A Convenient Method for Synthesis of Novel 3-(1,3,4-Oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines: Regioselective Cyclization of 3-Ethoxyhydrazonocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline

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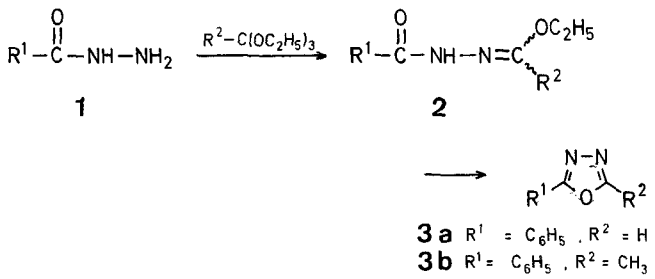
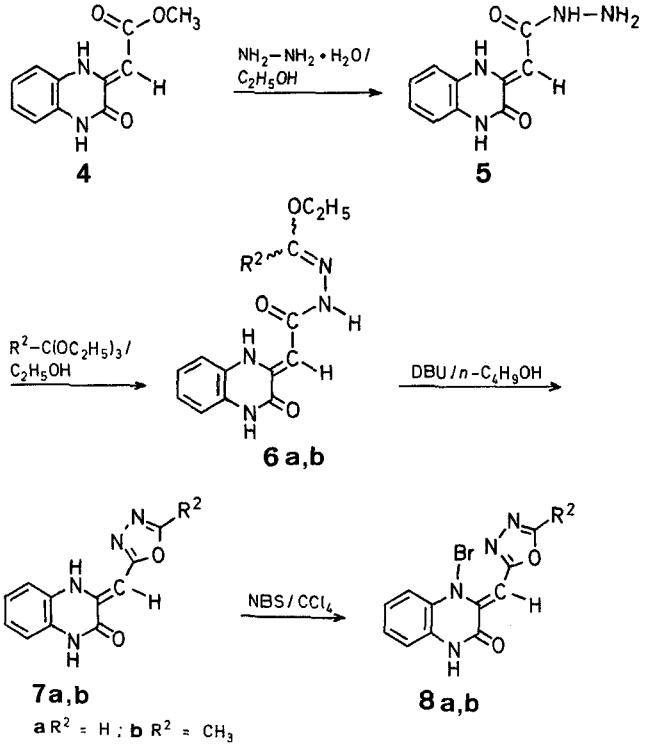
Ainsworth[1] reported a simple and general method for the preparation of various 2-aryl- and 2-alkyl-5-aryl-1,3,4-oxadiazoles **(3)** by refluxing of acylhydrazides **(1)** in orthoesters.

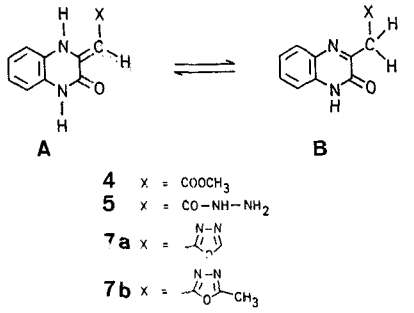


However, this method is inconvenient when the intermediary *N*-acylhydrazonic esters **(2)** are insoluble in the orthoesters at their reflux temperatures. In fact, our novel *N*-acylhydrazonic esters **(6)** are insoluble in refluxing orthoesters, and their cyclizations to 1,3,4-oxadiazoles **(7)** cannot be accomplished despite prolonged reaction time. However, this problem was solved by refluxing of the insoluble *N*-acylhydrazonic esters **6** in *n*-butanol in the presence of a base such as 1,8-diazabicyclo[5.4.0]-7-undecene (DBU). This method enabled us to prepare novel 1,3,4-oxadiazole derivatives, and it was further found that the method effected the cyclization of **2** to **3** within 1 h.

