

Trimethylsilyl Iodide As A Versatile Reagent for the Synthesis of 4-Iodopiperidine Derivatives Via Aza-Prins Cyclization

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ABSTRACT

A series of 4-Iodopiperidine derivatives have been synthesised in good yields by employing a catalytic amount of Trimethylsilyl iodide as a versatile reagent via Aza-Prins cyclization under mild reaction conditions. All the synthesised compounds were characterized using ¹H NMR, ¹³C NMR and MASS spectral methods.

INTRODUCTION

Heterocyclic compounds, primarily those containing nitrogen are found in nature and synthetic drugs. These are crucial for drug development as well as chemical biology. The majority of them have excellent physiological properties and play significant roles in the human body. One of such nitrogen containing heterocyclic compound is Piperidine which is common structural unit in many of the naturally occurring alkaloids and is a useful building block in the synthesis of organic compounds, including pharmaceuticals [1]. Piperidine derivatives show wide spectrum of biological activities such as anti-cancer [2-3], anti-viral [4], anti-microbial [5,6], antimalarial [7], antifungal [8], antihypertension [9], anti-Alzheimer [10], antipsychotic [11], anticoagulant [12] activities. Due to the variety of biological and pharmaceutical activities piperidine derivative have attracted the attention of the researchers. Consequently, a number of techniques have been devised for the stereo- and enantioselective synthesis of substituted piperidines [13-15]. The aza-Prins cyclization is one of these straightforward and easy ways to make trans-2,4-disubstituted piperidines [16]. Furthermore, trans-2,6-disubstituted tetrahydropyridine derivatives can be prepared using the aza-silyl-Prins process [17]. Recently, there has been a report on the synthesis of iodopiperidines via the aza-Prins-cyclization utilizing gallium(III) iodide as a catalyst [18].

Trimethylsilyl iodide ((CH₃)₃SiI) is a versatile catalyst [19-21] in many of the organic transformations which can work under mild reaction conditions, often leading to high regio and stereoselectivity.

Following our interest on Aza-Prins type cyclizations, we herein report an efficient method for the synthesis of substituted piperidines from homoallylic amines and aldehydes by means of Aza-Prins type cyclization using Trimethylsilyl iodide under mild conditions. Accordingly, the corresponding 4-iodo-2-arylpiperidine derivatives **5a-j** were produced in good yields with trans selectivity when benzaldehyde was treated with N-tosylhomoallyl amine at room temperature in the presence of catalytic amount of Trimethylsilyl iodide.

EXPERIMENTAL

All the reagent grade chemicals were acquired from the available commercial suppliers. No additional pu-

rification was done before their use. All the Solvents used, were distilled according to standard protocols before their use. TLC was used for tracking the progress of the reaction and also for testing the purity of the compounds. Merck silica gel 60-120 mesh Was used for carrying out column chromatography for the purification of crude product. Using a Buchi 530 melting point device, melting points were determined in open capillary tubes. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 on Bruker spectrometer at 400 MHz and 101 MHz, respectively. NMR spectra were recorded using tetramethylsilane (TMS) as an internal reference. The Bruker Micro TOF spectrometer was used to get the high-resolution mass (ESI).

Synthesis of N-tosyl homoallylic amine (3)

Triethylamine (3.86 mL, 27.72 mmol) was added to a stirred solution of but-3-enamine hydrochloride (1) (1.00 g, 9.25 mmol) in dry dichloromethane (10 mL) at room temperature in a dry environment. The mixture was agitated for 40 minutes and then cooled to 0 °C and again stirred for an additional 20 minutes. Tosyl chloride (2) (2.29 g, 12.03 mmol) was added to the above solution at 0 °C. The resulting mixture was stirred at r.t. for 5 h, after the completion of reaction monitored by TLC, reaction was quenched by the addition of water (3 mL). The organic layer was washed with water (3 × 10 mL), brine (3 × 10 mL), and dried over anhydrous sodium sulphate and concentrated in *vacuo*. The crude product obtained was purified by column chromatography (20 % EtOAc/Hexane) giving the target compound (3) (1.87 g 90 %) as a syrup.

