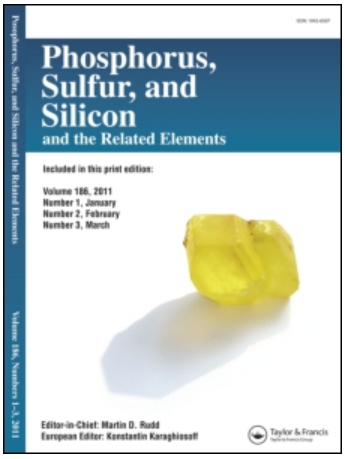

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REACTIONS WITH HETEROCYCLIC DIAZONIUM SALTS: SYNTHESIS OF SEVERAL NEW THIAZOLO[2,3-*c*]AS-TRIAZINES AND THIAZOLO [2,3-*c*]1,2,4-TRIAZOLE DERIVATIVES

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Several new thiazolo[2,3-*c*]as-triazines and thiazolo[2,3-*c*]1,2,4-triazole derivatives were synthesized utilizing 4-methyl-5-ethoxy carbonylthiazol-2-diazonium sulphate and active methylene reagents.

Key words: Activated nitriles; heterocyclic diazonium salts; thiazolo[2,3-*c*]as-triazines.

INTRODUCTION

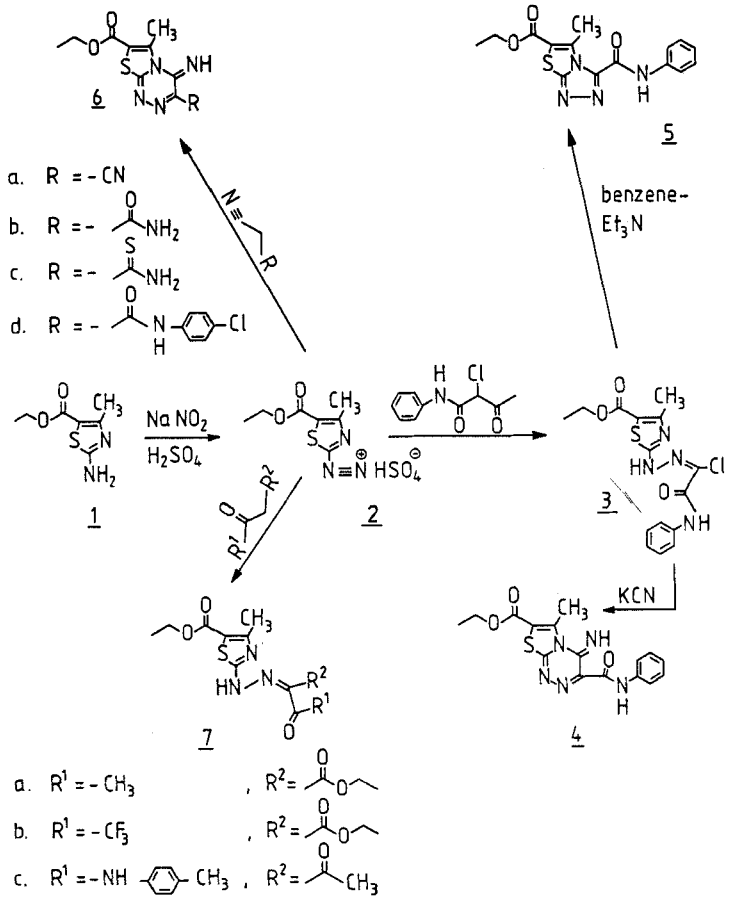
Thiazole[1–3] as well as triazine[4–6] are known to possess biological activity. In the hope to achieve higher activity, we have synthesized thiazolo-triazine derivatives.[7–8] In our synthetic scheme, we have employed the well known reaction of diazonium salt with active methylene compounds. However, the initial products formed with the thiazole 2 have been further cyclized to provide several novel bicyclic compounds.

RESULTS AND DISCUSSION

In continuation of this work we report here a novel synthesis of some thiazolo[2,3-*c*]as-triazines and thiazolo[2,3-*c*]1,2,4-triazoles. Thus diazotization of 2-amino-4-methyl-5-ethoxycarbonylthiazole (**1**) by the action of sodium nitrite and sulphuric acid, afforded the corresponding diazonium sulphate (**2**)[7–9] which coupled with chloroacetoacetanilide in ethanol-sodium acetate solution to yield the corresponding thiazol-2-yl hydrazidoyl chloride (**3**).

The formation of compound (**3**) from this reaction is assumed to proceed via coupling with the active hydrogen in the chloro derivative followed by a Japp-Klingman acetyl group cleavage.

Treatment of hydrazidoyl chloride (**3**) with potassium cyanide in aqueous etha-



Scheme 1

nolic solution afforded the thiazolo[2,3-*c*]as-triazine derivative (**4**), the reaction proceeding via a nucleophilic substitution reaction followed by cyclization. Also it has been shown that cyclization of (**3**) in triethylamine-benzene solution yielded the corresponding thiazolo[2,3-*c*]1,2,4-triazole derivative (**5**). It is clear that the cyclization of (**3**) in a basic medium takes place via elimination of hydrogen chloride.

