

COUPLING KINETICS OF 4-SULFOBENZENEDIAZONIUM ION WITH 2,4-THIAZOLIDINEDIONE, ITS 3-METHYL DERIVATIVE AND 3-METHYL-5-ISOXAZOLONE

Jaromir KAVALEK, Vladimir MACHACEK and Vojeslav STERBA

Department of Organic Chemistry,

University of Pardubice, 532 10 Pardubice, The Czech Republic

Received May 9, 1994

Accepted May 23, 1994

3- and 4-substituted 5-phenylazo derivatives of 2,4-thiazolidinedione were prepared as potential biologically active fungicides. The kinetics of coupling of 4-sulfobenzenediazonium salt with 2,4-thiazolidinedione and 3-methyl-2,4-thiazolidinedione have been studied and the results have been compared with kinetic data of coupling reaction of 3-methyl-5-isoxazolone.

A detailed account of reactions of substituted thioureas with chloroacetic acid giving 2-imino-4-thiazolidinedione derivatives has been given in the reviews^{1,2}. As many of the reaction products exhibit biological activity, most of the references cited there deal with the synthesis of compounds with potential biological activity.

Arylazo compounds or their hydrazo tautomers are mostly prepared by reaction of arenediazonium salts with aromatic hydroxy and amino compounds or by reaction with compounds containing methylene group activated by one or two neighbouring, strongly electron-attracting groups³⁻⁶.

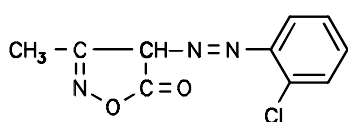
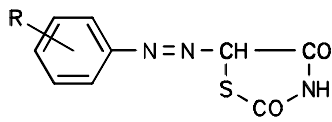
Substituted 2,4-thiazolidinediones have the methylene group activated by the neighbouring carbonyl group and sulfur atom. It is easily deprotonated to give the carbanion which can react with electrophilic agents¹ inclusive of benzenediazonium ions. The base-catalyzed reaction of 3-methyl-5-isoxazolone (which also has an activated methylene group) with some substituted benzenediazonium ions gives azo compounds with high fungicidal activity (e.g. commercial derivative⁷ "Drazoxolon", *I*).

The present paper deals with the synthesis of a series of substituted phenylazo derivatives of 2,4-thiazolidinedione *Ila* – *IIf* which were submitted to biological screening tests. At the same time, kinetics of coupling of 4-sulfobenzenediazonium salt with 2,4-thiazolidinedione (*III*) and 3-methyl-2,4-thiazolidinedione (*IV*) was studied. The results were compared with analogous data on the coupling reaction with 3-methyl-5-isoxazolone (*V*).

EXPERIMENTAL

Reagents

2,4-Thiazolidinedione (*III*) was prepared from chloroacetic acid and thiourea by boiling on water bath for 12 h according to the known procedure⁸. 3-Methyl-2,4-thiazolidinedione (*IV*) was prepared by methylation of the dione *III* according to the known procedure⁹. 3-Methyl-5-isoxazolone (*V*) was prepared from hydroxylamine hydrochloride and ethyl 3-oxobutanoate according to reported procedure¹⁰. 5-(Substituted phenylazo)-2,4-thiazolidinediones (*IIa – II f*) were prepared by coupling of the respective diazonium salts with the dione *III* in acetate buffer solution. For their melting points and elemental analyses see Table I.

*I**IIa–II f*

a, R = 2-Cl; **b**, R = 3-Cl; **c**, R = 4-Cl;
d, R = 4-Br; **e**, R = 3-NO₂; **f**, R = 3-COCH₃

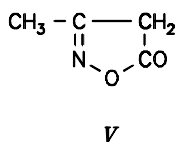
TABLE I

Physico-chemical properties of 5-(substituted phenylazo)-2,4-thiazolidinediones *IIa – II f*

Compound	M.p., °C	Yield, %	Calculated/Found	
			% C	% H
<i>IIa</i>	194.5 – 196	60	42.28	2.36
			42.50	2.46
<i>IIb</i>	232 – 233	30	42.28	2.36
			42.40	2.20
<i>IIc</i>	247 – 249	85	42.28	2.36
			42.00	2.52
<i>IId</i>	265 – 268	85	36.02	2.01
			36.23	2.09
<i>IIe</i>	113 – 115	70	40.60	2.27
			40.90	2.39
<i>II f</i>	220 – 223	75	50.18	3.44
			49.92	3.30

