Research Article

A Concise Synthesis of 3-piperdinones and 4-Methyl 3-piperdinones via Aldol Strategy

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ABSTRACT

Synthesis of 3-Piperidinone and 4-Methyl 3-piperdinone has been described, which are key intermediates in the synthesis ofglycosil and glycosidase inhibitors such as Nojirimycin, deoxymannojirimycin, deoxygalactaostatin, fagomine...etc, the main intermediates were prepared in minimum number of steps by applying Sharpless asymmetric epoxidation and intramolecular Aldol condensation.

Keywords: Glycosil and Glycosidase inhibitors, Sharpless epoxidation, Aldol condensation.

1. INTRODUCTION

Glycobiology is a rapidly growing research area where carbohydrates play a major role. Low molecular-weight polyhydroxylated alkaloidal monosaccharides, with nitrogen atom in the place of the ring oxygen of the corresponding carbohydrates are known as imino sugars. Iminosugars have emerged as important tools for glycobiology research.[1-2]In recent years, polyhydroxylatediminosugars have attracted a great deal of attention due to their ability to mimic sugars and thereby competitively and selectively inhibit glycosidases and glycosyltransferases. In the case of iminosugars, ring oxygen substituted with nitrogen renders the imino sugars metabolically inert, but it does not prevent their recognition by glycoprocessing enzymes. The resemblance of iminosugars to carbohydrates and their polar nature might be responsible for endowing them with several special attributes as potential drug candidates, at the same time; they remain sufficiently distinct from carbohydrates to avoid processing by other carbohydrate-modifying systems and have both chemical and biological stability. This unique combination of properties singles out iminosugars as a special class in the search for new drug molecules.[3-5]Protonated, imino sugars resemble the transient oxocarbonium ion involved in glycoside hydrolysis and thus can act as transition-state analogues for the competitive inhibition of the glycosidases and glycosyltransferases. Inhibition of these enzymes affects the maturation, transport, secretion, and function of glycoproteins and could alter cell-cell or cell-virus recognition processes.[6-7] Glycosidase inhibitors have been shown to interact with receptors related to a wide range of prominent diseases including viral infections, cancer, diabetes and other metabolic disorders and are expected to find an increasing number of applications as beneficial drugs[8]. Polyhydroxylatedpiperdine alkaloids have received much importance due to their importance as glycosidase inhibitors, among themgalactonojirimycin, Fagomine, Nojirimycin,Deoxymannojirimycin,Deoxygalact ostatin because of their biological activities,

Piperdines ability of complex formation is main reason for different biological activities, The ability of selective glycosidase inhibitor activities[9-11]and consequently exhibit significant Anticancer, antitumor, Animalistic, immunoregulating and Anti-HIV properties, It is believed that their activity is result of their ability to mimic the transition state involved in substrate hydrolysis, which have led to many stereo selective synthesis of this natural alkaloids to date.

The absolute configuration of steriogenic centres are absolutely crucial for their biological activity, and therefore many stereo selective synthesis of these natural alkaloids have been described to date, to develop the biological activities continuous efforts are going on these compounds in the form of derivatives and stereo isomers, and analogues of this family. Most of the synthetic approaches involve the synthetic transformations of monosaccharide's and amino acids with considerable number of steps. Due to the biological and synthetic activitiesof piperdines,wehad developed this methodology to the synthesis of piperdinones and 3-methyl piperdinones

2. EXPERIMENTAL SECTION

General: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 500 MHz (^{1}H) or 75 MHz (^{13}C) spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constant *J* are in Hz. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and High (HRMS) resolution, *m/z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified elsewhere. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