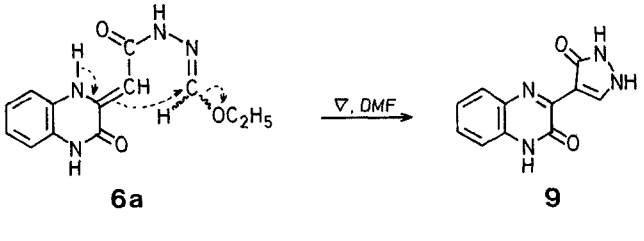
3-Methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(4)** hardly reacts with most amines or an equimolar to 5-fold molar amount of hydrazines[2]. In the present investigation, however, **4** is found to be converted easily to 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(5)** in the presence of 10-fold molar amount of hydrazine hydrate. Reactions of **5** with triethyl orthoformate and triethyl orthoacetate afford 3-ethoxyhydrazonocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(6a)** and 3-methylethoxyhydrazonocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(6b)**, respectively, which are cyclized to 3-(1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(7a)** and 3-(5-methyl-1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(7b)**, respectively, by heating under reflux in *n*-butanol in the presence of DBU. In contrast, the cyclization to compounds **7a, b** is not completed by heating of **6a, b** under reflux in the orthoesters. The reaction of **7a, b** with *N*-bromosuccinimide affords 4-bromo-3-(1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(8a)** and 4-bromo-3-(5-methyl-1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(8b)**, respectively[3]. The analytical and spectral data (Table) are in accord with the proposed structures of **7a, 7b, 8a,** and **8b.**



As shown by ^{1}H-N.M.R. spectrometry, the ester **4** exhibits a tautomeric equilibrium between the forms **A** and **B** in DMSO-d_6 solution[4]. Similarly, compounds **5, 7a,** and **7b** exist as tautomeric pairs in DMSO-d_6, which are characterized by vinyl and methylene proton signals, respectively (Table).



When compound **6a** is heated in dimethylformamide instead of *n*-butanol/DBU, 3-(5-oxopyrazolin-4-yl)-2-oxo-1,2-dihydroquinoxaline **(9)**[2] results as the cyclization product. Presumably, due to steric hindrance by the methyl group, this cyclization route cannot be realized in **6b.** Thus, heating of **6b** in dimethylformamide results in the formation of **7b** in 60% yield.



3-Hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (5):

A solution of compound **4** (10 g, 45.9 mmol) with hydrazine hydrate (22.95 g, 45.9 mmol) in ethanol (200 ml) is refluxed for 3 h on a boiling water bath to precipitate colorless needles of **5,** which are collected by suction filtration (9.07 g). Evaporation of the filtrate gives additional product **5** (0.73 g); total yield: 9.80 g (98%). An analytically pure sample is obtained by washing with hot ethanol a few times.

3-Ethoxyhydrazonocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (6); General Procedure:

A solution of **5** (5 g, 22.9 mmol) with the appropriate orthoester (50 ml) in ethanol (700 ml) is refluxed for 3 h on a boiling water bath. When triethyl orthoformate is used, the solvent is evaporated to afford yellow needles of **6a,** which are treated with hexane/ethanol and collected by suction filtration; yield: 6.18 g (98%).

When triethyl orthoacetate is employed, yellow needles of **6b** precipitate during the reaction. The needles are collected by suction filtration (5.53 g), and the filtrate is evaporated to provide additional product **6b** (0.93 g); total yield: 6.46 g (98%).

Analytically pure samples of **6a** and **6b** were obtained by washing with hot ethanol a few times.

3-(1,3,4-Oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (7):

Method A: A solution of **6a** or **6b** (5 g) with DBU (5 ml) in *n*-butanol (500 ml) is refluxed for 20 h in an oil bath at 160–180 °C. The sol-

Table. Analytical and Spectral Data for Compounds **5**, **6a, b**, **7a, b**, **8a, b**

Product	m.p. [°C][a]	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
5	264–265°	$C_{10}H_{10}N_4O_2$ (218.2)	1665, 1630	11.67 (s, 1H); 11.40 (s, 1H); 9.13 (s, 1H); 7.83–6.70 (m, 4H$_{arom}$); 5.60 (s)[c]; 4.33 (br. s, 2H); 3.66 (s)[c]
6a	213–214°	$C_{13}H_{14}N_4O_3$ (274.3)	1690, 1630	—[d]
6b	248–249°	$C_{14}H_{16}N_4O_3$ (288.3)	1690, 1630	—[d]
7a	290–292°	$C_{11}H_8N_4O_2$ (228.2)	1695, 1640	11.67 (s, 1H); 10.57 (s, 1H); 9.13 (s, 1H); 7.80–6.87 (m, 4H$_{arom}$); 6.12 (s)[e], 4.47 (s)[e]
7b	255–256°	$C_{12}H_{10}N_4O_2$ (242.2)	1695, 1640	11.67 (s, 1H); 10.43 (s, 1H); 7.77–6.83 (m, 4H$_{arom}$); 6.02 (s)[f]; 4.37 (s)[f]; 2.50 (s, 3H)
8a	223–224°	$C_{11}H_7BrN_4O_2$ (307.1)	1670	12.83 (s, 1H); 9.40 (s, 1H); 7.90–7.10 (m, 4H$_{arom}$); 6.90 (s, 1H)
8b	214–216°	$C_{12}H_9BrN_4O_2$ (321.2)	1670	12.82 (s, 1H); 7.90–7.20 (m, 4H$_{arom}$); 6.83 (s, 1H); 2.55 (s, 3H)

