Synthesis of Biologically Active Triazenes from Isolable Diazonium Salts

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(Z. Naturforsch. **27 b**, 1183—1185 [1972]; received March 13/Juli 11, 1972)

Synthesis, triazene, diazonium tetrafluoroborate, and hexafluorophosphate

Alkaryl triazenes were synthesized in two steps from the isolated intermediary diazonium tetrafluoroborates and hexafluorophosphates by coupling the arenediazonium cations with dimethylamine in an aqueous solution but without the use of mineral base. The method enables the preparation of triazenes which are not readily accessible by conventional procedures; it also leads to higher yields and purer products in the preparation of known compounds.

The 1,1-dialkyl-3-aryltriazenes are potent carcinogens in rats [1] and mutagens in *Drosophila* [2], *Neurospora* [3], and yeast [4]. The unexpectedly high toxicity of 1-(4-hydroxyphenyl)-3,3-dimethyltriazene [5] in rats stimulated interest in the preparation of the phenolic triazenes which were expected to exhibit distinct biological activity in living organisms. Because of the inherent reactivity of the phenolic group, above all its susceptibility to oxidation in alkali, the phenolic compounds could not be readily prepared by standard methods.

The direct synthetic route to aromatic monoalkyl (R = alkyl, R′ = H) or dialkyl (R = R′ = alkyl) triazene derivatives [6] depends upon the reaction of an arenediazonium cation with the nucleophilic nitrogen atom of a primary or secondary aliphatic amine (Fig. 1).

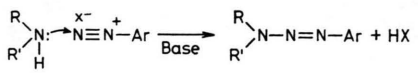

Fig. 1. Formation of alkaryl triazenes in the reaction between the nucleophilic nitrogen atom of an aliphatic amine and an arenediazonium cation.

In conventional preparations of alkaryl triazenes the arenediazonium solution is reacted with the corresponding aliphatic amine in the presence of excess inorganic base to consume the acid used in diazotization. These procedures [7–9] lead to satisfactory results in the preparation of readily accessible diazoamino compounds but they are less suitable for the synthesis of triazenes derived from aromatic or heterocyclic amines the diazotization of which is accompanied by side-reactions. However, the most serious difficulties arise in the preparation of triazenes from aromatic amines containing functional groups sensitive to alkali, such as the phenolic hydroxyls. Even when these diazonium solutions are coupled with the passive component in an inert atmosphere, the sensitive products deteriorate rapidly under the alkaline reaction conditions.

This paper describes a useful modification of triazene synthesis from the isolated intermediary diazonium tetrafluoroborates [10] and hexafluorophosphates [11]. The arenediazonium salts were obtained by direct diazotization of the aromatic amines with sodium nitrite in tetrafluoroboric or hexafluorophosphoric acid which technique has not been previously reported. Under controlled reaction conditions, the method yielded isolable arenediazonium salts ($X^- = BF_4^-$ or PF_6^-, Fig. 1) even from water-soluble aromatic amines in yields ranging from 58 to 89% of the theoretical amount. After crystallization or precipitation, the purified diazonium salts became a readily available source of the required arenediazonium cation. Since no excess acid had to be neutralized in the subsequent step and, provided the nucleophilic activity of the aliphatic amine was sufficiently high, the coupling occurred readily without the use of mineral base.

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Materials and Methods

General

Synthetic grade amines, chemically pure tetrafluoroboric acid, D_{20} 1,22, 32% (Riedel-de Haen), and technical hexafluorophosphoric acid, 70% (Fluka), were used as supplied. Transition points were observed on a Mettler FP1 melting and boiling point apparatus. UV spectra were recorded in methanolic solutions on a Zeiss DMR 21 recording spectrophotometer.

Preparation of arenediazonium fluoroborates

The arylamine (0.1 mole) was dissolved in fluoroboric acid (0.2 mole, 44.9 ml) and the solution was cooled in an ice-salt bath to $-5°$. Sodium nitrite (0.1 mole, 6.9 g) in water (15 ml) was added dropwise over 30 min with mechanical stirring. The separated diazonium salt was collected on a filter, sucked as dry as possible and washed with ice-cold ether-methanol mixture (4 : 1).

Preparation of arenediazonium fluorophosphates

The arylamine (0.1 mole) was dissolved in fluorophosphoric acid (0.11 mole, 13.9 ml) diluted to 40 ml, and the cooled solution was diazotized as described above. The isolated diazonium fluorophosphate was washed first with cold water and then with ether-methanol to facilitate drying.

The crude salts crystallized readily from acetone-methanol (1:1) or were precipitated from a saturated acetone solution by the addition of ether and light petroleum. The purified diazonium fluoroborates and fluorophosphates could be stored at $-12°$ without appreciable loss.

Coupling of arenediazonium salts with dimethylamine

Dimethylamine (0.22 mole, 24.8 ml, 40%) was diluted with an equal volume of water in a 500 ml reaction flask fitted with a gas inlet tube, a dropping funnel, and a mechanical stirrer. The finely powdered diazonium salt (0.1 mole) was covered with water (about 50 ml) and the suspension was added, under a stream of nitrogen, to the cooled stirred solution of dimethylamine. After the reactants had been combined (about 1 hr), the reaction was stirred for additional 10 min after which it was saturated with carbon dioxide. The product was either collected on a filter or extracted with ether. The reaction mixture was clarified with charcoal and concentrated under reduced pressure to obtain the water-soluble compounds.

