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A practical regioselective ring-opening of activated aziridines with organoalanes

Ferruccio Bertolini [a,b], Simon Woodward [b,*], Stefano Crotti [a], Mauro Pineschi [a,*]

[a] Dipartimento di Scienze Farmaceutiche, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy
[b] School of Chemistry, The University of Nottingham, Nottingham NG7 2RD, United Kingdom

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ABSTRACT

The regioselective ring-opening of N-protected 2-phenylaziridines is accomplished by the addition of organoalanes in dichloromethane. With this simple method it is possible to introduce alkyl, alkenyl and alkynyl substituents at the benzylic position of the phenylaziridine to give the corresponding β-phenyl-β-substituted amines, as useful precursors for intramolecular hydroaminations, in high yields.

The ring-opening of aziridines with carbon nucleophiles represents a useful entry into substituted amines.[1] Several organometallic reagents have been used for this purpose, with the notable exception of organoaluminium reagents. For example, organocuprates are particularly well suited for the ring-opening of *N*-tosyl phenylaziridine, albeit with modest regioselectivity, and with predominant attack at the less-hindered position.[2] More recently, a completely reversed regioselectivity (1:5), favouring the benzylic position was obtained with Me_2CuLi in the ring-opening of 2-pyridinesulfonamide-protected phenylaziridine, due to the chelating properties of the protecting group.[3] It should be noted that aziridine ring-cleavage with metal acetylides to form homopropargylic amines has scarcely been described,[4] notwithstanding the synthetic potential of these in the preparation of heterocycles by intramolecular amination,[5] or 'click chemistry' manipulation of the triple bond.[6] Furthermore, when *N*-tosyl phenylaziridine was used, a regioisomeric mixture, with predominant attack of the potassium or lithium acetylide at the less-hindered position, was obtained.[4]

We report here a novel method for the ring-opening of aryl and vinyl aziridines with alkyl, alkenyl and alkynyl organoaluminium reagents to give the corresponding substituted amines with modest to complete regioselectivity.

In preliminary experiments, we found that the reaction of a variety of *N*-tosyl aziridines with $AlMe_3$ under different reaction conditions gave only trace amounts of alkylated products with very low conversions (<10%) even with prolonged reaction times. Finally, we found that the reaction between $AlMe_3$ and *N*-tosyl phenylaziridine **1a** was solvent dependent. A very low conversion occurred when the reactions were carried out in THF and Et_2O, but when CH_2Cl_2 or toluene were used, complete conversion was obtained in 1 h at 0 °C. To our delight, the ring-opening occurred via completely selective attack of the methyl fragment at the benzylic position (Table 1, entry 1). The use of $AlEt_3$ afforded the corresponding adduct **3a**, albeit with reduced regioselectivity (entry 2). When these reactions were carried out on enantiomerically pure aziridine (*R*)-**1a** (>98% ee), the corresponding products **2a** and **3a** were obtained with low enantioselectivity (14% ee).

However, it was possible to employ the Cbz-protected phenylaziridine **1b**, even if a lower yield of the corresponding adduct **2b** was obtained. Also in this case, when enantiomerically pure (*R*)-**1b** was used, extensive racemization (25% ee) was observed. The high extent of racemization, together with the selective attack at the benzylic position, point to ring-opening under electronic control. Probably, the high affinity of aluminium for oxygen allows coordination of AlR_3 to the oxygen lone-pairs of the protecting group,[8] thus creating a more reactive 'ate complex', which delivers the methyl fragment intramolecularly onto the benzylic carbenium ion (Fig. 1), with a substantial loss of stereochemical integrity of the starting aziridine (57% inversion, 43% retention, as determined by HPLC on a chiral stationary phase).

