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Ring opening of 2-phenylazetidines with allylsilanes

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Abstract—N-Activated 2-phenylazetidines were opened regioselectively at the benzylic carbon with various allylsilanes or propargylsilane in the presence of $BF_3{\cdot}Et_2O$, providing amino olefins, precursors of biomolecules such as phenyl-homo-kainoids.

Over the years the reactivity and/or use of aziridines and azetidines have been addressed by several groups.[1–13] Shortly we and others have reported on new reactivities of N-activated 2-phenylaziridines and 2-phenylazetidines towards various nucleophiles. These three and four membered heterocycles have been identified, respectively, as masked 1,3 and 1,4 dipoles in the presence of selected dipolarophiles.[14–18] Recently we focused on the reactivity of 2-phenylazetidines (**1a**–**b**) as electrophiles towards various allylsilanes, and report here our preliminary results on the successful ring opening of the azetidines **1a**–**b** together with relevant applications towards the preparation of biomolecules.

The two starting azetidines **1a** (NTs) and **1b** (NNos), selected for our study can be readily obtained from styrene following reported procedures.[19] The reaction of **1a** or **1b** with trimethylallylsilane **2** was performed at room temperature in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (Scheme 1). After 30 min reaction time, no starting azetidine was apparent on TLC. From the reaction mixture two adducts could be isolated by column chromatography, and identified as **3a**–**a′**, a mixture of inseparable silylated piperidines, and **4a** the open chain allylated adduct in a ratio **3a**–**a′**/**4a**: 1/4. This first experiment established that azetidine **1a** is ring opened with allylsilane at the benzylic carbon via a S_E2' pathway where azetidine **1a** is the electrophilic substrate (Eq. 1). The piperidine adducts **3a**–**a′** is resulting from an internal collapse of the silicon stabilized β-carbenium on the transient amide anion. A similar result was observed with the corresponding aziridine.[7] It is noteworthy that the silylated piperidines **3a**–**a′** could be transformed quantitatively into **4a** via a brief heating in a TBAF solution. Interestingly if the initial reaction mixture was aged overnight only the allylated adduct **4a** was isolated, in situ desilylation being promoted by the fluorinated Lewis acid. This observation will simplify the purification step, because at that time the allylated adducts were our targets for further applications (vide infra). Very similar results in reaction rates and yields were obtained with **1b**, the nosyl activated azetidine, in this case we isolated the adducts **3b**–**b′** and **4b**, respectively, the piperidine and the allylated adducts. The mixture of piperidines **3b**–**b′** is cleanly converted to **4b** by a TBAF treatment or more conveniently with the overnight ageing procedure. As anticipated the tosyl or nosyl activations in **1a** or **1b** are similarly effective for the azetidine ring opening with allylsilane **2**. Conversely when different Lewis acids ($TiCl_4$, $MgBr_2$, $ZnBr_2$) were experimented, we observed severe contaminations with byproducts, mainly halogenated adducts at the benzyl carbon. Therefore $BF_3{\cdot}Et_2O$ was favoured as a good compromise between electronic assistance and intrinsic reactivity. The temperature seemed not to be a critical factor but we found that the ideal conditions are to mix azetidine (**1a**) and allylsilane (**2**) at −78 °C, followed by dropwise addition of the Lewis acid. The mixture was then left to warm up to room temperature overnight. The remarkable regioselectivity in the ring opening at the benzylic carbon is best explained by the release of the cyclic constraint and the polarization of the benzylic C–N bond with the Lewis acid.[20]

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✠ Philippe Klotz died suddenly on June 9, 2005.