Kinetic Measurements

All kinetic experiments were carried out at 25 °C, using the VSU-2P apparatus (Zeiss, Jena). Coupling of 4-sulfobenzediazonium salt with the dione III and its methyl derivative IV was carried out in a quartz cell located in thermostated cell compartment of the spectrophotometer; 1 ml of aqueous solution of substrate (III or IV) and potassium chloride was mixed with 1 ml of acetate or phosphate buffer. After temperature, 0.1 ml $1 \cdot 10^{-3}$ M diazotized sulfanilic acid solution was added, and absorbance was measured at 365 nm. The ionic strength was adjusted at 0.5 by addition of potassium chloride. Kinetic experiments of 4-sulfobenzediazonium salt with isoxazolone V were carried out in the same way as those of the compounds III and IV. The buffer used was chloroacetate, the absorbance changes were followed at 400 nm. Sulfanilic acid was diazotized by the procedure given in ref.¹¹.



RESULTS AND DISCUSSION

Coupling reactions of diazotized sulfanilic acid with the compounds III – V were studied in aqueous buffer solutions at 25 °C. In all the cases, concentration of the substrates was at least ten times higher than that of the diazonium salt, the reactions proceeding thus as pseudomonomolecular. The time dependence of $\log(A_\infty - A_t)$ was linear in the whole conversion range investigated (80 to 90% conversion). Influence of pH and concentrations of the mentioned reactants on the rate constant was determined, and the results are presented in Tables II and III. The experimental rate constants are

TABLE II

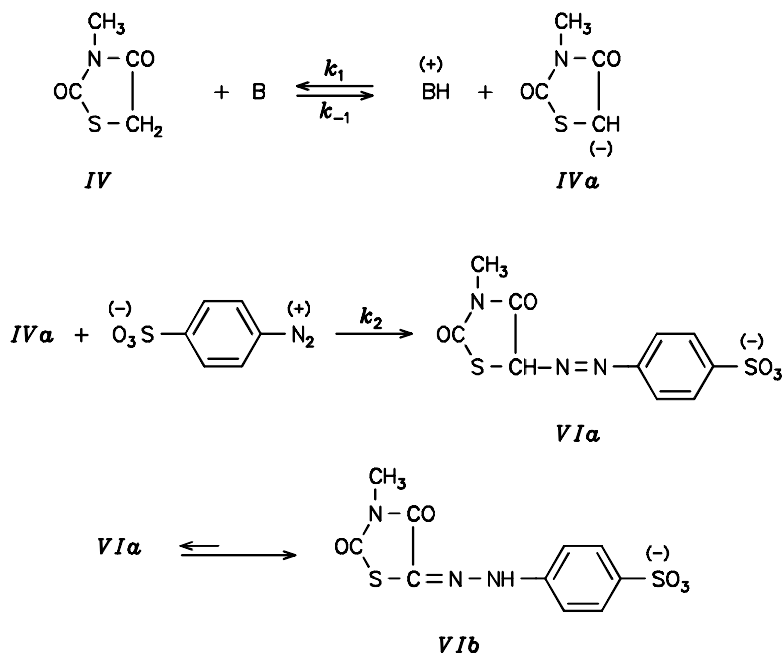
Rate constants $k_{\text{exp}}(\text{s}^{-1})$ of coupling of diazotized sulfanilic acid with isoxazolone V, dione III and its methyl derivative IV at various substrate concentrations

Entry	$k_{\text{exp}} \cdot 10^{3,a}$		
	V ^b	III ^c	IV ^d
1	2.5 (0.5)	0.33 (0.1)	2.0 (1.5)
2	5.4 (1.0)	0.67 (0.2)	4.5 (3.0)
3	7.8 (1.5)	1.01 (0.3)	7.2 (4.5)
4	–	1.98 (0.6)	10.0 (6.0)
5	–	2.42 (0.75)	12.2 (7.5)
6	–	5.15 (1.6)	–
7	–	6.00 (2.0)	–
8	–	8.5 (3.0)	–

