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Regiochemical control of the ring-opening of aziridines by means of chelating processes. Part 4: Regioselectivity of the opening reactions with MeOH of 1-(benzyloxy)-2,3- and -3,4-*N*-(methoxycarbonyl)aziridoalkanes under condensed and gas-phase operating conditions

Paolo Crotti,[a,*] Gabriele Renzi,[b,*] Graziella Roselli,[b] Valeria Di Bussolo,[a] Sandra Giuli,[b] Sofia Tsitsigia[a] and Maria Rosaria Romano[a]

[a]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy*
[b]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy*

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Abstract—The regioselectivity of the addition reaction of MeOH both in the condensed phase ($MeOH/H_2SO_4$) and in the gas-phase ($MeOH/D_3^+$) was examined in a series of activated aziridines. The results indicate that gas-phase operating conditions are particularly favorable for the occurrence of D^+-mediated chelated bidentate species, which influence the regioselectivity of the opening process. In the condensed phase, the chelating $MeOH/LiClO_4$ protocol turned out to be decidedly less effective for regioselectivity and also in determining the composition of the reaction mixture.

1. Introduction

In gas-phase operating conditions, characterized by the presence of a gaseous acid ($GA^+=D_3^+$), without the complicating interference of the solvent and counterion effects, we recently observed the incursion of intramolecular chelating processes mediated by the proton (actually D^+) in epoxide ring-opening reactions with MeOH of the open-chain epoxides **1**–**6** bearing a heterofunctionality (CH_2OBn or CH_2CH_2OBn relative to the oxirane ring).[1] All the epoxides (**1**–**6**) examined showed, in the gas-phase, a regioselectivity toward the oxirane carbon furthest from the heterofunctionality decidedly superior to that obtained in the condensed phase (cd phase), not only under standard conditions (H_2SO_4/MeOH) but also under chelating conditions ($LiClO_4$/MeOH) by the promoting action of Li^+.[1,2]

In order to verify how the coordinating ability of both Li^+ in the cd phase and D^+ in the gas-phase could be influenced by the nature of the small-ring heterocycles and by the conformational freedom of a non-cyclic system, we have now examined the regiochemical behavior in the acid methanolysis of open-chain *N*-(methoxycarbonyl)-substituted aziridines **7**–**12** (activated aziridines), structurally related to the previously examined epoxides **1**–**6**, both in the cd phase and in the gas-phase.[3]

Studies on the regio- and stereoselectivity of the ring-opening process of aziridines under different conditions are an area of increasing interest, due to the synthetic potential of these heterocycles for the stereo-controlled introduction of a nitrogen-containing functionality into a molecule. Relevant applications of the ring-opening reactions of activated and unactivated aziridines have recently been described for the synthesis of sulfur-containing heterocycles,[4a] 2-alkylaziridines, symmetrical α-branched-*N*-tosylamides, and unsymmetrical amines;[4b] chiral 2-(2-pyridyl)-[4c] and 2-(aryloxymethyl)-aziridines[4d] were used for the synthesis of chiral amines, while a fluoride-promoted ring-opening of a 2-(2-acylaminophenyl)aziridine was employed for the stereoselective construction of the Communesin ring system.[4e] Aziridines react also with silylated nucleophiles (Me_3SiN_3, Me_3SiCl, Me_3SiCF_3) in DMF to give the corresponding addition products.[4f]

Keywords: Aziridines; Regioselectivity; Gas-phase reactions; Chelation.
* Corresponding authors. Tel.: +39 050 2219 690; fax: +39 050 2219 660 (P.C.); tel./fax: +39 0737 402219 (G.R.); e-mail addresses: crotti@farm.unipi.it; gabriele.renzi@unicam.it

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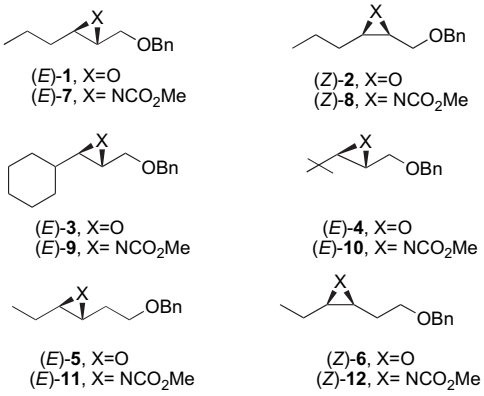
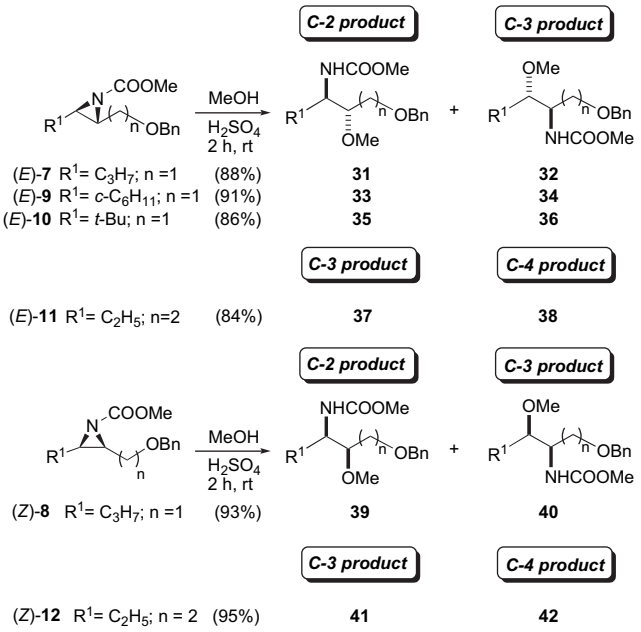


2. Results

An application of the Staudinger reaction (PPh_3 in MeCN at 80 °C)[3] to the pairs of regioisomeric azido alcohols **13**–**24** obtained in the azidolysis (NH_4Cl/NaN_3) of the corresponding epoxides **1**–**6**[2,5] afforded the unactivated aziridines **25**–**30**, which were N-protected by treatment with ClCOOMe to give the activated aziridines **7**–**12** (Scheme 1).

