This article was downloaded by: [Nanyang Technological University] On: 25 April 2015, At: 02:54 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

Convoniont Mothod for the

Convenient Method for the Synthesis of N-(Ethyloxycarbonyl) Ester Derivatives from Amino Acids

J. V. Bhaskar Kanth ^a & Marzappan Periasamy ^a ^a School of Chemistry, University of Hyderabad, Central University P.O., Hyderabad, 500-134 Published online: 23 Sep 2006.

To cite this article: J. V. Bhaskar Kanth & Marzappan Periasamy (1995) Convenient Method for the Synthesis of N-(Ethyloxycarbonyl) Ester Derivatives from Amino Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:10, 1523-1530, DOI: <u>10.1080/00397919508011764</u>

To link to this article: http://dx.doi.org/10.1080/00397919508011764

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

Terms & Conditions of access and use can be found at <u>http://www.tandfonline.com/page/terms-and-conditions</u>

SYNTHETIC COMMUNICATIONS, 25(10), 1523-1530 (1995)

CONVENIENT METHOD FOR THE SYNTHESIS OF N-(ETHYLOXYCARBONYL) ESTER DERIVATIVES FROM AMINO ACIDS

J.V.Bhaskar Kanth and Mariappan Periasamy*

School of Chemistry, University of Hyderabad, Central University P.O., Hyderabad-500 134.

Abstract: Amino acids upon treatment with ethyl chloroformate in methanol in the presence of potassium carbonate give the corresponding N-(ethyloxycarbonyl) amino acid ester derivatives in good yields. These derivatives can be also synthesized by performing the reaction in THF in the presence of alcohols.

Protection of amino and carboxylic functional groups in amino acids is an important transformation, since it helps in carrying out selective reactions at either of the reactive centers. In recent years, the N- and O-protected esters 1 and 2 derived from L-valine and L-proline were widely used in the synthesis of important chiral auxiliaries such as 3 and 4.

1523

Copyright @ 1995 by Marcel Dekker, Inc.



In connection with studies towards the synthesis of chiral amino alcohols,^{2,3} we were looking for a simple procedure for the synthesis of 1 & 2. Usually, these N- and O-protections are carried out in two steps as outlined in Scheme-1.⁴

We wish to report a simple one pot method for simultaneous Nand O-protection of amino acids under mild conditions as outlined in Scheme 2.





S.No	Amino acid	Product ^b	Yield(%) ^C
1		H₂C COOCH3 H₂C NHCOOC₂H5	94
2	Ph-COOH	Ph NHCOOC ₂ H ₅	91
3	н соон		91
4	Соон Н	Соосн ₃ соос ₂ н ₅	95

Table 1: Simultaneous N- and O-protection of amino acids^a

- a. Reactions were carried out using amino acid (10mmol), ethyl chloroformate (22mmol), potassium carbonate (10mmol) in dry methanol (20ml) for 12h at room temperature.
- b. Products were identified by IR, NMR (¹H & ^{13}C)
- c. Yields are of isolated and purified products.





This procedure was found to be a general one and a few other carbamate esters of amino acids have been synthesized. The results are summarized in Table 1.

This single pot N- and O-protection process would most probably go through the intermediacy of the anhydride shown in Scheme 3.

If this is the case, it should be possible to synthesize different carboxylic esters using the corresponding alcohols. Indeed, this was observed. The N-protected benzyl ester of L-valine (1, R = C_2H_5 , R' = CH_2Ph) can be readily prepared in 84% yield by the addition of two equivalents of ethyl chloroformate to a mixture of L-valine and K_2CO_3 in dry THF followed by benzylalcohol at room temperature. Following a similar procedure, menthyl ester of L-valine (1, R = C_2H_5 , R' = -menthyl, yield = 68%) and benzyl ester of L-proline (2, $R = C_2H_5$, $R = -CH_2Ph$, yield = 85%) were also synthesized.

Attempted preparation of the phenolic esters using phenol in the place of alcohols was not successful.



This method was also found to be useful for esterification of carboxylic acids under mild conditions. When capric acid and undecylenic acid were treated with ethyl chloroformate in the presence of $K_2^{CO}_3$ in methanol, the corresponding methyl esters were obtained in good yields.



In conclusion, the present method should serve as a convenient method for simultaneous N- and O-protection of amino acids and also for the esterification of carboxylic acids under mild conditions.

Experimental Section

Preparation of N-(ethyloxycarbonyl)-L-valine methyl ester (1, R = C_2H_5 , R = CH₃).

L-Valine (1.17g, 10mmol) in dry methanol (20ml) was taken in a two-necked RB flask. Anhydrous K_2CO_3 (1.32g, 10mmol) was added followed by ethyl chloroformate (2.5g, 22mmol) under nitrogen atmosphere. The reaction mixture was stirred for 12h at r.t. Methanol was evaporated and distilled water (10ml) was added. The contents were extracted with chloroform (3x15ml). The combined organic extract was washed with brine and dried over anhydrous MgSO₄. Evaporation of the solvent afforded essentially pure N- and O-protected L-valine.