[a] All m.p. are uncorrected.
[b] Satisfactory mass spectral and microanalytical data were obtained: C, ±0.3; H, ±0.3; N, ±0.3.
[c] Vinyl and methylene signal in the ratio 1:1.
[d] Insoluble in DMSO-d_6.
[e] Vinyl and methylene signal in the ratio 3.75:1.
[f] Vinyl and methylene signal in the ratio 3:1.

vent is evaporated to give an oily substance which is dissolved in chloroform/ethanol (10:1) to precipitate the crystalline product **7a** or **7b**. After the product has been collected by suction filtration, the filtrate is passed through a silica gel column using the same mixture as eluent. The eluate is evaporated to afford additional product **7a** or **7b**; total yields: 3.80 g (91%) of **7a**; 3.85 g (91%) of **7b**. Recrystallization from ethanol provides yellow needles of **7a** and **7b**.

Method B: A solution of **6b** (3 g) in dimethylformamide (300 ml) is refluxed for 20 h in an oil bath at 160–180 °C. Evaporation of the solvent and column chromatography as described above gives **7b**; yield: 1.52 g (60%).

4-Bromo-3-(1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (8); General Procedure:

A suspension of **7a** or **7b** (1 g) with *N*-bromosuccinimide (1.2 eq.) in tetrachloromethane (100 ml) is refluxed for 4 h on a boiling water bath to precipitate colorless crystals of **8a** or **8b**, which are collected by suction filtration. The crystals of **8a** or **8b** are taken up in ethanol by heating, and the solution is immediately filtered. Evaporation of the filtrate gives analytically pure sample of **8a** or **8b**; yields: 1 g (74%) of **8a**; 1 g (80%) of **8b**.

3-(Pyrazolin-5-on-4-yl)-2-oxo-1,2-dihydroquinoxaline (9):

A solution of **6a** (3 g) in dimethylformamide (300 ml) is refluxed for 20 h in an oil bath at 160–180 °C. Evaporation of the solvent gives the crystalline product **9**, which is treated with hexane/ethanol to leave a yellow powder; yield: 2.15 g (86%); m.p. 305 °C (Ref.[2], m.p. 305 °C).

2-Phenyl-1,3,4-oxadiazole (3a) and 2-Methyl-5-phenyl-1,3,4-oxadiazole (3b):

A solution of appropriate *N*-acylhydrazonic ester **2a**[5] or **2b**[5] (3 g) in *n*-butanol (300 ml) and DBU (3 ml) is refluxed for 1 h in an oil bath at 160–180 °C. Evaporation of the solvent gives an oily residue, which is dissolved in chloroform. After washing with water (2 × 150 ml) two times to exclude DBU and drying with sodium sulfate, evaporation of the solvent affords the crystalline products **3a** and **b**, respectively.

3a: yield 1.70 g (77%); m.p. 36–37 °C (Ref.[1], m.p. 34–35 °C)

3b: yield 2.04 g (90%); m.p. 66–68 °C (Ref.[1], m.p. 67–68 °C)

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[1] C. Ainsworth, *J. Am. Chem. Soc.* **77**, 1148 (1955).
[2] Y. Kurasawa, A. Takada, *Chem. Pharm. Bull.* **29**, 2871 (1981).
[3] The bromination at N-4 has been confirmed; unpublished data by the authors.
[4] R. Mondelli, L. Merlini, *Tetrahedron* **22**, 3253 (1966).
[5] C. Runti, L. Sindellari, C. Nisi, *Ann. Chim. (Rome)* **49**, 1649 (1959).

