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Alkylative Ring Opening of *N*-Methylaziridinium Ions and a Formal Synthesis of Tyroscherin

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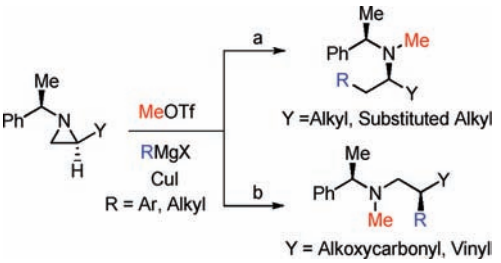
ABSTRACT



Alkylative ring-opening reactions of stable 2-substituted *N*-methylaziridinium ions proceeded with various alkyl- or arylmagnesium bromides in the presence of CuI to yield synthetically valuable and optically pure alkylated acyclic amines in a completely regio- and stereoselective manner. This was applied to a formal synthesis of the cytotoxic natural product tyroscherin.

Aziridine, a nitrogen-containing three-membered ring, is synthetically valuable for the preparation of various cyclic and acyclic molecules via the processes including regioselective ring-opening and ring-extension reactions.[1] Alkylative aziridine ring openings with carbon nucleophiles may provide a very efficient route toward nitrogen-containing acycles with an extension of the carbon chain.[2] A few cases have been reported for activated aziridines bearing electron-withdrawing groups (EWGs), such as carbonyl, sulfonyl, or phosphinyl, at the ring nitrogen, with a limited range of applicable nucleophiles without high regio- and stereoslectivity in general.[1f,2,3] Further, the activated aziridines are relatively unstable and difficult to prepare in optically pure forms.[2] However, aziridines with an electron-donating substituent (EDG) like a phenylethyl group at the ring nitrogen is very stable and readily accessed in optically pure forms.[4] Those aziridines should be activated to an aziridinium ion intermediate, as shown in the bracket of Scheme 1, prior to the nucleophilic ring-opening reactions.[2,5,6]

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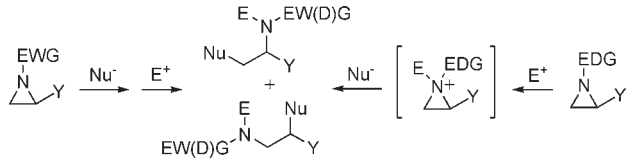
Scheme 1. Ring-Opening Reactions of Aziridines



Recently, we have developed a reliable method for the activation of aziridines by reaction with methyltrifluoromethanesulfonate to form a stable *N*-methylaziridinium ion.[7] The *N*-methyl aziridinium ion readily reacts with various nucleophiles including amine, azide, alkoxide, and cyanide to provide the corresponding ring-opening product as single isomer in a completely regio- and stereoselective manner, depending on the nature of the substituent at C-2 of the aziridine ring. Only a few halide nucleophiles showed exceptional selectivity.[8] Although most heteroatom nucleophiles can be applicable, carbon nucleophiles, especially alkyl metals, have not been successful in the aziridine opening reaction. This communication describes an efficient method allowing rapid introduction of carbon nucleophiles from alkyl or arylmagnesium bromide to unactivated aziridine en route to the synthesis of various functionalized aminoalkanes.

The nucleophilic ring-opening reaction of the unactivated aziridine **1** bearing a benzyl group at the ring nitrogen was initiated by the reaction with methyl trifluoromethanesulfonate to form conformationally stable *N*-methylaziridium ion **2** (Scheme 2).[7] Using aziridine **1A** (Y = methoxymethyl) as a model, we have investigated the reactions with various alkyl metal compounds including alkyllithium, alkyl Grignard, and alkylzinc, upon formation of *N*-methylaziridinium ion intermediate **2A** (Y = methoxymethyl). However, the reaction did not give the desired product **3**, but **5** resulted from the ring opening by a triflate anion in all cases.

