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APPLICATION OF AZA-TRANSFER TO ORGANIC COMPOUNDS

REACTIONS BETWEEN HETEROCYCLIC DIAZO COMPOUNDS AND HYDRAZINES

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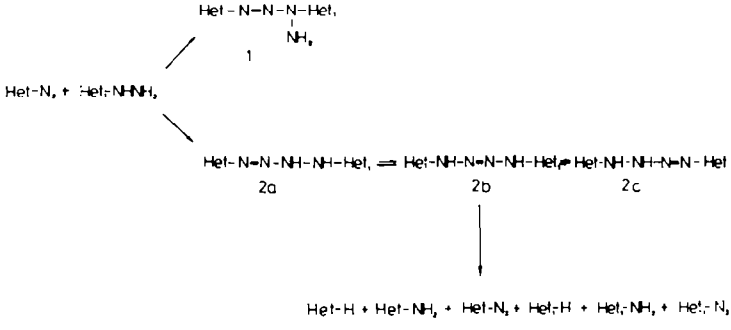
Abstract—Aza-transfer reactions between heterocyclic hydrazines and diazonium salts or between heterocyclic diazo compounds and substituted hydrazines have been investigated. The reaction proceeds via intermediate tetrazenes and labelled compounds have been used to elucidate the reaction mechanism.

Although heterocyclic diazo compounds are valuable synthons for the preparation of heterocyclic systems[1-5] few reactions of these compounds with amino or hydrazino compounds have been investigated. Recently, we demonstrated[6] that heterocyclic hydrazines react with benzenediazonium tetrafluoroborate to give a mixture of products formed from and by decomposition of the intermediate tetrazene.

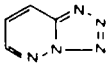
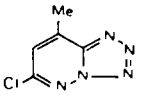
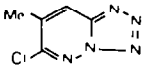
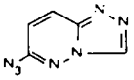
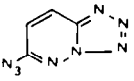
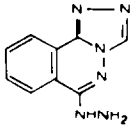
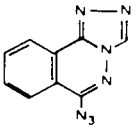
We have now investigated the reaction between heterocyclic diazo compounds and hydrazines and the reaction between heterocyclic hydrazines and diazo compounds or diazonium salts, in order to determine factors which influence aza-transfer[7] within these molecules. Although preliminary investigations on the reaction of heterocyclic diazo compounds with heterocyclic hydrazines showed that aza-transfer occurred to both reactant sides[6] (Scheme 1) we have now established that the reaction can be conducted so as to proceed only in one direction. Various heterocyclic hydrazines, when treated with aryldiazonium salts in an alcoholic solution, where transformed almost quantitatively into the corresponding heterocyclic azides or tetrazoloazines, if azido-tetrazolo isomerization is possible. These transformations are summarized in Table 1. If these reactions were monitored in a NMR probe, it could be established that most of these transformations were complete in a few minutes and products, as indicated in Table 1, were almost quantitative.

These results also indicate that a 1,3-tetrazene (**1**) intermediate is very improbable since azides or tetrazoloazines can be generated only from 1,4-tetrazenes (**2**). This was confirmed by following the progression of the reaction in a NMR probe. If 6-chloro-3-hydrazinopyridazine (**3**) was treated with benzenediazonium tetrafluoroborate at −20° one could observe the immediate formation of a 1,4-tetrazene which is stable at this temperature. If the temperature was gradually raised, the tetrazine slowly decomposed into the final products, 6-chlorotetrazolo(1,5-b)pyridadazine and aniline. At −10°, about 50% of the tetrazene was decomposed after 25 min. At 0° the conversion into the final products was complete in about 35 min. No other intermediates could be detected. A NMR investigation of the $^{15}N_2$-labelled tetrazene (**4**) did not reveal ^{15}N–H coupling which could be expected for a tautomer corresponding to the structure **4b**. The same observations are valid for the tetrazene formed with benzenediazonium tetrafluoroborate labelled either at $^{15}N_1$ or $^{15}N_1$–$^{15}N_2$ in the diazonium group. Therefore we must accept that even at low temperatures the prototropic changes were fast and that a rapid equilibrium between the corresponding tautomeric forms (**4a**, **4b** and **4c**) existed. 3-Hydrazino-6-chloropyridazine and benzene diazonium tetrafluoroborate were selected as model compounds for the above NMR spectroscopic investigation of aza-transfer because the starting hydrazino



Scheme 1.

