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Gallium iodide/iodine as a versatile reagent for the aza-Prins cyclization: an expeditious synthesis of 4-iodopiperidines

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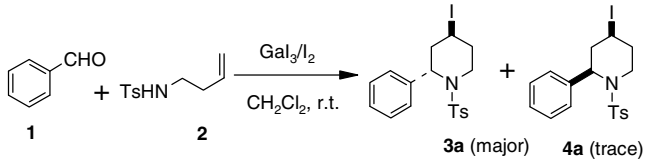
Abstract

4-Iodopiperidines are prepared in good yields and with high selectivity by means of aza-Prins-cyclization using a catalytic amount of gallium(III) iodide and a stoichiometric amount of iodine under mild reaction conditions. This is the first report on the preparation of 4-iodopiperidines via aza-Prins-cyclization.

Keywords: Aza-Prins-cyclization; Molecular iodine; Homoallylic amines; 4-Iodopiperidine

The piperidine ring is a common structural feature of numerous naturally occurring alkaloids such as coniine, sedamine, sedridine, (−)-allosedamine, (−)-allosedridine, halosaline, and many others.[1] They are very useful for the treatment of respiratory illnesses such as asthma, bronchitis, and pneumonia.[2] Both enantiomers of allosedridine exhibit memory-enhancing properties and may be effective for the treatment of Alzheimer's disease.[3] As a result, various methods have been developed for the synthesis of substituted piperidines in a stereo- and enantioselective manner.[4] Of these, the aza-Prins cyclization is a simple and direct method for the preparation of *trans*-2,4-disubstituted piperidines.[5] In addition, the aza-silyl-Prins reaction is a method for the preparation of *trans*-2,6-disubstituted tetrahydropyridine derivatives.[6] In spite of its potential utility in natural product synthesis, only a few reports exist on aza-Prins-cyclizations.[5,6] Furthermore, there have been no reports on the synthesis of iodopiperidines via the aza-Prins-cyclization. Recently, there has been considerable interest in gallium-mediated transformations.[7] Owing to their unique catalytic properties, gallium halides have been widely used for a variety of organic transformations. In particular, gallium(III) compounds are considered as effective Lewis acids to activate alkynes under extremely mild conditions.[8]

In continuation of our research program on the Prins-cyclization,[9] we herein report an efficient method for the synthesis of substituted piperidines from homoallylic amines and aldehydes by means of aza-Prins-cyclization using gallium(III) iodide/molecular iodine under mild conditions. Accordingly, treatment of benzaldehyde with *N*-tosylhomoallyl amine in the presence of 10 mol % of GaI_3 and a stoichiometric amount of molecular iodine at ambient temperature over 6.5 h gave the corresponding 4-iodo-2-phenylpiperidine **3a** in 91% yield with *trans*-selectivity (Scheme 1).



Scheme 1. Preparation of **3a**.

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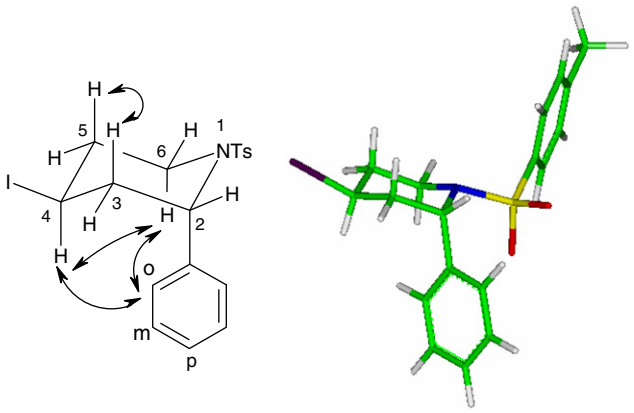
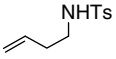
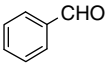
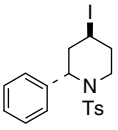
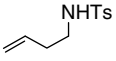
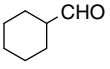
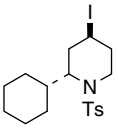
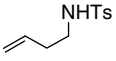
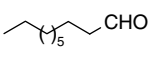
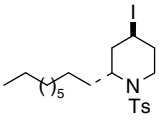
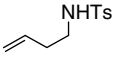
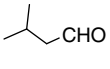
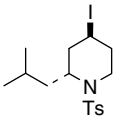
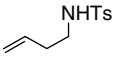
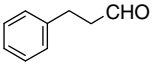
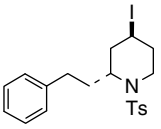
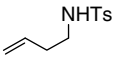
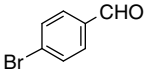
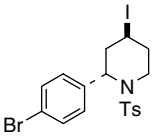
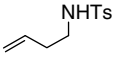
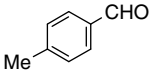
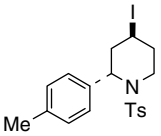
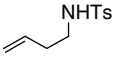
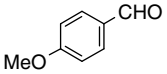
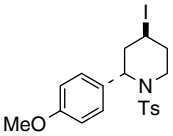


Fig. 1. Characteristic NOEs and energy-minimized structure of **3a**.

