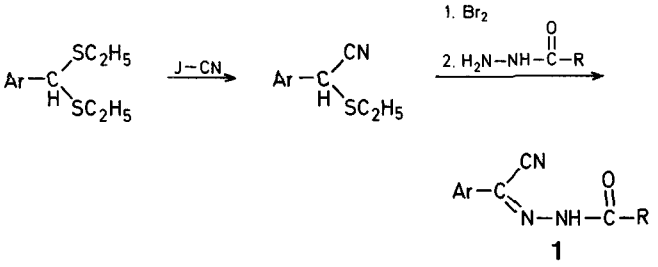
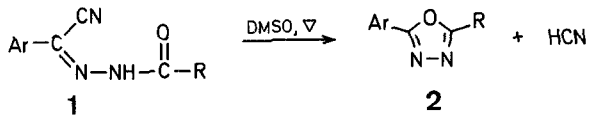


Compounds **1** have been shown to be converted into 1,2,4-triazine derivatives upon treatment with sodium hydroxide in dimethyl sulfoxide at 110°C[1]. We now report that heating of compounds **1** in boiling dimethyl sulfoxide for 0.5–2 hours results in intramolecular cyclocondensation with loss of hydrogen cyanide to give 1,3,4-oxadiazoles **(2)** in a clean reaction.



There are only two reports on analogous cyclocondensations with elimination of hydrogen cyanide, i.e., the conversion of *N''*-acryloylcyanoformamidrazone into 5-amino-2-vinyl-1,3,4-oxadiazole[2] by heating in pyridine for 18 hours and the conversion of α-oxonitrile thiosemicarbazones into 2-amino-1,3,4-thiadiazoles[3] by heating in glycol.

We have found that the cyclization **1** → **2** proceeds 10 times faster in dimethyl sulfoxide than in pyridine. Thus, heating of hydrazone **1b** at 108°C for 22 h gave a 33% yield of 1,3,4-oxadiazole **2b** when dimethyl sulfoxide was used and only a 3% yield when pyridine was used [in these cases, the yields are based on integration of the $CH_3$ peaks in the $^1$H-N.M.R. spectrum]. In boiling dimethyl sulfoxide, the reaction of **1b** (and also that of **1a**) is complete after only 10 minutes.

In most cases, the use of dimethyl sulfoxide as solvent seems only to enhance the nucleophilicity of the "enolic" form of **1** whereby the reaction is accelerated. However, with compound **1c** the reaction requires 2 hours to go to completion; in this case, it proceeds through an intermediate *N*-acyl-*N*-methylthiomethylhydrazone **(3c)** which could be isolated by stopping the reaction after 12 minutes. Since no other by-product was observed the following mechanism may be suggested for this particular case:

## A New Access to Unsymmetrical 2,5-Disubstituted 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

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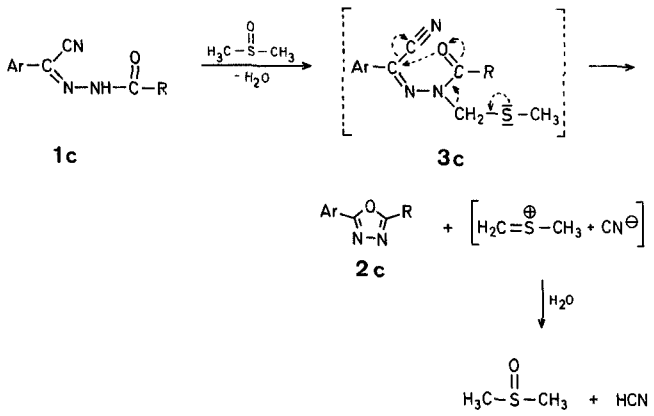
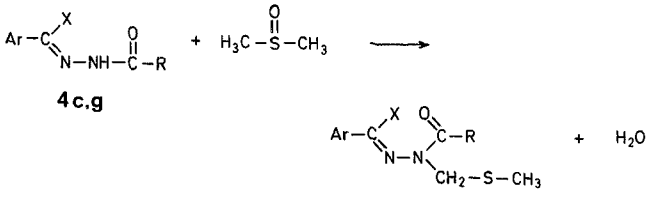
α-Cyanobenzylidenehydrazides **(1)** are readily obtained from the *S,S*-dialkyl acetals of aromatic aldehydes.



