Stereospecific aziridination of olefins *via* electrophile-induced cyclization of γ,δ-unsaturated imines and subsequent hydrolytic rearrangement†

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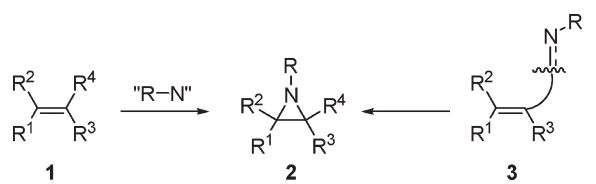
The olefinic bond of γ,δ-unsaturated aldehydes underwent a net aziridination through electrophile-induced cyclization and subsequent rearrangement of the resulting cyclic iminium salts: this methodology allows the stereospecific introduction of aziridine moieties into cyclic systems.

Due to the well-known synthetic flexibility of aziridines,[1] the aziridination of olefins **1** towards azaheterocycles **2** is a highly useful transformation in synthetic organic chemistry (Scheme 1).[2] One-step procedures include, among others, the reaction of olefins with nitrenes,[2,3] with *N*(,*N*)-(di)halogenated amines,[4] with palladium complexes and bromine,[5] with [*N*-(4-toluenesulfonyl)imino]-phenyliodinane[6] and related species.[7] The formation of aziridines from olefins and nitrenes, the latter generally synthesized from azides, by α-elimination reactions and by oxidation of primary amines, is well studied.[2a,8] When azides serve as precursors, the alternative of 1,3-dipolar cycloaddition must be envisaged. The aziridination works well for certain aminonitrenes, in which the amino group apparently stabilizes the singlet state, but the nature of the amino substituent is crucial.[2a] Additionally, such *N*-amino aziridines have most often an undesirable substituent which is difficult to remove or replace by more general substituents.[2a,8] An alternative method for the synthesis of aziridines from olefins consists of the regio- and stereospecific reaction with halo azides or iodo isocyanate, the resulting β-halo azides[9] and β-iodo isocyanates[10] being ring closed subsequently.

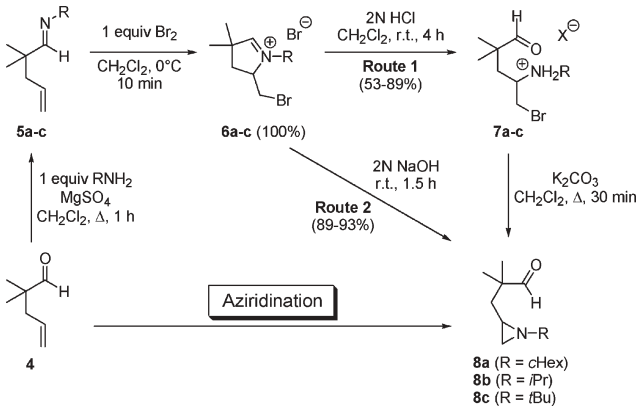
In the present report, a new and efficient method is disclosed for the intramolecular aziridination of olefins by transfer of alkylamine moieties (N–R) from a remote position in the molecule (see compound **3**) to the alkene, the net result being the conversion of an unactivated carbon–carbon double bond into an aziridine **2** (Scheme 1). This approach offers a suitable alternative for the aziridination of olefins by means of copper-catalyzed reactions of intermediate oxaziridines.[11]



Scheme 1

N-(2,2-Dimethyl-4-penten-1-ylidene)amines **5**, prepared from 2,2-dimethyl-4-pentenal **4**[12] upon treatment with 1 equiv. of a primary amine in dichloromethane in the presence of $MgSO_4$, react very smoothly with bromine in dichloromethane at 0 °C for 10 min to afford cyclic iminium salts **6** in essentially quantitative yields (Scheme 2).[13] The functionalized 1-pyrrolinium salts **6** are easily converted into aziridines **8** by a two-step process, involving (i) hydrolysis of the iminium function with aqueous hydrogen chloride in a two-phase system with dichloromethane as a co-solvent, and (ii) ring closure of the resulting intermediate β-bromoammonium salts **7** with potassium carbonate in dichloromethane (Scheme 2).[14] The functionalized aziridines **8** were isolated, after distillation, in 53–89% overall yields from the starting α-allylisobutyraldimines **5** (Scheme 2, Route 1). This initially followed route could be improved considerably by treatment of the iminium salts **6** with aqueous sodium hydroxide, directly affording the rearranged end-products **8** in 89–93% yield (Scheme 2, Route 2).

