Studies on Pyrrolidinones. A Convenient Synthesis of 2-Methyl-5-(5-oxo-1-benzyl-2-pyrrolidinyl)-1,3,4-oxadiazole

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2-Methyl-5-(5-oxo-1-benzyl-2-pyrrolidinyl)-1,3,4-oxadiazole is easily obtained by dehydration of *N*-acetyl-1-benzylpyroglutamic acid hydrazide with a methanesulfonic acid/phosphoric anhydride mixture.

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1,3,4-Oxadiazole derivatives are reported to show broad spectrum of biological activities [1]; some of these compounds exhibit herbicidal properties [2]. It has also been reported that molecules formed by attachment of some 1,3,4-thiadiazoles to the nitrogen of a lactam type heterocycle have phytosanitary activity [3]. These observations, and our interest in pyroglutamic acid chemistry [4], prompted us to study the synthesis of compound **1**, an 1,3,4-oxadiazole linked to a lactam ring, as a model for products with posssible fungicidal and/or herbicidal properties.

The diacylhydrazine **3**, easily obtained from readily available *N*-benzylpyroglutamic acid hydrazide **2** [5], cannot be efficiently cyclized by conventional methods (Table 1, runs 1 to 12). However, by using a mixture of phosphoric anhydride/methanesulfonic acid (1/10, W/W) [6] (Table 1, run 13) the oxadiazole **1** is obtained in good yield (84%). The conditions of this reaction (75°, 4 hours), have been chosen in order to avoid benzylic cleavage by the methanesulfonic acid, which could occur at higher temperature [7]. This result shows the superiority of the phosphoric anhydride/methanesulfonic acid mixture over polyphosphoric acid to promote such easy and clean dehydra-

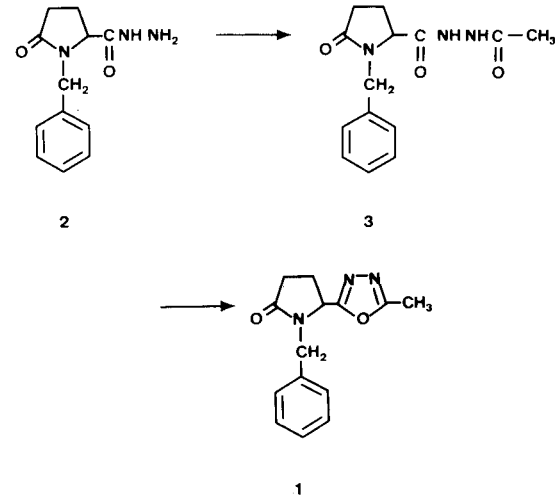

Figure 1

Table 1

Cyclization of Compound **3**

Run No.	Solvent (ml)	Hydrazide **3** : 0.1 mole P_2O_5 (mole)	PPA (ml)	$MeSO_3H$ mole (ml)	$POCl_3$ (ml)	Other reactif	Reaction time (hours)	Temperature (° C)	Yield %	Reference of the Method
1						H_2SO_4: 70 ml	5	25	0	[8]
2						Ac_2O: 250 ml	15	140	0	[9]
3	$CHCl_3$ 300				20		2	61	0	[10]
4			360				3	160	0	[11]
5	$C_2H_2Cl_2$ 220	0.3					4	110	11	[12]
6	$CHCl_3$ 220	0.3					2	61	17	[12]
7		0.18	68				12	160	18	
8		1.3			250		2	60	0	
9		0.1			220		0.5	95	37	
10	Toluene 250	0.18				PTSA 0.08	6.5	110	49	[13]
11	Toluene 100			0.22 (14.5)			6.5	110	0	[14]
12			730	0.14 (9.1)			70	85	53	
13		0.45		4.6 (300)			4	75	84	

Table 2

Cyclization of Diacylhydrazines

4a R = CH_3

4b R = C_6H_5

Compound No.	$P_2O_5/MeSO_3H$ method [a] Yield %	Method	Literature Yield	Reference
4a	78	Ac_2O, Reflux	30%	[15]
		Ac_2O, $HClO_4$	43%	[16]
4b	77	PPE, 100°	65%	[17]
		Ac_2O, $HClO_4$	48%	[16]

[a] **4a,b**: 0.055 *M*; $MeSO_3H$: 160 g; P_2O_5: 36 g; 70° (4H).

tion reactions [6]. To our knowledge, this reagent has never been used in the synthesis of oxadiazoles, and we have found that this reaction is quite general and gives good yields of other oxadiazoles (Table 2).

The excellent yield obtained for these dehydration reactions makes it possible to consider generalization of this method to the synthesis of oxadiazoles bearing other substituants capable of providing interesting biological properties.

EXPERIMENTAL

Melting and boiling points reported are uncorrected. The ir spectra were recorded on a Perkin-Elmer 398 spectrometer. The nmr spectra were obtained on a Hitachi Perkin-Elmer R-600 instrument at 60 MHz. All nmr spectra were obtained in deuteriochloroform solution and are reported in parts per million downfield from tetramethylsilane as an internal standard. Elemental analyses were performed by the "Central Microanalytical Department" of CNRS in Vernaison, France.

N-Acetyl-1-benzylpyroglutamic Acid Hydrazide (**3**).

A mixture of 35 g (0.15 mole) of hydrazide **2** [5] and acetic acid anhydride (70 ml) was kept at room temperature during 19 hours. The product was obtained by filtration and washed with ether, yield, 95%, mp 189° (water); ir (nujol): ν cm^{-1} 3225 (NH), 1715-1700 (C=O), 1620 (C=C); nmr (deuteriomethanol): δ ppm 1.97 (s, 3H), 2.05-2.80 (m, 4H), 3.84 (d, 1H, J = 15 Hz), 4-4.3 (m, 1H), 5.06 (d, 1H, J = 15 Hz), 7.35 (s, 5H).

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.09; H, 6.32; N, 15.08.

2-Methyl-5-(5-oxo-1-benzyl-2-pyrrolidinyl)-1,3,4 oxadiazole (**1**).

A suspension of 360 g (2.54 moles) of methanesulfonic acid and 36 g (0.25 mole) of phosphoric anhydride was stirred at room temperature during 1 hour, then 15 g (0.055 mole) of compound **3** was added. After heating at 70-80° during 4 hours and neutralization in aqueous sodium carbonate (1000 ml) the product was extracted with dichloromethane. The solvent was evaporated and the residue distilled, yield 84%, bp 180° (0.15 mm), mp 86° (water); ir (nujol): ν cm^{-1} 1680 (C=O), 1585-1565-1495 (C=C, C=N); nmr (deuteriochloroform): δ ppm 2-2.9 (m, 4H), 2.36 (s, 3H), 4.24 (d, 1H, J = 14.4 Hz), 4.65 (d, 1H, J = 14.4 Hz), 4.7-5 (m, 1H), 7.25 (s, 5H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.24; H, 5.98; N, 16.27.

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