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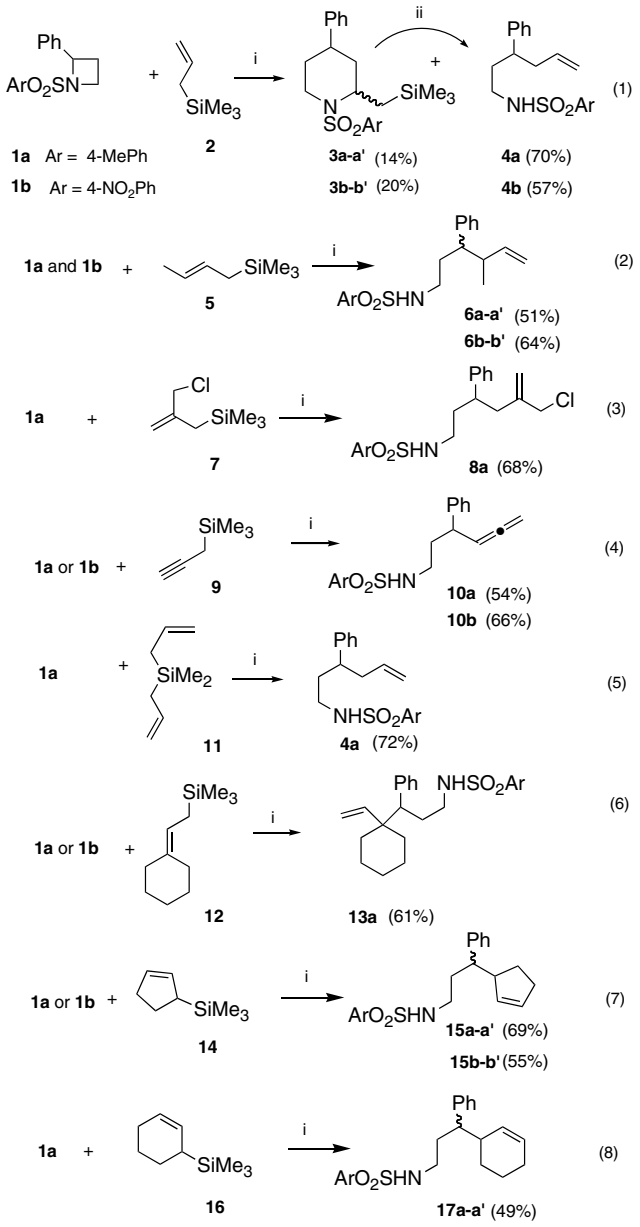
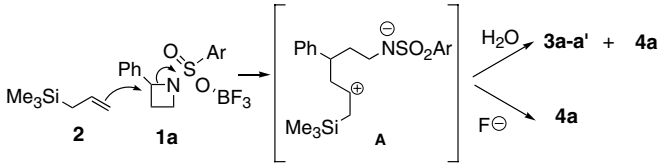


Scheme 1. Reagents and conditions: (i) BF_3Et_2O, CH_2Cl_2 from −78 °C to rt; (ii) TBAF in THF reflux 1 h.

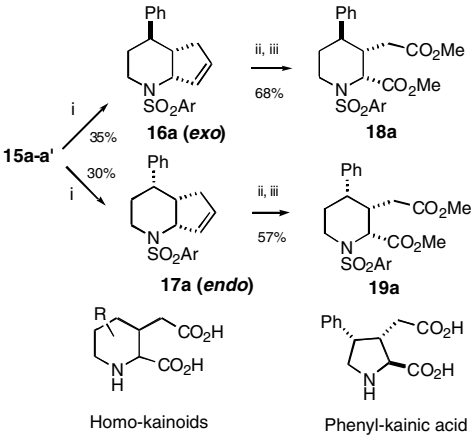
Next the reactivity of easily accessible allylsilanes namely the *E* crotylsilane (**5**), or 2-chloromethyl-3-trimethylsilylpropene (**7**) towards **1a**–**b** was explored (Eqs. 2 and 3). In each case the expected transformations were operative and delivered the allylated adducts **6a**–**a′**, **6b**–**b′**, mixtures of diastereomers (1/1 ratio), and **8a**. In a complementary study, we decided to oppose propargylsilane (**9**) to azetidine **1a** and **1b** (Eq. 4). Surprisingly even if propargylsilane is known to be less nucleophilic than allylsilane, the allenyl adducts **10a** and **10b** were isolated in acceptable yields. These data demonstrated that azetidines of type **1a** or **1b** are of great value as masked electrophiles.

To explain the regioselective ring opening of azetidines **1a**–**b**, with allylsilanes or propargylsilane, we propose the mechanism depicted in Scheme 2. The Lewis acid ($BF_3{\cdot}Et_2O$) may have a double function (i) first in coordinating the sulfonyl appendage that stretch out the benzylic C–N bond leading to the electrophilic substitution; (ii) second in stabilizing the transient amide in intermediate **A**, which can then evolve to a mixture of **3a** and **4a**, or solely to **4a**, respectively, if the reaction is quenched after 1 h, or left overnight (Scheme 2). Then we decided to prepare more complex allylsilanes **11**, **12**, **14** and **16**[21] in order to extend the scope of the reaction and to apply it to the synthesis of scaffolds occurring in biomolecules (Eqs. 5–8). Each reaction with these allylsilanes deserves special comments. With bis-allylsilane **11** only adduct **4a** was obtained, the expected cooperativity and/or double addition of the two allylsilane residues embedded in **11** was not detected. Considering the peculiar reactivity of azetidine **1a** with methylenecyclohexane,[15] allylsilane **11** is combining two potential nucleophilic centres one on the alkene and one on the allylsilane. Therefore a multi-path reaction was awaited for **11** towards **1a**, via two putative carbenium ions on the β- or γ-carbon next to the silicon atom.

