HETEROCYCLES, Vol. 53, No. 1, 2000, pp. 191 - 195, Received, 2nd August,1999

5-BUTYL-3,5-DIARYL-4,5-DIHYDRO-1,2,4-OXADIAZOLES, AND A ONE–STEP SYNTHESIS OF 4,4-DIBUTYL-2-PHENYLBENZO-1,3-OXAZINE

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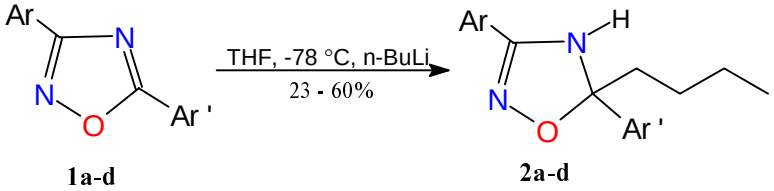
Abstract - *The synthesis of 5-butyl-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles is described. The present work also describes the discovery of a reaction leading to the conversion of 5-butyl-5-(2-hydroxyphenyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole **(1d)** to 4,4-dibutyl-2-phenylbenzo-1,3-oxazine **(3)**.*

Many 1,2,4-oxadiazoles have been prepared and their properties studied,[1] some of them presenting applications as optical brighteners.[2] However, the corresponding partially reduced derivatives, 4,5-dihydro-1,2,4-oxadiazoles, have received little attention. Although, studies of absorption and fluorescence have shown that 1,2,4-oxadiazoles often behave quite differently from their corresponding 4,5-dihydro–1,2,4-oxadiazoles, few efforts[3] have been made to learn more about their respective behaviors.

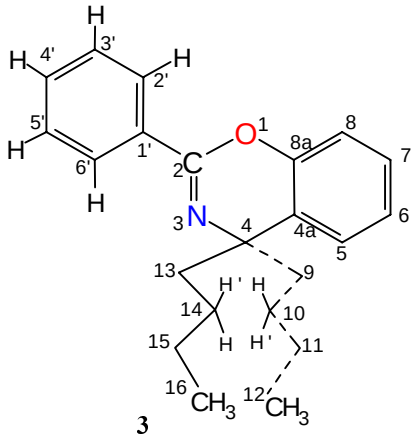
This note reports the preparation of four 5-butyl-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles **(2a–d)** from n-butyllithium and 3,5-diaryl-1,2,4-oxadiazoles **(1a-d) (Scheme I)**.

