Tetrahedron Letters,Vol.26,No.36,pp 4387-4390,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

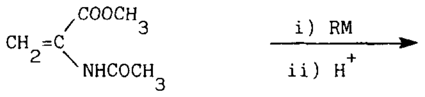
SYNTHESIS OF α-AMINO ACID DERIVATIVES BY COPPER(I)-CATALYZED CONJUGATE ADDITION OF GRIGNARD REAGENTS TO METHYL 2-ACETAMIDOACRYLATE

C. Cardellicchio, V. Fiandanese, G. Marchese, F. Naso*, and L. Ronzini

Centro CNR di Studio sulle Metodologie Innovative di Sintesi Organiche
Dipartimento di Chimica, Università di Bari, via Amendola 173, 70126 Bari, Italy

Summary: *The reactions of Grignard reagents with methyl 2-acetamidoacrylate in the presence of CuI give fair to good yields of α-amino esters; the corresponding α-deutero- or α-methyl-derivatives are obtained upon quenching with D^+ or CH_3I, respectively.*

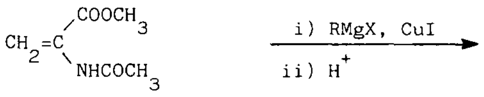
In principle, α-amino acid derivatives could be prepared by conjugate addition of suitable organometallic reagents to an α,β-unsaturated ester such as methyl 2-acetamidoacrylate (eq.1).



$$CH_2{=}C\begin{smallmatrix}COOCH_3\\ NHCOCH_3\end{smallmatrix} \xrightarrow[\text{ii) } H^+]{\text{i) RM}} R{-}CH_2{-}C{-}H\begin{smallmatrix}COOCH_3\\ NHCOCH_3\end{smallmatrix} \qquad (1)$$

However, it has been reported that no product resulting from a simple 1,4-addition is obtained in the reactions between N-acylaminoacrylic acids[1] or related methyl esters[2] with lithium diorganocuprates.

Due to our interest in the synthesis of α-amino acids or of their precursors,[3] we undertook an investigation of the above reaction and now we report that the process can be performed in a convenient manner by copper(I)-catalyzed conjugate addition of Grignard reagents[4] (eq. 2).



$$CH_2{=}C\begin{smallmatrix}COOCH_3\\ NHCOCH_3\end{smallmatrix} \xrightarrow[\text{ii) } H^+]{\text{i) RMgX, CuI}} R{-}CH_2{-}C{-}H\begin{smallmatrix}COOCH_3\\ NHCOCH_3\end{smallmatrix} \qquad (2)$$

As illustrated by the results in the Table, various α-amino esters can be synthesized by this process in THF (with the exception of the 1-naphtyl-derivative), in ether/benzene or in THF/benzene, in most cases higher yields being obtained in the mixed solvents. The reaction works well with aromatic and primary, secondary, and tertiary aliphatic Grignard reagents.

In order to understand the factors determining the success of our transformation, we performed a few experiments using methyl 2-acetamidoacrylate and lithium diorganocuprates (Ph_2CuLi and $\underline{n}$-Bu_2CuLi) in ether, THF, and ether/benzene. The results showed that either no 1,4-addition occurred or mixtures of products, including the products of 1,4-addition, were formed. Therefore, we conclude that the type of organometallic reagent used plays a crucial role in the conjugate addition.

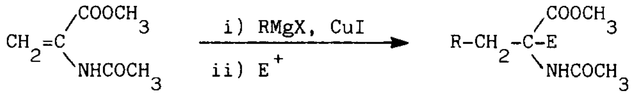
An additional interesting feature of our procedure is represented by the possibility of preparing α-deutero- or α-methyl-α-amino esters upon quenching with D^+ or methyl iodide, respectively (entries 7-9,12,17,18 and 24).

