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Zinc mediated transesterification of β-ketoesters and coumarin synthesis

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Abstract—The transesterification of ketoesters using zinc and iodine is described. The reaction has been done on a variety of alcohols and phenols. Alcohols furnish transesterified products whereas phenols gave 4-methylcoumarins. The method is highly promising compared with existing methods. © 2002 Elsevier Science Ltd. All rights reserved.

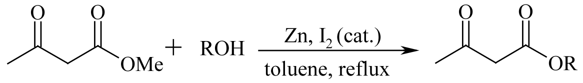
The electrophilic and nucleophilic sites of β-ketoesters are valuable tools in synthesis. Facile reactions on the two electrophilic carbonyls and the two nucleophilic carbons[1] have made β-ketoesters popular synthons. Many biologically active systems are accessible from β-ketoesters of different alcohols.[1b] Usually, β-ketoesters can be readily prepared from the reactions of diketene with alcohols to furnish the desired esters. However, diketene poses practical problems due to its reactivity, corrosiveness and handling difficulties. Methyl or ethyl acetoacetates are commercially available and are stable. Although *tert*-butyl acetoacetate can be readily transformed to the corresponding esters in the absence of any catalyst,[2] this method is restricted to *tert*-butyl esters, which in turn are not readily available. A great deal of attention has been given to effect transesterification of methyl or ethyl acetoacetate employing homogeneous catalysts like DMAP,[3] DBU,[4] titanium tetraoxide[5] and *p*-TSA.[6,7] We were the first to describe the utility of a heterogeneous catalyst viz. S-SnO$_2$ as an efficient heterogeneous catalyst in effecting transesterification[8a] as well as deprotection of crotyl, cinnamoyl and dimethylallyl esters.[8b] After our publication several other catalysts were also shown to be effective.[9] We have also shown commercially available Amberlyst-15 to be an efficient catalyst[10] for transesterification.

The use of zinc has gained popularity of late in effecting synthetically useful transformations like the ene cyclization,[11] the Diels–Alder reaction,[12] the synthesis of AF4,[13] and the synthesis of benzhydrols[14] to name a few.

In this communication we report the use of zinc as an efficient mediator for transesterification reactions. The reaction has been performed on a standard substrate, namely methyl acetoacetate with various alcohols (Scheme 1).

The results are summarized in Table 1. The use of activated zinc[15] and the conditions used for the reaction are some of the highlights. A noteworthy feature of the present protocol is that benzyl, allyl and propargyl, esters (entries 3, 5 and 7, respectively) become readily accessible. The allyl and propargyl esters are known to be difficult to prepare as they readily undergo the Carroll rearrangement.[3] From Table 1, it is evident that both primary as well as secondary alcohols participate well in the reaction. However a tertiary alcohol i.e. *tert*-butanol, did not lead to the formation of the corresponding *tert*-butyl ester.

In a typical example, zinc (1.10 g, 16.95 mmol) was taken in a round bottom flask attached to a reflux and a distillation condenser. Methyl acetoacetate (1 g, 8.47 mmol) in toluene (10 ml) was added followed by the addition of cyclohexanol (0.93 g, 9.32 mmol) in toluene (5 ml). A catalytic amount of iodine was added and the reaction was heated under reflux for 5 h whilst being



Scheme 1.

Keywords: zinc; iodine; transesterification; coumarins.

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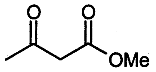
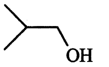
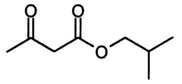
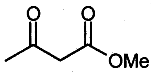
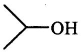
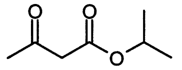
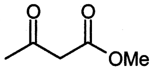
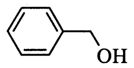
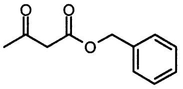
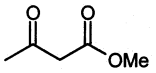
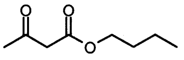
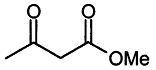
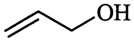
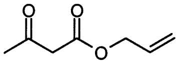
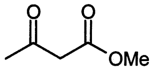
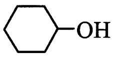
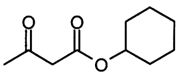
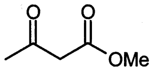
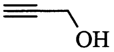
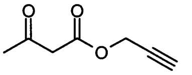
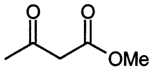
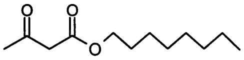
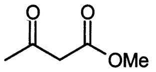
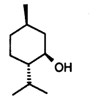
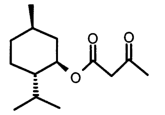
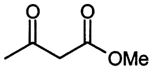
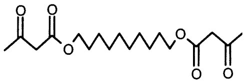
Table 1.

