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FACILE SYNTHESIS OF THIADIAZOLO[2,3-b] QUINAZOLINE DERIVATIVES *VIA* THE JAPP-KLINGEMANN REACTION

ABDOU O. ABDELHAMID, HAMDI M. HASSANEEN, IKHLASS M. ABBAS and AHMAD S. SHAWALI*
Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

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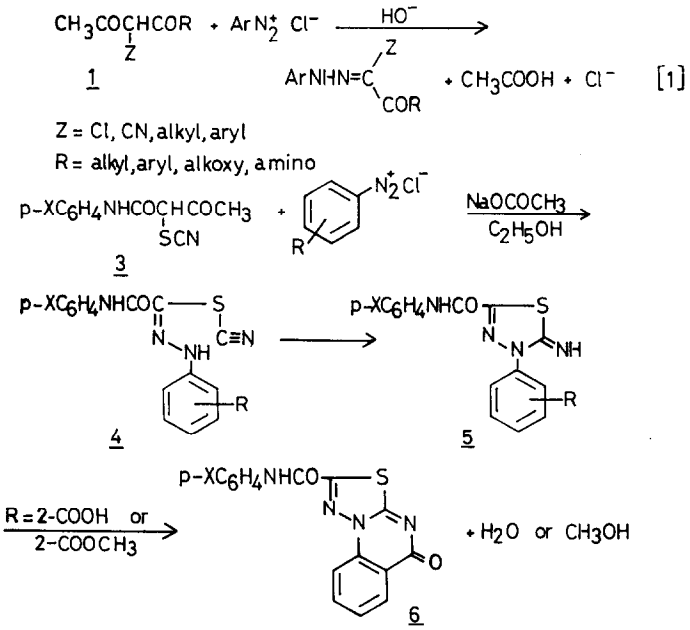
Abstract—Diazotized anathranilic acid and its methyl ester react with substituted α-thiocyanatoacetoacetanilides **3a–c** to give in both cases the corresponding thiadiazolo[2,3-*b*] quinazolines **6a–c**, respectively. A mechanism is proposed and it is substantiated by synthesis of **6a** from N-(2-carboxyphenyl)-C-phenylcarbamoyl hydrazidoyl chloride **8a** or its N-(2-methoxycarbonylcarbonylphenyl) analogue **8d**.

The Japp–Klingemann reaction[1] of active methine compounds **1** has been long known and much studied (eqn 1, Scheme 1). In this paper, we report on an investigation of the use of this reaction in synthesis of the title compounds (Scheme 1). The class of thiadiazolo[2,3-*b*] quinazoline derivatives in this report represents a novel ring system that has not yet been reported.

RESULTS AND DISCUSSION

Treatment of α-thiocyanatoacetoacetanilide **3a** with diazotized anthranilic acid in ethanilic sodium acetate buffered solution gave a pale coloured product. Mass spectral and combustion analyses data indicated its molecular formula as $C_{16}H_{10}N_4O_2S$. The IR spectrum of this product was free of SCN (2165 cm^{-1}), NH (3340 cm^{-1}) and OH (3100–2450 cm^{-1}) bands. It revealed, however, two carbonyl bands near 1680 and 1705 cm^{-1}. Thus, it was clear that the hydrazone **4a** was not the end product of the reaction.

Our first consideration for the structure of this product was **6a** which is shown in Scheme 1. It was thought that **4a** undergoes spontaneous cycloaddition[2] to give the iminothiadiazoline derivative **5a**, which completes the reaction by the loss of elements of water to yield the final product **6a**. The proposed structure of **6a** was confirmed by our finding that **6a** was also obtained by coupling of **3a** with diazotized methyl anthranilate. Compounds **3b–c** reacted similarly with diazotized anthranilic acid or its methyl ester and gave the corresponding products **6b–c**, respectively (Scheme 1).