The process described here, because of its procedural simplicity and the use of readily available chemicals, appears to be a promising and useful route (after hydrolysis) to a wide variety of DL-α-amino acids of both uncommon and proteinogenic types.[5] Also, it is worth noting the interest connected with the synthesis of α-deuterated α-amino acids which have attracted considerable attention[6] and of the α-alkyl-derivatives[7] which present a potential as therapeutically useful drugs.[8]

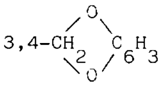
The following procedure for the synthesis of $\underline{N}$-acetyl-DL-leucine methyl ester and of the corresponding α-deuterated or α-methyl-substituted derivative is representative. 0.27 g (1.4 mmol) of CuI were placed in a 250 ml round-bottom flask, equipped with a magnetic stirrer and maintained under a nitrogen atmosphere. Dry ether (10 ml) was added to the flask and the resulting slurry was stirred and cooled to 0°C in an ice bath. A solution of isopropylmagnesium chloride (35 ml of 0.80 M, 28 mmol) in ether/benzene (3:1) was added and, after 10 min, methyl 2-acetamidoacrylate[9] (2 g, 14 mmol) dissolved in 15 ml of ether was dropped. Stirring was continued for additional 30 min at 0°C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and the aqueous layer extracted with ether (three times). After drying over anhydrous sodium sulfate, the combined organic extracts were concentrated in vacuo and the residue was crystallized from petroleum ether to give 1.57 g (60% yield) of $\underline{N}$-acetyl-DL--leucine methyl ester, m.p. 76.5-77°C (lit.[10] m.p. 77°C). The same procedure was followed for the reactions performed in THF and in THF/benzene. In the latter case the solvent for preparing the Grignard reagent was THF only.

To obtain the corresponding deuterated derivative, the reaction was quenched with an excess of D_2O (10 ml) and the same work-up procedure was followed.[11] In the case of the alkylation, the reaction, carried out as above described in ether/benzene, was quenched with an excess of methyl iodide (10 ml) dissolved in 10 ml of THF and stirring was continued for additional 8 h at 0° C. The residue, isolated in the usual manner, was purified by distillation

Table. Conjugate addition of Grignard reagents to methyl 2-acetamidoacrylate[a]



$$CH_2{=}C\begin{smallmatrix}/COOCH_3\\ \backslash NHCOCH_3\end{smallmatrix} \xrightarrow[\text{ii) } E^+]{\text{i) RMgX, CuI}} R{-}CH_2{-}\overset{/COOCH_3}{\underset{\backslash NHCOCH_3}{C}}{-}E$$

Entry	R	Electrophile E^+	Solvent[b]	Yield[c] %
1	CH_3CH_2	H^+	THF	47
2		H^+	Et_2O/C_6H_6	80 (60)
3	$CH_3(CH_2)_2$	H^+	THF	60 (53)
4		H^+	Et_2O/C_6H_6	60 (50)
5	$(CH_3)_2CH$	H^+	THF	93 (61)
6		H^+	Et_2O/C_6H_6	90 (60)
7		D^+	Et_2O/C_6H_6	(62)
8		CH_3I	THF	(63)[d]
9		CH_3I	Et_2O/C_6H_6/THF[e]	(63)[d]
10	$CH_3(CH_2)_3$	H^+	THF	65 (53)
11		H^+	Et_2O/C_6H_6	75 (65)
12		D^+	Et_2O/C_6H_6	(65)
13	$(CH_3)_3C$	H^+	THF	54[d]
14		H^+	Et_2O/C_6H_6	78 (67)[d]
15	C_6H_5	H^+	THF	61
16		H^+	Et_2O/C_6H_6	76 (63)[f]
17		CH_3I	THF	(45)
18		CH_3I	Et_2O/C_6H_6/THF[e]	(62)
19	$2\text{-}CH_3C_6H_4$	H^+	THF	60[d]
20		H^+	Et_2O/C_6H_6	95 (80)[d,f]
21	$4\text{-}CH_3OC_6H_4$	H^+	THF	76 (58)[f]
22	$1\text{-}C_{10}H_7$	H^+	Et_2O/C_6H_6	93 (63)[f]
23		H^+	THF/C_6H_6	75 (50)[f]
24		CH_3I	THF/C_6H_6	51