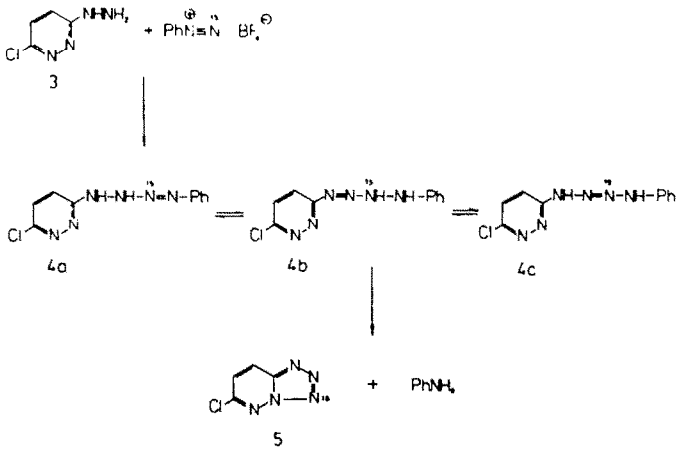
Table 1.

Hydrazine	Diazonium salt	Temp.(°C)	Reaction time[a](min)	Product	Lit.
16	A	R.T.	5	17	13
	B	65	30	17	
3-Hydrazinopyridazine	A	R.T.	10		14
	B	65	20		
3	A	R.T.	>3	12	15
	B	R.T.	>3	12	
	C	R.T.	10	12	
3-Hydrazino-4-methyl-6-chloropyridazine	A	R.T.	3		16
	B	R.T.	10		
3-Hydrazino-5-methyl-6-chloropyridazine	A	R.T.	5		16
	B	65	13		
7	A	R.T.	>3	8	17
	B	65	20	8	
6-Hydrazino-s-triazolo-(4,3-b)pyridazine	A	R.T.	15		18
	B	65	20		
6-Hydrazinotetrazolo-(1,5-b)pyridazine	A	R.T.	>3		18
	B	60	13		
22	A	R.T.	3	23	19
	B	65	10	23	
	A	65	10		b)
	B	65	30		

a) Reactions were followed in a nmr probe until complete conversion. Methanol was used as solvent.
b) M.p. 181° (from EtOH). (Found: C, 51.14; H, 2.50; N, 46.39. Calc. for $C_6H_5N_7$: C, 51.18; H, 2.39; N, 46.43%).
A = Benzenediazonium tetrafluoroborate; B = diazotized sulfanilic acid; C = o-nitrobenzenediazonium tetrafluoroborate.

compound and the product, 6-chlorotetrazolo(1,5-b)pyridazine (**5**), gave two well defined and separated AB type NMR spectra. In this connection it has been reported that tetrazene was prepared[8] and it decomposed by two paths into nitrogen and hydrazine (75%) or into ammonium and azide ion (25%). In methanolic solution the ratio was changed to 2:3. Some heteroaryl substitued tetrazenes are stable at room temperature and can be isolated and characterized. In this case, a heterocyclic diazo compound and not a diazonium salt must be used as starting material and the reaction should take place in a less polar solvent.[9]

Further support for a 1,4-tetrazene intermediate is afforded by the reaction of labelled benzenediazonium tetrafluoroborate. The isotopic N atom was found incorporated almost quantitatively in the corresponding

