SYNTHESIS OF 4-CHLORO-PIPERIDINE DERIVATIVES VIA NbCl₅ MEDIATED AZA-PRINS TYPE CYCLIZATION OF EPOXIDES AND HOMOALLYLIC AMINES

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ABSTRACT

4-Chloro-piperidine derivatives were synthesized in good yield by the reaction of epoxides and homoallylic amines using Niobium pentachloride reagent under the mild reaction condition

Keywords: Aza Prins, Epoxides, Homoallylic Amines, Piperidines, Niobium Pentachloride

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INTRODUCTION

The piperidine ring is an important class of nitrogen-containing six-member ring system present in many natural products like Coniine and related alkaloids,¹ Solenopsin A,² Piperine,³ Anabesine,⁴ Lobeline,⁵ Lobelanine and Lobelanidine.⁶ Especially, N-protected piperidine is an important intermediate and can easily be converted to different amide functionalities. Hence, the method that can easily access to this structure would be much useful. In this aspect, aza Prins reaction is well known stereo-selective methods used for the construction of piperidine ring using aldehydes and homoallylic amines.⁷⁻²⁵ Even though the outcome of this reaction is piperidine derivative, the substitution at the 4th position depends on the availability of nucleophiles to the cyclic carbonium ion. In general, 4-hydroxy and 4-halo piperidine derivatives are the common products in the aza Prins cyclization. Among them, the 4-halo piperidine derivatives are the more demanding intermediates because of labile halo substituent which can easily be converted to different functionalities. Because of the numerous application of aza Prins reaction for construction of 4-halo piperidine ring, many modified methods were reported.²⁶⁻³¹ Alternately, 4-halopiperidine derivatives can be synthesized using epoxides and homoallylic amines.³² Due to the increasing demand of piperidine derivatives in the synthesis of natural products prompted us to develop the alternate method that successfully minimizes the use of Lewis acid with increased yield. For this purpose, Niobium (V) chloride has been found as an effective Lewis acid due to easy handling, less catalytic loading and high stability. Particularly, Niobium (V) chloride has been used in various reactions like Diels-Alder reaction, Allylation of aldehydes, Aldol reaction and epoxides ring-opening reactions.³³

EXPERIMENTAL

Material and Methods

All chemicals, solvents and reagents purchased from commercial sources. ¹H and ¹³CNMR spectral data were recorded on a Bucker 300 instrument. The mass spectra were recorded on an Agilent 1100 Series HPLC system equipped with a diode matrix and the ionization method is atmospheric-pressure chemical ionization (APCI). Elemental analyses were recorded using the 2400 model Perkin-Elmer CHN analyzer.

General Procedure

To a solution of styrene oxide (0.4 g, 3.33 mmol) and homoallylic amine **2a** (0.5 g, 2.22 mmol) in anhydrous methylene chloride (10 mL) under nitrogen atmosphere, was added Niobium (V) chloride

Rasayan J. Chem., 13(1), 494-498(2020)

<http://dx.doi.org/10.31788/RJC.2020.1315392>

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(0.325 g, 1.2 mmol) with stirring. The reaction mixture was stirred at room temperature and monitored by TLC (Ethylacetate/ Hexane 3:1). After 15 min, the reaction mixture was quenched with water and the organic layer was separated. The aqueous layer was extracted twice with methylene chloride (2 X 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product. The crude product was purified by column chromatography over Silicagel (100-200 mesh) and eluted with Ethyl acetate / Hexane to afford pure compound **3a** as gummy liquid (0.71 g, Yield 88%).

