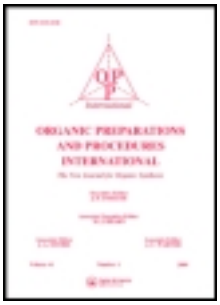

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

AN EFFICIENT LARGE SCALE SYNTHESIS OF NATEGLINIDE

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Version of record first published: 18 Feb 2009.

To cite this article: Batchu Chandrasekhar, Mangesh S. Sawanth, Sameer J. Naik, Nandakumar B. Gaikwad, Pramila V. Kulkarni & Shekar B. Bhirud (2004): AN EFFICIENT LARGE SCALE SYNTHESIS OF NATEGLINIDE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 36:5, 459-467

To link to this article: http://dx.doi.org/10.1080/00304940409356630

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (5), 459-467 (2004)

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A new generation of sulfonylurea (SU)[1] type agents have recently become available and have been found to be highly useful as oral hypoglycemic agents in the treatment of Type 2 *diabetes mellitus*. Another structurally distinct class of compounds belonging to the family of carbamoylmethylbenzoic acid (*glinides*) derivatives are also known to be useful in the treatment of Type 2 diabetes mellitus. Nateglinide (**1**) and repaglinide (**2**) [*Fig. 1*] appear to stimulate first

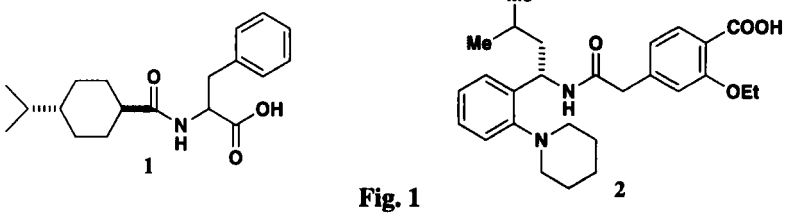
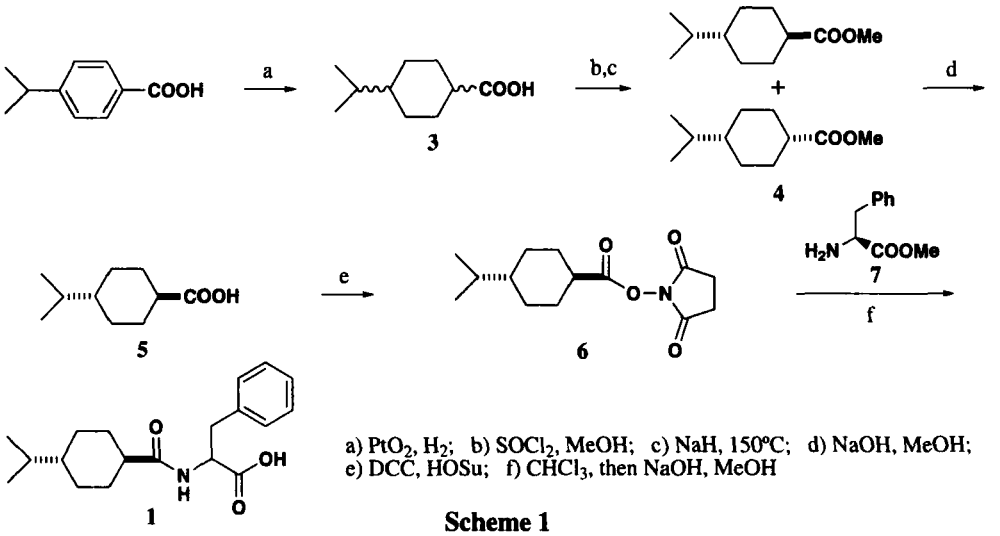


Fig. 1

phase insulin secretion. Glinides may be used either as monotherapy or in combination with biguanides or thiazolidinediones. Nateglinide [brand name: *Starlix*, *N*-[(*trans*-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine (AY4166)] is a novel amino acid derivative, expected to be a promising insulinotropic agent for reducing post-prandial hyperglycaemia.[2] Due to this property of nateglinide, its synthesis,[3] spectral[4] and analytical data,[5] as well as its polymorphism[6] have been thoroughly investigated.

