2-Imino-2,5-dihydro-1,3,4-thiadiazoles: Synthesis of 5-Oxo-1-thia-4-azaspiro[2,3]hexanes and 4-Alkylidene-2-oxoazetidines

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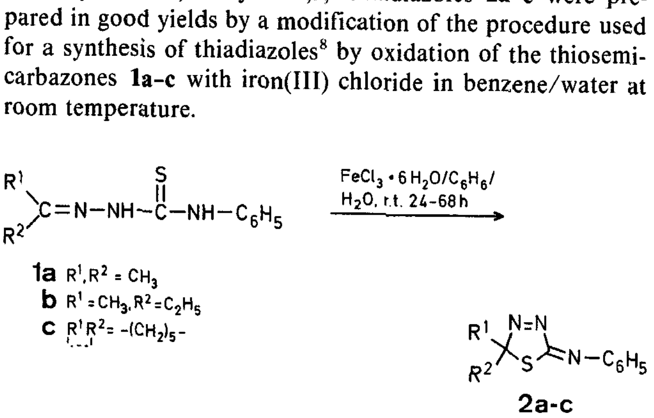
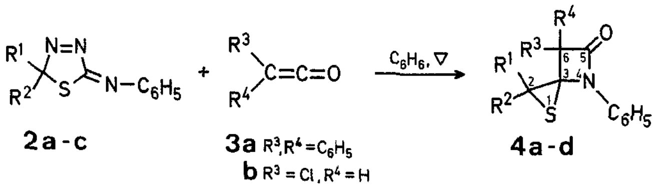
Thiadiazolines and oxadiazolines are useful reagents for carbon-carbon bond formation[1-4] and for syntheses of the other types of heterocycles[5,6,7]. In this communication, we report a synthesis of 2-imino-2,5-dihydro-1,3,4-thiadiazoles and their applications to the synthesis of 5-oxo-1-thia-4-azaspiro[2,3]hexanes (spiro-β-lactams) and 4-alkylidene-β-lactams.

2-Phenylimino-2,5-dihydro-1,3,4-thiadiazoles **2a–c** were prepared in good yields by a modification of the procedure used for a synthesis of thiadiazoles[8] by oxidation of the thiosemicarbazones **1a–c** with iron(III) chloride in benzene/water at room temperature.

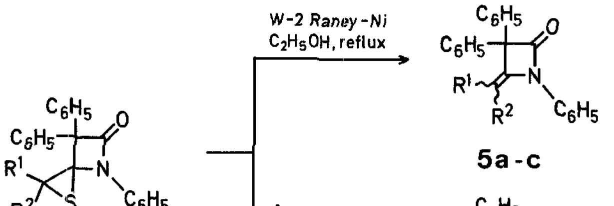


The thiadiazoles **2a–c** were characterized by spectral data and microanalysis. Compounds **2a–c** reacted smoothly with diphenylketene (**3a**) in boiling benzene to give the 5-oxo-1-thia-4-azaspiro[2,3]-hexanes **4a–c** in excellent yields (Table 2). Using chloroketene (**3b**), generated *in situ* from chloroacetyl chloride and triethylamine at −70 °C instead of **3a**, the corresponding spiro-β-lactam product **4d** was obtained in 54% yields. These products are assumed to be formed via [2π+2π]cycloaddition followed by elimination of nitrogen gas.



The structural confirmations for **4a–d** were based on satisfactory microanalysis, I.R., ¹H-N.M.R., ¹³C-N.M.R., and mass spectra as well as chemical properties. The I.R. spectrum of **4a**, for example, showed a strong absorption at 1750 cm⁻¹ (C═O) and its ¹³C-N.M.R. spectrum contained four singlets at δ = 168.8, 72.3, 86.8, 46.8 ppm which are assigned to the carbonyl(C-5), C-6, and C-3(spiro), and C-2 carbon atoms, respectively. The mass spectral fragmentation pattern of **4a** (*m/e* = 371, 331, 252, 194, 177, 119, 74) is also in agreement with the proposed structure.