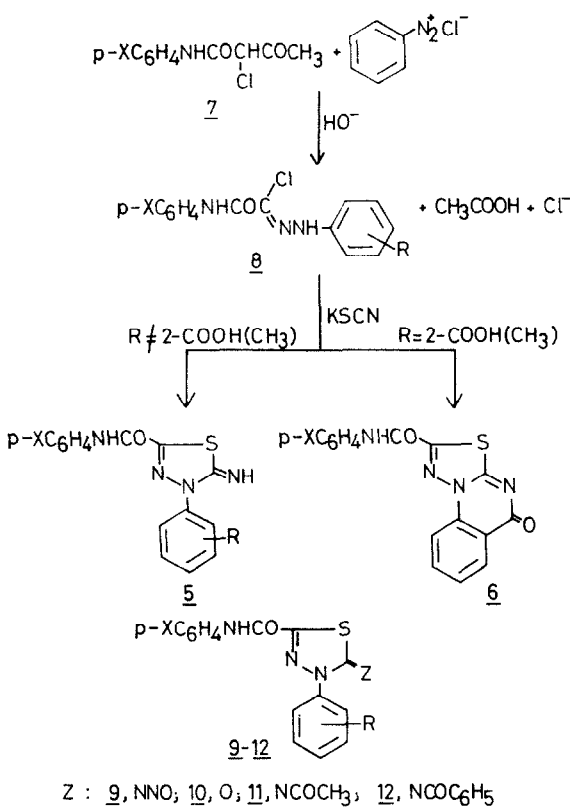
X/R : a) H/2-COOH
b) CH_3/ 2-COOH
c) Cl / 2-COOH
d) H/2-$COOCH_3$
e) H/H
f) H/4-CH_3
g) H/ 3-CH_3
h) H/ 4-Cl
i) H/ 3-Cl
j) H/ 4-NO_2
k) H/3- NO_2

Scheme 1

To substantiate the involvement of **5** as intermediate in the present reaction, coupling of **3a** with other diazotized anilines was investigated under similar conditions. In this case the corresponding thiadiazoline derivatives **5** was isolated. In no case, the open chain thiocyanatohydrazone **4** was isolated. The structures of the products **5e–k** were established by spectroscopic and chemical evidence and alternate synthesis (Scheme 2). Thus, the IR spectra of **5** (KBr) revealed the absence of free SCN band (2165 cm^{-1})[3] and the presence of two NH bands near 3280 and 3340 cm^{-1} assignable to the anilide and imino NH groups respectively. The products **5e–k** can be nitrosated to give the corresponding N-nitroso derivatives **9**, which upon thermolysis in xylene yield the thiadiazolin-5-ones **10**. Acylation of **5** in acetic anhydride and with benzoyl chloride in pyridine gave the N-acyl derivatives **11** and **12**, respectively. Both spectral and elemental analyses data were compatible with the structures of the products **9–12** (see Experimental).

Conclusive evidence for the structure of the product **6a** was obtained by synthesis using the hydrazidoyl chloride **8d** obtained from coupling of α-chloroacetoacetanilide **7a** with diazotized methyl anthranilate. Reaction with potassium thiocyanate at room temperature gave a produce identical in all respects (Spectra, m.p. and mixed m.p.) with compound **6a** obtained from **3a** and diazotized anthranilic acid or its methyl ester. Similar treatment of **8a** with potassium thiocyanate in ethanol on hot yielded **6a**, whereas other compounds in series **8** gave the corresponding thiadiazoline derivatives **5**.[4]

The foregoing results indicate that coupling of α-thiocyanato derivatives of active methylene compounds with diazotized anthranilic acid or its methyl ester seems to be an efficient and rapid experimental procedure for synthesis of thiadiazolo[2,3-*b*] quinazoline derivatives.