Two synthetic routes to **1** were selected from the literature based on their simplicity. In the original synthesis (*Scheme 1*),[3a-c] **1** was prepared in low overall yield (45%) in five steps employing classical reactions. The first step is the catalytic reduction of cumic acid[7] using Adams' catalyst to afford a mixture of *trans*- and *cis*-4-isopropylcyclohexanecarboxylic acid (**3**)



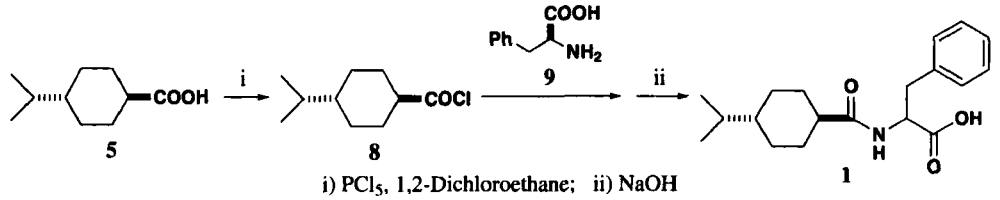
a) PtO_2, H_2; b) $SOCl_2$, MeOH; c) NaH, 150°C; d) NaOH, MeOH; e) DCC, HOSu; f) $CHCl_3$, then NaOH, MeOH

Scheme 1

in a ratio of 1:3. The second step, esterification of **3** followed by isomerization with NaH at 150°C yielded a mixture of *trans*-and *cis*-methyl ester in a ratio of 6:1 (**4**). The fourth step, the hydrolysis of the ester mixture, followed by crystallization yielded the corresponding pure *trans*-isomer of acid (**5**). Nateglinide was synthesized by coupling[8] activated ester of the *trans*-acid (**5**) obtained from **5**, *N,N'*-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu) with D-Phe-OMe (**7**). Hydrolysis of the resulting ester with sodium hydroxide gave nateglinide (**1**).

Although reproducible at lab level, the scale-up of this process proved to be difficult. Here are some of the drawbacks of the method: (a) The process involves a tedious and cumbersome multi-step synthesis (b) The isomerization of the mixture of the esters (**4**) is carried out with sodium hydride and high vacuum distillation, resulting in the partial charring and diminished yields. (c) The coupling of acid (**5**) is accomplished with *N,N'*-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide. DCC is an acute irritant and a hygroscopic reagent difficult to handle. (d) The purity of the nateglinide was not satisfactory, a series of purification steps being demanded in order to meet quality requirements for active pharmaceutical ingredients.

The second route[3d,e] consist of the reaction of *trans*-4-isopropylcyclohexanecarboxylic acid (**5**) with phosphorus pentachloride to give the corresponding acid chloride (**8**) which by reaction with D-phenylalanine (**9**) in 1,2-dichloroethane gave sodium salt of nateglinide (**1**). Although the procedure presented in *Scheme 2* appeared to be straightforward with an overall



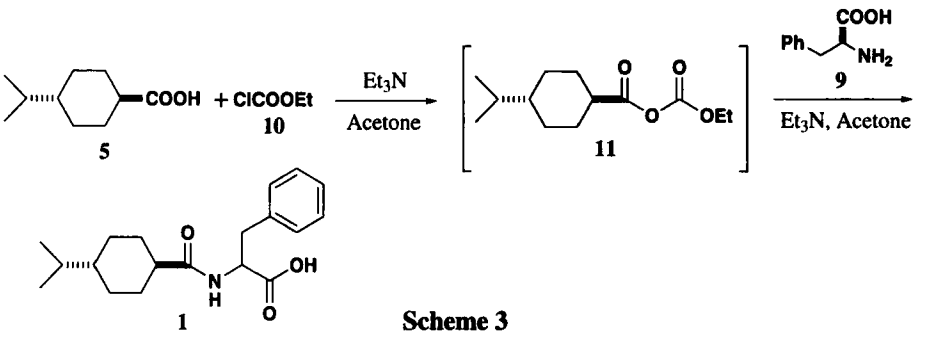
i) PCl_5, 1,2-Dichloroethane; ii) NaOH

Scheme 2

yield of (94%), the following shortcomings were noticed: (a) The acid chloride has limited value in peptide coupling because of the danger of hydrolysis, isomerization and other side-products.[9] (b) Phosphorus pentachloride is extremely corrosive and hygroscopic which makes its handling during scale-up operations very difficult. (c) The use of 1,2-dichloroethane a category of class I solvents in the final step of the process is not acceptable as its limit is 5 ppm in the product.

Very recently, Teva investigators[3f] described the use of thionyl chloride in the presence of catalysts such as dimethylformamide and N-methylpyrrolidine for the preparation of **8** and nateglinide (**1**) was obtained by acylation of sodium or triethylamine salt of D-phenylalanine (**9**) with **8** in both aqueous and biphasic systems. The *cis*-isomer was not formed during the process. However, the method has the following shortcomings: (a) The excess thionyl chloride used in the reaction was reported to be removed under reduced pressure. However complete removal of thionyl chloride in large scale operations is very difficult. Even small amounts of thionyl chloride can increase the impurity levels in the product.

