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A NEW SYNTHESIS OF 1,3,4-OXADIAZOLES. CYCLIZATION OF N,N'-DIACYLHYDRAZINES CATALYZED BY PALLADIUM(0).

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Abstract: Several 1,3,4-oxadiazoles were synthetized by cyclization of N,N'diacylhydrazines catalyzed by palladium(0). Water formed during the reaction is responsible for the hydrolysis of the products. To avoid it, we introduced benzoic anhydride into the medium and obtained an increased yield of oxadiazoles.

1,3,4-oxadiazoles are generally obtained by intramolecular dehydration of N,N'diacylhydrazines with or without dehydrating agents¹. They also may be prepared by oxidative cyclization of hydrazones or semicarbazones², by cyclization of N,N'diacylhydrazines using silylated compounds³, by rearrangements of tetrazoles⁴ or by addition of one-carbon fragment on a N-acylhydrazine⁵. It is difficult to find a method that permits so easily the synthesis of 2,5-diaryl-, 2-alkyl-5-aryl- or 2,5dialkyl-1,3,4-oxadiazoles. We describe here a new method to prepare oxadiazoles by cyclization of N,N'-diacylhydrazines using palladium reagents.

At the beginning of the eighties, a synthesis of furans was developped in our laboratory⁶. During this study, it was shown that it is possible to produce

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2,5-dimethylfuran by cyclization of 2,5-dioxohexane catalysed by palladium. The analogy of structure led us to imagine the formation of 1,3,4-oxadiazoles starting from N,N'-diacylhydrazines in presence of palladium(0).

The first tests were run using a symmetrical hydrazine, N,N'-dibenzoylhydrazine **1a**. They were run in an apolar and aprotic solvent which permits a high reaction's temperature, anhydrous decalin (mixture of isomers). A catalytic system, often used in organic synthesis, was tested : $Pd(PPh_3)_4/PPh_3$. Besides 2,5-diphenyl-1,3,4-oxadiazole **2a**, we detected by HPLC the presence of both Nbenzoylhydrazine **3** and benzoic acid **4** (FIG.1, Table 1).



Table 1 : Palladium(0) Catalyzed Cyclization of diacylhydrazine 1a

Catalyst	Time	T°	Yield 2a	Yield 3	Yield 4
(molar ratio)	(hour)	(°C)	(%)	(%)	(%)
Pd(PPh ₃) ₄ /PPh ₃ (1/30)	12	175	10	64	48

The presence of two by-products is explained by the partial hydrolysis, of 1a and 2a, due to water formed during the cyclization reaction⁷. We have to remove, totally or partially, water from the medium. The efficiency of several azeotropes

or dehydrating agents was tested unsuccessfully. Finally, we added benzoic anhydride into the medium. It reacts with water to give benzoic acid. Its use increased the yield of **2a** during the cyclization of **1a** (Table 3). We applied this method to the synthesis of 2-methyl-5-phenyl-1,3,4-oxadiazole **2b** starting from N-acetyl,N'-benzoylhydrazine **1b**. Besides predicted products, **2a** was formed during the reaction (FIG.2, Table 2). This last one was formed by cyclization of **1a** produced from **3** and benzoic anhydride (FIG.3). This model may be extended to the synthesis of further oxadiazoles.



Table 2 : Palladium(0) Catalyzed Cyclization of diacylhydrazine 1b



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FIG.3

We have extended the cyclization reaction to further diacylhydrazines (FIG.4, Table 3). The moderate 2,5-disubstituted-1,3,4-oxadiazoles's yields were due their sensitivity to hydrolysis^{7a,b}.



FIG.4

Table 3 : Palladium(0) Catalyzed Cyclization of N,N'-diacylhydrazine 1a-h

1	R	R'	Time	T°	product	by-product
			(nour)	$(^{\circ}\mathrm{C})$	(%)	(%)
a	-Ph	-Ph	12	175	2a (84)	1
b	-Me	-Ph	7	170	2b (76)	2a (19)
c	-4-Ph-CH ₃	-4-Ph-CH ₃	15	170	2c (50)	2i (42)
d	-4-Ph-OMe	-4-Ph-OMe	12	170	2d (/)	2j (/)
e	-4-Ph-NO ₂	-4-Ph-NO ₂	12	170	2e (55)	2k (36)
f	-Et	-Ph	7	170	2f (71)	2a (25)
g	-Me	-Me	4	170	2g (25)	2b (28)
h	-Et	-Et	6	170	2h (30)	2f (33)

EXPERIMENTAL

All commercially available reagents were used as received from the suppliers. Products were isolated using a Waters PrepLC/System 500A (Cartridge Waters PrepPak[™]-500/Silica; Dichloromethane/Ethyl Acetate : 96/4). Melting points (°C) were determined with a Mettler FP1 and are uncorrected. ¹H and ¹³C spectra were recorded on a Brucker AC300 spectrometer operating at, respectively, 300.133 and 75.47 MHz. Chemical shifts are given in part per million positive values down field from internal TMS (¹H and ¹³C). Coupling constants are given in Hz.

Synthesis of 1,3,4-oxadiazoles 2a-h

4.2 mmoles of diacylhydrazine **1a-h** are introduced, under a N₂ atmosphere, into 80 ml of anhydrous decalin which contains 0.13 mmole of Pd(PPh₃)₄, 3.8 mmoles of PPh₃ and 5 mmoles of benzoic anhydride. The temperature is raised up at the rate of 2 °C/min. The reactions are monitored by HPLC (C₁₈ column, UV detection 204 or 250 nm). After cooling, products were isolated by preparative liquid chromatography. Results are given in Table 3. Physical constants of 1,3,4oxadiazoles **2a-k** are given in Table 4.

