PREPARATION OF SOME PYRAZOLE DERIVATIVES BY EXTRUSION OF ELEMENTAL SULFUR FROM 1,3,4-THIADIAZINES

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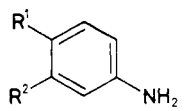
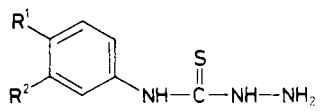
Received May 17, 1991
Accepted June 18, 1991

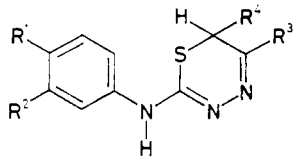
In connection with our research of pyrazolo[3,4-*b*]quinolines we were also interested in the preparation of various pyrazole intermediates. In some cases we found a method useful based on extrusion of elemental sulfur from intermediate 1,3,4-thiadiazines (for a review on the preparation of five-membered heterocycles by the extrusion reaction see ref.[1]). This short contribution describes the preparation of some new 3-anilino-4-pyrazolecarboxylic acid derivatives using this method. We started from corresponding anilines *Ia–Ic* which were transformed to respective 4-phenylthiosemicarbazides *IIa–IIc* by the usual way[2]. The compounds of this type are known to react with α-halo ketones, yielding 1,3,4-thiadiazoles of general formula *III*.



I

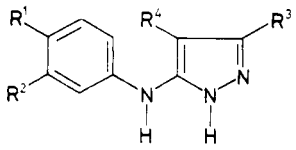


II



III

In formulae *I* and *II*: *a*, $R^1 = R^2 = H$; *b*, $R^1 = H$; $R^2 = Cl$; *c*, $R^1 = F$; $R^2 = Cl$



IV a, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COOC_2H_5$
IV b, $R^1 = H$; $R^2 = Cl$; $R^3 = CH_3$; $R^4 = COOC_2H_5$
IV c, $R^1 = R^2 = H$; $R^3 = R^4 = COOC_2H_5$
IV d, $R^1 = H$; $R^2 = Cl$; $R^3 = R^4 = COOC_2H_5$
IV e, $R^1 = F$; $R^2 = Cl$; $R^3 = R^4 = COOC_2H_5$
IV f, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COOH$
IV g, $R^1 = H$; $R^2 = Cl$; $R^3 = CH_3$; $R^4 = COOH$
IV h, $R^1 = R^2 = H$; $R^3 = COOH$; $R^4 = H$
IV i, $R^1 = R^2 = H$; $R^3 = COOC_2H_5$; $R^4 = H$

Compounds having an electron-withdrawing group in the neighbourhood of the sulfur atom extrude spontaneously elemental sulfur to provide corresponding

pyrazoles *IV*. In our hands the treatment of *IIa* and *IIb* with ethyl 2-chloroacetoacetate yielded pyrazole derivatives *IVa* and *IVb*, respectively. Similar treatment of *IIa*–*IIc* with diethyl 2-chlorooxalylacetate provided *IVc*–*IVe*, respectively.

Saponification of *IVa* and *IVb* with a boiling solution of sodium hydroxide in aqueous ethanol gave corresponding acids *IVf* and *IVg*, respectively. However, the

TABLE I

Yields, meting points and elemental analyses of compounds *IIa*–*IVi*

Compound	Yield, % M.p., °C	Formula (M.w.)	Calculated/Found					
			% C	% H	% N	% Cl	% F	% S
IIa	60	$C_7H_9N_3S$	50·28	5·42	25·13	—	—	19·17
	130–140[a]	(167·2)	49·95	5·23	25·33	—	—	19·55
IIb	47	$C_7H_8ClN_3S$	41·69	4·00	20·84	17·58	—	15·90
	135–136[b]	(201·7)	41·89	3·97	21·01	17·33	—	16·10
IIc	54	$C_7H_7ClFN_3S$	38·28	3·21	19·13	16·14	8·65	14·60
	166–167[c]	(219·7)	38·29	3·24	19·17	16·49	8·74	14·43
IVa	68	$C_{13}H_{15}N_3O_2$	63·66	6·16	17·13	—	—	—
	166–168	(245·3)	63·48	6·21	17·25	—	—	—
IVb	47	$C_{13}H_{14}ClN_3O_2$	55·82	5·04	15·02	12·67	—	—
	158–164	(279·7)	55·58	5·16	15·28	12·49	—	—
IVc	49	$C_{15}H_{17}N_3O_4$	59·40	5·65	13·85	—	—	—
	151–152	(303·3)	59·61	5·70	14·05	—	—	—
IVd	57	$C_{15}H_{16}ClN_3O_4$	53·34	4·77	12·44	10·50	—	—
	165–166	(337·8)	52·89	4·89	12·82	10·72	—	—
IVe	53	$C_{15}H_{15}ClFN_3O_4$	50·64	4·25	11·81	9·97	5·34	—
	184–185	(355·7)	50·43	4·13	11·95	10·04	5·39	—
IVf	88	$C_{11}H_{11}N_3O_2$	60·82	5·10	19·34	—	—	—
	190–195[d,e]	(217·2)	60·55	5·23	19·47	—	—	—
IVg	91	$C_{11}H_{10}ClN_3O_2$	52·50	4·00	16·70	14·09	—	—
	222–223	(251·7)	52·47	4·17	16·97	14·04	—	—
IVh[f]	63	$C_{10}H_9N_3O_2$	59·11	4·46	20·68	—	—	—
	260–280[g]	(203·2)	58·82	4·65	20·65	—	—	—
IVi	69	$C_{12}H_{13}N_3O_2$	62·33	5·67	18·17	—	—	—
	156–157	(231·2)	62·30	5·62	17·74	—	—	—

[a] Ref.[5] gives m.p. 140°C. [b] Ref.[3] gives m.p. 130°C. [c] Ref.[4] gives m.p. 171°C. [d] Ref.[4] gives m.p. 195°C (decomposition). [e] Decomposition. [f] *IVc* was used as a starting compound. [g] Decomposition to a compound not melting up to 300°C.

same treatment of *IVc* afforded *IVh*, a product of hydrolysis, and led to decarboxylation at position 4. Owing to the low solubility of *IVh* we prepared its ethyl ester *IVi* for the structural assignment by ^{13}C NMR spectrum.

