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MOLECULAR IODINE CATALYSED SYNTHESIS OF TETRAHYDROAZEPINES FRAMEWORKS *VIA* SILYL AZA-PRINS CYCLIZATION

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ABSTRACT: A new methodology for the synthesis of seven- membered unsaturated aza cycles (tetrahydroazepines) was developed. It is based on the powerful Aza-Prins cyclization in combination with the Peterson-type elimination reaction. In a single reaction step, a C−N, C− C bond and an endocyclic double bond are formed. Under mild reaction conditions,using Molecular Iodine as sustainable catalysts, tetrahy- droazepines with different degrees of substitution are obtaineddirectly and efficiently. DFT calculations supported the proposed mechanism.

KEYWORDS: Tetahydroazepines, Silyl Aza Prins, Molecular Iodine

INTRODUCTION:

Unsaturated seven-membered ring azacycles (tetrahydroazepines) are found in numerous natural and non-natural products with remarkable pharmaceutical activity.[i] Also, they serve as substructures of more complex molecules or as precursors of hydroazepines with different biological proper- ties.[ii] Most of these natural products come from terrestrial sources such as balanol (1), an unusual metabolite isolated from fungus *Verticillium balanoides*, which is a potent inhibitor of PKC[1] or (−)-galanthamine (2), commercially known as Reminyl and used for the symptomatic treatment of Alzheimer's (Figure 1).[iii] The unnatural azepane **3** proved to be an excellent agent against lung cancer, where the heterocyclic nitrogenous core is essential for its bioactivity (IC_{50} of 4.18 nM) (Figure 1).

Classical methods to synthesize this type of heterocycles include Bronsted or Lewis acid-mediated cyclizations, atom transfer radical cyclization (ATRC), cycloadditions,[iv] conjugate addition cyclizations, ring expansions (cyclopropanes, aziridines, azetidines, 2-cyano-6-oxazolopi- peridine [v]), and ring-closing metathesis.[vi] Among the different types of acid-mediated cyclizations, the aza Prins cyclization is a powerful tool for obtaining nitrogenated heterocycles. It has been widely used for the synthesis of piperidines and pyrrolidines.[vii] However, there are few examples of synthesis of tetrahydroazepines through this methodology[viii, ix] .In 2016, Barbero and co- workers achieved the synthesis of azepane rings, with an exocyclic double bond, through a diastereoselective silyl aza-Prins cyclization mediated by $InCl_3$ Nevertheless, this reaction, inspired by the work of the Dobbs' group, is a relatively high energy demanding reaction[x].

Therefore, new methods for the synthesis of seven-membered azacycles via Prins cyclizations remain challenging and highly desirable.

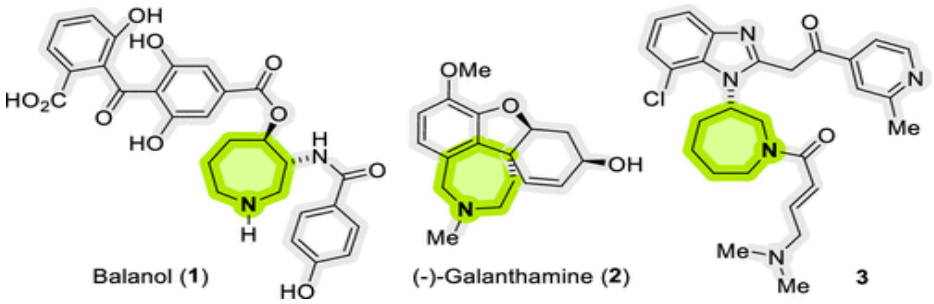


Figure 1. Representative bioactive hydroazepines/tetrahydroazepines.

EXPERIMENTAL SECTION:

Reagents were obtained from commercial sources (Sigma-Aldrich, Merck, Alfa Aesar), without further purification. Solvents (DCM, Et_2O, THF, and DMF) were used from the Pure Solv system. The dispensing system allows easy access to the anhydrous solvents. EtOH was purified by distillation and dried following the procedure in the literature.[35] Chemical reactions and the separation of the crudes were monitored by thin-layer chromatog- raphy (TLC). TLC was performed on aluminum foil sheets 60 F254 manufactured by MERCK. The solvent or solvent mixture was *n*- hexane/ethyl acetate (EtOAc) in different ratios. Flash column chromatography was performed using silica gel (0.015−0.04 mm) and *n*-hexane/EtOAc solvent systems. Automated flash column chromatography was performed using the Biotage Isolera System (Isolera Prime). It includes simultaneous UV detection on all wavelengths and baseline correction, which enable detection of poor UV absorbing compounds. NMR spectra were recorded on Bruker Avance instruments. ^{1}H NMR spectra were recorded at 400, 500, and 600 MHz, and ^{13}C NMR spectra were recorded at 100, 125, and 150 MHz, VTU 298.0 K. The residual solvent peak was used as an internal reference ($CDCl_3$:δH 7.26, δC 77.0). High-resolution mass spectra were recorded on an LCT Premier XE mass spectrometer. It is provided with different ionization sources: electrospray (ESI), an atmospheric pressure chemical ionization (APCI)source, and an orthogonal acceleration time of flight analyzer that provides high sensitivity, resolution, and accurate mass measurement.

GENERAL PROCEDURE:

FOR SILYL AZA-PRINS CYCLIZATION OF 1-AMINO-3-TRIPHENYLSILYL-4-PENTENES (4 A−B):

To a solution of amines 6a−b (0.30−0.12 mmol, 1.0 equiv) in dry DCM (3.0−1.2 mL, 0.1 M) at 0°C were added the aldehyde (0.45−0.18 mmol,1.5 equiv) and the catalyst (0.030−0.012 mmol, 0.1 equiv). Once the reaction was complete, checked by TLC, it was quenched with water. The layers were separated, and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (n-hexane/EtOAc solvent system).

2-ISOBUTYL-1-TOSYL-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5A):

Following the general procedure (1), to a solution of amine 4a (80 mg, 0.16mmol, 1.0 equiv) in 1.6 mL of dry DCM (0.1 M) at 0 °C were added isovaler aldehyde (21 μL, 0.19 mmol, 1.2equiv) and I_2 (4.8 mg, 0.019 mmol, 0.1 equiv) to obtain 45 mg of tetrahydroazepine 5a as a pale yellow oil (0.147 mmol, 92%). *R*f = 0.63 (*n*-hexane/EtOAc 80:20), ^{1}H NMR ($CDCl_3$, 400

MHz): δ = 7.69 (d, *J* = 8.1 Hz, 2H), 7.26(d, *J* = 7.3 Hz, 2H), 5.70 (m, 1H), 5.55 (m, 1H), 4.13 (m, 1H), 3.66 (brddd, *J* = 14.5, 4.8 & 3.4 Hz, 1H), 3.14 (brddd,*J* = 14.0, 11.0 & 2.2 Hz, 1H), 2.40 (s, 3H), 2.38−2.27 (m, 2H), 2.15 (m, 2H), 1.37(m, 3H), 0.82 (d, *J* = 6.4 Hz, 3H),0.80 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$- NMR ($CDCl_3$, 125 MHz): δ = 142.8 (C), 138.6 (C), 130.7 (CH),129.5 (2× CH),127.2 (CH), 127.1 (2× CH), 53.4 (CH), 41.2(CH), 40.2 (CH), 32.5 (CH), 30.3 (CH), 24.6 (CH), 22.9(CH_3),22.3 (CH_3), 21.5 (CH_3); HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{25}NO_2NaS$, 330.1505; found, 330.1504.

2-HEXYL-1-TOSYL-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5B):

Following the general procedure (1), to a solution of amine 4a (0.150 mg, 0.30 mmol, 1.0 equiv) in 3.0 mL of dry DCM (0.1 M) at 0 °C were added heptanal (51 μL, 0.36 mmol, 1.2 equiv)and I_2 (9.0 mg, 0.030 mmol, 0.1 equiv) to obtain 81 mg of tetrahydroazepine 5b as a pale yellow oil (0.24 mmol,80%). *R*f = 0.57 (*n*-hexane/EtOAc 80:20); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J*= 8.3Hz, 2H), 5.69 (m, 1H), 5.56 (m, 1H), 4.03 (m, 1H), 3.68 (brddd, *J* = 14.5, 5.1 & 3.1 Hz, 1H), 3.14 (brddd, *J* = 13.3,10.9 & 2.1Hz, 1H), 2.41 (s, 3H), 2.38−2.28 (m, 2H), 2.19 (m, 2H), 1.46 (m,2H), 1.29−1.11 (m, 6H), 1.10−0.98 (m,2H), 0.85 (t, *J* = 7.0 Hz,3H); $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): δ = 142.7 (C), 138.5 (C),130.6 (CH), 129.4 (2×CH), 127.0 (CH), 126.9 (2× CH), 55.4(CH), 41.3 (CH_2), 32.3 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 30.5(CH_2), 29.0 (CH_2), 26.1 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 14.0 (CH_3); HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{29}NO_2NaS$, 358.1817; found, 358.1821.$C_{19}H_{29}NO_2NaS$, 358.1817; found, 358.1821.

