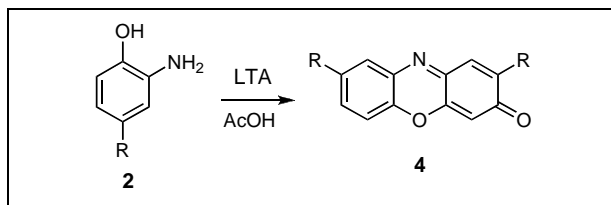


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Received June 29, 2006



A one-pot synthesis of some new 2,8-disubstituted 3*H*-phenoxazin-3-ones from 4-substituted-2-aminophenols through a selective oxidative condensation by lead tetraacetate in acetic acid is described.

J. Heterocyclic Chem., **44**, 491 (2007).

INTRODUCTION

Naturally occurring phenoxazines such as the ommochromes are pigments responsible for the colorations of certain arthropods [1]. A series of antibiotic substances known as actinomycins are the derivatives of phenoxazin-3-one. Though actinomycins are toxic, their derivatives have been shown to be useful anticancer agents [2,3]. Thus it could be seen that the phenoxazine and its 3-oxo derivative are useful candidates both as dye stuffs and antibiotics. Traditional routes to phenoxazine include thermolysis of 2-aminophenol and catechol, the latter acting as an acid catalyst. The various synthetic routes for tricyclic oxazines have been reviewed in detail [4]. Among the approaches to phenoxazines, the reductive cyclisation of 2-nitrodiphenyl ether with trialkyl phosphites is the most interesting. Simple oxidation of phenoxazine gives phenoxazin-3-one and several oxidizing agents have been used for this conversion, one of them being hypervalent iodine compounds such as iodosyl benzene [5]. Oxidation of phenoxazine with perdisulphate yielded the corresponding phenoxazin-3-one and a possible mechanism involving electron transfer followed by proton transfer with an intermediate radical formation has been suggested on the basis of kinetic data [6].

RESULTS AND DISCUSSION

In continuation of our recent research on the synthesis of five membered heterocyclic compounds containing at least two heteroatoms such as isoxazolidines [7-9], benzimidazoles [10] and benzoxazoles [11,12], it has been planned to synthesize some more new benzoxazoles from the respective aldehydes and amines without isolating the imine intermediate by lead tetraacetate oxidation. When equimolecular amounts of the corresponding aldehydes (1) and amines (2) were irradiated in a domestic

microwave oven and the crude reaction mixture was treated with LTA in acetic acid, the expected benzoxazoles (3) were obtained [13] (Scheme 1) along with a small amount of a byproduct, which has been identified as substituted phenoxazin-3-ones (4).

It has been realized that this 2,8-disubstituted phenoxazin-3-one could have been formed from the unreacted 4-substituted-2-aminophenols and this has been confirmed by treating the latter compounds with LTA directly in acetic acid. To substantiate the above conversion, a set of substituted phenoxazin-3-ones was synthesized in good yield from the corresponding aminophenols through a facile one-pot lead tetraacetate oxidation (Scheme 2).

All the compounds isolated (4a-e) are new. Assignment of the phenoxazin-3-one structure was based on ¹H, ¹³C NMR and mass spectra. In the mass spectrum of the compound 4a, recorded in EI mode, the molecular ion peak is at 337 m/e suggesting the presence of single nitrogen. The molecular weight also suggests that a compound is a derived dimer of the starting 2-aminophenol. The characteristic M-15 (322 m/e) and M-29 (308 m/e) peaks strongly suggest the loss of methyl and ethyl groups respectively from molecular ion. The presence of a relatively strong peak at m/e 281 could be ascribed to the species obtained by the loss of two ethylene molecules from the *t*-amyl groups in the molecular ion.

The ¹H NMR spectrum of 4a shows two quartets at 1.89 ppm and 1.69 ppm and two triplets at 0.70 and 0.68 ppm each with a coupling constant of 7.5 Hz. The two triplets are overlapping with each other making a nice six line signal with an intensity ratio of 1:1:2:2:1:1. There are two singlets each accounting for six hydrogen atoms at 1.33 and 1.34 ppm. The above sets of signals clearly show the presence of two non-equivalent 1,1-dimethylpropyl

groups in the molecule. There are two one-hydrogen singlets at 6.23 ppm and 7.27 ppm. The set of a doublet (7.71 ppm, 2.4 Hz), a doublet of doublet (7.49 ppm, 8.7 Hz and 2.4 Hz) and a doublet (7.24 ppm, 8.7 Hz) each accounting for one hydrogen indicate that one 4-substituted aminophenol skeleton is there.