Spectral Data

trans-2-benzyl-4-chloro-1-tosylpiperidine (3a): ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, J = 8.6 Hz, 2H), 7.28 (m, 5H), 7.15 (d, J = 6.5 Hz, 2H), 4.42 (m, 1H), 4.13 (m, 1H), 3.74 (dd, J = 11.6, 2.8 Hz, 1H), 3.23 (td, J = 11.3, 3.0 Hz, 1H), 2.82 (m, 2H), 2.38 (s, 3H), 2.17 (m, 1H), 2.05 (m, 1H), 1.62 (m, 2H); ^{13}C NMR (400 MHz, CDCl_3): δ 21.4, 35.8, 36.6, 37.0, 40.4, 52.9, 55.4, 127, 129, 129.2, 131; HRMS: m/z = 364.80 (M^+ +H); Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{ClNO}_2\text{S}$: C, 62.71; H, 6.09; N, 3.85. Found: C, 62.78; H, 6.13; N, 3.89.

trans-2-Benzyl-4-chloro-1-(methylsulfonyl)piperidine (3b): ^1H NMR (400 MHz, CDCl_3): δ 7.32 (m, 5 H), 4.46 (s, 1 H), 4.22 (m, 1H), 3.89 (d, J = 12.2 Hz, 1H), 3.18 (m, 1H), 2.89 (m, 1H), 2.86 (m, 1H), 2.27 (m, 5H), 1.92 (m, 1H), 1.88 (m, 1H); ^{13}C NMR (CDCl_3 , 400 MHz): δ 138.3, 129.2, 128.9, 126.2, 56.5, 53.2, 40.8, 40.8, 39.6, 37.4, 36.8; Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{ClNO}_2\text{S}$: C, 54.25; H, 6.30; N, 4.87; found C, 54.28; H, 6.37; N, 4.79.

trans-tert-butyl 2-benzyl-4-chloropiperidine-1-carboxylate (3c): ^1H NMR (400 MHz, CDCl_3): δ 7.25 (m, 3H), 7.10 (m, 2H), 4.68 (m, 1H), 3.78 (m, 1H), 3.42 (m, 2H), 2.87 (m, 2H), 1.96 (m, 1H), 1.75 (m, 3H), 1.32 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3): δ 155.85, 135.46, 129.23, 128.65, 81.86, 58.45, 56.78, 47.28, 38.46, 30.95, 28.60; HRMS: m/z = 310.50 (M^+ +H); Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{ClNO}_2$: C, 65.90; H, 7.81; N, 4.52; Found C, 66.20; H, 7.76; N, 4.57.

trans-4-chloro-2-(4-methoxybenzyl)-1-tosylpiperidine (4a): ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, J = 8.2 Hz, 2H), 7.45 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.56 (m, 1H), 4.23 (m, 1H), 3.76 (s, 3H), 3.64 (m, 1H), 3.48 (m, 1H), 2.63 (m, 2H), 2.42 (s, 3H), 1.75 (m, 4H); ^{13}C NMR (400 MHz, CDCl_3): δ 160.8, 144.4, 137.9, 134.1, 128.2, 127.7, 113.8, 59.2, 58.8, 56.6, 47.4, 37.6, 31.3, 22.9; HRMS: m/z = 394.80 (M^+ +H); Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{ClNO}_3\text{S}$: C, 60.98; H, 6.14; N, 3.56; Found C, 60.86; H, 6.22; N, 3.45.

trans-4-chloro-2-(4-methoxybenzyl)-1-(methylsulfonyl)piperidine (4b): ^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.54, (m, 1H), 4.26 (m, 1H), 3.78 (s, 3H), 3.42 (m, 1H), 3.19 (s, 3H), 2.68 (m, 2H), 1.79 (m, 4H); ^{13}C NMR (400 MHz, CDCl_3): δ 161.2, 136.8, 130.4, 115.1, 59.2, 57.9, 55.7, 44.4, 38.1, 29.5; HRMS: m/z = 318.40 (M^+ +H); Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{ClNO}_3\text{S}$: C, 52.91; H, 6.34; N, 4.41; Found C, 52.98; H, 6.27; N, 4.46.