Compounds *IIa* (ref.[2]), *IIb* (ref.[3]), *IVa* (ref.[4]), and *IVf* (ref.[4]) have been previously described in the literature.

EXPERIMENTAL

The melting points were determined on a Mettler FP 5 apparatus and were not corrected. The ^1H NMR spectra (100 MHz) and the ^{13}C NMR spectra (25·14 MHz) were measured on an apparatus BS-487 (Tesla Brno) 100 MHz in deuteriochloroform, using tetramethylsilane as a standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz.

General Procedure for the Preparation of 4-Phenylthiosemicarbazides *II*

A concentrated aqueous solution of ammonia (200 ml) was added to a solution of aniline *I* (1 mol) in ethanol (320 ml) and this mixture was stirred at room temperature for 1 h. Then carbon disulfide (60 ml, 1 mol) was added dropwise over 30 min, the mixture was stirred at room temperature for 4 h and then left to stand overnight. A solution of sodium chloroacetate, prepared by neutralization of a solution of chloroacetic acid (94·5 g, 1 mol) in water (200 ml) with solid sodium carbonate (53 g, 0·5 mol), was added and the reaction mixture was stirred for 1 h. Then hydrazine monohydrate (75 ml, 1·5 mol) was added and the mixture stirred at room temperature for 4 h and left to stand overnight in a refrigerator. The product was filtered off and crystallized from ethanol. Yields, melting points and elemental analyses of thiosemicarbazides *II* are summarized in Table I.

TABLE II

^1H NMR Data of 3-anilinopyrazoles *IVa*–*IVe*

Compound	Aromat. H	CH_3CH_2	CH_3CH_2	3-CH_3[a]
IVa	6·80–7·35 m, 5 H	4·32 q, 2 H, J = 7	1·42 t, 3 H, J = 7	2·44 s, 3 H
IVb	6·80–7·30 m, 4 H	4·32 q, 2 H, J = 7	1·40 t, 3 H, J = 7	2·46 s, 3 H
IVc	6·90–7·50 m, 5 H	4·42 q; 4·34 q, 4 H, J = 7	1·42 t; 1·40 t, 6 H, J = 7	—
IVd	6·80–7·30 m, 4 H	4·44 q; 4·36 q, 4 H, J = 7	1·42 t; 1·40 t, 6 H, J = 7	—
IVe	6·75–7·40 m, 3 H	4·42 q; 4·36 q, 4 H, J = 7	1·42 t; 1·40 t, 6 H, J = 7	—

[a] Pyrazole ring.

General Method of Preparation of *IVa—IVe*

Ethyl 2-chloroacetoacetate or diethyl 2-chlorooxalylacetate (0·1 mol) was added to a stirred suspension of 4-phenylthiosemicarbazide *IIa—IIc* (0·1 mol) in ethanol (130 ml) and the mixture was stirred at room temperature for 8 h and then refluxed for 2 h. Amorphous sulfur was filtered off from the hot mixture, the filtrate was cooled and the product filtered off and crystallized from ethanol (additional elemental sulfur was filtered off). Yields, m.p. and elemental analyses are given in Table I, ^{1}H NMR data are given in Table II.

General Method for Alkaline Saponification of *IVa*, *IVb* and *IVc*

A mixture of the respective starting ester (10 mmol), ethanol (100 ml) and 5% aqueous solution of sodium hydroxide (75 ml) was refluxed for 8 h and then acidified with concentrated hydrochloric acid to pH 4 and cooled. The precipitate formed was filtered off, washed with cold water and crystallized from methanol. Yields, m.p. and elemental analyses are given in Table I.

Ethyl 5-Anilinopyrazole-3-carboxylate (*IVi*)

A mixture of *IVh* (1 g, 5 mmol) and 30% ethanolic solution of hydrogen chloride (30 ml) was refluxed for 50 h, the solution was evaporated to dryness, the residue dissolved in methylene chloride (100 ml) and washed twice with 10% aqueous solution of potassium carbonate (10 ml) and water (10 ml). After drying over magnesium sulfate the solution was evaporated and the residue crystallized from ethanol; yield 0·8 g (69%), m.p. 156—157°C. ^{1}H NMR spectrum: 1·44 t, 3 H (CH_3, $J = 7$); 4·45 q, 2 H (CH_2, $J = 7$); 6·56 s, 1 H (H-4); 7·00—7·40 m, 5 H (aromat. H). ^{13}C NMR spectrum: 14·27 q (CH_3); 61·47 t (CH_2); 92·77 d (C-4); 116·00 d (C-2′, C-6′ of phenyl); 120·48 d (C-4′ of phenyl); 129·37 d (C-3′, C-5′ of phenyl); 140·80 s (C-3); 142·44 (C-1′ of phenyl); 147·23 s (C-5); 163·21 s (COO).

Our thanks are due to Dr J. Holubek for the measurement and the interpretation of the NMR spectra.

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Translated by the author.