Anais da Academia Brasileira de Ciências (2007) 79(1): 29-33
(Annals of the Brazilian Academy of Sciences)
ISSN 0001-3765
www.scielo.br/aabc

1,4- Addition of diazomethane to a heterodiene: a direct preparation of the oxazolic ring

FLÁVIO DA S. EMERY[1], RAPHAEL S.F. SILVA[1], KELLY C.G. DE MOURA[1], MARIA C.F.R. PINTO[1], MAURO B. AMORIM[1], VALÉRIA R.S. MALTA[2], REGINA H.A. SANTOS[2], KÁTIA M. HONÓRIO[2], ALBÉRICO B.F. DA SILVA[2] and ANTONIO V. PINTO[1]

[1]Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde
Universidade Federal do Rio de Janeiro, Ilha do Fundão, 21944-970 Rio de Janeiro, RJ, Brasil
[2]Departamento de Química e Física Molecular, Instituto de Química de São Carlos, Universidade de São Carlos
Av. Trabalhador São Carlense, 400, Centro, 13566-590 São Carlos, SP, Brasil

Manuscript received on July 29, 2005; accepted for publication on May 2, 2006;
presented by ELOISA B. MANO

ABSTRACT

The reaction of naphthoquinone-oximes (**3**) and (**4**) with diazomethane yields directly, in one step, the oxazoles (**5**) and (**6**), respectively.

Key words: quinones, oximes, diazomethane, oxazoles.

INTRODUCTION

Despite the many advanced strategies available today in the state-of-the-art of ring junction construction in organic synthesis, the pursuit of heterocyclic appendages by new routes has been receiving considerable attention (Turchi and Dewar 1975, Kreisberg et al. 2002). The major interest in heterocycles derives from their presence in various naturally occurring compounds and by their biological activities, (de Oliveira et al. 2002, Millan et al. 2000).

Due to the relevant biological properties of so many compounds containing heterocyclic rings, we have, in the last few years, focused our attention on a program of synthesis of heterocyclic compounds that takes into account the use of naturally occurring raw materials from the Brazilian flora. For example, β-lapachone **2** as a simple building block was used to synthesize several biologically active heterocyclic naphthalene derivatives, (de Moura et al. 2001, Pinto et al. 2000).

Dedicated to Prof. Walter B. Mors on the occasion of his 85th birthday
Correspondence to: Antonio Ventura Pinto
E-mail: ventura@nppn.ufrj.br

MATERIALS AND METHODS

GENERAL EXPERIMENTAL PROCEDURES

The mono oxime **4** was synthesized by the reaction of the β-lapachone with $NH_2OH.HCl$ in etanol and triethylamine for 36h under stirring to room temperature. The formed insoluble solid was filtered yielding 95%. The syntesis was performed as described in the German patent: *Europäisches Patentamt* N° 85810555.4.

The mono oxime **3** was synthesized by the reaction of the nor-β-lapachone with $NH_2OH.HCl$ in etanol and triethylamine for 36h under stirring to room temperature. The formed insoluble solid was filtered yielding 90%.

3 Spectral data. **U.V.**λ_{max} **nm (log** ε**) EtOH:** 358 (3.64), 291(4.86), 271(4.97), 262(4.96), 225(5.13) **I.R.(KBr)cm^{-1}:** 3426, 2977, 2931, 1626, 1591, 1529, 1424, 1371, 1279, 1103, 975, 840, 766. **MS (70 eV) m/z (resl.ab.%):** 243(82), 226(100), 198(28), 183(27), 170(20), 153(21), 130(53), 115(32), 102(42), 63(21). **NMR^{1}H (200 MHz, CDCl$_3$)** δ **ppm *J* Hz:** 18.0(s, 1H), 8.3(d, 1H J=7.5), 7.8(d, 1H J=7.5), 7.5(t, 1H J=7.4), 3.0(s, 2H), 1.6(s, 6H).

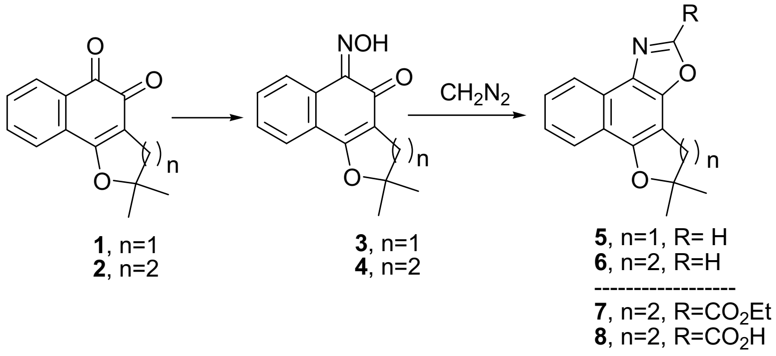


Fig. 1 – Preparation of naphthoxazoles from quinones.