The methanolysis opening compounds, the pairs of regioisomeric methoxyurethanes (MUs), *C-2* and *C-3 products* from aziridines **7**–**10** and *C-3* and *C-4 products* from aziridines **11** and **12**, were prepared, when possible, by separation (preparative TLC) of the mixture of MUs obtained in the methanolysis under standard conditions (H_2SO_4/MeOH) of the corresponding aziridines: MUs **32** (*C-3 product*) from (*E*)-**7** (*C-3 product*/*C-2 product*=90:10), **40** (*C-3 product*) from (*Z*)-**8** (*C-3 product*/*C-2 product*=94:6), **33** (*C-2 product*) and **34** (*C-3 product*) from (*E*)-**9** (*C-3 product*/*C-2 product*=75:25), **35** (*C-2 product*) from (*E*)-**10** (*C-3 product*/*C-2 product*=3:97), **37** (*C-3 product*) and **38** (*C-4 product*) from (*E*)-**11** (*C-4 product*/*C-3 product*=61:39), and **41** (*C-3 product*) and **42** (*C-4 product*) from (*Z*)-**12** (*C-4 product*/*C-3 product*=48:52) (Scheme 2).

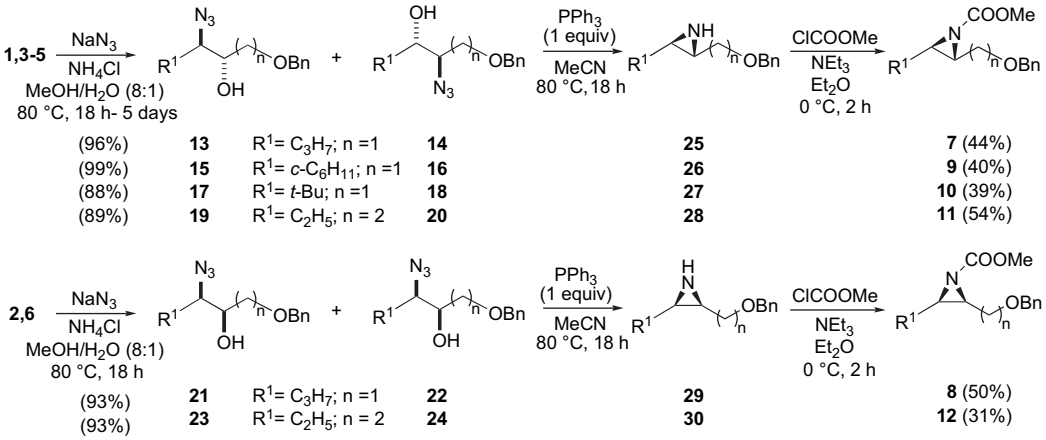
The regioisomeric MUs **31** [*C-2 product* from (*E*)-**7**], **36** [*C-3 product* from (*E*)-**10**], and **39** [*C-2 product* from (*Z*)-**8**] were prepared by alternative similar synthetic procedures



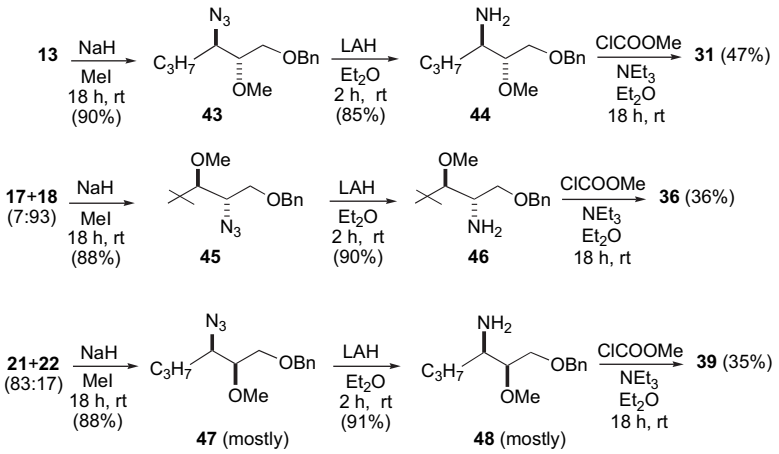
Scheme 2.

starting from the corresponding azido alcohols. In this way, the *anti* azido alcohol **13**[2,6] was O-methylated by the MeI/NaH protocol to give the corresponding methoxy azide **43**. The $LiAlH_4$ reduction of **43** afforded the corresponding methoxy amine **44**, which was treated with ClCOOMe to give the desired MU **31**. The same procedure (methylation, reduction, and N-protection) applied to the 83:17 mixture of *syn* azido alcohols **21** and **22** and to the 93:7 mixture of *anti* azido alcohols **18** and **17** obtained in the azidolysis of epoxides **2** and **4**, respectively,[2] afforded the corresponding reaction mixtures from which MUs **39** and **36** were separated pure (TLC) (Scheme 3).

The exact structure, regio-, and stereochemistry of each pair of regioisomeric MUs **31**–**42** were determined on the basis of the configuration of the starting aziridine, the completely anti-stereoselective ring-opening process commonly observed in aliphatic aziridines, and by appropriate ^1H NMR decoupling experiments.



Scheme 1.



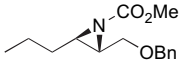
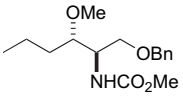
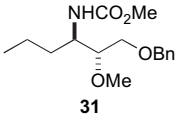
Scheme 3.

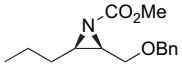
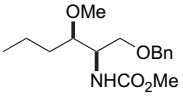
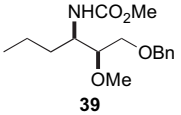
3. Discussion

Aziridines **7–12** were subjected to ring-opening reactions with MeOH in the cd phase [standard (0.2 N H_2SO_4/MeOH) and chelating conditions (10 N $LiClO_4$/MeOH)] and in the gas-phase (D_3^+/MeOH in D_2). The results obtained in these different reaction conditions are shown in Tables 1–3.

