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# Novel Rearrangement During the Reaction of Diethylmalonate with α-(5-Substituted 2-hydroxyphenyl)-N-phenyl Nitrones

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# NOVEL REARRANGEMENT DURING THE REACTION OF DIETHYLMALONATE WITH α-(5-SUBSTITUTED 2-HYDROXYPHENYL)-N-PHENYL NITRONES

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***The hydroxyl group at the* ortho *position of the α-aryl ring of α-(2-hydroxyaryl)-N-aryl nitrones altered the expected course of the reaction between differently substituted α-(2-hydroxyaryl)-N-aryl nitrones and diethylmalonate, leading to the formation of an enamine involving an interesting rearrangement under microwave irradiation. The enamines have been characterized by NMR and x-ray analyses, and a reasonable mechanism has been put forwarded to explain the rearrangement.***

***Keywords***: Diethyl malonate; enamine formation; microwave-assisted organic reactions; nitrone addition

The enamine group is one of the most versatile functionalities available to the synthetic chemist for different transformations.[1] Enamines have been intensively studied in organic synthesis after Stork's report on the application of enamines for the alkylation and acylation of carbonyl compounds.[2] Enamines have been used in natural product synthesis, including total synthesis of fabianine[3] and quaipyridines.[4]

β-Functionalized enamines or the corresponding imine tautomers derived from phosphonium salts,[5] phosphine oxides,[6] phosphonates,[7–10] and phosphazenes[11] have been employed in the synthesis of phosphorus substituted three-, five-, and six-membered nitrogen heterocycles. The heterocyclic frameworks available through this methodology include azirines, pyrazoles, pyrroles, 2-pyrrolones, dihydro- and tetrahydropyridines, 2-pyridones, quinolines, and pyrimidin-2,4-diones. Phosphorus functionalized enamines are also useful starting materials for the preparation of phosphorus-containing heterocycles.[12] Very recently, the unexpected diversity of reaction patterns of heterocyclic enamines when treated with aliphatic and aromatic dicarboxylic acid chlorides has been discovered.[13] We report the unexpected formation of ethyl 3-(2-hydroxy-5-substituted phenylanilino)-2-propenoate, a set of novel enamines obtained by the addition of diethylmalonate to C-aryl-N-aryl nitrones.

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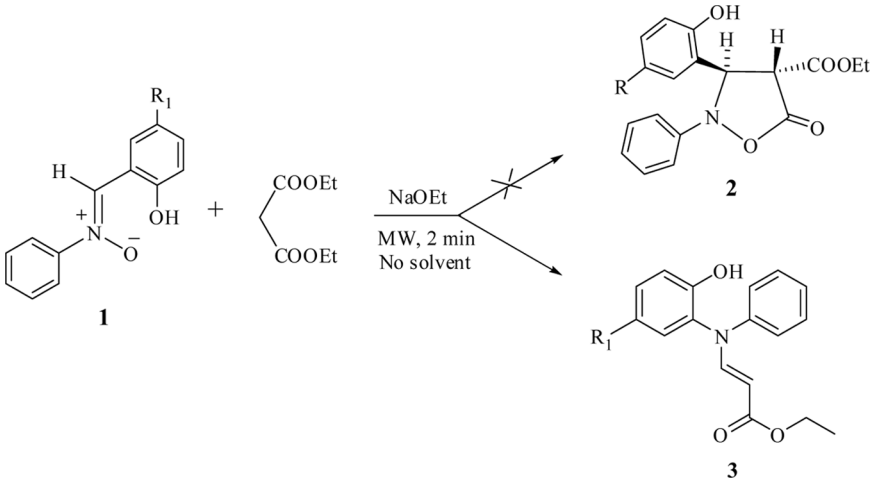
Our experience with 2-hydroxy/methoxy-substituted C-aryl-N-aryl nitrones giving unexpected products during attempted 1,3-dipolar addition reactions[14] prompted us to investigate the behavior of these nitrones toward other reactions involving nucleophiles. Addition of carbon nucleophiles to electron-deficient olefins is a classical and fundamental carbon–carbon bond-forming reaction.[15] This reaction and its close variants have been extensively used in organic synthesis.[16] Diethyl malonate adducts have been used in the preparation of a very wide variety of heterocycles. Addition of diethylmalonate with simple nitrones, leading to the formation of isoxazolidinone, has already been described.[17,18] In the present work, when α-(2-hydroxyaryl)-N-aryl nitrones **1** were allowed to react with diethyl malonate in the hope of preparing 5-oxo-2-phenyltetrahydro-4-isoxazole **2** with 2-hydroxyaryl group at the 3-position and carbethoxy group at the 2-position, the expected cyclic compound was not obtained, but a novel rearrangement occurred that led to a new set of enamines.