2-(BUT-3-EN-1-YL)-1-TOSYL-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5C):

Following the general procedure (1), to a solution of amine4a (0.150 mg, 0.30 mmol, 1.0 equiv) in 3.0 mL of dry DCM (0.1 M) at 0 °C were added 4-pentenal (61 μL, 0.60 mmol,2.0 equiv) and I_2 (9.0 mg, 0.030 mmol, 0.1 equiv) to obtain 61 mg of tetrahydroazepine 5c as a pale yellow oil (0.20 mmol, 67%). *R*f = 0.54 (*n*-hexane/EtOAc 80:20); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.26 (d,*J* = 7.8 Hz, 2H), 5.71 (m, 2H), 5.54 (m, 1H), 4.94 (m, 2H),4.06 (m, 1H), 3.65 (ddd, *J* = 14.5, 5.4 & 3.3 Hz, 1H), 3.18(ddd, *J* =14.6, 10.6 & 2.4 Hz, 1H), 2.40 (s, 3H), 2.37−2.26 (m, 2H), 2.18 (m,2H), 1.90 (m, 2H), 1.59 (m, 2H); $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100MHz): δ = 142.8 (C), 138.3 (C), 137.8 (CH), 130.8 (CH), 129.5(2× CH), 127.0 (2× CH), 126.7 (CH), 114.8 (CH_2), 55.2 (CH),41.5 (CH_2), 31.8 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 21.4 (CH_3);HRMS (ESI^+): *m*/*z* [*M* + Na]$^+$ calcd for $C_{17}H_{23}NO_2NaS$, 328.1347; found, 328.1349.

2-BENZYL-1-TOSYL-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5D):

Following the general procedure (1), to a solution of amine 4a (0.150g, 0.30 mmol, 1.0 equiv) in 3.0 mL of dry DCM (0.1 M) at 0 °C were added phenyl acetaldehyde (43 μL, 0.36 mmol,1.2 equiv) and I_2 (9.0 mg, 0.030 mmol, 0.1 equiv) to obtain 67 mg of tetrahydroazepine 5d as a pale yellow oil (0.195 mmol, 65%). *R*f = 0.46 (*n*-hexane/EtOAc 80:20); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (m, 2H), 7.23 (m,5H),7.12 (m, 2H), 5.73 (m, 1H), 5.55 (m, 1H), 4.30 (m, 1H), 3.64(ddd, *J* = 14.4, 5.7 & 3.4 Hz, 1H), 3.33 (ddd, *J* = 14.4,10.4 & 2.6 Hz, 1H), 2.84 (m, 2H), 2.47−2.34 (m, 4H), 2.26 (m, 2H), 2.09 (m, 1H); $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz):δ = 142.8 (C), 138.5 (C), 137.9(C), 130.8 (CH), 129.5 (2× CH), 129.2 (2× CH), 128.4 (2× CH), 127.0 (2× CH), 126.5 (CH), 126.4 (CH), 58.1 (CH), 41.9 (CH_2), [M + Na] calcd for $C_{20}H_{23}NO_2NaS$, 364.1347; found, 364.1349.

2-ISOBUTYL-1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZEPINE(5E):

Following the general procedure (1), to a solution of amine 4b (0.500 g, 1.19 mmol, 1.0 equiv) in 12 mL of dry DCM (0.1 M) at 0°C were added iso valeraldehyde (0.19 mL, 1.79mmol, 1.5 equiv) and I_2 (35 mg, 0.12 mmol, 0.1 equiv) to obtain 0.201 g of tetrahydroazepine 5e as a pale