1c 3c 2c

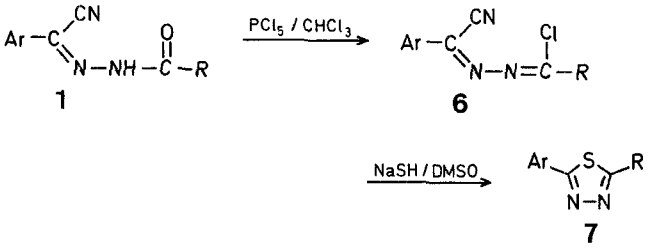
The formation of the methylthiomethyl compound **3c** is not surprising since educt **1c** possesses a somewhat acidic NH group. This type of *N*-substitution has already been described for phthalimide and related compounds[4,5]. We have found that this methylthiomethylation can also be performed with other acylhydrazones (**4c,g**).



4c,g 3c, 5c, 5g

| | Ar | X | R |
|---|---|---|---|
| 3c |  | —CN |  |
| 5c |  | H |  |
| 5g |  | H | —$CF_3$ |

The principle of the conversion of hydrazones **1** into 1,3,4-oxadiazoles (**2**) can be modified for the conversion of hydrazones **1** into *1,3,4*-thiadiazoles (**7**). Compounds **1** are first converted into the hydrazonic chlorides (**6**) which are then, without previous purification, treated with sodium hydrogen sulfide in dimethyl sulfoxide to give the disubstituted 1,3,4-thiadiazoles (**7**).



1 6 7

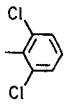
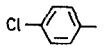
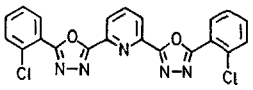
**1,3,4-Oxadiazoles (2); General Procedure:**

A solution of the carboxylic acid α-cyanobenzylidenehydrazide (**1**) in dimethyl sulfoxide (8 ml/g of **1**) is heated to reflux for the time given in Table 1. The solution is then allowed to cool and is poured into water (80 ml/g of **1**). In the case of **2a, b, c**, the mixture is saturated with sodium chloride and extracted with ether (2 × 5 ml/10 ml of mixture), washed with saturated sodium chloride solution (8 ml/10 ml of extract), dried with sodium sulfate, and evaporated. In the case of **2e, f**, the precipitated solid is isolated by suction and washed with water. The products are recrystallized from the solvents given in Table 1.

**1,3,4-Thiadiazoles (7):**

*1,3,4-Thiadiazoles* **7a, b:** A mixture of the carboxylic acid α-cyanobenzylidenehydrazide (**1**), chloroform (15 ml/g of **1**), and phosphorus(V) chloride (2 mol/mol of **1**) is stirred at slight reflux for 20 min. It is then allowed to cool, diluted with dichloromethane (30 ml/g of **1**), washed with ice water (50 ml/g of **1**), and dried with sodium sulfate. The solvents are evaporated and the remaining crude imidoyl chloride **6** is dissolved in the minimum amount of dimethyl sulfoxide (10–20 ml/g of **1**). This solution is stirred at room temperature and water (0.5 ml/10 ml of dimethyl sulfoxide) and sodium hydrogen sulfide hydrate ($NaSH \cdot H_2O$, Aldrich; 2.1 mol/mol of **1**) are added. Stirring is continued for 30 min, the mixture diluted with water (80 ml/10 ml of mix-

**Table 1.** 1,3,4-Oxadiazoles (**2**) prepared

| 2 | Ar | R | Reflux time in DMSO [h] | Yield[a] [%] | m.p. [°C] (solvent) | Molecular Formula[b] or m.p. [°C] reported | |
|---|---|---|---|---|---|---|---|
| a |  |  | 0.5 | 94 | 108–109° (methanol) | 110°[6], 102–104°[7] | |
| b |  | $CH_3$ | 0.5 | 75 | 65–66° (*pentane*) | 65–66°[8], 61–64°[9] | |
| c |  |  | 2 | 76 | 138.5–139.5° (methanol) | $C_{14}H_7Cl_3N_2O$ | (325.6) |
| d |  |  | 1 | 93 | 177.5–178° | $C_{13}H_8ClN_3O$ | (257.7) |
| e |  |  | 1 | 65 | 200–202° (acetonitrile) | $C_{13}H_{12}N_4O_2$ | (256.3) |
| f[c] |  | | 1 | 90 | 261–262° (DMSO/ethanol) | $C_{21}H_{11}Cl_2N_5O_2$ | (436.3) |