A mixture of α-(2-hydroxyaryl)-N-aryl nitrone **1**, diethyl malonate, and solid sodium ethoxide was irradiated with microwaves for 2 mins. Only one product, **3,** was obtained in very good yield as evidenced by thin-layer chromatography (TLC) (Scheme 1 and Table 1). The $^{1}H$ and $^{13}C$ NMR spectra along with the two-dimensional NMR spectra were helpful in assigning the structure of the product, and the product obtained was enamine **3** and not the expected **2**. In the $^{1}H$ NMR spectrum of **3a**, there is a triplet at 1.17 ppm ($J = 7.2$ Hz) and a quartet at 3.98 ppm ($J = 7.2$ Hz), indicating the presence of a carbethoxy group in the molecule. There is a singlet appearing at 1.26 ppm for nine hydrogens, due to the *t*-butyl group. Two doublets at 4.74 ppm ($J = 13.2$ Hz) and 8.22 ppm ($J = 13.2$ Hz) show the presence of *trans* coupled olefinic hydrogens. Obviously one is under the influence of an electron-releasing group and the other is under the influence of an electron-withdrawing group, shown by the large difference in their chemical shift. All the aromatic hydrogens appear between 6.97 and 7.35 ppm.




**Scheme 1.** Reaction of C-(2-hydroxyaryl)-N-aryl nitrone with diethyl malonate.

**Table 1.** Reaction time and yield of enamine formation

| Compound | $R_1$ | Reaction time (min) | Yield (%) |
|---|---|---|---|
| **3a** | $C(CH_3)_3$ | 2 | 85 |
| **3b** | $CH_2CH_3$ | 2 | 83 |
| **3c** | $OCH_3$ | 2 | 78 |
| **3d** | $C(CH_3)_2CH_2CH_3$ | 2 | 80 |
| **3e** | $CH(CH_3)_2$ | 2 | 85 |

In the $^{13}C$ NMR spectrum of **3a**, signals appear at 14.3, 31.4, 34.2, 59.6, 94.6, 117.1, 118.5, 123.8, 125.5, 126.5, 127.0, 129.5, 144.5, 145.3, 146.0, 149.3, and 169.0 ppm. The presence of 2-hydroxy-5-substituted aryl group and the phenyl group are evident from the spectral pattern. The deshielded doublet at 8.22 ppm has hetero-nuclear multiple bond correlation (HMBC) contours with the carbons at 169.0, 145.3, and 126.5 ppm. All the three carbons are quaternary carbons and have three bond connectivities with this hydrogen. This clearly suggests that the two aryl groups and the vinyl group are attached through a common atom. The elemental analysis performed on the compound indicates the presence of nitrogen, and hence this common atom could be nitrogen. There are two other quaternary carbons at 144.5 and 149.3 ppm. The former carbon is *ipso* to the *t*-butyl group, as it gives a HMBC contour with the methyl hydrogens of the *t*-butyl group, and the latter carbon must be *ipso* to hydroxyl group. Thus, we conclude the structure of **3** to be that shown in Fig. 1.

To confirm the assigned structure, single-crystal x-ray analysis was carried out for compound **3a**, ethyl 3-[5-*tert*-butyl)-2-hydroxyphenylanilino]-2-propenoate. (Crystallographic data for the structure **3a** have been deposited with the Cambridge Crystallographic Centre as supplementary publication number CCDC 710035.) The x-ray structure is shown in Fig. 2, confirming the assignments. The crystal data are provided in Table 2.

