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Synthesis of N-Methoxy and N-H Aziridines from Alkenes

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Key Words: Aziridine; N-Methoxyaziridine; N-Methoxycaprolactam; Dimethoxyamine; Nitrenium Ion

Abstract: Electron-rich alkenes are converted into N-methoxyaziridines by treatment with $HN(OCH_3)_2$ and trimethylsilyl triflate. Reduction with Li/ammonia affords the N-H aziridines.

Recent publications by Rudchenko et al. report that N-methoxyaziridines can be prepared in a single step from alkenes using $HN(OCH_3)_2/BF_3$ in ether.[1] This reagent acts as a source of methoxynitrenium tetrafluoroborate, a highly reactive electrophile. Thus, N-methoxyaziridinium salts **1a** and **1b** are obtained from tetramethylethylene and cis-2-butene, respectively, and the corresponding N-methoxyaziridines **2a** and **2b** are isolated in 26% and 20% yield after neutralization with ammonia and distillation.

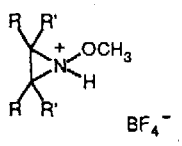
We have been interested in the direct aziridination of alkenes in connection with previous work in our laboratory.[2] Compared to other direct aziridinations,[3] the Rudchenko method is appealing because of its simplicity. However, we were not able to achieve practical yields of the N-methoxyaziridines[4] using the original procedure with cyclooctene as the test substrate. Some improvement in yield was observed in dichloromethane vs. ether, and by adding $HN(OCH_3)_2$ slowly to the alkene and BF_3•etherate, but extensive optimization gave no more than 50% of the methoxyaziridine after neutralization of salts.

The BF_3•etherate activation method is somewhat complicated by the disproportionation process that must occur on the way to the tetrafluoroborate salt **3a**. To circumvent this potential problem, we examined several other activating agents. A marginal improvement in the yield of aziridine was obtained using methanesulfonic acid in place of BF_3•etherate, but trimethylsilyl triflate (TMSOTf) proved to be the best activating agent. A stoichiometry of 1.2:1 of TMSOTf : $HN(OCH_3)_2$ gave practical results, presumably via the initial formation of a triflate salt **3b**. After neutralization with dilute NaOH, the crude N-methoxyaziridine **4** was recovered in 86% yield (ca. 95% pure by NMR). Purification by chromatography (77% isolated) or by distillation (64% isolated overall) afforded **4** that was >98% pure according to NMR analysis.

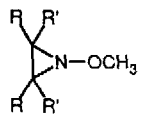
The optimized procedure[5] works with other simple alkenes, but there are limitations in the functionality that can be present. Thus, reasonable yields of the N-methoxyaziridines **5** or **6** were obtained with cis or trans 2-octenes (78% and 74%, respectively), and the aziridine ester **7** was prepared in somewhat lower yield from methyl crotonate (51%).[4] However, complex product mixtures resulted with allyl or crotyl alcohols, or with cyclohexenone as the substrates. Furthermore, no conversion to methoxyaziridine was detected with the

electron deficient substrate dimethyl fumarate.

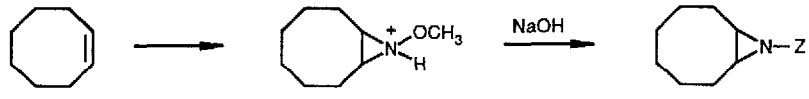
Further transformation from the N-methoxyaziridine **4** into N-H aziridine **8**[3d] is possible using Na/NH_3 reduction. The two-step sequence from $HN(OCH_3)_2$ to **8** proceeds in ca. 50% overall yield based on the dimethoxyamine reagent, and provides access to aziridines with overall retention of alkene stereochemistry.



1a R= R'= CH_3
1b R= CH_3, R'= H

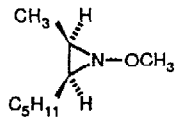


2a R= R'= CH_3
2b R= CH_3, R'= H



3a X= BF_4^-
3b X= $CF_3SO_3^-$

4 Z= OCH_3
8 Z= H



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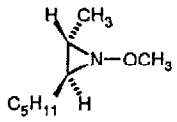

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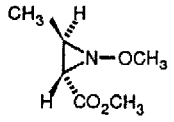