Scheme 2

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP1000 spectrophotometer, PMR ($CDCl_3$) spectra on a Varian-T60A spectrometer, UV spectra (EtOH) on a Pye Unicam SP8000 spectrophotometer and mass spectra on a Perkin–Elmer RMU-6E spectrometer (Ionization energy 70 eV). Elemental analyses were performed at the Microanalytical laboratory at the University of Cairo, Giza, Egypt. α-Chloroacetoacetanilides **7a–c** and the hydrazidoyl chlorides **8a,e–k** were prepared by previously described methods.[5–6]

α-Thiocyanatoacetoacetanilides **3a–c**. To a suspension of the appropriate α-chloroacetoacetanilide **7** (0.005 mole) in ethanol (20 ml) a solution of potassium thiocyanate (0.01 mole) in water (10 ml) was added and the mixture was stirred for 1 h at room temperature. Upon dilution of the reaction mixture with water, a yellow solid precipitated. It was collected and recrystallized from cyclohexane to give **3** in 60–70% yield. Compound **3a** had m.p. 110°. Found: C, 56.15; H, 4.12; N, 11.72; S, 13.91; calc. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.95; S, 13.91%. Compound **3b** had m.p. 127°. Found: C, 58.21; H, 4.78; N, 11.15; S, 12.72; calc. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28; S, 12.91%. Compound **3c** had m.p. 125°. Found: C, 49.32; H, 3.30; N, 10.24; S, 11.61; calc. for $C_{11}H_9N_2O_2SCl$: C, 49.14; H, 3.30; N, 10.42; S, 11.93%.

Hydrazidoyl Chlorides **8b–d**. These new compounds were prepared by coupling α-chloroacetoacetanilides **7a–c** with diazotized anthranilic acid or its methyl ester following our previously described procedure.[6] Compound **8b** had m.p. 238°. Found: C, 57.7; H, 4.2; N, 12.5; Cl, 10.8; calc. for $C_{16}H_{14}N_3O_3Cl$: C, 57.92; H, 4.25; N, 12.66; Cl, 10.68%. Compound **8c** had m.p. 227°, Found: C, 51.27; H, 3.00; N, 11.75; Cl, 20.31; calc. for $C_{15}H_{11}N_3O_3Cl_2$: C, 51.15; H, 3.14; N, 11.93; Cl, 20.13%. Compound **8d** had m.p. 147°. Found: C, 57.68; H, 4.31; N, 12.51; Cl, 10.86; calc. for $C_{16}H_{14}N_3O_3Cl$: C, 57.92; H, 4.25; N, 12.66; Cl, 10.68%.

Thiadiazolo[2,3-b] *quinazolinones* **6a–c**. *Method A*. To a cold solution of the appropriate α-thiocyanatoacetoacetanilide **3** (0.01 mole) and sodium acetate (1.3 g) in ethanol (50 ml) was added dropwise a solution of diazotized anthranilic acid or methyl anthranilate (0.01 mole) while stirring. After the addition was complete (30 min), the reaction mixture was left overnight in a refrigerator. The pale yellow solid which precipitated was collected and crystallized from dimethylformamide. Compound **6a** had m.p. 281°, MS: *m/e* 294 (M^+). Found: C, 59.7; H, 3.2; N, 17.51; S, 10.0; calc. for $C_{10}H_{10}N_4O_2S$: C, 59.61; H, 3.2; N, 17.38; S, 9.94%. Compound **6b** had m.p. 270°. Found: C, 60.51; H, 3.4; S, 9.6; calc. for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.59; S, 9.53%. Compound **6c** had m.p. 295°. Found: C, 53.68; H, 2.45; S, 8.89; calc. for $C_{16}H_9N_4O_2S$ Cl: C, 53.86; H, 2.54; S, 8.98%.

Method B. To a suspension of **8b** (0.005 mole) in ethanol (30 ml) a solution of potassium thiocyanate (1.7 g, 0.01 mole) in water (10 ml) was added. The mixture was stirred for 4 h at room temperature. The crude product was collected, washed with water and crystallized from dimethylformamide. The product obtained was found to be identical in all respects (m.p. mixed m.p. and spectra) with that obtained above by coupling **3a** with diazotized anthranilic acid or methyl anthranilate.

