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Synthesis of oxygen-containing heterocyclic compounds via α-chloro-δ-(trimethylsilyloxy)imines

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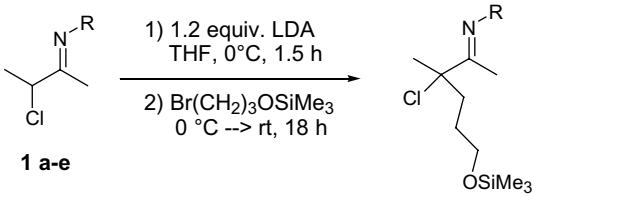
Abstract—Treatment of α-chloro-δ-(trimethylsilyloxy)ketimines, obtained by regiospecific alkylation of α-chloroketimines with 3-bromo-1-(trimethylsilyloxy)propane, with bases and nucleophiles leads to a variety of oxygen-containing heterocycles, including tetrahydrofurans and tetrahydropyrans.

The combination of a carbon nitrogen double bond, a halogen atom and a protected alcohol function in one molecule offers the potential to provide access to a variety of functionalized heterocyclic compounds, for example, cyclic ethers. Previously, we have reported the synthesis of 2,3-disubstitued oxolanes from α-chlorinated-γ-(trimethylsilyloxy)ketimines.[1] In the present paper, the reactivity of α-chloro-δ-(trimethylsilyloxy)ketimines, bearing one more C-atom in the alkyl chain, towards nucleophiles and bases is investigated. These reactions should provide the corresponding 6-membered rings, that is aminotetrahydropyrans, which are related to aminosugars, displaying important biological activities, such as activity against a broad range of tumurs and soft tissue sarcomas.[2]

α-Chloro-δ-(trimethylsilyloxy)ketimines **2a**–**e** were synthesized by regiospecific alkylation[3] of α-chloroketimines[4] **1a**–**e** with 3-bromo-1-(trimethylsilyloxy)propane via the intermediacy of 3-chloro-1-azaallylic anions, generated with lithium diisopropylamide in tetrahydrofuran (Scheme 1). These new α,δ-difunctionalized ketimines **2** were purified by vacuum distillation (Table 1) and have a reasonable shelf life, provided they are well protected from moisture, that is under a nitrogen atmosphere in the refrigerator (−20 °C).



Scheme 1.

Treatment of α-chloroketimines **2a**,**b** (R = *i*-Pr, *t*-Bu) with two molar equivalents of potassium *t*-butoxide in tetrahydrofuran at room temperature yielded almost exclusively (90–95%) 2-(*N*-alkylacetimidoyl)-2-methyltetrahydrofurans **4a**,**b** (Table 2, entries 1 and 3). The latter compounds resulted from deprotection of the trimethylsilylether and subsequent intramolecular nucleophilic substitution of the α-chloro atom (Scheme 2). Thus, it seems that this method has a potential for the synthesis of 2-imidoyl- and 2-acyltetrahydrofurans. 2-Acetimidoyl-2-methyloxolanes **4** were hydrolyzed with water in a two-phase system with ether at room temperature for 4 h to give 2-acetyl-2-methyloxolane **5** in 90–94% yield. It should be mentioned that the 2-acetimidoyloxolanes **4** are extremely sensitive to hydrolysis

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Table 1. Synthesis of α-chloro-δ-(trimethylsilyloxy)ketimines **2**[a]

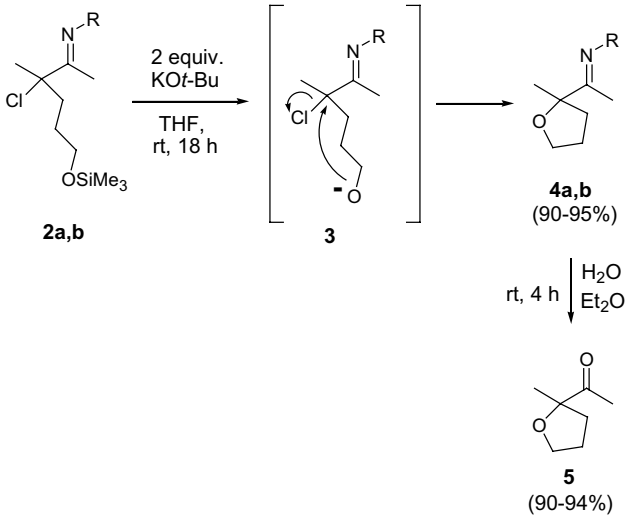
Substrate	R	Equivalents of bromide[b]	Yield (%)[c]	Bp (°C/mmHg)
1a	*i*-Pr	1.1	62	74–80/0.07
1b	*t*-Bu	1.1	70	79–88/0.05
1c	Cyclohex	1.05	48	87–93/0.01
1d	*i*-Bu	1.1	14[d]	70–73/0.02
1e	*s*-Bu	1.1	60	67–72/0.04

[a] Deprotonation: 1.2 equiv LDA, THF, 0 °C, 1.5 h; addition of the bromide; 0 °C to room temperature, 18 h.
[b] 3-Bromo-1-(trimethylsilyloxy)propane.
[c] Yield after distillation.
[d] Spectral data of **2d**: see Ref. 5.

