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Solid Phase Synthesis of Ketones from Esters

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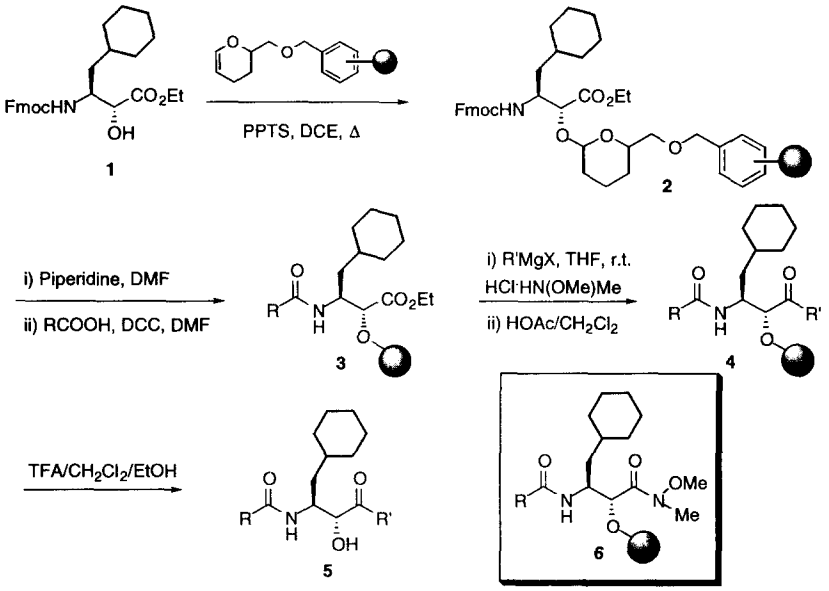
Abstract: A one-pot procedure for the solid phase synthesis of ketones from the corresponding esters, via *in situ* formation of the *N*-methoxy-*N*-methylamide, is described. © 1997 Elsevier Science Ltd.

Solid phase organic synthesis[1] is an important and evolving tool in the search for novel, biologically active compounds.[2,3] Methods for the preparation of ketones on solid support include oxidation,[4] C-acylation,[5] Stille coupling[6] and cleavage of resin-bound *N*-methoxy-*N*-alkylamides using Grignard reagents.[7] In the search for unique protease inhibitors based on α-hydroxyketones, a one-pot procedure for the conversion of polymer-supported esters to ketones was developed.[8,9]

Fmoc-protected cyclohexyl norstatine ethyl ester (**1**)[10] was coupled to DHP-linked polystyrene resin (Scheme 1) using catalytic PPTS in 1,2-dichloroethane (DCE).[11] Deprotection of the amine (20% piperidine/DMF), followed by acylation (RCOOH) afforded resin-bound ester **3**. Treatment of ester **3** with excess Grignard reagent (R'MgX) and *N,O*-dimethylhydroxylamine hydrochloride afforded ketone **4**,[12] via the intermediate *N*-methoxy-*N*-methylamide **6** (*vide infra*). Cleavage from the resin gave the desired ketone **5** in good purity and yield.[13] The scope and limitations of the procedure were explored further (Table 1). The reaction is particularly successful with non-hindered primary Grignard reagents, and generally yields products of excellent purity (>80%), considering the purity is based on a four step sequence.[14] Secondary Grignard reagents afford lower yields of ketone (entries 6, 9), as do hindered primary nucleophiles (entry 4). The nature of the nitrogen acyl group (aromatic or aliphatic) appears to have little effect on the efficiency of the transformation.

Addition of excess Grignard reagent (20 equivalents) is necessary to afford the desired ketone in high purity. In a study where 6 equivalents of $PhCH_2MgCl$ and 2 equivalents of HCl·HN(OMe)Me were employed, a 2:1 mixture of the desired ketone and the corresponding *N*-methoxy-*N*-methylamide was obtained after cleavage from the resin. The isolation of these two products confirms that the reaction proceeds via the intermediate *N*-methoxy-*N*-methylamide.