F. Babudri, L. Di Nunno, S. Florio, *Synthesis* **1983** (3), 230–231:

The title compounds **5** and **7** should be named (*Z*)-2-alkylidene-4-methyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines; compound **10** as 11-methyl-3-(2-methylaminophenylthio)-2-oxo-4,5-diphenyl-2,5-dihydro-11*H*-oxepino[3,2-*b*][1,4]benzothiazine.

Y. Kurasawa, Y. Moritaki, A. Takada, *Synthesis* **1983** (3), 238–240:

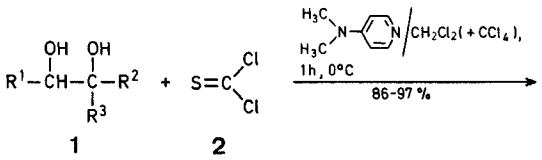
The title compounds **6** and **7** should be named 3-(1-ethoxyalkylidenehydrazinocarbonylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines, respectively.

Abstract **6589**, *Synthesis* **1983** (3), 247:

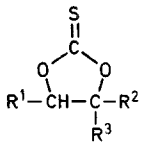
The title should be *N*-(1-Aroyloxyalkyl)-pyridinium and *P*-(1-Aroyloxyalkyl)-phosphonium Salts.

Abstract **6593**, *Synthesis* **1983** (4), 335:

The formula scheme **1** + **2** ⟶ **3** should be:



1 **2**



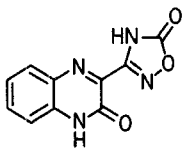
3

Y. Otsuji, S. Nakanishi, N. Ohmura, K. Mizuno, *Synthesis* **1983** (5), 390:

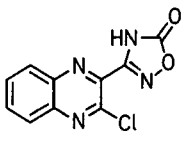
The substituents for compound **2g** (Table) should be R=H, X=H, n=1.

Y. Kurasawa, M. Ichikawa, A. Sakakura, A. Takada, *Synthesis* **1983** (5), 399–400:

The structures of products **4**, **8**, **9**, and **10** given have since been found to be erroneous, the corrected structures are given below. A revision will be published in *Chem. Pharm. Bull.* in 1984.



4



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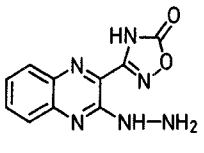
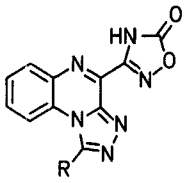


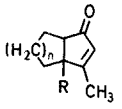
9



10a R = H
b R = CH_3

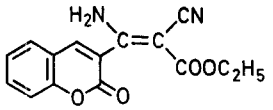
C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983** (6), 429–442:

The structure of the third product in Table 4 (p. 435) should be:



S. M. Fahmy, R. M. Mohareb, *Synthesis* **1983** (6), 478–480:

The structure of product **5** should be:



L. Jacob, M. Julia, B. Pfeiffer, C. Rolando, *Synthesis* **1983** (6), 451–452:

The first three entries in Table 1 (p. 451) should be as follows:

Table 1. Demethylation of Mixed Alkyl Methyl Phosphates **(1, 3, 4)** and of Dimethyl Heptanephosphonate **(5)** using Dimethyl Sulfide (2.5 equiv) and Methanesulfonic Acid (10 equiv)

Substrate	Product	Reaction conditions		Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c] or m.p. [°C] reported
		Scale [mmol]	Time [h]			
1a $n\text{-}C_6H_{13}\text{-}O\text{-}P(=O)(OCH_3)_2$	**2a** · $H_2N\text{-}C_6H_5$	10	22	82 (93)	133–134° (ethanol)	$C_{12}H_{22}NO_4P$ (275.3)
1b $n\text{-}C_8H_{17}\text{-}O\text{-}P(=O)(OCH_3)_2$	**2b** · $H_2N\text{-}C_6H_5$	5	7	(88)	135–137° (acetone)	129–130°[22] (ethanol)
		5	12	(93)		
		5	48	(98)		
		5	19	65		
		10	92	83		
		10	52[c]	83		
1c $n\text{-}C_6H_{13}\text{-}CH(CH_3)\text{-}O\text{-}P(=O)(OCH_3)_2$	**2c** · $H_2N\text{-}C_6H_5$	5	19	68	154° (ethanol)	$C_{14}H_{26}NO_4P$ (303.3)
		10	92	79		