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Synthesis of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile: A key intermediate for Vildagliptin

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ABSTRACT

An alternative and practical synthesis of (*S*)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile was achieved. Reaction of L-proline with SOCL2 (Thionyl Chloride), DMF (Di-methyl Formamide) and methanol was followed by conversion of the L-Proline Methyl Ester hydrochloride. Then further reaction of l-proline methyl ester HCl with NH3 Gas was followed by conversion of L-Proline Amide. Then further reaction of l-proline amide with CAC (Chloro Acetyl Chloride) was followed by conversion of (S) 1-(Chloroacetyl) Pyrolidine 2-Carboxamide. Then further reaction of (S) 1-(Chloroacetyl) Pyrolidine 2-Carboxamide with POCL3 (Phosphorous Oxychloride) of the resulting product into the 1-(Chloroacetyl) Pyrolidine 2-Carbonitrile (CPC) via the corresponding amide intermediate. The synthesized pyrrolidine derivative was utilized to prepare DPP-IV inhibitor Vildagliptin. This review includes the analytical methodologies in which synthesis methods the different Analytical techniques Like HPLC, GC, IR and SOR etc. and the detection of compound by mean of FTIR, NMR,MS and ICP-MS.

KEYWORDS:

CPC, L-Prolinenitrile, Pyrrolidine, Vildagliptin & DPP-IV inhibitor.

INTRODUCTION:

One of the emerging and mechanism based approaches for the treatment of type-II diabetes is dipeptidyl peptidase IV (DPP-IV; CD26; E.C. 3.4.14.5) inhibition with the help of small molecules [1-3]. DPP-IV, a member of the prolyl oligopeptidase family of serine protease, cleaves the *N*-terminal dipeptide from peptides with proline or alanine in the second position. As a result of intense pharmaceutical research, several DPP-IV inhibitors have been discovered and a few of them entered clinical development recently. Vildagliptin and Sitagliptin are presently under review by US FDA as new treatment options for type-II diabetes

The active form of glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by intestinal L-cells in response to food intake [4], is a 30-amino acid peptide that stimulates insulin release, inhibits glucagon release, and slows gastric emptying. Each of these effects is beneficial in the control of glucose homeostasis in patients with type-II diabetes. However, in the presence of plasma DPP-IV the active form of GLP-1 is inactivated rapidly ($t_{1/2}$~1 min) due to the cleavage of a dipeptide from the *N*-terminus [5-6]. Thus inhibition of DPP-IV extends the half-life of endogenously secreted GLP-1, which in turn enhances insulin secretion and improves the glucose tolerance. DPP-IV inhibitors offer several potential advantages over existing therapies including decreased risk of hypoglycemia, potential for weight loss, and the potential for regeneration and differentiation of pancreatic β-cells [1].

CHEMICAL & PHYSICAL PROPERTY:

Chemical Name: (2S)-1-(2-Chloroacetyl)-2-9-pyrrolidinecarbonitrile [11]

Synonyms: (2S)-1-(Chloroacetyl)-2-pyrrolidinecarbonitrile;

(2S)-1-Chloroacetylpyrrolidine-2-carbonitrile;

(S)-1-(2-Chloroacetyl) pyrrolidine-2-carbonitrile;

1-Chloroacetyl-2-(S)-cyanopyrrolidine. [11]

Appearance: Pale Beige to Light Brown Solid. [11]

Molecular Formula: $C_7H_9ClN_2O$ [7]

Molecular Weight: 172.61 g/mol [7]

Melting Point: 52°-53°C [7]

Density: 1.27 g/cm^3 [7]

Stability: Hygroscopic. [11]

Storage: Hygroscopic, Refrigerator, under inert atmosphere. [11]

Solubility: Chloroform (Slightly), DMSO (Slightly), Methanol (Slightly). [11]

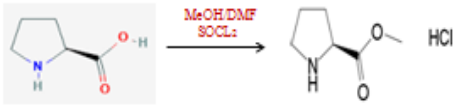
Hydrogen Bond Donor Count: 0 [7]

Hydrogen Bond Acceptor Count: 2 [7]

Rotatable Bond Count: 1 [7]

EXPERIMENTAL WORK:

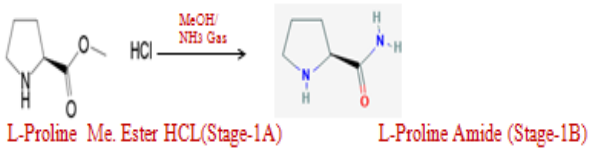
Stage-1A:



Scheme (1.0)

Arranged 1.0 liter Assembly. Charged MeOH (1.5 Volume) at 20° to 35°C.Charged L-Proline (1.0 Liter) at 20° to 35°C.Charged DMF (1.0%) at 20° to 35°C.Start drop wise addition of $SOCL_2$(1.06 Liter) at 20° to 45°c (Exothermic Reaction)Addition over maintain reaction mass for 2hrs.Maintaining over check, TLC, TLC complies. Distilled out MeOH under vacuum at below 45°C.Charged MeOH (1.0Volume) and distilled out MeOH proper under vacuum at below 45°C. [8, 9, 10]

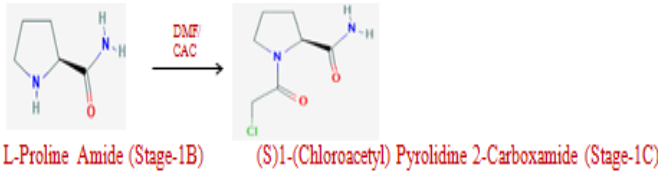
Stage -1B:



Scheme (2.0)

Arranged 2.0 liter Assembly. Charged MeOH (3.0 Volume) at 20° to 35°cChilled up to -5°c and temp achieved start NH3 purging at -5° to 10°C.After preparation of Methanolic Ammonia solution check NH_3 (%), NLT=20%Dump stage -1A in to methanolic ammonia solution (Add drop wise) at 0° to 30°C.Dumping over charged purified water at 20° to 30°C.Start NH3 purging for 6hrs at 20° to 30°C.Purging over check TLC, TLC complies. Distilled out MeOH under vacuum up to 95°C. [8, 9, 10]

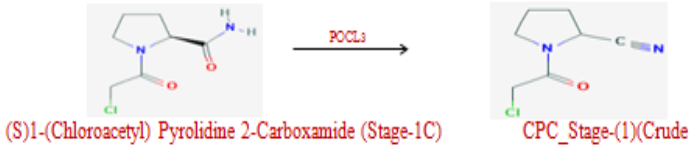
Stage -1C:



Scheme (3.0)

Charged DMF in to assembly (4.0 Volume).Charged L-Proline Amide at 20° to 35°C.Cooled up to 0° to 5°C.Temp achieved start addition of CAC (Chloro Acetyl Chloride) at 0° to 20°C.Addition over maintain Reaction mass for 2hrs at 10° to 20°C.Take sample and send for HPLC result complies.[8, 9, 10]

Stage -1:

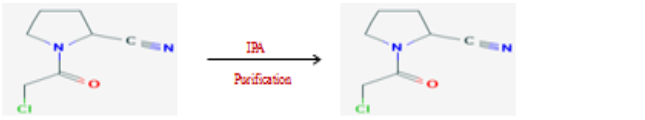


Scheme (4.0)

Take above RxM and chilled up to 0° to 5°C. Temperature achieved and starts addition of $POCL_3$ at 0° to 15°C.Addition over maintain 1hrs at 0° to 15°C.Take a sample and send for HPLC, HPLC complies. Arranged 3.0 lit assembly changed purified water (6.0 Volume) at 20° to 35°c. Cooled the Reaction

Mass up to 0° to 5°C. Dump RxM in to chilled water at 0° to 15°C. Quenching over maintain for 30min at 0° to 15°C.Charged MDC at 0° to 20°C and maintain for 30min. Apply layer separation. Arranged distillation and distilled out Organic layer under vacuum at 90°c.Distillation over weight of product (crude) [8, 9, 10]

Stage -Final:



Scheme (5.0)

Charged IPA (2.0 Volume) at 20° to 35°C.Charged crude at 20° to 35°.Heat up to 85°C temp achieved charged carbon at 65°C.Stir for 1hrs.Apply hyflow filter at 75° to 85°C.Take ml and charged in to assembly. Cooled up to 0° to 5°C temp. Maintain for 1hrs.Filter the Reaction Mass and wash with IPA. Dry product in to Oven at 50°C.

