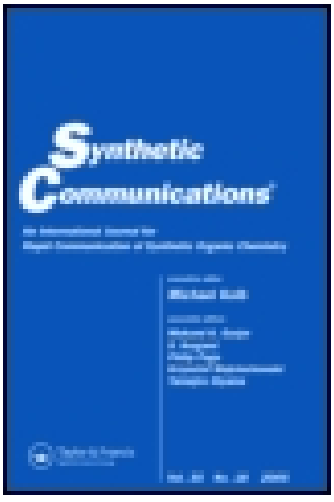

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Reaction of β-Lapachone with 1,2-Diamines: Facile Synthesis of Novel Tetracyclic Pyrazines

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Reaction of β-Lapachone with 1,2-Diamines: Facile Synthesis of Novel Tetracyclic Pyrazines

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Abstract: The reactions of β-lapachone (**1**) with 1,2-diaminoethane (**2**) and 1,2-diaminopropane (**4**) gave the tetracyclic pyrazine derivatives (**3**) and mixtures of (**5**) and (**6**), respectively, while reaction with o-phenylene diamine (**7**) gave the quinoxaline derivative (**8**). The structure of pyrazine derivative (**3**) is confirmed by single-crystal X-ray diffraction study.

Keywords: β-lapachone, 1,2-diamines, carbonyl reactivity, regioisomer

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1. INTRODUCTION

A number of prenyl naphthoquinone congeners such as lapachol, deoxylapachol, α- and β-lapachones, dehydro-α-lapachone, and dehydroiso-β-lapachone have been isolated from the woods of various *Bignoniaceae*[1–5] *Malvaceae*,[6] and *Verbenaceae*[7] plants. β-Lapachone (**1**), a 1,2-naphthoquinone, is obtained in low yield naturally and was synthesized from lapachol through cyclization of the isoprenyl side chain of lapachol under microwave irradiation.[8]

We report the reactions of β-lapachone with different 1,2-diamines using conventional heating and microwave irradiation.

2. RESULTS AND DISCUSSION

The reaction of β-lapachone (**1**) with 1,2-diaminoethane (**2**) at room temperature gave the corresponding tetracyclic pyrazine derivative **3** (Scheme 1). This observation is in contrast to what Di Chenna et al. observed.[9] We have not found the formation of a monoarylimine-*o*-quinone derivative.

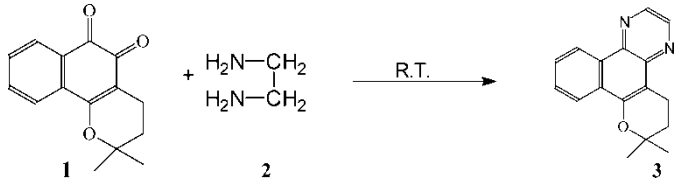
We extended our studies to the reaction of β-lapachone with 1,2-diaminopropane. Similar results involving the formation of the pyrazine derivatives (**5** and **6**) were noticed (Scheme 2).

The reaction of o-phenylene diamine (**7**) with (**1**) gave the quinoxaline derivative **8** (Scheme 3).

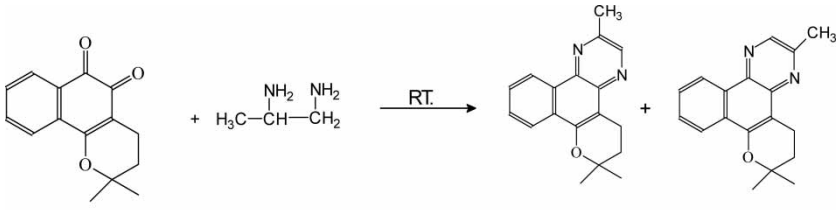
The structure of **3**, involving facile dehydrogenative cyclocondensation even under mild conditions, was confirmed by single-crystal X-ray diffraction (Fig. 1).

3. EXPERIMENTAL

Melting points were determined in soft-glass capillaries in an electrothermal melting-point apparatus and are uncorrected. Qualitative and quantitative thin-layer chromatography (TLC) was conducted on TLC aluminium sheets, Kieselgel $60F_{254}$ (E. Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 300 instrument using $CDCl_3$ as solvent. Mass spectra (EIMS) were generated on a Jeol D-300 spectrometer. All compounds were homogeneous on TLC plates in various solvent systems.



Scheme 1.