Finally, we found that the arylative ring opening with phenylmagnesium bromide in the presence of 3 mol equiv of CuI in dioxane yielded the expected product **3Aa** in 61% yield (Table 1, entry 1).[9]

Scheme 2. Alkylative Ring-Opening Reactions of 2-Substituted (1*R*)-1-Phenylethylaziridine **1** after Formation of *N*-Methylaziridinium Ion **2**

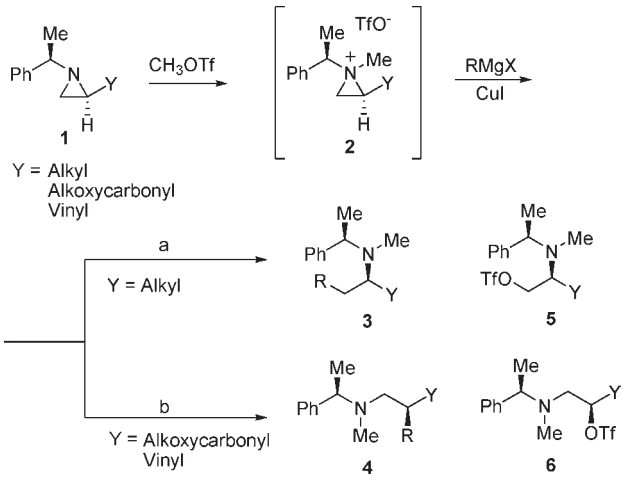


Table 1. Alkylative Ring-Opening of the Aziridiniums **2** with Various Alkyl and Arylmagnesium Bromides in the Presence of CuI as in Scheme 2

no.[a]	sm.	Y	R	prod.	%[b]
1	**1A**	CH_2OMe	C_6H_5	**3Aa**	61
2	**1A**	CH_2OMe	2-$MeOC_6H_4$	**3Ab**	69
3	**1A**	CH_2OMe	$CH_3(CH_2)_2$	**3Ac**	44
4	**1A**	CH_2OMe	$(CH_3)_2CHCH_2$	**3Ad**	88
5	**1A**	CH_2OMe	$C_6H_5C{\equiv}C$	**3Ae**	90
6	**1A**	CH_2OMe	$CH_2CH{=}CH_2$	**3Af**	68
7	**1B**	CH_2OBn	C_6H_5	**3Ba**	89
8	**1B**	CH_2OBn	2-$MeOC_6H_4$	**3Bb**	52
9	**1B**	CH_2OBn	$CH_3(CH_2)_2$	**3Bc**	60
10	**1B**	CH_2OBn	$(CH_3)_2CHCH_2$	**3Bd**	75
11	**1B**	CH_2OBn	$C_6H_5C{\equiv}C$	**3Be**	83
12	**1B**	CH_2OBn	$CH_2CH{=}CH_2$	**3Bf**	80
13	**1C**	$(CH_2)_3CH_3$	C_6H_5	**3Ca**	50
14	**1C**	$(CH_2)_3CH_3$	$CH_3(CH_2)_2$	**3Cc**	78
15	**1C**	$(CH_2)_3CH_3$	C_6H_5CC	**3Ce**	52
16	**1D**	$(CH_2)_3OBn$	C_6H_5	**3Da**	51
17	**1D**	$(CH_2)_3OBn$	$CH_3(CH_2)_2$	**3Dc**	74
18	**1E**	CO_2Et	C_6H_5	**4Ea**	43
19	**1E**	CO_2Et	$CH_3(CH_2)_2$	**4Ec**	49
20	**1F**	$CH{=}CHC_3H_7$	C_6H_5	**4Fa**	76
21	**1F**	$CH{=}CHC_3H_7$	$C_6H_5C{\equiv}C$	**4Fc**	55

[a] All reactions were carried out in dioxane except entries 18 and 19. [b] The isolated yield was not optimized.

Under these conditions, the ring-opening reactions with alkylmagnesium bromides also proceeded, affording the corresponding products **3Ac**, **3Ad**, and **3Ae** in 44, 88, and 90% yield, respectively (entries 3−5). Allylmagnesium bromide was also applicable and yielded the product **3Af** in 68% yield (entry 6). (2*R*)-Benzyloxymethylaziridine also underwent similar arylative as well as alkylative ring-opening reactions with various carbon nucleophiles to provide the corresponding ring-opening products **3B**,

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(7) Kim, Y.; Ha, H.-J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363. The *N*-methyl group and the substituent at C-2 are in a *cis* relationship. We observed correlation signals in NOESY spectra between the *N*-methyl and methylene protons bearing OMe in **2A**.