An examination of the results obtained in the cd phase under standard conditions indicates that the regioselectivity of the addition reaction of aziridines **7–12** is consistently influenced by the electron-withdrawing inductive effect of the terminal OBn functionality, actually by its distance from the aziridine carbons, and by the presence of serious steric encumbrance around the aziridine ring. In this framework, the high, electronically favored, C-3 regioselectivity

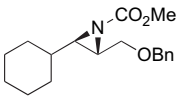
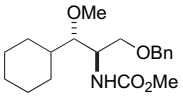
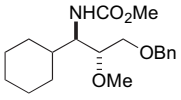
Table 1. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of aziridines (*E*)-**7** and (*Z*)-**8**

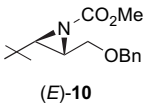
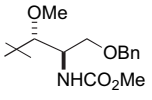
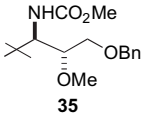
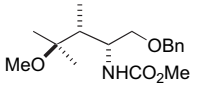
System composition (Torr)[a]				Product distribution[b]				
				C-3 Product		*C-2 Product*		Total abs yield[c] (%)
 (*E*)-**7**				 **32**		 **31**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	
Gas-phase								
(0.64)	D_2 (760)	—	(1.90)	(1.69)	97	(0.05)	3	58
(0.68)	D_2 (760)	3	(2.02)	(0.57)	>**99**	—	<**1**	19
Condensed phase								
	0.2 N H_2SO_4/MeOH				**90**		**10**	
	10 M $LiClO_4$/MeOH				**95**		**5**	

System composition (Torr)[a]				Product distribution[b]				
				C-3 Product		*C-2 Product*		Total abs yield[c] (%)
 (*Z*)-**8**				 **40**		 **39**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	
Gas-phase								
(0.49)	D_2 (760)	—	(1.49)	(1.77)	97	(0.05)	3	61
(0.56)	D_2 (760)	3	(1.70)	(0.54)	>**99**	—	<**1**	18
Condensed phase								
	0.2 N H_2SO_4/MeOH				**94**		**6**	
	10 M $LiClO_4$/MeOH				**96**		**4**	

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.
[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature *G*(D_3^+) values.[7]

Table 2. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of aziridines (*E*)-**9** and (*E*)-**10**

System composition (Torr)[a]				Product distribution[b]				
				C-3 product		*C-2 product*		Total abs yield[c] (%)
 (*E*)-**9**				 **34**		 **33**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	
Gas-phase								
(0.51)	D_2 (760)	—	(1.55)	(1.75)	87	(0.26)	13	67
(0.56)	D_2 (760)	3	(1.69)	(0.56)	**95**	(0.04)	**5**	20
Condensed phase								
	0.2 N H_2SO_4/MeOH				**75**		**25**	
	10 M $LiClO_4$/MeOH				**88**[d]		**12**[d]	

System composition (Torr)[a]				Product distribution[b]						
				C-3 Product		*C-2 product*				Total abs yield[c] (%)
 (*E*)-**10**				 **36**		 **35**		 **50**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	*G*	%	
Gas-phase										
(0.59)	D_2 (760)	—	(1.76)	(0.18)	11	(1.07)	64	(0.43)	25	56
(0.55)	D_2 (760)	3	(1.67)	(0.09)	**25**[e]	(0.28)	**55**[e]	(0.11)	**20**	16
Condensed phase										
	0.2 N H_2SO_4/MeOH				**3**		**97**			
	10 M $LiClO_4$/MeOH				**0.2**[f]		**0.8**[f]		**15**[f]	

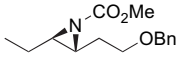
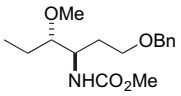
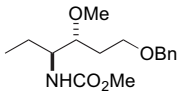
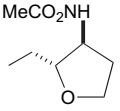
[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.
[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature $G(D_3^+)$ values.[7]
[d] Complex reaction mixture: the addition product constitute only 20% of the crude reaction product.
[e] *C-2 Product*/*C-3 product* ratio=69:31.
[f] The crude reaction product mostly consists of the unreacted aziridine (*E*)-**10** (84%).

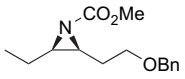
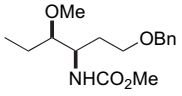
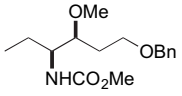
(90–94%) found in the simple, unencumbered 2,3-aziridines (*E*)-**7** and (*Z*)-**8** consistently decreases (75%) on passing to aziridine (*E*)-**9**, in which the corresponding C(3) aziridine carbon is partly hindered by the β-branching corresponding to the cyclohexane ring. In aziridine (*E*)-**10**, in which the C(3) aziridine carbon corresponds to a neopentyl carbon, the regioselectivity of the methanolysis is completely inverted and an almost complete C-2 regioselectivity is observed (97%). Consistent with these results, in the open-chain 3,4-aziridines (*E*)-**11** and (*Z*)-**12**, in which the OBn group is more distant from the aziridine carbons and no steric encumbrance is present around the aziridine moiety, only a scarce regioselectivity from (*E*)-**11** (*C-4 product*/*C-3 product*=61:39) or practically none from (*Z*)-**12** (*C-4 product*/*C-3 product*=48:52) is observed.