The thiazolo[2,3-*c*]as-triazines (**6**) were produced via coupling of (**2**) with active nitrile reagents in ethanol-sodium acetate solution. The reaction is assumed to proceed via coupling of compound (**2**) with the active methylene group to give the corresponding hydrazone derivatives, which cyclise to afford the corresponding thiazolo[2,3-*c*]as-triazine derivatives (**6**)*. In contrast to the above results compound (**2**) was coupled with ethylacetoacetate and ethyl 1,1,1-trifluoro-acetoacetate and aceto-(4-ethyl)-anilide to yield the corresponding hydrazones (**7**)*. Also it has been found that diazonium salt (**2**) can be coupled with active methylene heterocycles

*The structures were established on the basis of elemental analysis and spectral data (cf. Tables I and II).

such as 3-methylpyrazol-5-one, *N*-phenyl-3-methylpyrazol-5-one and rodamin to yield the corresponding acyclic hydrazones (**8, 9**), respectively.

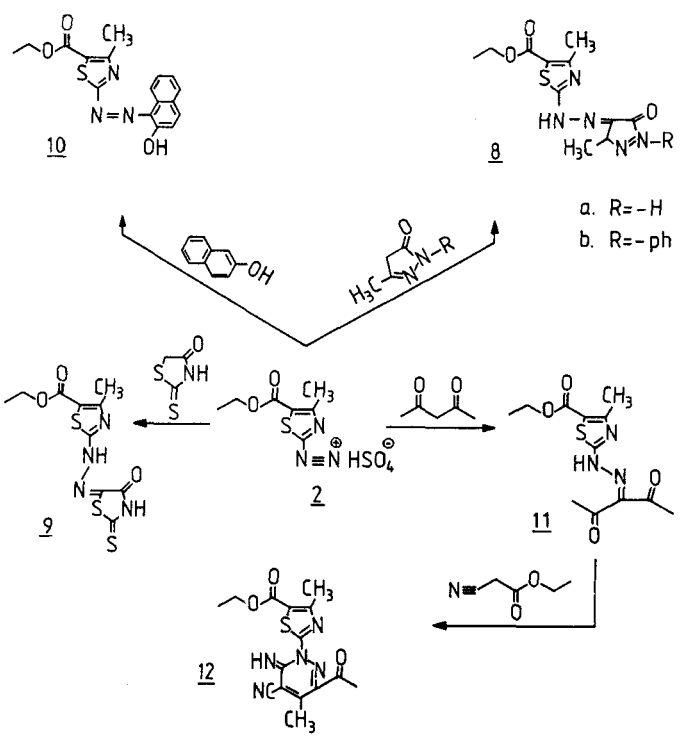
The diazonium sulphate (**2**) can be coupled with electron rich aromatic rings such as that of β-naphthol to give the acyclic hydrazone (**10**)*. The thiazol-2-yl-*N*-pyridazine (**12**)* could be obtained through fusion of hydrazone (**11**)[8-9] with ethyl cyanoacetate in presence of ammonium-acetate. Similar reactions have been previously observed.[10-11]

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on Pye Unicam Sp-1100 spectrophotometer. Elemental analysis has been carried out by the Microanalytical Center at Cairo University. Compound (**2**) was prepared following literature procedures.[7-8]

Preparation of thiazol-2-yl hydrazidoyl chloride derivative (**3**): A suspension of α-chloro acetoacetate anilide (0.01 mole) in ethanol (100 ml) and anhydrous sodium acetate (0.01 mole) was cooled (0–5°C). To this mixture a solution of diazonium sulphate (**2**) (0.01 mole) was added dropwise over 30 minutes with continuous stirring for 2 hrs. The solid product, so formed, was collected by filtration and crystallized from ethanol to give the thiazol-2-yl hydrazidoyl chloride (**3**) (cf. Tables I and II).

Coupling of the diazonium salt (**2**) *with active methylene reagents*: General procedure: A suspension of diazonium sulphate (**2**) (0.01 mole) was gradually added to a cold solution (0–5°C) of each one of the following active methylene reagents (malononitrile, cyanoacetamide, cyanothioacetamide, cyanoaceta (p-Cl) anilide, ethylacetoacetate, ethyl 1,1,1-trifluoroacetoacetate, acetoacet-(p-CH_3)anilide, 3-methylpyrazol-5-one, *N*-phenyl 3-methylpyrazol-5-one, rodamine and β-naphthol (0.01 mole) in ethanol (30