N-tosyl homoallylic amine (3): Colourless syrupy liquid, 90 % yield. IR (KBr, ν_{max} , cm^{-1}): 3286, 2926, 1642, 1603, 1328, 1154, 1090, 919, 814, 760, 662, 549. ^1H NMR (300 MHz, CDCl_3) δ ppm: 7.75 (d, 2H, $J = 8.3$ Hz), 7.32 (d, 2H, $J = 8.3$ Hz), 5.54-5.68 (m, 1H), 5.00-5.07 (m, 2H), 4.72 (t, 1H, $J = 6.1$ Hz), 2.96-3.02 (q, 2H), 2.45 (s, 3H), 2.15-2.22 (q, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 21.3, 33.5, 42.1, 117.5, 126.5, 129.2, 133.8, 136.3, 142.9; Mass (HRMS-ESI): m/z (M + Na) : 248.07.

General procedure for the Synthesis of (2R,4R)-4-iodo-2-aryl-1-tosylpiperidine scaffolds (5 a-j):

A mixture of N-tosyl homoallylic amine (3) (1 mmol), aldehyde (4a-j) (1 mmol) and trimethylsilyl iodide (0.1 mmol) in dichloromethane (5 mL) was subjected to stirring at 25 °C for about 6-8.5 h. The progress of the reaction was monitored play TLC. When the reaction was complete as indicated by TLC, the reaction mixture was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to purification by column chromatography using 5% Ethyl acetate and Hexane as eluent resulting in pure (2R,4R)-4-iodo-2-aryl-1-tosylpiperidine derivatives (5a-j) in good yields. The products thus obtained were characterized by IR, NMR, and mass spectroscopy.

(2R,4R)-4-Iodo-2-propyl-N-tosylpiperidine(5a):

IR (neat): ν_{max} 2923, 2853, 1739, 1461, 1374, 1216, 1170, 1119, 759, 668 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ 7.67 (d, 2H, $J = 8.3\text{Hz}$), 7.30 (d, 2H, $J = 7.9$ Hz), 4.24 (tt, 1H, $J = 12.4, 3.8$ Hz), 3.89 (brq, 1H), 3.63 (ddt, 1H, $J = 14.6, 4.4, 2.3$ Hz), 3.02 (ddd, 1H, $J = 15.2, 12.4, 2.9$ Hz), 2.40 (s, 3H), 2.12-2.20 (m, 2H), 2.02 (ddt, 1H, $J = 13.4, 4.2, 2.1$ Hz), 1.87 (dq, 1H, $J = 4.6, 12.3$ Hz), 1.25-1.60 (m, 4H), 0.90 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 13.6, 19.6, 21.4, 31.6, 37.9, 41.3, 42.2, 55.1, 126.8, 129.6, 138.1, 143.2.

LCMS: m/z : 408 (M + H); 430 (M + Na).

(2R,4R)-4-iodo-2-cyclohexyl-1-tosylpiperidine (5b): White syrup, 88 % yield. IR (KBr, ν_{max} , cm^{-1}): 3435, 2923, 2847, 1597, 1452, 1321, 1257, 1150, 1084, 1039, 969, 924, 817, 704. ^1H NMR (300 MHz, CDCl_3) δ ppm: 7.76 (d, $J = 7.8$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 4.23 (tt, $J = 12.3, 3.7$, Hz, 1H, H4a), 3.67 (ddt, $J = 14.2, 4.5, 2.4$ Hz, 1H, H6e), 3.50 (ddd, $J = 14.2, 12.2, 2.5$ Hz, 1H, H6a), 3.04 (ddt, $J = 13.1,$

4.2, 2.3 Hz, 1H, H2), 2.52 (s, 3H, CH₃), 2.47 (dt, $J = 5.2, 13.2$ Hz, 1H, H3), 2.15 (m, 1H, H5), 1.52-1.96 (m, 13H); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 18.9, 21.7, 38.0, 40.5, 43.2, 57.5, 126.6, 127.0, 127.2, 128.8, 130.0, 136.9, 138.1, 143.7; Mass (LCMS): m/z ([M+H]⁺): 448.