The use of chelating conditions in the cd phase by the usual $LiClO_4$/MeOH protocol (80 °C) is not so effective in the present aziridines **7**–**12** as in the previously studied oxiranes **1**–**6**,[1] and contrasting results were obtained, depending on the structure of the starting aziridine. In the simple 2,3-aziridines (*E*)-**7** and (*Z*)-**8**, mixtures of the corresponding *C-3* and *C-2 products*, in a ratio very similar to the one observed under standard conditions, were obtained. With the cyclohexyl-substituted aziridine (*E*)-**9** the chelating ability of Li^+ is clearly revealed, as expected, by a consistent increase in the C-3 regioselectivity (*C-3 product*/*C-2 product*=88:12), but the reaction is not clean, and the addition products constitute only 20% of the crude reaction mixture. With *tert*-butyl-substituted aziridine (*E*)-**10**, the $LiClO_4$/MeOH protocol is practically ineffective, and only a complex reaction mixture, mostly consisting of the unreacted aziridine (*E*)-**10** (84%) and the rearranged addition product **50** (15%), was obtained: only a practically inconsistent amount (1%) of the addition products, the MUs **35** and **36**, was present.[8a] The rearranged product **50**, formed in this reaction, reasonably derives from a 1,2-methylide shift on the Li^+-coordinated aziridine and the subsequent attack of MeOH on the developing tertiary carbocation, as tentatively shown in **49** (Scheme 4).[8b]

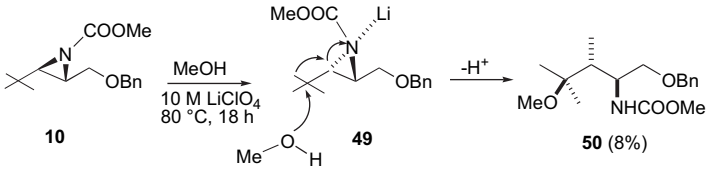
The behavior of 3,4-aziridines (*E*)-**11** and (*Z*)-**12** under these chelating opening conditions is completely different. While, on one hand, the aziridine (*Z*)-**12** behaves as expected, affording a clear 25:75 mixture of the corresponding *C-3* and *C-4 products*, with a marked increase in the *C-4 product* compared with the same reaction carried out under standard conditions (*C-3 product*/*C-4 product*=52:48), on the other hand the diastereoisomeric aziridine (*E*)-**11** affords the *trans*-1,2-disubstituted tetrahydrofurane derivative **53**

Table 3. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of aziridines (*E*)-**11** and (*Z*)-**12**

System composition (Torr)[a]				Product distribution[b]						
				C-4 product		*C-3 product*				Total abs yield[c]%
 (*E*)-**11**				 **38**		 **37**		 **53**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	*G*	%	
Gas-phase										
(0.53)	D_2 (760)	—	(1.61)	(0.91)	44	(0.33)	16	(0.83)	40	69
(0.57)	D_2 (760)	3	(1.70)	(0.36)	**55**[d]	(0.06)	**9**[d]	(0.24)	**36**[e]	22
Condensed phase										
	0.2 N H_2SO_4/MeOH				**61**		**39**			
	10 M $LiClO_4$/MeOH				**2**		**1**		**97**[e]	

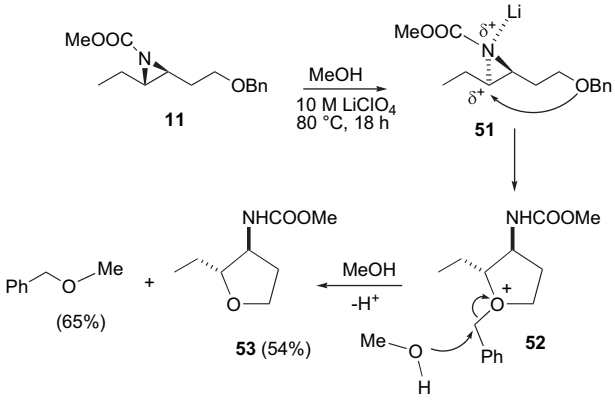
System composition (Torr)[a]				Product distribution[b]				
				C-4 Product		*C-3 Product*		Total abs yield[c] (%)
 (*Z*)-**12**				 **42**		 **41**		
Aziridine	Bulk gas	NMe_3	MeOH	*G*	%	*G*	%	
Gas-phase								
(0.58)	D_2 (760)	—	(1.72)	(1.32)	77	(0.39)	23	57
(0.61)	D_2 (760)	3	(1.85)	(0.60)	**87**	(0.09)	**13**	23
Condensed phase								
	0.2 N H_2SO_4/MeOH				**48**		**52**	
	10 M $LiClO_4$/MeOH				**75**		**25**	

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.
[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature $G(D_3^+)$ values.[7]
[d] *C-3 Product*/*C-4 product*=14:86.
[e] A similar amount of benzyl methyl ether is detected (GC).

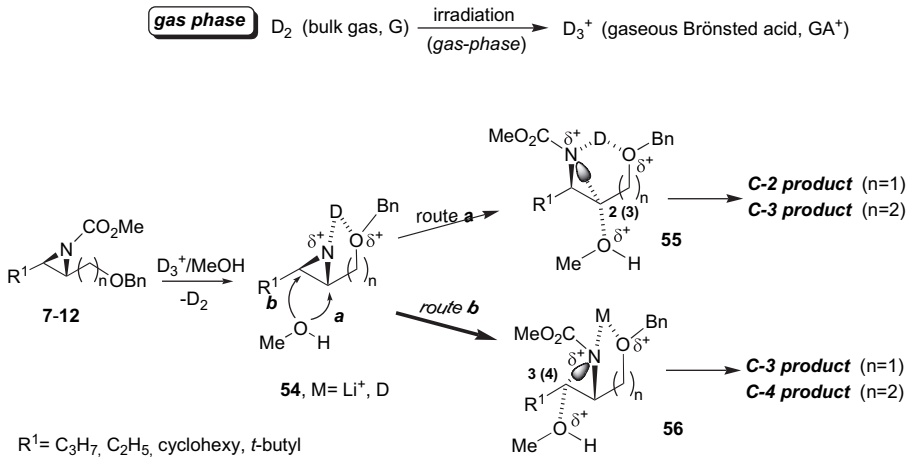


Scheme 4.

(97%), as practically the only reaction product, accompanied by only a small amount (3%) of the addition products, the MUs **37** and **38**. The formation of the cyclic compound **53** may be rationalized by admitting a coordination of the metal (Li^+) to the aziridine nitrogen with partial polarization along the C(4)–nitrogen bond, as shown in structure **51** (Scheme 5). Subsequent entropically favored attack of the oxygen of the terminal OBn group on the partially positive C(4) aziridine carbon of **51**, followed by S_N2 attack of MeOH on the intermediate oxonium ion **52** determines the formation of the cyclic product **53** and the delivery of benzyl methyl ether, which, actually, can be recovered from the crude reaction mixture. The occurrence of a certain steric hindrance between the two aliphatic chains in the formation of the corresponding cyclic product, may be the cause of the



Scheme 5.



