THE PREPARATION OF N- AND C-HALOGEN DERIVATIVES OF 1,2,4-TRIAZOLE

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The action of halogens in an alkaline medium on 1,2,4-triazoles has given their N-chloro, N-bromo, and N-iodo derivatives. The formation of C-halogen derivatives of some 1,2,4-triazoles from their N-halogen derivatives has been studied, and also the action of halogens on 1,2,4-triazoles at elevated temperatures. It has been shown that N-bromo-1,2,4-triazoles very readily form 1,2,4-triazole and 3,5-dibromo-1,2,4-triazole in approximately equimolar proportions. N-Chloro-1,2,4-triazole is more stable to the action of heat and forms 3-chloro-1,2,4-triazole with a yield of 40%. It was impossible to convert N-iodo-1,2,4-triazole into C-derivatives.

The numerous investigations of the 1,2,4-triazole system collected particularly in reviews [1,2] have led to the technical use of a number of its derivatives in the synthesis of polymers, photographic materials, herbicides, and insecticides. However, the halogenation of the triazole ring has hitherto been studied little. The usual method for obtaining 3(5)-halogeno-1,2,4-triazoles is the replacement of the amino groups in 3(5)-amino-1,2,4-triazoles by halogen via diazonium salts [3–5] or by the action of halogen derivatives of phosphorus on 1,2,4-triazolones [6,7].

On reaction with halogens, the azoles very readily form C-halogen derivatives. The treatment of 1,2,4-triazole (Ia) with bromine in aqueous solution gave 3,5-dibromo-1,2,4-triazole (IIa) with a yield of 24–29%. Subsequently [9], the synthesis of IIa and a number of 5(3)-substituted 3(5)-bromo-1,2,4-triazoles by the bromination of the triazoles in an alkaline medium with a yield of 80–100% was described. We have carried out similar work on compounds IIa and IVa [10]. We have also observed that the bromination of Ia in an alkaline medium at an elevated temperature takes place very readily with the formation of IIa with an almost quantitative yield. The bromination of Va and VIa has given their 5(3)-bromo derivatives. The bromination of the triazole ring in an alkaline medium takes place more readily than that of the methyl group of 3-methyl-1,2,4-triazole. We were unable to obtain C-halogen derivatives by the chlorination and iodination of Ia in neutral and alkaline media. Thus, the halogenation of the 1,2,4-triazoles takes place with greater difficulty than that of the majority of other azoles, which is in harmony with theoretical ideas [11] on the greater difficulty of electrophilic substitution reactions with an increase in the number of nitrogen atoms in the azole ring. In connection with this, our attempts to obtain methyl triazolyl ketone from N-acetyl-1,2,4-triazole may be mentioned. It was found that the reaction does not take place even under severe conditions (100° C, in a sealed tube) in the presence of catalysts for the Friedel-Crafts reaction.

In view of the high electron density on the "pyridine" nitrogen atoms in the azoles, it may be assumed that the electrophilic attack of a halogen must take place more readily at these nitrogen atoms, with the formation of N-halogen derivatives, than at the carbon atoms of the ring. N-Halogen derivatives of a number of azoles have been obtained, but some of them are unstable. Thus, N-halogen derivatives of pyrazole have been obtained in the form of pyrazolinium salts [12], but N-chloro- and N-bromo-1,2,3-triazoles have not been obtained in the pure form [13]. The preparation of N-chloro-1,2,4-triazole was recently reported [14]. We have developed a method for obtaining various N-halogen derivatives of the 1,2,4-triazoles [10]. N-Chloro-1,2,4-triazoles are obtained by the action of chlorine on 1,2,4-triazoles in the presence of bases in water or an organic solvent. N-Bromo-1,2,4-triazoles are obtained by the action of bromine water on 1,2,4-triazoles in an alkaline medium. N-Iodo and also N-bromo derivatives are obtained by the treatment of 1,2,4-triazoles in the presence of potassium iodide or bromide in an alkaline medium with a more electronegative halogen (chlorine or bromine). An analogous synthesis of N-halogenoamines has been described in the literature [15].

The N-halogen derivatives of the 1,2,4-triazoles possess halogenating and oxidating properties. Thus, N-chloro-1,2,4-triazole (Ib) reacts vigorously with a number of compounds containing active functional groups such as phenols and dimethyl sulfoxide. The halogen atom is slowly split off by cold water and rapidly by hot water and various reagents such as acids and sodium bisulfite; on salts of the hydrohalic and hydropseudohalic acids it acts oxidatively with the partial formation of new N-halogen derivatives containing the more electropositive halogen atom.

I-VII

I $R = R' = H$; II $R = R' = Br$; III $R = Br$, $R' = H$;
IV $R = Cl$, $R' = Br$; V $R = Cl$, $R' = H$; VI $R = CH_3$, $R' = H$;
VII $R = R' = C_5H_5CH_2$: a $X = H$; b $X = Cl$; c $X = Br$; d $X = I$

The N-chloro derivatives are readily soluble in organic solvents, and their solubilities in water are approximately the same as those of the initial triazoles. On the other hand, the N-bromo and N-iodo derivatives are sparingly soluble and do not sublime in vacuum. Their thermal instability and the presence of the reactive halogen atom prevented us from obtaining some N-bromo and N-iodo derivatives in the pure state.