Scheme I



1a-d **2a-d**

Ar	Ar '
a: Ph	Ph
b: 2-ClPh	Ph
c: Ph	2-ClPh
d: Ph	2-HOPh



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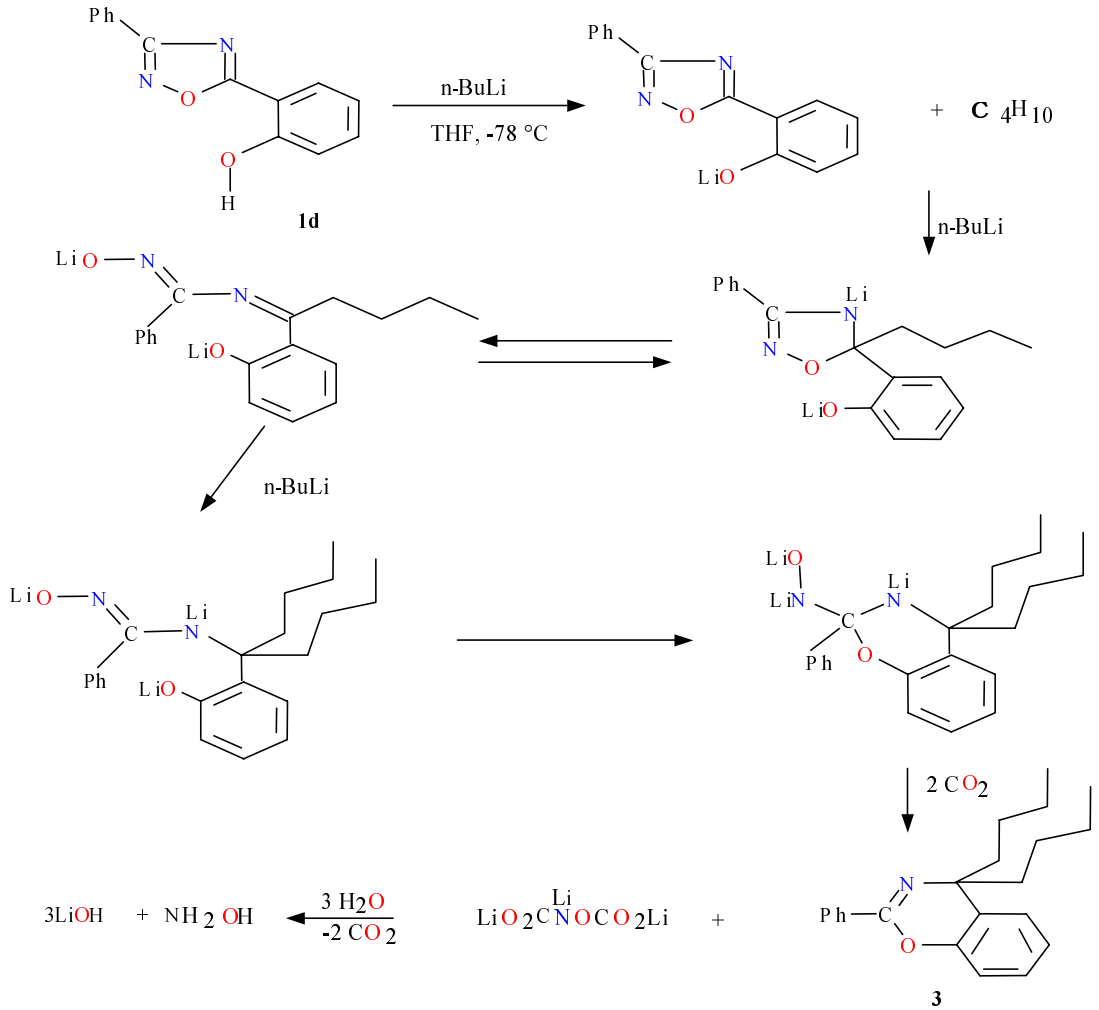
Previously, only two 1,2,4-oxadiazoles, i.e., 3-methyl-5-phenyl- and 5-methyl-3-phenyl-1,2,4-xadiazoles, have been subjected[4] to this type of reaction. However, only the former reacts with n-butyllithium at C-5. The reaction of n-butyllithium with oxadiazoles **(1a-c)**, following the reported[4] method, with some

modification, proceeded in 46-60% yields, but with **1d,** the yield was low (23%). There appears to be two following reasons for the low yield of compound(**2d**):

1. Since the reaction has been carried out using 1 to 2 mol eq of **1d** and n-butyllithium, 1 mol eq of the base has been consumed quickly for abstracting the -OH proton to form the anion. Formation of this anion makes the addition of the remaining n-butyllithium slower, and 2. Presumably, the reaction time has been insufficient. TLC analysis of the reaction products shows the presence of a large quantity of the starting material.

The reaction of n-butyllithium with **1d** was investigated more thoroughly in order to improve the yield. Adding an excess of n-butyllithium led to the formation of a fast running spot (R_f = 0.86) and only a little bit of **2d** (R_f = 0.1) as evidenced by TLC, $CHCl_3$/EtOAc (9:1). These compounds were separated by liquid chromatography using silica gel as adsorbent. The IR spectrum of the fast running spot (liquid) showed a strong absorption at 1675 cm^{-1} due to ν-O-C=N- characteristic of an 1,3-oxazine.[5] The analytical and spectroscopic results leave no doubt about the structure of compound **(3)**. This is the first example where a 5-(2-hydroxyphenyl)-3-phenyl-1,2,4-oxadiazole **(1d)** has been transformed to 4,4-dibutyl-2-phenylbenzo-1,3-oxazine **(3)**. 1,3-Oxazines are an interesting class of compounds and the

Scheme II



subject has been reviewed recently.[6] Some modified benzoxazines have been prepared and are effective[7] in the treatment of subjects suffering from impaired nervous or intellectual functioning due to deficiencies in the number or strength of excitatory synapses or in the number of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors. A mechanism for the formation of **3** from the starting material **(1d)** and n-butyllithium is suggested **(Scheme II)**. In one of the proposed mechanistic steps, the adjacent nitrogen and oxygen atoms have been shown to have negative charges. In support of this proposal, we can say that such dianions have been observed[8] when oximes are converted to hydroxylamines by treatment with 2 moles of alkyllithium reagent.

In summary, n-butyllithium has been added regiospecifically to C-5 of 3,5-diaryl-1,2,4-oxadiazoles **(1a-d)**. Also, a new synthesis of 4,4-dibutyl-2-phenylbenzo-1,3-oxazine **(3)** has been discovered.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Bruker IFS66 (FT) spectrophotometer, ^{1}H NMR spectra of **2a-d** on a Bruker AC-200 (200 MHz), ^{1}H and ^{13}C NMR of **3** on a Varian Unity plus instruments using TMS as an internal standard. Analytical TLC was carried out on precoated Kieselgel 60 F_{254} plates (Merck) using an appropriate solvent system and UV was used for revelation of the spots. Chemical Ionization (CI) MS of compounds **(2a-c)** were obtained on a Finnigan MAT GCQ (Model: Ion Trap) instrument at 70 eV using methane as the reagent gas. No satisfactory CIMS of **2d** could be obtained inspite of our best efforts.