The reaction of vinyl aziridines with organometallic reagents has often been promoted by copper salts and this usually results in selective *anti*-S_N2' reactions,[9] even if particular steric bias can induce a *syn*-stereoselective pathway.[10] The uncatalyzed addition of $AlMe_3$ to 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**1c**) proceeded with full conversion in 1 h at 0 °C and with good regioselectivity ($S_N2/S_N2' = 93/7$). Unfortunately, the product consisted of a mixture of *cis*-**6a** (60%) and *trans*-**7a** (40%) diastereoisomers, which was not separable by chromatographic purification (entry 6). On the other hand, the uncatalyzed addition of $AlMe_3$ to the five-membered analogue **1d** gave the *cis*-S_N2 adduct **6a** with good stereo- and regioselectivity, in fair isolated yield (entry 7). The stereochemistry of adduct **8a** was confirmed by ^1H NMR examination and by comparison with the data of the corresponding trans adduct.[11] The cis 1,2-opening is a mode of reaction rarely observed with alkyl carbanions,[12] and can be explained via coordination of the organoalane to the aziridine-protecting group with subsequent intramolecular transfer of the R group from the same side.

* Corresponding authors. Tel.: +39 (0)502219668; fax: +39 (0)502219660 (M.P.).
E-mail address: pineschi@farm.unipi.it (M. Pineschi).

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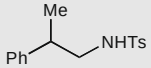
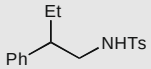
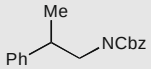
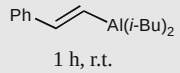
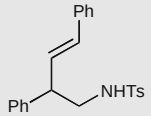
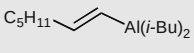
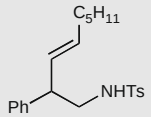
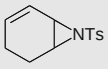
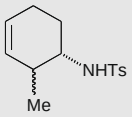
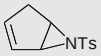
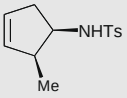
Table 1
Ring-opening of aryl and vinyl aziridines with alkyl and alkenyl alanes[a]

Entry	Aziridine	AlR_3 conditions	Regioselectivity[b]	Product yield[c] (%)
1	 **1a**	$AlMe_3$ 1 h, 0 °C	>95/<5	 **2a**, (92)
2	 **1a**	$AlEt_3$ 1 h, 0 °C	88/12	 **3a**, (70)
3	 **1b**	$AlMe_3$ 1 h, 0 °C	>95/<5	 **2b**, (58)
4	 **1a**	 1 h, r.t.	>95/<5	 **4a**, (85)[d]
5	 **1a**	 1 h, r.t.	>95/<5	 **5a**, (60)[d]
6	 **1c**	$AlMe_3$ 1 h, 0 °C	93/7	 **6a**,**7a** mixture
7	 **1d**	$AlMe_3$ 1 h, 0 °C	91/9	 **8a**, (62)

[a] All reactions were carried out in CH_2Cl_2 in accordance with the typical procedures.[7]
[b] Regioselectivity determined by ^1H NMR examination of the crude mixture.
[c] Isolated yield of pure product after chromatographic purification on silica gel.
[d] The product was recovered contaminated (ca. 10%) with the corresponding alkynylated compound.

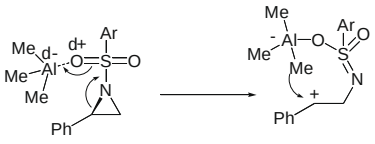
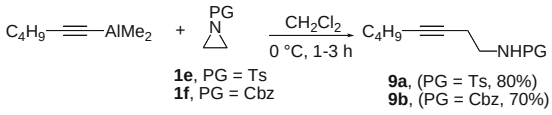


Figure 1. A plausible mechanism for the ring-opening of *N*-tosyl phenylaziridine.

Alkynylaluminium reagents, which can be prepared from the corresponding alkynyllithium and dialkylaluminium chlorides,[13] have found widespread use in organic synthesis.

Interestingly, the increased reactivity of these reagents allowed the reaction with protected aziridines **1e** and **1f** to occur at 0 °C in CH_2Cl_2, to give good yields of homopropargylamines **9a**,**b** (Scheme 1). It should be noted that the reaction of $AlMe_3$ with the same



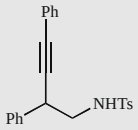
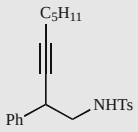
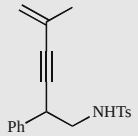
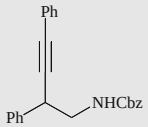
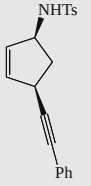
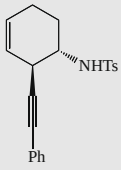
Scheme 1. Alkynylation of protected aziridines **1e** and **1f**.

aziridines afforded only trace amounts of alkylated products. Although it is not a normal procedure to carry out an alkyne deprotonation in CH_2Cl_2, the use of this solvent is mandatory here to obtain high yields of alkynylated products. No evidence of competing CH_2Cl_2 deprotonation was observed.