2 - *Phenylcarbamoyl* - 4 - *aryl* - 5 - *imino* - Δ^2 - 1,3,4 - *thiadiazolines* **5e–k**. *Method A*. A cold solution of **3a** (2.3 g, 0.01 mole) and sodium acetate (1.3 g) in ethanol (50 ml) was treated, while stirring, with the appropriate diazonium salt (0.01 mole) and left in the ice bath for 3 h. The precipitate was collected, washed with water and recrystallized from methanol or ethanol. The compounds prepared are listed in Table 1. IR (KBr) spectra of **5e–k** reveals bands at 1680 (NHCO), 3280 (– NH) and 3340 cm^{-1} (CONH). PMR ($CDCl_3$) of **5e** 7.2–7.9 (m, 11H, ArH, NHCO, imino NH); UV (Ethanol) λ_{max} 350–335, 255–240, 230–215 nm.

Table 1.

Compound	M.p.°C	Method	Molecular Formula	C,% Calcd.	C,% Found	H,% Calcd.	H,% Found	S,% Calcd.	S,% Found
5e	127	A,B	$C_{15}H_{12}N_4OS$	60.79	60.90	4.08	3.90	10.82	10.76
5f	192	A,B	$C_{16}H_{14}N_4OS$	61.91	61.80	4.54	4.30	10.33	10.40
5g	147	A	$C_{16}H_{14}N_4OS$	61.91	61.70	4.54	4.50	10.33	10.35
5h	168	A,B	$C_{15}H_{11}ClN_4OS$	54.46	54.60	3.35	3.20	9.69	9.60
5i	126	A	$C_{15}H_{11}ClN_4OS$	54.46	54.29	3.35	3.21	9.69	9.66
5j	220	A,B	$C_{15}H_{11}N_5O_3S$	52.77	52.55	3.25	3.15	9.39	9.27
5k	209	A,B	$C_{15}H_{11}N_5O_3S$	52.77	52.90	3.25	3.13	9.39	9.25
9e	144		$C_{15}H_{11}N_5O_2S$	55.37	55.31	3.41	3.30	9.85	9.70
9f	148		$C_{16}H_{13}N_5O_2S$	56.62	56.48	3.86	3.69	9.45	9.27
9g	152		$C_{16}H_{13}N_5O_2S$	56.62	56.50	3.86	3.70	9.45	9.30
9h	146		$C_{15}H_{10}ClN_5O_2S$	50.07	50.10	2.80	2.50	8.91	8.77
9i	136		$C_{15}H_{10}ClN_5O_2S$	50.07	50.03	2.80	2.67	8.91	8.80
9j	150		$C_{15}H_{10}N_6O_4S$	48.65	48.40	2.72	2.52	8.65	8.70
9k	158		$C_{15}H_{10}N_6O_4S$	48.65	48.60	2.72	2.62	8.65	8.55
10e	129		$C_{15}H_{11}N_3O_2S$	60.59	60.40	3.73	3.50	10.78	10.67
10f	148		$C_{16}H_{13}N_3O_2S$	61.72	61.55	4.21	4.12	10.29	10.10
10g	104		$C_{16}H_{13}N_3O_2S$	61.72	61.80	4.21	4.30	10.29	10.20
10h	136		$C_{15}H_{10}ClN_3O_2S$	54.30	54.15	3.04	3.00	9.66	9.56
10i	133		$C_{15}H_{10}ClN_3O_2S$	54.30	54.25	3.04	2.98	9.66	9.60
10j	216		$C_{15}H_{10}N_4O_4S$	52.63	52.54	2.94	2.79	9.37	9.30
10k	194		$C_{15}H_{10}N_4O_4S$	52.63	52.40	2.94	2.81	9.37	9.28
11e	216		$C_{17}H_{14}N_4O_2S$	60.34	60.40	4.17	4.10	9.47	9.38
11f	221		$C_{18}H_{16}N_4O_2S$	61.35	61.25	4.58	4.70	9.10	8.99
11g	237		$C_{18}H_{16}N_4O_2S$	61.35	61.20	4.58	4.71	9.10	9.07
11h	188		$C_{17}H_{13}ClN_4O_2S$	54.77	54.60	3.51	3.40	8.60	8.52
11i	236		$C_{17}H_{13}ClN_4O_2S$	54.77	54.56	3.51	3.50	8.60	8.53
11j	224		$C_{17}H_{12}N_5O_4S$	53.26	53.24	3.42	3.29	8.36	8.29
11k	249		$C_{17}H_{13}N_5O_4S$	53.26	53.30	3.42	3.40	8.36	8.31
12e	229		$C_{22}H_{16}N_4O_2S$	65.98	66.10	4.03	3.80	8.01	8.00
12f	216		$C_{23}H_{18}N_4O_2S$	66.65	66.70	4.38	4.40	7.73	7.67
12g	221		$C_{23}H_{18}N_4O_2S$	66.65	66.50	4.38	4.30	7.73	7.70
12h	234		$C_{22}H_{15}ClN_4O_2S$	60.76	60.50	3.47	3.35	7.37	7.28
12i	210		$C_{22}H_{15}ClN_4O_2S$	60.76	60.55	3.47	3.37	7.37	7.26
12j	223		$C_{22}H_{15}N_5O_4S$	59.32	59.20	3.39	3.29	7.19	7.10
12k	185		$C_{22}H_{15}N_5O_4S$	59.32	59.19	3.39	3.40	7.19	7.20