Indeed the reaction proceeded, but only adduct **13a** could be characterize, accounting that a carbenium stabilized by the silicon atom ranked over a tertiary one. Similarly as in our work with aziridines azetidines **1a** and **1b** were treated with cyclopentenyl- (**14**) and cyclohexenyltrimethysilane (**16**), the allylation worked efficiently, delivering inseparable mixtures (always in 1/1 ratio) of **15a**–**a′**, **15b**–**b′** and **17a**–**a′**, respectively, in 65% and 70% yield. Indeed we found a practical and efficient reaction for the regioselective ring opening of azetidines with allylsilanes. As we are currently interested in the preparation of kainoids,[22] we considered that **15a**–**a′** may constitute ideal starting materials for the obtention of homo-kainoids (Scheme 3). Kainoids have been used as successful probes to understand the excitatory functions of glutamic acid in the mammalian central nervous system.[23–25] But there is still a demand for more selective ligands towards the kainate receptors, especially for antagonists, and homo-kainoids may be potential candidates. Indeed following our previous reported sequence for the synthesis of phenyl-kainic acid, we used **15a**–**a′** towards the formal synthesis of



Scheme 2. Proposed mechanism for the regioselective opening of azetidine **1a**.



Scheme 3. Reagents and conditions: (i) $Pd(OAc)_2$, O_2, DMSO, 40 °C, 4 h, separation via chromatography; (ii) $RuCl_3$, $NaIO_4$; (iii) CH_2N_2 in Et_2O.

phenyl-homo-kainic acid. Using the hydroamination reaction assisted by Pd(II),[26] the mixture of diastereomers (**15a**–**a′**) was converted into bicyclic adducts **16a** and **17a**, which could be separated by column chromatography and identified by extensive NMR (COSY and NOESY experiments) to be, respectively, the *exo* (**16a**) and *endo* (**17a**) adducts with a cis ring junction. Finally, a single crystal X-ray analysis of **17a** confirmed our NMR analysis.[27] Then each diastereomer could be transformed into the fully protected phenyl-homokainoids **18a**–**19a** in a two step sequence: Sharpless oxidation and diazomethane esterification, awaiting final deprotection.[28,29]

In conclusion in this work on N-activated azetidines, we have demonstrated that the regioselective ring opening with allysilanes is realized at the benzylic carbon under smooth reaction conditions in a good yielding sequence. Our work is probably giving a new vitality to the azetidine chemistry, indeed some of the described adducts have a real chemical potential. We are currently using the above methodology towards the synthesis of biological active compounds.

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28. *Typical experimental conditions for the preparation of* **4a**. A mixture of azetidine **1a** (100 mg, 0.35 mmol) and trimethylallylsilane **2** (85 µl, 0.53 mmol, 1 equiv) in CH_2Cl_2 (5 ml) is cooled at −78 °C and a solution of $BF_3{\cdot}Et_2O$ (100 µl, 0.8 mmol, 2.3 equiv) in CH_2Cl_2 (1 ml) is added dropwise. After 1 h, H_2O (2 ml) was added and the mixture was left overnight at room temperature. More water was added and the organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with heptane/Et_2O 8:2 to yield **4a** (70%).
29. Selected physical data: Compound **4a** mp 76–78 °C; IR (KBr) ν (cm^{-1}) 3270, 3090, 1320, 1170; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.68 (d, J 8.5 Hz, 2H) 7.38–7.12 (m, 5H), 7.11–7.02 (m, 2H), 5.68–5.52 (m, 1H), 4.95 (d, J 6 Hz, 1H), 4.73 (br s, 1H), 2.74–2.85 (m, 2H), 4.86–4.83 (m, 1H), 2.62–2.58 (m, 1H), 2.42 (s, 3H), 2.29 (dt, J 7.0 and 1.5 Hz, 2H), 1.97–1.60 (m, 2H); ^{13}C NMR (75 Hz, $CDCl_3$, 25 °C) δ 143.7, 143.4, 137.1, 136.4, 129.8, 128.7,

127.7, 127.2, 126.6, 116.6, 43.1, 41.6, 41.3, 35.6, 21.7; *m*/*z* (FAB-MS) [M+H$^+$] 330.