Table 2. Reaction of α-chloro-δ-(trimethylsilyloxy)ketimines **2** with bases and nucleophiles

Entry	R	Reaction conditions	Yield (%)[a]	**4** (%)[b]	**6** (%)[b]	**7** (%)[b]
1	*i*-Pr	2 equiv KO*t*-Bu, THF, rt, 18 h	100	90[c]	—	—
2	*i*-Pr	2 equiv KO*t*-Bu, THF, Δ, 1 h	100	81	19	—
3	*t*-Bu	2 equiv KO*t*-Bu, THF, rt, 18 h	100	95	3	—
4	*t*-Bu	2 equiv KO*t*-Bu, THF, Δ, 1 h	100	73	27	—
5	Cyclohex	2 equiv KO*t*-Bu, THF, Δ, 1 h 30 min	76	81	9	—
6	*t*-Bu	2 equiv KO*t*-Bu, THF, Δ, 2 h	90	43	43	—
7	*s*-Bu	2 equiv KO*t*-Bu, THF, Δ, 1 h 30 min	80	74[e]	14[f]	—
8	*i*-Pr	2 equiv K_2CO_3, MeOH, Δ, 1 h	100	18	2	80[d]
9	*i*-Pr	4 equiv NaOMe (2 N), MeOH, Δ, 1 h 30 min	100	85	—	14
10	*s*-Bu	3 equiv K_2CO_3, MeOH, Δ, 2 h 30 min	97	18	—	66
11	*s*-Bu	MeOH, Δ, 2 h 30 min	95	26	—	67[g]

[a] Yield, crude material.
[b] GLC.
[c] Distilled: yield = 72%; bp 65–70 °C/11 mmHg.
[d] Distilled: yield = 65%; bp 30–33 °C/0.07 mmHg; one stereoisomer.
[e] Spectral data of **4d**: see Ref. 10a.
[f] Spectral data of **6d**: see Ref. 10b.
[g] Isolated after treatment with K_2CO_3.

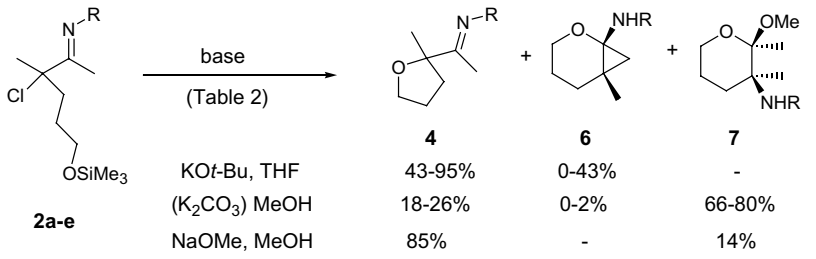


Scheme 2.

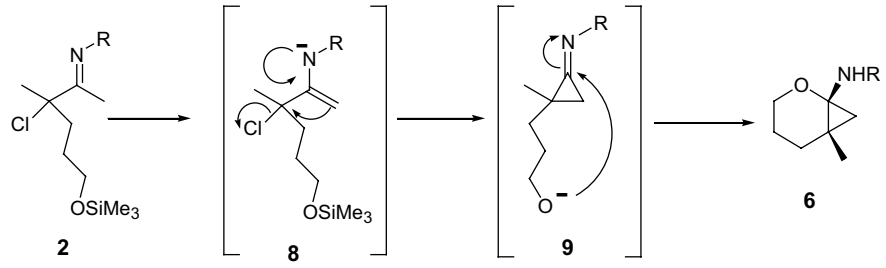
of the imino function, yielding 2-acetyl-2-methyltetrahydrofuran **5**. This chemical property seems to be a general phenomenon of α-alkoxyimines.[6]

Refluxing the functionalized α-chloroketimines **2** with the same strong base (KO*t*-Bu) in THF for 1–2 h resulted in 9–43% of *cis*-1-(*N*-alkylamino)-6-methyl-2-oxabicyclo[4.1.0]heptanes **6** in addition to 43–81% of the above discussed 2-imidoylsubstituted oxolanes **4** (Scheme 3, Table 2, entries 2, 4–7). From a mechanistic point of view, the formation of the 2-oxabicyclo[4.1.0]heptanes **6** is explained by a Favorskii-type rearrangement, followed by intramolecular trapping of the intermediate cyclopropylideneamines[7] **9** by the desilylated alcohol function (Scheme 4).[8] It was previously demonstrated that a strong base at higher temperature is required for the Favorskii rearrangement of tertiary α-chloroketimines.[9]

