Mannich Cyclizations Promoted by Ce(IV) Oxidations of α-Aminocarboxylates and α-Stannylamines

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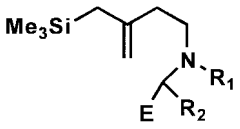
Mannich cyclizations are highly versatile reactions that are used often to prepare structurally complex nitrogen heterocycles. A number of approaches have been developed to initiate and terminate these processes.[1] Particularly elegant methodology for these purposes have come from studies by Overman and his coworkers.[2] One example is found in the transformation of the allysilane linked amine **1** to the functionalized piperidine **2** (Scheme 1).

Several years ago, we developed new strategies to initiate Mannich cyclizations, which are based on the use of α-silyamine and α-silylamide oxidations to generate the key iminium and N-acyliminium ion intermediates.[3] Formation of iminium ions in these reactions follows the sequential SET-desilylation pathway depicted in Scheme 2. Ensuing investigations showed that the oxidative Mannich cyclization methodology is applicable to stereoselective piperidine ring formation[4] and it serves as an alternative procedure to promote Pictet-Spengler cyclization.[5] Also, we found that this aproach can be extended to Prins cyclizations where key oxonium ion intermediates are generated by oxidation of α-stannyl ethers.[6]

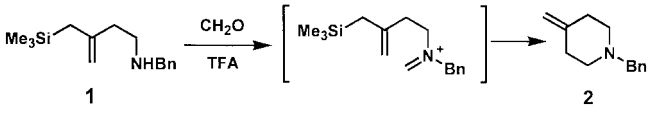
A limitation of this methodology, when applied to Mannich cyclizations, results from the shortage of methods to synthesize α-C-branched α-silylamine substrates **3** (E = $SiMe_3$, R_2 = alkyl or aryl).[7] In contemplating remedies to this problem, we relied on the results of our earlier mechanistic investigations of amine and amide SET-promoted oxidation reactions. By using laser flash photolysis techniques, we demonstrated that cation radicals derived by photoinduced one electron oxidation of α-aminocarboxylates undergo exceedingly fast, unimolecular decarboxylation to form α-amino radicals.[8] Since radicals of this type are in the pathway for oxidative iminium ion formation (Scheme 2), we expected that Ce(IV) oxidations of α-aminocarboxylates (**3**, E = CO_2Metal) would serve as an efficient procedure to promote Mannich cyclizations. This method would be flexibile since α-C-substituted α-aminocarboxylates can be readily prepared starting with natural and unnatural α-amino acids.



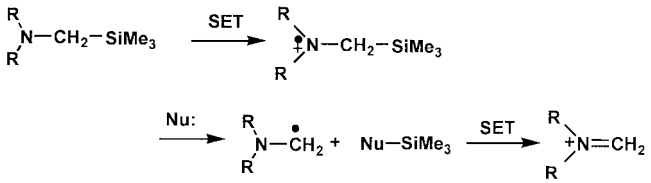
3

In a similar manner, a variety of high yielding sequences have been developed for synthesis of α-substituted α-stannyl amines.[9] Based on a consideration of oxidation potential data and the reactivity of intermediate amine cation radicals, we felt that α-stannyl amines (**3**, E = $SnBu_3$) would also be versatile substrates for Mannich cyclization reactions.

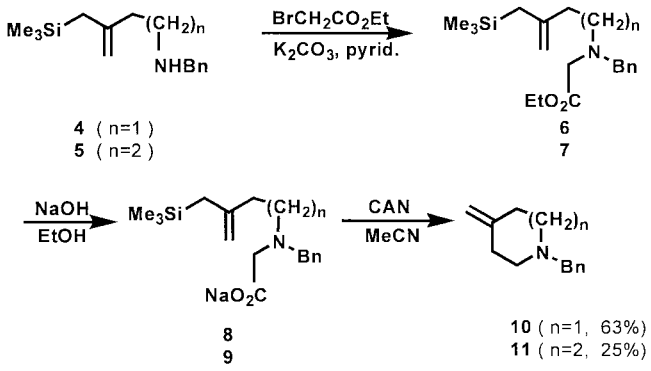
The foundations of these proposals have been evaluated in preliminary studies with the allysilane tethered α-aminocarboxylates **8** and **9** (Scheme 3) and α-stannylamine **12** (Scheme 4). The substrates for this study are prepared by using the routes outlined in Schemes 3 and 4. As anticipated, independent treatment of **8** and **9** with $Ce(NH_4)_2(NO_3)_6$ (3 molar excess) in anhydrous MeCN at 25 °C for 6h, followed by silica gel chromatography, affords the piperidine **10**