[a] Yield of recrystallized product.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.26; H, ±0.18; N, ±0.09. Exception: **2e** ($M^+ = 256$), C, −0.52.

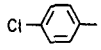
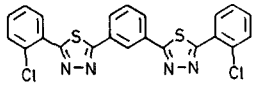
[c] The precursor **1f** (m.p. 215–217°C) was prepared from pyridine-2,6-dicarboxylic acid dihydrazide and bromo-(2-chlorophenyl)-ethylthioacetonitrile.

**Table 2.** *N*-Acyl-*N*-(methylthiomethyl)-hydrazonoarylacetonitriles prepared

| Product | Reflux Time in DMSO | Yield [%] | m.p. [°C] | Molecular Formula[a] | I.R. (Nujol) $\nu_{C=O}$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$) $\delta$ [ppm] | |
|---|---|---|---|---|---|---|---|
| | | | | | | $CH_2$ | $CH_3$ |
| **3c** | 12 min | 17[b] | 123.5–125° | $C_{17}H_{12}Cl_3N_3OS$ (412.7) | 1715 | 5.82 | 2.4 |
| **5c** | 24 h | 54 | 115–116° | $C_{16}H_{13}Cl_3N_2OS$ (387.7) | 1690 | 5.38 | 2.37 |
| **5g** | 6 h | 12[c] | 109–110° | $C_{11}H_{11}F_3N_2OS$ (276.3) | 1720 | 5.16 | 2.18 |

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.25; H, ±0.12; N, ±0.23; S, ±0.22.
[b] Isolated from a mixture of **1c**, **2c**, and **3c**.
[c] The low yield is due to decomposition with formation of a large amount of benzaldehyde.

**Table 3.** 1,3,4-Thiadiazoles (**7**) prepared

| 7 | Ar | R | Yield[a] [%] | m.p. [°C] (solvent) | Molecular Formula[b] or m.p. [°C] reported | M.S. *m/e* ($M^+$) |
|---|---|---|---|---|---|---|
| **a** |  |  | 92 | 113–114° (methanol) | $C_{15}H_{11}ClN_2S$ (286.8) 139–141°[6] | 286 |
| **b** |  |  | 83 | 107–108° (hexane) | 102–103°[9], 105–106°[10] | |
| **d** |  |  | 62 | 188–189° (methanol) | 187.6–188.4°[11] | |
| **h**[c] |  | | 78 | 223.5–225° (DMSO, washed with ethanol) | $C_{22}H_{12}Cl_2N_4S_2$ (467.4) | 466 |

[a] Yield of recrystallized product.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.15; H, ±0.09; N, ±0.12; S, ±0.15.
[c] The precursor **1h** (m.p. 188–191°C) was prepared from isophthalic dihydrazide and bromo-(2-chlorophenyl)-ethylthioacetonitrile.

ture), and extracted with ether (2 × 25 ml/10 ml of diluted mixture). The extract is washed with saturated sodium chloride solution (8 ml/10 ml of extract) and dried with sodium sulfate. The solvent is evaporated and the residual product **7** recrystallized from the solvent given in Table 3.

*Bis-thiadiazole* **7h**: The procedure is the same as that for **7a, b**, except larger amounts of phosphorus(V) chloride (4 mol/mol of **1**) and sodium hydrogen sulfide hydrate (4.2 mol/mol of **1**) are used. After dilution of the mixture with water, product **7h** is isolated by suction and washed with water.

*1,3,4-Thiadiazole* **7d**: The procedure is the same as that for **7a, b**, except that in the preparation of the imidoyl chloride **6d** pyridine (6 ml/g of **1**) is added to the chloroform solution of **1** before phosphorus(V) chloride is added with water cooling; the mixture is stirred at room temperature for 30 min and then refluxed for 2 min to give the imidoyl chloride **6d** which is further treated as above. After dilution of the final reaction mixture with water, product **7d** is isolated by suction and washed with water.