The triazenes were purified by crystallization from ethanol or benzene, or by distillation under reduced pressure.

Results and Discussion

The success of the modified triazene synthesis depends primarily on the diazotization of the water-soluble aromatic amines in tetrafluoroboric or hexafluorophosphoric acid and on the isolation and purification of the intermediary arenediazonium salts. Although solid diazonium salts derived from water-soluble aromatic amines have been prepared by diazotization in organic solvents [12], the described method afforded good yield of isolable arenediazonium fluoroborates and fluorophosphates in an aqueous phase even from the three isomeric aminophenols. Despite its corrosive properties, it was expected that fluorophosphoric acid could be a more suitable reagent than fluoroboric acid since its arenediazonium salts were reported [11] to be even less soluble than the corresponding fluoroborates. Nevertheless, in this series, conventional method of preparation yielded isolable diazonium hexafluorophosphate from 4-aminophenol only.

The results of diazotization of ten representative aromatic amines in tetrafluoroboric and hexafluorophosphoric acid are summarized in Table I. Contrary to expectation, the yields of arenediazonium fluorophosphates by direct diazotization in hexafluorophosphoric acid were not significantly higher than those of the corresponding fluoroborates. This result was possibly due to the lower purity grade of hexafluorophosphoric acid which was available.

Table I. Diazotization of arylamines in tetrafluoroboric and hexafluorophosphoric acid.

Arylamine	Yield of $Ar\text{-}N_2^+BF_4^-$ [%]	Transition * temperature		Yield of $Ar\text{-}N_2^+PF_6^-$ [%]	Transition * temperature	
Aminobenzene	89	97	Lit. [13]	85	91	
2-Aminophenol **	86	89– 90		80	108–109	
3-Aminophenol	72	72– 73	Lit. [14]	71	105–106	
4-Aminophenol	74	114–115		84	130–131	Lit. [11]
2-Aminobenzoic acid	64	124–125	Lit. [11]	81	128–129	Lit. [11]
3-Aminobenzoic acid	89	133–134		78	119–120	
4-Aminobenzoic acid	82	101–102	Lit. [11]	81	145–146	Lit. [11]
2-Aminobenzene sulphonic acid	67	123–125		71	120–121	
3-Aminobenzene sulphonic acid	74	125–127		58	118–120	
4-Aminobenzene sulphonic acid	87	128–129		82	166–168	

* Decomposition temperature of recrystallized air-dried salt. ** Absence of heavy metals and efficient cooling are essential for a successful reaction.

Table II. Coupling of isolated arenediazonium salts with dimethylamine.

Arenediazonium	Yiel of 1-aryl-3,3-dimethyl-triazene from diazonium		Solvent of crystal-lization	Transition temperature	UV-absorption (MeOH)	
	tetrafluoroborate [%]	hexafluorophosphate [%]			λ_{max} (nm)	log ε
Benzene-	68	70		b. 115/14 mm	223	3.98
				Lit.[7] 125–127/19 mm	283	4.12
2-Hydroxybenzene-	Failed	Failed				
3-Hydroxybenzene-	54	63	Benzene	d. 110–111	217.5	4.02
					293	4.04
					308	4.04
4-Hydroxybenzene-	79	75	Benzene	d. 93–94	218	3.97
				Lit.[8] 93–93.5	289	4.12
					324	4.09
2-Carboxybenzene-	70	72	Ethanol	d. 126	241	4.05
				Lit.[7] 124–126	316	4.19
3-Carboxybenzene-	70	71	Ethanol	d. 115–116	218	4.30
					322	4.33
4-Carboxybenzene-	71	73	Ethanol	d. 171	228	3.93
					321	4.36
2-Sulphoxybenzene-	73	74	Ethanol	d. 206–207	228	3.83
					297	4.07
3-Sulphoxybenzene-	67	68	Ethanol	d. 185–186	231	3.79
					287	3.95
					313	3.87
4-Sulphoxybenzene-	76	77	Ethanol	d. 138–139	217	4.23
					312	4.13

In all cases but one, the coupling of the isolated arenediazonium salts with dimethylamine in an aqueous phase yielded the corresponding alkaryl triazenes. The data are collected in Table II. The reaction of 3-hydroxybenzenediazonium fluoroborate and fluorophosphate yielded the novel 1-(3-hydroxyphenyl)-3,3-dimethyltriazene in 54% and 63% yield, respectively. Similarly, 1-(4-hydroxyphenyl)-3,3-dimethyltriazene was obtained in 79% and 75% yield. Since RONDESTVEDT and DAVIS[8] prepared 1-(4-hydroxyphenyl)-3,3-dimethyltriazene in 19% yield, the reported modification offers a considerable improvement in the preparation of this compound. Although HADFIELD and LEGG[15] claim to have prepared triazene derivatives by the coupling of diazotized 2-hydroxyaniline with unspecified primary and secondary amines, the reaction between 2-hydroxybenzenediazonium fluoroborate or fluorophosphate and dimethylamine did not yield any isolable product.

This work was greatly facilitated by the able technical assistance of Mr. W. MÖSSNER.

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