Trimethylsilyl Iodide-Promoted Aza-*Prins* Cyclization for the Synthesis of 4-Iodopiperidines

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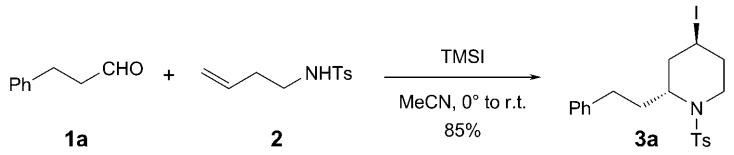
The aza-*Prins* cyclization of homoallyl *N*-tosylamine with aliphatic aldehydes gives *trans*-2-alkyl-4-iodo-1-tosylpiperidines. This method is chemoselective as it works only with the aliphatic aldehydes, and, in the case of aromatic aldehydes, the starting materials are recovered.

The aza-*Prins* cyclization [1], in which alkenes are used as intramolecular nucleophile, is a simple and direct method for the preparation of *trans*-2,4-disubstituted piperidines. Earlier, we have studied [2] the use of Me_3SiI (TMSI) in *Prins* cyclization reactions for the synthesis of tetrahydropyrans. In continuation, here we report TMSI-promoted aza-*Prins* reaction for the synthesis of 4-iodopiperidines from *N*-tosyl homoallylic amines and aldehydes.

Thus, treatment of 3-phenylpropanal with *N*-tosylbut-3-enamine in the presence of 1 equiv. of TMSI in MeCN at 0° to room temperature was found to be completed in 2 h, and the corresponding *trans*-4-iodo-2-(2-phenylethyl)-1-tosylpiperidine (**3a**) was isolated as the major isomer in 85% yield (*Scheme 1*). The structure of the product was established by NMR spectroscopy and NOE studies.

Scheme 1



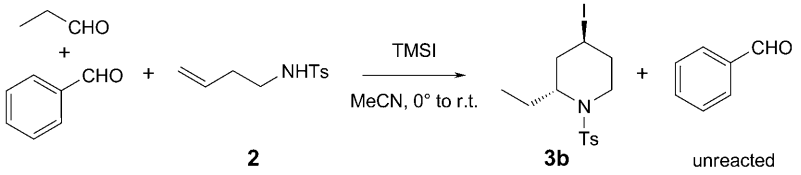
1a **2** **3a**

To evaluate the scope of the reaction, several aliphatic aldehydes such as butanal, hexanal, isobutanal, cyclopentanecarbaldehyde, and cyclohexanecarbaldehyde were studied, and they were found to give the corresponding piperidines in good yields when treated with *N*-tosylbut-3-enamine. In all cases, the *trans*-diastereoisomer was obtained as the major product, and the *trans*-configuration was confirmed by NOE experiments. This reaction does not require any additives. Under these conditions, the aza-*Prins* cyclization works well only with aliphatic aldehydes, whereas, the reaction does not work with the aromatic aldehydes. Accordingly, the aza-*Prins* reaction using TMSI is selective. Reactions of aldehydes containing aromatic rings located in a distal position (*Entries a* and *e*; *Table* in *Exper. Part*) relative to the C=O group, proceeded

satisfactorily. It is important to mention that no *N*-tosyl deprotection was observed during the aza-*Prins* cyclization.

The high chemoselectivity of the method is demonstrated by competitive reactions between aliphatic and aromatic aldehyde. Accordingly, the reaction of **2** with a mixture containing equal amounts of propanal and benzaldehyde in the presence of TMSI proceeded to give **3b**, and unreacted benzaldehyde was recovered (*Scheme 2*).

Scheme 2



In conclusion, we have described a very simple, efficient, and practical method for the synthesis of *trans*-4-iodo-2-alkyl-1-tosylpiperidines *via* aza-*Prins* reaction using TMSI. The significant features of this method are *a*) operational simplicity, *b*) commercial availability of TMSCl, *c*) no need for any additive to promote the reaction, *d*) chemoselectivity, and *e*) high yields of products.