The structure of **3a** shown in Figure 1 was deduced from the NMR data, where the two substituents, iodo and phenyl, are trans to each other. Proton H4 has 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 additional support for the structure.

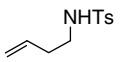
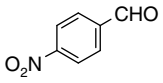
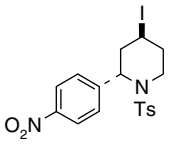
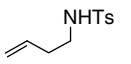
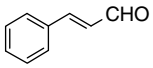
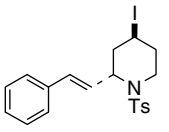
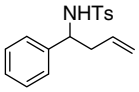
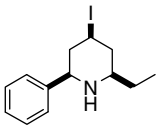
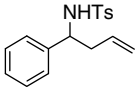
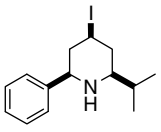
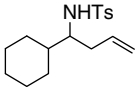
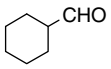
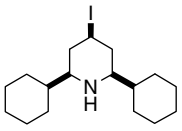
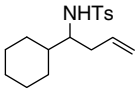
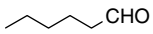
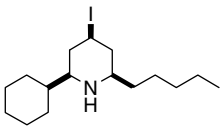
This result provided incentive for further study of reactions with other aldehydes such as cyclohexanecarboxaldehyde, *n*-decanal, isovaleraldehyde, and hydrocinnamal-

Table 1
Gallium(III) iodide/iodine promoted aza-Prins cyclization

Entry	Homoallyl amine	Aldehyde	Iodopyridine[a]	Time (h)	Yield[b] (%)	Trans/cis[c]
a				6.5	91	96:4
b				6.0	88	97:3
c				6.5	90	98:2
d				6.5	89	98:2
e				7.0	91	98:2
f				6.0	89	97:3
g				6.5	92	96:4
h				8.0	83	96:4

(*continued on next page*)

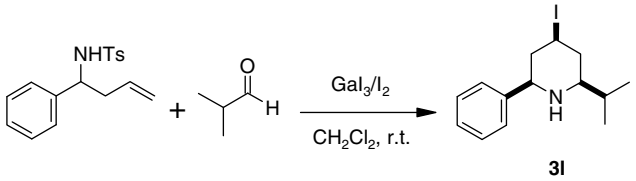
Table 1 (*continued*)

Entry	Homoallyl amine	Aldehyde	Iodopyridine[a]	Time (h)	Yield[b] (%)	Trans/cis[c]
i				8.5	82	96:4
j				7.5	90	97:3
k				7.5	86	—
l				8.0	90	—
m				7.0	85	—
n				7.5	88	—

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] The diastereoselectivity was determined by HPLC.

dehyde to produce the respective *trans*-2-alkyl-4-iodopiperidines in excellent yields (Table 1, entries **b**–**e**). Aromatic aldehydes such as *p*-bromobenzaldehyde, *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 the corresponding *trans*-4-iodo-2-styrylpiperidine in 90% yield (Table 1, entry **j**). The use of the substituted homoallylic amines afforded 2,4,6-trisubstituted piperidines with all *cis*-configuration (Table 1, entries **k**–**n**, Scheme 2).

The NMR data suggested the structure for **3l** (Fig. 2), where the three 2-, 4-, and 6-substituents are in equatorial positions.



3l

Scheme 2. Preparation of **3l**.

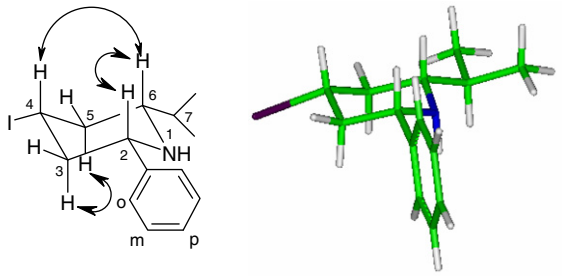
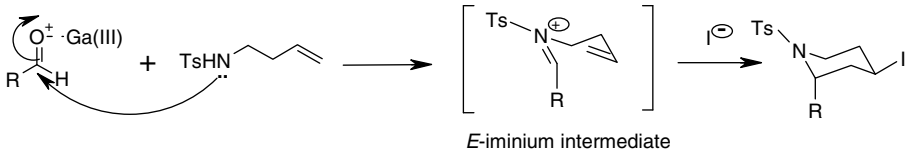


Fig. 2. Characteristic NOEs and energy-minimized structure of **3l**.

The H2 and H6 protons showed large couplings ($J = 11.0$ Hz) whereas H4 has two large couplings ($J = 12.4$ Hz) indicating the axial positioning of these protons, and thereby the equatorial orientation of the substituents at the 2-, 4-, and 6-positions. The structure was further confirmed by NOESY cross peaks between H4a/H6a, H2a/H6a, and H3a/H5a. Further, the equatorial position of the Ph group was confirmed by NOESY cross peaks, H-*ortho*/H3e and H-*ortho*/H3a. It is important to mention that *N*-tosyl deprotection was observed during the aza-Prins-cyclization of substituted homoallylic amides (Table



Scheme 3. A plausible reaction mechanism.