(2R,4R)-4-iodo-2-phenyl-1-tosylpiperidine (5d): Colourless solid, 91 % yield. IR (KBr, ν_{\max} , cm⁻¹): 3027, 2923, 2870, 1598, 1493, 1449, 1335, 1285, 1157, 1090, 1058, 951, 833, 700. ¹H NMR (300 MHz, CDCl₃) δ ppm: d 7.76 (d, $J = 7.7$ Hz, 2H, tos-o), 7.34 (m, 4H, tos-m, Ph-m), 7.29 (m, 3H, Ph-o,p), 5.20 (br m, 1H, H2e), 4.14 (tt, $J = 12.6, 3.9$ Hz, 1H, H4a), 3.72 (ddt, $J = 14.8, 4.6, 2.3$ Hz, 1H, H6e), 3.01 (ddd, $J = 15.2, 12.6, 2.9$ Hz, 1H, H6a), 2.94 (ddt, $J = 13.4, 4.2, 2.1$ Hz, 1H, H3e), 2.44 (s, 3H, CH₃), 2.27 (dt, $J = 5.4, 13.4$ Hz, 1H, H3a), 2.09 (m, 1H, H5e), 1.96 (dq, $J = 4.6, 12.6$ Hz, 1H, H5a); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 18.9, 21.7, 38.0, 40.5, 43.2, 57.5, 126.6, 127.0, 127.2, 128.8, 130.0, 136.9, 138.1, 143.7; Mass (LCMS): m/z ([M+H]⁺): 442.

(2R,4R)-4-iodo-2-((E)-styryl)-1-tosylpiperidine (5j): Yellow syrup, 90 % yield. IR (KBr, ν_{\max} , cm⁻¹): 2917, 2856, 1646, 1491, 1384, 1334, 1191, 1153, 1087, 931, 703, 654. ¹H NMR (300 MHz, CDCl₃) δ ppm: δ 7.65 (d, 2H, $J = 8.7$ Hz), 7.13-7.24 (m, 7H), 6.42 (d, 1H, $J = 16.2$ Hz), 5.91 (dd, 1H, $J = 5.6, 16.1$ Hz), 4.65-4.75 (m, 1H), 4.27 (tt, 1H, $J = 12.3, 3.9$ Hz), 3.66 (ddt, 1H, $J = 14.5, 4.3, 2.3$ Hz), 3.11 (ddd, 1H, $J = 15.1, 12.2, 2.8$ Hz), 2.11- 2.55 (m, 7H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ ppm: 21.1, 32.0, 33.6, 39.0, 44.4, 55.4, 125.7, 127.1, 128.0, 129.1, 130.5, 133.1, 134.4, 136.2, 137.3, 143.1; Mass (LCMS): m/z ([M+Na]⁺): 490.

RESULTS AND DISCUSSION

N-tosyl homoallylic amine **3** was prepared by tosylation of but-3-en amine hydrochloride **1** at 0 °C to room temperature for 5 h yielding 90%. Treatment of aldehydes **4a-j** with N-tosylhomoallyl amine **3** in the presence of catalytic amount of Iodotrimethylsilane (TMSI) at ambient temperature gave the corresponding 4-iodo-2-arylpiperidine derivatives (**5 a-j**) in good yields with *trans* selectivity. The scope and generality of this process was illustrated with respect to various aldehydes. The structures of all the final products were established by ¹H, ¹³C NMR and mass spectral analysis. The structure of **5a** shown in **Figure 1** was deduced from the NMR data, where the two substituents, iodo and phenyl, were *trans* to each other. Proton H4 had two large couplings ($J = 12.6$ Hz) indicating it to be in an axial position, with diaxial couplings to H3a and H5a, implying that the iodo group adopts the equatorial position at C4. This was further confirmed by a NOESY cross peak, H4/H6a. The axial orientation of the Ph group was confirmed by the NOESY cross peaks, H-ortho/H4 and also H-ortho/ H6a. In addition, the couplings and H3a/H5a NOE correlation provided an additional support for the structure.

