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A Simple Preparation of Ketones. *N*-Protected α-Amino Ketones from α-Amino Acids

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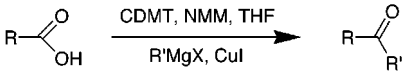
ABSTRACT



Carboxylic acids and amino acids are readily converted, under mild conditions, into the corresponding activated esters, which are reacted with Grignard/CuI reagent to give the corresponding ketones in nearly quantitative yields. The compounds were recovered substantially pure from the reaction mixtures.

N-Protected α-amino ketones are very important compounds in synthetic organic chemistry. In fact, they are interesting as intermediates in natural product synthesis[1] and as starting materials for nitrogen-containing heterocycles.[2]

Several methods for the synthesis of α-amino ketones have been reported starting from α-amino acids.[3] Recently, a conversion of α-amino acids into NH-Boc[3d] and NH-Cbz[3e] protected α-amino ketones via imidazolides with Grignard reagents under Cu(I) catalysis or by palladium-catalyzed reaction of thiol esters with organozinc reagents, respectively, were reported. The yields were in general satisfactory, but the final product had to be purified on silica gel. A valuable method to obtain ketones and in particular *N*-protected α-amino ketones[2,4] is based on the reaction between Grignard or organolithium reagents and *N*-protected α-amino Weinreb amides.[5] At present, this route might not suffer any more from drawbacks since we have very recently reported an easy one-flask procedure that allows one to obtain quantitatively the amide without any purification.[6] However, it requires a large excess of the organometallic reagent.[2,4]

On this basis of and following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,[7] we describe herein an alternative approach that avoids the formation of the Weinreb amide and provides an efficient and cheap conversion of acids and in particular of α-amino acids into the corresponding ketones via direct reaction with Grignard/CuI reagents.

The procedure is based on the treatment of the carboxylic acid with 2-chloro-4,6-dimethoxy[1,3,5]triazine (CDMT) and *N*-methylmorpholine (NMM) in THF, which gives the corresponding activated ester quantitatively in ca. 1 h (monitored by TLC) at room temperature.[6] After filtering the white precipitate, 1 equiv of anhydrous CuI is added to the solution, containing the activated ester, followed by 1 equiv of freshly prepared Grignard reagent, slowly and at 0 °C (Scheme 1).

(1) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. Angle, S. R.; Boyle, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185.

(2) (a) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039. (b) De Luca, L.; Falorni, M.; Giacomelli, G.; Porcheddu, A. *Tetrahedron* **1999**, *40*, 8701.

(3) (a) Mayer, D. In *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1977; Vol. 7, 2c, p 2253. (b) Fischer, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399. (c) Pace, R. D.; Kabalka, G. W. *J. Org. Chem.* **1995**, *60*, 4838. (d) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A., Varchi, G. *Synlett* **1998**, 1013. (e) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

(4) Sawamura, M.; Nakayama, Y.; Kato, T.; Ito, Y. *J. Org. Chem.* **1995**, *60*, 1727.

(5) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(6) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534.

(7) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395. Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275.

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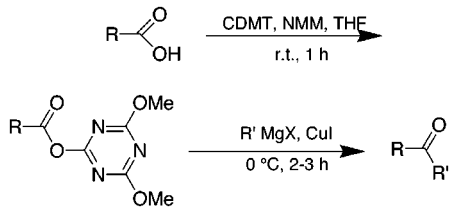
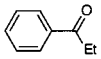
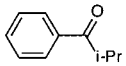
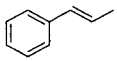
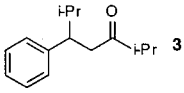
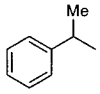
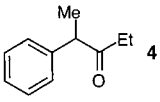
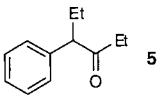
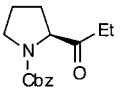
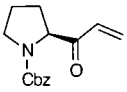
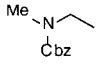
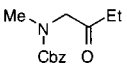
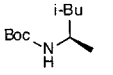
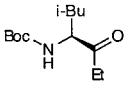
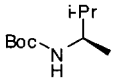
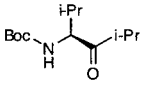
Scheme 1



As shown in Table 1, a variety of ketones and *N*-protected α-amino ketones were prepared from commercially available carboxylic acids and amino acids. In the most of the cases, the yields were nearly quantitative and the conversion very high.