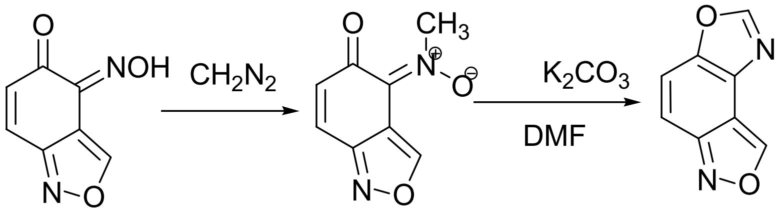


Fig. 2 – Katristzky's proposition of oxazole formation.

The synthesis of the naphthoxazoles **5** and **6** were accomplished by the addition of 10ml of an eter solution of diazomethane to 1.0mmol of the oximes **3** and **4** at 0°C. The reactions were maintained in this temperature for 12h in both cases. After the vacuum evaporation of the solvent, the products were isolated by column cromatography over silica gel, eluted with mixtures of hexane/ ethyl acetate with increased gradient of polarity. In the mixtures of hexane/ ethyl acetate 98:02 the oxazoles were eluted, and after recrystallization in etanol were obtained in 52% of yield for **5** and 56% for **6**.

The synthesis of the oxazoles **7** and **8** was performed by the reaction of the β-lapachone **2** with ethyl ester of glicine as described earlier (Pinto et al. 1997).

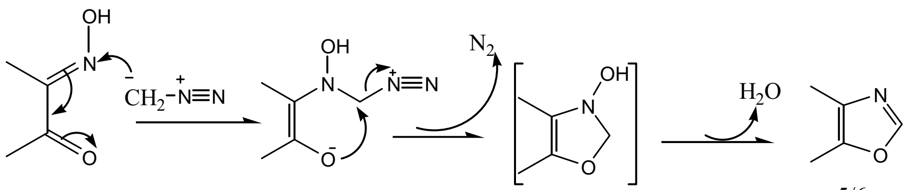
All the physical data for **5**, **6**, **7** and **8** are already described in the literature (Pinto et al. 1997).

RESULTS AND DISCUSSION

In our studies the electrophilic chemical behavior of quinoid carbonyl systems was exploited in order to construct imidazole, oxazole and phenazine rings attached to the naphthalene skeleton of the original naphthoquinone. In this paper we report a simple and direct alternative to the construction of oxazole appendages, using the mono oxime of β-lapachone **2** and one of its semisynthetic inferior homolog **1** which were converted to the pyran[4,3-*b*]naphtho[1,2-*d*]oxazole compound **6** and the furan[4,3-*b*]naphtho[1,2-*d*]oxazole compound **5** respectively, *via* their reactions with diazomethane.

In both cases, the reaction of **3** or **4** (1.0 mmol) is conducted in ether, with diazomethane free from base in slight excess, at low temperature. After the reactions take place (monitored by TLC) the solutions in each case are vacuum evaporated and the products isolated by column chromatography (eluted with a mixture of hexane/ethyl acetate of increasing polarity). Subsequent crystallization from ethanol furnishes respectively **5** (mp=117°C, 50-60%) and **6** (mp=120°C, 50-60%) in pure forms. To the best of our knowledge, the directed conversion of mono oximes of *ortho*-quinones to oxazole rings using diazomethane represents a new type of reaction, without precedent in the literature.

Recently, the cyclization of an α-oxo-oxime to 2-substitued benzoxazoles was reported, but in two stages, through a stable N-methylnitrone intermediate, followed by treatment with base, (Katristzky et al. 2003).



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5/6

Fig. 3 – Mechanistic proposition of oxazole formation.

Mechanistically, we propose that the reaction reported here, leading directly to the N- hydroxy oxazole ring appendage as shown in **9**, goes by a 1,4 nucleophylic diazomethane attack on the nitrogen of the heterodiene groups in compounds **3** and **4**, respectively. Differing from the Katristzky reaction for the formation of oxazole rings, in our case, the reactions do not proceed in two stages, and do not need the presence of a strong base for the formation of the oxazolic ring. We assume that the driving force for the 1, 4 nucleophilic attack of the diazomethane is the aromatization of the naphthalene structures in going from **3** and **4**, respectively, to the intermediate **9**, which then continues on to a fully unsaturated oxazolic ring by elimination of water.

The ^{1}H-NMR spectrum indicated that the corresponding oxazoles 5 and 6 are already present in the crude reaction mixtures.

Oximes **3** (mp=164°C) and **4** (mp=144°C) can be synthesized easily from the corresponding *ortho*-quinones **1** (4.4 mmol) and **2** (4.1mmol) respectively, by reacting them at room temperature with hydroxylamine hydrochloride (13 mmol) in the presence of trimethylamine (2.5 mL) as acid scavenger and ethanol (30 mL) as solvent, with stirring during 2h. In both cases the products are easily and directly crystallized from the reaction mixture in high yield. The proof of the regiorientation junction of the oxazolic ring fused to the naphthalene skeleton in **6** came from its chemical correlation with the ester **7**, whose structure was finally confirmed by X-Ray crystallography. Fig. 4 shows the ORTEP projection for **7** and Table I contains the crystal data and details of its structure determination.