On the other hand, *cis*-3-(*N*-alkylamino)-2,3-dimethyl-2-methoxy-tetrahydropyran derivatives **7**, as well as oxolanes **4**, were formed by reaction of the δ-(trimethylsilyloxy)ketimines **2** with methanol under reflux in the presence of bases such as sodium methoxide or potassium carbonate (Table 2, entries 8–11). 2-Alkoxy-3-aminotetrahydropyrans **7** were obtained in pure form by distillation of the crude reaction mixture under reduced pressure, as demonstrated for the *N*-isopropyl derivative **7a** (Table 2; entry 8), which was isolated in 65% yield. Closely related aminotetrahydropyranyl ethers, which have been prepared as aminosugar and acetylcholine analogues, showed acetylcholine esterase inhibiting activity.[11] Other 2-alkoxy-3-aminopyranoses are cysteine protease inhibitors, useful in treating Alzheimer's disease.[12]



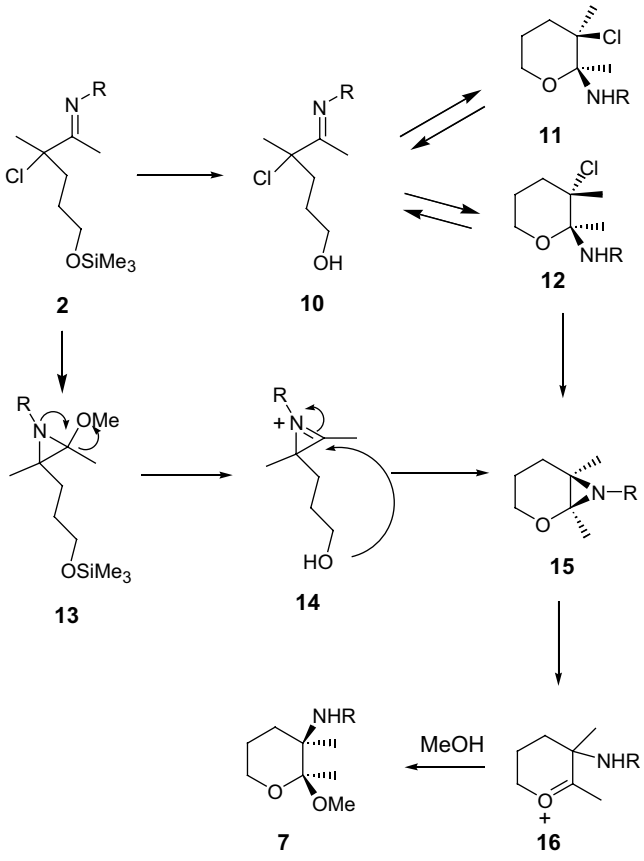
Scheme 3.



Scheme 4.

The first step of the reaction mechanism, leading to tetrahydropyranyl compounds **7** is interpreted as an oxygen desilylation and addition of the alcohol function across the imino bond to give tetrahydropyranyl ethers **11** and **12** or, alternatively, attack of methanol (or methoxide) across the imino bond with subsequent ring closure to α-alkoxyaziridines **13** (Scheme 5). In the former case, the formation of tetrahydropyranyl ethers **11** and **12** is subject to reversible processes. However, only the *trans*-isomer **12** is able to give a ring closure to the bicyclic aziridine **15**, which suffers ring opening to the oxonium ion **16**. This reactive species undergoes a stereospecific attack of the alcohol to provide *cis*-3-alkylamino-2-methoxytetrahydropyrans **7**. The stereospecificity of this process stems from hydrogen bond guided approach of the alcohol with the alkylamino group. The plausible mechanism via 2-methoxyaziridines **13** demands a *O*-desilylation process and the generation of azirinium ion **14**. The latter reactive species undergoes intramolecular addition of the alcohol to the iminium function providing the same bicyclic aziridine **15** as in the first mechanistic route. Both mechanistic proposals are equally plausible and supported by known reactions with α-haloimines. As a consequence, it might be that both routes are operative. This conversion into 2,3-disubstituted tetrahydropyrans bears similarity with the formation of 2-alkoxy-3-alkylaminotetrahydrofurans from α-chloro-γ-(trimethylsilyloxy)ketimines.[1a] Of course, in the latter case, the competitive intramolecular nucleophilic substitution of the α-chloro atom, with generation of imidoyloxetanes, did not occur because of ring strain.