1 4 5 6

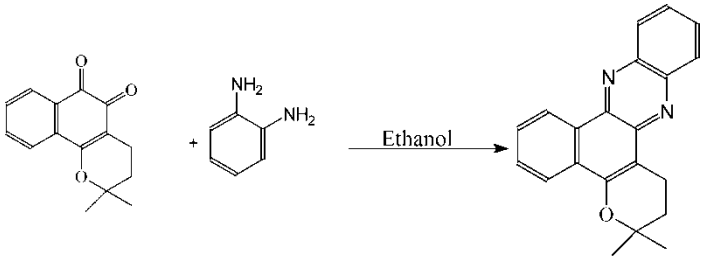
Scheme 2.

3.1. Reaction of β-Lapachone with 1,2-Diaminoethane (1)

β-Lapachone (61 mg, 0.25 mmol) and 1,2-diaminoethane (2 mL) were stirred at room temperature for 24 h until completion of the reaction (TLC). Petroleumether (60–80°C, 10 mL) was added to the reaction mixture. Crude product is separated by filtration and purified by preparative TLC (benzene, R_f 0.29). Yield (54.9 mg, 90%).

3.2. 5,6-Dihydro-7,7-dimethyl-7H-pyrano[3′,2′:4]naphtha[1,2-b]-pyrazine (3)

Physical properties: yellow needles, mp 77–80°C; (found: C, 77.03; N, 10.57; $C_{17}H_{16}N_2O$ requires C, 77.27; N, 10.60%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.50 (6H, s, 2Me), 2.04 (2H, t, *J* 7.0, -CH_2-), 3.24 (2H, t, *J* 7.0, -CH_2-), 7.73 (2H, m, 2Ar-H), 8.33 (1H, m, 1Ar-H), 8.76 (2H, m, N-CH═CH-N), 9.14 (1H, br d, 1 × Ar-H); δ_C (300 MHz; $CDCl_3$; Me_4Si) 18.26 (C_7-CH_3), 26.80 (C_7-CH_3), 32.39 (C_5 and C_6), 75.37 (C_7), 110–130 (aromatic-C), 138.19 (-C═N of C_{4a}), 139.99 (C_3), 143.93(C_2), 150.43 (C_{8a}); MS (m/z, rel. int. %) 264



1 7 8

Scheme 3.

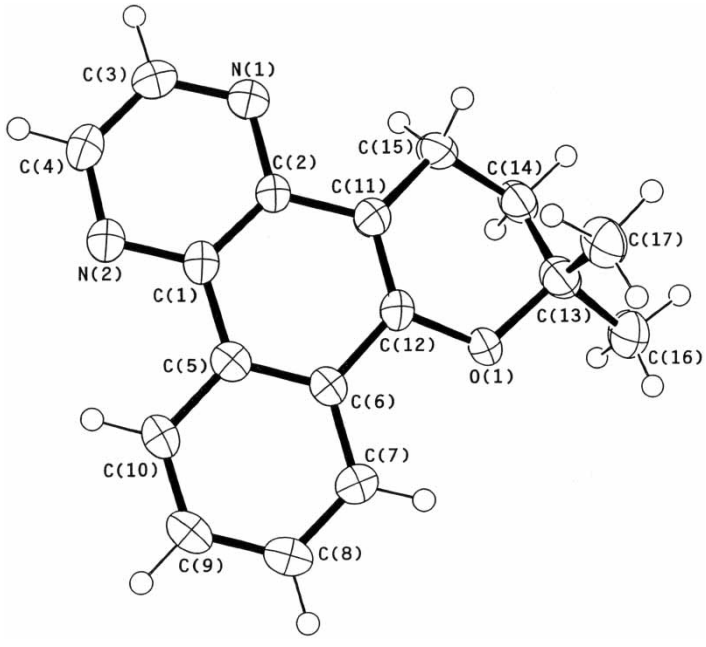


Figure 1. ORTEP plot of the asymmetric unit of $C_{17}H_{16}N_2O$. The nonhydrogen atoms are drawn with 50% probability ellipsoids.

$[M]^+$ ($C_{17}H_{16}N_2O$) (55), 249 $[M\text{-}Me]^+$ (15), 235 $[249\text{-}CH_2]^+$ (10), 221 $[235\text{-}CH_2]^+$ (100), 209 (60), 188, 127; X-ray analysis: the C(3)–C(4) bond length (1.362 Å) was found to be very close to the aromatic C-C bond length.

