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1-DIPHENYLPHOSPHINYL-2,2-DIMETHYLAZIRIDINE - A NEW PRECURSOR OF α,α-DIMETHYLARYLALKYLAMINES

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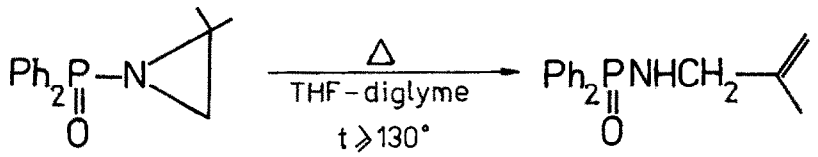
Abstract: The new synthesis of α,α-dimethylarylalkylamines from 1-diphenylphosphinyl-2,2-dimethylaziridine is described.

Among the variety of sympathomimetic amines, α,α-dimethyl-β-phenylethylamine derivatives (phenthermine analogues) exhibit relatively wide range of biological activity. They possess CNS-stimulant activity[1,2] and antidepressant properties[1-3]. Some of them (e.g. chlorphenthermine, mephenthermine) are known as appetite-suppressing agents[1,2,4,5]. Recently, phenthermine analogues are used in the synthesis of new β-blockers[6-8].

Synthesis of this class of compounds is usually achieved by Ritter reaction[4,9,10], by Hofmann amide degradation[2,11] or by reduction of tertiary nitro compounds[12,13], but these methods are not applicable in all cases.

Our interest in the preparation of new compounds with β-adrenergic antagonist activity, prompted us to search for the more general method of the synthesis of α,α-dimethylarylalkylamines. One of the possibilities seemed to be the reaction of N-activated 2,2-dimethylaziridines with C-nucleophilic reagents. Although the cleavage of various N-substituted aziridines by nucleophiles is well documented[14], almost no data pertinent to the reaction with Grignard compounds are so far available[15,16]. We now report the reaction of readily accesible[17] 1-diphenylphosphinyl-2,2-dimethylaziridine 1 with some selected Grignard reagents.

In the preliminary experiments, we have found, that the reaction of 1 with phenylmagnesium bromide does not occur in boiling tetrahydrofuran but requires higher temperatures. Considering the possibility of thermal rearrangement[18] of starting aziridine in the course of Grignard reaction, we have checked the behaviour of compound 1 in the pyrolytic conditions.



1 2

We have found, that continous heating of 1-diphenylphosphinyl-2,2-dimethylaziridine 1 in the mixture of THF-diglyme (1:5) at the temperature range from 120° to 150° produces increasing amounts of N-(2-methylallyl)diphenylphosphinamide 2[19] (see Table 1), accompanied by starting material 1 and two unidentified minor products.

Table 1

^{31}P-NMR determined yields of 2 depending on temperature and time of reaction

120°/0.5h	130°/0.5h	140°/0.5h	150°/0.5h	150°/1h
0%	6%	23%	33%	50%

It becomes clear from the above experiments, that the temperature of the mixture during Grignard reaction should not exceed 130°.

On the basis of these results we have performed the reaction of 1 with various Grignard reagents according to the following general procedure: To a solution of Grignard reagent (prepared from 20 mmoles of the respective halide) in dry tetrahydrofuran (20 ml), 1-diphenylphosphinyl-2,2-dimethylaziridine (4 mmoles) and diglyme (20 ml) were added. Tetrahydrofuran was then distilled off to achieve the required temperature of the mixture (120°-130°).

The mixture was refluxed with stirring as this temperature for 3h. The progress of the reaction was controlled by TLC. Saturated ammonium chloride solution (50 ml) was then added, followed by chloroform extraction. The extract was washed with water, dried (Na_2SO_4) and evaporated in vacuo (1 mm Hg) to give an oil purified by column chromatography on silica and subsequent crystallization. The yields and melting points of products 3 and 4 are summarized in Table 2.