When Ib was heated in an inert solvent in the presence of peroxides or with irradiation by UV light, 3-chloro-1,2,4-triazole (Va) was obtained; this reaction has been carried out by a different method previously [14]. N-Bromo-1,2,4-triazole (IIc) is rapidly converted on being heated in an inert solvent or

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Compound	Mp, °C (conditions of purification)	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	halogen	N	C	H	halogen	N	
Ib	81-82 (decomp. after a few sec)	$C_2H_2ClN_3$	23.73	2.36 2.03	35.00* 34.55*	40.41	23.21	1.94	34.30	40.55	
Ic	136-138 (decomp.)	$C_2H_2BrN_3$	16.44	1.53	54.15 52.15*	28.43	16.22	1.37	54.0	28.35	
Id	about 187 (decomp.)	$C_2H_2IN_3$			64.3*	22.08			65.18	21.52	
IIb	129; two vacuum (5 mm) sublimations at 110-120° °C (bath temp.) and 126.5-127.5	$C_2Br_2ClN_3$	8.64		74.11 13.72*	16.43	9.19		74.73 13.19*	16.08	
IIc	about 135 (decomp.)	$C_2Br_3N_3$	7.71		77.66	14.77	7.85		78.45	13.72	78
IId	decomp. above 230	$C_2Br_2IN_3$	7.51		80.31	12.27	6.82		81.29	11.89	60
IIIb	90-92, twice sublimed in vacuum	$C_2HBrClN_3$			19.80*	22.78			19.45*	23.01	86
IVa	191.5; sublimed in vacuum (5 mm) at 170° C (bath temp.)	$C_2HBrClN_3$	13.15	0.70	63.07		13.16	0.55	63.35		90
IVb	103-104, twice sublimed in vacuum	$C_2BrCl_2N_3$	11.36		69.47	19.07	11.06		69.60	19.35	92
VIIb	60-60.5 (from petroleum ether)	$C_{16}H_{14}ClN_3$	67.56	5.23	12.45*		67.65	4.94	12.50		96.5

*Active halogen.

when an attempt is made to sublime it in vacuum into a mixture of Ia and IIa in approximately equimolar proportions. Under similar conditions, 5(3)-substituted N-bromo-1, 2, 4-triazoles form 5(3)-substituted 3(5)-bromo-1, 2, 4-triazoles in good yields. N-Iodo-1, 2, 4-triazole (Id) could not be converted into its C-iodo derivative on thermal treatment. It may be concluded that in a number of cases the halogenation of the 1, 2, 4-triazoles takes place in the same way as the reaction of their N-halogeno derivatives.

The considerable differences in physical and chemical properties between the N-halogeno derivatives of the 1, 2, 4-triazoles can be explained by the different polarities of the nitrogen–halogen bonds. The structure and possibility of obtaining the isomeric N-halogeno derivatives require further study.

EXPERIMENTAL

3, 5-Dibromo-1, 2, 4-triazole (IIa). A solution of 1.38 g (0.02 mole) of Ia in 20 ml of water was treated with 4–5 g of $KHCO_3$ (or the corresponding amount of sodium carbonate or KOH) and was then heated to 80° C, and, with stirring, 2.1–2.4 ml (about 0.044 mole) of bromine in an aqueous solution of potassium bromide was added. The reaction mixture was brought to the boil to eliminate the excess of bromine, filtered with the addition of active carbon, acidified, and left in the refrigerator for 2 hr. The precipitate was filtered off with suction and washed on the filter with cold water. Yield 4.4 g (97%), mp 209–210° C. It crystallizes from water or ethanol. Mp 211–212° C [8]. The substance is very readily soluble in tetrahydrofuran, readily soluble in ethanol, to the extent of about 1% in boiling water, and very slightly in CCl_4 and benzene.

N-Acetyl-3, 5-dibromo-1, 2, 4-triazole. At 0° C, a solution of 0.8 ml (0.011 mole) of acetyl chloride in 3 ml of tetrahydrofuran was added to a solution of 2.27 g (0.01 mole) of IIa in 5 ml of dry tetrahydrofuran and 1.105 ml (0.011 mole) of pyridine. The colorless precipitate was filtered off, the filtrate was evaporated in vacuum, and the residue was added to the precipitate and this mixture was treated with ice water. The colorless substance was filtered off, washed with ice water, and dried over P_2O_5. Yield 2.6 g (96.5%), mp 137–139° C; 0.8 g was crystallized from 30 ml of petroleum ether. Mp 140–141° C. Found, %: C 18.20; H 1.37; Br 59.06; N 15.82. Calculated for $C_4H_3Br_2N_3O$, %: C 17.86; H 1.12; Br 59.35; N 15.62.

5(3)-Bromo-3(5)-chloro-1, 2, 4-triazole (IVa). This was obtained similarly from Va.

