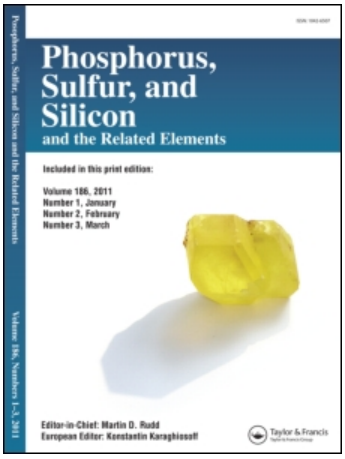

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Kamal, Mohamed and Ibrahim, Ahmed(1990) 'REACTIONS WITH HETEROCYCLIC DIAZONIUM SALTS: SYNTHESIS OF SEVERAL NEW THIAZOLO[2,3-c]AS-TRIAZINES AND THIAZOLO [2,3-c] 1,2,4-TRIAZ OLE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 47: 1, 61 — 65
To link to this Article: DOI: 10.1080/10426509008046847
URL: http://dx.doi.org/10.1080/10426509008046847

Phosphorus, Sulfur, and Silicon, 1990, Vol. 47, pp. 61–65
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REACTIONS WITH HETEROCYCLIC DIAZONIUM SALTS: SYNTHESIS OF SEVERAL NEW THIAZOLO[2,3-c]AS-TRIAZINES AND THIAZOLO[2,3-c]1,2,4-TRIAZOLE DERIVATIVES

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(Received March 20, 1989; in final form April 28, 1989)

Several new stable thiazolo[2,3-c]as-triazines could be synthesized via coupling of diazotized aminothiazole with active nitrile reagents. On the other hand, several new thiazolyl hydrazonyl chlorides and thiazolyl pyridazine could be synthesized via coupling of thiazole diazonium sulfate with α-chloro diketone, α-chloro β-ketoester compounds and active methylene reagents. The structural assignments were based on the elemental analysis and IR data.

Key words: Reactions with heterocyclic diazonium salts; synthesis of thiazolo[2.3-c]as-triazines; heterocyclic diazonium salts; synthesis of thiazolo[2,3-c]1,2,4-triazoles; utility of thiazol-2-yl diazonium sulphate; synthesis of thiazol-2-yl hydrazonoyl chlorides.

INTRODUCTION

In spite of recent interest in the synthetic potentialities of carbo-aryl hydrazonyl halides,[1] very little attention has been paid to the chemistry and synthetic potentialities of their heterocyclic analogues. We have already described the synthesis of carbo(3-phenylpyrazol-5-yl-hydrazonyl) chlorides and their conversion into pyrazolo[1,5-c]1,2,4-triazoles and pyrazolo[1,5-c]as-triazines.[1–3] We continued this work[4–5] because of the considerable biological activities of thiazole derivatives, which possess insecticidal,[6] pesticidal[7] and fungicidal[8] activity.

RESULTS AND DISCUSSION

We report here the results of our further investigation on the synthesis of other heterocyclic hydrazonyl halides. The work has resulted, in addition to synthesis of several new thiazolo[2,3-c]as-triazines, in the clarification of the mechanistic pathways for the reaction of diazotized 2-aminothiazoles with activated nitrile compounds. Thus, bromination reaction of benzaldehyde (4-phenylthiazol-2-yl)hydrazone (**1**) in acetic acid/acetic anhydride mixture yielded the corresponding thiazolo[2,3-c]1,2,4-triazole derivative (**3**). The attempts to isolate the thiazol-2-yl hydrazonyl bromide derivative (**2**) were unsuccessful.

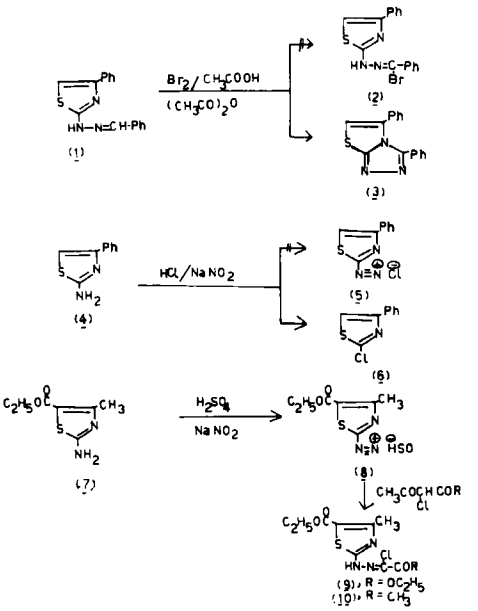
We supposed that it may be possible to isolate thiazol-2-yl hydrazonyl halide via coupling reaction of thiazolyl diazonium salt with α-chloro derivatives of ethyl