We next examined the reaction of dimethyl(alkynyl)alanes with aryl and vinyl aziridines, and the results are reported in Table 2.

Apart from the reaction of the organoalane derived from heptyne (Table 2, entry 2), all the other reactions were complete in

Table 2
Ring-opening of aryl and vinyl aziridines with R-CCAlMe$_2$[a]

Entry	R (Aziridine)	Conditions	Regio-selectivity[b]	Product yield[c] (%)
1	Ph (**1a**)	1 h, 0 °C	>95/<5	 **10**, (85)
2	C_5H_{11} (**1a**)	18 h, rt	>95/<5	 **11**, (70)
3	C_3H_5 (**1a**)	1 h, 0 °C	>95/<5	 **12**, (88)
4	Ph (**1b**)	1 h, 0 °C	>95/<5	 **13**, (60)
5	Ph (**1d**)	1 h, 0 °C	89/11 (S_N2'/S_N2)	 **14**, (60)
6	Ph (**1c**)	1 h, 0 °C	7/93 (S_N2'/S_N2)	 **15**, (45)

[a] All reactions were carried out in CH_2Cl_2 in accordance with the typical procedure.[14]
[b] Regioselectivity determined by ^{1}H NMR examination of the crude mixture.
[c] Isolated yield of pure product after chromatographic purification on silica gel.

1 h at 0 °C after the addition of the dimethyl(alkynyl)alane to the aziridine. The regioselectivity of the ring-opening was excellent in all cases for phenylaziridines **1a** and **1b** (entries 1–4), whereas the use of cyclic vinyl aziridines **1d** and **1c** gave minor amounts of regioisomeric products (entries 5 and 6). Moreover, the alkynyl group of the reagent was found to have a significant influence on the regio- and stereoselectivity of the ring-opening depending on the substrate used. In fact, the reaction of the alkynyl alane derived from phenylacetylene with the cyclohexene-derived aziridine **1c** proceeded with high S_N2 regioselectivity. The 1,2-addition path was not completely stereoselective (ca. 9:1 trans/cis), but the major product isolated in pure state by chromatographic purification was the *trans*-homopropargyl amine **15** (entry 6). To our surprise, the reaction with the five-membered analogue **1d** exhibited unusual *cis*-S_N2' stereoselectivity, which might be ascribed to the increased soft character of this reagent with respect to $AlMe_3$ (entry 5). The 1,4-cis relationship of the substituents was deduced from the large chemical shift difference (0.91 ppm) between the two ring methylene protons and by their characteristic coupling patterns.[15] This stereoselective outcome nicely complements the recently developed synthetic protocol for alkynylated 1,4-trans-disubstituted cyclopentenes by desymmetrization of bicyclic hydrazines.[16]

In conclusion, the ring-opening of aryl and vinyl aziridines with organoalanes proceeds with high yields and regioselectivity in a weakly coordinating non-ethereal solvent. This simple protocol allows the introduction of alkyl, alkenyl and alkynyl substituents at the benzylic position of the phenylaziridine to give the corresponding β-phenyl-β-substituted amines in high yields. Of particular interest is the practical synthesis of novel homopropargylic and homoallylic amines which can be used for intramolecular hydroaminations.

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Supplementary data

Supplementary data (detailed experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.081.