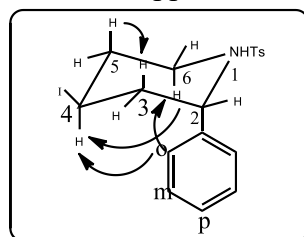


Figure 1. Characteristic NOE's of 5a

This result provided incentive for further study of reactions with other aldehydes such as cyclohexanecarboxaldehyde, n-decanal, isovaleraldehyde, and hydrocinnamaldehyde to produce the respective *trans*-2-alkyl-4-iodopiperidines in excellent yields (Table 1, entries b–e). Aromatic aldehydes such as p-bromo-benzaldehyde, p-methylbenzaldehyde, p-methoxybenzaldehyde, and p-

nitrobenzaldehyde underwent smooth coupling with N-tosylhomoallylic amine to furnish the corresponding *trans*-2-aryl-4-iodopiperidines (Table 1, entries f–i). Similarly, *trans*-cinnamaldehyde gave corresponding *trans*-4-iodo-2-styrylpiperidine in 90 % yield (Table 1, entry j).

Mechanism

Mechanistically, the formation of the products may be explained by initial iminium intermediate formation and subsequent Prins-type cyclization (Figure 2). The scope and generality of this process is illustrated in Table 1.

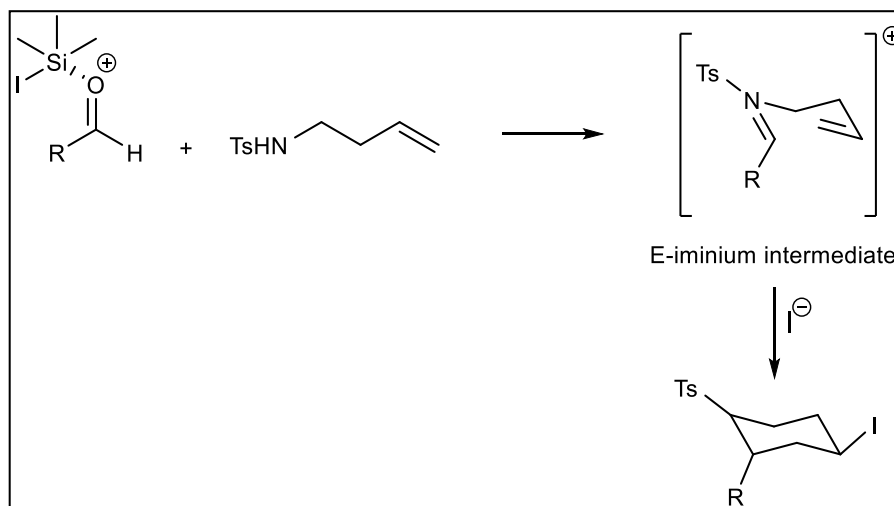


Figure 2: A plausible reaction pathway

Scheme 1. The synthetic route for the preparation of (2*R*,4*R*)-4-iodo-2-aryl-1-tosylpiperidine

