Direct NH-aziridination of α,β-unsaturated ketones

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1-Aryl-α,β-unsaturated ketones were directly aziridinated, *N*-unsubstituted, in a one-pot reaction with satisfactory yields by *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate, a nitrogen–nitrogen ylide precursor, in the presence of sodium hydride.

Introduction

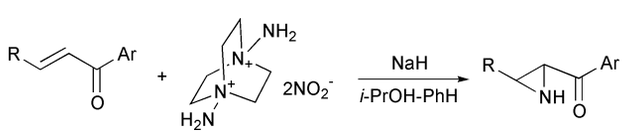
Aziridines are very important intermediates in organic synthesis[1] and have found widespread use in asymmetric synthesis.[2] A variety of methods for the preparation of aziridines have been developed.[3] However, most of the methods produce *N*-substituted aziridines, such as *N*-arenesulfonyl, alkoxycarbonyl, or aryl substituted aziridines. Removal of these substituents is carried out, in most cases, under harsh conditions. Only a few methods have been reported for the direct preparation of *N*-unsubstituted aziridines until now. The early preparative routes to *N*-unsubstituted aziridines involved cycloelimination processes in which one, sometimes two, bonds were formed directly to the nitrogen atom. These routes include two intramolecular cyclization pathways involving either nucleophilic displacement by the amine nitrogen on the β-carbon in the cycloelimination of β-haloamines, β-aminohydrosulfate esters and their equivalents, or nucleophilic displacement by a β-carbanionic center (rendered suitably acidic by the presence of a contiguous carbonyl function) on the amine nitrogen with concomitant departure of a suitable leaving group (alkoxy, trialkylammonium or halide).[3a] As an alternative route, both 1,2-dihalides[4] and α-halo-α,β-unsaturated carbonyl compounds[5] react with ammonia to give *N*-unsubstituted aziridines. It was also reported that oximes could be converted into *N*-unsubstituted aziridines by treatment with Grignard reagents[6] or by reduction with lithium aluminium hydride in certain cases.[7] 3,3-Pentamethyleneoxaziridine can transfer its NH group to electron-deficient olefins to give *N*-unsubstituted aziridines in low yields and with a limited group of substrates.[8] 3,3-Pentamethylenediaziridine can only transfer its NH group to the C=C double bond of α,β-unsaturated *N*,*N*-disubstituted amides.[9]

Nitrogen ylides are another kind of potential NH transfer agent. Free sulfimides $HN{=}SR_2$, sulfur–nitrogen ylides, are used for the direct synthesis of *N*-unsubstituted aziridines. However, the yields are unsatisfactory and enaminoketones are obtained as major byproducts in moderate yields.[10] A direct aziridination of chalcone is needed in order to prepare *N*-unsubstituted aziridines in satisfactory yields by an amine imide, which is formed *in situ* from *N*,*N*-dimethylhydrazine and oxirane (propene oxide).[11] The search for nitrogen transfer agents for the direct aziridination of olefins to prepare *N*-unsubstituted aziridines is currently an attractive field of research.

Results and discussion

An amine imide, as a type of nitrogen–nitrogen ylide, is an effective NH source for *N*-unsubstituted aziridination of electron-deficient olefins. Hydrazinium nitrates are readily prepared from tertiary amines and hydroxylamine-*O*-sulfonic acid.[12] We rationalize that hydrazinium nitrates could become amine imides, which could aziridinate olefins with electron-withdrawing groups, after reaction with bases. We therefore decided to investigate this aziridination and undertake a survey of various olefins to ascertain the generality of the reaction.

A hydrazinium nitrate, *N*,*N*′-diamino-1,4-diazoniabicyclo-[2.2.2]octane dinitrate, was prepared from 1,4-diazabicyclo[2.2.2]octane (DABCO) and hydroxylamine-*O*-sulfonic acid in the presence of calcium oxide and calcium nitrate according to the literature procedure.[12] A solution of equimolar *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate and chalcone in a mixture of isopropanol and benzene (2 : 1, v/v) was added portionwise to sodium hydride over 30 min while stirring at room temperature. Chalcone was converted to aziridine in a yield of 63%. After the ratio of *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate and chalcone was increased to 2 : 1 and the reaction was carried out at 0 °C, the aziridinated product was obtained in 95% yield (Scheme 1). A



Scheme 1

variety of chalcone derivatives were also aziridinated in high yields following the same procedure except for nitro substituted chalcones (15–17%, Table 1 entries 12 and 13). For aziridination of aliphatic α,β-unsaturated ketones (but-3-en-2-one and cyclohex-2-en-1-one) with *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate, no aziridination products were isolated. Although 4-phenylbut-3-en-2-one did not give the desired aziridine product in this aziridination, 1-arylbut-2-en-1-ones [1-phenylbut-2-en-1-one and 1-(4-methoxyphenyl)but-2-en-1-one] were aziridinated in almost quantitative yields. The results are summarized in Table 1.[11,13,14] A comparison of the coupling constants of their methine protons with those reported in the literature[10b,15] demonstrates that the aziridines have a *trans*-configuration.