5-Butyl-3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazole (2a). General Procedure for the Synthesis of Compounds (2). To a cold (-78 °C) and stirred solution of 3,5-diphenyl-1,2,4-oxadiazole **(1a)** (0.20 g, 0.9 mmol) in dry THF (6 mL) under N_2 was added n-butyllithium (1.8 mL 1.8 mmol, 0.5 M solution in hexane) dropwise in a few minutes. After stirring the contents for 30 min at this temperature, some dry ice pieces were added and the temperature was allowed to attain rt. Addition of water (10 mL) followed by extraction with ether and work-up provided 0.27 g of crude material. TLC, $CHCl_3$/EtOAc (3:1), showed some starting material (R_f = 0.65) and a new product with R_f = 0.38. Chromatography over a silica gel column eluting first with hexane-chloroform (1:1), later with chloroform and finally with $CHCl_3$/EtOAc (9.7:0.3) provided the desired compound. Crystallization and recrystallization from acetone-water gave **2a** (0.15 g, 60%): mp 134-136°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68-7.72 (m, 2H, Ar), 7.55-7.58 (m, 2H, Ar), 7.30-7.50 (m, 6H, Ar), 4.82 (br, 1H, NH), 2.17 (t, J = 8.00 Hz, 2H, $-CH_2-(\alpha)$), 1.26-1.47 (m, 4H, $-CH_2-CH_2-(\beta,\gamma)$), 0.90 (t, J = 6.98 Hz, 3H, CH_3); IR (Nujol) 3248 (NH), 1599 (C=N) cm^{-1}, MS (CI) m/z 281 (M+1, 93), 263 (20), 223 (31), 163 (19), 119 (25), 105 (100). *Anal*. Calcd for $C_{18}H_{20}N_2O$: C, 77.13; H, 7.19; N, 9.99. Found: C, 76.77; H, 7.23; N, 9.78.

5-Butyl-3-(2-chlorophenyl)-5-phenyl-4,5-dihydro-1,2,4-oxadiazole (2b): R_f = 0.19, $CHCl_3$/Hexane (1:1); mp 134-135 °C (chloroform); 53.3% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (m, 1H, Ar), 7.52-7.57 (m, 3H, Ar), 7.27-7.44 (m, 5H, Ar), 5.49 (br, 1H, NH), 2.18 (t, J = 8.05 Hz, 2H, -CH_2-(α)), 1.26-1.46 (m, 4H, -CH_2CH_2-(β,γ)), 0.90 (t, J = 6.99 Hz, 3H, CH_3); IR (Nujol) 3186 (NH), 1590 (C=N) cm^{-1}; MS (CI) m/z 315 (M+1, 100), 297(20), 257 (29), 163 (16), 153 (20), 105 (15). *Anal*. Calcd for $C_{18}H_{19}N_2OCl.1/4H_2O$: C, 67.71; H, 6.15; N, 8.77. Found: C, 68.11; H, 5.97; N, 8.38.

5-Butyl-5-(2-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole (2c): R_f = 0.41, CH_2Cl_2/Hexane (1:1); mp 130-131 °C (benzene); 45.7% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.41 Hz and J = 2.07 Hz, 1H, Ar), 7.65 (m, 2H, Ar), 7.23-7.47 (m, 6H, Ar), 5.82 (br s, 1H, NH), 2.17-2.43 (m, 2H, -CH_2- (α)), 1.26- 1.40 (m, 4H, -CH_2-CH_2- (β,γ), 0.86 (t, J = 7.02, 3H, CH_3); IR (Nujol) 3222 (NH), 1602 (C=N) cm^{-1}; MS (CI) m/z 315 (M + 1, 94), 297 (28), 279 (49), 257 (47), 197 (6), 139 (100), 119 (28). *Anal*. Calcd for $C_{18}H_{19}N_2OCl$: C, 68.68; H, 6.08; N, 8.89. Found: C, 68.36; H, 6.19; N, 8.54.

