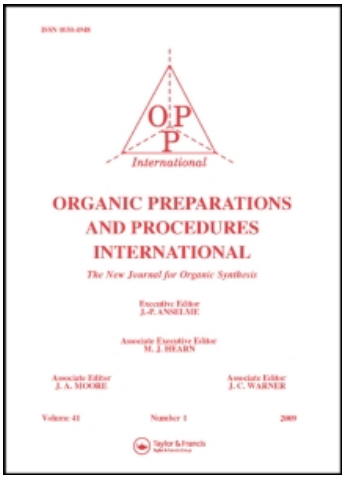

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

IMPROVED PROCEDURE FOR THE ONE-STEP SYNTHESIS OF α-KETOESTERS

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To cite this Article Singh, Janak , Kissick, Thomas P. and Mueller, Richard H.(1989) 'IMPROVED PROCEDURE FOR THE ONE-STEP SYNTHESIS OF α-KETOESTERS', Organic Preparations and Procedures International, 21: 4, 501 — 504
To link to this Article: DOI: 10.1080/00304948909356417
URL: http://dx.doi.org/10.1080/00304948909356417

ORGANIC PREPARATIONS AND PROCEDURES INT. 21(4), 501-504 (1989)

IMPROVED PROCEDURE FOR THE ONE-STEP SYNTHESIS OF α-KETOESTERS

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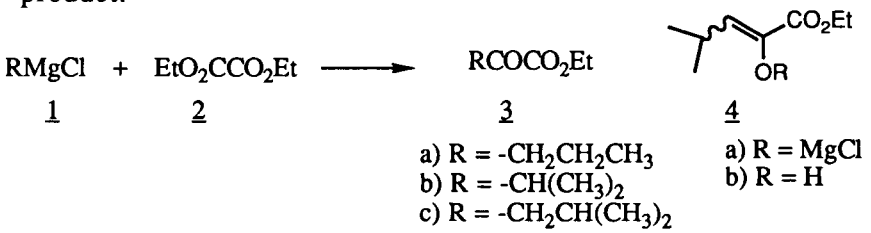
α-Ketoesters are useful synthetic intermediates that have been employed recently for the synthesis of angiotensin converting enzyme (ACE) inhibitors.[1] These compounds have been accessed by several new methods.[2-9] The most direct preparation by the addition of Grignard reagents 1 to diethyl oxalate 2, which gives α-ketoesters in low to moderate yields,[5,6] has been investigated for improvement in the yield of the product.



1 2 3 4

a) R = $-CH_2CH_2CH_3$
b) R = $-CH(CH_3)_2$
c) R = $-CH_2CH(CH_3)_2$

a) R = MgCl
b) R = H

It has been reported[6] that during Grignard reactions with diethyl oxalate in ether the primary alkyl α-ketoesters are obtained in 5-20% yield. The use of excess diethyl oxalate (1.1 to 2 molar equivalents) and THF as solvent gave α-ketoesters in 40 to 76% yield.[1,6] Isolation of the more volatile products, e.g., ethyl 2-oxovalerate (3a, yield 65%), was difficult due to the presence of unreacted 2. Yulin and coworkers[7] carried out the reaction with 30% excess Grignard reagent in ether and obtained products in 51-98% yields. The lower alkyl ketoesters ethyl 2-oxovalerate (3a) and ethyl 4-methyl-2-oxovalerate (3c) were produced in only 51% and 61% yields, respectively. Very recently Villiers[8] described the preparation of various α-ketoesters in high yields by reactions of 2 with 20% excess Grignard reagents at -80°. Since an α-ketoester could possibly react further with a Grignard reagent, the presence of excess reagent[7] could lead to unwanted byproducts.[9]

We required α-ketoesters 3b and 3c for various projects and have independently developed reaction conditions to produce these compounds in high yields. We found that control of the stoichiometry (1 molar equivalent 1) and low temperatures (-78° to -60°C) produced very clean products. α-Ketoesters 3a-3c were prepared in this manner in 92% (85% distilled), 90% (89% distilled) and 98% yields, respectively.