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7. *Typical procedure for alkylation* (entry 1, Table 1): $AlMe_3$ (0.5 mmol, 0.25 mL of a 2 M solution in hexanes) was added at 0 °C under an argon atmosphere to a solution of racemic or (*R*)-**1a** (68.3 mg, 0.25 mmol) in dichloromethane (1.0 mL). The mixture was allowed to react at 0 °C for 1 h and then quenched with 1 M hydrochloric acid (2.0 mL). The aqueous phase was extracted with dichloromethane (5.0 mL) and diethyl ether (5.0 mL). The combined organic fractions were dried over magnesium sulfate and filtered. Evaporation of the organic solution afforded a crude residue which was purified by silica gel column chromatography (hexane/EtOAc: 9/1), to give 4-methyl-*N*-(2-phenylpropyl)benzenesulfonamide (**2a**) (66.5 mg, 92%).[2,3] HPLC analysis of the product was performed on a Chiralpak ® AD-H column, flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 95/5, retention times (min): 49.0 (*R*, minor stereoisomer); 54.1 (*S*, major stereoisomer). *Typical procedure for alkenylation* (entry 4, Table 1): to a solution of DIBAL-H in hexanes (0.6 mmol, 0.6 mL of a 1 M solution in hexanes) was added phenylacetylene (0.6 mmol, 3.0 equiv) dropwise. The solution was allowed to react at 55 °C for 3 h. At this point, the solution was cooled to room temperature and a solution of aziridine **1a** (54.6 mg, 0.2 mmol) in dichloromethane (0.6 mL) was added dropwise at 0 °C. The mixture was allowed to react at room temperature for 1 h and then quenched with 1 M hydrochloric acid (2.0 mL). The aqueous phase was extracted with dichloromethane (5.0 mL) and diethyl ether (5.0 mL). The combined organic fractions were dried over magnesium sulfate and filtered.

Evaporation of the organic solution afforded a crude residue which was purified by silica gel column chromatography (petroleum ether/EtOAc: 85/15) to give **4a** (64 mg, 85%) as a white solid (contaminated with 10% of **10**). Mp = 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H, Ar-C*H*$_3$); 3.22–3.40 (m, 2H, C*H*$_2$–NH); 3.55–3.66 (m, 1H, Ph-C*H*); 4.48 (br s, 1H, CH$_2$–N*H*); 6.29 (dd, J_1 = 17.7 Hz, J_2 = 8.6 Hz, 1H, Ph-CH=C*H*–); 6.53 (d, J = 17.7 Hz, 1H, Ph-C*H*=CH); 7.12–7.43 (m, 12H, Ar-*H*); 8.00 (d, J = 9.0 Hz, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 48.5, 48.7, 126.3, 127.2, 127.4, 127.7, 127.8, 128.6, 129.0, 129.8, 131.8, 132.3, 136.6, 137.0, 140.3, 143.5. ESIMS (+) *m/z* 400.1345 (M+Na).

8. As the nitrogen of protected aziridines is very poorly basic, its direct interaction with a Lewis acid is not likely. See also Ref. 1a.
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14. *Typical Procedure for alkynylation* (entry 1, Table 2): In a dry Schlenk tube, a solution of BuLi (0.5 mmol, 0.3 mL of a 1.6 M solution in hexanes) was added under an argon atmosphere at 0 °C to a solution of phenylacetylene (0.5 mmol) in freshly distilled dichloromethane (1.0 mL). This mixture was allowed to react for 15 min at 0 °C. To this solution, dimethylaluminium chloride (0.5 mmol, 0.5 mL of a 1 M solution in hexanes) was then added dropwise at 0 °C. The resulting suspension was stirred for 25 min at room temperature and added via *cannula* to a solution of aziridine **1a** (68.3 mg, 0.25 mmol) in dichloromethane (0.6 mL) at 0 °C. The mixture was allowed to react for 1 h at 0 °C. Column chromatography (petroleum ether/EtOAc: 9/1) afforded *N*-(2,4-diphenylbut-3-ynyl)-4-methylbenzenesulfonamide (**10**), (80 mg, 85%) as a white solid. Mp = 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, Ar-C*H*$_3$); 3.26–3.33 (m, 1H, C*H*$_2$–NH); 3.36–3.43 (m, 1H, C*H*$_2$–NH); 4.02 (dd, 1H, J_1 = 8.0 Hz, J_2 = 6.4 Hz, Ph-C*H*); 4.80–4.84 (m, 1H, CH$_2$–N*H*); 7.28–7.39 (m, 10H, Ar-*H*); 7.41–7.48 (m, 2H, Ar-*H*); 7.76 (d, 2H, J = 8.0 Hz, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 39.0, 49.3, 85.1, 87.5, 122.6, 127.0, 127.7 (2 carbons), 128.3, 128.4, 128.8, 129.7, 131.7, 137.0, 137.7, 143.5. ESIMS (+) *m/z* 398.1173 (M+Na).
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