5-Butyl-5-(2-hydroxyphenyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole (2d): R_f = 0.1, Hexane/AcOEt (9:1); mp 149-151 °C (dichloromethane); 23% yield; ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.64-7.72 (m, 2H, Ar), 7.33-7.50 (m, 4H, Ar), 7.18 (dt, J = 7.88 Hz and J = 1.80 Hz, 1H, Ar), 6.92 (dt, J = 8.00 Hz and 1.30 Hz, 1H, Ar), 6.84 (dd, J = 7.91 Hz and J = 1.30 Hz, 1H, Ar), 5.48 (br, s, 1H, NH), 2.15-2.30 (m, 2H, -CH_2- (α)), 1.60 (s, 1H, OH),1.20-1.50 (m, 4H, -CH_2CH_2- (β,γ)), 0.85 (t, J = 6.95 Hz, 3H, CH_3). Both NH and OH signals disappeared when D_2O was added in the NMR tube. IR (Nujol) 3000-3330 br (OH), 3122 (NH), 1601.4 (C=N) cm^{-1}. *Anal*. Calcd for $C_{18}H_{20}N_2O_2.1/4\ H_2O$: C, 71.86; H, 6.87; N, 9.31. Found: C, 71.90; H, 6.82; N, 9.20.

4,4-Dibutyl-2-phenylbenzo-1,3-oxazine (3): To a cold solution (–78 °C) of compound **(1d)** (0.15g, 0.6 mmol) in dry THF (6.0 mL) under an argon atmosphere was added *N*-butyllithium (1.5 mL, 2.4 mmol, 1.6 M solution in hexane) dropwise during 45 min under stirring and the contents were brought up to rt. Work-up as described above left 200 mg of a mixture, which showed three spots on TLC with R_f values of 0.10 **(2d)**, 0.70 **(1d)** and 0.86 **(3)** in the solvente system hexane/AcOEt (9:1). Separation on a silica gel using hexane as eluent column provided 93 mg (46%) of pure **3** as a colorless liquid**;** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (m, 2H, H-2' and H-6'), 7.45 (m, 3H, H-3', H-4' and H-5'), 7.10-7.22 (m, 3H, H-5, H-6, H-7), 7.00 (unres. d, J ≈ 7.50 Hz, 1H, H-8), 1.84 (t, J = 7.95 Hz, 4H, H-11 and H-11'; H-13 and H-13'), 1.21 (m, 6H, H-10', H-14', H-11 and H-11'; H-15, H-15'), 0.95 (m, 2H, H-10 and H-14), 0.78 (t, J = 7.05 Hz, 6H, 2CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.04 (C-12 and C-16), 22.92 (C-11 and C-15), 26.57 (C-10 and C-14), 44.31 (C-9 and C-13), 115.12 (C-8), 124.47 (C-6), 124.56 (C-4), 125.51 (C-5), 127.33 (C-

3' and C-5'), 127.40 (C-1'), 128.12 (C-2' and C-6'), 130.57 (C-4'), 132.73 (C-4a), 149.62 (C-8a), 150.35 (C-2); IR (Neat) 3061 and 3033 (C-H, Ar), 1675.4 (-O-C=N) cm^{-1}; MS (EI) m/z (M^+ < 0.5), 264 (100), 222 (12), 208 (8), 161 (4), 91 (8). *Anal*. Calcd for $C_{22}H_{27}ON$: C, 82.20; H, 8.46; N, 4.36. Found: C, 82.36; H, 8,42; N, 4.47. The ^1H NMR spectrum of compound **(3)** showed an interesting phenomenon which merits comment. Four methylene protons of C-9 and C-13 appeared at δ 1.84 as a triplet and were easy to identify, but the other eight methylene protons of C-10, C-11, C-14 and C-15 gave two sets of narrow multiplets – one at δ 1.21 (6H) and the other at δ 0.95 (2H). Initially, it was difficult to know the correct identify of these two higher field protons. However HETCOR experiment (^1H-^{13}C) helped in making assignments for these two upfield protons, which are due to H-10 and H-14. Further elution of the column by increasing solvent polarity gave **1d** (10 mg, 6.7%), and **2d** (33 mg, 18%) respectively.

ACKNOWLEDGEMENT

Financial assistance from the Brazilian National Research Council (CNPq) and the Pernambuco Foundation for Science and Technology (FACEPE) is gratefully acknowledged. Our thanks are also due to Mr. Eduardo Miguez of the Natural Products Research Institute (NPPN) of the Federal University of Rio de Janeiro, Rio de Janeiro, for recording the 200 MHz ^1H NMR spectra of compounds **(2a-d)**, and to Fernando Hallwass of the Fundamental Chemistry Department (DQF) for obtaining the ^1H and ^{13}C NMR and Hetcor spectra of compound **(3)**. Finally, we would like to thank Érida Maria Alves Pequeno for measuring the IR spectra.

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