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A PROCESS FOR THE SYNTHESIS OF β-KETOESTERS USING *IN-SITU* GENERATED (TRIMETHYLSILYL)MALONATES.

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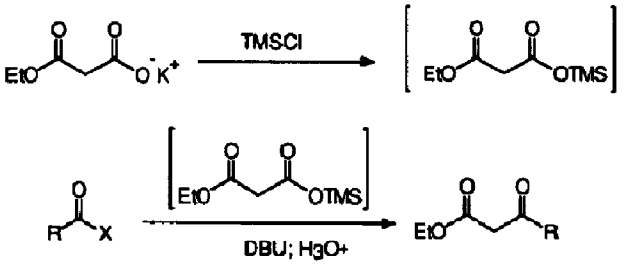
Abstract: (TMS)ethyl malonate can be generated *in-situ* by treating potassium ethyl malonate with trimethylsilyl chloride and acylated with aliphatic or aromatic acyl imidazoles or chlorides in the presence of DBU to prepare a variety of β-ketoesters. This constitutes a high yield method for preparing β-ketoesters, which also can be extended to the formation of alkylidene malonates.

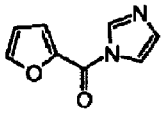
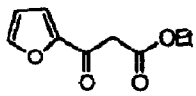
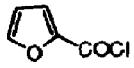
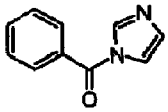
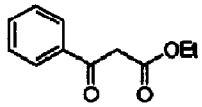
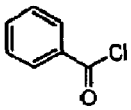
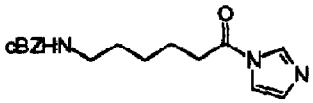
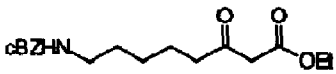
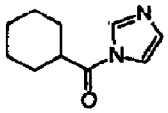
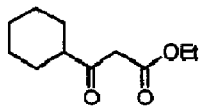
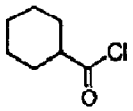
β-ketoesters are useful synthetic intermediates for the preparation of a variety of complex organic structures.[1] The development of versatile methods for preparing β-ketoesters extend their value as synthetic tools. A number of methods involving the acylation of the enolates of malonates leading to β-ketoesters have been reported.[2] The often difficult task of avoiding cleavage of the acyl group on base or acid catalyzed hydrolysis for decarboxylation has lead to various alternative methodologies such as acylation of Meldrums acid,[3] mixed malonate esters,[4] and bis-trimethylsilylmalonates.[5,6] Often a chelating effect has been employed to lock in the enolate anion of malonate using lithium and magnesium salts.[7] However, these methods often have the limitation that aliphatic acylation do not give consistent yields. These difficulties lead us to develop a novel preparation of β-ketoesters by acylating the potassium salt of ethyl malonate in the presence of TMSCl and DBU.

Scheme 1



Under anhydrous conditions potassium ethyl malonate readily reacts with TMSCl in acetonitrile at room temperature. The resulting *in-situ* generated (trimethylsilyl)ethyl malonate undergoes a facile reaction with acyl imidazoles or chlorides in the presence of DBU (Scheme 1). On aqueous workup β-ketoesters are isolated in greater than 90% yields. Noteworthy is that both aromatic and aliphatic families of acylating species are compatible with this methodology and both give high yields. Listed in Table 1 are a variety of aliphatic and aryl acylating agents successfully utilized with this methodology.

Table 1. Preparation of β-ketoesters with (TMS)ethyl Malonate Intermediate.

Entry	Acyl Reactant*	Product	Isolated yield (%)
1a			93
1b			90
2a			96
2b			91
3			95
4a			92
4b			92

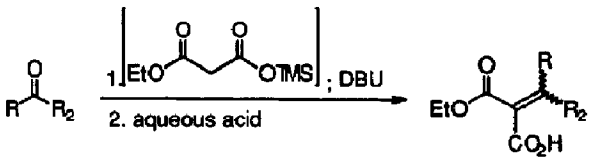
*For acyl imidazoles: $KO_2COCH_2CO_2Et$, TMSCl (1 equiv.), DBU (2 eqiv.);
For acyl chlorides: $KO_2COCH_2CO_2Et$, TMSCl (2 equiv.), DBU (3 eqiv.).[8]

Note that the conditions can accommodate a variety of funtionalities. Acyl imidazoles used were easily prepared from the carboxylic acid using 1,1'-carbonyldiimidazole (CDI) in THF at room temperature or from the acyl chlorides and imidazole/triethyl amine in THF. The acylation reactions were all done at 0-22°C and the products isolated by extractive work up. DBU is used as both a base and acid scavenger. The advantages of this methodology is the variety of organic classes which can be accommodated, the ability to use the (trimethylsilyl)ethyl malonate intermediate without isolation, and the isolation of product in high purity by a simple extractive workup. This methodology is particularly suited for a sequential one-pot scale-up process.