a) At 0°C; reaction time 30 min. The molar ratio between Grignard reagent and substrate was 2:1 (3:1 for entry 21) and 5 mol % of CuI with respect to the Grignard reagent was used. b) For reactions in mixed solvents, solutions of Grignard reagents in ether were diluted with benzene (ether:benzene 3:1). In the case of entries 23 and 24 the Grignard reagent was prepared in THF and the reactions were carried out in THF/benzene. c) Yields determined by G.L.C. analysis; yields of isolated purified products are given in parentheses. d) The new compounds exibited ^{1}N.M.R. spectroscopic properties consistent with their structures and gave satisfactory molecular weight determinations (mass spectrometry). e) THF used as solvent for CH_3I. f) The product was purified by crystallization after isolation by medium pressure column chromatography through silica gel (ether/petroleum ether 8/2 as eluant).

(bp 82-83°C/ 1 mmHg) to give 1.77 g (63% yield) of the α-methyl-derivative.

Acknowledgement: This work was supported by a grant from the "Progetto Finalizzato di Chimica Fine e Secondaria" of the Italian National Research Council (CNR).

References and Notes

1) K.D. Richards, A.J. Kolar, A. Srinivasan, R.W. Stephenson, and R.K. Olsen, J. Org. Chem., 41, 3674 (1976).

2) J.A. Bajgrowicz, A. El Hallaoui, R. Jacquier, Ch.Pigière, and Ph. Viallefont, Tetrahedron Lett., 25, 2759 (1984); A. Bernardini, A. El Hallaoui, R. Jacquier, Ch. Pigière, Ph. Viallefont, and J. Bajgrowicz, ibid., 24, 3717 (1983).

3) V. Fiandanese, F. Naso, and A. Scilimati, Tetrahedron Lett., 25, 1187 (1984); M. Cutolo, V. Fiandanese, F. Naso, and O. Sciacovelli, ibid., 24, 4603 (1983).

4) For reviews see: G.H. Posner, "An Introduction to Synthesis using Organocopper Reagents", John Wiley, 1980; G.H. Posner, Org. Reactions, 19, 1 (1972).

5) For a comprehensive review on α-amino acids synthesis see: G.C.Barrett,"Synthesis of Amino Acids" in Chemistry and Biochemistry of the Amino Acids, G.C.Barrett Ed., Chapman and Hall, 1985, Chap.8.

6) H. Fujihara and R.L. Schowen, J. Org. Chem., 49, 2819 (1984); D.M. Yamamoto, D.A. Upson, D.K. Linn, and V.J. Hruby, J. Am. Chem. Soc., 99, 1564 (1977); D.A. Upson and V.J. Hruby, J. Org. Chem., 41, 1353 (1976); H. Matsuo, Y. Fujimoto, and T. Tatsuno, Tetrahedron Lett., 3465 (1965).

7) S. Karadi, J.S. Amato, and L.M. Weinstock, Tetrahedron Lett., 25, 4337 (1984); M. Kolb and J. Barth, Liebigs Ann. Chem., 1668 (1983), and references therein; J.A. Bajgrowicz, B. Cossec, Ch. Pigière, R. Jacquier, and Ph. Viallefont, Tetrahedron Lett., 24, 3721 (1983); I. Hoppe, U. Schöllkopf, and R. Tölle, Synthesis, 789 (1983); U. Schöllkopf, W. Hartwig, K-H Pospischil, and H. Khene, ibid., 966 (1981); J-P. Branquet, H. Pacheco, and A. Cier, Bull. Soc. Chim. Fr., 2942 (1965).

8) R.C. Sheppard (Ed.), "Amino Acids, Peptides and Proteins" (Specialist Periodical Reports) The Chemical Society, London, 10, 11 (1979).

9) Methyl 2-acetamidoacrylate was prepared by esterification of a commercial sample of the corresponding acid according to E. Rothstein, J. Chem. Soc., 1968 (1949).

10) N.A. Smart, G.T. Young, and M.W. Williams, J. Chem. Soc., 3902 (1960).

11) For the labelled compounds, the deuterium content at the α-position was 97 % as determined by mass spectrometry analysis.

(Received in UK 20 May 1985)