***N*-Acyl-*N*-(methylthiomethyl)-hydrazonoarylacetonitriles 3c, 5c, 5g**: A solution of the carboxylic acid α-cyanobenzylidenehydrazide (**1c**) or benzylidenehydrazide (**4c, g**) in dimethyl sulfoxide (15 ml/g of hydrazide) is refluxed for the time given in Table 2. After cooling, the mixture is poured into water (30 ml/10 ml of mixture) and extracted with ether (2 × 5 ml/10 ml of aqueous mixture). The extract is washed with water (2 × 8 ml/10 ml of extract), dried with sodium sulfate, and evaporated. Products **5c** and **5g** are recrystallized from a small volume of methanol; product **3c** requires two recrystallizations from methanol, the second one being performed by keeping the solution at 38°C to prevent precipitation of the oxadiazole **2c**.

Received: May 25, 1983
(Revised form: June 26, 1983)

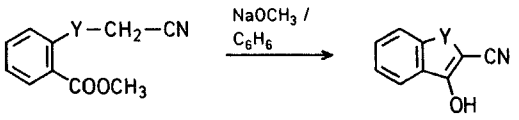
[1] F. Pochat, *Tetrahedron Lett.* **22**, 3595 (1981).
[2] K. Matsuda, L. T. Morin, *J. Org. Chem.* **26**, 3783 (1961).
[3] H. Willitzer, M. Tonew, E. Tonew, *German Patent (DDRP)* 136963 (1979); *C. A.* **92**, 41963 (1980).
[4] H. H. Otto, *Pharm. Zentralh.* **107**, 444 (1968).
[5] C. Chen, C. H. Wang, *Bull. Inst. Chem. Acad. Sinica* **18**, 30 (1970); *C. A.* **75**, 20166 (1971).
[6] R. L. N. Harris, J. L. Huppatz, *Aust. J. Chem.* **30**, 2225 (1977).
[7] W. G. Brouwer, E. J. McPherson, R. B. Ames, R. W. Neidermyer, *Canadian Patent* 966490 (1975), Uniroyal; *C. A.* **83**, 114415 (1975).
[8] F. Povanazec, J. Kovac, J. Svoboda, *Collect. Czech. Chem. Commun.* **45**, 1299 (1980).
[9] H. Weidinger, J. Kranz, *Chem. Ber.* **96**, 1049, 1059 (1963).
[10] S. F. Moss, D. R. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1990.
[11] E. Siegrist, E. Maeder, M. Dünnenberger, P. Liechti, *Swiss Patent* 411906 (1966), CIBA; *C. A.* **67**, 64406 (1967).

**Errata and Addenda 1984**

M.H. Elnagdi, M.R.H. Elmoghayar, G.E.H. Elgemeie, *Synthesis* **1984** (1), 1–26:

The second paragraph on page 2 should read:
Cyclic 3-oxoalkanenitriles **11** are obtained via cyclisation of methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**)[61a], methyl 2-(cyanomethoxy)-benzoate (**10b**)[61b], or methyl 2-(cyanomethylthio)-benzoate (**10c**)[61] under basic conditions.

The formula scheme **10** → **11** (p. 3) should be:




**10a** Y = N–CO–CH$_3$
**b** Y = O
**c** Y = S

**11a-c**

The experimental procedure for **11a** (p. 3) should read:

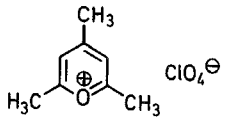
**2-Cyano-3-hydroxyindole (11a; Y = NH)[61]:**
A mixture of freshly prepared sodium methoxide (10 mmol) and methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**; 10 mmol) in benzene (25 ml) is stirred for 2 h at room temperature then left for 12 h at room temperature. The mixture is poured into water. Carbon dioxide is bubbled into the resulting solution till no more solid separates. The product is collected and recrystallised; yield: 64%; m.p. 165–167°C (dec.).