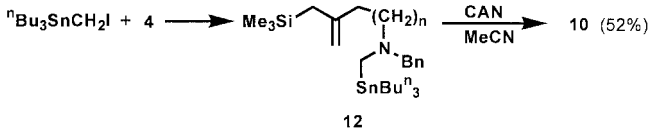
Scheme 1



Scheme 2



Scheme 3



Scheme 4

(63%) and hydroazepine **11** (25%), respectively. The efficiencies of these reactions are comparable to those recorded earlier for Ce(IV) oxidation of the corresponding α-silylamines (45-62%).[4] Likewise, CAN oxidation of α-stannyl amine **12** under similar conditions leads to isolation of piperidine **10** in a 52% yield.

The results of this preliminary effort demonstrate that Ce(IV) oxidations of α-aminocarboxylates and α-stannylamines serve as useful procedures to initiate Mannich cyclization reactions. Owing to the relative simplicity of substrate synthesis and the variety of conditions that can be employed for these oxidations (*e.g.*, photochemical,[11] electrochemical,[12] iodonium ion[13]), these approaches should be applicable to complex *N*-heterocycle synthesis.

Experimental Section

***N*-Benzyl-*N*-(trimethylsilylmethylalkenyl)amino Carboxylate Esters 6 and 7**. To independent solutions of the known[4] *N*-benzyl-*N*-(trimethylsilymethylalkenyl)amines **4** (3.38 g, 14.6 mmol) and, **5** (3.82 g, 14.6 mmol) and potassium carbonate (4.04 g, 29.3 mmol) in 70 mL of acetonitrile at 0 °C were slowly added a solution of ethylbromoacetate (1.78 mL, 16.0 mmol) in 40 mL of acetonitrile. The resulting mixtures was stirred for 30 min at 0 °C, pyridine (1.30 mL, 16.0 mmol) was added and the mixtures were stirred at 0 °C for 4h. The resulting solutions were filtered through celite and the filtrates were concentrated *in vacuo* to give a residues which were subjected to column chromatography (silica, 1 : 7 CH_2Cl_2 : hexane) to yield 3.03 g (62%) of **6** and 2.64 g (52%) of **7**, respectively.

6: ^{1}H-NMR ($CDCl_3$) 0.01 (s, 9H, $Si(CH_3)_3$), 1.26 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.51 (s, 2H, $C\underline{H}_2Si(CH_3)_3$), 2.18 (t, J = 7.7 Hz, 2H, $C\underline{H}_2CH_2N$), 2.80 (t, J = 7.7 Hz, 2H, $CH_2C\underline{H}_2N$), 3.33 (s, 2H, $NC\underline{H}_2CO_2$), 3.82 (s, 2H, $ArC\underline{H}_2N$), 4.16 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.57 (d, J = 12.5 Hz, 2H, vinyl CH_2), 7.25-7.37 (m, 5H, Ar-$\underline{H}$); ^{13}C-NMR ($CDCl_3$) 1.4 ($Si(CH_3)_3$), 14.3 ($OCH_2\underline{C}H_3$), 26.8 ($\underline{C}H_2Si(CH_3)_3$), 36.0 ($\underline{C}H_2CH_2N$), 52.5 ($CH_2\underline{C}H_2N$), 54.1 ($N\underline{C}H_2CO_2$), 58.0 ($Ar\underline{C}H_2N$), 60.2 ($O\underline{C}H_2CH_3$), 108 ($\underline{C}H_2$=C), 127,.0, 128.2 and 128.9 (aromatic), 138.9 (Ar, C-ipso), 145.5 (CH_2=$\underline{C}$), 171.4 (CO_2); MS (FAB), m/z (rel. intensity) 334 (M^++1, 23), 260 (10), 244 (6), 219 (3), 205 (100); HRMS(FAB), m/z 334.2213 ($C_{19}H_{32}NO_2Si$ requires 334.2202)

