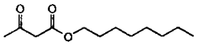
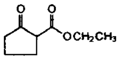
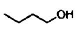
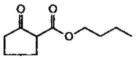
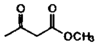
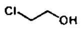
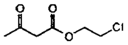
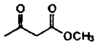
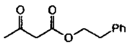
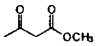
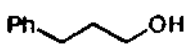
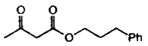
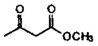
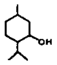
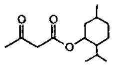
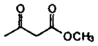
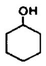
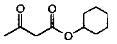
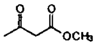
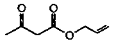
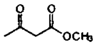
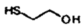
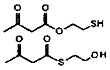
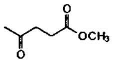
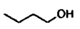
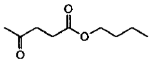
Table 1.



S. No.	Substrate	Alcohol	Product	Time (h)	Yield (%)
1				10.0	85
2				5.5	85
3				2.0	89
4				3.0	90
5				3.0	75
6				4.0	88
7				2.0	64
8		** 		6.0	94
9				6.0	65
10				8.0	42
11			# 	2.0	86*
12				10.0	54

* Combined yields; **2 eq of alcohol. # 1:1 ratio of products.

oxide, which has been effectively utilized for transesterification of β-ketoesters with excellent results, and, as part of our continued interest in finding cheaper alternatives for effecting this transesterification, we found that Amberlyst-15 was more effective with primary, secondary, and allylic alcohols (see Table 1). Several related reports have also appeared (10,11).

Amberlyst-15 is a macro reticular ion exchange resin that contains strongly acidic sulfonic groups and has been widely used for a variety of reactions: preparation of acetals from carbonyls and alcohols (12); esters from alcohols and acids (13); tetrahydropyranylation of alcohols and phenols (14); hydrolysis of acetals to carbonyls (15); and dethioacetalization (16). In this communication, a facile inter conversion of β-ketoesters using Amberlyst-15 is described.

Mixing an equimolar mixture of ketoester and alcohol in the presence of 10% Amberlyst-15, heating in toluene, while removing the methanol/ethanol formed, led to the formation of the transesterified β-ketoesters in good to excellent yields. A noteworthy feature of the present protocol is that not only β-ketoesters but also a γ-ketoester (entry 12) can be transesterified. Another example of interest is the transesterification of N-(2-hydroxy ethyl)phthalimide to furnish the 2-phthalimido ethyl acetoacetate ester (entry 1). This product is an important reagent for the synthesis of 1,4-dihydropyridine derivatives (17), which are effective calcium channel blockers and have antihypertensive activities. Another point worth mentioning is that only a 1:1 ratio of ketoester and alcohol is required for a facile exchange to occur. Chiral alcohols also participate efficiently in this reaction, giving access to chiral ketoesters. Interestingly, when mercapto ethanol is used, an equimolar amount of thio ester and ester are obtained in good yields.

This catalyst, being heterogeneous in nature, offers advantages over conventional methods, not only in terms of yields and reaction times, but also in ease of work-up and retrieval of products, in addition to the reusability of catalyst, which can be of tremendous commercial importance. The short reaction times and high yields emphasize the attractive feature of this protocol.

The ready availability of this catalyst commercially and its superiority over the existing methods (1) should make the present protocol an attractive addition to conventional methods.

EXPERIMENTAL

General Procedure for Transesterification

A mixture of ketoester (1 eq), alcohol (1 eq), and catalyst (100 mg, 10% by weight of ketoester) in toluene (20 mL) was heated to 110°C in a two-necked round-bottom flask provided with a distillation condenser to remove MeOH/EtOH. After completion of the reaction (as monitored by TLC), the catalyst was filtered and the filtrate concentrated and chromatographed on SiO_2 (95:5 pet.ether: ethyl acetate) to afford the ester as a viscous liquid in excellent yields.

1. N-(2-Phthalimidoethyl)-3-oxo Butanoate (17)

M.p.: 88°–89°C. IR (neat) cm^{-1}: 3022, 1755, 1744, 1712, 1428, 1395, 1365, 1319, 1216, 754, 720. ^{1}H NMR (200 MHz) $CDCl_3$ (δ): 2.25 (s, 3H); 3.45 (s, 2H); 4.0 (t, J = 5.4 Hz, 2H); 4.4 (t, J = 5.4 Hz, 2H); 7.7–7.9 (m, 4H, aromatic). Mass (m/z): 275 (M^+). Analysis: Calculated C = 61.09; H = 4.83; N = 5.05. Found C = 60.82; H = 4.76; N = 4.65.

2. Butyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 2980, 2950, 1750, 1730, 1650, 1420, 1350, 1320, 1250, 1180, 1150, 1050, 1020, 950, 820, 750. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 0.9 (t, 3H, -CH$_3$); 1.35 (m, 2H, -CH$_2$-); 1.6 (m, 2H, CH$_2$-); 2.25 (s, 3H, -CH$_2$-); 3.4 (s, 2H, -CH$_2$-), 4.1 (t, 2H, -OCH$_2$-). Mass (m/z): 158 (M$^+$).

3. Octyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 2950, 2850, 1750, 1720, 1650, 1450, 1400, 1350, 1300, 1220, 1150, 1020. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 0.9 (t, 3H); 1.3 (m, 10H, -CH$_2$-); 1.6 (t, 2H); 2.6 (s, 3H); 3.4 (S, 2H); 4.1 (t, 2H). Mass (m/z): 214 (M$^+$).

4. Butyl-2-oxo Cyclopetanecarboxylate (18)

IR (neat) cm^{-1}: 2950, 2850, 1750, 1720, 1640, 1610, 1450, 1350, 1250, 1180, 1050, 920. ^{1}H NMR (200 MHz) CDCl$_3$ (δ) : 0.9 (t, 3H); 1.3 (m, 2H); 1.6 (m, 2H); 2.1 (m, 2H); 2.3 (m, 4H); 3.15 (t, 1H); 4.2 (t, 2H). Mass (m/z): 184 (M$^+$).

5. 2-Chloroethyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 2950, 1750, 1720, 1650, 1450, 1420, 1350, 1320, 1250, 1150, 1020, 780, 650. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 2.1 (s, 3H); 3.4 (s, 2H); 3.6 (t, 2H); 4.3 (t, 2H). Mass (m/z): 167 (M + 2), 165 (M$^+$).

6. 2-Phenyl Ethyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 3020, 2900, 1750, 1720, 1620, 1400, 1300, 1250, 1200, 1050, 1020, 920, 810, 720, 580, 550. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 2.15 (s, 3H); 3.0 (t, 2H); 3.4 (s, 2H); 4.4 (t, 2H), 7.5 (m, 5H). Mass (m/z): 206 (M$^+$).

7. 3-Phenyl Propyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 3030, 2860, 1740, 1720, 1650, 1600, 1500, 1455, 1360, 1260, 1170, 1150, 1030, 750, 700. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 2.0 (m, 2H); 2.2 (s, 3H); 2.7 (t, 2H); 3.5 (s, 2H); 4.2 (t, 2H); 7.25 (m, 5H). Mass (m/z): 220 (M$^+$).

8. 5-Methyl-2-(1-methylethyl)cyclohexyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 2980, 2820, 1740, 1700, 1650, 1450, 1400, 1350, 1300, 1240, 1120, 1080, 1020, 980, 950, 900, 850. ^{1}H NMR (200 MHz) CDCl$_3$ (δ): 0.80

(d, 3H); 1.1 (d, 6H); 1.2 (m, 4H); 1.35 (m, 2H); 1.55–1.85 (m, 3H), 2.3 (s, 3H), 3.5 (s, 2H), 4.7 (dt, J = 4.4 & 10.9, 1H). Mass (m/z): 240 (M^+).

9. Cyclohexyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 3010, 2980, 1750, 1720, 1650, 1560, 1420, 1350, 1250, 1180, 1020, 920, 850, 780, 700. ^1H NMR (200 MHz) $CDCl_3$ (δ): 1.35 (m, 6H); 1.70 (m, 2H); 1.80 (m, 2H); 2.4 (s, 3H), 3.4 (s, 2H), 4.8 (m, 1H). Mass (m/z): 184 (M^+).

10. Allyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 2950, 1750, 1720, 1640, 1420, 1380, 1280, 1020, 1000, 950, 780, 550. ^1H NMR (200 MHz) $CDCl_3$ (δ): 2.2 (s, 3H); 3.4 (s, 2H); 4.6 (d, 2H); 5.25 (d, 2H); 5.8 (m, 1H). Mass (m/z): 142 (M^+).

11(a). 2-Mercapto Ethyl-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 1740, 1710, 1600, 1400, 1350, 1300, 1250, 1150, 1020. ^1H NMR (200 MHz) $CDCl_3$ (δ): 1.5 (t, -SH); 2.25 (s, 3H); 2.7 (dt, 2H); 3.5 (s, 2H); 4.3 (t, 2H). Mass (m/z): 162 (M^+).

11(b). 2-Hydroxy Thio-3-oxo Butanoate (18)

IR (neat) cm^{-1}: 3400, 1740, 1710, 1600, 1400, 1350, 1300, 1250, 1150, 1020. ^1H NMR (200 MHz) $CDCl_3$ (δ): 1.7 (s, 3H); 2.8 (s, -OH); 3.1 (t, 2H); 3.7 (s, 2H); 4.2 (t, 2H). Mass (m/z): 162 (M^+).

12. Butyl-4-oxopentanoate (18)

IR (neat) cm^{-1}: 2950, 2800, 1740, 1720, 1620, 1450, 1350, 1180, 1150, 1050, 1020, 950, 780, 650. ^1H NMR (200 MHz) $CDCl_3$ (δ): 0.90 (t, 3H); 1.5 (m, 4H); 2.1 (s, 3H); 2.5 (t, 2H); 2.7 (t, 2H), 4.1 (t, 2H). Mass (m/z): 172 (M^+).

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