Method B. To a suspension of the appropriate **8** (0.005 mole) in ethanol (50 ml) a solution of potassium thiocyanate (0.01 mole) in water (10 ml) was added, and the mixture was stirred for 4 h at room temperature. During this period, the material went into solution and a new solid precipitated. It was collected, washed with water, and crystallized from ethanol. The properties of the compounds obtained were identical with those of the products obtained by Method A (Table 1).

Nitrosation of **5e–k**. A solution of **5** (1.0 g) in acetic acid (30 ml) was treated with a saturated sodium nitrite solution while stirring. The reddish product which precipitated was collected and recrystallized from acetone. The 2-phenylcarbamoyl - 4 - aryl - 5 - nitrosoimino - 1,3,4, - thiadiazolines **9e–k** prepared are listed in Table 1 together with their physical constants. UV (ethanol) of **9**: λ_{max} (log ϵ) 510–470 (<2.0) ($n-\pi^*$) and 340–360 (>4) ($\pi-\pi^*$) nm.[7]

2-Phenylcarbamoyl-4-aryl-Δ^2-1,3,4-thiadiazolin-5-ones **10e–k**. The appropriate nitrosoimino derivative **9** (0.5 g) was refluxed in xylene (20 ml) for 30 min and the solvent was then removed under reduced pressure. Trituration of the residue with ligroin (40/60) caused precipitation of **10** which was collected and crystallized from ethanol. The compound prepared are listed in Table 1. IR (KBr) 3330, 1680 cm^{-1} (CONH), 1705 cm^{-1} (5–CO). PMR ($CDCl_3$) of **10f**: 2.4 (3H, s, CH_3Ar), 7.0–8.5 ppm (10H, m, ArH and CONH). UV (ethanol) λ_{max}: 340–300, 290–250 and 240–200 nm.

Acylation of **5e–k**. Compound **5** (0.5 g) was refluxed in acetic anhydride (10 ml) for 20 min and the mixture was then poured onto ice. The crude product was collected and crystallized from acetic acid. The N-acetyl derivatives **11e–k** were obtained almost in quantitative yield (Table 1). IR (KBr) 3320, 1680 (CONH), 1630 cm^{-1} (CH_3CON–). PMR ($CECl_3$) of acetyl derivative of **10f** 2.34 (3H, s, CH_3CON–), 2.41 (s, 3H, CH_3Ar), 7.0–8.5 ppm (m, 10H, ArH and anilide NH).

The benzoyl derivatives **12e–k** were obtained by refluxing equimolecular amounts of **5** and benzoyl chloride in pyridine for 20 min. Work up of the reaction mixture and crystallization from acetic acid gave **12e–k** in almost quantitative yield, Table 1.

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