An Attempt to Convert Heterocyclic Amines into Azides by an Aza-transfer Reaction under Phase-transfer Reaction Conditions

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The conversion of heterocyclic amines into the corresponding azides or tetrazoloazines under phase transfer reaction conditions is described. It was found that this transformation is limited only to aminopyridine (**1a-d**) aminoisoquinoline (**1e**) and 2-aminobenzothiazole (**1f**) derivatives, while other heterocyclic amines (**1g-w**) could not be transformed under these conditions.

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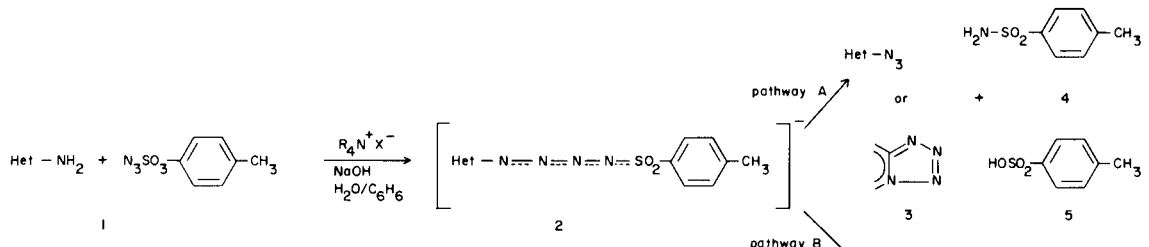
There are several methods for the preparation of organic azido compounds. They include the nitrosation reaction of hydrazines, the reaction of hydrazoic acid with nitroso compounds, the reaction of diazonium salts with nucleophiles such as ammonia, chloramine, hydroxylamine, hydrazine and azide ion, and the substitution of halogen and some other groups by azide ion (1). Arylazides and 3-azido- and 4-azidopyridine have been prepared from *N*-aminopyridinium chloride and the corresponding diazonium salts (2). Recently, the diazo transfer reaction (3) has been extended to the nitrogen containing groups. In this way aliphatic and aromatic primary amines have been converted with *p*-toluenesulphonyl azide into the corresponding azides in the presence of strong bases such as methyllithium or methylmagnesium chloride (4, 5,6). The reaction has been simplified in such a way that instead of organometallic reagents the phase transfer catalysis, which has aroused much interest as a synthetic tool in recent years (7), has been utlized in order to generate the amine anions (8). In this manner a number of aniline derivatives has been converted into the corresponding aryl azides, isolated as triphenylphosphine imine adducts (8).

It seemed worthwhile to extend this latter reaction, as a continuation of our work on the synthetic applications of the aza-transfer reaction (9-17), and to study its scope and limitations in heterocyclic series. Therefore, a number of heterocyclic amino compounds was selected and the transformation was carried out with *p*-toluenesulphoneazide in a two phase system in the presence of a tetraalkylammonium salt as a phase transfer catalyst according to Scheme **1**.

In this reaction, first an anion is formed from the heterocyclic amino compound which reacts with tosylazide to form the 1,4-disubstituted tetrazene anion **2**. This then decomposes in two different ways, dependent on the stability of the anion of the heterocyclic amine, $HetNH^-$, relative to the tosylamine anion, $TosNH^-$. When the relative stability of the heterocyclic amine anion is low, the reaction pathway A is operating. In this way aminopyridine derivatives **1a-d** were converted into the corresponding tetrazolo[1,5-*a*]pyridine derivatives **3a-d**, 1-aminoisoquinoline (**1e**) into tetrazolo[5,1-*a*]isoquinoline (**3e**), and 2-aminobenzothiazole (**1f**) into 2-azidobenzothiazole (**3f**) and tosylamide (**4**). (Table 1).