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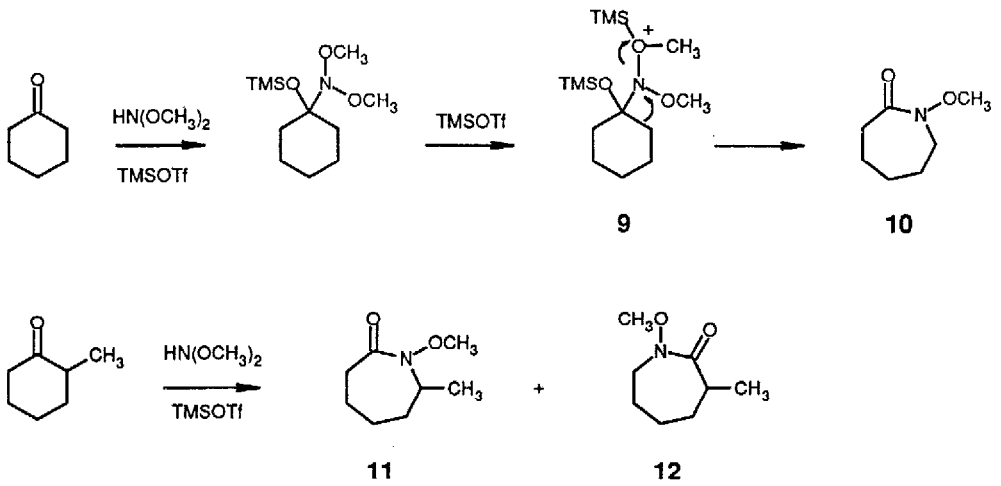
In the course of these studies, 1-trimethylsiloxycyclohexene was treated with $HN(OCH_3)_2$ and TMSOTf in an attempt to prepare α-(N-methoxyamino)cyclohexanone or other aziridine-derived products. Instead of the expected α-methoxyamino ketone, we isolated N-methoxycaprolactam **10**, a substance previously obtained from reaction of cyclohexanone with H_2NOCH_3/tert-C_4H_9-OCl.[6] Apparently, this product is formed via silyl enol ether cleavage. Thus, a similar experiment using $HN(OCH_3)_2$/TMSOTf with cyclohexanone as the starting material gave **10** in 84% yield, and a reaction catalyzed by methanesulfonic acid afforded 92% of **10** (isolated) after 18 hours at room temperature in CH_2Cl_2. This reaction is related mechanistically to the Beckmann rearrangement, and probably involves carbon migration via **9** as shown. A similar reaction was observed starting with 2-methylcyclohexanone, resulting in a 2:1 mixture of regioisomers **11** and **12**.



In summary, the modified Rudchenko method is competitive with other direct aziridination procedures in overall yield.[3] The procedure is believed to generate the reactive N-methoxynitrenium ion CH_3O-N-H^+ $F_3CSO_3^-$ *in situ*,[7] and allows stereospecific aziridination of electron-rich alkenes. Ketone functionality can interfere with the reaction due to a competing Beckmann-type rearrangement. However, this latter process provides access to N-methoxy lactams that are otherwise difficult to prepare.

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4. All N-methoxyaziridines were characterized by satisfactory high resolution MS (molecular ion) and by NMR spectroscopy. Each was observed as a mixture of two N-methoxy invertomers with characteristic N-methoxy chemical shifts as follows ($CDCl_3$, δ): **4**, 3.51 and 3.52 ppm; **5**, 3.51 and 3.53 ppm; **6**, 3.53 and 3.54 ppm; **7**, 3.53 and 3.60 ppm.

5. A 50 mL flask was equipped with a dropping funnel and was charged with cyclooctene (2.5 mL, 19.5 mmol) and dichloromethane (20 mL). After cooling to -14 °C (ice-ethanol bath), trimethylsilyl triflate (Aldrich; 3.0 mL, 15.5 mmol) was added. A solution of $HN(OCH_3)_2$ (1.0 g, 13 mmol)[1] in dichloromethane (5 mL) was then added slowly to the stirred mixture over a period of 30 min (CAUTION! the neat reagent must not be used! Contact with acids or with other electrophilic catalysts can result in an exothermic decomposition. Solutions of dimethoxyamine can be handled safely, but the rate of addition must be controlled). After addition was complete, the solution was allowed to warm to room temperature and was stirred 1 h. The dichloromethane was then removed (aspirator), the residue was stirred with NaOH (1 M, 20 mL), and the organic products were extracted with dichloromethane (3 x 10 mL). Drying (Na_2SO_4), solvent removal, and distillation gave **4** (1.28 g, 64%, b.p. 90-93 °C at 30 mm Hg), > 98% pure by NMR. Chromatographic purification over silica gel gave better recovery (77%) of **4**, estimated to be 98% pure by NMR spectroscopy.

   Reduction of **4** to **8**. Liquid ammonia (5 mL) was condensed into a 25 mL flask at -78 °C. A solution of **4** (0.08 g, 0.52 mmol) in THF (4 mL) was added and was followed by the addition of sodium metal (0.1 g, 4.3 mmol). The blue mixture was allowed to warm to -30 °C while stirring and was kept at this temperature for 1 h. A solution of ethanol in hexane (1.5 mL, 1:3) was added to quench the reaction, and the mixture was allowed to warm to room temperature as the ammonia was vented into the hood using a nitrogen stream. Aqueous ether workup followed by chromatography over silica gel (elution with chloroform:ethanol, 20:1) gave **8**[3d] (0.045 g, 70%), > 97% pure by NMR.

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