Pergamon

Tetrahedron Letters, Vol. 36, No. 31, pp. 5461-5464, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01089-0

A New General Method for Preparation of *N*-Methoxy-*N*-Methylamides. Application in Direct Conversion of an Ester to a Ketone.

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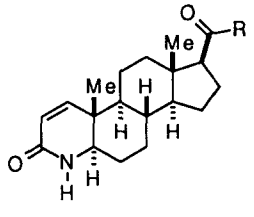
Abstract: The reaction of an ester with *N,O*-dimethylhydroxylamine and a suitable organomagnesium reagent or lithium amide base provides a general method for the preparation of *N*-methoxy-*N*-methylamides. Application in the direct conversion of a highly hindered ester to a ketone, the azasteroid 5α-reductase inhibitor MK-0434, is described.

The Δ^1-3-keto-4-azasteroid structural unit **1** is the basis for a series of potent 5α-reductase inhibitors differing only in the C17 side-chain which have been evaluated for the treatment of Benign Prostatic Hyperplasia (BPH).[1] Finasteride (**1a**, MK-0906), the active ingredient in Proscar™, emerged as the first drug therapy for BPH.[2] The final intermediate in the process for making finasteride is the methyl ester **1b** which is converted to the *tert*-butylamide using EtMgBr and *tert*-butylamine, the Bodroux reaction.[3] Among the other drug candidates in this series, the phenyl ketone **1c** (MK-0434) presented a particularly challenging synthetic problem. The ketone had been originally prepared from the thiopyridyl ester **1d** which served as a pivotal intermediate in the preparation of a wide variety of analogs.[1] This approach, however, was not practical for large scale production. With a well-developed process for producing large quantities of **1b**,[4] we set out to develop a method for converting the ester to the required ketone. Success depended primarily on our ability to limit reaction of an organometallic reagent with the ketone product.[5]



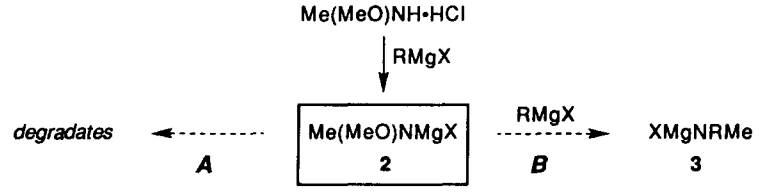
R	1
NH*t*-Bu	**a**
OMe	**b**
Ph	**c**
2-*S*-pyridyl	**d**
N(OMe)Me	**e**
H	**f**

We now wish to report a practical method for accomplishing this transformation with minimal side-reactions. Amide **1e** can be prepared from ester **1b** by reaction with Me(MeO)NH and an organomagnesium reagent. Without isolation, subsequent reaction with PhMgCl provides ketone **1c**.[6] In broader application, this method proved to be general for preparation of *N*-methoxy-*N*-methylamides from enolizable as well as hindered esters.

The use of *N*-methoxy-*N*-methylamides as isolated intermediates in the conversion of esters to ketones has become widely practiced.[7] The tetrahedral intermediate formed on reaction of the *N*-methoxy-*N*-methylamide with an organometallic reagent resists collapse to form the ketone under the reaction conditions thereby preventing the subsequent reaction of the ketone and organometallic. The *N*-methoxy-*N*-methylamide is generally prepared from the ester using an aluminum-based reagent.[8] In application of this method to the azasteroid **1b**, we observed none of the desired amide possibly as a result of steric hinderance about the carbonyl.

Our experience with the Bodroux reaction in making finasteride suggested that the magnesium amide derived from Me(MeO)NH would have the Lewis acidity and nucleophilicity required to attack the hindered carbonyl of the steroidal ester.[9] Initial attempts to make **1e**, however, were disappointing. When EtMgBr was added to a

slurry of Me(MeO)NH•HCl in THF at 0 °C and the resulting solution was added immediately to a slurry of the ester, only low yields of the desired amide **1e** were produced. We suspected that the magnesium amide **2** had been consumed by self-decomposition (path *A*)[10] or reaction with the organomagnesium reagent (path *B*)[11].



If, however, the desired reactions, formation of the magnesium amide **2** and addition to the ester carbonyl, were fast relative to the competing undesired reactions, *A*, *B* and the addition of the organomagnesium reagent to the ester carbonyl, it would be possible to form **2** in the presence of the ester and achieve the desired result. When EtMgBr was added to a slurry of the ester **1b** and Me(MeO)NH•HCl in THF at 0 °C, the ester was rapidly converted to amide **1e** which was isolated in 91% yield.