The ^{13}C NMR spectrum has 8 carbons at 39.82, 38.28, 37.19, 33.29, 28.85, 27.73, 9.88 and 9.47 ppm in the aliphatic region corresponding to two 1,1-dimethylpropyl units. There are five CH carbon atoms at 131.63, 130.67, 127.66, 115.83, and 108.35 ppm in the aromatic/olefinic region (DEPT spectrum) all of them are almost equally intense. The aromatic/olefinic/ carbonyl quaternary-carbons appear at 186.44, 153.93, 149.69, 148.98, 147.37, 142.03, and 133.40 ppm. The data are in good agreement with the assigned structure **4a**. The formation of the product can be explained by the initial formation of phenoxazine by the dimerisation of 2-aminophenol in acetic acid followed by oxidation to phenoxazin-3-one. The other pathway of initial oxidation of 2-aminophenol to give 2-hydroxy-5-alkylbenzoquinone followed by the reaction with another molecule of 4-alkyl-2-aminophenol is unlikely, although simple benzoquinone and 2-aminophenol combination has led to phenoxazin-3-one. However, it must be mentioned that the oxidation of simple 2-aminophenol leads to 2-aminophenoxazin-3-one and not to unsubstituted phenoxazin-3-one [14] through a radical mechanism [15]. Such a direct oxidation would have led to a bridgehead-substituted phenoxazine in the present case. It is pertinent to quote that 4-methyl-2-aminophenol in acetic acid has been shown to undergo

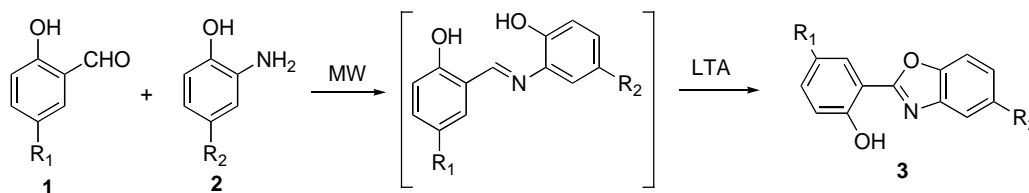
slow oxidation to give several products, one among them being 2,8-dimethylphenoxazin-3-one, obtained in very minor quantity [16]. Even oxidation by ferricyanide in acetic acid has not improved the yield of this product among others. However, in the present investigation, lead tetraacetate was found to selectively effect the tandem oxidative condensation to give mainly 2,8-disubstituted-3H-phenoxazin-3-ones with no other oxidized products in traceable amount, thus providing a new one-pot synthesis of disubstituted phenoxazin-3-ones.

EXPERIMENTAL

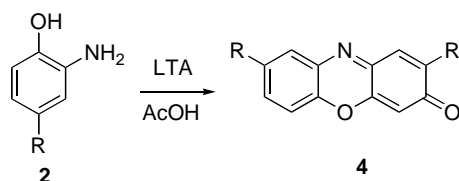
All chemicals were of reagent grade quality and used without further purification. All melting points reported in this work were measured in open capillaries and are uncorrected. NMR spectra were recorded on a Bruker 300 MHz (Ultrasield) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. The reactions were routinely monitored by thin layer chromatography (TLC) on silica gel plates.

General Procedure for the preparation of 2,8-disubstituted-3H-phenoxazin-3-ones (4a-e). A mixture of 4-substituted-2-aminophenol (10 mmol) and lead tetraacetate (10 mmol) was stirred in 50 mL of acetic acid for 30 minutes at room temperature. After completion of the reaction, as indicated by tlc, the mixture was poured in to ice water and extracted with chloroform. The chloroform layer was washed twice with cold water and sodium bicarbonate solution, dried with anhydrous sodium sulphate and evaporated. The crude reaction mixture was purified through silica column using petroleum ether-ethyl acetate as eluent.