The net result of this rearrangement constitutes a transfer of an alkylamino group to the olefinic double bond with concomitant generation of an aldehyde functionality. Because of the fact that enimine **5** is easily accessible from 2,2-dimethyl-4-pentenal **4** by a simple imination procedure in nearly quantitative yields, the net transformation of pentenal **4** to aziridines **8** comprises an aziridination of the olefinic double bond by primary amines under mild conditions, *ie via* electrophile-induced cyclization of enimines **5** and subsequent hydrolysis and ring closure.



Scheme 2

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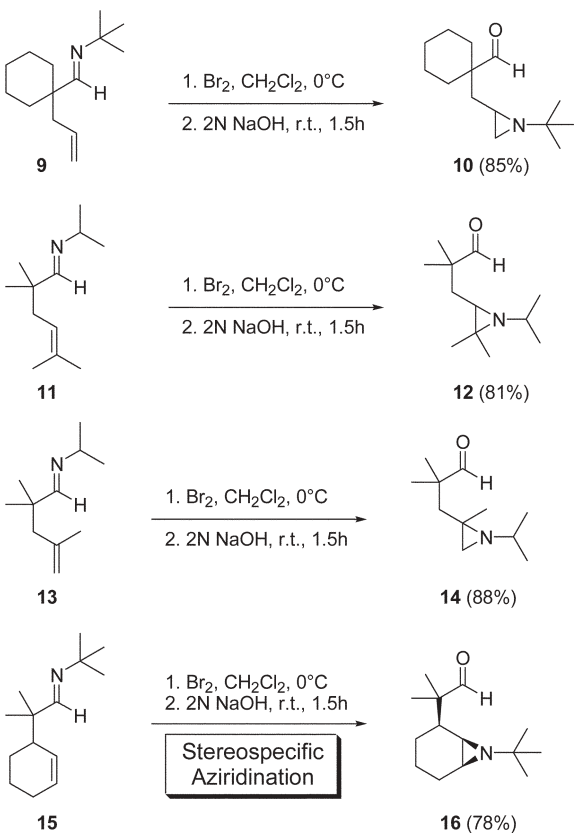
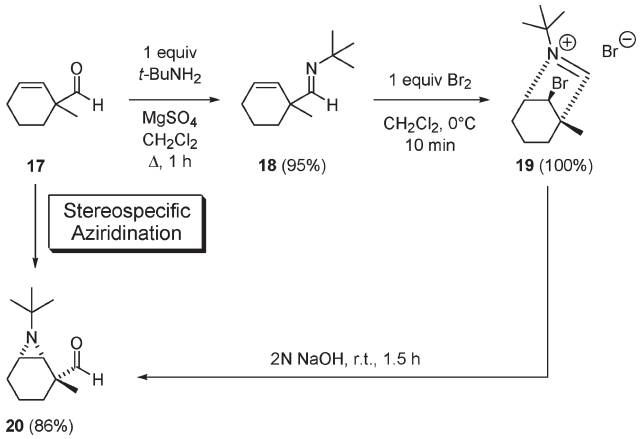
This intramolecular aziridination was extended to other imines such as α-allylcyclohexanecarbaldimine **9**, isobutyraldimines **11** and **13**, and α-(2-cyclohexen-1-yl)isobutyraldimine **15**, which were, after electrophile-induced cyclization with bromine and hydrolytic alkylamino transfer, converted into aziridines **10**, **12**, **14** and **16** (Scheme 3). Due to the nature of the cyclization process, the conversion of **15** into 7-azabicyclo[4.1.0]heptane derivative **16**[15] occurs stereospecifically with the aziridino moiety positioned *cis* with respect to the alkyl substituent.

In order to underline the synthetic potential of this stereospecific construction of aziridines *via* an intramolecular rearrangement process, 1-methyl-2-cyclohexenecarbaldehyde **17** was converted to β,γ-unsaturated imine **18** upon treatment with 1 equiv. of *t*-$BuNH_2$ in dichloromethane in the presence of $MgSO_4$. The latter imine underwent smooth electrophile-induced cyclization with bromine to afford the bicyclic iminium salt **19** in quantitative yield (Scheme 4). Alkaline hydrolysis of this iminium salt **19** with aqueous sodium hydroxide at room temperature produced the rearranged 7-aza-7-*t*-butyl-2-methylbicyclo[4.1.0]heptane-2-carbaldehyde **20** in 86% yield (Scheme 4). Again, the conversion of **17** into **20** consists of a net aziridination process in which the aziridine moiety is stereospecifically positioned *cis* with respect to the carbaldehyde group. This stereospecific aziridination is a useful synthetic procedure for the functionalization of cycloalkenes due to the chemical behaviour of (non-activated) aziridines in ring opening reactions.[16]

In conclusion, a novel aziridination of olefins *via* electrophile-induced cyclization of unsaturated imines towards cyclic iminium salts and subsequent hydrolytic rearrangement has been presented.