The conversion of esters to *N*-methoxy-*N*-methylamides proved to be general with the proper choice of base. *i*-PrMgCl is preferred. Using MeMgCl and EtMgBr small amounts (2-5%) of the corresponding ketones were observed with less hindered esters and this problem was completely eliminated by using the more hindered base. Although the non-nucleophilic bases mesitylmagnesium bromide and lithium hexamethyldisilazide (LHMDS) gave comparable yields, *i*-PrMgCl provides the cleanest crude product simplifying purification. The chemistry works well with both enolizable and hindered esters (Table 1).[12] The lower yields observed in entries 4 and 5 appear to be the result of base-promoted elimination of formaldehyde.[13]

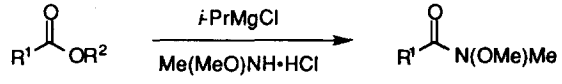


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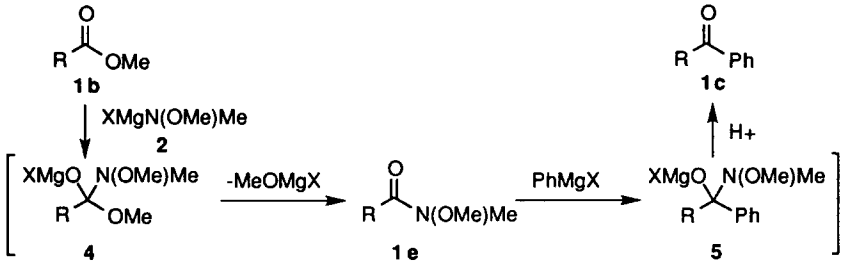
Table 1. Preparation of *N*-Methoxy-*N*-methylamides from Esters using Isopropylmagnesium Chloride

entry	R^1	R^2	amide **6**	yield[a] (%)
1	Ph	Me	**a**	100[b]
2	$PhCH_2$	Me	**b**	92
3	$PhCH_2CH_2$	Et	**c**	97
4	$PhCH_2CMe_2$	Et	**d**	85
5	PhCH=CH	Me	**e**	88
6	C_6H_{11}	Me	**f**	94
7	3,5-$(MeO)_2$Ph	Me	**g**	98

[a]Yield after chromatographic purification. [b]HPLC assay yield.

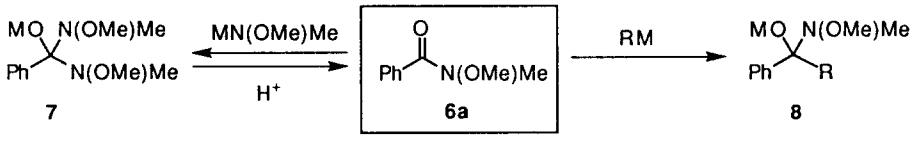
Returning to the problem of making ketone **1c**, reaction of the isolated amide **1e** with PhMgCl gave the desired product and less than 2% tertiary alcohol, the predominant product observed on reaction of 1 equiv of PhMgCl with **1c**. With the prospect for avoiding isolation of **1e**, we then proposed to use PhMgCl both to

generate **2** and convert **1e** to **1c**. We recognized that success would depend upon the relative stability of intermediates **4** and **5**. Intermediate **4** must eliminate MeOMgX to give **1e** under conditions where **5** is stable.



PhMgCl was added at -5 °C and the ester was consumed almost immediately. Complete conversion of **1e** to **1c** required 8 h at 20 °C, but less than 2% of the tertiary alcohol was formed. The major steroidal side-product was identified as the aldehyde **1f** which was not observed when isolated amide **1e** was reacted with PhMgCl suggesting that **2** or **3** (R=Ph) is responsible for the reduction observed.[14] The aldehyde formed was proportional to the excess of amine hydrochloride used and was minimized (<2%) by determining the minimum amount of amine hydrochloride required to complete conversion to **1e** (1.25 equiv). With the optimal charges of amine hydrochloride and PhMgCl the direct conversion afforded 87% yield of **1c** after isolation. The method is practical for large scale production as demonstrated in the direct conversion of 16 kg of ester to ketone.

