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The Formation of 1,4-Disubstituted Piperazines from 1-Substituted Aziridines

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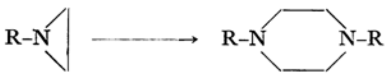
The dimerization of aziridines to piperazines has received little attention.[1-5] Heine and his co-workers reported that 1-arylsulfonylaziridines and 1-phenylaziridine, on treatment with sodium iodide, were dimerized to the corresponding piperazines.[6] Recently, Dick found the reaction of certain 1-alkylaziridines with alkyl or alkenyl halides gave nearly quantitatively the corresponding 1,1,4-trialkylpiperazinium halides.[7]

In the course of our study we found that the treatment of 1-cyclohexylaziridine with four equivalents of phenylmagnesium bromide gave a 41% yield of 1,4-dicyclohexylpiperazine. The structure of this piperazine was established by a study of the melting point,[8] by its elemental analysis and by a study of its infrared spectrum. Similarly, 1-benzylaziridine was dimerized to the corresponding 1,4-disubstituted piperazine. Control runs in the absence of the Grignard reagent resulted in the recovery of aziridines. Using half an equivalent of magnesium bromide instead of the Grignard reagent, 1-substituted aziridines in refluxing methanol were dimerized to the corresponding 1,4-disubstituted piperazines in 50—70% yields. The dimerization of aziridines also occurred with a catalytic amount of other Lewis acids. These results are summarized in Table 1.

TABLE 1. REACTION OF 1-SUBSTITUTED AZIRIDINES WITH LEWIS ACIDS OR PHEYLMAGNESIUM BROMIDE



Reaction	Substituent	Catalyst	Yield %	Mp°C or Bp°C/mmHg
1	i-C_3H_7	$MgBr_2$	70	97/20
2	n-C_4H_9	$MgBr_2$	43	134/27[c]
3	C_6H_{11}	$MgBr_2$	72	117–118[d,e]
4		$SnCl_4$	60	
5		$ZnCl_2$	50	
6		$BF_3O(C_2H_5)_2$	52	
7		$AlCl_3$	66	
8		C_6H_5MgBr	41	
9	$C_6H_5CH_2$	$MgBr_2$[a,b]	66	90–91[f,g]
10		C_5H_6MgBr	15	

	Formula	Elemental analysis					
		Calcd, %			Found, %		
		C	H	N	C	H	N
1	$C_{10}H_{22}N_2$	70.53	13.02	16.45	70.20	12.93	16.16
2	$C_{12}H_{26}N_2$	72.66	13.21	14.12	72.78	13.17	13.82
8	$C_{16}H_{30}N_2$	76.74	12.08	11.19	76.66	11.81	10.98
10	$C_{18}H_{22}N_2$	81.16	8.33	10.52	81.01	8.70	10.35

a) THF as solvent. b) See Experimental. c) Lit. bp 114°C/10 mmHg.[7] d) Lit. mp 118°C.[8]
e) Recrystallized from acetonitrile. f) Lit. mp 92°C.[9]
g) Recrystallized from ethanol.

It is well known that the reaction of ethylene oxide with a Grignard reagent gives a primary alcohol. However, the reaction of aziridines with this reagent did not give secondary amines, but piperazines. The catalytic action of the Grignard

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[9] Heilbron, "Dictionary of Organic Compounds," ed. by A. H. Cook and E. R. H. Jones, Oxford University Press, New York, N. Y. (1953), p. 216.

reagent seems to be the following: Initially, the magnesium of this reagent coordinates to the basic aziridine nitrogen; then the electrophilic ring carbon attacks not the carbon of the Grignard reagent, but another aziridine nitrogen, and a piperazine is formed. The reason for this seems to be that the nucleophilicity of the Grignard reagent is less strong than that of aziridine nitrogen. In view of this, it is obvious that Lewis acids are also more effective catalysts than the Grignard reagent.

Experimental

Reaction of 1-Substituted Aziridines with Phenylmagnesium Bromide. An 80 m*l* portion of a dry ether solution containing 0.16 mol of phenylmagnesium bromide was prepared, and to this solution there was added rapidly 0.04 mol of aziridine dissolved in 50 m*l* of dry ether. The mixture was then refluxed for 7 hr and allowed to stand at room temperature overnight. The solution was decomposed by pouring in 40 g of ammonium chloride and ice. The ether layer was washed with water and dried over anhydrous potassium carbonate. The solvent was evaporated and allowed to stand in a refrigerator overnight. The oily brown residue was treated with 10 m*l* of acetonitrile. A white precipitate was separated by filtration and recrystallized.

Reaction of 1-Substituted Aziridines with Magnesium Bromide. A mixture of 0.02 mol of the aziridine, 1.84 g of magnesium bromide, and 40 m*l* of methanol was refluxed for 7 hr. The solvent was evaporated, and the residue was treated with a slight excess of potassium hydroxide and water. The solution was extracted several times by ether. The ether layer was dried over anhydrous potassium carbonate and evaporated. The crude product was recrystallized or distilled. In the case of 1-benzylaziridine, a white crystal was obtained as a by-product; mp 141—142°C.