Exp. No	β-Ketoester	Alcohol	Product	Yield (%) (isolated)
1				85
2				62
3				66
4				78
5				45
6				60
7				71
8				79
9				89
10				66[#]

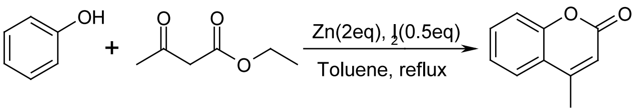
[#] 2eq. of methyl acetoacetate were used.

monitored by TLC. The reaction was quenched with dil. HCl (20 ml) or with saturated aqueous NH_4Cl, filtered, and the compound was extracted in ether and purified by chromatography using silica gel (60–120 mesh).

Having obtained encouraging results in the formation of ketoesters, it was decided to study the reactivity of phenols in the transesterification reaction. The same protocol with a slight modification was used for the phenols. It was found that under the reaction conditions, coumarins were efficiently formed. Coumarins form an elite class of compounds, occupying a special place in nature as they form sub-units of many natural compounds.[16b] They exhibit a broad spectrum of biological activity profiles such as anthelmintic, anticoagulants, hypnotic and insecticidal properties.[16] Coumarins have been synthesized using various reactions conditions such as the Pechmann condensation,[17] the Knoevenagal condensation,[18] the Wittig reaction[19] and by flash-vacuum pyrolysis.[20]

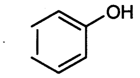
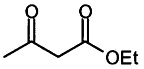
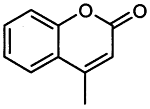
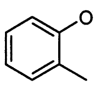
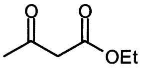
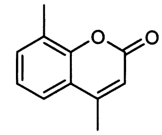
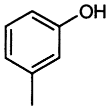
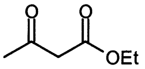
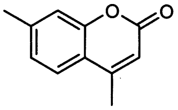
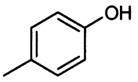
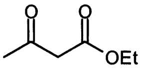
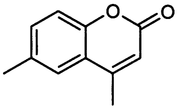
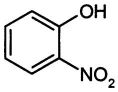
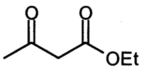
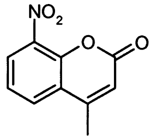
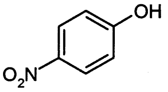
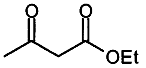
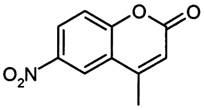
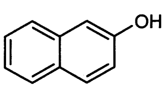
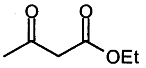
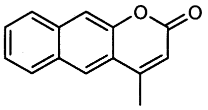
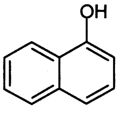
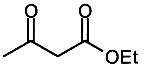
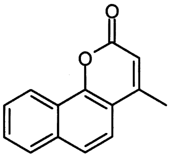
In the class of coumarins, 4-methylcoumarins have enjoyed a special status as they form the core of industrially important coumarins like 7-hydroxy-4-methylcoumarin (coumarin 47 or coumarin 460)[16b] and 7-diethylamino-4-methylcoumarin (umbelliferon-47).[16b] The synthesis of 4-methylcoumarin has been mainly reported via the Pechmann condensation using various catalyst like H_2SO_4-microwave,[21] montmorillonite clay[22] and PPA.[23] In this communication we describe a protocol to effect a Pechmann condensation using zinc and iodine (Scheme 2).

The use of 0.5 equiv. of iodine in the reaction leading to the coumarins was arrived at after considerable experimentation, during which it was also observed that the use of an excess of iodine did not increase the yield.



Scheme 2.

Table 2. Synthesis of 4-methylcoumarins

Exp. No	Starting material: Phenol	Starting material: β-Ketoester	Product	Yield (%) (isolated)
1				40
2				77
3				65
4				78
5				25
6				40
7				50
8				63

A wide variety of phenols were subjected to the conditions and the results obtained are tabulated in Table 2. It was observed that the reaction goes better with cresols. However with *o*-chlorophenol, no corresponding coumarin was obtained.

In a typical procedure, ethyl acetoacetate in toluene was added zinc (2 equiv.). α-Naphthol was added followed by the addition of iodine (0.5 equiv.). The reaction mixture was refluxed for 5 h and monitored by TLC. The reaction was worked up using either dil. HCl (10%) or using saturated aqueous NH_4Cl. The compound was extracted with ethyl acetate. The solvent was then concentrated under reduced pressure and the residue thus obtained was precipitated using pet. ether. The compound was then filtered and dried to furnish the corresponding coumarin (see entry 8).

In conclusion, the ready availability of zinc coupled with the ease of operation of their reactions should make the present methodology an attractive one as it offers both coumarin synthesis as well as transesterificaiton.

Acknowledgements

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