In modern practice, acid chlorides are considered as overly reactive species leading to undesired side-reactions, therefore alternative carboxy activation methods are preferred.[10] A new route has been developed[11] to simplify the process and to make it cost effective and feasible for scale up operations (*Scheme 3*). This involves the mixed carbonic anhydride method of peptide



Scheme 3

synthesis[12] which is superior in rate, yield and relative purity of the product. To achieve acceptable reaction rates and to drive the reaction to completion the formation of mixed carbonic anhydride **11** was carried out at –15°C in a Dry Ice-acetone bath in presence of ethyl chloroformate (**10**). The reaction was performed without isomerization in presence of tertiary amine. The most important factor in yield was the nature of tertiary amine used. Indeed optimum activation times varied with the tertiary amine used; In our study, when triethylamine was the base, the activation time was 60-75 min (5% excess of chloroformate was used to ensure that no excess acid was present). Further study has shown that a 5% excess triethylamine gave satisfactory results in avoiding isomerization. It is convenient to add the amine reactant as a salt of sodium.

In the initial stages of process development work, this coupling was done with sodium salt of nateglinide, since it is known that bases used may cause isomerization. Therefore the initial mixed anhydride from *trans*-4-isopropyl-cyclohexane carboxylic acid (**5**) was prepared at

–15°C in acetone (1:8 w/v) with 1.05 equivalent of triethylamine and ethyl chloroformate (**10**). A solution of the sodium salt D-phenylalanine (**9**) with 1 equivalent of sodium hydroxide in acetone, water mixture (1:10 w/v) was prepared separately at –5 to 0°C and added in one portion and the procedure described in the experimental section was followed thereafter. This resulted in a 90% yield of crude nateglinide (94-95%) from which only a yield of 60% of pure nateglinide was isolated because of the difficulty in purifying the nateglinide from the both polar and non-polar impurities (*Fig. 2*).

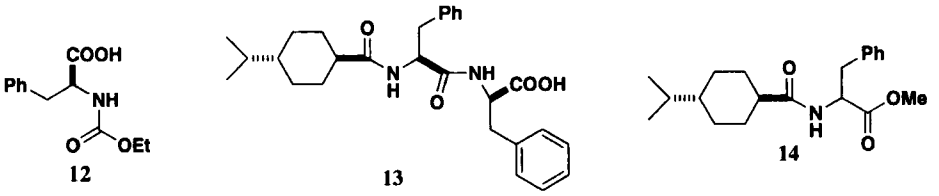
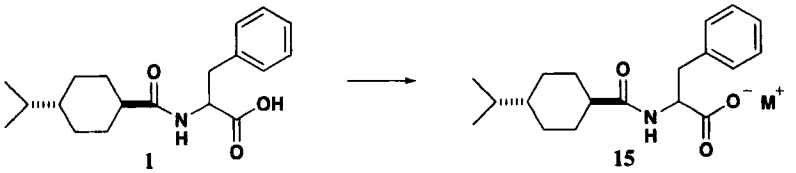


Fig. 2

Although these impurities are process-related, during development process, the impurities were identified. The impurity **12** formed during reaction of D-phenylalanine and ethyl chloroformate comes as polar one in HPLC with respect to nateglinide. The impurities **13** and **14** appearing during synthesis, are found to be non polar. Typical methods to improve the quality of the drug substances are recrystallization of the drug itself. This has been examined in this study. Since the product and the impurities have considerable solubility in most of the effective solvents, a single recrystallization was not sufficient. Although many impurities (2-3%) such as **12** could be removed by crystallization in methanol, water (1:1) mixture, the major non-polar impurity such as **13** (0.8-1%) could not be lowered. To improve the purity of the product, it was slurried in a mixture of *n*-hexane and dichloromethane and hence the total level of impurities thus reduced by a factor of about 5-10. The efficiency of removal of individual impurities is also important to the development chemist, since already the publication[13] was known especially in the announcement of methods to examine this point. Nateglinide has many polymorphs such as A^{6j}, $B^{6a,b}$, C^{6i}, H^{6c}, M^{6j}, P^{6j}, R^{6k}, $S^{6d\text{-}f}$, X^{6l}, Z^{3f} and AL^{6g} and the required H form is obtained in 45% yield, in spite of initial yield of 90% crude but in 95% purity of nateglinide was achieved. In this connection, it should be mentioned that the multiple purifications made the process less attractive.