^a Substrate concentrations ($c \cdot 10^3$ mol l⁻¹ for V and IV, and $c \cdot 10$ mol l⁻¹ for III) are given in parenthesis. ^b pH 2.70; $k_2 K_a = 1 \cdot 10^{-2}$ s⁻¹. ^c pH 5.17; $k_2 K_a = 2.2 \cdot 10^{-7}$ s⁻¹. ^d pH 6.48; $k_2 K_a = 5.5 \cdot 10^{-7}$ s⁻¹.

directly proportional to concentration of the substrates except for higher concentrations of the compound *III*. In this case the k_{exp} value increases more slowly due probably to association of the compound *III*. The dependence $\log k_{\text{exp}}$ vs pH is linear with the slope equal to unity.

In the cases of the methyl derivative *IV* and isoxazolone *V* the deprotonation of CH_2 group gives only one monoanion from each compound. The coupling reaction mechanism of the substrate *IV* is given in Scheme 1, the mechanism for the isoxazolone *V* being similar.



SCHEME 1

The final tautomer equilibrium is very rapid and is shifted almost completely in favour of the hydrazone compound¹² which thus represents the main reaction product. The rate-limiting step can be either deprotonation of CH_2 group or the reaction of the formed anion with diazonium ion. In the former case, the reaction rate would be directly proportional to buffer concentration and independent of diazonium salt concentration; i.e. with excess substrate, the reaction would be of zero order. So far, this mechanism was observed only in reactions of benzenediazonium ions with nitroethane¹³. In the latter case, i.e. if the reaction of the carbanion with diazonium cation were rate-limiting, the k_{exp} values would be directly proportional to concentration of substrate and inversely proportional to the proton concentration (for pH lower than pK_a

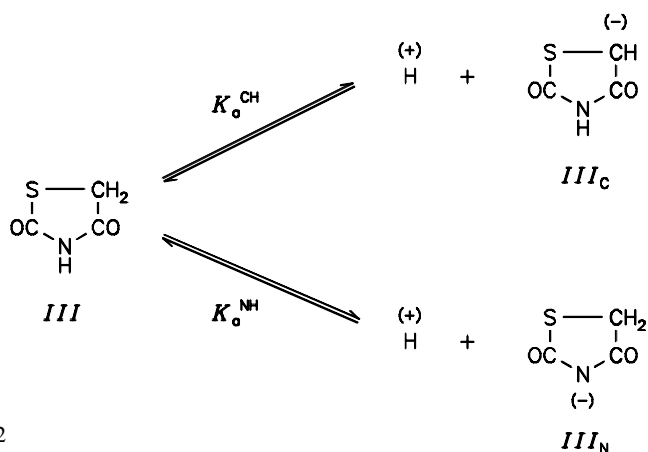
of the substrate). This dependence was observed in coupling reactions of all three substrated *V*, *III* and *IV*. The reaction rate is given by Eq. (1):

$$r = k_{\text{exp}}[\text{ArN}_2^+] = k'_2[\text{ArN}_2^+][\text{SH}] = k_2[\text{ArN}_2^+][\text{S}^-] . \quad (1)$$

For $\text{pH} \ll \text{p}K_a$ of the substrate SH , $[\text{S}^-] = K_a[\text{SH}]/[\text{H}^+]$, so that $k_{\text{exp}} = k_2K_a[\text{SH}]/[\text{H}^+]$.

Dissociation of the dione *III* is represented in Scheme 2, and experimental dissociation constant is defined by Eq. (2):

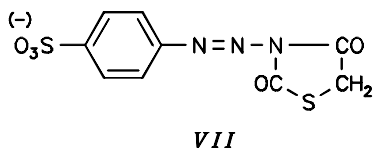
$$K_{a,\text{exp}} = ([\text{III}_C] + [\text{III}_N]) [\text{H}^+]/[\text{III}] . \quad (2)$$



SCHEME 2

As hydrogen atom at the NH group is much more acidic than that at CH_2 group, concentration of the anion III_N is higher than that of III_C by many orders of magnitude. But for $\text{pH} \ll \text{p}K_{a,\text{exp}}$ it is $[\text{III}_C] = K_a^{\text{CH}} [\text{III}]/[\text{H}^+]$, as it is the case with the *N*-methyl derivative *IV*. The K_a^{CH} value should be comparable with the K_a value of the methyl derivative *IV*.