trans-tert-butyl 4-chloro-2-(4-methoxybenzyl)piperidine-1-carboxylate (4c): ^1H NMR (400 MHz, CDCl_3): δ 7.19 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.1 Hz, 1H), 4.56 (m, 1H), 3.62 (s, 3H), 3.57 (m, 1H), 3.45 (m, 2H), 2.68 (m, 2H), 2.05 (m, 1H), 1.74 (m, 3H), 1.27 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3): δ 162.1, 156.4, 136.8, 128.7, 113.9, 80.3, 59.2, 57.6, 54.4, 48.9, 36.4, 30.7, 26.8; HRMS: m/z = 340.70 (M^+ +H); Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{ClNO}_3$: C, 63.61; H, 7.71; N, 4.12; Found C, 63.52; H, 7.86; N, 4.04.

trans-4-chloro-2-cyclohexyl-1-tosylpiperidine (5a): ^1H NMR (400 MHz, CDCl_3): δ 7.64 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 3.58-3.95 (m, 3H), 2.80-3.00 (td, J = 2.6 and 13.5 Hz, 1H), 2.38 (s, 3H), 2.10 (dd, J = 1.7 and 11.9 Hz, 1H), 1.85 (m, 1H), 1.77 (m, 4H), 1.65 (m, 1H), 1.50 (m, 3H), 1.20 (m, 3H), 0.88 (m, 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 143.2, 138.5, 129.8, 126.9, 59.0, 52.7, 41.0, 35.9, 35.3, 34.8, 30.5, 29.5, 25.8, 25.6, 25.5, 21.2; HRMS: m/z = 356.90 (M^+ +H); Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{ClNO}_2\text{S}$: C, 60.74; H, 7.36; N, 3.94. Found: C, 60.83; H, 7.45; N, 3.85.

RESULTS AND DISCUSSION

In order to check the feasibility of reaction, a mixture of styrene oxide and homoallylic amine in anhydrous methylene chloride was stirred under nitrogen atmosphere at room temperature. To this mixture, Niobium pentachloride was added and continued stirring at room temperature till the completion of the reaction. After 15 min, TLC indicated the completion of both starting materials. After workup, the product was purified by column chromatography over silica gel (100-200 mesh) to afford the pure product. The product was characterized by relevant spectroscopic data and confirmed the product as **3a**. The spectroscopic data were compared with the literature data and further confirmed the product **3a** (Fig.-1).^{17,21,33}

Fig.-1: Synthesis of Compounds 3a-5a

With this cheerful result in hand, the reaction was further applied to various epoxides and homoallylic amines as illustrated in Fig.-3. In all these cases, the reaction worked efficiently with good yield ranging from 80 to 93% showing the applicability of this method. It is noticed that the nature of substituent shows some effect on the yield and reaction time. The epoxides containing electron-donating group gave slightly lower yield with longer reaction time than the un-substituted epoxides. Similarly, it is observed that the nature of protection on amine also makes a mild effect on the yield. The bulky protecting group gives lower yield compared to the tiny protecting groups.

The provisional mechanism for the formation of 4-chloropiperidine derivative could be explained by the NbCl_5 mediated opening of epoxides ring followed by intra-molecular migration of hydrogen, which is after the nucleophilic attack of amine and re-arrangement gives piperidine carbonium ion. The substitution in the 4th position depends on the availability of nucleophiles. As the chloride ion is readily available from NbCl_5 the preferred product would be the 4-chloro piperidine derivative (Fig.-2).

Fig.-2: The Provisional Mechanism for the 4-Chloro piperidine Derivatives Formation

It has been confirmed that the formation of *trans*-isomer predominantly by ¹HNMR data and further compared with those reported. The formation of *trans* isomer predominantly could possibly due to the formation of more stable *E*-iminium intermediate.¹⁷

CONCLUSION

In summary, we have developed NbCl_5 mediated mild and highly efficient method for the synthesis of 4-Chloro-piperidine derivatives by the cyclization of epoxides and homoallylic amines. The attractive

features of this process are mild reaction conditions, good yields and less reagent loading makes it useful process for the synthesis of 4-Chloro-piperidine derivatives

ACKNOWLEDGMENT

Kamesu Koyiri thank KLEF for permitting the research work.

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[RJC-5392/2019]