3.3. Reaction of β-Lapachone with 1,2-Diaminopropane (2)

1,2-Diaminopropane (2 mL) was added to β-lapachone (61 mg, 0.25 mmol), and the mixture was stirred at room temperature. The progress of the reaction was examined on TLC plate, which after 5 min indicated the formation of two products in a ratio of 1:3. These two products were separated by preparative TLC and characterized as regioisomers **5** and **6** (benzene, R_f 0.48, 0.36 respectively) on the basis of spectral studies. Yield: 14.33 mg, 23.5% of **5**; 43 mg, 70.5% of **6**.

The reaction was also carried out under microwaves, where it was completed in 15 s. However, under MW irradiation, the reaction showed the formation of the two products, **5** and **6**, in a 2:3 ratio, indicating the enhanced yield of regioisomer **5**. To check the possibility of conversion of **6** to **5**, the reaction mixture was further irradiated for a longer period of 10 min, but no change was found in the product ratio. Yield: 23.42 mg, 38.4% of **5**; 35.13 mg, 57.6% of **6**.

3.4. 5,6-Dihydro-2,7,7-trimethyl-7H-pyrano[3′,2′:4] naphtha [1,2-b]-pyrazine (5)

Physical properties: pale yellow needles, mp 75–78°C; found: C, 77.44; N, 10.04; $C_{18}H_{18}N_2O$ requires C, 77.69; N, 10.07%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49 (6H, s, 2Me), 2.03 (2H, t, *J* 7.0, -CH_2-), 2.76 (3H, br s, N═C-CH_3), 3.21 (2H, t, *J* 7.0, CH_2-), 7.71 (2H, m, 2Ar-H), 8.32 (1H, m, 1Ar-H), 8.60 (1H, br s, N-CH═C-N), 9.07 (1H, m, 1Ar-H).

3.5. 5,6-Dihydro-3,7,7-trimethyl-7H-pyrano[3′,2′:4] naphtha [1,2-b]-pyrazine (6)

Physical properties: bright yellow needles, mp 70–72°C; found: C, 77.93; N, 10.07; $C_{18}H_{18}N_2O$ requires C, 77.69; N, 10.05%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49 (6H, s, 2Me), 2.02 (2H, t, *J* 7.0, -CH_2-), 2.79 (3H, br s, N═C-CH_3), 3.22 (2H, t, *J* 7.0, -CH_2-), 7.71 (2H, m, 2Ar-H), 8.32 (1H, m, 1Ar-H), 8.69 (1H, br s, N-C═CH-N), 9.16 (1H, m, 1Ar-H).

3.6. Reaction of β-Lapachone with *o*-Phenylene Diamine (3)

The analogous reaction of *β*-lapachone (61 mg, 0.25 mmol) with *o*-phenylene diamine (21 mg, 0.25 mmol) in ethyl alcohol (15 mL) was carried out at room temperature. The reaction was examined on a TLC plate, which indicated product **8** with minor impurities. This compound was purified by preparative TLC (benzene R_f 0.76). Yield: 56.12 mg, 92%.

3.7. 7,8-Dihydro-9,9-dimethyl-9H-pyrano[3′,2′:4] naphtha [1,2-b]-quinoxaline (8)

Physical properties: bright yellow needles, mp 113–115°C; found: C, 80.51; N, 8.93; $C_{21}H_{18}N_2O$ requires C, 80.25; N, 8.91%. δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.53 (6H, s, 2Me), 2.07 (2H, t, *J* 7.0, -CH_2-), 3.35 (2H, t, *J* = 7.0, -CH_2-), 7.80 (3H, m, 3Ar-H), 8.30 (1H, m, 1Ar-H), 9.33 (1H, m, 1Ar-H); δ_C (300 MHz; $CDCl_3$; Me_4Si) 18.33 (C_9-CH_3), 26.86 (C_9-CH_3), 32.52 (C_7 & C_8), 76.03 (C_9), 109–130 (aromatic-C), 140.79 (-C═N of C_{14b}), 142.59 (-C═N of C6a), 144.55 (C_{10a}); MS (m/z, rel. int. %) 314 $[M]^+$ ($C_{21}H_{18}N_2O$) (75), 299 $[M\text{-}Me]^+$ (15), 285 $[299\text{-}CH_2]^+$ (10), 271 $[285\text{-}CH_2]^+$, 229 (20).

4. CONCLUSION

We have developed a facile method for quantitative synthesis of a novel tetracyclic ring system involving the formation of the pyrazine ring in the

absence of any solvent/catalyst by reaction of β-lapachone with various amines at room temperature.

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