Scheme 6.

different behavior of aziridine (*Z*)-**12** under the same reaction conditions (Tables 1–3).

Application of the gas-phase opening conditions to aziridines **7–12** (Scheme 6) results in a general increase in the C-3 (from aziridines **7–9**) and C-4 regioselectivity (from aziridines **11** and **12**), which corresponds to a decidedly preferential attack of the nucleophile on the aziridine carbon further from the OBn heterofunctionality. In this respect, the complete C-3 regioselectivity obtained under these conditions with aziridines (*E*)-**7** and (*Z*)-**8**, and the large increase in C-4 regioselectivity observed with aziridines (*E*)-**11** and (*Z*)-**12** are noteworthy, considering that, commonly, it is difficult to obtain a complete or high regioselectivity in aziridine systems that are not affected by serious electronic and/or steric effects.

Due to the serious steric hindrance by the *tert*-butyl group around the aziridine C(3) carbon, the opening reaction of aziridine (*E*)-**10** is still largely C-2 regioselective (69%) also under gas-phase opening conditions, but a clear increase in C-3 regioselectivity is observed if compared with the corresponding opening reaction carried out in the cd phase under standard conditions (H^+/MeOH) (from 3 to 31%). This is the best demonstration that the gaseous operating conditions are particularly effective in promoting the bidentate chelating ability of the proton (actually D^+ in the gas-phase) between the two basic centers of the molecule, the aziridine nitrogen and the ether oxygen (–OBn), with a consequent clear influence on the regioselectivity of the addition process.[1]

As previously admitted for the corresponding oxirane systems,[1] the results obtained in the gas-phase with aziridines **7–12** can be rationalized by invoking the occurrence of a chelated bidentate species through D^+, such as **54**. The stereoelectronic factors associated with the nucleophilic opening process of the intermediate **54** through the corresponding regioisomeric partially polarized species **55** (*route **a***) and **56** (*route **b***) favor **56** and, as a consequence, the formation of the *C-3 product*, from aziridines **7–10** (n=1), and the *C-4 product*, from aziridines **11** and **12** (n=2), with an increased preferential attack of the nucleophile (MeOH) on the aziridine carbon further from the terminal –OBn group (Scheme 6).[1,2]

It is interesting to note that the 1,2-adducts/rearranged product ratio [namely, (MUs **35**+**36**)/**50** ratio] and the 1,2-adducts/cyclic product ratio [namely, (MUs **37**+**38**)/**53** ratio] found in the opening reactions of aziridines (*E*)-**10** and (*E*)-**11**, respectively, under chelating conditions in the cd phase ($LiClO_4$/MeOH), consistently increase under gas-phase operating conditions: from 1:15 to 80:20 for (*E*)-**10** and from 3:97 to 64:36 for (*E*)-**11**. Moreover, aziridine (*E*)-**10**, which is recovered as mostly unreacted under $LiClO_4$/MeOH conditions in the cd phase, completely reacts under gas-phase operating conditions. Similarly, the reaction of aziridine (*E*)-**9** in the gas-phase is particularly clean, if compared with that under chelating conditions in the cd phase, and the corresponding addition products (the MUs **33** and **34**) are the only constituents of the crude reaction mixture.

All these results indicate that in the cd-phase chelating conditions ($LiClO_4$/MeOH), probably as a result of the presence of MeOH as the solvent, and its competitive coordination with the metal cation (Li^+), the aziridine nitrogen–Li^+ coordination and the subsequently induced polarization of the aziridine C–N bond are consistently lower than that determined by the D^+ in the gas-phase (D_2 as the bulk gas), to the point that attack by the external nucleophile (MeOH, intermolecular addition reaction) can be consistently precluded. Consequently, under these conditions, low yields of direct addition products (the corresponding MUs) are obtained and/or competitive reaction pathways, such as rearrangement processes or entropically favored intramolecular addition reactions, can more extensively occur, with the formation, in general, of complex reaction mixtures. No similar behavior was observed in the opening reactions of the structurally related epoxides **1–6**, where the corresponding 1,2-addition products were the *only reaction products*, independent of the reaction conditions. This observation points to a coordinating ability of the oxirane oxygen of epoxides **1–6** toward Li^+ in the cd phase and D^+ in the gas-phase decidedly superior to that of the nitrogen of aziridines **7–12**, as a consequence of the inductive and conjugative electron-withdrawing effects of the methoxycarbonyl group, which makes the lone pair of the aziridine nitrogen less available for coordination.[9]

4. Conclusions

The results obtained in the opening reactions with MeOH of activated aziridines **7–12**, both in the cd phase (MeOH/H_2SO_4 and $LiClO_4$/MeOH) and in the gas-phase operating conditions (MeOH/D_3^+ in D_2) indicate that the gas-phase opening protocol is particularly effective in promoting the occurrence of chelated bidentate species through D^+, and as a consequence determining an increased regioselectivity in favor of that regioisomer deriving from an attack of the nucleophile (MeOH) on the aziridine carbon further from the terminal OBn group. Interestingly, this effect is consistently found also in a sterically hindered aziridine system, such as the *tert*-butyl-substituted aziridine (*E*)-**10**. In spite of the well-known chelating ability of Li^+, the $LiClO_4$/MeOH protocol turned out to be decidedly less effective than the gas-phase protocol as regards the regioselectivity (a scarce increase in the *C-3 product*/*C-2 product* or *C-4 product*/*C-3 product* ratio), and in determining even the result of the addition reaction. In fact, in some cases, complex reaction mixtures are obtained in which very low amount of the expected 1,2-addition products (the corresponding MUs) is present, whereas rearranged or intramolecular addition products are the main reaction products.