On the other hand, the increased relative stability of

Scheme I



Ia Pyridyl-2
b 4-Methylpyridyl-2
c 5-Methylpyridyl-2
d Pyridyl-3
e Isoquinolyl-1
f Benzothiazolyl-2
g Pyrimidinyl-2
h 4,6-Dimethylpyrimidinyl-2
i 5-Bromopyrimidinyl-2
j Pyridazinyl-3
k 6-Chloropyridazinyl-3
l 6-Chloro-4-methylpyridazinyl-6
m 6-Chloro-5-methylpyridazinyl-6
n 6-Chloro-4,5-dimethylpyridazinyl-6
o Pyrazinyl-2
p 4-Quinolonyl-3
r 1,2,4-Triazinyl-3
s 5,6-Dimethyl-1,2,4-triazinyl-3
t 1,2,4 (1H)-Triazolyl-3
u 4-Phenylthiazolyl-2
v 5-Nitrothiazolyl-2
w Pyrazolo/3,4-b/pyridyl-3

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Table 1

Conversion of Heterocyclic Amines into Azides or Tetrazoloazines with Tosylazide under the Phase-transfer Reaction Conditions.

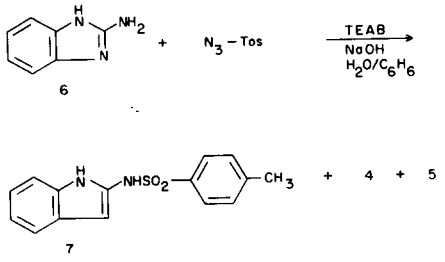
Starting compound	Product		Catalyst	Reaction time (hours)	Yield (a) (%)	m.p.	Literature m.p. (b)
1a	Tetrazolo[1,5-*b*]pyridine	(**3a**)	BTEAC	20	35	152-155°	154-156° (26) 159° (27)
1b	6-methyltetrazolo[1,5-*b*]pyridine	(**3b**)	TEAB	12	39	135-137°	139-141° (28)
1c	7-methyltetrazolo[1,5-*b*]pyridine	(**3c**)	BTEAC	20	40	98-100°	95-97° (28) 97° (27)
1d	3-azidopyridine	(**3d**)	BTEAC	2.5	30	b.p. 76-78° (3 torr)	b.p. 75° (2 torr) (29)
1e	tetrazolo[5,1-*a*]isoquinoline	(**3e**)	BTEAC	6	74	138-140°	140-142° (30)
1f	2-azidobenzothiazole	(**3f**)	TEAB	1	27	110-112°	110-112° (29)

(a) Yield of purified product. (b) Isolated products are in all respects (ir, nmr, ms) identical with the compounds cited in the literature.

the heterocyclic amine anion forces the reaction pathway B, in which heterocyclic amine (**1**), tosylamide (**4**) and nitrogen are formed from the intermediate **2** (18). The formation of the intermediate tetrazene anion **2** in this latter reaction is supported by the following experimental observation. Tosylazide itself decomposes slowly under the experimental conditions. It was found by a separate experiment that 18% of tosylazide was decomposed after 20 hours at reflux temperature if the catalyst was omitted. On the other hand, 78% of the tosylazide was transformed into the tosylamide in the presence of TEAB in the same time, while in the presence of a heterocyclic amine (**1q-w**) tosylazide decomposed quantitatively in 1-3 hours. The transformation of amines into azides does not proceed without the catalyst. Different catalysts have been used in these experiments: tetraethylammonium bromide (TEAB), benzyltrimethylammonium chloride (BTMAC), benzyltriethylammonium chloride (BTEAC) and tetra-*n*-butylammonium bromide (TBAB). The best results were obtained with benzyltriethylammonium chloride and tetraethylammonium bromide as shown in Table 2.

Some side reactions were also observed. When 2-aminobenzimidazole treated under these conditions *N*-(benzimidazolyl-2′)-p-toluenesulphonamide (**7**) (43%) was isolated besides 2-aminobenzimidazole (13%), tosylamide (5.1%) and *p*-toluenesulphonic acid (13%) (Scheme 2). Bedises the azide or tetrazolo compound and tosylamide a small amount of *p*-toluenesulphonic acid (∿3%) was isolated in all cases. (Scheme 2).