1, entries **k**–**n**). In the absence of gallium(III) iodide, no aza-Prins-cyclization was observed even with stoichiometric amounts of iodine. The use of gallium(III) iodide alone gave the products in low yields (20–35%). Therefore, addition of 1 equiv. of iodine was crucial to obtain high conversion. Thus, the combination of gallium(III) iodide and iodine worked efficiently to furnish the corresponding di- and tri-substituted piperidines in good to high yields. The effects of various metal iodides such as GaI_3, InI_3, AlI_3, and MgI_2 were screened. Of these metal iodides, gallium(III) iodide was found to be superior in terms of conversion. For example, the reaction between benzaldehyde and *N*-tosylhomoallyl amine in the presence of 1 equiv of molecular iodine and 10 mol % of metal iodides such as GaI_3, InI_3, AlI_3, and MgI_2 gave product **3a**, in 91%, 75%, 69%, and 62% yields, respectively. The combination of 10 mol % of $FeCl_3$ and 1 equiv of iodine also gave 4-iodopiperidines along with 4-chloropiperidines. In addition, *N*-tosyl deprotection was observed in aza-Prins-cyclization when using $FeCl_3/I_2$. As solvent, dichloromethane gave the best results. In all cases, the reactions proceeded readily at room temperature under mild conditions to give the products in good yields and with high diastereoselectivity. The formation of the products may be explained by initial aminal formation and subsequent Prins-type cyclization (Scheme 3). The scope and generality of this process is illustrated in Table 1.[10]

In summary, we have developed an efficient protocol for the synthesis of 2,4-di- and 2,4,6-trisubstituted piperidines by means of aza-Prins-cyclization using gallium(III) iodide/molecular iodine as a novel catalytic system. The method is mild, selective, and convenient and the reaction conditions are amenable to scale-up.

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10. *General procedure*: A mixture of homoallylic amine (1 mmol), aldehyde (1 mmol), and gallium iodide (0.1 mmol) and iodine (1.0 mmol) in dichloromethane (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction 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. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 0.5–9.5) gave the pure 4-iodopiperidine. The products thus obtained were characterized by IR, NMR, and mass spectroscopy. The spectral data were found to be consistent with authentic samples. Compound **3a**: 4-Iodo-1-(4-methylphenylsulfonyl)-2-phenylhexahydropyridine: solid, mp 102–104 °C. IR (KBr): ν_{max} 3029, 2924, 2870, 1598, 1494, 1448, 1336, 1285, 1156, 1091, 1059, 950, 930, 834, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, $J = 7.7$ Hz, 2H, tos-*o*), 7.34 (m, 4H, tos-*m*, Ph-*m*), 7.28 (m, 3H, Ph-*o*, *p*), 5.21 (br m, 1H, H2e), 4.13 (tt, $J = 12.6$, 3.9, Hz, 1H, H4a), 3.74 (ddt, $J = 14.8$, 4.6, 2.3 Hz, 1H, H6e), 3.04 (ddd, $J = 15.2$, 12.6, 2.9 Hz, 1H, H6a), 2.95 (ddt, $J = 13.4$, 4.2, 2.1 Hz, 1H, H3e), 2.46 (s, 3H, CH_3), 2.28 (dt, $J = 5.4$, 13.4 Hz, 1H, H3a), 2.10 (m, 1H, H5e), 1.95 (dq, $J = 4.6$, ~12.6 Hz, 1H, H5a). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 21.6, 38.0, 40.6, 43.4, 57.6, 126.6,

127.0, 127.4, 129.0, 129.9, 137.1, 138.0, 143.6. LCMS: *m*/*z*: (M^++H) 442. Compound **3l**: 4-Iodo-2-isopropyl-6-phenylhexahydropyridine: liquid IR (KBr): ν_{max} 3451, 2959, 2923, 2850, 1451, 1156, 1129, 1063, 1001, 754 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H, Ph-*m*), 7.28 (m, 3H, Ph-*o*, *p*), 4.43 (tt, $J = 12.4$, 4.2 Hz, 1H, H4a), 4.36 (dd, $J = 11.0$, 2.2 Hz, 1H, H2a), 3.23 (ddd, $J = 11.0$, 5.9, 1.8 Hz, 1H, H6a), 2.57 (ddt, $J = 12.8$, 4.2, 2.1 Hz, 1H, H3e), 2.39 (ddt, $J = 12.6$, 4.2, 2.1 Hz, 1H, H5e), 2.14 (q, $J \sim 13.0$ Hz, 1H, H3a), 2.01 (q, $J \sim 12.0$ Hz, 1H, H5a), 1.81 (q, $J \sim 6.8$ Hz, 1H, H7), 0.98 (d, $J = 6.8$ Hz, 3H, CH_3), 0.96 (d, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 18.4, 23.4, 29.7, 32.9, 41.6, 47.5, 80.3, 83.8, 125.5, 127.4, 128.3, 141.6. LCMS: *m*/*z* (%): (M^++H) 330.