An alternative method of purification was investigated to simplify the above process and to make it more cost effective as shown in *Scheme 4*. The presence of an ionizable moiety



M+ = Na, K, Ca, Mg, Li, Zn, Dicyclohexyl amine, α-methyl benzyl amine, L-Arg, Lys

Scheme 4

and also crystallinity in a salt afforded a means of purification and removal of unwanted impurities for an acidic drug prompted us to purify the nateglinide by preparing its salt[14-16] with a suitable base. To form a salt, the pH of the solution of the drug must be adjusted above its pH_{max} value, counterions used to form salts must be suitable to achieve such pH condition, otherwise salts would not be formed. As a result of this consideration, we selected salt formers such as metallic cations (sodium, potassium, calcium, magnesium, lithium, zinc), organic amines (dicyclohexylamine, α-methylbenzylamine), cationic amino acids (L-arginine, lysine). To examine the impact of purification by salt formation, the sodium salt was chosen as the case study due to its wide application and the ability to achieve a recovery of the drug. The sodium salt can be prepared by means of sodium hydroxide in polar organic solvent. Interestingly, 95% pure nateglinide was enriched to 99.8% and both polar, non-polar impurities were minimized in the process. Nateglinide purified by this method is produced in the required H form of pharmaceutically acceptable quality and was obtained in 60% yield. The salt formation and subsequent regeneration of nateglinide, made the process less attractive and less profitable.

The various methods to improve the quality of the drug substances such as recrystallization, salt formation, proved to be ineffective. Thus the optimization of the above mentioned new route became inevitable. Since the major side-products were found to be base-promoted, it was of interest to test the system by addition of triethylamine salt of D-phenylalanine as a reactant to the mixed anhydride, in peptide synthesis. In the current procedure, first the mixed anhydride was prepared from *trans*-4-isopropylcyclohexanecarboxylic acid, at −15°C in acetone with 1 equiv. of triethylamine, ethyl chloroformate. A mixture of D-phenylalanine, 1-equiv. of triethylamine, with catalytic amount of *N*-methylmorpholine in aqueous acetone was added and the procedure described in the experimental section was followed thereafter. The result was a >90% yield of nateglinide in >99% purity. This clearly shows that sodium hydroxide is a strong base and addition to D-phenylalanine to generate the sodium salt resulted in difficulties to remove impurities. The use of triethylamine for forming salt of D-phenylalanine along with hitherto mentioned mixed anhydride formation in acetone medium simplified the peptide formation, resulting in a purer product.[17]

EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and were used as such without any further purification unless required. The melting points were recorded on Mettler Toledo FP90 apparatus and are uncorrected. The ^1H NMR spectra were obtained using a 300 MHz Varian spectrometer using tetramethylsilane as internal standard. Infrared spectra were determined as KBr pellets using a Perkin-Elmer spectrum1 instrument. Mass spectra were recorded on an Applied Biosystem API 3000. HPLC analysis was performed using Shimadzu LC-8A, UV-vis detector, SPD-10A, *VP*data module and a Hypersil C^{18} column.

Preparation of *N* [(*trans*-4-Isopropylcyclohexyl)carbonyl)]-D-phenylalanine (1).- Part A: 500 g (2.95 moles) of *trans*-4-isopropylcyclohexane carboxylic acid, 5 L of acetone and 313 g

(3.09 moles) of triethylamine were placed, in a 20 L 4-necked round bottom flask, stirred and cooled to –20°C. 335 g (3.10 moles) of ethyl chloroformate was added slowly from –10 to –15°C over 30 min. After the addition the reaction mixture was stirred at –5 to –10°C for 75 min.

Part B: 510 g (3.09 moles) of D-phenylalanine, 1 L of acetone, 4 L of water, 500 g (4.95 moles) of triethylamine were placed in a 10 L four neck round bottom flask, stirred for 30 min at 25-30°C and cooled to 0-5°C for 30 min. A 100 mL mixture containing water (89 mL), acetone (10 mL), *N*-methylmorpholine (1 mL) was added and stirred for 10 min.

The part B solution was added slowly to part A solution in about 15 min, while maintaining the temperature to –5°C to –10°C for 75 min. 6 L of water was added slowly to part A solution in about 15 min, while maintaining the temperature to –5°C to –10°C for 75 min. Another 6 L of water was added, followed by addition of 5% hydrochloric acid (5 L), in about 1 h at 25-30°C. The reaction mixture was stirred for 60 min, filtered, washed with water (3 x 1 L). The wet cake was slurried in 10 L of water, stirred for 30 min, collected, dried to give 850 g (91%) of **1** in 99.2% purity as determined by HPLC [HPLC system: HypersilC^{18} 250 mm column; mobile phase: 0.05 M NH_4OAc/MeOH in 28:72 ratio; flow rate 1 mL/min; UV: λ_{max} 215 nm, retention time 8.1 min. The dried product appears as white crystalline solid, mp 130-132°C, *lit*[6a] mp 129-130°C. The resultant product was converted into H form as follows.

