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Expeditious, large scale preparation of ethyl (*R*)-5-methyl-3-oxo octanoate via a cross Claisen reaction between *N*-acyl oxazolidinone derivatives and the magnesium enolate of potassium ethyl malonate

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Abstract

A new and efficient method for the direct conversion of *N*-acyl oxazolidinones to a β-keto ester is disclosed. The one-pot transformation is effected by the utilization of an excess of Lewis acid along with base and potassium ethyl malonate. This methodology has been applied to the large scale preparation of ethyl (*R*)-5-methyl-3-oxooctanoate.

Keywords: β-Keto ester; Claisen; Oxazolidinone; Magnesium enolate; Malonic acid ester

β-Keto esters are important intermediates in organic synthesis and their preparation have attracted considerable interest. The most traditional method is the Claisen condensation, where an ester displaces an alkoxy or aryloxy group.[1] Another very popular methodology is the acylation of diethyl malonate followed by the hydrolysis and the decarboxylation of one of the two ester groups in the acylated malonate intermediate,[2] but a drawback is the potential formation of a methyl ketone by-product. Many other methods have been developed that employ diverse approaches[3] but, unfortunately, very few of them are amenable to be scaled up in a safe and cost effective manner. A notable exception involves the use of the magnesium enolate of the half ester of malonic acid prepared by using magnesium chloride and triethylamine. This has been shown to react with acid chlorides or imidazolides to provide β-keto esters.[4]

As part of an on-going project in our laboratories, we had the need for large quantities of enantioenriched ω-branched alkyl β-keto esters and, in particular, we were interested in ethyl (*R*)-5-methyl-3-oxo-octanoate (**9**). The introduction of the chiral center in the molecule was accomplished through the Michael addition of organocopper species to crotonyl derivatives of oxazolidinones (Scheme 1).[5] Both the phenylglycinol and the norephedrin-derived oxazolidinones auxiliaries (**1** and **2**, respectively) were successfully used to prepare enantioenriched materials. The typical method of transforming these intermediates into keto esters is shown in Scheme 2 and involves the following: (1) the preparation of lithium peroxide; (2) the reaction of lithium peroxide with the substrate; (3) the reductive decomposition of the peroxy acyl intermediate as well as the excess peroxide; (4) workup in order to achieve an anhydrous solution of the corresponding acid; (5) activation of the acid by making, for example, an imidazolide, a mixed anhydride or an *N*-acyl urea, and (6) reaction with the magnesium enolate of malonic ester.[6]

Even though this sequence has been safely and effectively performed by our group many times on 100s of moles scale, there are several important drawbacks, such as a tedious reaction sequence that takes several days of

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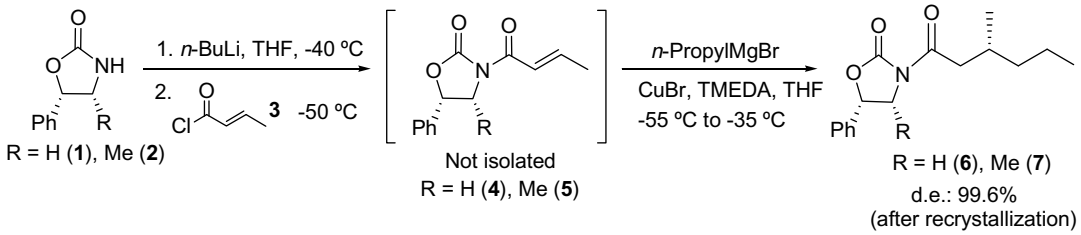
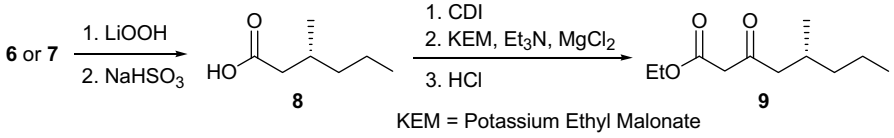
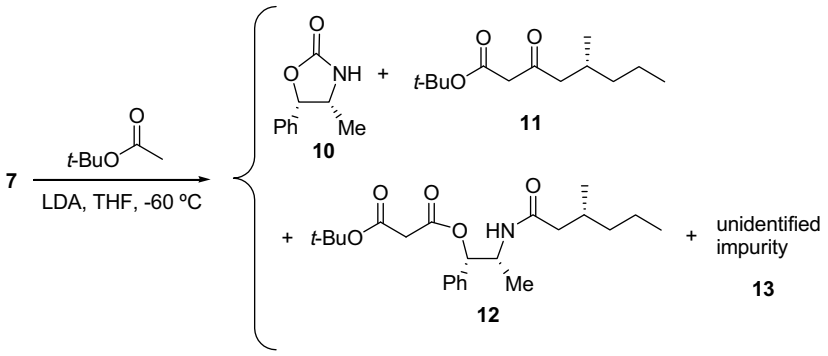