Alkaline hydrolysis of **7**, followed by acid workup, gave a crude unstable acid, **8**, that on tentative crystallization in hot hexane, suffered decarboxylation to produce crystals of pure **6** in high yield. Consideration of the chemical origin of **6** (from **4**) defines the exact location of the oxime functional group in this compound. This leads to the structural assignments for the corresponding homologous compounds **3** and **5**. Ester **7** was prepared as previously published, (Pinto et al. 2000), from the reaction of **2** with the ethyl ester of glycine. A compound that should correspond to **6** was already cited in the literature from the reaction of **2** with free glycine in pyridine, but in poor yield and without a correct assignment of its structure, (Pinto et al. 2000). Nevertheless, all of the physical data for this compound are fully in accord with the structure presented here for **6**.

CONCLUSION

Due to the trypanocidal action of some drugs, which contain the basic heterocyclic skeleton present in **6**, we propose that the easy access to **5** and **6** from simple naphthoquinone mono oximes can open a line to prepare 2-alkyl substituted derivatives with potential biological activity. The metalation of oxazoles, which are unsubstituted in the 2-position to produce carbanion intermediates at low temperatures (butyllithium/THF), support the proposal that these reactions offer a probable chemical route to such derivatives by simple alkylations, (Hodges et al. 1991). These studies, as well as the extension of the use of the methodology with oxazoles described here to other naphthoquinone mono oximes, are now in progress. All compounds gave spectroscopic and spectrometric data in accord with the described structures.

ACKNOWLEDGMENTS

We thank Prof. Ira Brinn (Instituto de Química/ UFRJ) for a critical revision of the original manuscript. This research was supported by grants from Conselho Nacional

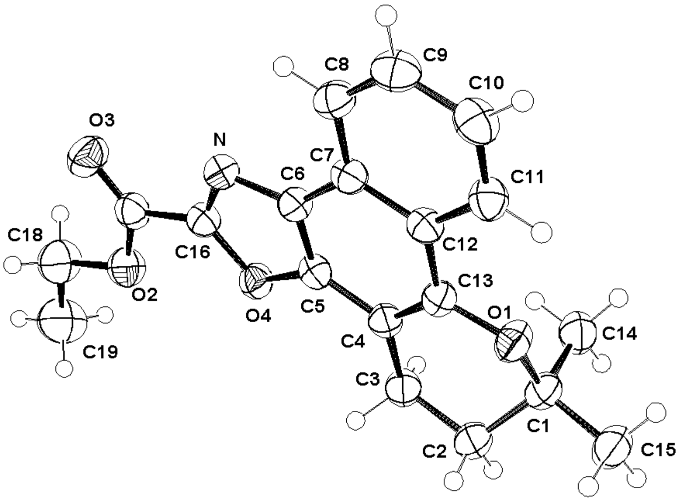

Fig. 4 – Crystal structure of **7** (ORTEP Diagram, thermal ellipsoids at 50% probability, H atoms omitted for clarity.

TABLE I
Crystal data for structure determination of 7.

Empirical Formula	$C_{19}H_{19}NO_4$
Formula Weight	325.35
Crystal System	Monoclinic
Space group	P21/n
a [Å]	12.590(2)
b [Å]	7.864(3)
c [Å]	17.106(3)
β[°]	107.79(1)
V [Å^3]	1612.7(7)
Z	4
D(calc) [Mg/m^3]	1.340
F(000)	688
μ(MoKα) [/mm]	0.094
Crystal Size [mm]	0.05 x 0.10 x 0.10
Temperature (K)	243
λ MoKα [Å]	0.71073
θ min-max [°]	2.4, 28.0
hkl max and min	0: 16 ; $\overline{10}$: 0 ; $\overline{22}$: 21
Tot., Uniq. Data, R(int)	4067, 3896, 0.024
Observed data [I > 2.0 σ(I)]	2704
Nref, Npar	3896, 220
R, wR, S	0.0499, 0.153, 1.04
w = 1/[σ^2(Fo^2)+(0.0779P)^2+0.4813P] where	P=(Fo^2+2Fc^2)/3
Min. and Max. resd. dens. [e/Å^3]	–0.37, 0.48

de Desenvolvimento Científico e Tecnológico (CNPq), Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Fundação Universitária José Bonifácio/UFRJ (FUJB).

RESUMO

A reação das naphthoquinona-oximas (**3**) e (**4**) com diazometano fornece diretamente, em uma etapa, os oxazóis (**5**) e (**6**), respectivamente.

Palavras-chave: quinonas, oximas, diazometano, oxazóis.

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