5. Experimental

5.1. General

^1H and ^{13}C NMR spectra were determined with a Bruker AC 200 spectrometer on a $CDCl_3$ solution using tetramethylsilane as the internal standard. FTIR spectra for comparison between compounds were taken with a Mattson 3000 FTIR spectrophotometer. All reactions were followed by TLC on Alugram SIL G/UV_{254} silica gel sheets (Macherey–Nagel) with detection by UV or by 0.5% phosphomolybdic acid in 95% EtOH. Preparative TLC was performed on 2.0 or 0.5-mm Machery–Nagel DC-Fertigplatten UV_{254} silica gel plates. Flash chromatographies were performed by using silica gel 60 (Macherey–Nagel 230–400 mesh). Epoxides **1–6** and the corresponding mixtures of regioisomeric azido alcohols **13–24** were prepared as previously described.[2,5]

5.1.1. Synthesis of aziridines 7–12: typical procedure. A solution of the 87:13 mixture of azido alcohols **13** and **14** (0.69 g, 2.77 mmol)[2] in MeCN (3 mL) was treated with PPh_3 (0.73 g, 2.77 mmol) and the reaction mixture was stirred at room temperature until the evolution of N_2 was observed (30 min), then gently refluxed overnight. After cooling, the solvent was removed under vacuum (rotating evaporator) and the residue was repeatedly extracted with boiling petroleum ether (bp 40–60 °C). Evaporation of the organic extracts afforded an oily residue consisting of the unactivated aziridine (*E*)-**25** (0.60 g) [FTIR ν 3286, 1454, 1377, 1201, 1099 cm^{-1}; ^1H NMR δ 7.19–7.28 (m, 5H), 4.47 (s, 2H), 3.52 (dd, 1H, J=10.5, 4.4 Hz), 3.33 (dd, 1H, J=10.5, 5.9 Hz), 1.84–1.90 (m, 1H), 1.68–1.76 (m, 1H), 1.13–1.60 (m, 4H), 0.86 (t, 3H, J=6.8 Hz)] in a mixture with PPh_3 and Ph_3PO, which was dissolved in anhydrous Et_2O (30 mL) and treated at 0 °C with ClCOOMe (0.34 mL, 4.34 mmol) in the presence of NEt_3 (0.61 mL, 4.34 mmol). After 2 h stirring at the same temperature, dilution with Et_2O, and evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution yielded a crude liquid product (0.63 g) consisting of aziridine (*E*)-**7**, which was subjected to flash chromatography. Elution with a 9:1 hexane/AcOEt mixture afforded pure *(E)-1-(benzyloxy)-2,3-[(N-methoxycarbonyl)azirido]-hexane* (**7**) (0.32 g, 44% yield), as a liquid. (Found: C, 68.73; H, 7.87; N, 5.09. $C_{15}H_{21}NO_3$ requires: C, 68.42; H, 8.04; N, 5.32.) FTIR ν 1722, 1454, 1307, 1205 cm^{-1}; ^1H NMR δ 7.22–7.40 (m, 5H), 4.51 (s, 2H), 3.76 (dd, 1H, J=10.8, 3.8 Hz), 3.67 (s, 3H), 3.58–3.70 (m, 1H), 2.43–2.60 (m, 2H), 1.21–1.75 (m, 4H), 0.96 (t, 3H, J=7.2 Hz). ^{13}C NMR δ 162.4, 137.9, 128.5, 127.7, 127.6, 73.0, 67.5, 53.3, 42.6, 40.5, 33.2, 20.3, 13.9. MS (*m*/*z*) 59, 77, 91, 114, 142, 263 (M^+).

Aziridines **8–12** were prepared following the typical procedure (see Supplementary data).

5.1.2. Methanolysis of aziridines 7–12 with 0.2 N H_2SO_4 in MeOH: typical procedure. A solution of aziridine (*E*)-**7** (0.072 g, 0.27 mmol) in 0.2 N H_2SO_4 in MeOH (3 mL) was stirred at room temperature for 2 h. Dilution with Et_2O and evaporation of the washed (saturated aqueous $NaHCO_3$ and saturated aqueous NaCl) organic solution afforded a crude liquid product (0.070 g, 88% yield) consisting of a 9:1 mixture of regioisomeric methoxyurethanes (MUs) **32** (*C-3 product*) and **31** (*C-2 product*) (GC), which was subjected to preparative TLC using a 9:1:0.1 hexane/AcOEt/MeOH mixture as the eluant. Extraction of the most intense band afforded pure *anti 1-(benzyloxy)-3-methoxy-2-N-(methoxycarbonylamino)-hexane* (**32**) (0.035 g, 44% yield), as a liquid. (Found: C, 64.74; H, 8.22; N, 4.58. $C_{16}H_{25}NO_4$ requires: C, 65.06; H, 8.53; N, 4.74.) FTIR ν 3435, 1712, 1537, 1454, 1251, 1085 cm^{-1}; ^1H NMR δ 7.16–7.41 (m, 5H), 5.07 (d, 1H, J=8.7 Hz, NH), 4.51 (s, 2H), 3.85–3.90 (m, 1H), 3.66 (s, 3H), 3.60–3.70 (m, 1H), 3.49 (dd, 1H, J=9.3, 4.1 Hz), 3.35 (s, 3H), 3.25–3.40 (m, 1H), 1.19–1.56 (m, 4H), 0.85 (t, 3H, J=6.2 Hz). ^{13}C NMR δ 157.0, 138.3, 128.6, 127.9, 80.8, 73.4, 69.1, 58.5, 53.1, 52.4, 32.9, 18.8, 14.5. MS (*m*/*z*) 77, 91, 101, 142, 174, 295 (M^+).

The methanolysis reactions of aziridines **8–12** were carried out following the typical procedure (see Supplementary data).

5.1.3. Separation of the mixture of azido alcohols 13 and 14. The 87:13 mixture of azido alcohols **13** and **14** (0.20 g)[2] was subjected to preparative TLC (a 9:1:0.1 hexane/AcOEt/MeOH mixture was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **13**) afforded pure azido alcohols **13** (0.13 g, 65% yield) and **14** (0.012 g, 6% yield).

anti 1-(Benzyloxy)-3-azido-2-hexanol (**13**): a liquid. (Found: C, 62.59; H, 7.92; N, 16.57. $C_{13}H_{19}N_3O_2$ requires: C, 62.63; H, 7.68; N, 16.85.) FTIR ν 3445, 2102, 1454, 1290, 1098 cm^{-1}; ^1H NMR δ 7.26–7.31 (m, 5H), 4.51 (s, 2H), 3.59–3.68 (m, 1H), 3.53 (d, 2H, J=3.0 Hz), 3.35–3.48 (m, 1H), 1.29–1.58 (m, 4H), 0.92 (t, 3H, J=6.4 Hz). ^{13}C NMR δ 137.6, 128.4, 127.8, 73.4, 72.4, 71.0, 63.9, 32.3, 19.4, 14.1.

anti 1-(Benzyloxy)-2-azido-3-hexanol (**14**): a liquid. (Found: C, 62.46; H, 7.51; N, 16.49. $C_{13}H_{19}N_3O_2$ requires: C, 62.63; H, 7.68; N, 16.85.) FTIR ν 3450, 2102, 1454, 1287, 1099 cm^{-1}; ^1H NMR δ 7.30–7.36 (m, 5H), 4.58 (s, 2H), 3.73 (d, 2H, J=6.0 Hz), 3.48–3.69 (m, 2H), 1.26–1.65 (m, 4H), 0.94 (t, 3H, J=6.8 Hz). ^{13}C NMR δ 137.6, 128.7, 128.1, 73.8, 71.9, 70.1, 65.4, 35.7, 19.1, 14.2.

5.1.4. Synthesis of MUs 31, 36, and 39: typical procedure. A solution of azido alcohol **13** (0.094 g, 0.38 mmol) in anhydrous THF (1 mL) was added to a stirred suspension of NaH (0.030 g of a 60% dispersion in mineral oil, 0.75 mmol) in anhydrous THF (3 mL). After 30 min stirring at room temperature, MeI (0.568 g, 0.25 mL, 4.0 mmol) was added and stirring was prolonged for 18 h at the same temperature. Dilution with ether and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude product consisting of methoxy azide **43** (0.090 g, 90% yield), which was directly used in the next step without any further purification. FTIR ν 3368, 2104, 1454, 1280, 1099 cm^{-1}; ^1H NMR δ 7.30–7.36 (m, 5H), 4.58 (s, 2H), 3.65 (d, 2H, J=3.4 Hz), 3.55–3.76 (m, 1H), 3.39 (s, 3H), 3.25–3.34 (m, 1H), 1.27–1.63 (m, 4H), 0.94 (t, 3H, J=6.3 Hz).

A solution of **43** (0.090 g, 0.34 mmol) in anhydrous Et_2O (1 mL) was added to a stirred suspension of $LiAlH_4$ (0.053 g, 1.39 mmol) in anhydrous Et_2O (3 mL). After 2 h stirring at the same temperature, the reaction mixture was diluted with Et_2O and carefully treated with water and 10% aqueous NaOH in order to destroy the excess of hydride. Evaporation of the organic solution afforded a crude product, consisting of amine **44** (0.069 g, 85% yield) [FTIR ν 3410, 3340, 1456, 1398, 1099 cm^{-1}; ^1H NMR δ 7.29–7.33 (m, 5H), 4.54 (s, 2H), 3.60–3.63 (m, 2H), 3.44 (s, 3H), 3.21 (dd, 1H, J=9.3, 4.4 Hz), 2.92–3.03 (m, 1H), 1.52–1.67 (m, 2H, NH_2), 1.20–1.50 (m, 4H), 0.92 (t, 3H, J=6.3 Hz)], which was dissolved in anhydrous Et_2O (3 mL) and treated with ClCOOMe (0.024 mL, 0.32 mmol) in the presence of Et_3N (0.044 mL, 0.32 mmol). After 18 h stirring at room temperature, dilution with Et_2O and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solution afforded a crude product (0.077 g), which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *anti 1-(benzyloxy)-2-methoxy-3-(methoxycarbonylamino)-hexane* (**31**) (0.048 g, 47% yield), as a liquid. (Found: C, 65.37; H, 8.28; N, 4.50. $C_{16}H_{25}NO_4$ requires: C, 65.06; H, 8.53; N, 4.74.) FTIR ν 3441, 1714, 1546, 1454, 1249, 1089 cm^{-1}; ^1H NMR δ 7.27–7.32 (m, 5H), 5.20 (d, 1H, J=9.3 Hz, NH), 4.54 (d, 1H, J=12.3 Hz), 4.50 (d, 1H, J=12.3 Hz), 3.74–3.97 (m, 1H), 3.64 (s, 3H), 3.51–3.60 (m, 2H), 3.42 (s, 3H), 3.31–3.37 (m, 1H), 1.24–1.47 (m, 4H), 0.88 (t, 3H, J=6.3 Hz). ^{13}C NMR δ 157.3, 138.0, 128.6, 127.9, 81.5, 73.7, 70.3, 58.6, 52.1, 51.8, 33.1, 19.4, 14.1. MS (*m*/*z*) 77, 87, 91, 142, 177, 295 (M^+).

MUs **36** and **39** were prepared following the typical procedure (see Supplementary data).

5.1.5. Methanolysis of aziridines 7–12 with 10 M $LiClO_4$ in MeOH: typical procedure. A solution of aziridine (*E*)-**7** (0.032 g, 0.12 mmol) in 10 M $LiClO_4$ in MeOH (1 mL) was stirred at 80 °C for 18 h. After cooling, dilution with Et_2O and evaporation of the washed (water) organic solution afforded a crude liquid product (0.034 g, 96% yield) consisting of a 95:5 mixture of MUs **32** (*C-3 product*) and **31** (*C-2 product*) (GC).