acetoacetate and acetylacetone. Thus, diazotization of 2-amino-4-phenylthiazole (**4**) in presence of hydrochloric acid has afforded the corresponding 2-chloro-4-phenylthiazole (**6**). It was found that the thiazol-2-yl diazonium chloride derivative (**5**) was decomposed under reaction conditions to give the corresponding 2-chloro-4-phenylthiazole (**6**). On the other hand, diazotization of 4 in presence of oxyacids produced unstable diazonium salts. These readily decomposed under the coupling reaction conditions and no coupling products could be obtained.

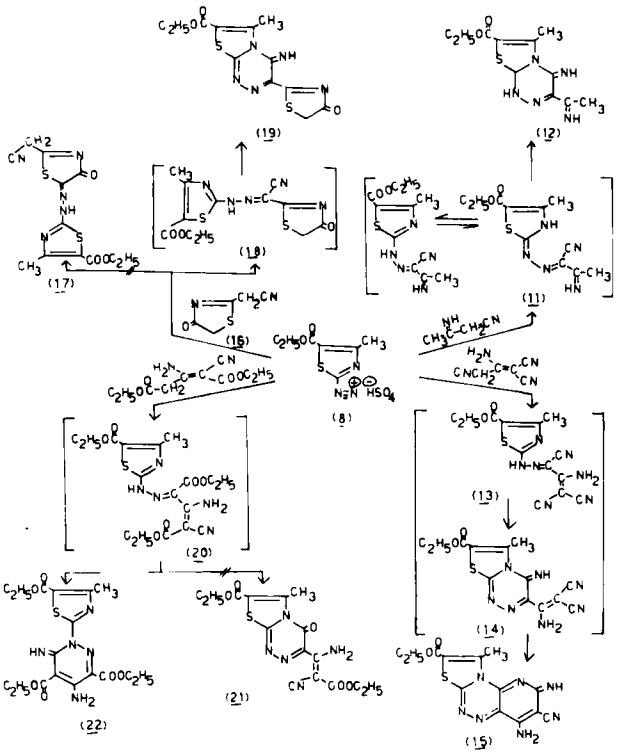
In contrast to the behaviour of (**4**), compound (**7**) could be diazotized in presence of sulfuric acid. The diazonium sulfate (**8**) could be successfully coupled with the ethyl α-chloroacetoacetate and α-chloroacetylacetone to yield the corresponding thiazol-2-yl hydrazonyl chloride derivatives (**9** and **10**). The formation of compounds **9** and **10** from this reaction is assumed to proceed via coupling with the active hydrogen in the α-chloro derivatives followed by a Japp-Klingman acetyl group cleavage. (cf. Scheme 1).

In continuation of this work we report here the results of our further investigation on the reactions of diazotized aminothiazole (**8**). Thus, diazonium sulfate (**8**) could be coupled with 3-iminobutane nitrile to yield the final product **12**. The IR spectrum of 12 revealed the absence of CN group. We suggest that the reaction first involved coupling with active methylene of 3-iminobutane nitrile to yield the corresponding hydrazone (**11**) or azine as intermediate which then cyclised to afford the final reaction product **12**.

On the other hand, diazotized 8 could be coupled with malononitrile dimer to yield a product of molecular formula $C_{13}H_{11}N_7O_2S$. The IR spectrum of the product revealed strong absorptions at 1720, 2222, 3000, 3250 and 3440 cm^{-1}



SCHEME 1



SCHEME 2

indicating the presence of $COOC_2H_5$, CN, CH_3, NH_2, NH groups, respectively. Based on these data, the structure 15 was suggested for this product. We assume that the reaction proceeds via coupling of **8** with active methylene of malononitrile dimer to afford hydrazone **13**, which cyclises to afford the thiazolo[2,3-c]as-triazine derivative (**14**) as intermediate followed by cyclisation to the final product **15**. (cf. Scheme 2).

Also it has been found that diazotized 8 can be coupled with the thiazolin-4-one derivative (**16**) to give **19**. IR data of **19** revealed the absence of cyano group indicating that a coupling reaction occurred at active methylene to afford hydrazone (**18**) as intermediate, which cyclized in acid medium to yield the final product thiazolo[2,3-c]as-triazines derivative (**19**).