Table 1. Synthesis of Ketones from Carboxylic Acids

entry	R	R'	Product	yield conversion[a]
1		Et	 **1**	98 (100)
2	"	"	**1**	98[b] (65)
3	"	"	**1**	35[c] (97)
4	"	"	**1**	25[d] (76)
5	"	*i*-Pr	 **2**	99 (83)
6		"	 **3**	90[e] (47)
7		Et	 **4**	97 (95)
8		Et	 **5**	94 (74)
9		Et	 **6**	95[f] (100)
10	"	vinyl	 **7**	48[g] (35)
11		Et	 **8**	97 (80)
12		Et	 **9**	97 (65)
12		*i*-Pr	 **10**	98 (55)

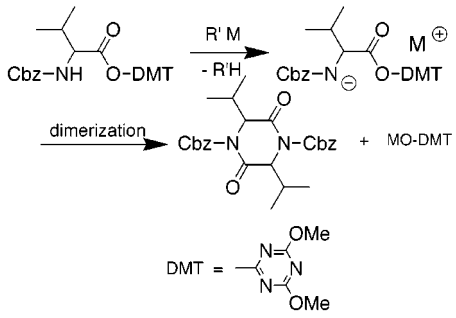
[a] %, after 3 h. [b] Inverse addition. [c] Reaction run without CuI (10% mol). [e] 10% of isopropyl *trans*-cinnamate. [f] $[\alpha]^{20}_D$ −43.0° (*c* 0.76, $CHCl_3$). [g] $[\alpha]^{20}_D$ −36.3° (*c* 0.56, $CHCl_3$).

It is interesting to note that the inversion of the addition of the reagents (entry 2) does not influence the yield of the reaction; however, the completion of the reaction requires longer times. The presence of a stoichiometric amount of CuI is necessary as the reaction of the Grignard reagent with the activated ester furnished an extensive amount of the tertiary alcohol even at low temperature (entry 3). Addition of a catalytic amount (10%) of CuI to the Grignard reagent led to grossly similar results, and the alcohol was the main compound recovered (entry 4).[8]

Aromatic and aliphatic carboxylic acids are cleanly converted to the corresponding ketones. In the case of cinnamic acid, the reaction afforded mainly 2,6-dimethyl-5-phenylheptan-3-one, corresponding to a Michael-type 1,4-addition product, which undergoes a successive reaction of the Grignard/CuI reagent with its activated carboxylic group.

This methodology is applicable to NH-Boc and N-Cbz protected α-amino acids having secondary amino groups. With N-Cbz primary α-amino acids the only product recovered is the dimeric N-Cbz diketopiperazine, which presumably proceeds via the formation of the N-anion that condenses with another molecule (Scheme 2).

Scheme 2



The reaction proceeds with satisfactory rates with alkyl organometallic derivatives, whereas vinyl metal compounds seem to react slowly and with poor yields. The reaction is very slow with alkynyl metal reagents, so that the corresponding alkynyl ketone is formed only in negligible amounts.[9] In these last cases the reaction is not competitive with the corresponding procedure via the Weinreb amides.[6]

According to what is already reported,[6] significant racemization of the chiral center of the α-amino acids did not occur under these conditions, as revealed by the optical rotation values of the product **6** if compared with that reported in the literature.[3e,6]

The procedure for the synthesis of *N*-benzyloxycarbonyl-pyrrolidin-2-yl-propan-1-one **6** is representative. CDMT (0.74 g, 4.4 mmol) and NMM (1.2 mL, 11.1 mmol) were added to a solution of *N*-benzyloxycarbonyl-L-proline (0.89 g, 3.7 mmol) in THF (11 mL) maintained at room temper-

(8) All unknown compounds in the table were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis.

(9) The product of self-coupling of the terminal alkyne used is the main one in the hydrolyzed reaction mixture after usual workup.

ature. The white precipitate formed during 1 h of stirring was filtered off under argon, CuI (0.70 g, 3.7 mmol) was added to this solution, and then at 0 °C, slowly, a THF solution (5 mL) of ethylmagnesium bromide (1.24 mL of 3 N Et_2O solution, 3.7 mmol) was added. After an additional 2−3 h of stirring at room temperature, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted two times with 10 mL of diethyl ether. The combined organic phases were washed with 15 mL each of saturated Na_2CO_3, 1 N HCl, and brine. The organic layer was dried over anhydrous Na_2SO_4 to give, after evaporation of solvent, compound **6** (95%), nearly pure by TLC.[10]

Key features of this method, which leads in good yields within a short period to the desired ketones, are the mild conditions and, owing to the high reactivity of the activated ester, the reduced amount of the Grignard reagent. The yields are generally comparable to those obtained via the Weinreb amides according to the recently reported method,[6] without using the expensive *N*,*O*-dimethylhydroxylamine hydrochloride or converting the acid into a more complex derivative. In conclusion, we believe that the simple method here described is very useful for the preparation of NH-Boc protected α-amino ketones under mild conditions even in large scale.

(10) The crude products can be further purified by short-path silica gel. The yield in the table refers to isolated yields, obtained after purification.

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Supporting Information Available: Physical and spectroscopic data for all unknown compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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