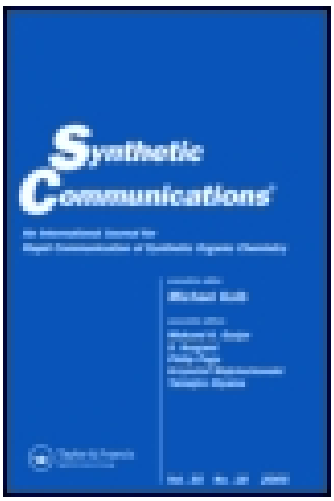

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Convenient Method for the Synthesis of N-(Ethyloxycarbonyl) Ester Derivatives from Amino Acids

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

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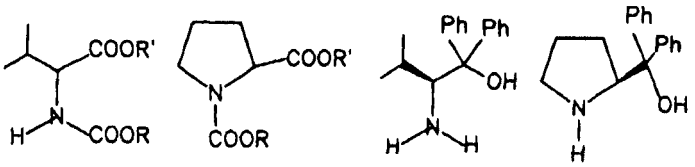
Abstract: Amino acids upon treatment with ethyl chloroformate in methanol in the presence of potassium carbonate give the corresponding N-(ethyloxycarbonyl) amino acid ester derivatives in good yields. These derivatives can be also synthesized by performing the reaction in THF in the presence of alcohols.

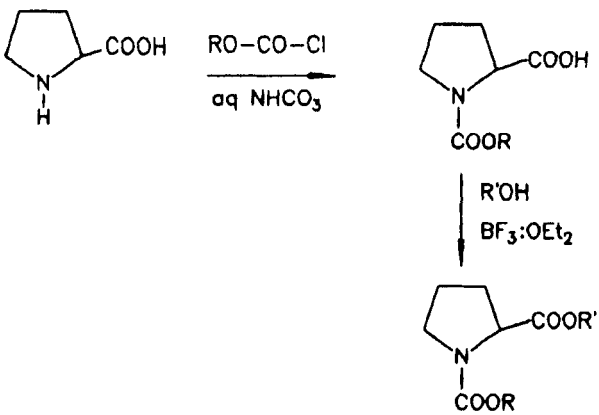
Protection of amino and carboxylic functional groups in amino acids is an important transformation, since it helps in carrying out selective reactions at either of the reactive centers. In recent years, the N- and O-protected esters 1 and 2 derived from L-valine and L-proline were widely used in the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



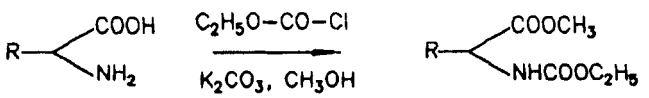
1 2 3 4

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 N- and O-protection of amino acids under mild conditions as outlined in Scheme 2.

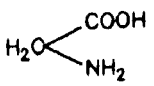
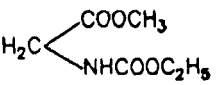
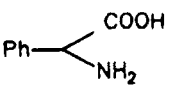
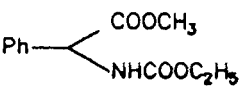
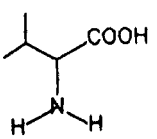
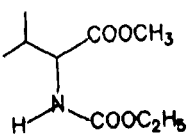
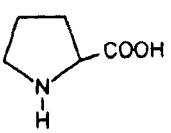
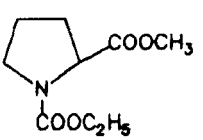


Scheme 1



Scheme 2

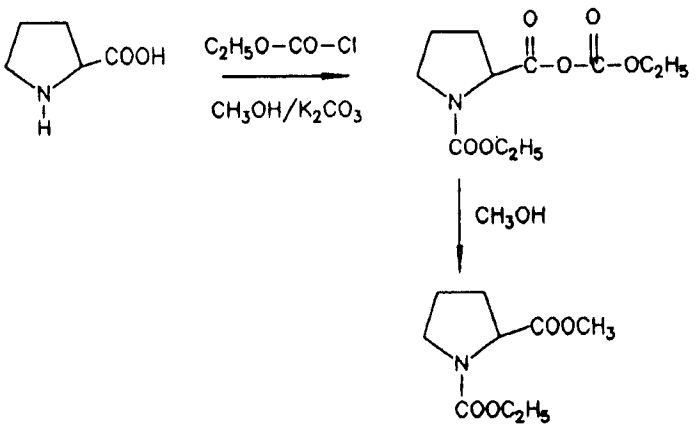
Table 1: Simultaneous N- and O-protection of amino acids[a]

S.No	Amino acid	Product[b]	Yield(%)[c]
1			94
2			91
3			91
4			95

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 (^{1}H & ^{13}C)

c. Yields are of isolated and purified products.



Scheme 3

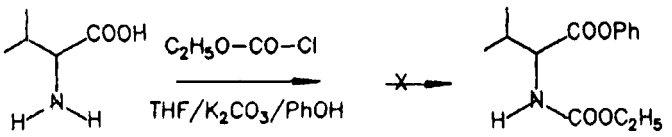
This procedure was found to be a general one and a few other carbamate esters of amino acids have been synthesized. The results are summarized in Table 1.

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

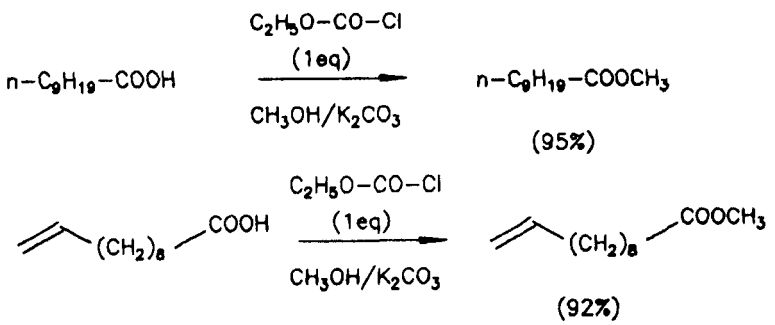
If this is the case, it should be possible to synthesize different carboxylic esters using the corresponding alcohols. Indeed, this was observed. The N-protected benzyl ester of L-valine (1, R = C_2H_5, R' = CH_2Ph) can be readily prepared in 84% yield by the addition of two equivalents of ethyl chloroformate 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_2CO_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' = CH_3).

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 $MgSO_4$. 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, $CDCl_3$) : 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

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)ν_{max}:3350, 3100, 2900, 2850, 1700, 1680, 1600 cm^{-1}

^1H NMR(200MHz, $CDCl_3$)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).

^{13}C NMR(50.0MHz, $CDCl_3$)δppm: 14.4, 17.3, 18.8, 58.9, 60.9, 66.8, 128.2, 128.4, 135.4, 156.7, 171.9.

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

N-(Ethyloxycarbonyl)-glycene methyl ester: (50.0MHz, $CDCl_3$) δppm 13.9, 42.0, 51.5, 60.5, 156.4, 170.4.

N-(Ethyloxycarbonyl)-(L)-phenylglycene methyl ester: (50.0MHz, $CDCl_3$) 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: (25.0MHz, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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.

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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.
3. Periasamy, M.; Kanth, J.V.B.; Prasad, A.S.B.; *Tetrahedron*, 1994, 50, 6411.
4. Corey, E.J.; Shibata, S.; Bakshi, R.K.; *J. Org. Chem.*, 1988, 53, 2861.

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