Thus, though we aimed at a cyclic compound from the open-chain precursor nitrone, a different compound was obtained involving an interesting rearrangement. Obviously, the hydroxyl group present at the *ortho* position has some role to play directing the course of the reaction along a different path. Such an influence by the *ortho* methoxy group during the 1,3-dipolar cycloaddition reaction of

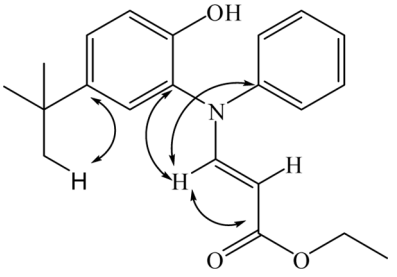



**Figure 1.** Selected HMBC correlations of **3a.**

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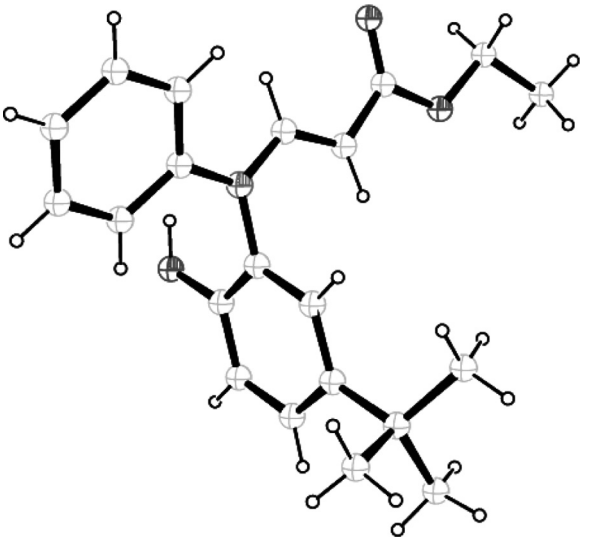

**Figure 2.** ORTEP diagram of ethyl (*E*)-3-[5-*tert*-butyl)-2-hydroxyphenylanilino]-2-propenoate **3a.**

**Table 2.** Summary of crystal data, data collection, and structure refinement for **3a**

| Crystal data | Compound **3a** |
|---|---|
| Empirical formula | $C_{21}H_{25}NO_3$ |
| Formula weight | 339.42 |
| Temperature | 298(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Triclinic, P-1 |
| Unit cell dimensions | a = 8.4086(4) A, alpha = 73.921(2)° |
| Volume | b = 11.0725(5) A, beta = 84.265(2)° |
| Z, Calculated density | c = 11.3982(5) A, gamma = 70.723(2)° |
| Absorption coefficient | 962.49(8) $A^3$ |
| F(000) | 2, 1.171 $mg/m^3$ |
| Crystal size | 0.078 $mm^{-1}$ |
| Theta range for data collection | 364 |
| Limiting indices | 0.28 × 0.25 × 0.22 mm |
| Reflections collected (unique) | 2.36 to 27.23° |
| Completeness to theta | $-10 \le h \le 10$, $-14 \le k \le 14$, $-14 \le l \le 14$ |
| Absorption correction | 12273/4208 [R(int) = 0.0259] |
| Max. and min. transmission | 25.00 and 99.0% |
| Refinement method | None |
| Data/restraints/parameters | 0.9831 and 0.9786 |
| Goodness of fit on $F^2$ | Full-matrix least-squares on $F^2$ |
| Final R indices [I > 2sigma(I)] | 4208/1/260 |
| R indices (all data) | 0.783 |
| Largest diff. peak and hole | R1 = 0.0522, wR2 = 0.1359 |
| | R1 = 0.0937, wR2 = 0.1740 |
| | 0.292 and −0.201 $eA^{-3}$ |