In beginning to assess broader application in the direct conversion of esters to ketones we chose methyl benzoate as substrate. On adding excess MeMgCl to a mixture of Me(MeO)NH•HCl and methyl benzoate, rapid and complete conversion to amide **6a** was observed. Conversion of **6a** to acetophenone, however, stopped at 90%. With extended aging at 20 °C, tertiary alcohol began to appear. Insight into the source of this problem came from a report that tetrahedral intermediate **7** (M=Li), formed by addition of PhLi to the urea, is remarkably stable.[15] This observation suggested that amide anion **2** adds to **6a** to give **7** competitive with the addition of RM to give **8** (M=MgX). The appearance of tertiary alcohol suggests that **7** is more stable than **8**.



Consistent with this interpretation, the reaction of excess MeMgCl with amide **6a** was inhibited by **2** generated from Me(MeO)NH•HCl. A signal for the carbonyl carbon of **6a** was not observed by ^{13}C NMR. Using LHMDS as base a new signal at 108.3 ppm corresponding to tetrahedral intermediate **7** (M=Li) appeared.

Successful conversion of an ester to a ketone by this method then depends upon the relative stability of tetrahedral intermediates and the relative rates of addition of **2** and RM to the *N*-methoxy-*N*-methylamide carbonyl. In preliminary survey of a series of ester/organomagnesium pairs using the protocol developed for the preparation of **1c**, it was apparent that reaction parameters must be defined for each case.[16]

In conclusion, the reaction of an ester with Me(MeO)NH•HCl and a suitable organomagnesium reagent or lithium amide base provides a general method for the preparation of *N*-methoxy-*N*-methylamides that can be applied in the direct conversion of an ester to a ketone.

General Procedure for the Conversion of Esters to *N*-Methoxy-*N*-methylamides. The ester (10 mmol) and 1.51 g (15.5 mmol) of Me(MeO)NH•HCl were slurried in 20 mL of THF cooled to -20 °C under nitrogen. A solution of *i*-PrMgCl in THF (15 mL, 2.0 M) was added over 15 min maintaining the temperature below -5 °C. The mixture was aged for 20 min at -10 °C and quenched with 20 wt % aqueous NH_4Cl. The product was extracted using *tert*-butylmethyl ether and the organic solution was dried over Na_2SO_4 and concentrated. Chromatographic purification (silica gel) afforded the reported yields of analytically pure product.

Direct Conversion of Methyl Ester 1b to 17β-Benzoyl-4-aza-5α-androst-1-ene-3-one (1c). To a slurry of Me(MeO)NH•HCl (3.71 g, 37.9 mmol) and ester **1b** (10.0 g, 30.2 mmol) in 400 mL of THF at -5 °C under nitrogen was added PhMgCl in THF (126 mL, 2.0 M) over 2 h maintaining the temperature between -2 and -5 °C. After 1h at -5 °C the reaction mixture was warmed to 25 °C over 1 h, aged for 8 h then quenched into 1 N HCl. The mixture was heated to 30-35 °C. The layers were separated and the THF solution was concentrated. The product was crystallized by adding isopropanol and water and cooling to 0 °C, isolated by filtration washing with cold isopropanol, and dried at 80 °C under vacuum to give 9.9 g (87% yield) of the phenyl ketone **1c**. $[\alpha]_{405}$ +94.5° (25 °C, c = 1, glacial acetic acid); IR (nujol) 3170, 1665, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.90-7.82 (2H), 7.60-7.39 (3H), 6.71 (1H, d, *J* = 10.0 Hz), 6.27 (1H, bs), 5.77 (1H, dd, *J* = 1.8, 10.0 Hz), 3.49 (1H, m) 3.32 (1H, m), 2.47 (1H, m), 0.92 (3H, s), 0.62 (3H, s); ^{13}C ($CDCl_3$, 62.5 MHz) δ 201.8, 166.7, 150.8, 139.2, 132.6, 128.3, 128,1, 122.9, 59.5, 57.0, 56.5, 47.5, 45.2, 39.2, 39.0, 35.4, 29.4, 25.8, 24.5, 23.7, 21.2, 13.8, 11.9. Anal. Calcd for $C_{25}H_{31}N_1O_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.51; H, 8.26; N, 3.58.

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(*Received in USA* 15 *December* 1994; *revised* 1 *June* 1995; *accepted* 8 *June* 1995)