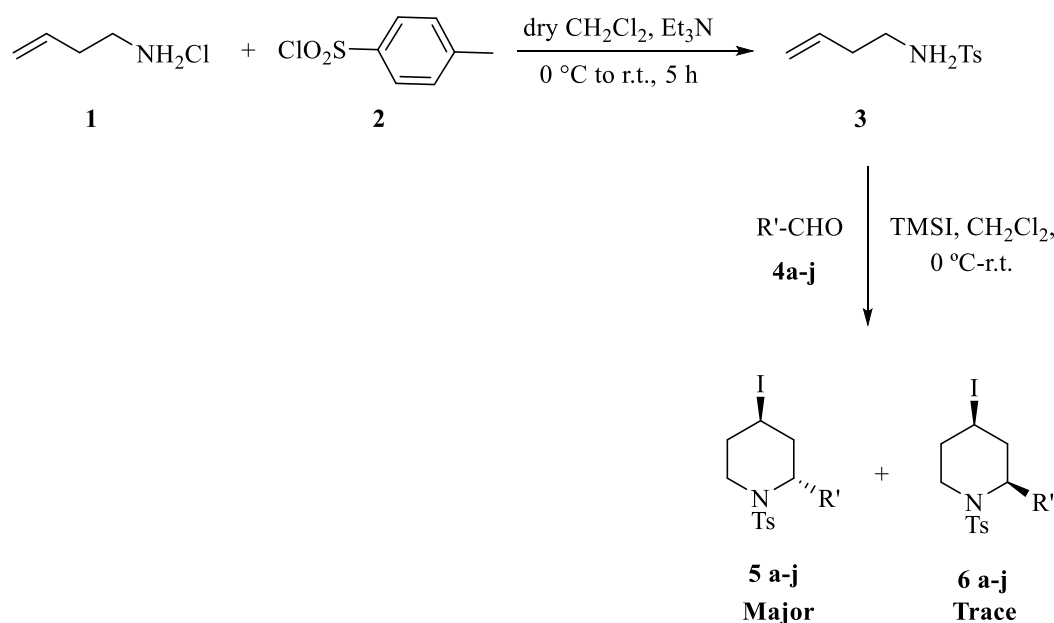
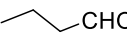
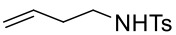
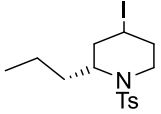
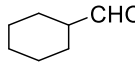
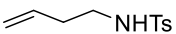
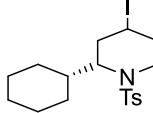
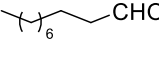
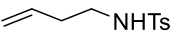
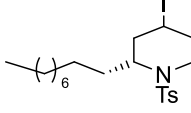
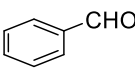
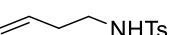
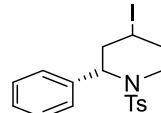
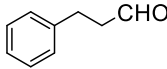
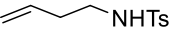
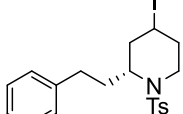
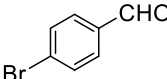
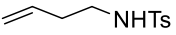
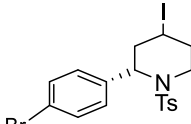
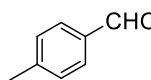
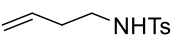
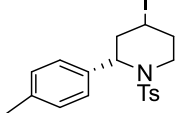
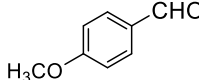
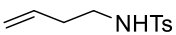
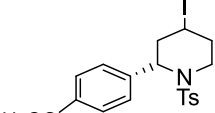
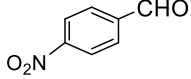
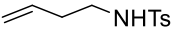
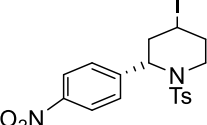
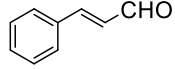
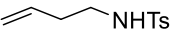
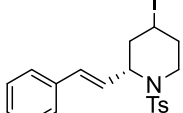


Table 1:

Entry	Aldehyde=R'	Homoallylamine	Product (5)	Time (h)	Yield (%)	<i>Trans:cis</i> Ratio
a				6.5	89	98 : 2
b				6.0	88	97 : 3
c				6.5	90	98 : 2
d				6.5	91	96 : 4
e				7.0	91	98 : 2
f				6.0	89	97 : 3
g				6.5	92	96 : 4
h				8.0	83	96 : 4
i				8.5	82	96 : 4
j				7.5	90	97 : 3

Conclusion

A series of 2, 4-disubstituted iodopiperidine derivatives have been synthesised utilizing iodotrimethyl silane as a novel catalytic system by means of aza-Prins-cyclization. The approach was convenient, mild, scalable, and selective.

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