Scheme 2

TABLE I

List of new prepared compounds

Compd. No.	M.P. °C.	Yield %	M. Formula and M. Weight	Found Calcd. C.	Analysis H.	N.	S.
3	165	72	$C_{15}H_{15}N_4O_3SCL$ (366.5)	49.0 49.1	3.9 4.1	15.4 15.3	8.6 8.7
4	>260	80	$C_{16}H_{15}N_5O_3S$ (357)	54.1 53.8	4.4 4.2	19.5 19.6	9.6 9.6
5	>260	60	$C_{15}H_{14}N_4O_3S$ (330)	54.3 54.5	4.3 4.2	16.8 17.0	9.6 9.7
6a	235	75	$C_{10}H_9N_5O_2S$ (263)	45.4 45.6	3.1 3.4	26.3 26.6	12.0 12.2
6b	128	82	$C_{10}H_{11}N_5O_3S$ (281)	42.5 42.7	3.7 3.9	24.6 24.9	11.2 11.4
6c	120	72	$C_{10}H_{11}N_5O_2S$ (297)	40.4 40.4	3.8 3.7	23.3 23.6	21.5 21.5
6d	>260	85	$C_{16}H_{14}N_5O_3SCL$ (391.5)	48.8 49.0	3.3 3.6	17.7 17.9	8.0 8.2
7a	105	60	$C_{13}H_{17}N_3O_5S$ (327)	47.5 47.7	5.2 5.2	13.1 12.8	9.6 9.8
7b	100	55	$C_{13}H_{14}N_3O_5SF_3$ (381)	40.8 40.9	3.5 3.7	10.8 11.0	8.4 8.4
7c	180	75	$C_{18}H_{20}N_4O_4S$ (388)	55.5 55.7	5.3 5.2	14.2 14.4	8.1 8.2
8a	142	66	$C_{11}H_{13}N_5O_3S$ (295)	44.6 44.7	4.1 4.4	23.7 23.7	10.9 10.8
8b	110	70	$C_{17}H_{17}N_5O_3S$ (371)	55.3 55.0	4.3 4.6	18.6 18.9	8.5 8.6
9	170	68	$C_{10}H_{10}N_4O_3S_3$ (330)	36.4 36.4	2.8 3.0	16.9 17.0	28.8 29.0
10	175	90	$C_{17}H_{16}N_3O_3S$ (342)	59.4 59.6	4.6 4.7	12.0 12.3	9.2 9.4
12	127	56	$C_{15}H_{15}N_5O_3S$ (345)	52.1 52.2	4.3 4.3	20.1 20.3	9.2 9.3

TABLE II

List of IR data for the prepared compounds

Compd. No.	cm^{-1} (ν) selected bands
3	1605 (C=N), 1685 (CO), 1720 (ester) and 2900–3100 (CH_3, CH_2, NH)
4	1610 (C=N), 1690 (CO), 1720 (ester) and 2850–3100 (CH_3, CH_2, NH)
5	1600 (C=N), 1680 (CO), 1715 (ester) and 2900–3200 (CH_3, CH_2, NH)
6a	1610 (C=N), 1720 (ester), 2220 (CN), 2850–3100 (CH_3, CH_2, NH)
6b	1600 (C=N), 1680 (CO), 1720 (ester), 2900–3300 (CH_3, CH_2, NH)
6c	1630 (C=N), 1720 (ester) and 2850–3200 (CH_3, CH_2, NH)
6d	1605 (C=N), 1680 (CO), 1720 (ester), 2900–3300 (CH_3, CH_2, NH)
7a	1660 (CO), 1700, 1720 (2 ester) and 2850–3200 (CH_3, CH_2, NH)
7b	1620 (C=N), 1700, 1720 (2 ester) and 2900–3400 (CH_3, CH_2, NH)
7c	1605 (C=N), 1680 (CO), 1720 (ester), 2900–3100 (CH_3, NH)
8a	1610 (C=N), 1670 (C=O), 1720 (ester), 2850–3200 (CH_3, NH)
8b	1605 (C=N), 1678 (C=O), 1720 (ester) and 2900–3100 (Ch_3, NH)
9	1630 (C=N), 1720 (ester), 2900–3300 (CH_3, NH)
10	1610 (C=N), 1720 (ester), 2850–3450 (CH_3, NH, OH)
12	1609 (C=N), 1686 (CO), 1720 (ester), 2200 (CN), 2900–3300 (CH_3, CH_2, NH)

ml) containing anhydrous sodium acetate (0.015 mole) with continuous stirring for 2 hrs to yield the coupling products (6–10), respectively.

Reaction of the hydrazidoyl chloride **(3)** *with potassium cyanide*: A solution of **(3)** (0.01 mole) in ethanol (20 ml) was treated with a solution of potassium cyanide (0.03 mole) in water (5 ml). The reaction mixture was refluxed for 2 hrs and then poured into ice/water. The solid product, so formed, was collected by filtration and recrystallized from ethanol to yield **(4)** (cf. Tables I and II).

Cyclization of the hydrazidoylchloride **(3)**: A suspension of **(3)** (0.01 mole) in dry benzene (20 ml) was treated with triethylamine (0.015 mole). The reaction mixture was refluxed for 3 hrs. The solvent was then removed in vacuo. The remaining solid product was washed with pet.ether (60/80°C) and collected by filtration and recrystallized from ethanol to yield compound **(5)** (cf. Tables I and II).

Reaction of hydrazone **(11)** *with ethylcyanoacetate*: Equimolar amounts (0.01 mole) of ethylcyanoacetate and the hydrazone **(11)** (0.01 mole) were heated in presence of ammonium acetate (0.01 mole) at 160°C for 30 minutes. The resulting solid product was crystallized from ethanol to give pyridazine derivative **(12)**.

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