Coupling with the compound *III* can take place both at carbon atom of the anion III_C and at nitrogen atom of the anion III_N ; the latter alternative results in formation of triazene *VII*. In contrast to the products of C-coupling, triazenes are unstable in acidic media, being split into the respective starting components.

*VII*

The coupling kinetics was pseudomonomolecular in all the cases. Spectrum of the product formed was similar to that of the coupling product from the *N*-methyl derivative *IV*. It did not change after acidification of the reaction product, which indicated that no triazene was practically formed.

As the coupling mechanism is the same for both compounds *III* and *IV*, and substitution of NH hydrogen atom by methyl group does not influence fundamentally the reactivity of the formed carbanion, the coupling rates (defined by e.g. k_2K_a) should be similar, which is in accord with the values found (Table II).

The isoxazolone *V* reacts faster than the diones *IV* and *III* by about 4.5 orders of magnitude. The isoxazolone is a much stronger C-acid (pK_a 5.56; ref.¹⁰) than the diones *III* and *IV* (rough estimate – by about 10 orders of magnitude). On the other hand, the carbanion of isoxazolone is far more stable and, hence, less reactive toward diazonium ions. The both factors act in opposite directions, but the former (i.e. magnitude of dissociation constant) predominates.

Kinetic study of these azo coupling reactions had a practical purpose, viz. estimation of optimum reaction conditions for preparation of these azo compounds which are potential biologically active agents (fungicides)⁷.

TABLE III

Rate constants $k_{\text{exp}}(\text{s}^{-1})$ of coupling of diazotized sulfanilic acid with isoxazolone *V*, dione *III* and its methyl derivative *IV* at various pH

Entry	$k_{\text{exp}} \cdot 10^{3,a}$		
	<i>V</i> ^b	<i>III</i> ^c	<i>IV</i> ^d
1	2.0 (2.34)	0.21 (4.74)	0.38 (5.39)
1	2.5 (2.40)	0.32 (5.05)	0.62 (5.50)
3	2.7 (2.51)	0.67 (5.35)	1.33 (6.50)
4	5.2 (2.71)	2.35 (5.85)	8.20 (6.80)
5	–	4.50 (6.35)	–
6	–	6.95 (6.80)	–
7	–	8.75 (7.05)	–

^a pH given in parentheses. ^b $[V] = 1 \cdot 10^{-3} \text{ mol l}^{-1}$. ^c $[III] = 1 \cdot 10^{-2} \text{ mol l}^{-1}$. ^d $[IV] = 3 \cdot 10^{-3} \text{ mol l}^{-1}$.

This work was supported by the Grant Agency for Science of the Czech Republic, No. 203/93/2065.

REFERENCES

1. Brown F. C.: *Chem. Rev.* 61, 463 (1961).
2. Kavalek J., Said El Bahaie, Sterba V.: *Collect. Czech. Chem. Commun.* 45, 263 (1980).
3. Houben-Weyl: *Methoden der organischen Chemie*, Vol. X/3. Thieme, Stuttgart 1965.
4. Patai S. (Ed.): *The Chemistry of Diazonium and Diazo Groups*. Wiley, London 1978.
5. Saunders K. H., Allen R. L. M.: *Aromatic Diazo Compounds*, 3rd ed. Arnold, London 1985.
6. Zollinger H.: *Diazo and Azo Chemistry*. Interscience, New York 1961.
7. Imperial Chemical Industries Ltd.: *Belg.* 617, 389; *Chem. Abstr.* 59, 6413 (1963).
8. Hamed A. E.: *Thesis*. University of Cairo, Cairo 1975.
9. Lo C. P., Shrophire E. Y.: *J. Org. Chem.* 22, 999 (1957).
10. Katritzky A. R., Oeksne S., Boulton A. J.: *Tetrahedron* 18, 777 (1962).
11. Putter R. in: *Methoden der organischen Chemie* (E. Müller, Ed.), Vol. X/3, p. 20. Thieme, Stuttgart 1965.
12. Zollinger H.: *Azo and Diazo Chemistry; Aliphatic and Aromatic Compounds*. Interscience, New York 1961.
13. Machacek V., Panchartek J., Sterba V., Vecera M.: *Collect. Czech. Chem. Commun.* 33, 3154 (1968).

Translated by the author (V. S.).