yellow oil (0.87 mmol, 73%). *R*f =0.49 (*n*-hexane/EtOAc 70:30); ^{1}H NMR ($CDCl_3$, 400 MHz): δ =(dt, *J* = 14.9 & 4.0 Hz, 1H), 3.21 (ddd, *J* = 14.6, 11.5 & 2.9 Hz, 1H),2.87 (s, 3H), 2.48 (m, 2H), 2.28 (m, 2H), 1.53 (m, 2H), 1.38(m,1H), 0.93 (brd, *J* = 1.6 Hz, 3H), 0.91 (brd, *J* = 1.6 Hz, 3H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ = 130.5 (CH),127.1 (CH), 54.1 (CH),41.3 (CH_2), 40.6 (CH_3), 40.5 (CH_2), 33.1 (CH_2), 30.7 (CH_2), 24.7(CH), 22.9 (CH_3), 22.3 (CH_3); HRMS (ESI$^+$): *m*/*z* [*M* + Na]$^+$ calcd for $C_{11}H_{21}NO_2NaS$, 254.1191; found, 254.1191.

2-HEXYL-1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5F):

Following the general procedure (1), to a solution of amine 4b (50 mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0 °C were added heptanal (25 μL, 0.18 mmol,1.5 equiv) and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 25 mg of tetrahydroazepine 5f as a pale yellow oil (0.097 mmol, 81%). *R*f = 0.62 (*n*-hexane/EtOAc 70:30); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.76 (m, 1H), 5.68 (m, 1H), 3.95 (m, 1H), 3.68 (dt, *J* = 14.9 & 4.1 Hz, 1H), 3.22 (ddd, *J* =14.7, 11.5 & 3.0 Hz, 1H), 2.86 (s, 3H), 2.47 (m, 2H), 2.31 (m, 2H),1.66 (m, 1H), 1.52 (m, 1H), 1.27 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ = 130.5 (CH), 126.9 (CH),56.3 (CH), 40.7 (CH_2), 40.4 (CH_3), 32.7 (CH_2), 32.5 (CH_2), 31.8(CH), 30.8 (CH), 29.2 (CH), 26.2 (CH), 22.6 (CH), 14.1(CH_3); HRMS (ESI): *m*/*z* [*M* + Na] calcd for $C_{13}H_{25}NO_2NaS$: 282.1504; found, 282.1506.

2-(BUT-3-EN-1-YL)-1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZE- PINE (5G):

Following the general procedure (1), to a solution of amine 4b (50 mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0°C were added 4-pentenal (18 μL, 0.18mmol, 1.5 equiv) and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 19 mg of tetrahydroazepine5g as a pale yellow oil (0.084 mmol, 70%). *R*f = 0.51 (*n*-hexane/ EtOAc 70:30); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.79 (m, 2H), 5.68(m,1H), 5.04 (dq, *J* = 17.1 & 1.6 Hz, 1H), 4.98 (dd, *J* = 10.3 & 1.6Hz, 1H), 3.98 (dq, *J* = 7.0 & 4.2 Hz, 1H), 3.70 (dt, *J* =15.0 & 4.3 Hz,1H), 3.25 (ddd, *J* = 14.6, 11.4 & 3.0 Hz, 1H), 2.87 (s, 3H), 2.48 (m,2H), 2.33 (m, 2H), 2.04 (m, 2H),1.79 (m,1H), 1.63 (m,1H);^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ = 137.7 (CH), 130.6 (CH),126.7 (CH), 115.1(CH_2), 55.9 (CH), 40.8 (CH_2), 40.4 (CH_3), 32.4(CH_2), 31.8 (CH_2), 30.7 (CH_2), 30.3 (CH_2); HRMS (ESI$^+$): *m*/*z* [*M*+Na]$^+$ calcd for $C_{11}H_{19}NO_2NaS$, 252.1034; found, 252.1035.

2-BENZYL-1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5H):

Following the general procedure (1), to a solution of amine 4b (50mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0 °C were added phenylacetaldehyde (20 μL, 0.18 mmol, 1.5 equiv) and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 20 mg of tetrahydroazepine 5h as a pale yellow oil (0.076 mmol, 63%). *R*f =0.44 (*n*-hexane/EtOAc 70:30); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33−7.27 (m, 2H),7.25−7.19 (m, 3H), 5.81 (m, 1H), 5.69 (m, 1H), 4.25 (dq, *J* = 7.0 & 4.2 Hz, 1H), 3.64 (dt, *J* = 15.0 & 4.1 Hz, 1H), 3.28(ddd, *J* = 14.5, 11.4 & 2.9 Hz, 1H), 3.03 (dd, *J* = 13.4 & 7.0 Hz,1H), 2.82 (dd, *J* = 13.5 & 7.5 Hz, 1H), 2.56−2.44 (m,4H), 2.43−2.26 (m, 3H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ = 138.4 (C),130.7 (CH), 129.3 (2× CH), 128.5 (2×CH), 126.7 (CH), 126.6(CH), 58.5 (CH), 41.0 (CH_2), 39.3 (CH_3), 39.1 (CH_2), 32.4 (CH_2),30.9 (CH_2); HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{19}NO_2NaS$, 288.1034; found, 288.1036.