General procedure for the synthesis of compound 9 and 4

To a suspension of activated and powdered molecular sieves (4 A°) (10.4 g) in dryCH_2Cl_2 (200 ml) were added at 20° C a solution of (+)-diethyltartrate (5.98 g, 29.07 mmol) in dry CH2Cl2 (10 ml) and $Ti(O^{i}Pr)_4$ (6.68g, 23.6 mmol). Then a solution of ^{t}BuOOH (5.5 M in toluene, 31.38 gr, 34.86 mmol) was added dropwise over 10 min.The resulting mixture was stirred for 30 min at - 20° C, and a solution of allyl alcohol(10.0 g, 116.27 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise over 40 minutes with vigorous stirring. After stirring for 5 h at -20° C, the reaction mixture was warmed to 0° C and poured into a mixture of $FeSO_4 \cdot H_2O$ (50 g) and tartaric acid (15 g) in deionized water (70 mL) at 0° C. After stirring for 10 min, organic layer was separated and aqueous layer was extracted with diethyl ether (100 mL). The combined organic layers were cooled to 0° C and to this were added 30% NaOH in saturated brine (20 mL). After stirring vigorously at 0° C for 1 h, this mixture was diluted with water (100 mL), the organic layer was separated, and the aqueous layer was extracted twice with diethyl ether (100 mL). The combined organic layers were dried with sodium sulphate and concentrated in vacuo to get 9.89 g of epoxide with 80% of yield.

((2S, 3S)-3-ethyloxiran-2-yl)methanol (9)

1H NMR (300 MHz, CDCl3): 3.85 (dd, J=12.6 Hz, 1H), 3.57 (dd, J = 12.78Hz,1H),2.85(dd, J=4.57, 2H), 1.60 (m, J = 7.3 Hz, 2H), 1.01 (t, J = 7.3, 3H) 13CNMR (75MHz,CDCl3): 65.3, 57.6, 55.7, 24.7, 9.9. MS (ESI): m/z 102.0 [M+H]+

General procedure for the synthesis of compound 5 and 10

To a solution of epoxy alcohol (5.0 g, 49.01 mmol) in anhydrous Et_2O (80 mL) was added NEt_3 (10.39 g, 102.9 mmol) and the resulting solution was stirred at room temperature. After 30 min, allyl isocyanate (6.10 g, 173.55 mmol) was added to the solution and the clear colourless solution was stirred at 65 ^{o} C until TLC showed complete conversion (4 h). The reaction mixture was diluted with Et_2O and quenched with saturated aqueous NH_4Cl (25 mL). The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether (60 mL). The combined organic layers were dried with sodium sulphate and concentrated in vacuo to get the crude compound of which was purifies by column chromatography (hexane/ethyl acetate) gave (8.24 g, 90%) as a colourless syrup.

((2S,3S)-3-methyloxiran-2-yl)methyl allylcarbamate(5)

1H NMR (300 MHz, CDCl3): δ 5.8-6 (m, 1H), 5.25-5.4 (m, 1H), 4.99 (brs, 1H), 4.4 (dd, J = 2.64 Hz, 1H), 3.95 (dd, J = 5.84 Hz, 1H), 3.81 (t, J = 5.47 Hz, 1H), 3.81 (t, J = 5.47 Hz, 2H), 2.95-? (m, 2H), 1.38 (d, J = 5.01 Hz, 3H). 13CNMR (75 MHz, CDCl3):171.8,129.8, 126.5, 72.1, 61.4, 59.5, 52.0, 25.4 MS(ESI): m/z 171.0 [M+H]+

((2S,3S)-3-ethyloxiran-2-yl)methyl allylcarbamate(10)

1H NMR (300 MHz, CDCl3): 5.84 (m, J = 5.4 Hz,14.3 Hz, 1H), 5.28 (dd, J = 14.1 Hz, 1 H), 5.25-5.02 (dd, J = 8.87, 2 H), 4.42 (d, J = 9.27 Hz, 1 H), 3.9 (dd, J = 6.23 Hz, 11.89 Hz, 1 H), 3.80 (dd, J = 3.96 Hz, 6.63 Hz, 1 H), 2.99 (dd, J = 4.52, 7.55 Hz, 1H), 2.82 (dd, J = 5.46 Hz, 1 H), 1.66 (m, J = 6.42 Hz, 12.56 Hz, 2 H). 13CNMR (75 MHz, CDCl3):155.9, 134.2, 115.7, 64.9, 57.2, 55.2.MS (ESI): m/z 185.0 $[M+H]^+$

General procedure for the synthesis of compound 6 and 11

A solution of sodium bis(trimethylsilyl)amide (2.3 g, 12.97 mmol) in anhydrous THF (15 mL) was added to a solution of carbamate (2.0 g, 12.97 mmol) in anhydrous THF (15 mL). The resulting mixture was stirred at room temperature until TLC showed completion of the reaction (30 min). The yellow solution was quenched with saturated NH_4Cl (15 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried and evaporated and the crude product was chromatographed (hexane/ethyl acetate) yielding the product as a white solid (1.73 g, 86% yield).