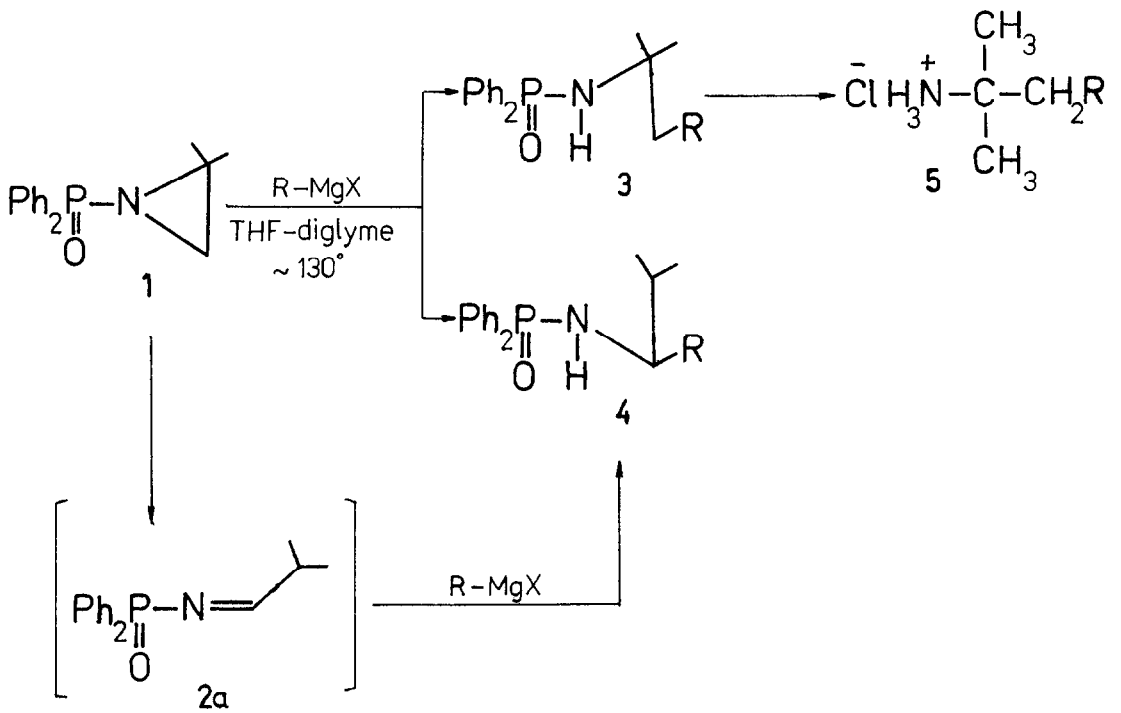
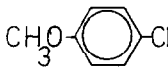
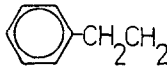
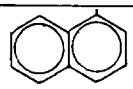
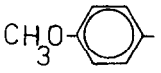
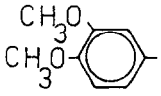


Table 2*

Entry	R	3 **		4		Other compounds
		yield (%)	m.p. (°C)	yield (%)	m.p. (°C)	
a		75	110-12	-	-	
b		65	116-18	-	-	
c		26	***	-	-	25% of $Ph_2P(O)CH_2CH_2CH_2Ph$***
d		42	171-74	28	162-64	
e		30	oil	15	168-71	
f		26	143-45	10	***	
g		25	***	25	***	25% of 1
h		traces	-	21	137-39	43% of 1

* satisfactory IR, NMR (^1H and ^{31}P) spectra and elemental analysis were obtained for compounds 3a,b,d-f and 4d,e,h.

** all compounds exhibit identical chemical shift in their ^{31}P-NMr spectra (δ=19.4±0.1 ppm; $CHCl_3$/85% H_3PO_4).

***not isolated in pure form; structures and yields based on ^1H and ^{31}P-NMR spectra of partially purified compounds.

As indicated in Table 2, the reaction with benzylic Grignard reagents gives the products 3a and 3b in good yield. In the case of less reactive aromatic Grignard reagents, the reaction is more complicated and gives usually the mixture of products 3d-h and 4d-h as well as some amounts of unchanged starting material 1. The product 4 is probably formed by thermal rearrangement of aziridine 1 to N-(2,2-dimethylethylidene)diphenylphosphinamide 2a and subsequent addition of Grignard reagent[20]. Nucleophilic attack on phosphorus was observed only in the case of primary-alkyl type Grignard reagent (c), where 3c and the respective phosphine oxide were formed.

Compounds 3a-g were transformed to amine hydrochlorides 5 in high yields by treatment with methanolic HCl[21].

Acknowledgments

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17. Compound 1 was prepared in 80% yield from 2,2-dimethylaziridine (0.6 mole) and diphenylphosphinic chloride (0.4 mole) in the presence of triethylamine (0.5 mole) (CH_2Cl_2,-5°, 2-3h); m.p. 132°-135°, δ ^{31}P-NMR($CHCl_3$) 27.8 ppm
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19. Compound 2 was isolated in pure form, m.p. 105°-106°, δ ^{31}P-NMR($CHCl_3$) 23.7 ppm, δ ^{1}H-NMR($CDCl_3$) 1.67(s,3H,CH_3), 3.40(m,2H,CH_2), 4.80 and 4.94 (ms,2H, vinylic protons), 7.20-7.96 ppm (m,10H, aromatic protons)
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