1-(METHYLSULFONYL)-2-PHENETHYL-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5I):

Following the general procedure (1), to a solution of amine 4b (50 mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0°C were added hydro cinnamaldehyde (26 μL,0.18 mmol, 1.5 equiv) and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 20 mg of tetrahydroazepine 5i as a paleyellow (0.072 mmol, 60%). *R*f = 0.39(*n*-hexane/EtOAc 70:30); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28 (m, 2H), 7.19 (m, 3H), 5.79 (m, 1H), 5.70 (m, 1H), 4.04 (dq, *J* = 6.9 &4.1 Hz, 1H),

3.74 (dt, *J* = 14.8 & 4.2 Hz, 1 Hz), 3.29 (ddd, *J* = 14.7,11.5 & 3.0 Hz, 1H), 2.86 (s, 3H), 2.61 (m, 2H), 2.51 (m, 2H), 2.39(m, 1H), 2.36−2.28 (m, 1H), 2.01 (m, 1H), 1.86 (m, 1H); $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ = 141.4 (C), 130.7 (CH), 128.4 (2×CH), 128.2 (2× CH), 126.6 (CH), 126.0 (CH), 56.0 (CH), 40.9(CH_2), 40.4 (CH_3), 34.3 (CH_2), 32.5 (CH_2), 30.6 (CH_2); HRMS(ESI^+): *m*/*z* [*M*+ Na]$^+$ calcd for $C_{15}H_{21}NO_2NaS$, 302.1191; found, 302.1193.

2-CYCLOHEXYL-1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZEPINE (5J):

Following the general procedure (1), to a solution of amine 4b (50 mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0°C were added cyclohexane carbox aldehyde (36μL, 0.30 mmol, 2.5 equiv) and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 16 mg of tetrahydroazepine 5j as a pale yellow oil (0.064 mmol, 53%). *R*f = 0.56 (*n*-hexane/EtOAc 70:30); ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.82 (m, 1H), 5.72(m, 1H), 3.72−3.66 (dt, *J* = 15.1 & 3.9 Hz, 1H), 3.65−3.60(m, 1H), 3.09 (ddd, *J* = 14.6, 11.9 & 2.5 Hz, 1H), 2.88 (s, 3H),2.53−2.44 (m, 2H), 2.44−2.38 (m, 1H), 2.25 (m, 1H), 1.78−1.63 (m, 6H),1.16 (m, 3H), 0.92 (m, 2H); $^{13}C\{^1H\}$-NMR($CDCl_3$, 125 MHz): δ =131.1 (CH), 127.5 (CH), 60.8 (CH), 41.3 (CH_2), 40.7 (CH_3), 37.2(CH), 30.8 (CH_2), 30.6(CH_2), 30.1 (CH_2), 29.3 (CH_2), 26.2(CH_2), 26.1 (CH_2), 26.0 (CH_2); HRMS (ESI^+): *m*/*z* [M + Na]$^+$calcd for $C_{13}H_{23}NO_2NaS$, 280.1347; found, 280.1348.

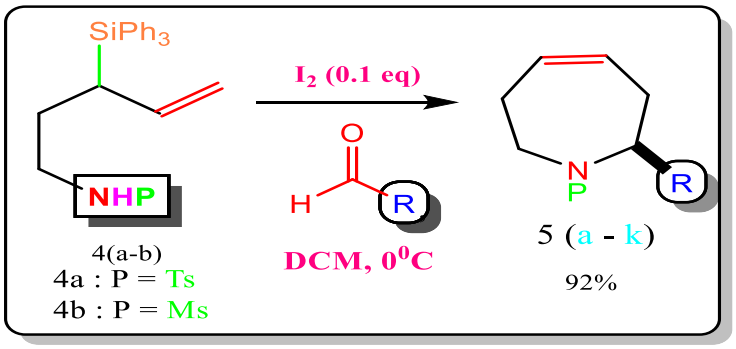
3-(1-(METHYLSULFONYL)-2,3,6,7-TETRAHYDRO-1H-AZEPINE-2-YL)PROPYL BENZOATE (5K):