Desulfurization of **4a–c** by Raney-nickel W-2 in boiling ethanol afforded the 4-alkylidene-β-lactams **5a–c** in excellent yields. In the I.R. spectrum, **5a** showed strong absorptions at 1780 (C═O) and 1695 (C═C) cm⁻¹ which are comparable to those of 3-methylenecyclobutanone[7] (1790 cm⁻¹ for C═O and 1675 cm⁻¹ for C═C). Isopropylidene-β-lactam (**5a**) was also obtained in 66% yield when **4a** was refluxed in dimethylformamide for 2.5 h.



5,5-Dimethyl-2-phenylimino-2,5-dihydro-1,3,4-thiadiazole (2a); Typical Procedure:

To an aqueous solution (100 ml) of iron(III) chloride hexahydrate (28.8 g. 0.105 mol) is added a solution of acetone-4-phenyl-3-thiosemicarbazone (**1a**; 10.72 g, 0.052 mol) in benzene (400 ml) and the mixture is stirred at room temperature for 24 h. Then the organic layer is separated and the aqueous layer is extracted with benzene (100 ml × 2). The combined organic layer is washed with water (100 ml × 2) and dried with anhydrous sodium sulfate. The benzene is evaporated in vacuo to give **2a**; yield: 9.65 g (90%); m.p. 100–100.5 °C.

$C_{10}H_{11}N_3S$	calc.	C 58.53	H 5.40	N 20.48	S 15.59
(205.3)	found	58.45	5.38	20.40	15.50

M.S. (75 eV): *m/e* = 177 ($M^{\oplus} - N_2$); 74 [$(H_3C)_2CS$].

I.R. (Nujol): ν = 1640 (C═N); 1535 cm⁻¹ (N═N).

¹H-N.M.R. (CDCl₃): δ = 1.80 (s, 6H, CH₃); 6.95–7.5 ppm (m, 5 H_{arom}).

¹³C-N.M.R. (CDCl₃): δ = 28.2 (CH₃); 106.9 (ring sp³ carbon); 121.0, 126.8, 129.3, 148.1 (aromatic carbons); 174.3 ppm (C═N).

***2,2-Dimethyl-4,6,6-triphenyl-5-oxo-1-thia-4-azaspiro[2,3]hexane* (4a); Typical Procedure:**

A mixture of thiadiazole **2a** (2.5 g, 12 mmol) and diphenylketene (**3a**; 2.4 g, 12 mmol) in benzene (50 ml) is refluxed for 3 h and then the solvent is evaporated in vacuo to give **4a**; yield: 4.5 g (100%); m.p. 157–158 °C.

$C_{24}H_{21}NOS$	calc.	C 77.59	H 5.70	N 3.77
(371.5)	found	77.75	5.42	3.73

M.S. (75 eV): *m/e* = 371 ($M^{\oplus}$); 252 ($M^{\oplus} - C_6H_5NCO$).

¹H-N.M.R. (CDCl₃): δ = 1.25 (s, 3 H, CH₃); 1.50 (s, 3 H, CH₃); 7.5–7.9 ppm (m, 15 H_{arom}).

¹³C-N.M.R. (CDCl₃): δ = 25.3 (q, CH₃); 30.1 (q, CH₃); 46.8 (s, C-2), 72.3 (C-6); 86.8 (C-3); 125.3 (d), 127.3 (d), 127.8 (d); 127.9 (d), 128.2 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.6 (d), 135.5 (s), 135.9 (s), 138.5 (s, aromatic carbons); 168.8 ppm (C-5).

0039-7881/81/1032-0813 $ 03.00

Table 1. 2-Phenylimino-2,5-dihydro-1,3,4-thiadiazoles **2a–c**

Product	Reaction time [h]	Yield [%]	m.p. [°C][a]	Molecular formula[b]		I.R. (nujol) [cm⁻¹] $\nu_{C=N}$	$\nu_{N=N}$
2a	24	90	100–100.5°	$C_{10}H_{11}N_3S$	(205.3)	1640	1535
2b	68	85	47.5–49°	$C_{11}H_{13}N_3S$	(219.3)	1620	1530
2c	24	88	76.5–78°	$C_{13}H_{15}N_3S$	(245.4)	1630	1530

[a] Not corrected.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.30, N ±0.30.