Experimental Part

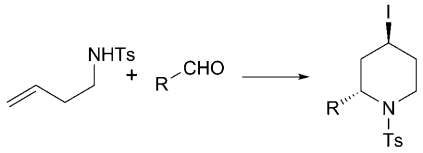
General. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh; *Merck*). M.p.: *Fisher Johns* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 683* spectrometer. NMR Spectra: in $CDCl_3$; *Varian Gemini 200*, *Bruker 300*, or *Varian Unity 400* NMR spectrometers; chemical shifts (δ) in ppm, referenced to tetramethylsilane (TMS) as internal standard; coupling constants (J) in Hz. MS: *Finnigan MAT 1020B* or *micro mass VG 70-70 H* spectrometers operating at 70 eV using a direct inlet system.

General Procedure. A mixture of N-*tosylbut-2-enamine* (**2**; 1 mmol), aldehyde **1** (1 mmol), and TMSI (1 mmol; prepared *in situ* from TMSCl and NaI) in MeCN (5 ml) was stirred at 0° for the specified amount of time (*Table*). After completion of the reaction (TLC), the mixture was extracted with CH_2Cl_2 (2×10 ml). The combined org. layers were dried (Na_2SO_4). Removal of the solvent followed by purification on SiO_2 (AcOEt/hexane 0.5 : 9.5) gave the corresponding pure 2-alkyl-4-iodo-*N*-tosylpiperidine **3**. The products thus obtained were characterized by IR, NMR, and mass spectrometry. The spectral data were found to be consistent with those of authentic samples.

4-Iodo-1-[(4-methylphenyl)sulfonyl]-2-(phenylethyl)piperidine (**3a**; *Entry a*): IR (KBr): 3026, 2926, 1598, 1494, 1451, 1338, 1156, 1093, 975, 917, 815, 694. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.73–7.64 (*m*, 2 H); 7.34–7.08 (*m*, 6 H); 4.47–4.22 (*m*, 1 H); 4.12–3.92 (*m*, 1 H); 3.78–3.65 (*m*, 1 H); 3.53–3.41 (*m*, 1 H); 2.70–2.51 (*m*, 2 H); 2.45–2.40 (*d*, $J = 6.4$, 3 H); 2.34–1.7 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 143.2; 141.1; 137.9; 129.8; 128.1; 126.8; 126; 53.3; 42.3; 41.5; 38.9; 33.6; 32.7; 31.7; 21.8. ESI-MS: 492 ($[M + Na]^+$).

4-Iodo-1-[(4-methylphenyl)sulfonyl]-2-(1-methylethyl)piperidine (**3d**; *Entry d*): IR (KBr): 2962, 2926, 2871, 1598, 1454, 1337, 1156, 1092, 1043, 963, 922, 818, 747. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.75–7.69 (*m*, 2 H); 7.34–7.25 (*m*, 2 H); 4.38–4.20 (*m*, 1 H); 3.80–3.61 (*m*, 1 H); 3.50–3.29 (*m*, 1 H); 3.07–2.72 (*m*, 1 H); 2.45–2.40 (*d*, $J = 6.4$, 3 H); 2.30–1.7 (*m*, 3 H); 1.29–1.21 (*m*, 1 H); 0.99–0.88 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 143.4; 138.2; 129.8; 126.9; 61.7; 42.8; 38.98; 32.2; 29.3; 21.5; 19.7. ESI-MS: 430 ($[M + Na]^+$).

Table. *TMSI Promoted Synthesis of 4-Iodopiperidines.* Reaction duration: 2 h.



2 **1** **3**

Entry	R	Yield [%][a])	*trans*/*cis* Ratio
a	$PhCH_2CH_2$	85	95 : 5
b	Et	88	97 : 3
c	Pentyl	85	97 : 3
d	i-Pr	82	96 : 4
e	$PhCH_2$	80	95 : 5
f	Pr	82	96 : 4
g	Cyclopentyl	82	94 : 6
h	Cyclohexyl	80	94 : 6
i	Ph	no reaction	

[a]) The yields are given for isolated pure products. The products were characterized by spectral data, and known compounds were compared with authentic samples.

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