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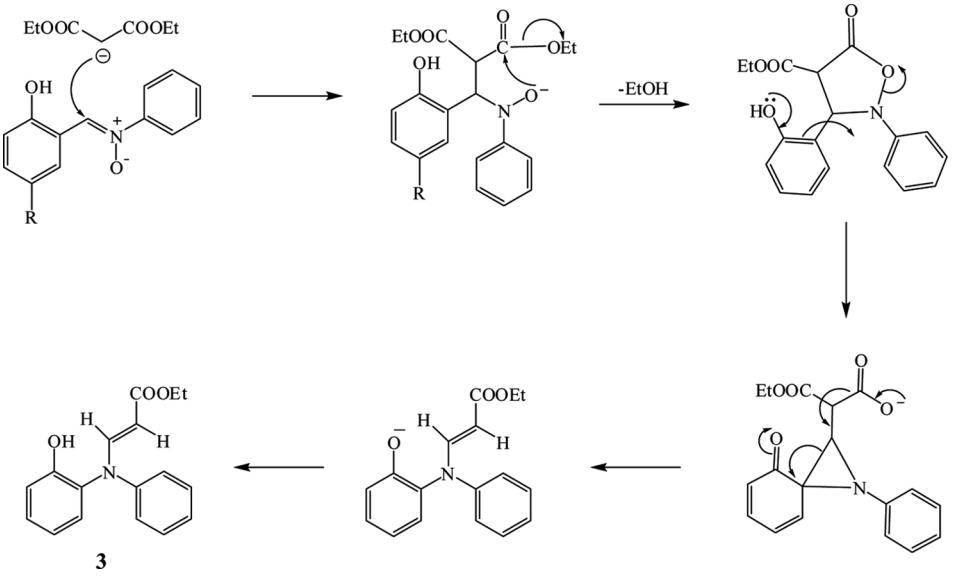
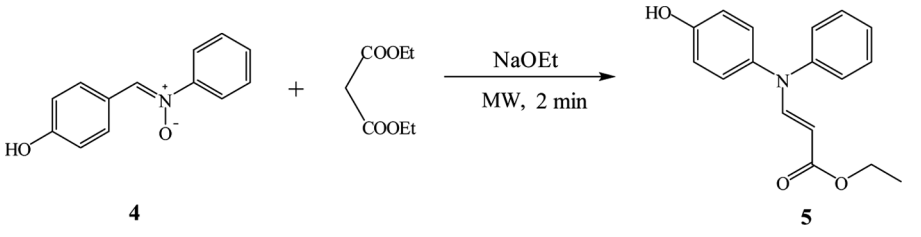



**Scheme 2.** Mechanism for the formation of product **3**.

α-(2-methoxyphenyl)-N-aryl nitrone with maleic anhydride has already been noticed.[14] A reasonable mechanism can be provided for the conversion (Scheme 2).

The hydroxyl group present at the 4-position of the nitrone was also expected to influence the course of the reaction in a similar fashion, and hence the reaction was carried out with the nitrone **4** generated from 4-hydroxybenzaldehyde. In this case also, the expected cycloaddition did not take place; the molecule underwent a rearrangement to give the enamine **5** (Scheme 3). The structure of **5** was confirmed by $^{1}H$ and $^{13}C$ NMR spectral analysis.

It must be mentioned that the reaction of nitrone generated from 2/4-methoxy benzaldehyde with diethyl malonate did not proceed to give either a cyclized product or an enamine. The additions of different nucleophiles with one carbethoxy group and another electron-withdrawing group [*viz.*, ethylchloro acetate and ethylcyano acetate on α-(2-hydroxyaryl)-N-aryl nitrone] have not yielded any recognizable products.




**Scheme 3.** Reaction of C-(4-hydroxyphenyl)-N-aryl nitrone with diethyl malonate.

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## EXPERIMENTAL

All chemicals were of reagent-grade quality and used with out further purification. All melting points were recorded in open capillaries and are uncorrected. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 300-MHz spectrometer at 300 MHz and 75 MHz respectively in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. The related two-dimensional (2D) NMR spectra were also recorded on the same instrument. Chemical shifts are given in parts per million (δ scale), and coupling constants are given in hertz. Microanalyses were carried out on a Perkin-Elmer instrument. The single-crystal x-ray data set was collected on a Bruker AXS diffractometer with radiation of $\lambda = 0.71073$ A°. All chromatographic separations were performed on 60- to 120-mesh silica gel using petroleum ether/ethyl acetate as eluent.

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### General Procedure for the Preparation of Ethyl 3-[5-Substituted)-2-hydroxy phenylanilino]-2-propenoate (3)

Diethylmalonate (0.32 g, 0.002 mol) and a catalytic amount of sodium ethoxide were subjected to microwave irradiation for 1 min, and the resultant mass was taken out. An equimolar amount of α-(5-substituted-2-hydroxyphenyl)-N-phenyl nitrone **1** was then added and mixed well. The reaction mixture was again irradiated for 1 min, and the mixture was worked out using petroleum ether to yield the white crystalline mass of the product ethyl 3-[5-substituted)-2 hydroxy phenylanilino]-2-propenoate **3**.

### Ethyl 3-[5-*tert*-Butyl)-2-hydroxyphenylanilino]-2-propenoate (3a)

White crystals (85%), mp 137°C. Anal. calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.40; H, 7.45; N, 4.23. $^{1}H$ NMR (300 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.2$ Hz, 3H); 1.26 (s, 9H), 3.98 (q, $J = 7.2$ Hz, 2H); 4.74 (d, $J = 13.2$ Hz, 1H); 6.97–7.35 (m, 8H), 8.22 (d, $J = 13.2$ Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.3, 31.4, 34.2, 59.6, 94.6, 117.1, 118.5, 123.8, 125.5, 126.5, 127.0, 129.5, 144.5, 145.3, 146.0, 149.3, 169.0 ppm.