Scheme 3



Scheme 4

By means of this methodology, a stereospecific introduction of aziridine moieties in cyclic systems can be accomplished in an efficient and straightforward manner.

Notes and references

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14 General procedure (Route 1). To a stirred solution of imine **5** (34 mmol) in dry dichloromethane (60 mL) at 0 °C was added slowly an equimolar amount of bromine (5.44 g, 34 mmol) in dichloromethane (20 mL). After stirring for 10 min at 0 °C, an aqueous hydrogen chloride solution (170 mL, 2 M) was added, and the resulting mixture was stirred for 4 h at room temperature. Then, the reaction mixture was basified by adding an aqueous sodium hydroxide solution (4 M), and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried (K_2CO_3), followed by filtration of the drying agent and evaporation of the solvent. The residue was dissolved in dry dichloromethane (80 mL), K_2CO_3 (10 g) was added and the mixture was heated under reflux for 30 minutes. After filtration and evaporation of the solvent in vacuo, distillation of the crude reaction mixture yielded the anticipated aziridines **8**. Spectroscopic data of 3-(1-cyclohexylaziridin-2-yl)-2,2-dimethylpropanal **8a**. Yield 53%. Bp. 75–77 °C/0.075 mmHg. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.10 (3H, s, Me); 1.13 (3H, s, Me); 1.0–2.0 (16H, m, C_6H_{11}, NCH_2, CH_2); 9.40 ppm (1H, s, HC=O). ^{13}C NMR (20 MHz, $CDCl_3$): δ 21.36, 22.13 (Me_2); 24.90 (CH_2); 26.19 (CH_2); 32.49 (NCH_2); 33.00 (NCH); 41.52 (CH_2CMe_2); 45.78 (CMe_2); 69.24 (NCH); 204.63 ppm (HC=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1718. MS (70 eV) *m*/*z* (%): 209 (M^+, 3); 191 (32); 166 (18); 138 (55); 124 (18); 110 (46); 109 (45); 108 (55); 99 (27); 99 (27); 98 (27); 94 (18); 83 (23); 70 (18); 67 (18); 57(18); 56 (100); 55 (45). Anal. Calcd for $C_{13}H_{23}NO$: C 74.59%; H 11.08%. Found: C 74.41%; H 11.19%.

15 General procedure (Route 2). To a stirred solution of imine **9**, **11**, **13** or **15** (1 mmol) in dry dichloromethane (3 mL) at 0 °C was added slowly an equimolar amount of bromine (0.16 g, 1 mmol) in dichloromethane (2 mL). After stirring for 10 min at 0 °C, the solvent was evaporated *in vacuo*. Subsequently, an aqueous sodium hydroxide solution (5 mL, 2 M) was added to the residual oil, and the mixture was stirred for 1.5 h at room temperature. The aqueous reaction mixture was then extracted with chloroform (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$. After filtration and evaporation, the nearly pure reaction mixture was purified by Kugelrohr distillation, yielding pure aziridine **10**, **12**, **14** or **16**. Spectroscopic data of 2-(7-*t*-butyl-7-azabicyclo[4.1.0]hept-2-yl)-2-methylpropanal **16**. Yield 78%. Bp. 85 °C/0.2 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (9H, s, Me_3); 1.14 and 1.17 (2 × 3H, 2 × s, Me_2); 1.08–1.90 (9H, m, $NCH(CH_2)_3CHCH$); 9.67 ppm (1H, s, HC=O). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.53, 20.24 (Me_2); 20.99, 22.91, 24.37 ($(CH_2)_3$); 27.03 (Me_3); 28.20 (CH); 32.78 and 42.18 (2 × NCH); 48.81 (CMe_2); 53.48 (CMe_3); 206.95 ppm (HC=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1718. MS (70 eV) *m*/*z* (%): no M^+; 195 (11); 194 (8); 152 (23); 138 (13); 96 (100); 67 (12); 58 (19); 57 (19); 56 (14); 55 (12). Anal. Calcd for $C_{14}H_{25}NO$: C 75.28%; H 11.28%. Found: C 75.17%; H 11.40%.

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