N-Chloro-1, 2, 4-triazole (Ib). A) A solution of 13.8 g (0.2 mole) of Ia in 20 ml of water was treated with 20–30 g of ice and 20 g (0.2 mole) of comminuted $KHCO_3$, and chlorine was passed through with stirring and cooling until a faint permanent yellowish coloration appeared. The colorless precipitate formed was filtered off, washed with the minimum amount of ice water, and dried in a thin layer over H_2SO_4. Yield 12-16 g (58–77.4%). It was crystallized from CCl_4 or petroleum ether, or was purified by vacuum sublimation (5 mm) at 40–50° C.

B) A solution of 6.9 g (0.1 mole) of Ia in 100 ml of absolute ether was treated with 20–30 g of dry comminuted $KHCO_3$, the mixture was cooled to −5°C, and, with vigorous stirring, chlorine (slightly more than the calculated amount) was passed through the solution, the temperature of which was kept at about 0° C. The mixture was filtered and the residue was washed several times with absolute ether. The combined filtrate was concentrated in the vacuum of a water pump at 0° C to a volume of 20–30 ml, diluted with petroleum ether, and frozen out at −20° C. The colorless crystals were filtered off at 0° C. The mother solution was concentrated in vacuum, and diluted with petroleum ether, an additional amount of Ib being isolated similarly. The total yield was 8.5–9.3 g (82–90%). The substance is very readily soluble in the majority of organic solvents and also in water. Even in the well-purified form it had a strong smell of chlorine.

N-Bromo-1, 2, 4-triazole (Ic). With stirring, 500 ml of bromine water (17 ml (0.33 mole) of bromine and 20 g of KBr) was added to a solution of 20.0 g (0.29 mole) of Ia and 16.8 g (0.30 mole) of KOH in 600 ml of water at 0° C. The colorless or faintly yellowish precipitate formed was filtered off and washed with ice water. It was dried in a thin layer in a desiccator over H_2SO_4. Yield 38 g (88.6%). By treatment of the filtrate with sodium carbonate solution and bromine water it was possible to obtain another 2–3 g of Ic. The total yield was about 97%. The product was sometimes contaminated with adsorbed bromine, but this could be eliminated by washing with organic solvents. The substance was unstable on storage.

N-Iodo-1, 2, 4-triazole (Id). Chlorine was passed through a solution of 3.0 g (43.5 mM) of Ia, 3.2 g (57 mM) of KOH, and 10 g of potassium iodide in 80 ml of water at 0° C with stirring until the reaction was neutral. The black precipitate was filtered off, washed with water, dried in vacuum over H_2SO_4, and triturated with dry acetone, ethyl acetate, and chloroform. This gave 8–9 g of a yellowish substance. For further purification, 3.4 g was dissolved in 50 ml of dry pyridine at room temperature, the solution was filtered through a glass filter, and 200 ml of benzene was added to the filtrate. The precipitate was filtered off and washed several times with benzene. It was dried over H_2SO_4 in vacuum. The total yield of colorless substance was 5–7 g (58–82%).

3, 5-Dibromo-N-chloro-1, 2, 4-triazole (IIb). With stirring, chlorine in slightly more than the calculated amount was passed through a solution of 2.27 g (0.01 mole) of IIa and 1.5 g of sodium acetate in 10 ml of water and 50 ml of acetone at 0° C. The solution was concentrated in vacuum at 0° C, and the precipitate that deposited was filtered off and washed with ice water (2–3 x 10 ml). The product was dried in vacuum over H_2SO_4. Yield 2.3 g (88.5%). Colorless crystalline substance.

Compounds IIIb and IVb were obtained similarly. Compound IIc was obtained from IIa by the same method but using bromine. Compound VIIb was obtained in the same way as IIb, but without evaporation in vacuum. The oil formed rapidly crystallized, and the product was filtered off. Compound IId was obtained by dissolving IIa in acetone, adding the calculated amount of bromine at 0° C, and pouring the mixture into an aqueous solution of potassium iodide and sodium acetate. The brown precipitate was treated with organic solvents as in the production of Id (table).

3-Chloro-1, 2, 4-triazole (Va). A solution of 1.03 g of Ib in 10 ml of dichloroethane was boiled for 1.5 hr, 0.05 g of benzoyl peroxide being added in two portions. The solvent was distilled off in vacuum and the residue was treated with a solution of alkali, neutralized, and evaporated in vacuum, and the new residue was sublimed in vacuum (5 mm). Yield 0.45 g (about 40%). Mp 158–161° C (from ethanol). Mp of a mixture 161–163° C. According to the literature [3], mp 167° C.

Transformation of N-bromo-1, 2, 4-triazole (Ic). After Ic had been stored for six months in a sealed vessel at room temperature, the active halogen had disappeared. 4.75 g of the product (0.032 mole calculated to Ic) was boiled with 10 ml of water, and the mixture was cooled and filtered. The filtrate was evaporated in vacuum and crystallized from ethyl acetate. This gave 0.8 g of Ia with mp ~119° C. The residue was crystallized from ethanol, giving 2.95 g (0.0130 mole) of IIa with mp 209–210° C. Neither substance gave a depression of the melting point with the corresponding authentic substance.

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