Judicious use of base appears critical to the success of this methodology, especially with aliphatic acylating agents. For example, when trimethylamine/$MgCl_2$ was used in place of DBU as the base, aliphatic acylation did not occur. This is in agreement with previous reports by Rathke.[5] With acyl imidazoles, 1 equivalent of TMSCl and 2 equivalents of DBU are necessary for optimum results. In contrast, acylation of the (trimethylsilyl)ethyl malonate intermediate with acid chlorides requires two equivalents of TMSCl and three equivalents of DBU, one being used as the acid scavenger, to give best results. The acylation intermediate derived with acid chlorides shows a propensity for rapid cleavage of the acyl group, which is mitigated if the intermediate enolate is trapped with the additional TMSCl.

The ability to trap an intermediate enolate species as a trimethylsilyl derivative also provides a handle to extend the utility of this methodology to prepare alkylidene malonates. By treating the *in-situ* generated (trimethylsilyl)ethyl malonate with an aldehyde or ketone in the presence of DBU leads to the formation of alkylidene malonates (Table 2).[9] And unlike the classical Knoevenagel reaction,[10] aliphatic aldehydes and ketones are suitable substrates for condensation with this malonate variant . This method has the advantage over other reported methods[11] developed for the condensation of aliphatic aldehydes and ketones with malonates in it's mild reaction conditions and high yields. The (TMS)ethyl malonate method offers a useful scale-up procedure for the preparation of α, β-unsaturated malonates.

Table 2. Preparation of Alkylidene Malonates with (TMS)ethyl Malonate Intermediate.



Entry	R	R_2	Isolated Yield (%)	E:Z
1	Ph	H	74	2:1
2	C_4H_9	CH_3	81	1:1

In summary, a new versatile process is reported for the preparation of β-ketoesters by generating (trimethylsilyl)ethyl malonate *in-situ* and treating this species with either acyl chlorides or acyl imidazoles in the presence of DBU. This method is a high yielding reaction and can accommodate both alkyl and aryl acylating agents. In addition, the (TMS)ethyl malonate intermediate can be used to prepare alkylidene malonates by condensation with aryl or alkyl aldehydes and ketones. Further studies to extend this reaction's usefulness are underway.

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[8] A typical preparation of β-ketoesters from acyl imidazoles: An acyl imidazole solution was prepared by treating 6-(carbobenzyloxyamino)caprioic acid (20 g, 75.4 mol) in 80 mL THF with CDI (14 g, 86.3 mmol) and a catalytic amount of DMAP at rt and stirring 24 h. A (TMS)ethyl malonate solution was prepared by treating potassium ethyl malonate (14 g, 82.4 mmol) in 50 mL acetonitrile with TMSCl (9 g, 82.7 mmol) at rt and stirring for 4-8 h. The solution was cooled to 0 °C and DBU (25 g, 164 mmol) was added and stirred at 0 °C for 0.5 h. The 6-(carbo-benzyloxyamino)caprioic imidazole solution was added dropwise to the (TMS)ethyl malonate solution at 0 °C. The reaction mixture was stirred for 17 h at rt and was quenched by adding 10 % aqueous citric acid (pH 4-5) and extracted with ethyl acetate. The ethyl acetate extract was washed with dil. $NaHCO_3$ and then with water. On concentration of the solvent 25 g (100 %) of the desired product was isolated without need for further purification. All compounds reported exhibited ^1H NMR spectra consistent with their assigned structures.

A typical preparation of β-keto esters from acyl chlorides: A TMS-malonate solution was prepared by treating potassium ethyl malonate (1.8 g, 10.6 mmol) in 20 mL acetonitrile with TMSCl (2.4 g, 22.1 mmol) at rt and stirred for 4 h. This mixture was cooled to 0 °C and DBU (5.1 g, 33.6 mmol) was added dropwise and mixed for 0.5 h at rt. Benzoyl chloride (1.45 g, 10.3 mol) was added at 0 °C and the solution was stirred for 5 h. The reaction was quenched by adding 10 % aqueous citric acid (pH 4-5) and extracted with ethyl acetate. The ethyl acetate extract was washed with dil. $NaHCO_3$, then water, followed by drying and concentration to afford 1.8 g (92%) of the desired product without need for further purification. ^1H NMR was consistent with previously prepared material.

[9] A typical reaction for the preparation of α,β-unsaturated esters: A TMS-malonate solution was prepared by treating potassium ethyl malonate (1.8 g, 10.6 mmol) in 20 mL acetonitrile with TMSCl (1.2 g, 11 mmol) at rt and stirred for 4 h. The solution was cooled to 0 °C and DBU (1.6 g, 10.5 mmol) was added. The mixture was stirred at 0 °C for 5 min and benzaldehyde (1.1 g, 9.4 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then at rt for 2 h. The reaction was quenched by adding 10 % aqueous citric acid (pH 4-5) and extracted with ethyl acetate. On concentration of the solvent 2.2 g (96 %) of the desired product was isolated without need for further purification. All compounds reported in Table 2 exhibited ^1H NMR spectra consistent with their assigned structures.

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