Scheme 1. The synthesis of ω-branched alkyl β-keto esters.



Scheme 2. Typical transformation sequence to prepare β-keto esters from *N*-acyl oxazolidinones.



Scheme 3. Direct conversion using the lithium *tert*-butyl acetate enolate.

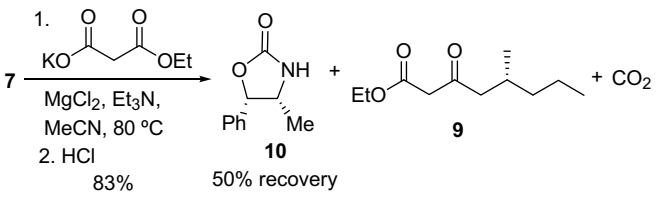
processing to effect complete conversion, the fact that the aqueous hydrogen peroxide and the resulting lithium derivative and acylperoxy intermediate are both high-energy species capable of rapid decomposition, the need for expensive reagents (*N*,*N*′-dicyclohexylcarbodiimide, 1,1′-carbonyldiimidazole) to activate the acid for displacement, a low throughput and large amounts of waste.

There are several reports on the direct reaction of ester enolates in order to accomplish the above conversion more efficiently through the use of magnesium *p*-nitrobenzyl malonate,[7] but only in the presence of benzylic oxazolidinones, or allylzinc to afford the corresponding allylic alcohol.[8] The use of lithium *tert*-butyl acetate has also been reported[9] and, when tested on *N*-acyl oxazolidinone **7** as a representative example, the reaction was complete in less than 30 min at −60 °C and afforded the desired β-keto ester **11** but, also, gave up to 20% of undesired by-product **12** (Scheme 3) and up to 30% of an unidentified impurity **13**.

The use of $MgCl_2$ in the reaction gave similar results and $ZnCl_2$ gave a much slower reaction (no reaction at −60 °C) with similar levels of **12**. A summary of the conditions that were screened is shown in Table 1. The low conversions with $ZnCl_2$ as an additive are likely due to water being present.

Table 1
Conditions screen for the displacement of the oxazolidinone moiety in **7** with the lithium enolate of *tert*-butyl acetate

Entry	Additive	Enolate equivalents	Conversion (%)	*T* of addition	**12** (%)	**13** (%)
1	None	2	100	−70 °C	20	30
2	None	1.15	60	−65 °C	20	30
3	$MgCl_2$	1.44	80	−60 °C to rt	20	20
4	$ZnCl_2$	1.44	40	−60 °C to rt	20	0
5	$ZnCl_2$	2.3	70	−60 °C to rt	20	0



Scheme 4. Direct conversion of **7** to β-keto ester **9** using the magnesium enolate of KEM.