Scheme 1

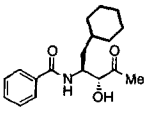
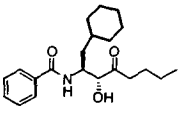
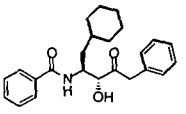
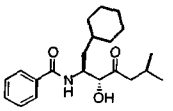
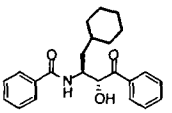
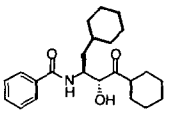
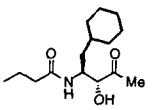
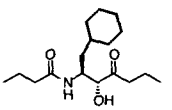
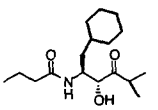
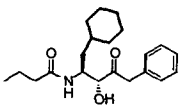
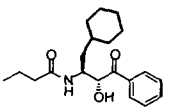
Evidence for the intermediacy of the amide was also gathered from an experiment where the HCl·HN(OMe)Me was omitted completely, which resulted in a complex mixture (HPLC and TLC analysis) on cleavage from the resin.

The purity of the product appears to be independent of reaction temperature. Addition of the Grignard reagent to the resin-bound ester and *N,O*-dimethylhydroxylamine hydrochloride at either -15 °C or at room temperature afforded products of equal purity after cleavage from the resin. The fact that the conversion proceeds efficiently at room temperature significantly increases the utility of this methodology.

The reaction is much less successful with organolithium reagents than with Grignard reagents. For example, treatment of a mixture of resin-bound ester **3** (R = C_3H_7) and HCl·HN(OMe)Me with MeLi, followed by cleavage from the resin resulted in a multi-component mixture (HPLC and TLC analysis). Column chromatography afforded the desired methyl ketone in only 9% yield. It has been demonstrated that reaction of HN(OMe)Me with organolithiums affords the *N*-methyl-*N*-substituted amine[15] which may account for the low efficiency in this case.

The following experimental procedure is representative. To a stirred mixture of resin-bound ester **3** (150 mg, 0.5 mmol/g) and HCl·HN(OMe)Me (14.6 mg, 2 equiv.) in THF (1.2 mL) at room temperature was added MeMgCl (0.5 mL, 3 M/THF, 20 equiv.) dropwise over 20 minutes. The reaction mixture was stirred at room temperature for 15 hours. The resin was washed with THF to remove unreacted Grignard reagent. It was then washed with DMF/H_2O (3:1), CH_2Cl_2,

Table 1

Entry	RMgX	Product	Crude Purity[a]	Yield[b]
1	MeMgCl		86.0%	52%
2	*n*-BuMgCl		85.6%	59%
3	$PhCH_2MgCl$		85.7%	68%
4	*i*-BuMgCl		35.0%	31%
5	PhMgBr		69.9%	54%
6	$C_6H_{11}MgCl$		22.5%	14%
7	MeMgCl		83.1%	67%
8	*n*-PrMgCl		68.5%	49%
9	*i*-PrMgCl		26.6%	13%
10	$PhCH_2MgCl$		91.9%	65%
11	PhMgBr		70.0%	39%

[a] Determined by reverse phase HPLC. [b] Isolated yield after column chromatography (4 step reaction sequence).

HOAc/CH_2Cl_2 (9:1), followed by multiple washings with CH_2Cl_2 and EtOH.[16] The ketone product was then cleaved from the resin using TFA/CH_2Cl_2/EtOH (2:2:1, 2 mL).

In summary, a one-pot procedure for the solid phase synthesis of ketones from the corresponding esters has been developed. The procedure can be conveniently carried out at room temperature and generally affords ketones of high purity when unhindered, primary Grignard reagents are employed.

Acknowledgments

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11 Thompson, L.A.; Ellman, J.A. *Tetrahedron Lett.* **1994**, *35*, 9333.

12 Examination of the resin-bound materials by IR spectroscopy showed the disappearance of the ester (1743 cm^{-1}) and the appearance of a methyl ketone (1719 cm^{-1}).

13 Yields were calculated based on the initial loading of the resin.

14 All compounds were characterised by ^1H NMR, ^{13}C NMR and MS.

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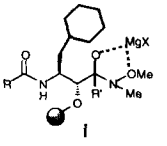
16 The acetic acid/CH_2Cl_2 washing step is of critical importance. If it is omitted, an insoluble precipitate and higher than expected mass return are seen on cleavage of the product from the resin. Presumably, this is due to magnesium salts resulting from collapse of the tetrahedral intermediate **i** on exposure to the acidic cleavage conditions.



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