MATERIALS AND METHODS

Procedure for searching information:

Relevant literature survey was done by scientific websites and tabs i.e. Google Scholar, Scientific journal. Information was also obtained from books and e-articles. The chemical name of the chemical was validated using the chemical List. Published review papers on *Synthesis of (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile: A key intermediate for dipeptidyl peptidase IV inhibitor* were used as guidelines to design the present study and also to add missing data to ensure a more comprehensive and up-to-date review is obtained. The reference lists of review and research papers were searched for further relevant information. Regarding the search methodology, the following keywords were searched: "*(2S)-1-(2-Chloroacetyl)-2-9-pyrrolidinecarbonitrile* ". (Google = 2670 search results, Articles = 287).

SEPARATION METHOD:

Isocratic Method:

Buffer Preparation: 1.0 ml Triethylamine in 1000ml glass bottle and make up to 1000ml with Water. Adjust pH 5.0 ±0.05 with diluted Orthophosphoric acid. Mobile Phase Preparation: Buffer: Acetronitrile (900:100) v/v. Diluents Preparation: Water: Acetronitrile (800:200) v/v.

Chromatographic Condition: Column- Intertsil ODS-3, (250 x 4.6mm) 5µm.Wave-Length- UV Spectrometer at 200.0nm. Flow-rate– 1.0 ml/ min. Injection Volume– 20.0µl.Column oven temp. – Ambient. Runtime – 60.0min. Retention time of CPC is about 18.5 min.

OR

Gradient Method:

Buffer Preparation: 1.0 ml Triethylamine in 1000ml glass bottle and make up to 1000ml with Water. Adjust pH 4.0 ±0.05 with diluted Orthophosphoric acid. Mobile Phase (A): Buffer (100%), Mobile Phase (B): Methanol (100%). Diluents Preparation: Water: Acetronitrile (800:200) v/v.

Chromatographic Condition: Column- Intersil C-8, (250 x 4.6mm) 5µm. Wave-Length- UV Spectrometer at 210.0nm. Flow-rate– 0.8 ml/ min. Injection Volume– 20.0µl. Column oven temp. – 50.0°C Runtime – 20.0min. Retention time of CPC is about 14.8 min.

Gradient Program:

Sr No.	Time	Flow	%A	%B	%C	%D
1	0.0	0.8 ml/min	90.0	10.0	0.0	0.0
2	10.0	0.8 ml/min	80.0	20.0	0.0	0.0
3	12.0	0.8 ml/min	90.0	10.0	0.0	0.0
4	20.0	0.8 ml/min	90.0	10.0	0.0	0.0

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Material & Chemical:

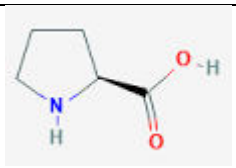
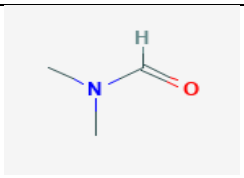
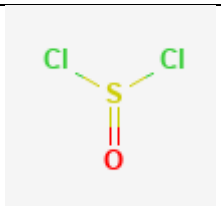
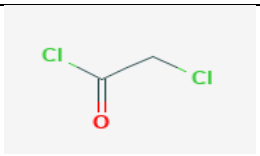
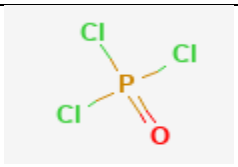
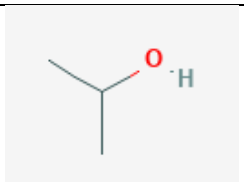
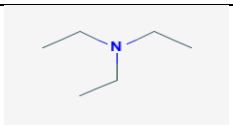
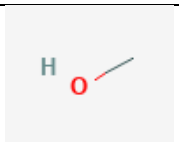
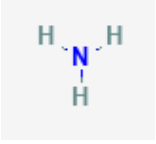
Name of Compound	Chemical Structure	Molecular Weight g/mol	Molecular Formula	PubChem CID
L-Proline		115.13	$C_5H_9NO_2$	145742
DMF(Di-methyl Formamide)		73.09	C_3H_7NO	6228
SOCL2 (Thionyl Chloride)		118.97	$SOCL_2$	24386
CAC (Chloro Acetyl Chloride)		112.94	$C_2H_2Cl_2O$	6577
POCL3 (Phosphorous Oxychloride)		153.33	POCL3	24813
IPA(Isopropyl Alcohol)		60.1	C_3H_8Os	3776
TEA(Triethylamine)		101.19	$C_6H_{15}N$	8471
Methanol		32.042	CH_3OH	887
Ammonia		17.031	NH3	222