### Ethyl 3-[5-Ethyl)-2-hydroxyphenylanilino]-2-propenoate (3b)

White crystals (83%), mp 125°C. Anal. calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.80; N, 4.55. $^{1}H$ NMR (300 MHz, $CDCl_3$): δ 1.15 (t, $J = 7.5$ Hz, 3H); 1.21 (t, $J = 7.5$ Hz, 3H); 2.56 (q, $J = 7.5$ Hz, 2H); 4.00 (q, $J = 7.2$ Hz, 2H); 4.76 (d, $J = 13.8$ Hz, 1H); 6.90–7.34 (m, 8H); 8.19 (d, $J = 13.8$ Hz, Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.0, 14.3, 27.7, 59.6, 94.5, 117.4, 118.8, 123.8, 126.9, 127.8, 129.4, 129.5, 137.9, 144.5, 146.1, 149.8, 169.1 ppm.

### Ethyl 3-(2-Hydroxy-5-methoxyphenylanilino)-2-propenoate (3c)

White crystals (78%), mp 143°C. Anal. calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.05; H, 6.20; N, 4.40. $^{1}H$ NMR (300 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.2$ Hz, 3H); 4.05 (q, $J = 7.2$ Hz, 2H); 3.80 (s, 3H); 4.83 (d, $J = 13.2$ Hz,

1H); 7.00–7.60 (m, 8H); 8.20 (d, $J = 13.2$ Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 13.9, 41.5, 55.6, 61.3, 94.5, 113.2, 115.9, 117.7, 118.3, 118.6, 119.4, 119.5, 122.5, 123.7, 125.4, 128.7, 129.3, 131.4, 145.9, 154.1, 169.0 ppm.

### Ethyl 3-[2-Hydroxy-5-(*tert*-pentyl)phenylanilino]-2-propenoate (3d)

White crystals (80%), mp 139°C. Anal. calcd. for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.80; H, 7.65; N, 4.05. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, $J = 7.2$ Hz, 3H); 1.30 (s, 6H); 1.40 (t, $J = 6.9$ Hz, 3H); 4.01 (q, $J = 7.2$ Hz, 2H); 4.40 (q, $J = 6.9$ Hz, 2H); 4.75 (d, $J = 13.2$ Hz, 1H); 7.00–7.60 (m, 8H); 8.25 (d, $J = 13.2$ Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 8.9$, 13.8, 14.3, 28.3, 36.8, 59.5, 94.2, 117.2, 123.5, 125.4, 126.4, 127.5, 129.3, 132.6, 146.2, 149.2, 157.1, 169.2 ppm.

### Ethyl 3-(2-Hydroxy-5-isopropylphenylanilino)-2-propenoate (3e)

White crystals (85%), mp 139°C. Anal. calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.90; H, 7.20; N, 4.40. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, $J = 7.2$ Hz, 3H); 1.25 (d, $J = 7.2$ Hz, 6H); 2.70 (sep, $J = 7.2$ Hz, 1H); 3.95 (q, $J = 7.2$ Hz, 2H); 4.77 (d, $J = 13.2$ Hz, 1H); 6.85–7.58 (m, 8H); 8.40 (d, $J = 13.2$ Hz, Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 14.2, 23.8, 33.0, 59.5, 94.0, 117.4, 118.4, 123.5, 126.4, 127.8, 129.2, 142.4, 144.5, 146.3, 150.0, 169.3 ppm.

### Ethyl 3-[4-Hydroxy(phenyl)anilino]-2-propenoate (5)

White crystals (80%), mp 135°C. Anal. calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.99; H, 6.95; N, 4.83. $^1$H NMR (300 MHz, $CDCl_3$): 1.28 (t, $J = 7.2$ Hz, 3H); 4.20 (q, $J = 7.2$ Hz, 2H); 4.83 (d, $J = 13.2$ Hz, 1H); 6.90–7.38 (m, 9H); 8.15 (d, $J = 13.2$ Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): 14.4, 59.6, 93.1, 116.5, 122.2, 125.4, 127.3, 128.6, 128.7, 129.3, 147.9, 155.0, 169.8 ppm.

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