The following references should be added (p. 23):

[61] (a) D. Vorländer, *Ber. Dtsch. Chem. Ges.* **35**, 1683, 1696 (1902).
(b) R. Bryant, D.L. Haslam, *J. Chem. Soc.* **1965**, 2361.

P. Molina, A. Tárraga, E. Romero, M.L. Peña, *Synthesis* **1984** (1), 71–73:

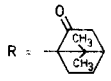
The structure of compound **6** (p. 71) should be:




**6**

Abstract 6803, *Synthesis* **1984** (1), 82:

The substituent R should be:

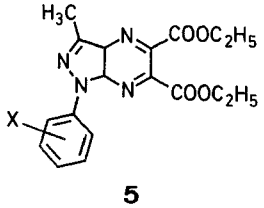



F. Pochat, *Synthesis* **1984** (2), 146–148:

Compounds **3c**, **5c**, and **5g** (p. 147 and 148) should be named as *N'*-acyl-*N'*-(methylthiomethyl)-hydrazones.

P.G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, *Synthesis* **1984** (2), 148–149:

The structure of compound **5** (p. 149) should be:




**5**

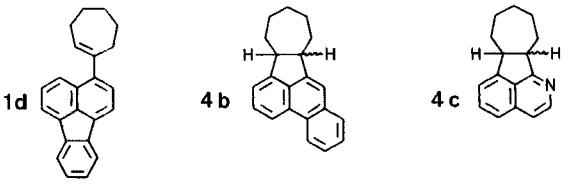
S.C.W. Coltman, S.C. Eyley, R.A. Raphael, *Synthesis* **1984** (2), 150–152:

The first line of the experimental procedure for esters **4** should read:
To a solution of **2** (0.1 mol) in absolute ethanol (30 ml) is added a 1

R. Lapouyade, A. Nourmamode, *Synthesis* **1984** (2), 161–164:

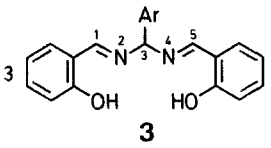
The title should read:
A New Synthesis of 6b,8,9,10,11,11a-Hexahydro-7*H*-cyclohepta[*a*]acenaphthylenes by Base-Catalyzed Photocyclization of 1-Arylcycloheptenes

The structures of products **1d**, **4b**, and **4c** in Tables 2 and 3 (p. 163) should be:




T. Takajo, S. Kambe, W. Ando, *Synthesis* **1984** (3), 256–259:

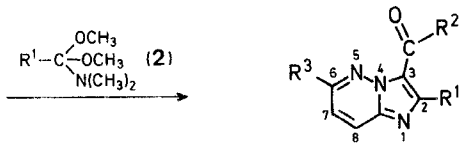
The structure of product **3** (p. 257, left) should be:




**3**

S. Podergajs, B. Stanovnik, M. Tišler, *Synthesis* **1984** (3), 263–265:

The structures of reagent **2** and products **5a–d** (p. 264) should be:




**5a-d**

U. Schöllkopf, U. Busse, R. Kilger, P. Lehr, *Synthesis* **1984** (3), 271–274:

The heading for the first experimental procedure (p. 274) should be:
(3*S*,6*S*)-3,6-Diisobutyl-2,5-dioxohexahydropyrazine (**9**):

J. Cabré, A.L. Palomo, *Synthesis* **1984** (5), 413–417:

The authors' address should read:
Gema S.A., Beethoven-15, Barcelona-21; Centro Marga para la Investigación, Muntaner 212, Barcelona-36, Spain
The formulae of Schemes **A** and **B** (p. 413) should be interchanged.
The following experimental procedure should be added:

**Cyclohexylammonium Carboxylates (Tables 3); General Procedure:**
To a solution of cyclohexylamine (1.15 ml, 10.0 mmol) in the solvent (20 ml, Table 3), the carboxylic acid is added at room temperature. The mixture is stirred for 15 min at room temperature and then cooled to 0–5°C. The precipitate is filtered and washed with cold (0 to −5°C) solvent (10 ml).

D.P. Stack, R.M. Coates, *Synthesis* **1984** (5), 434–436:

The structure of product **2e** (Table, p. 435) should be: