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SYNTHESIS OF 1,1'-BIPIPERIDINES BY THE DIRECT N,N-COUPLING OF PIPERIDINES

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Oxidation of piperidines with aqueous alkaline solution of sodium peroxodisulfate in the presence of silver nitrate gave 1,1'-bipiperidines.

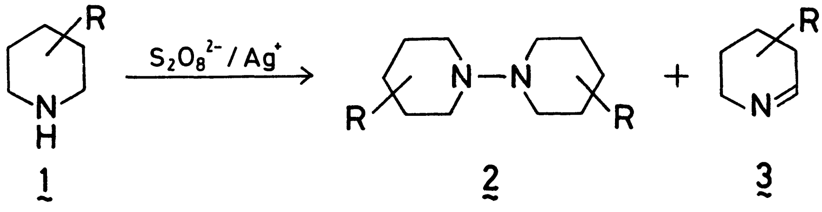
While oxidative N,N-coupling of aromatic secondary amines to the corresponding hydrazines has been accomplished with various oxidizing agents,1) that of aliphatic or cyclic secondary amines has not been known so far. We now wish to report the first example of direct oxidative N,N-coupling of piperidines (1) leading to 1,1'-bipiperidines (2).

The new reaction involves the silver-catalyzed oxidation of piperidines with peroxodisulfate. Thus a 25 % aqueous solution of sodium peroxodisulfate (11.9 g, 0.05 mol) was added dropwise at 0 °C to a stirred mixture of piperidine (4.3 g, 0.05 mol), sodium hydroxide (4.0 g, 0.10 mol) and a catalytic amount of silver nitrate (43 mg, 0.25 mmol) in water (50 ml) and the mixture was stirred for additional 2.5 hr. After saturating the reaction mixture with sodium chloride, it was extracted with ether. The ethereal extract was dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica-gel column using hexane/ethyl acetate (10 : 1) as an eluent to give 1,1'-bipiperidine (2a) (2.0 g, yield 48 %) which was found to be gas chromatographically pure. Evaporative distillation (room temp./0.5 Torr) gave analytically pure sample as colorless needles (mp 19.5 ~ 20.5 °C), which was hitherto regarded as liquid.

Three new dimethyl-1,1'-bipiperidines were prepared in a similar fashion and their structures were established by elemental analyses and spectroscopic properties (MS, IR, ^{1}H- and ^{13}C-NMR). The yields and physical constants of these hydrazines are shown in the Table along with the yield of the only by-products of these reactions, 2,3,4,5-tetrahydropyridines (3).

Although a number of preparative methods have been utilized to prepare 1,1'-bipiperidine (2a),2)~5) all of these require several tedious and costly steps if one wants to start with piperidines (1). Furthermore the overall yields obtained by using these known procedures are usually low (at most 10 %).3),5) By contrast, our present method involves only very simple preparative procedure which guarantees the product (2a) of high purity as well as the high yield (48 %).

Table. Oxidative N,N-coupling of piperidines with peroxodisulfate in the presence of silver nitrate



1 ~ 3	Reaction condition[a]	2			3
		Bp (°C/Torr)	Mp (°C)	Yield(%)[b]	Yield(%)[b]
a (R=H)	A	52.0/0.3	19.5~20.5	61 (48)	1.9
b (R=2-Me)	B	70.0/0.9	liquid[c]	15 (4.5)	26
		71.5/0.9	liquid	(3.5)	
c (R=3-Me)	A	106/17	liquid[d]	62 (30)	1.9
d (R=4-Me)	A	63/0.5	27.0~28.0	39 (24)	8.3

a) Reactions were run at 0~5 °C for 3 hr using the following molar ratio of 1 : $Na_2S_2O_8$: NaOH : $AgNO_3$ = 1 : 1 : 2 : 0.005 (A) and = 1 : 1.5 : 3 : 0.05 (B). b) Yields were determined by GLC. Values in parentheses are isolated yields. c) Diastereomers. d) Unseparable diastereomeric mixture.

The fact that the corresponding 2,3,4,5-tetrahydropyridines (3) were also produced[6] might well be compared with the silver-catalyzed oxidation of pyrrolidine[7] or aliphatic amines[8] with peroxodisulfate in which the products were derived only from imine intermediates and N,N-coupling was not observed. Hence it is particularly noteworthy that the high ratio of the N,N-coupling products was observed in the oxidation of piperidines except for 2-methylpiperidine (1b). The mechanism for the present reaction is now under investigation.

References and Note

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