Yield : 1.84g (91%)

IR (neat) ν_{max} : 3350, 2910, 2850, 1720, 1680 cm⁻¹

¹H NMR (200MHz, $CDCl_3$): 0.9(m,6H), 1.2(t,3H), 2.15(m,1H), 3.75(s,3H), 4.1-4.35(m,3H), 5.25(bs,1H).

 13 C NMR(25.0MHz, CDCl₃) : 14.2, 17.3, 18.7, 30.9, 51.8, 58.8, 60.8, 156.5, 172.7.

Preparation of N-(ethyloxycarbonyl)-L-valine benzyl ester (1, R = C_2H_5 , R = CH_2Ph).

L-Valine (1.17g, 10mmol) in dry THF (30ml) was taken in a two-necked RB flask. Anhydrous K_2CO_3 (1.32g, 10mmol) and benzyl alcohol ((1.1g, 10mmol) were added under nitrogen atmosphere at

N-(ETHYLOXYCARBONYL) ESTER DERIVATIVES

room temperature. Ethyl chloroformate (2.5g, 22mmol) was added during 5min. The contents were further stirred for 12h at room temperature. Water (10ml) was added and the organic layer was extracted with chloroform (2x10ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent efforded crude product which was further purified by column chromatography on silica gel using hexane:ethyl acetate / 90:10 as eluent.

Yield : 2.34g, (84%)

 $IR(neat)\nu_{max}$:3350, 3100, 2900, 2850, 1700, 1680, 1600 cm⁻¹

¹H NMR(200MHz, CDCl₃)δppm: 0.9(m,6H), 1.2(t,3H), 2.1(m,1H), 4.2(m,3H), 4.7(s,2H), 5.2(s,1H), 7.3(m,5H).

¹³C NMR(50.0MHz, CDCl₃)δppm: 14.4, 17.3, 18.8, 58.9, 60.9, 66.8, 128.2, 128.4, 135.4, 156.7, 171.9.

¹³C NMR data of other carbamate-esters synthesized following the procedures described here are listed below.

N-(Ethyloxycarbonyl)-glycene methyl ester: (50.0MHz, CDCl₃) δppm 13.9, 42.0, 51.5, 60.5, 156.4, 170.4.

N-(Ethyloxycarbonyl)-(L)-phenylglycene methyl ester: (50.0MHz, CDCl₃) δppm 14.2, 37.9, 51.8, 54.7, 60.8, 126.7, 128.2, 128.9, 135.9, 155.7, 171.9.

N-(Ethyloxycarbonyl)-(L)-proline methyl ester: $(25.0 \text{ MHz}, \text{ CDCl}_3)$ δppm 13.5, 22.4, 23.3, 28.8, 29.8, 45.3, 45.7, 50.9, 58.1, 57.8, 60.0, 153.5, 154.0, 172.2, 172.4

N-(Ethyloxycarbonyl)-(L)-proline benzyl ester: (25.0MHz, CDCl₃) δppm 13.4, 13.9, 22.7, 23.5, 29.2, 30.1, 45.7, 46.1, 58.3, 58.6, 60.4, 60.7, 66.0, 126.3, 126.6, 127.4, 127.7, 128.0, 141.1, 154.2, 154.8, 172.2, 173.1.

N-(Ethyloxycarbonyl)-(L)-valine menthyl ester: (50.0MHz, CDCl₃) δppm 14.5, 16.1, 17.5, 18.9, 21.0, 22.2, 23.2, 25.8, 31.3, 31.7, 34.6, 45.1, 50.2, 58.9, 61.1, 71.5, 156.5, 172.0.

Acknowledgement: We are grateful to the CSIR and DST, New Delhi for financial support. We are also thankful to the UGC for special assistance and COSIST programs.

References

- 1. (a) Itsuno, S.; Ito, K.; J.Org.Chem., 1984, 49, 555.
 - (b) Itsuno, S.; Nakano, M.; Masuda, H.; Ito, K.; J. Chem.
 Soc., Perkin Trans. I, 1985, 2039.

(c) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Bull. Chem. Soc. Jpn., 1987, 60, 395.

(d) Corey, E.J.; Bakshi, R.K.; Shibata, S.; J. Am. Chem.
 Soc., 1987, 109, 5551.

- (e) Corey, E.J.; Pure and Appl. Chem., 1990, 62, 1209.
- (f) Singh, V.K.; Synthesis, 1992, 602.
- 2. Kanth, J.V.B.; Periasamy, M.; Tetrahedron, 1993, 49, 5127.
- Periasamy, M.; Kanth, J.V.B.; Prasad, A.S.B.; Tetrahedron, 1994, 50, 6411.
- Corey, E.J.; Shibata, S.; Bakshi, R.K.; J. Org. Chem., 1988, 53, 2861.

(Received in the UK 20 July 1994)