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NOTE

A Simplified Process for High Purity of N-[1-(s)-Ethoxycarbonyl-3-phenylpropyl]-(s)-alanine-N-carboxyanhydride

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N-[1-(s)-Ethoxycarbonyl-3-phenylpropyl]-(s)-alanine-N-carboxyanhydride is prepared in very high purity by intramolecular cyclization of carbamate (**I**) using N,N-dimethyl aniline as base and without any tedious purification.

Key Words: N-[1-(s)-Ethoxycarbonyl-3-phenylpropyl]-(s)-alanine-N-carboxyanhydride, High purity.

N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanine-N-carboxyanhydride (NEPA-NCA) is a well-known chemical intermediate in the pharmaceutical industry, which play an important role in synthesizing Angiotensin-I converting enzyme (ACE) Inhibitors such as delapril, enalapril, imidapril, indolapril, moexipril, quinapril, ramipril and trandolapril. The demand of NEPA-NCA has been increasing during the past few years and will continue to grow in the near future.

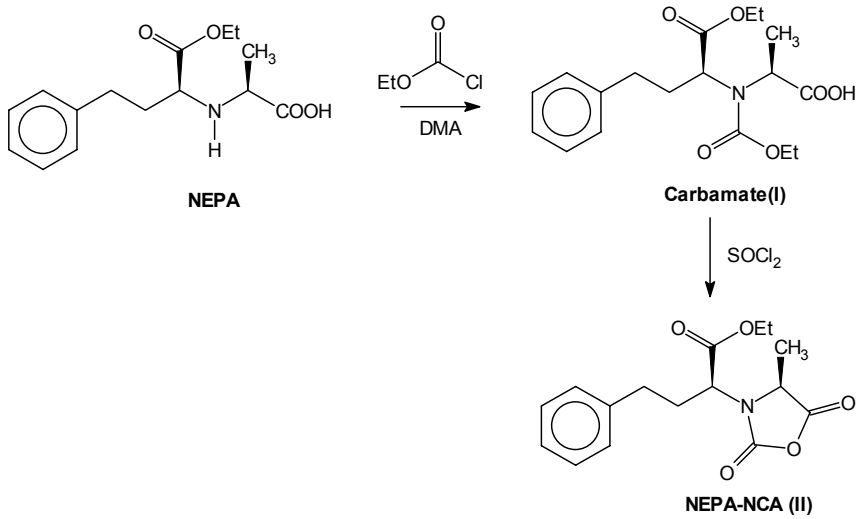
The most common method of producing NEPA-NCA is the reaction of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanine (NEPA) with phosgene[1,2] or N,N'-carbonyldiimidazole (CDI)[3]. The yield by this method is relatively high, however it involves the use of either highly toxic phosgene or expensive CDI. Other methods which are reported in the literature are intramolecular cyclization of carbamate with an acyl group activation reagent[4] and reductive amination Schiff's base with Pd/C[5].

Preparation of NEPA-NCA: To a stirred mixture of NEPA (100 g, 0.36 mol) and DMA (56.6 g, 0.47 mol) in DCM (550 mL) was added ethyl chloroformate (50.8 g, 0.47 mol) in DCM (50 mL) at 0-5 °C during a period of 20-30 min. Reaction mixture was stirred at 20-25 °C till complete consumption of NEPA on HPLC (*ca.* 3h). The reaction mixture was washed with 4 N HCl (2 × 250 mL) and then with H_2O (2 × 250 mL). The organic layer was separated and stirred with $SOCl_2$ (64 g, 0.54 mol) at room temperature till complete consumption of carbamate on HPLC (*ca.* 24 h). The reaction was quenched by addition of H_2O (300 mL) at 0-5 °C, organic layer was separated and finally washed with H_2O (2 × 150 mL). DCM was evaporated

to give residue which on stirring with cyclohexane (800 mL) gave 94.6 g (86 %) of white solid (m.p. 70-72 °C) of NEPA-NCA (HPLC purity: > 99 %). ^{1}H NMR ($CDCl_3$) data of the compound was consistent with literature[4].

The present work is related to intramolecular cyclization of carbamate[4], since it does not involve the use of expensive CDI and toxic phosgene for preparation of NEPA-NCA. However as per the literature reaction of NEPA with alkyl chloroformate is carried out in presence of base such as Et_3N, poly-vinylpyridine or 10 % NaOH to form carbamate which is then cyclized in presence of acyl group activation reagent such as thionyl chloride, acetyl chloride or acetic anhydride.

When NaOH is used as base for N-acylation of NEPA with ethyl chloroformate, reaction showed the multiple spots on TLC which could be attributed to alkaline hydrolysis of ester group in NEPA. When Et_3N is used as base, the NEPA-NCA isolated after intramolecular cyclization of carbamate (**I**) with $SOCl_2$ was dark brown in description with only 94 % purity on HPLC and 64 % yield. Attempts to decolorize brown material with charcoal treatment also failed to give white product. As NEPA-NCA of high purity without any colouring impurity is required in order to minimize the purification steps in final active pharmaceutical ingredients (API), it was necessary to search for an alternative base instead of Et_3N. N, N-Dimethylaniline (DMA) has been used extensively as base for acylation reaction[6] and is cheap and nonvolatile (BP 193-194 °C), which therefore can be recovered easily. It was therefore thought worthwhile to explore the feasibility of DMA as a base in the reaction of NEPA with ethyl chloroformate to form carbamate, which could be further converted to NEPA-NCA in presence of $SOCl_2$. Towards this end, NEPA in DCM was stirred with ethyl chloroformate in



Scheme: Preparation of NEPA-NCA from NEPA

presence of DMA till complete consumption of NEPA on HPLC. The reaction mass was washed with dilute HCl and then finally with water. The organic layer was stirred with $SOCl_2$ till complete consumption of carbamate on HPLC. The reaction mass on aqueous work-up followed by distillation of solvent afforded residue which on stirring with cyclohexane gave white solid of NEPA-NCA (HPLC purity: > 99 %) in 86 % yield.

In conclusions use of DMA as a base gives high purity and almost white in description of NEPA-NCA without undergoing any reprocessing or tedious purification by any conventional methods.

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ERRATUM

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Derivative Spectrophotometric Determination of Uranium(VI) using 2-Hydroxy-3-methoxybenzaldehydeisonicotinoyl-hydrazone Reagent

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In Table-1, please read as

***Masked with fluoride 50 µg/mL; **Masked with thiourea 700 µ/mL**
instead of *Masked with fluoride 6 µg/mL; **Masked with 917 µg/mL.