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(9) When the aziridinium ion is formed the ring becomes sufficiently reactive to be attacked by the carbon nucleophile as shown in the CuOTf catalyzed alkynylation of activated aziridines reported in the literature. Ding, C.-H.; Dai, L.-X.; Hou, X-.L. *Synlett* **2004**, 1691. Due to the low solubility of the aziridinium ion at 0 °C, there is a limitation to the solvent to be used. Among them dioxane was the best for most reactions.

in good to moderate yields (entries 7–12). The reactions of the aziridines with a simple alkyl substituent at C2, (2*R*)-butylaziridine (**1C**), also proceeded to afford **3Ca**, **3Cc**, and **3Ce** in 50, 78, and 52% yield, respectively (entries 13–15). The aziridine **1D** bearing benzyloxypropyl group at C2 also underwent the ring-opening reactions with phenyl- and propylmagnesium bromide to afford the products **3Da** and **3Dc** in 51 and 74% yield, respectively (entries 16 and 17). The reaction of ethyl (2*R*)-aziridine-2-carboxylate (**1E**) with phenylmagnesium bromide in the presence of CuI in dioxane yielded the triflated compound **6E** and a trace amount of arylative product **4Ea** with the carboxylate group remaining intact. Changing the reaction solvent to $CHCl_3$ improved the product yield up to 43% (entry 18). The same reaction conditions yielded the alkylated product **4Ec**, when applied to the reaction with propylmagnesium bromide (49% yield, entry 19). 2-(Penten-1-yl)aziridine (**1F**) was also reacted with phenyl- and phenylacetylidylmagnesium bromide to yield the expected product **4Fa** and **4Fc** in 76 and 55% yield, respectively (entries 20 and 21).

This method is applicable for the synthesis[10] of tyroscherin **12**, a natural product shown to be a potent and selective inhibitor of IGF-1-dependent growth in human breast cancer cell MCF-7 (Scheme 3).[11]

Its synthesis was achieved from *N*-methylation and the arylative ring-opening reaction of aziridine **9**, which was prepared by the known method involving alkylation of aziridine-2-(*N*-methoxymethyl)carboxamide (**7**) followed by stereoselective reduction of 2-acylaziridine (**8**).[12] *N*-Methylative and arylative aziridine ring opening of **9** with (4-methoxymethyloxyphenyl)magnesium bromide provided the corresponding product **10** in 75% yield. The removal of TIPS with HF and debenzylation in the presence of $(Boc)_2O$ afforded **11**, constituting a formal synthesis of natural product tyroscherin **12**.

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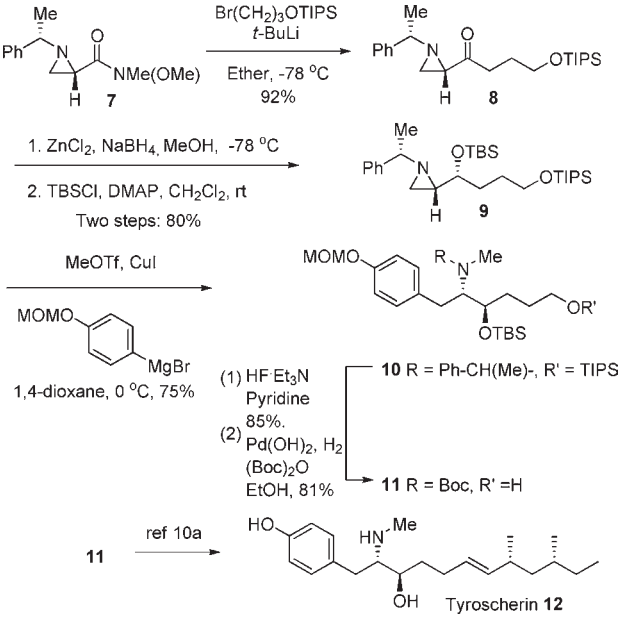
In conclusion, alkylative ring-opening reactions of 2-substituted aziridinium ions were successfully carried out with various alkyl or arylmagnesium bromides in the presence of CuI to yield synthetically valuable and optically pure alkylated acyclic amine derivatives in a completely regio- and stereoselective manner.

Scheme 3. Formal Synthesis of Tyroscherin (**12**)



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Supporting Information Available. Experimental procedures, spectral data, ^1H and ^{13}C NMR, NOESY spectra and optical rotation values. This material is available free of charge via the Internet at http://pubs.acs.org.