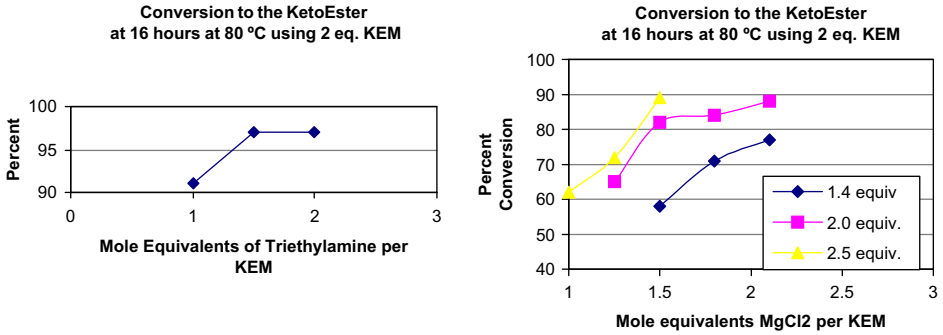


Fig. 1. Optimization results for the direct conversion of **7** to **9** using KEM.

In view of the above results, we turned our attention to the direct reaction of the *N*-acyl oxazolidinones with the dianion of the half ester of malonic acid (Scheme 4).[4] To our delight, the reaction gave high conversion and a very good yield of β-keto ester **9** after acidic workup under simple conditions. In addition, the chiral oxazolidinone could be recovered in high purity and fair yield after precipitating it out from hexanes.

After optimizing the reaction conditions, it was found that the desired ratio of reagents is 2 equiv of potassium ethyl malonate (KEM), 3 equiv of triethylamine and 4 equiv of $MgCl_2$. Under these conditions, the reaction is nearly complete in 16 h at 80 °C. It was speculated that the reason for needing 2 equiv of KEM was due to the fact that the CO_2 from the imidazolide solution might form the carbonate adduct of KEM. This was confirmed through additional experiments that showed that when the vessel was purged with nitrogen gas, the reaction proceeded at a faster rate than when CO_2 was added to the tank. Also, it is noteworthy to point out that a reaction carried out at 100 °C under 10 psi of pressure did not seem to have a faster rate. The results of the study are shown in Figure 1 for *N*-acyl oxazolidinone **7**.

In order to illustrate the feasibility of this technology, a typical experimental procedure is as follows:

To a stirred mixture containing 34 kg (117 moles) of *N*-acyl oxazolidinone **7** and 40 kg (235 moles) of ethyl malonate potassium salt in 230 kg of acetonitrile was added 45 kg (470 moles) of magnesium chloride in portions while keeping the temperature below 30 °C. The slurry was diluted with 24 kg (235 moles) of triethylamine and heated to 80 °C for 20 h. After cooling to 10 ± 5 °C, the reaction was quenched by the addition of a cooled mixture of 140 L of water and 80 kg of 35% aqueous hydrochloric acid. The lower layer was separated and the upper layer was diluted with 90 kg of ethyl acetate. The organic layer was washed with a solution of aqueous sodium bicarbonate (20.2 kg), water (120 L) and water (60 L). The organic solvents were removed by vacuum distillation, 400 L of hexanes was added and the distillation was resumed until a volume of about 100 L remained. After cooling to 10 °C for 1 h, the resulting slurry was filtered and the cake was washed with 60 L hexane(wash saved with the original liquor), followed by a 60 L isopropanol wash (discarded). The solids were dried at 45 °C resulting in 10 kg (50% recovery) of 90% pure oxazolidinone **10**.[10] The filtrates were concentrated and the product was distilled under vacuum (boiling point range: 40–60 °C at 0.1 mm of Hg) to give 19.6 kg (83% yield) of β-keto ester **9**.

In conclusion, we have developed an efficient method for the preparation of ethyl (*R*)-5-methyl-3-oxo-octanoate by a novel methodology that simplifies the process when *N*-acyl oxazolidinones are used as starting materials. This protocol has been demonstrated on pilot plant scale to produce multi-kilogram quantities of this important intermediate to support our research projects. Further applications of this methodology will be reported in due course.

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10. The recovered yield of oxazolidinone was lower than usual in this case because the reaction temperature was run on the high end (80 °C instead of 60 °C).