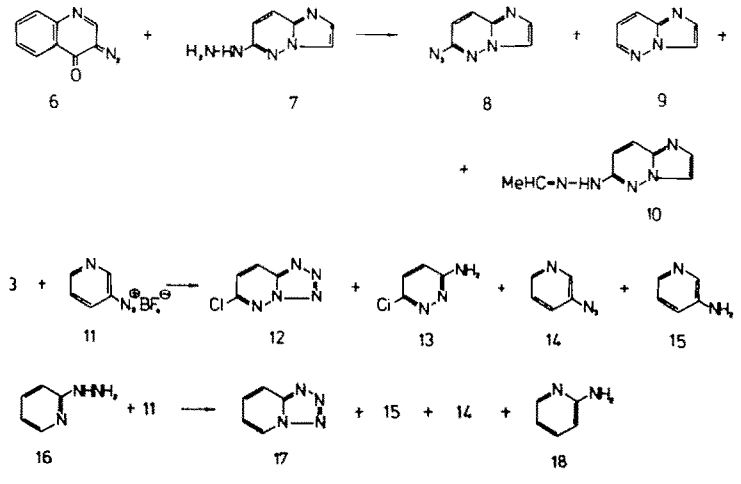


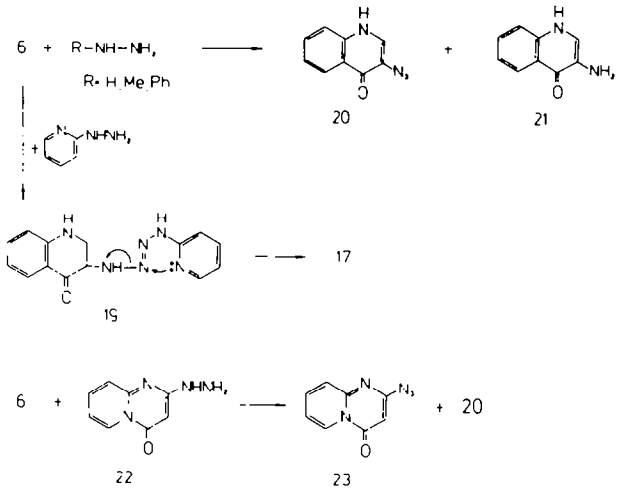
tetrazolopyridazine (**5**) and only traces of 3-amino-6-chloropyridazine and phenyl azide could be detected. This can be reconciled only with one decomposition path of **4** and similar experiments with the $^{15}N_1$-label or $^{15}N_1$–$^{15}N_2$-label in benzenediazonium tetrafluoroborate presented additional evidence for a clear-cut decomposition. It should be mentioned, however, that labelled 1,4-diphenyltetrazene was used in order to monitor its decomposition. It was shown that fission into phenyl azide and aniline took place by two paths almost statistically.[10]

In the reaction between 3-diazo-4-quinolone (**6**) and 6-hydrazinoimidazo(1,2-b)pyridazine (**7**), a mixture of products, when separated by tlc afforded the: 6-azidoimidazo(1,2-b)pyridazine (**8**), imidazo(1,2-b)pyridazine (**9**) and the ethylidene derivative of the starting hydrazino compound (**10**) as the main product. The first two compounds were formed in an aza-transfer reaction, whereas the formation of the hydrazone was explained by oxidation of ethanol into acetaldehyde. This evidently reacted faster with the starting hydrazine than the competitive aza-transfer took place.