Table 1.0[7]

GHS Classification of Product:

1) GHS Hazard Statements:

Harmful if swallowed [Warning Acute toxicity, oral]

Causes skin irritation [Warning Skin corrosion/irritation]

May cause an allergic skin reaction [Warning Sensitization, Skin]

Causes serious eye irritation [Warning Serious eye damage/eye irritation]

May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation][12]

Results and Discussion:

In our strategy, we decided to use L-proline in starting from less expensive and readily available. Additionally, Charged MeOH (1.5 Volume) at 20° to 35°C.Charged L-Proline (1.0 Liter) at 20° to 35°C.Charged DMF (1.0%) at 20° to 35°C.Start drop wise addition of $SOCL_2$(1.06 Liter) at 20° to 45°c (Exothermic Reaction)Addition over maintain reaction mass for 2hrs.Maintaining over check, TLC, TLC complies. Distilled out MeOH under vacuum at below 45°C.Charged MeOH (1.0Volume) and distilled out MeOH proper under vacuum at below 45°C (Scheme 1.0). Charged MeOH (3.0 Volume) at 20° to 35°C Chilled up to -5°C and temp achieved start NH3 purging at -5° to 10°C.After preparation of Methanolic Ammonia solution check NH_3 (%), NLT=20%Dump stage -1A in to methanolic ammonia solution (Add drop wise) at 0° to 30°C.Dumping over charged purified water at 20° to 30°C.Start NH3 purging for 6hrs at 20° to 30°C.Purging over check TLC, TLC complies. Distilled out MeOH under vacuum up to 95°C (Scheme 2.0). Charged DMF in to assembly (4.0 Volume).Charged L-Proline Amide at 20° to 35°C.Cooled up to 0° to 5°C.Temp achieved start addition of CAC (Chloro Acetyl Chloride) at 0° to 20°C.Addition over maintain Reaction mass for 2hrs at 10° to 20°C.Take sample and send for HPLC result complies (Scheme 3.0). Take above RxM and chilled up to 0° to 5°C. Temperature achieved and starts addition of $POCL_3$ at 0° to 15°C.Addition over maintain 1hrs at 0° to 15°C.Take a sample and send for HPLC, HPLC complies. Arranged 3.0 lit assembly changed purified water (6.0 Volume) at 20° to 35°c. Cooled the Reaction Mass up to 0° to 5°C. Dump RxM in to chilled water at 0° to 15°C. Quenching over maintain for 30min at 0° to 15°C.Charged MDC at 0° to 20°C and maintain for 30min. Apply layer separation. Arranged distillation and distilled out Organic layer under vacuum at 90°c.Distillation over weight of product (crude) (Scheme 4.0). Charged IPA (2.0 Volume) at 20° to 35°C.Charged crude at 20° to 35°.Heat up to 85°C temp achieved charged carbon at 65°C.Stir for 1hrs.Apply hyflow filter at 75° to 85°C.Take ml and charged in to assembly. Cooled up to 0° to 5°C temp. Maintain for 1hrs.Filter the Reaction Mass and wash with IPA. Dry product in to Oven at 50°C (Scheme 5.0).

CONCLUSION

In Conclusion, we have demonstrated an alternative and practical route for the synthesis of CPC, a key intermediate for the synthesis of DPP-IV (Di-Peptidyl Peptidase) inhibitors, starting from less expensive and readily available L-Proline. In comparison to the earlier routes the present process involves neither N-protection/de protection strategy nor a complicated isolation method. The utility of this process has been demonstrated in the synthesis of Vildagliptin, a potent, selective and orally bio-available DPP-IV (Di-Peptidyl Peptidase) inhibitor currently waiting for FDA approval. We expect that this process would find application in the design and synthesis of novel DPP-IV (Di-Peptidyl Peptidase) inhibitor for the potential treatment of type-II diabetes.

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