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RING TRANSFORMATIONS IN REACTIONS OF HETEROCYCLIC HALOGENO COMPOUNDS WITH NUCLEOPHILES (XIV)(1)

Reactions of 6-substituted derivatives of 2-bromopyridine with potassium amide in liquid ammonia

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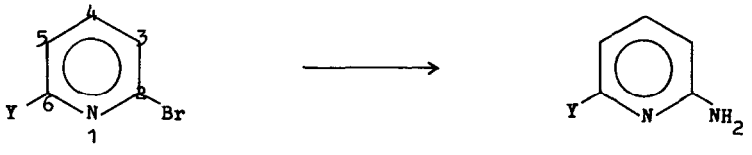
Following up some previous experiments (2,3,4), we reacted more than twenty 6-substituted 2-bromopyridines with the fourfold molar amount of potassium amide in liquid ammonia at -33°. Reaction mixtures were analyzed by GLC; components were isolated and identified by comparison with authentic specimins.

Five reaction types were observed, in two of which (numbers 3 and 5) ring fission taking place.

1. 

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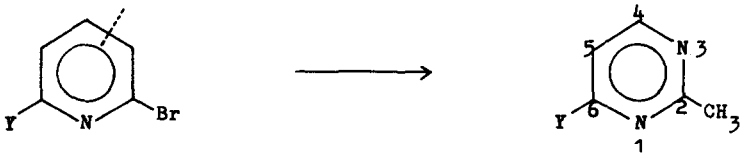
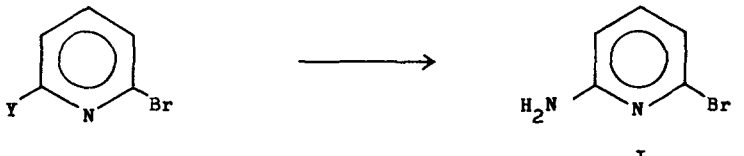
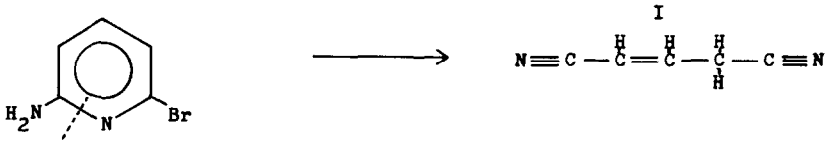
3. 

4. 

5. 

I VIII

Typical aminations are listed in the table.

TABLE

Action of potassium amide on	Reaction time	Reaction product			Reaction type
		Components	Ratio	Total yield	
6-Amino-2-bromopyridine(I)	1.5 min	1,3-Dicyanopropene (VIII)		5%[a]	5
2-Bromo-6-methylpyridine(II) (2)	8 hrs	2-Amino-6-methyl-pyridine(IX)	97-98	20-25%[b]	1 + 2
		4-Amino-6-methyl-pyridine(X)	2-3		
2-Bromo-6-phenylpyridine(III)	15 min	2-Amino-6-phenyl-pyridine(XI)	95	95%	1 + 3
		2-Methyl-6-phenyl-pyrimidine(XII)	5		
2-Bromo-6-ethoxypyridine(IV) (3)	15 min	2-Amino-6-ethoxy-pyridine(XIII)	85	80-85%	1 + 2
		4-Amino-6-ethoxy-pyridine(XIV)	15		
2-Bromo-6-phenoxypyridine(V)	15 min	2-Amino-6-phenoxy-pyridine(XV)	30	90-95%	3+1+2+4
		4-Amino-6-phenoxy-pyridine(XVI)	10		
		2-Methyl-6-phenoxy-pyrimidine(XVII)	55		
		Phenol(XVIII)	5		
2,6-Dibromopyridine(VI) (4)	2 hrs	6-Amino-2-methyl-pyrimidine(XIX)		20%[c]	3 + 1
2-Bromo-6-nitropyridine(VII)	2 min	6-Amino-2-bromo-pyridine(I)	50	10%[d]	4 (followed by 5)
		1,3-Dicyanopropene (VIII)	50		

a Together with polymers and unchanged I.
b Together with 20% unchanged II.
c Together with tar in the formation of which possible I is involved.
d Together with polymers.

Reactions are initiated by abstraction of a proton or addition of an amide ion.

A proton certainly is removed from the amino group in the conversion of 6-amino-2-bromopyridine(I) whereupon by fission of the 1-6 bond, elimination of the bromide ion and prototropy 1,3-dicyanopropene (VIII) is formed. Reactions of substances II, III, IV and V yielding the 2-amino compounds may be initiated by removal of a proton from carbon atom 3 if these transformations proceed via the 2,3-dehydro intermediates. Waiting for the results of aminations of the corresponding 3-deutero compounds, it is assumed, however, that these reactions start with the addition of an amide ion to carbon atom 2.

We are sure that addition of the amide ion to carbon atom 4 is the first step in the transformations of III, V and VI according to reaction type 3. Thereupon the derivatives of 2-methylpyrimidine XII, XVII and XIX are formed in a series of reactions involving the fission of the 3-4 bond (5).

The amide ion adds to carbon atom 6 of VII which is the most positive one in the nucleus of this substance. Thus from VII 6-amino-2-bromopyridine (1) is formed which changes into VIII as described above.

As for the mechanism of aminations of II, IV, V and analogous substances, according to reaction type 2, results of an investigation on these processes will be published shortly by one of us (d.H.) together with H. Boer.

Finally attention is drawn to the fact that the reaction pattern of substance V in our list (2-bromo-6-phenoxypyridine and also derivatives of this substance substituted in the benzene nucleus) is the most complex one.

Identification of products

1,3-Dicyanopropene (VIII, glutacononitrile), isolated by GLC, was identified by microanalysis, molecular weight determination (AEI mass spectrometer), IR and NMR spectroscopy. It was transformed into I again according to Johnson c.s.(5).

Ortho-cyanobenzyl cyanide, much more stable than VIII, was obtained in good yield very recently in this laboratory as a product from an analogous process (reaction of 3-amino-1-bromoisoquinoline with a potassium amide solution) by Miss Dr.G.M. Sanders.

Other products were identified by mixed melting point determinations with authentic specimina. The subsequent compounds were not described previously in the literature: VII (m.p. 133-135°C), XII (m.p. 54-55°C; picrate m.p. 205-206°C), XV (m.p. 62-63°C; picrate m.p. 208-209°C), XVI (m.p.57-58°C; picrate m.p. 176-177°C), XVII (oil; picrate m.p.171-172°C); 4-amino-2-phenylpyridine (m.p. 129-130°C).

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