Following the general procedure (1), to a solution of amine 4b (50 mg, 0.12 mmol, 1.0 equiv) in 1.2 mL of dry DCM (0.1 M) at 0 °C were added aldehyde 4- oxobutyl benzoate (34 mg, 0.18 mmol, 1.5 equiv), synthesized following the procedure described in the literature,[35] and I_2 (3.6 mg, 0.012 mmol, 0.1 equiv) to obtain 25 mg of tetrahydroazepine 5k as a pale yellow oil (0.074 mmol, 62%). *R*f= 0.29 (*n*-hexane/EtOAc 70:30); ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.03 (m, 2H), 7.56 (m, 1H), 7.44 (m,2H), 5.77 (m, 1H),5.68 (m, 1H), 4.3(m,2H), 4.03 (m, 1H), 3.72 (dt, *J* = 15.0 & 4.3Hz, 1H), 3.23 (ddd, *J* = 14.8, 11.6& 3.2 Hz, 1H), 2.88 (s, 3H), 2.55−2.43 (m, 2H), 2.41−2.27 (m, 2H), 1.89−1.73 (m, 3H), 1.71−1.60(m, 1H); $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): δ = 166.5 (C), 132.9(CH), 130.6 (CH), 130.2 (C), 129.5 (2× CH), 128.3 (2× CH),126.5(CH), 64.5 (CH_2), 56.0 (CH), 40.8 (CH_2), 40.4 (CH_3), 32.5(CH_2), 30.4 (CH_2), 29.2 (CH_2), 25.5 (CH_2); HRMS (ESI^+): *m*/*z* [M+ Na]$^+$ calcd for $C_{17}H_{23}NO_4NaS$, 360.1245; found, 360.1241.

RESULTS AND DISCUSSION:

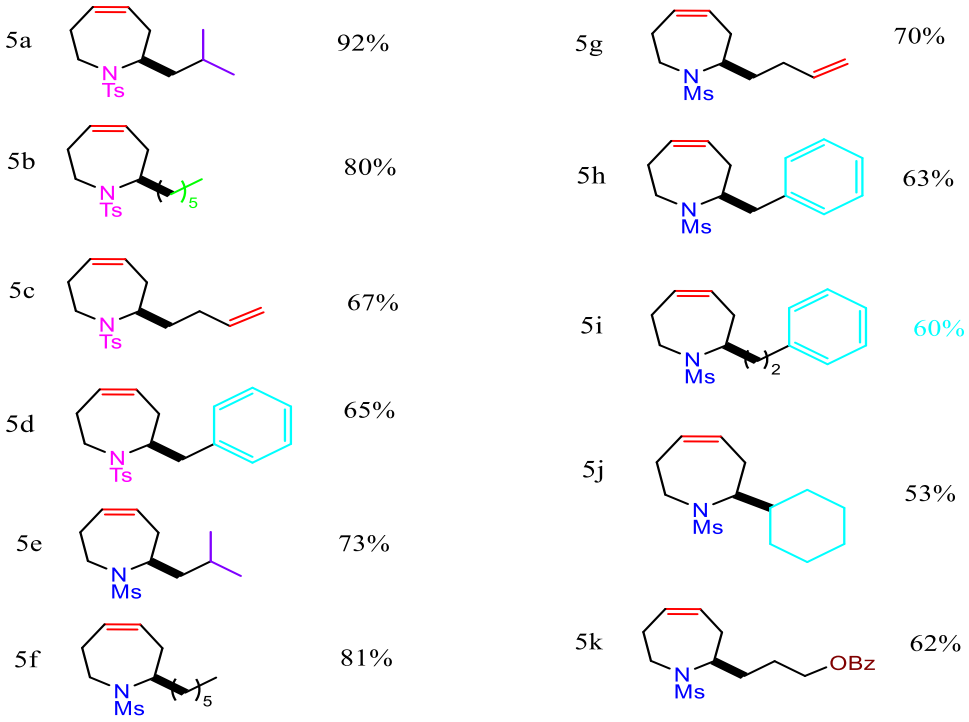
Based on our previous work, which allowed the diastereoselective synthesis of oxepenes through the Prins-Pinacol Cyclization (PPC) strategy, we decided to approach the nitrogen version and thus synthesize different tetrahydroazepines. If successful, it would constitute a direct and straightforward method that, using a sustainable Iron(III) catalyst, builds a C−N, C−C bond and an endocyclic double bond in a single reaction step (Scheme 1).