Scheme 1



Scheme 2



R

- a $\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$
- b $\text{C}(\text{CH}_3)_3$
- c $\text{CH}(\text{CH}_3)_2$
- d CH_2CH_3
- e $\text{C}(\text{CH}_3)_2\text{Ph}$

2,8-Di-*t*-pentyl-3H-phenoxazin-3-one (4a). This compound was obtained as a crystalline solid, Yield: 71%, mp 92-93 °C, ^1H nmr (300 MHz, CDCl_3) δ 0.68 (t, $J = 7.5$ Hz, 3H), 0.70 (t, $J = 7.5$ Hz, 3H), 1.33 (s, 6H), 1.34 (s, 6H), 1.69 (q, $J = 7.5$ Hz, 2H), 1.89 (q, $J = 7.5$ Hz, 2H), 6.23 (s, 1H), 7.24 (d, $J = 8.7$ Hz, 1H), 7.27 (s, 1H), 7.49 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.71 (d, $J = 2.4$ Hz, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ 9.47, 9.88, 27.73, 28.85, 33.29, 37.19, 38.28, 39.82, 108.35, 115.83, 127.66, 130.67, 131.63, 133.44, 142.03, 147.37, 148.98, 149.69, 153.93, 186.44; ms: m/z 337, 322, 308, 292, 281, 278, 264, 252. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_2$: C, 78.30; H, 8.06; N, 4.15%. Found: C, 78.22; H, 8.12; N, 4.11%.

2,8-Di-*t*-butyl-3H-phenoxazin-3-one (4b). This compound was obtained as a crystalline solid, Yield: 68%, mp, 142-43 °C, ^1H nmr (300 MHz, CDCl_3) δ 1.31 (s, 9H), 1.33 (s, 9H), 6.11 (s,

1H), 7.12 (d, $J = 8.7$ Hz, 1H), 7.26 (s, 1H), 7.50 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.62 (d, $J = 2.4$ Hz, 1H). *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53%. Found: C, 77.73; H, 7.55; N, 4.49%.

2,8-Diisopropyl-3H-phenoxazin-3-one (4c). This compound was obtained as a crystalline solid, Yield: 60%, mp, 97-98 °C, 1H nmr (300 MHz, $CDCl_3$) δ 1.26 (d, $J = 6.9$ Hz, 6H), 1.28 (d, $J = 6.9$ Hz, 6H), 2.91 (m, 2H), 6.13 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.24 (s, 1H), 7.42 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.60 (d, $J = 2.1$ Hz, 1H). *Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98%. Found: C, 76.90; H, 6.89; N, 4.92%.

2,8-Diethyl-3H-phenoxazin-3-one (4d). This compound was obtained as a crystalline solid, Yield: 55%, mp, 149-50 °C, 1H nmr (300 MHz, $CDCl_3$) δ 1.25 (t, $J = 7.5$ Hz, 3H), 1.27 (t, $J = 7.5$ Hz, 3H), 1.68 (q, $J = 7.5$ Hz, 2H), 1.70 (q, $J = 7.5$ Hz, 2H), 6.14 (s, 1H), 7.17 (d, $J = 8.7$ Hz, 1H), 7.25 (s, 1H), 7.43 (dd, $J = 8.7$, 2.1 Hz, 1H), 7.61 (d, $J = 2.1$ Hz, 1H). *Anal.* Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%. Found: C, 75.80; H, 5.92; N, 5.59%.

2,8-Bis(2-phenylpropan-2-yl)-3H-phenoxazin (4e). This compound was obtained as a crystalline solid, Yield: 70%, mp 79-80 °C; 1H nmr (300 MHz, $CDCl_3$): δ 1.73 (s, 6H), 1.74 (s, 6H), 6.16 (s, 1H), 7.14 (d, $J = 8.7$ Hz, 1H), 7.24-7.29 (m, 11H), 7.44 (dd, $J = 8.7$, 2.1 Hz, 1H), 7.62 (d, $J = 2.1$ Hz, 1H). *Anal.* Calcd. for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23%. Found: C, 83.20; H, 6.29; N, 3.20%.

Acknowledgment. The authors thank DST-IRHPA NMR facility at School of Chemistry, Madurai Kamaraj University, for recording NMR spectra.

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