(R)-3-allyl-4-((S)-1-hydroxyethyl) oxazolidin-2-one (6)

1H NMR (300 MHz, CDCl3): 5.77-5.8 (m, 1H), 5.25-5.3 (m, 2H), 4.35-4.4 (m, 1H), 4.3-4.1 (m, 3H), 3.73 (dd, J = 5.18 Hz, 2H), 1.12 (d, J = 6.4 Hz, 3H).13C NMR(75MHz,CDCl3) : 158.8, 131.9, 118.6, 63.2, 62.1, 59.45, 44.7, 25.6.MS(ESI): m/z 171.0 [M+H]+

(R)-3-allyl-4-((S)-1-hydroxypropyl) oxazolidin-2-one (11)

1H NMR (300 MHz, CDCl3) : 5.84 (m, 1H), 5.28 (m, 2H), 4.37 (dd, J = 6.42 Hz, 1H), 4.2 (m, 2H), 3.8-3.6 (m, 3H), 1.3-(m, 2H), 1.0(t,J= 7.35 Hz, H).13CNMR(75MHz,CDCl3): 158.7, 131.8, 118.6, 79.0, 68.2, 62.0, 44.7, 25.0.
MS (ESI): m/z 185.0 $[M+H]^+$

General procedure for the synthesis of compound 7 and 12

A solution of carbamate alcohol (1.5 g, 8.10 mmol) in anhydrous CH_2Cl_2 (40 mL) was added PCC (3.48 g, 16.23 mmol) at 0° C, The resulting mixture was stirred at room temperature for up to 12 h until TLC showed completion of the reaction, then filter the reaction mixture from celite pad ,and organic layer wash with brine solution and extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried and evaporated and the crude product was chromatographed (hexane/ethyl acetate) yielding the product as a white solid (1.25 g,92% yield).

(R)-4-acetyl-3-allyloxazolidin-2-one (7):

1H NMR (300 MHz, CDCl3) :δ5.76-5.8 (m,1H), 5.25- (s, 2H), 4.52 (t, J = 9.63 Hz, 1H), 4.40-4.18 (m, 3H), 3.64 (dd, J = 7.36, 1H), 2.22 (s, 3H).13C NMR (75 MHz, CDCl3): δ191.8, 127.8, 124.5, 73.1, 66.4, 60.1, 53.4, 26.12.MS (ESI): m/z 169.18 [M+H]+

(R)-3-allyl-4-propionyloxazolidin-2-one(12)

1H NMR (300 MHz, CDCl3) : δ 5.73-5.78(m, 1H), 5.24 (t, J = 9.25 Hz, 2H), 4.47 (t, J = 9.44 Hz, 1H), 4.20-4.28 (m, 1H), 4.09 (dd, J = 5.28 Hz, 1H), 3.58 (dd, J = 15.8 Hz, 1H), 2.47 (m, 1H), 2.47 (m, 2H), 1.1 (m, 1H).^{13}CNMR(300MHz,CDCl3):178.9,154.3,130.7,110.2,73.9,64.5,57.8,29.2,17.1MS(ESI):m/z 183.0 $[M+H]^+$

General procedure for the synthesis of compound 1 and 2

To a solution of ketone (1.0 g, 5.4 mmol) in CH_2Cl_2at 0° C was subjected in under ozone atmosphere for about for 5 to 10 minutes, turns to blackish colour to colourless, keep continue to apply oxygen for five minutes then added 10 mL of CH_2Cl_2 at 0° C and quench with dimethyl sulphide (each 1 mmol of compound added 1ml DMS) keep maintain cooling for 1hr then dried over the high vacuum pump for 1 hr, now added 20ml of water and extracted with CH_2Cl_2 (50 mL) separated organic layer dried over sodium sulphate and concentrated in vaccuo to get aldehyde of 0.8g