TABLE. Preparation of α-Ketoesters

Product	Yield (%)	lit. Yield (%)	Elemental Analyses calc. (found)
3a	92[a], 85[b]	65[5], 51[6]	C 58.32 (58.25); H 8.39 (8.55)[b]
3b	90[c], 89[d]	86[8,9], 88-92[9]	C 56.57 (56.34); H 8.47 (8.38)[d]
3c	98.4[e]	61[6]	C 59.52 (59.49); H 8.97 (8.56)[e]

a. Undistilled, yield corrected for 1 M% Et_2O and 1 M% diethyl oxalate. b. Distilled bp. 116°/35 mm; anal. calcd. for $C_7H_{12}O_3$ (144.2). c. Undistilled yield corrected for 5M% diethyloxalate. d. Distilled bp 110°/30 mm; anal. calcd. for $C_7H_{12}O_3 \cdot 0.25\ H_2O$ (144.17/148.67). e. Product was clean (^{1}HNMR, 270 MHz) and distillation was not necessary; anal. calcd. for $C_8H_{14}O_3 \cdot 0.18\ H_2O$ (158.19/161.43).

An interesting phenomenon was observed. When the reaction mixture was quenched at low temperature (-60°), only the keto form was obtained. However, a mixture of keto (3c) and enol (4b) forms of 3c was formed when the reaction mixture was warmed to ambient temperature and then quenched. The proportion of 3c (35%) and 4b (65%) was unchanged after distillation (yield 85%). However, treatment of the mixture of 3c and 4b with pyridine overnight caused complete tautomerisation of 4b to the thermodynamically more stable keto form 3c. Presumably, enolization is caused (during warming) by the EtOMgCl produced in the reaction; protonation of the enolate 4a then apparently occurs preferentially on oxygen, thus generating the enol form. At low temperature, this base is ineffective toward enolization and therefore, if the reaction mixture is quenched at low temperature, the keto form is the only component isolated.

In conclusion, a procedure is available for the preparation of α-ketoesters 3a-3c in high yields. This improved method should find general application for the synthesis of α-ketoesters.[8,9]

EXPERIMENTAL SECTION

Ethyl 2-oxovalerate 3a (Table, yield 92%, 85% distilled) and ethyl 2-oxo-isovalerate 3b (Table, yield 90%, 89% distilled) were prepared by the procedure described for the synthesis of α-ketoester 3c. For the preparation of 3a the temperature of the reaction mixture was maintained below -75° during the addition of propylmagnesium chloride. Satisfactory MS, IR, and NMR spectra were obtained for compounds 3a and 3b.

Preparation of Ethyl 4-Methyl-2-oxovalerate (3c).- A solution of diethyl-oxalate 2 (135.7 ml, 1.0 mole) in anhydrous ether (500 ml) was cooled to -78° under argon. A solution of isobutylmagnesium chloride (500 ml, 2M in ether, 1.0 mole) was added dropwise over 1 hr from an addition funnel. The internal temperature of the reaction mixture was monitored by a thermocouple and was maintained below -60° during the addition. After another 0.5 hr, the mixture was poured without warming into a rapidly stirred mixture of conc. HCl (85 ml), ice (400 ml) and ether (500 ml) in a 4 l beaker. The aqueous layer was separated. The ethereal layer was washed with water (500 ml), brine (2 x 500 ml), and dried ($MgSO_4$); the solvent was evaporated to give 155.4 g (yield 98%) of 3c. ^{1}HNMR (270 MHz, $CDCl_3$): δ 0.98 (6H, d, J = 7 Hz), 1.38 (3H, t, J = 8 Hz), 2.2 (1H, m), 3.72 (2H, d, J = 8 Hz), 4.32 ppm (2H, q, J = 8 Hz). ^{13}CNMR (68 MHz, $CDCl_3$): δ 13.9, 22.3, 24.1, 47.8, 62.2, 161.3, 194.2 ppm; IR ($CHCl_3$): 1740, 1730 (C=O) cm^{-1}; MS: (CI, NH_3) $(M+NH_4)^+$ = 176.

Acknowledgement.- We wish to thank Dr. Christopher M. Cimarusti for helpful suggestions. We thank our colleagues in Analytical Research & Development for their help and Ms. Jeannette Manello for literature searches.

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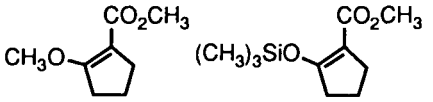
3. α-Keto diester (iii) was synthesized by ozonolysis of (i) or by

ozonolysis of (ii) followed by esterification with diazomethane. This work was carried out by one of us (JS) in the laboratory of Prof. Gilbert Stork at Columbia University in New York.



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(Received December 16, 1988; in revised form April 10, 1989)