A more or less pronounced aza-transfer in both directions, i.e. from the diazo compound to the hydrazino heterocycle and vice versa, was observed in the following reactions. 6-Chloro-3-hydrazinopyridazine (**3**) reacted with 3-pyridyldiazonium tetrafluoroborate (**11**) at room temperature to give 6-chlorotetrazolo(1,5-b)pyridazine (**12**), 3-amino-6-chloropyridazine (**13**), 3-azidopyridine (**14**) and 3-aminopyridine (**15**). The NMR evidence showed the ratio of the first two compounds was 1:1, 2, and therefore we concluded that aza-transfer proceeded in both directions to almost the same extent. In a similar aza-transfer reaction, using 2-hydrazinopyridine (**16**), a mixture of tetrazolo(1,5-a)pyridine (**17**), 3-aminopyridine (**15**), 3-azidopyridine (**14**) and 2-aminopyridine (**18**) was obtained. The NMR evidence showed that the reaction was complete in 3 min and that compounds **17** and **14** were formed in a ratio of 5:1. This indicated that the main aza-transfer reaction proceeded in the direction of 2-azidopyridine formation which instantly isomerized into **17**. In trifluoroacetic acid, however, the ratio of the above products was changed to 2:1. A possible explanation for this behaviour may be in the preferential protonation on the 2-substituted pyridine part of the molecule of tetrazene. By this process the free electron pair on the ring nitrogen was less available for cyclization (cf. **19**). Qualitatively, the preference for the protonation site could be estimated from the relative basicities of 2- and 3-aminopyridine (pK_a 6.86 and 5.98, respectively)[11] taking into consideration that these two molecules constitute part of the intermediate tetrazene **2**. Attempts to follow the decomposition path in strong mineral acid were unsuccessful.

Further investigations with 3-diazoquinolone (**6**) revealed that with hydrazine, methylhydrazine or phenylhydrazine the aza-transfer reaction proceeded predominantly in the direction of heterocycles. Thus in all cases investigated the main product was 3-azido-4-quinolone (**20**). A small amount of 3-amino-4-quinolone





(**21**) could be detected, presenting evidence for the other decomposition path as a minor reaction. With heterocyclic hydrazines, such as 2-hydrazinopyridine or **3** the aza-transfer occurred in the direction of the hydrazines and the corresponding tetrazolopyridine (**17**) or tetrazolopyridazine (**12**) were the main products. These observations indicated a cyclization process with participation of the free electron pair on the endocyclic nitrogen of the heterocycle (cf. **19**) which enhanced aza-transfer in one direction. Supporting evidence for this mechanism was afforded by the reaction between **6** and 2-hydrazinopyrido(1,2-a)pyrimidin-4-one (**22**). Here, the corresponding azido compounds, 3-azido-4-quinolone (**20**) and 2-azidopyrido(1,2-a)pyrimidin-4-one (**23**), were obtained in almost equal amounts. The lone pair of electrons at N_1-atom of the pyrido(1,2-a)pyrimidine ring could not participate in a cyclization process since a tetrazolopyridopyrimidine ring could not be formed on structural grounds and only the azido form could exist.[12] These results indicate that heterocyclic rings as substituents in 1,4-disubstituted tetrazenes play an important role in the direction of the aza-transfer.

EXPERIMENTAL

M.ps were determined on a Kofler hot plate m.p. apparatus. The NMR spectral measurements were performed on a JEOL JNM C-60 HL spectrometer with TMS as internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L spectrometer.

General procedure for the reaction between heterocyclic hydrazines and aryl diazonium salts. 0.01 mole of the corresponding heterocyclic hydrazine was dissolved in MeOH (3–10 ml) and 0.01 mole of diazonium tetrafluoroborate (or diazotized sulfanilic acid, or *o*-nitrobenzenediazonium tetrafluoroborate) in MeOH (10 ml) was added. The stirred mixture was left at room temp. or heated to 60–65°, the solvent was evaporated *in vacuo* and the residue was treated with 10 ml water and 0.5 ml conc. HCl. The resulting soln was extracted with chloroform (three times with 15 ml) and upon evaporation of the solvent the residue was crystallized from EtOH or aqueous EtOH.

These reactions were also monitored in a NMR probe. A soln of about 10 mg of the corresponding heterocyclic hydrazine in 0.5 ml of CD_3OD (with some TMS as internal standard) was prepared and the NMR spectrum recorded. Thereafter, about 20 mg of the corresponding diazonium salt was added and upon mixing, the NMR spectra were recorded continuously. After no changes were observed in the NMR spectra a small amount of the corresponding authentic azide or tetrazoloazine was added and the spectrum recorded again. This resulted in enhancement of signals which correspond to the anticipated product. The same procedure was then repeated with the addition of the corresponding amino compound resulting from the diazonium salt, added at the beginning. The starting compounds and the resulting products are given in Table 1.