7: ^{1}H-NMR ($CDCl_3$) 0.04 (s, 9H, $Si(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.50 (s, 2H, $C\underline{H}_2Si(CH_3)_3$), 1.60-1.72 (m, 2H, $CH_2C\underline{H}_2CH_2N$), 1.96 (t, J = 7.7 Hz, 2H, $C\underline{H}_2CH_2CH_2N$), 2.66 (t, J = 7.3 Hz, 2H, $CH_2CH_2C\underline{H}_2N$), 3.31 (s, 2H, $NC\underline{H}_2CO_2$), 3.80 (s, 2H, $ArC\underline{H}_2N$), 4.14 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.53 (d, J = 14.7 Hz, 2H, vinyl CH_2), 7.25-7.36 (m, 5H, Ar-$\underline{H}$); ^{13}C-NMR ($CDCl_3$) 1.22 ($Si(CH_3)_3$), 14.4 ($OCH_2\underline{C}H_3$), 25.9 ($\underline{C}H_2Si(CH_3)_3$), 26.9 ($CH_2\underline{C}H_2CH_2N$), 35.8 ($\underline{C}H_2CH_2CH_2N$), 53.7 ($CH_2CH_2\underline{C}H_2N$), 54.2 ($N\underline{C}H_2CO_2$), 58.3 ($Ar\underline{C}H_2N$), 60.1 ($O\underline{C}H_2CH_3$), 107.1 ($\underline{C}H_2$=C), 127.0, 128.3 and 129.0 (aromatic), 139.2 (Ar, C-ipso), 147.3 (CH_2=$\underline{C}$), 171.5 (CO_2); MS (FAB), m/z (rel. intensity) 348 (M^++1, 20), 319 (4), 274 (39), 219 (15), 206 (27), 91 (100); HRMS (FAB), m/z 348.2335 ($C_{20}H_{34}NO_2Si$ requires 348.2359).

Sodium *N*-Benzyl-*N*-(trimethylsilylmethylalkenyl)amino Carboxylates 8 and 9. Independent solutions of the esters **6** and **7** (1.82 g, 5.47 mmol and 1.90 g, 7.47 mmol, respectively) and sodium hydroxide in 30 mL of ethanol were stirred and reflux for 10 h and then concentrated *in vacuo* to give residues which were crystallized (ethylacetate) to yield 1.20 g (67%) of **8** and 1.12 g (60%) of **9**.

8: mp 249-250 °C; ^{1}H-NMR ($CDCl_3$) 0.02 (s, 9H, $Si(CH_3)_3$), 1.47 (s, 2H, $C\underline{H}_2Si(CH_3)_3$), 2.18 (t, J = 8.1 Hz, 2H, $C\underline{H}_2CH_2N$), 2.68 (t, J = 8.1 Hz, 2H, $CH_2C\underline{H}_2N$), 3.10 (s, 2H, $ArC\underline{H}_2N$), 3.75 (s, 2H, $NC\underline{H}_2CO_2$), 4.51 (d, J = 12.5 Hz, 2H, vinyl $C\underline{H}_2$), 7.26-7.41 (m, 5H, Ar-$\underline{H}$); ^{13}C-NMR (CD_3OD) 0.78 ($Si(CH_3)_3$), 28.2 ($\underline{C}H_2Si(CH_3)_3$), 36.5 ($\underline{C}H_2CH_2N$), 54.4 ($CH_2\underline{C}H_2N$), 59.3 ($Ar\underline{C}H_2N$), 59.8 ($N\underline{C}H_2CO_2$), 108.8 ($\underline{C}H_2$=C), 128.4, 129.5 and 131.0 (aromatic), 140.2 (Ar, C-ipso), 147.6 (CH_2=$\underline{C}$), 177.6 (CO_2); MS(FAB), m/z (rel. intensity) 328 (M^++1, 12), 250 (12), 242 (100), 184 (14), 115 (28); HRMS (FAB), m/z 328.1721 ($C_{17}H_{27}NO_2NaSi$ requires 328.1709).