We started with the simplest tetrahydroazepines, that is, bearing a single substituent that comes from the correspondingaldehyde. 1-Amino-3-triphenylsilyl-4-pentenes (6a-b), precursors of the silyl aza-Prins cyclization (SAPC), could be accessed in three reaction steps (see Supporting Information). Next, the SAPC assays were performed with different sustainablemetal catalysts, based on our previous experience for oxepene synthesis, affording the desired tetrahydroazepine.The best results were obtained using substoichiometric amounts (0.1 equiv) of I_2, the yield and ratio being slightly higherwhen the former was used.



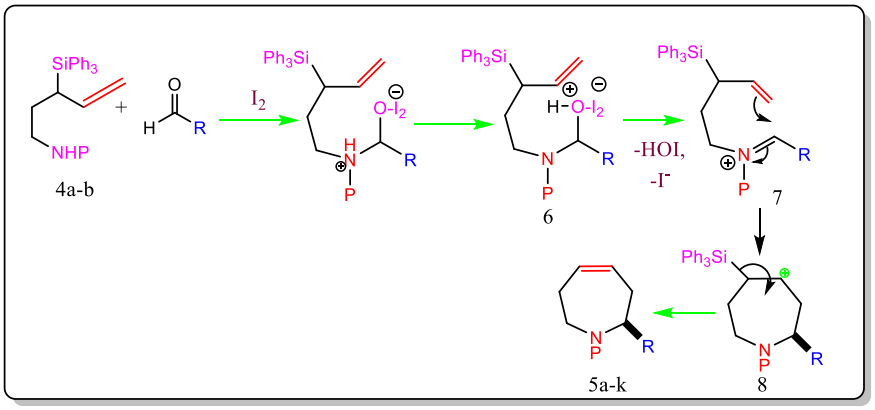
Scheme 1. Preparation of Unsaturated Seven-Membered Ring Azacycle

Table 1. ***Scope of Monosubstituted Tetrahydroazepines 7 Synthesis from SAPC***



[a]Reaction conditions: 4a−4b (0.20 mmol), aldehyde (0.24−0.40 mmol), I_2(0.02, mmol), dry DCM. Isolated yield. The conversion in all cases was 100%.
[b]2 g scale of 4a (4.0 mmol) afforded 60% yield of 5a (741 mg, 2.41 mmol).

Systems with aliphatic chains such as isovaleraldehyde and heptanal, with both tosylated and mesylated 1-amino-3-triphenylsilyl-4-pentenes 4a−b, respectively, gave yields of 92, 80, 73, and 81% (tetrahydroazepines 5a, 5b, 5e, and5f. Likewise, good results were observed with 4-pentenal, which led to tetrahydroazepines 5c and 5g with an endocyclic and an exocyclic olefin. Reaction with phenyl acetaldehyde and hydro cinnamaldehyde allowed a phenyl substituent to be incorporated into the heterocycles 5d, 5h, and 5i in 65, 63, and 60% yield, respectively. Our SAPC protocol also worked when using an aldehyde with a benzoate carrier chain, so future derivatizations of tetrahydroazepine 5k are feasible However, there was no reactivity with aromatic aldehydes.



Scheme 2. Mechanistic Proposal for SAPC

The mechanistic proposal for this transformation is based on that reported for the analogous process forming oxepenes (Scheme 2). First, a condensation occurs between the 1- amino-3-triphenylsilyl-4-pentene 4a and the Lewis acid− activated (Molecular Iodine) aldehyde. The zwitterionic species 6 leads to the amino-alcohol 13 and evolves to the iminium ion 7. This last species is intra molecularly trapped by the double bond, generating the carbocation 8, stabilized by the presence of the silyl group (β effect). Intermediate 8 undergoes a Peterson-type elimination, leading to tetrahydroazepines 5.

CONCLUSIONS:

we have developed an efficient and straightforward approach for the formation of mono and disubstituted seven-membered Δ^4-unsaturated azacycles. A variety of mono- and disubstituted tetrahydroazepines can beaccessed through SAPC, and in a single reaction step, C−C, C−N, and endocyclic C-C bonds are formed. In addition,it has been shown that the functionalization of the precursor amines determines their reactivity. Increasing the substitution of tetrahydroazepine up to three substituents is currently ongoing in our laboratory.

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