Scheme 2



This transformation is limited only to aminopyridine (**1a-d**), aminoisoquinoline (**1e**) and aminobenzothiazole (**1f**) derivatives. Other heterocyclic amines, such as aminopyrimidine (**1g-i**), aminopyridazine (**1j-n**), aminopyrazine (**10**), 3-amino-4-quinolone (**1p**), amino-1,2,4-triazine (**1r-s**), 3-amino-1,2,4(1*H*)triazole (**1t**), 2-aminothiazole (**1u-v**) and 3-aminopyrazolo(3,4-*b*]pyridine (**1w**) derivatives could not be converted into corresponding azides or tetrazoles under these conditions.

Table 2

Conversion of Heterocyclic Amines into Azides or Tetrazoles in the Presence of Various Catalysts after 20 Hours at Reflux

Product		Yield [%] BTMAC	BTEAC	BTEAB	TBAB
Tetrazolo[1,5-*b*]pyridine	(3a)	10	35	32	5
7-methyltetrazolo[1,5-*b*]pyridine	(3c)	24	40	36	20
tetrazolo[5,1-*b*]isoquinoline	(3e)	42	68	64	45

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, ir spectra were recorded on a Perkin-Elmer Infrared spectrophotometer 727B, nmr spectra on a JEOL JNM C60-HL spectrometer and mass spectra on a Hitachi-Perkin-Elmer RMU-6L instrument.

The amino compounds used in this study, and not available commercially, were prepared according to the procedures described in the literature: 3-aminopyridazine (19), 3-amino-6-chloro-4-methylpyridazine (21), 3-amino-6-chloro-5-methylpyridazine (21), 3-amino-6-chloro-4,5-dimethylpyridazine (22), 3-amino-4-quinolone (23), and 3-aminopyrazolo[3,4-*b*]pyridine (24).

General Procedure.

To an aqueous solution of sodium hydroxide (50%, 10 ml.) was added tetraalkylammonium salt (100 mg.), heterocyclic amino compound (2.5 mmoles) and *p*-toluenesulphonylazide (985 mg., 5 mmoles) in benzene (10 ml.). The reaction mixture was refluxed until tosylazide is present in the organic layer (1-20 hours). The reactions were followed by tlc (Merck, DC-Fertigplatten, Aluminiumoxid 150 F254 Typ T, with chloroform:methanol (9:1) as solvent). The organic layer was separated after cooling, the aqueous layer extracted several times with benzene or chloroform, the extracts washed with water and dried over anhydrous sodium sulphate. Evaporation of the combined extracts *in vacuo* yielded the corresponding azido compound or tetrazoloazine, which was purified by column chromatography using silicagel and a mixture of chloroform and methanol (9:1) as eluent. The experimental details are given in Table 1.

The aqueous layer was neutralized with hydrochloric acid (1:1) and extracted with chloroform (3 x 20 ml.). The combined extracts were washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The crude mixture was separated by tlc (Merck PSC Fertigplatten Alumina F254 and a mixture of chloroform and methanol (1:1) as solvent), affording tosylamide as the main byproduct, traces of the unreacted starting amine and traces of *p*-toluenesulphonic acid.

N-(Benzimidazolyl-2′)-*p*-toluenesulphonamide.

When 2-aminobenzimidazole (332.5 mg., 2.5 mmoles) was treated according to the above procedure the following compounds were isolated and identified. The benzene layer and combined chloroform extracts afforded crude *N*-(benzimidazolyl-2′)-*p*-toluenesulphonamide (314 mg., 43%). Recrystallization from ethanol produced a material which is identical in all respects with the compounds described in the literature (25).

The aqueous layer was acidified with hydrochloric acid (1:1) and extracted with chloroform (4 times, 20 ml.). The combined extracts were washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was separated by tlc (Merck, PSC Fertigplatten Alumina F254 and a mixture of chloroform and methanol (1:1) as solvent), affording the starting 2-aminobenzimidazole (43 mg., 13%), tosylamide (44 mg., 5.1%) and *p*-toluenesulphonic acid (110 mg., 13%).

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