H-form Preparation:- A mixture of 850 g of the product, 3.5 L of acetone in a 10 L four necked round-bottom flask was stirred for 10 min at 25-30°C. The acetone solution was added to the reaction flask containing 4 L water. The reaction mixture was stirred for 24 h at 25-30°C and the precipitated solid was collected, washed with 500 mL acetone + water mixture (1:1), and dried to give 745 g (80%) of **1**, purity >99.5% by HPLC [HPLC system: HypersilC^{18} 250 mm column; mobile phase: 0.05 M NH_4OAc/MeOH in 28:72 ratio, flow rate 1 mL/min; UV: λ_{max} 215 nm, retention time 8.1 min, mp 136-139°C, *lit.*[3b] mp 137-138°C. The $[\alpha]_D^{20} = -9.2$ (c = 1, methanol; *lit* $[\alpha]_D^{20} = -9.4$). IR (KBr): 3100, 2900, 1710, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.8 (d, 6H), 0.9-1.3 (m, 2H), 1.2-1.5 (m, 3H), 1.6-1.9 (m, 4H), 2.0-2.1 (m, 1H), 3.2-3.4 (m, 2H), 4.8 (q, 2H), 6.1 (d, 2H), 7.1-7.4 (m, 5H). Mass *m/z* 317 corresponding to $C_{19}H_{27}NO_3$.

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.79; H, 8.47; N, 4.35

Isolation and Identification of Major Impurities.- The mother liquor, (obtained from the batches and enriched in impurities) was concentrated under reduced pressure, and a few grams of the residue were dissolved in a minimal amount of methanol. Preparative HPLC (reversed–Phase) of this solution (eluent 0.05M NH_4OAc/MeOH in 28/72) carried in order of elution, samples of **12**, **13** and **14**.

2-[(Ethoxycarbonyl)amino]-3-phenylpropanoic Acid (12), a white, crystalline solid, mp. 83-84°C. IR: (KBr): 702, 929, 1425, 1532, 1688, 1721, 2994, 3109, 3308 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H), 3.06-3.2 (q, 2H), 4.0-4.6 (q, 1H), 5.0 (d, 1H), 7.1-7.3 (m, 5H), 8.5 (br, 1H). MS ($M+H^+$): *m/z* 238 corresponding to $C_{12}H_{15}NO_4$.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.27; N, 5.85

2-[2-[(*trans*-4-Isopropylcyclohexanecarbonyl)amino]-3-phenylpropionylamino]-3-phenylpropionic Acid (13), a white, crystalline solid, mp. 180-182°C. IR (KBr): 698, 749, 1212, 1455, 1538, 1640, 1725, 2930, 3109, 3289 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.79 (s, 3H), 0.81 (s, 3H), 0.89 (m, 2H), 0.9-1.2 (m, 2H),1.3-1.4 (m, 2H), 1.61-1.64 (m, 3H), 1.92-2.0 (m, 1H), 2.6-2.7 (m, 1H), 2.8-3.1 (m, 4H), 4.3-4.4 (m, 4H), 7.1-7.2 (m, 10H), 7.8 (d, 1H), 8.0 (d, 1H). MS (M+ H^+): *m/z* 465 corresponding to $C_{28}H_{36}N_2O_4$.

Anal. Calcd for $C_{28}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.28; H, 7.70; N, 5.98

2-[(*trans*-4-Isopropylcyclohexanecarbonyl)amino]-3-phenylpropionic Acid Methyl Ester (14), a white, crystalline solid, mp. 134-135°C. IR (KBr): 696, 1543, 1638, 1732, 3064, 3317 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (d, 6H), 1.06(m, 3H), 1.4 (m, 3H), 1.9 (m, 2H), 2.0 (m,1H), 3.2-3.0 (t, 2H), 3.7 (s, 3H). MS (M + H^+): *m/z* 332 corresponding to $C_{20}H_{29}NO_3$.

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.40; H, 8.75; N, 4.21

Acknowledgement.- The authors thank the Glenmark group of companies for supporting this work and Mr. Glen Saldanha, Managing Director of Glenmark Research Centre for permitting this work to be published. The authors acknowledge the help rendered by Dr. M. Khan and other colleagues of the analytical R&D Department of GRC.

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(Received June 30, 2004; in final form August 26, 2004)