Fully dried compound of aldehyde in round bottom flask was added with 15ml of dry toluene and catalytic dry *p*-TSA then heating continued at 90° C for four hours, after monitoring the TLC reaction mixture added with water extracted from ethyl acetate dried over sodium sulphate and concentrated in vacuum and purified by filter column with 50% ethyl acetate, hexane yields. (0.551 g, 3.24 mmol, 68% after two steps)

(R)-1H-oxazolo [3, 4-a] pyridine-3, 8(5H, 8aH)-dione (1)

1H NMR (300 MHz, CDCl3): δ 7.08-7.03 (m, 1H), 6.28-6.21 (m, 1H,), 4.72-4.51 (m, 2H), 4.48 (dd, J = 4.34 Hz, 1H), 4.32 (dd, J = 2.83 Hz, 1H), 4.12 (dd,J = 9.1Hz, 1H), 13C NMR (75 MHz, CDCl3): δ191.1, 157.5, 146.1, 124.2, 67.29, 56.2, 40.72. IR (KBr): λ_{max} 2931, 1752, 1668, 1109, 704 cm-1.MS (ESI): m/z 176 [M+Na]+

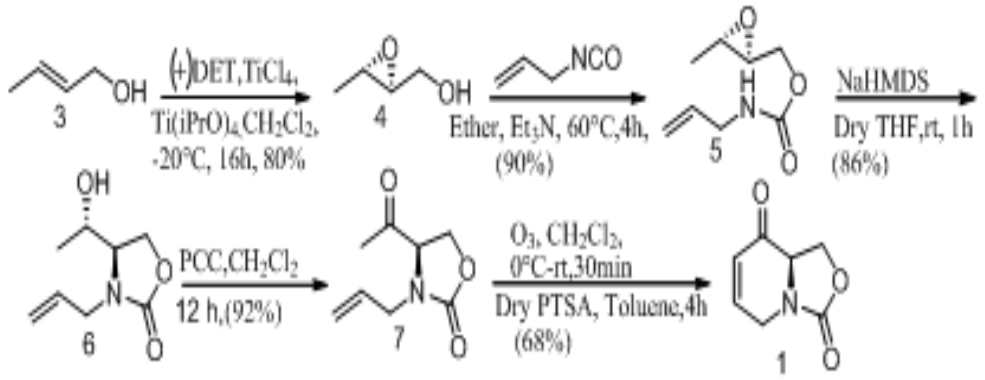
(R)-7-methyl-1H-oxazolo[3,4-a]pyridine-3,8(5H,8aH)-dione(2)

^{1}H NMR (300 MHz, CDCl3): 6.79 (s, 1H), 4.7 (dd, J = 4.3 Hz, 1H), 4.53 (dd, J = 4.9 Hz, 1H), 4.48 (dd, J = 4.34 Hz, 1H), 4.26 (dd, J = 2.04 Hz, 4.3 Hz, 1H), 4.09 (m, 1H), 1.87 (s, 3H).^{13}C NMR (75 MHz, CDCl3: δ192.7, 157.3, 141.0, 134.4, 64.3, 57.4, 41.1, 15.35. IR (KBr): λ_{max} 2923, 2853, 1752, 1696,772 cm^{-1}. MS (ESI): m/z185.0 [M+H]+