If the reaction between **3** and benzenediazonium tetrafluoroborate in alcohol was performed at room temp., **12** was formed in 64% yield. From the diazonium salt aniline was formed. The reaction, when monitored in a NMR probe, was shown to be complete in less than 3 min. However, at −20° in the NMR probe, an intermediate tetrazene was formed which was stable at this temp. With gradual increase of the temp. it decomposed slowly into the final products and at 0° the reaction was conplete after 35 min. The main products were **12** and aniline, whereas other products were formed in less than 1%.

3-Azido-4(1H) quinolone (**20**). A soln of 3-diazo-4-quinolone[12] (51 mg) in chloroform (3 ml) was placed in a separatory funnel and wrapped in aluminium foil. 80% Hydrazine hydrate (0.5 ml) was added dropwise under occasional shaking and EtOH was added until a soln resulted. Water was added to the mixture and the separated azide was filtered and crystallized from EtOH (40 mg, 95% yield). The azide was decomposed at a temp. above 85°; NMR (DMSO-d_6): δ = 7.89 (s, H_2), 8.10 (m, H_5), 7.65–7.16 (m, H_6, H_7 and H_8). (Found: C, 58.42; H, 3.63; N, 30.37. Calc. for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.10%).

If the same reaction was performed in EtOH, the azide was obtained in 39% yield.

The reaction between 3-diazo-4-quinolone and 6-hydrazinoimidazo(1,2-b)pyridazine. A soln of **6** (0.171 g) and **7** (0.149 g) in EtOH (10 ml) was heated under reflux for 1 hr. The solvent was evaporated and the residue was submitted to TLC (DC-Fertigplatten Kieselgel 60F-254, Merck, 0.25 mm, chloroform and MeOH (20:1) as solvent). The following products were obtained: **8**[17] (R_f = 0.72) (12 mg, 7.5% yield), **9**[20] (R_f = 0.60) (4 mg, 3% yield) and **10**[17] (R_f = 0.39) (69 mg, 40% yield).

Reaction between 3-diazo-4-quinolone and phenylhydrazine. A soln of phenylhydrazine (62 mg) in MeOH (1 ml) was added to a soln of **6** (98.5 mg) in MeOH (3 ml) and the mixture was left at room temp. for 1 hr. The solvent was evaporated and water was added to the residue. The precipitated azide **20** (15 mg) was filtered off, the filtrate was treated with few drops of HCl and extracted with ether. The ethereal soln afforded after evaporation a small amount of phenyl azide. The aqueous soln was evaporated to dryness and the residue sublimed *in vacuo* at 130°. The sublimate (4 mg) was identified as anilinium chloride, m.p. 192°, and the residue in the sublimation tube (33 mg) had m.p. 239–245° and was identified as 3-amino-4-quinolone hydrocholoride.[21]

A similar procedure was employed when other hydrazino compounds were treated with 3-diazo-4-quinolone or 3-diazoindazole (Table 2).

Table 2.

Diazo compound	Hydrazine	Temp.°C	Reaction time	Products	Yield, %[a]	Lit.
6	Methylhydrazine	R.T.	5 min	20	22	
				21	3	21
6	16	R.T.	30 min	17	28[b]	13
				21	14	21
6	3	R.T.	1 h	12	12[c]	15
				21	33	21
6	22	R.T.	1 h	20	4	
				21	4	21
				23	3	19
3-Diazoindazole	Methylhydrazine	0[d]	1 min	3-Azidoindazole	92	2

a) Methanol was used as solvent and yields are given for the isolated and purified compounds.

b) The reaction, when monitored in a nmr probe revealed a quantitative conversion of 16 into 17 at room temperature after 40 min.

c) From nmr spectroscopic examination the reaction was completed at 65° in 40 min.

d) Water was used as solvent.

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