It has been found that diazotized **8** can be coupled with ethyl cyanoacetate dimer to afford a product of molecular formula $C_{17}H_{21}N_5O_6S$. The IR spectrum of the product revealed the absence of cyano group. Based on this data, the structure **22** is suggested for this product. We assume that the reaction proceeds via coupling of **8** with the active methylene of ethyl cyanoacetate dimer to afford hydrazone **20** as intermediate, which cyclizes under the reaction condition to the thiazol-2-yl pyridazine derivative **22** via cyclization on the cyano group and not the ester group where the thiazolo[2,3-c]as-triazinone derivative **21** would be obtained (cf. Scheme 2).

EXPERIMENTAL

All melting point are uncorrected. IR spectra were recorded (KBr) on Pye Unicam sp-1100 spectrophotometer. Elemental analysis has been carried out by the Mircoanalytical center at Cairo University.

Diazotization of 2-Amino-4-ethoxycarbonyl-5-methylthiazole (**8**). Compound 2-amino-4-ethoxycarbonyl-5-methylthiazole (7) (0.01 mole) was transferred to a dry beaker, immersed in an ice-salt bath. To this was added concentrated sulfuric acid (1.5 ml) drop by drop with continuous stirring then ice (5 gm), followed by a solution of sodium nitrite (0.01 mol) dropwise over 15 minutes with continuous stirring to give the solution of diazotized (**8**).

Preparation of thiazol-2-yl hydrazonyl chloride derivatives (**9–10**). A suspension of α-chloro derivatives of ethyl acetoacetate and acetylacetone (0.1 mole) in ethanol (100 ml) and anhydrous sodium acetate (0.1 mole) was cooled (0–5°C). To this mixture a solution of diazotized (**8**) (0.1 mol) was added dropwise over 30 minutes with continuous stirring for 2 hrs. The solid product, so formed was collected by filteration and crystallised from ethanol to give the thiazol-2-yl hydrazonyl chloride derivatives (**9–10**) respectively (cf. Tables I and II).

Coupling of diazotized (**8**) *with different activated nitrile reagents.* A suspension of diazotized (**8**) (0.01 mole), was gradually added to a cold solution (0–5°C) of each of 3-iminobutane nitrile, malononitrile dimer, thiazolin-4-one derivatives (**16**) and ethyl cyanoacetate dimer (0.01 mole) in ethanol (30 ml) containing anhydrous sodium acetate (0.015 mole) with continuous stirring for 3 hrs.

TABLE I

List of new compounds

Compd. No.	m.p. C.	yield %	Solvent of Crystal.	M. Formula and M. Weight	Found Calcd. C.	Analysis H	N	S
9	150	63	EtOH	$C_{11}H_{14}N_3O_4SIC$ (319.5)	41.1 41.3	4.2 4.4	13.0 13.1	9.8 10.0
10	145	67	EtOH	$C_{10}H_{12}N_3O_3ClS$ (289.5)	41.3 41.4	3.9 4.1	14.3 14.5	11.1 11.0
12	230	70	EtOH	$C_{11}H_{13}N_5O_2S$ (279)	47.2 47.3	4.3 4.6	25.1 25.1	11.5 11.3
15	>260	65	EtOH	$C_{13}H_{11}N_7O_2S$ (329)	47.1 47.4	3.1 3.3	29.5 29.8	9.8 9.7
19	>260	73	C_5H_6N	$C_{12}H_{11}N_5O_3S$ (305)	46.9 47.2	3.5 3.6	22.7 22.9	10.3 10.5
22	215	60	EtOH	$C_{17}H_{21}N_5O_6S$ (423)	47.9 48.2	4.8 4.9	16.3 16.5	7.4 7.5

TABLE II

IR data of the newly prepared compounds

Compd. No.	IR, cm^{-1} (Selected bands)
9	1610 (C=N), 1710, 1720 (ester), 2900–3000 (CH_3, CH_2, NH)
10	1605 (C=N), 1665, 1720 (acetyl and ester groups), 2950, 3000 (CH_3, CH_2, NH).
12	1730 (ester), 2800–3100 (CH_3, CH_2), 3220 (NH).
15	1620 (C=N), 1720 (ester), 2222 (C=N), 3000 (CH_3, CH_2) 3250–3440 (NH, NH_2)
19	1686 (C=O of thiazole ring), 1710 (ester), 2850–3000 (CH_3, CH_2), 3200 (NH).
22	1690–1750 (ester), 2750–2950 (CH_3, CH_2), 3000–3250 (NH, NH_2).

The reaction product was formed and increased with dilution or adding of dilute solution of ammonia. The product was collected by filteration and recrystallized from the proper solvent to give the coupling products (**12**, **15**, **19** and **22**) respectively (cf. Tables I and II).

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