Table 2. 4-Phenyl-5-oxo-1-thia-4-azaspiro[2,3]hexanes **4a–d**

Product No.	R^1	R^2	R^3	R^4	Yield [%]	m.p. [°C][a]	Molecular formula[b]		I.R. (nujol) $\nu_{C=O}$ [cm⁻¹]	M.S. *m/e* (M^+)
4a	CH_3	CH_3	C_6H_5	C_6H_5	100	157–158°	$C_{24}H_{21}NOS$	(371.5)	1750	371
4b	CH_3	C_2H_5	C_6H_5	C_6H_5	71	184–187°	$C_{25}H_{23}NOS$	(385.5)	1760	385
4c	$-(CH_2)_5-$		C_6H_5	C_6H_5	100	197.5–199.5°	$C_{27}C_{25}NOS$	(411.6)	1755	411
4d	CH_3	CH_3	H	Cl	54	114.5–115.5°	$C_{12}H_{12}ClNOS$	(253.8)	1770	253

[a] Not corrected.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.30, N ±0.30.

Table 3. 4-Alkylidene-*β*-lactams **5a–c**

Product No.	R^1	R^2	Yield [%]	m.p. [°C][a]	Molecular formula	I.R. (nujol) [cm⁻¹] $\nu_{C=O}$	$\nu_{C=C}$	M.S. *m/e* ($M^{\oplus}$) found (calc.)
5a	CH_3	CH_3	97	105–106°	$C_{24}H_{21}NO$ (339.4)	1780	1695	339.1644 (339.1627)
5b	CH_3	C_2H_5	90	107–109°	$C_{25}H_{23}NO$ (353.5)	1780	1690	353.1759 (353.1783)
5c	$-(CH_2)_5)-$		89	153–155°	$C_{27}H_{25}NO$ (379.5)	1775	1685	379.1937 (379.1940)

[a] Not corrected.

4-Isopropylidene-2-oxo-1,3,3-triphenylazetidine (5a):

Spiro-azetidinone **4a** (1.3 g, 3.5 mmol) and Raney-nickel W-2 (3.4 ml) in ethanol (50 ml) are refluxed for 1 h. After cooling, insoluble material is removed by filtration and the filtrate is concentrated in vacuo to give **5a**; yield: 1.15 g (97%); m.p. 105–106 °C.

$C_{24}H_{21}NO$: calc. for $M^{\oplus}$, 339.1627 (found for $M^{\oplus}$, $m/e = 339.1644$).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.55$ (s, 6H, CH_3); 7.1–7.6 ppm (m, 15 H_{arom}).

We wish to thank Mr. T. Hinomoto, JEOL Co., for the ^{13}C-N.M.R. measurements.

Received: April 22, 1981

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[1] D. Daniil, U. Merkle, H. Meier, *Synthesis* **1978**, 535.

[2] H. Bühl, H. Gugl, H. Kolshorn, H. Meier, *Synthesis* **1978**, 536.

[3] J. Buter, S. Wassenaar, R. M. Kellogg, *J. Org. Chem.* **37**, 4045 (1972).

[4] R. M. Kellogg, W. L. Prins, *J. Org. Chem.* **39**, 2366 (1974).

[5] G. L'abbé, G. Verhelst, S. Toppet, *J. Org. Chem.* **41**, 3403 (1976).

[6] G. L'abbé, J.-P. Dekerk, J.-P. Declercq, B. Germain, M. V. Meerssche, *Angew. Chem.* **90**, 207 (1978); *Angew. Chem. Int. Ed. Engl.* **17**, 195 (1978).

[7] C. E. Diebert, *J. Org. Chem.* **35**, 1501 (1970).

[8] G. Ramachander, V. R. Srinivasan, *J. Sci. Ind. Res.* [C] **21**, 44 (1962).

0039-7881/81/1032-0814 $ 03.00