The same procedure applied to aziridine (*E*)-**10** (0.050 g, 0.19 mmol) at 80 °C for 5 days afforded a crude product (0.047 g) consisting of a very complex reaction mixture (GC), which was subjected to preparative TLC using a 7:3 hexane/AcOEt mixture.[8a] Extraction of the two most intense bands (the slower moving band contained **50**) afforded the unreacted aziridine (*E*)-**10** (0.030 g) and pure *syn 1-(benzyloxy)-3,4-dimethyl-4-methoxy-2-(methoxycarbonylamino)-pentane* (**50**) (0.005 g, 8% yield), as a liquid. (Found: C, 65.78; H, 8.71; N, 4.47. $C_{17}H_{27}NO_3$ requires: C, 65.99; H, 8.80; N, 4.53.) FTIR ν 3355, 1720, 1250, 1448, 1084 cm^{-1}; ^1H NMR δ 7.25–7.38 (m, 5H), 5.82–5.96 (m, 1H, NH), 4.56 (d, 1H, J=12.0 Hz), 4.46 (d, 1H, J=12.0 Hz), 3.47–3.82 (m, 3H), 3.65 (s, 3H), 3.17 (s, 3H), 1.97–2.12 (m, 1H), 1.18 (m, 3H), 1.12 (s, 3H), 0.90 (d, 3H, J=7.1 Hz). ^{13}C NMR δ 157.7, 128.6, 127.8, 127.7, 73.3, 70.8, 59.4, 53.7, 49.1, 42.0, 24.3, 21.5, 20.1. MS (*m*/*z*) 73, 91, 101, 188, 208, 309 (M^+).

The same procedure applied to aziridine (*E*)-**11** (0.050 g, 0.19 mmol) afforded a crude product (0.040 g) essentially consisting of the cyclic compound **53** and the benzyl methyl ether (^1H NMR), which was subjected to flash chromatography. Elution with a 9:1 hexane/AcOEt mixture afforded the benzyl methyl ether (0.014 g, 65% yield) [FTIR ν 1454, 1101 cm^{-1}; ^1H NMR δ 7.22–7.45 (m, 5H), 4.46 (s, 2H), 3.39 (s, 3H)] and *trans 2-ethyl-3-(methoxycarbonylamino)-tetrahydrofurane* (**53**) (0.018 g, 54% yield), as a liquid. (Found: C, 55.68; H, 8.64; N, 7.81. $C_8H_{15}NO_3$ requires: C, 55.47; H, 8.73; N, 8.09.) FTIR ν 3315, 2954, 2879, 1705, 1543, 1458, 1244 cm^{-1}; ^1H NMR δ 4.79–4.96 (m, 1H), 3.79–4.00 (m, 3H), 3.65 (s, 3H), 3.50 (dd, 1H, J=12.2, 5.3 Hz), 2.14–2.36 (m, 1H), 1.65–1.84 (m, 1H), 1.38–1.65 (m, 2H), 0.95 (t, 3H, J=7.4 Hz). ^{13}C NMR δ 154.7, 85.8, 66.2, 55.8, 52.3, 33.4, 26.7, 10.3. MS (*m*/*z*) 59, 70, 100, 115, 144, 173 (M^+).

5.2. Reactions in the gas-phase

5.2.1. Materials. Oxygen and trimethylamine were high-purity gases from Matheson Gas Products Inc., deuterium (99.98%) was purchased from Aldrich and all were used without further purification. The chemical purity of the starting activated aziridines **7–12** was verified by analytical gas chromatography on the same columns used for the analysis of their gas-phase products.

5.2.2. Procedure. The gaseous mixtures were prepared by conventional procedures with the use of a greaseless vacuum line. The selected aziridine derivative (0.007–0.009 mmol), methanol (0.021–0.026 mmol), the thermal radical scavenger O_2, and trimethylamine were introduced into carefully outgassed 250-mL Pyrex bulbs, each equipped with a break-seal arm. The bulbs were filled with D_2, and were then allowed to come to room temperature; the fragile ampoules were broken, and the gaseous components were

allowed to mix before being subjected to the irradiation (γ-rays). The gaseous mixtures were submitted to γ-irradiation at a constant temperature (37.5 °C) in a ^{60}Co 220 Gammacell from Nuclear Canada Ltd (dose: 1.5×10^4 Gy; dose rate: 1×10^4 Gy h^{-1}, determined with a Fricke dosimeter). Control experiments, carried out at doses ranging from 1×10^4 to 1×10^5 Gy, showed that the relative yields of products are largely independent of the dose. In order to verify the stability of the reaction products, the MUs **31**–**42** were placed with the gaseous members (D_2, O_2, and NMe_3) into Pyrex bulbs and γ-irradiated at the same experimental conditions adopted for the corresponding epoxides (37.5 °C, dose: 1.5×10^4 Gy). In all cases, the MUs **31**–**42** were recovered unchanged and no trace of isomerization products was found.

5.2.3. Product analysis. The radiolytic products were analyzed by injecting measured portions of the homogeneous reaction mixture into a Hewlett–Packard 5890 series II gas chromatograph, equipped with a flame ionization detector. In order to prevent selective loss of the reaction products by adsorption on the glass of the reaction bulb (and to obtain reproducible and meaningful reaction yields), the analysis was repeated after careful washing of the bulb walls with anhydrous ether. Satisfactory agreement between the results of the gaseous mixture and the ether solution analysis was found in all runs. The products were identified by comparison of their retention volumes with those of authentic reference compounds on the following columns:

(*i*) A 30 m long, 0.20 mm i.d. Carbowax 20™ Ultraperformance capillary column, operating at 180 °C; (*ii*) a 30 m long, 0.32 mm i.d. Supelcowax 10™ fused silica capillary column, operating at temperatures ranging from 50 to 200 °C, 4 °C min^{-1}. The identity of the products was further confirmed by GLC–MS, using a Hewlett–Packard 5890A gas chromatograph in line with a HP 5971A quadrupole mass spectrometer. Their yields were determined from the areas of the corresponding eluted peaks, using the internal standard method and individual calibration factors to correct for the detector response. The results given in Tables 1–3 are the average of at least three measurements taken on at least two different runs for each point.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2007.04.040.

References and notes

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