In conclusion, α-chloro-δ-(trimethylsilyloxy)ketimines **2** can be converted selectively to 2-imidoyltetrahydrofurans **4** or 2-alkoxy-3-aminotetrahydropyrans **7**, depending on the reaction conditions. 2-Oxabicyclo[3.1.0]hexanes **6** are side products (Favorskii rearrangement products) when a sterically hindered base is used.



Scheme 5.

Acknowledgements

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5. *N*-[3-Chloro-3-methyl-6-(trimethylsilyloxy)-2-hexylidene]-2-methylpropylamine **2d**: ^{1}H NMR ($CDCl_3$) δ 0.11 (9H, s, $SiMe_3$), 0.93 (6H, d, $J = 6.6$ Hz, $CHMe_2$), 1.24–1.79 (2H, m, $CH_2CH_2CH_2$), 1.68 (3H, s, MeCCl), 1.89–1.95 (1H, m, CH), 1.95 (3H, s, MeC=N), 1.97–2.07 (2H, m, CH_2CCl), 3.06 (2H, d, $J = 6.6$ Hz), 3.54–3.63 (2H, m, CH_2O); ^{13}C NMR ($CDCl_3$) δ −0.47 (Me_3), 13.8 (*Me*C=N), 20.70 and 20.74 (Me_2), 27.47 (*Me*CCl), 28.50 ($CH_2CH_2CH_2$), 29.74 (CH), 38.54 (CH_2CCl), 59.28 (=NCH_2), 62.46 (CH_2O), 76.55 (CCl), 167.67 (C=N); IR (NaCl): 1657 cm^{-1} (C=N); MS (70 eV): *m*/*z* (%): 291/3 (M^+, 2), 161/3 (35), 162 (6), 98 (58), 73 (19), 57 (100). Anal. Calcd for $C_{14}H_{30}ClNOSi$: C, 57.60; H, 10.36; N, 4.80. Found: C, 57.51; H, 10.33; N, 4.89.
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10. (a) *2*-Methyl-2-[*N*-(2-methylpropyl)acetimidoyl]tetrahydrofuran **4d**: ^{1}H NMR ($CDCl_3$) δ 0.91 and 0.92 (each 3H, d, $J = 6.4$ Hz, $CHMe_2$), 1.33 (3H, s, MeCO), 1.52–1.77 (3H, m, OCH_2CH_2CHCH), 1.83 (3H, s, MeC=N), 1.86–1.97 (1H, m, CH), 2.50–2.59 (1H, m, OCH_2CH_2CHCH), 3.06 (2H, d, $J = 6.93$ Hz, NCH_2), 3.69–3.91 (2H, m, CH_2O); ^{13}C NMR ($CDCl_3$) δ 12.45 (*Me*C=N), 20.72 ($CHMe_2$), 24.98 (*Me*CO), 25.84 (OCH_2CH_2), 29.76 (CH), 34.77 ($OCH_2CH_2CH_2$), 59.19 (=NCH_2), 67.73 (CH_2O), 87.28 (CO), 171.97 (C=N); IR (NaCl): 1660 cm^{-1} (C=N); MS (70 eV): *m*/*z* (%): 183 (M^+, 15), 168 (32), 140 (20), 85 (20), 69 (17), 57 (100). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.94; H, 11.51; N, 7.52; (b) *cis*-6-Methyl-1-[*N*-(2-methylpropyl)amino]-2-oxabicyclo[4,1,0]heptane **6d**: ^{1}H NMR ($CDCl_3$) δ 0.49 and 0.74 (2H, each d, $J = 4.62$ Hz, MeC*H*C*H*CN), 0.89 and 0.91 (each 3H, each d, $J = 6.6$ Hz, Me_2), 1.23 (3H, s, Me), 1.58–1.70 (2H, m, CH_2CH_2O), 1.87–2.01 (3H, m, NCH_2CH), 2.38–2.74 (2H, m, $CH_2CH_2CH_2O$), 3.34–3.73 (2H, m, CH_2O); ^{13}C NMR ($CDCl_3$) δ 20.70 and 20.81 (Me_2), 22.57 (*Me*C), 23.36 and 28.86 ($CH_2CH_2CH_2O$), 24.15 (*C*Me), 24.55 (CCH_2CN), 29.15 (CH), 53.21 (NCH_2), 65.78 (CH_2O); IR (NaCl): 3310 cm^{-1} (NH), 1120, 1075 and 1030 cm^{-1}; MS (70 eV): *m*/*z* (%): 183 (M^+, 13), 168 (32), 112 (14), 98 (14), 83 (19), 57 (100). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.18; H, 11.42; N, 7.52.
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