Attempts to aziridinate electron-rich olefins, styrene and allylbenzene, with *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]-octane dinitrate were unsuccessful indicating that this aziridination process is not a nitrene addition to an alkene, but a nitrogen ylide addition to an α,β-unsaturated ketone. It is assumed that *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate could convert into a diamine imide after reaction with sodium hydride. The diamine imide undergoes Michael addition to the α,β-unsaturated ketone followed by cyclization

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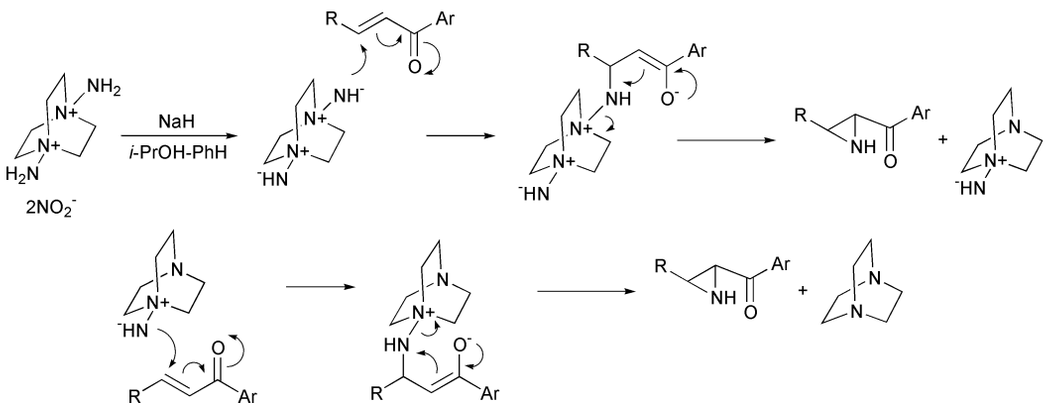
Table 1 Direct aziridination of α,β-unsaturated ketones with *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate

Aziridine	R	Substituent on Ar group	Yield (%)	Mp/°C (lit.)
1	Ph	H	95	100–101 (99–101[11])
2	Ph	4-Cl	79	76–78 (75–8[11])
3	2-ClPh	H	88	92–94 (92.5–4.5[11])
4	4-MeOPh	H	84	53–54
5	Ph	4-MeO	82	71–72 (71–2[13])
6	4-ClPh	H	79	88–89 (88.5[13])
7	Ph	4-Br	81	102–104 (98–104[13])
8	Ph	4-Me	89	89–90 (89–90[13])
9	4-BrPh	H	76	110–111 (111–2[13])
10	4-MePh	H	87	106–107 (105–6[13])
11	2-MeOPh	H	91	104–105 (104–5[13])
12	2-NO_2Ph	H	17	113–115 (113–5[13])
13	4-NO_2Ph	H	15	142–143 (142.5[13])
14	Me	H	99	oil[14]
15	Me	4-MeO	99	59–60



Scheme 2

to form an aziridine after departure of the good leaving-group tertiary amine, 1,4-diazabicyclo[2.2.2]octane (Scheme 2). The diamine imide can also decompose into 1,4-diazabicyclo[2.2.2]octane, which is a competitive reaction with aziridination, and is why excess hydrazinium nitrate is needed in the reaction. Scheme 2 shows both of the imide moieties in *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate participating in aziridination reactions. However, sometimes just one imide reacts. In the aziridination reactions in most cases Michael addition could be the rate-determining step. However, for the nitro substituted chalcones, ring-closure is possibly disadvantageous because the carbanion could be stabilized by a strong electron-withdrawing group, the nitro group. Thus, the yields of the corresponding aziridines are low.