9: mp 247-248 °C; ^{1}H-NMR ($CDCl_3$) 0.02 (s, 9H, $Si(CH_3)_3$), 1.50 (s, 2H, $C\underline{H}_2Si(CH_3)_3$), 1.73-1.61 (m, 2H, $CH_2C\underline{H}_2CH_2N$), 1.91 (t, J = 7.3 Hz, 2H, $C\underline{H}_2CH_2CH_2N$), 2.68 (t, J = 7.9 Hz, 2H, $CH_2CH_2C\underline{H}_2N$), 3.07 (s, 2H, $NC\underline{H}_2CO_2$), 3.74 (s, 2H, $ArC\underline{H}_2N$), 4.51 (d, J = 20.2 Hz, 2H, vinyl CH_2), 7.26-7.38 (m, 5H, Ar-$\underline{H}$); ^{13}C-NMR ($CDCl_3$) 1.0 ($Si(CH_3)_3$), 26.2 ($\underline{C}H_2Si(CH_3)_3$), 27.6 ($CH_2\underline{C}H_2CH_2N$), 37.4 ($\underline{C}H_2CH_2CH_2N$), 55.2 ($CH_2CH_2\underline{C}H_2N$), 58.9 ($Ar\underline{C}H_2N$), 59.7 ($N\underline{C}H_2CO_2$), 107.9 ($\underline{C}H_2$=C), 128.1, 129.3 and 130.9 (aromatic), 140.1 (Ar, C-ipso), 148.7 (CH_2=$\underline{C}$), 179.4 (CO_2); MS (FAB), m/z (rel. intensity) 342 (M^++1, 32), 274 (21), 137 (21), 115 (30), 73 (100); HRMS (FAB), m/z 342.1864 ($C_{17}H_{27}NO_2NaSi$ requires 342.1865).

Ceric Ammonium Nitrate Promoted Oxidative Cyclizations of 8 and 9. Independent solutions of **8** (0.33 g, 1.00 mmol) and **9** (0.34 g, 1.00 mmol) and ceric ammonium nitrate (1.64 g, 3.00 mmol) in 40 mL of anhydrous acetonitrile were stirred at 25 °C for 6 h, diluted with 40 mL of methylene chloride and filtered through celite. Aqueous NaCl was added and the organic layers were separated, dried over sodium sulfate and concentrated *in vacuo* giving residues which were subjected to column chromatography (silica, 1 : 1 ethyl acetate : hexane) to give 118 mg (63%) of the known[4] piperidine **10** and 50 mg (25%) of the known[4] hydroazepine **11**.

***N*-Benzyl-*N*-(3-trimethylsilylmethylbutenyl)stannylmethylamine 12**. A solution of the known[4] anine **4** (1.73 g, 7.00 mmol) and potassium carbonate (2.00 g, 14.0 mmol) in 50 mL of acetonitrile was stirred at 25 °C for 30 min. Tri-*n*-butylstannylmethyl iodide (3.45 g, 8.00 mmol) in 30 mL of acetonitrile was slowly added to this solution at 0 °C. The

resulting mixture was stirred at 0 °C for 30 min. Pyridine (0.65 mL, 8.00 mmol) was added and the mixture was stirred at 0 °C for 6 h, filtered through celite and filtrate was concentrated *in vacuo* to give a residue which was subjected to thin layer chromatography (silica, 1 : 9 CH_2Cl_2 : hexane) to yield 1.12 g (29%) of **12**.

12: ^{1}H-NMR ($CDCl_3$) 0.02 (s, 9H, $Si(CH_3)_3$), 0.86-0.95 (m, 15H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$), 1.22-1.40 (m, 6H, $CH_3C\underline{H}_2$-CH_2CH_2Sn), 1.43 (s, 2H, $C\underline{H}_2Si(CH_3)_3$), 1.45-1.58 (m, 6H, $CH_3CH_2C\underline{H}_2CH_2Sn$), 2.17 (t, J = 7.7 Hz, 2H, $C\underline{H}_2CH_2N$), 2.47 (t, J = 7.7 Hz, 2H, $CH_2C\underline{H}_2N$), 2.65 (s, 2H, $NC\underline{H}_2Sn$), 3.48 (s, 2H, $ArC\underline{H}_2N$), 4.56 (d, J = 8.8 Hz, 2H, vinyl CH_2), 7.24-7.33 (m, 5H, Ar-H)

Ceric Ammonium Nitrate Promoted Oxidative Cyclization of 12. A solutions of **12** (0.52 g, 0.94 mmol) ceric ammonium nitrate (1.56 g, 2.82 mmol) in 35 mL of anhydrous acetonitrile were stirred at 25 °C for 18 h, diluted with 20 mL of methylene chloride and filtered through celite. Aqueous NaCl was added and the organic layers were separated, dried over sodium sulfate and concentrated *in vacuo* giving residues which were subjected to column chromatography (silica, 1 : 1 ethyl acetate : hexane) to give 92 mg (52%) of the known[4] piperidine **10**.

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