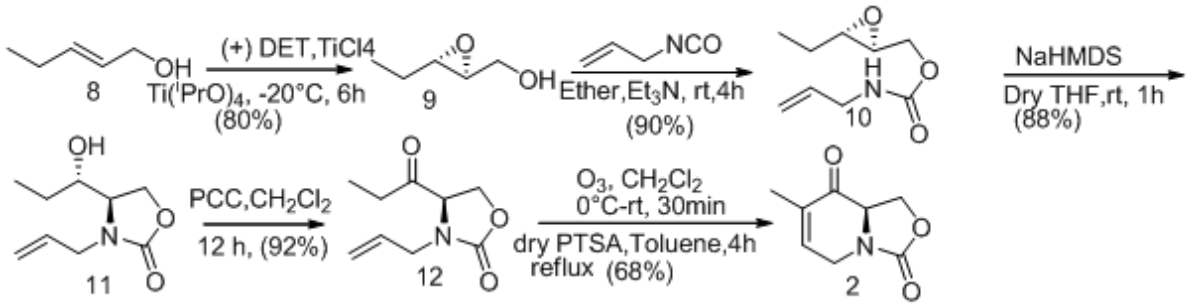
3. RESULTS AND DISCUSSION

Commercially available crotyl alcohol(3) was first submitted to Sharpless Asymmetric epoxidation[12-13],The process went on completion in 16 h at -20°C, which would be turned toAllyl carbamate[14]by treating under optimised condition at 60°C with allyl isocyanate / Et_3N in ether to get the 90% of yield. Then the crude product was subjected to subsequent intramolecular ring opening[15]with the standard condition of NaHMDS in dry THF gave the desired oxazolidinone(6) with good yield(80%) and treatment with other bases like KtBuO and NaH resulted very pooryield, Then carbamte alcohol(6) was subjected to PCC oxidation affords Methyl ketone(7) with 90% yield,Allylic double bond can be oxidised by using either the ozonolysisor Osmium tetraoxide/$NaIO_4$ to get the Aldehyde, But as per the observation Ozonolysis is the right option to get the good yield, the subsequent intramolecular aldol condensation requires extensive experimentation, Which was discussed in scheme-3, As per the results obtained finally pleased to find that the use of dry PTSA in toluene for Aldol condensation[16] resulted in two steps with very good yield(68%)of 3-piperdinones(1).

Scheme-1:



Scheme-2



To synthesise the 3-methyl piperdinones(2) same kind of strategy is employed ,which will starts by using commercially available pent-2-ene-1-ol(8),subjected to Sharpless asymmetric epoxidation to get pure ethyl epoxy alcohol(9), this subsequent treatment with Ally isocyanate /Et_3N in ether to produces the compound(10) with 75% of yield, then followed by treatment with NaHMDS in dry THF to give the carbamate(11) with good yield(92%). Thenoxidation[17] with PCCin DCM to give ketone (12), then olefin oxidation and subsequent aldol condensation with Anhydrous P in toluene[18] to afforded methyl-3piperdinone with 68% of yield. Different alternate conditions tried to improve the yield. And their results have been discussed below in scheme-3.

Different conditions for Aldol Reaction:Scheme-3:

Entry	Reaction condition	Temperature (°C)	Time (h)	Yields (%)
1	10% HCl in Dioxane	80 °C	12 h	27%
2	DMF, (D)-proline	60 °C	4 h	1%
3	DMF, (L)-proline	60 °C	1 h	0%
4	*p*-TsOH, MeOH	rt	24 h	38%
5	CSA, MeOH	rt	16 h	23%
6	*n*-BuLi, THF	0 °C - rt	3 h	17%
7	tBuOK, THF	0 °C - rt	2 h	13%
8	*p*-TsOH, Toluene	90 °C	4 h	**68%**
9	KOH, water	rt	3 h	4%

Different Aldol conditions were tried to get the better yields, by applying standard Aldolconditions with strong bases such as nBuLi, KtBuO, in dry THF produced very low yields, whereas by applying standard organo catalysts[19-20] such as D/L-Proline,is leads to develop multiple spots by TLC with no desire mass peaks, in other hand tried with acid catalysed Aldol[21-23]conditions like 10%HCl,dryCSA,dryPTSA provedworthful for Aldol and given up to 68% of yields. This was clearly mentioned in the above table.

4. CONCLUSION

In summary, we have developed a new, flexible route to synthesise 3-piperdinone and 4-Methyl 3-piperdinones in an extremely concise manner,This synthesis demonstrates that the Aldol condensation is the key step for the key intermediate piperdinones whichhas been prepared in limited no. of steps with very cheap rawmaterials; the present work is most concise entry to the synthesis of deoxy-azasugarsup to now.Therefore they appear as versatile intermediates for the synthesis of various types of bioactive molecules, such as 4-alkyl analogs of fagomine or other azasugars, and corresponding results will be reported in due course.

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