Two other hydrazinium salts, 1,1,1-triethylhydrazinium nitrate, an acyclic hydrazinium salt, and 1-aminopyridinium nitrate, an aromatic hydrazinium salt, were also prepared and were tested for aziridination. Aziridination of chalcone with 1,1,1-triethylhydrazinium nitrate gave a very low yield (12%). It might be assumed that the 1,1,1-triethylammonium imide anion attached to the nitrogen of triethylamine is more sterically hindered than those attached to the nitrogens of 1,4-diazabicyclo[2.2.2]octane. No desired aziridine was found in the reaction of 1-aminopyridinium nitrate with chalcone. This could be ascribed to the aromaticity of pyridine. After reaction with sodium hydride, the pyridinium *N*-imide anion is very unstable and is prone to forming stable aromatic pyridine by loss of imide. In competitive reactions, pyridinium *N*-imide decomposes faster than the Michael addition occurs.

In order to extend this aziridination, attempts to aziridinate α,β-unsaturated esters (ethyl cinnamate and ethyl acrylate) and α,β-unsaturated *N*,*N*-disubstituted amides (*N*,*N*-dimethylcinnamamide and *N*,*N*-dimethylacrylamide) with *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate failed.

In conclusion, *N*,*N*′-diamino-1,4-diazoniabicyclo[2.2.2]-octane dinitrate is an efficient reagent for the conversion of 1-aryl-α,β-unsaturated ketones to their *N*-unsubstituted aziridine derivatives.

Experimental

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 200 (200 MHz) spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. CHN analyses were recorded on an Elementar Vario EL analyzer. IR spectra were taken on a Bruker Vector 22 FT-IR spectrophotometer using KBr pellets.

Caution: Hydrazinium salts should be considered potential chemical hazards[16] and extreme care must be exercised in working with them. However no problems were encountered during our studies. *N*,*N*′-Diamino-1,4-diazoniabicyclo[2.2.2]-octane dinitrate was prepared according to the literature procedure and was reported stable, but highly energetic.[12] The known aziridine derivatives gave satisfactory data as reported in the literature.[11,13,14]

General aziridination procedure

N,*N*′-Diamino-1,4-diazoniabicyclo[2.2.2]octane dinitrate (268 mg, 1.0 mmol) and α,β-unsaturated ketone (104 mg, 0.5 mmol) were dissolved in 9 mL of a mixture of anhydrous isopropanol and benzene (2 : 1, v/v). NaH (30 mg, 95%, ~1.0 mmol) was added portionwise over 30 min with stirring at 0 °C. The mixture was stirred overnight. Water was added to the reaction mixture. After extracting with benzene, the organic layer was washed with water and brine and dried over sodium sulfate.

After removal of the solvent, the residue was recrystallized from methanol or separated on a silica gel column with hexane : AcOEt (10 : 1) as an eluent to give colorless crystals except for yellow nitro substituted aziridines.

2-Benzoyl-3-(4-methoxyphenyl)aziridine 4. Colorless crystals, yield 84%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02–7.23 (9H, m, ArH), 3.47 (dd, 1H, J = 2.4, 8.1 Hz, CH), 3.14 (dd, 1H, J = 2.4, 9.6 Hz, CH), 2.66 (dd, 1H, J = 8.1, 9.6 Hz, NH); IR (KBr) ν/cm^{-1} 3264 (N–H), 1667 (C=O); MS (*m*/*z*) 253 (M^+, 41), 238 (M^+ − Me, 100), 105 (PhCO, 75). Anal. calcd for $C_{16}H_{15}NO_2$ (253.30) C, 75.87; H, 5.97; N, 5.53. Found C, 75.60; H, 6.04; N, 5.61%.

2-(4-Methoxybenzoyl)-3-methylaziridine 15. Colorless crystals, yield 99%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, 2H, J = 9.3 Hz, ArH), 6.99 (d, 2H, J = 9.3 Hz, ArH), 3.90 (s, 3H, MeO), 3.18 (d, 1H, J = 2.5 Hz, CH), 2.19 (m, 1H, CH), 2.10 (br s, 1H, NH), 1.35 (d, 3H, J = 5.2 Hz, Me); IR (KBr) ν/cm^{-1} 3209 (N–H), 1653 (C=O); MS (*m*/*z*): 191 (M^+, 33), 176 (M^+ − Me, 100), 135 (MeOPhCO, 78). Anal. calcd for $C_{11}H_{13}NO_2$ (191.23) C, 69.09; H, 6.85; N, 7.32. Found C, 69.30; H, 6.60; N, 7.37%.

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