2	mp (litt.)	bp (litt.)	¹ H NMR (DMSO d6), δ, J	13 C NMR (DMSO d6), δ
a	138	1	7.46-7.5 (m, 6H), 8.08 (d, 4H,	123.3, 126.7, 129.4, 132.0, 164.0
	(138.5^{2c})		J = 7)	
Ь	67 (66.5 ^{4b})	1	2.57 (s, 3H), 7.46-7.51 (m, 3H),	10.6, 123.6, 126.3, 129.4, 131.7,
			7.86 (d, 2H, J = 7.9)	163.7, 163.8
с	175	1	2.40 (s, 6H), 7.43 (d, 4H,	21.2, 120.7, 126.6, 129.9, 142.2,
	(176^{3b})		J = 7.8), 8.00 (d, 4H, J = 7.8)	164.5
e	309 (309-	1	8.41 (d, 4H, J = 8.3), 8.56 (d,	124.4, 126.9, 129.3, 149.3, 162.6
	311 ^{8a}		4H, J = 8.3)	
f	1	276	1.28 (t, 3H, J = 7.6), 2.88 (q, 2H,	10.3, 18.4, 123.6, 126.2, 129.2,
		$(105^{0.18b})$	J = 7.6), 7.53-7.55 (m, 3H), 7.93	131.5, 163.8, 167.6
			(d, 2H, J = 6.8)	
g	1	178 (178-	2.42 (s, 6H)	10.2, 163.4
		179 ^{1a})		
h	1	198	1.09 (t, 6H, J = 7.6), 2.58 (q, 4H,	10.4, 18.7, 167.5
		(198 ⁸⁰)	J = 7.6)	
i	126	1	2.40 (s, 3H), 7.29 (d, 2H J =	21.7, 121.3, 124.0, 126.9, 129.1,
	(125.5 ²⁶)		7.8), 7.49-7.51 (m, 3H), 7.99 (d,	129.8, 131.6, 142.3, 164.3, 164.7
			2H, J = 7.8), 8.09 (m, 2H)	
k	206	/	7.62-7.69 (m, 3H), 8.17 (d, 2H,	123.3, 124.4, 127.2, 127.8,
	(206 ²⁶)		J = 6.3, 8.39 (d, 2H, $J = 8.4$),	129.3, 129.4, 132.3, 162.8, 165.6
			8.45 (d, 2H, J = 8.4)	

Table 4 : Caracterization of Products and By-Products 2a-k

References

- 1. See for examples : (a) Stollé, R. Chem. Ber. 1899, 32, 797 (b) Hetzheim, A. and Mockel, K. in Advances in heterocyclic chemistry; Katritzky A.R. and Boulton A.J. Eds.; Academic Press : New york and London, 1966, Vol. VII,pp 183-224.
- (a) Stollé, R. J. prakt. Chem. 1904, 70, 393 (b) Blankenstein, G. and Mockel, K. Chem. Ber. 1962, 2, 69 (c) Milcent, R. and Barbier, G. J. Heterocycl. Chem. 1983, 20, 77 (d) Jedlovska, E. and Gavlakova, E. Collect. Czek. Chem. Commun. 1994, 59, 1892.
- (a) Rigo, B.; Cauliez, P.; Vasseur, D. and Couturier, D. Synth. Comm. 1986, 16, 1665. (b) Chiriac, C. I. Rev. Roumaine Chim. 1987, 32, 223. (c) Rigo, B.; Cauliez, P.; Vasseur, D. and Couturier, D. Synth. Comm. 1988, 18, 1247 (d) Rigo, B.; Vasseur, D.; Cauliez, P. and Couturier, D. Synth. Comm. 1989, 19, 2321.
- (a) Huisgen, R.; Grashey, R.; Knupfer, H.; Kunz, R. and Seidel, M. Chem. Ber. 1964, 97, 1085 (b) Jursic, B. S. and Zdravkovsky, Z. Synth. Comm. 1994, 24, 1575.
- (a) Weidinger, H. and Kranz, J. Chem. Ber. 1963, 96, 1049 (b) Browne, E. J. and Pelya, J. B. J. Heterocycl. Chem. 1966, 523 (c) Gehlen, H. and Schade, W. Ann. 1964, 675, 176 (d) Golfier, M. and Milcent, R. Synthesis 1979, 946 (e) Shawali, A. S. and Fahmi, A.-G. A. J. Heterocycl. Chem. 1977, 14, 1089
- 6. Camus, F.; Hasiak, B. and Couturier, D. Synth. Comm. 1982, 12, 647.
- (a) Grekov, A. P. and Azen, R. S. *Zh. Obshch. Khim.* 1961, 31, 407 (b) Grekov, A. P. and Nesynov, E. P. *Zh. Obshch. Khim.* 1961, 31, 1122 (c) Tsuji, J.; Hayakawa, S. and Takayanagi, H. *Chem. Lett.* 1975, 437 (d) Tsuji, J.; Hayakawa, S. and Takayanagi, H. *Synthesis* 1976, 61.
- 8 (a) Baltazzi, E. and Wysocki, A. J. Chem. Ind. 1963, 1080. (b) Ainsworth, C. US 2,733,245 1956.

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