Compound **13a**, waxy solid; IR (KBr) *v* (cm^{-1}) 3360, 1640, 1600, 1170; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.64 (d, *J* 8.3 Hz, 2H), 7.34–7.11 (m, 5H), 7.08–6.97 (m, 2H), 5.49 (dd, *J* 11 and 17.7 Hz, 1H), 5.25 (dd, *J* 1.5 and 11.3 Hz, 1H), 4.87 (dd, *J* 1.5 and 18 Hz, 1H), 4.28 (m, 1H), 2.81–2.68 (m, 1H), 2.64–2.53 (m, 1H), 2.43 (s, 3H), 2.44–2.36 (m, 1H), 2.05–1.87 (m, 1H), 1.85–1.04 (m, 11H); ^{13}C NMR (75 Hz, $CDCl_3$, 25 °C) δ 143.6, 143, 140.8, 137.4, 130, 128.2, 127.5, 126.9, 116.4, 54.2, 42.4, 38.9, 29.6, 26.8, 22.6, 21.9; *m*/*z* (FAB-MS) [M+H$^+$] 398.

Compound **16a** (*exo*), mp 123–125 °C; IR (KBr) *v* (cm^{-1}) 3080, 1610, 1500, 1175; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.76 (d, *J* 8 Hz, 2H), 7.20–7.36 (m, 5H), 7.09 (d, *J* 7 Hz, 2H), 5.91 (m, 1H), 5.57 (m, 1H), 4.79 (d, *J* 5.5 Hz, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 2.90 (m, 1H), 2.76 (m, 1H), 2.46 (s, 3H), 2.25 (m, 1H), 1.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) d 21.6, 23.0, 32, 38.6, 41.0, 62.9, 126.4, 127. 3, 127.5, 128.5, 129.7, 135.3, 137, 143.2, 143.3; *m*/*z* (FAB-MS (M+H$^+$).

Compound **17a** (*endo*) mp 85–88 °C; IR (KBr) *v* cm^{-1}) 3080, 1615, 1520, 1180; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) d 7.68 (d, *J* 8.5 Hz, 2H), 7.35 (d, *J* 8 Hz, 2H), 7.18–7.31 (m, 3H), 7.08 (d, *J* 7 Hz, 2H), 5.80 (m, 1H), 5.38 (m, 1H), 5.07 (s, 1H), 3.97 (d, *J* 13 Hz, 1H), 2.91 (td, *J* 12 and 3 Hz, 1H), 2.47 (s, 3H), 2.38 (m, 2H), 2.17 (dd, *J* 165 and 2.5 Hz, 1H), 1.96 (dd, *J* 16 and 2.5 Hz, 1H), 1.59 (m, 2H); 13C NMR (75 MHz, $CDCl_3$, 25 °C) d 21.6, 23, 32, 38.6, 41, 62.9, 1216.4, 127.3, 127.5, 128.5, 129.7, 135.3, 137, 143.2, 143.3; *m*/*z* (FAB-MS) 354 (M+H).

Compound **18a** waxy solid; IR (KBr) *v* (cm^{-1}) 3015, 2950, 1710, 1580, 1170; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.82–8.73 (m, 2H), 7.51–7.43 (m, 2H), 7.37–7.18 (m, 3H), 7.17–6.99 (m, 2H), 4.61 (d, *J* 5.5 Hz, 1H), 4.18–4.01 (m, 1H), 3.62 (s, 3H), 3.42 (s, 3H), 3.58–3.39 (m, 1H), 3.18–2.89 (m, 2H), 2.79–2.58 (m, 1H), 2.45 (s, 3H), 2.39–2.24 (m, 1H), 2.19–2.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 33.1, 33.8, 40.8, 49.4, 50.5, 51.9, 52.2, 59.0, 64.7, 124.3, 124.5, 127.2, 127.4, 128.3, 128.5, 128.8, 140, 140.7, 145.4, 152.8, 170.2, 172.5; *m*/*z* (FAB-MS) 446 (M+H$^+$).

Compound **19a** waxy solid; IR (KBr) *v* (cm^{-1}) 3010, 2980, 1715, 1510, 1175; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.88 (d, *J* 8.6, 2H), 7.83 (d, *J* 9.0, 2H), 7.32–7.23 (m, 3H), 7.07 (d, *J* 6.7, 2H), 5.13 (d, *J* 4.9 Hz, 1H), 4.02 (d, *J* 2.6, 1H), 3.71–3.38 (m, 7H), 2.72–2.52 (m, 2H), 2.47 (s, 3H) 2.17–1.99 (m, 2H), 1.97–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 28.5, 33.8, 35.2, 39.9, 49.0, 41.9, 43.5, 52.4, 54.1, 126.5, 126.8, 127.1, 127.7, 128.0, 128.5, 128.9, 143.1, 144, 144.6, 155.1, 171.9, 172.5; *m*/*z* (FAB-MS) 446 (M+H$^+$).