A Facile Synthesis of Δ^2-1,3,4-Thiadiazolines Unsubstituted at the 4-Position

D. Michael Evans and David R. Taylor

Chemistry Department, University of Manchester Institute of Science and Technology, Manchester M60 1QD, U.K.

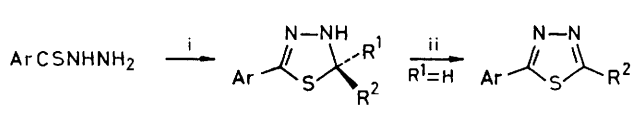
Contrary to many literature reports, the condensation of a wide variety of aldehydes and ketones with thioaroylhydrazines ($ArCSNHNH_2$) produces 2-aryl-Δ^2-1,3,4-thiadiazolines and not acyclic isomers.

A recent communication by Zelenin and co-workers[1] prompts us to disclose the preliminary results of our own investigation of reactions between aldehydes and ketones and thioaroylhydrazines ($ArCSNHNH_2$). Such reactions are commonly assumed, on the basis of several publications,[2–4] to yield acyclic condensation products (**1**) comparable to those obtained by the corresponding reactions (1) of aroylhydrazines.[5,6] In our hands, treatment of a thioaroylhydrazine at

$$ArCXNHNH_2 \xrightarrow[X = O \text{ or } S]{R^1COR^2} ArCXNHN{=}CR^1R^2 \quad (1)$$
(**1**)

ambient temperature with an ethanolic solution of an aliphatic or alicyclic ketone, or with an aromatic aldehyde, for up to 1 h even in the absence of acidic catalysts is sufficient to ensure virtually complete conversion into 2,5-substituted Δ^2-1,3,4-thiadiazolines (**2**). Although those thiadiazolines derived from aldehydes are somewhat prone to oxidation (prolonged reflux in ethanol may be sufficient to convert them into 2,5-disubstituted thiadiazoles), all the examples we have investigated may be isolated in 50—97% yield in the pure state without special precautions (Scheme 1).

Although our m.p. values for some of these compounds (**2**; Ar = Ph: R^1 = H, R^2 = Ph or 4-$MeOC_6H_4$: R^1 = R^2 = Me) agree with literature values cited[2,3] for isomeric thioaroylhydrazones (**1**), their cyclic structure is established beyond reasonable doubt by the characteristic n.m.r. shifts of their sp^3-hybridised 5-carbon atom and, where one is present, its attached methine proton (Table 1). The correctness of these assignments is supported by our earlier investigations[7] of the spectra of 4-amidino-Δ^2-1,3,4-thiadiazolines (**3**) and their comparison with 4-aryl-Δ^2-1,3,4-thiadiazolines (**4**) prepared by the method of Wuyts[8] from N^1-thioaroyl-N^2-arylhydrazines ($ArCSNHNHAr'$). An acyclic structure is denied to (**4**) by the presence of the 4-substituent while the cyclic structure of (**3**) is based ultimately upon an *X*-ray crystallographic analysis.[9]

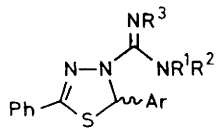


(**2**)

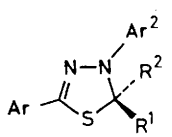
Scheme 1. i, R^1COR^2, EtOH, room temp.; ii, heat, [O].

The only reaction of thiobenzoylhydrazine with an aldehyde which we have so far found to proceed differently is that with formaldehyde, which yields the interesting bis-Δ^2-thiadiazoline (**5**). [Holmberg[2] made this compound but ascribed to it the rather improbable acyclic structure (**6**).]

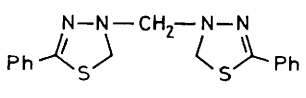
The only previous attempt to investigate the products of thioaroylhydrazine–aldehyde reactions by modern spectroscopic methods[10] concluded that a solvent-dependent equilibrium exists between the cyclic form (**2**) and the acyclic hydrazones (**1**; X = S). For the single compound (**2c**) that our series has in common with theirs, we are unable to reproduce the reported spectroscopic data which were claimed to demonstrate the existence of the acyclic isomer, and in none of our $CDCl_3$ solutions is there any evidence for the presence of even small concentrations of any isomer except the thiadiazolines (**3**). However, we do have evidence that very strong bases may initiate ring-opening reactions which commence by deprotonation at the 4-position: an attempt to



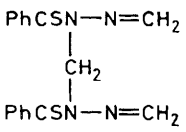
(**3**)



(**4**)



(**5**)



(**6**)

Table 1. Data for 2,5-substituted-Δ^2-1,3,4-thiadiazolines (**2a**—**k**) and (**5**).[a]

Compound	Ar	R^1	R^2	% yield	M.p. (°C)	^{13}C shift (C-5)[b]/p.p.m.	^{1}H shift (C-5-H)[c]
(2a)	Ph	H	Ph	88	78—80	74.65	6.3
(2b)	Ph	H	4-ClC_6H_4	64	106—108	73.74	6.32
(2c)	Ph	H	4-$MeOC_6H_4$	71	82—84	74.35	6.30
(2d)	Ph	H	4-MeC_6H_4	69	52—54	74.47	6.3
(2e)	Ph	Me	Me	64	49—51	79.94	—
(2f)	Ph	-$[CH_2]_5$-		52	52—54	85.77	—
(2g)	4-$MeOC_6H_4$	H	Ph	82	97—99	74.41	(6.3)[d]
(2h)	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	97	108—110	74.59	6.32
(2j)	4-$MeOC_6H_4$	Me	Me	87	44—46	79.88	—
(2k)	4-$MeOC_6H_4$	-$[CH_2]_5$-		51	65—67	85.59	—
(5)				69	86—88	59.16[e]	4.8 (4*H*)

[a] All new compounds had satisfactory elemental analyses, and were identified by i.r., ^{1}H and ^{13}C n.m.r. and mass spectroscopic analysis. [b] 20 MHz spectrum of $CDCl_3$ solution. [c] 90 MHz spectrum of $CDCl_3$ solution. [d] This signal is obscured by the N*H* resonance but is visible after D_2O exchange. [e] The bridging NCH_2N carbon resonates at 72.65 p.p.m. but is a less intense signal.

achieve *N*-methylation by treatment with sodium hydride followed by addition of iodomethane led to ring-opening and *S*-methylation.[11]

We are currently conducting an exploration of the synthetic potential of these Δ^2-1,3,4-thiadiazolines, which may readily be acetylated, benzoylated, and chloroacetylated without ring-opening, although an attempt to achieve *N*-methylation directly with iodomethane in the absence of sodium hydride was unsuccessful.

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