Microwave assisted synthesis of 4-alkyl-2-([5-substituted-2-hydroxyphenyl]iminomethyl)benzenols and their NMR characterization

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Imines, 4-alkyl-2-([5-substituted-2-hydroxyphenyl]iminomethyl)benzenols \(1\), have been obtained successfully in excellent yield from the corresponding aldehydes and amines by microwave irradiation. The resultant Schiff bases have been fully characterized by spectral data.

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Calixarenes are the third generation macromolecules of immense importance and the syntheses of modified calixarenes assume importance for their varying inclusion and associating characteristics.\(^1\) Though several aryl ring modified calixarenes have been synthesized,\(^2\) calixarenes modified at the side chain have not attracted the attention. During our attempt to prepare several side chain modified calixarenes with more than one atom and \(sp^2\) centres instead of the methylene bridge, we have synthesized a set of imine precursors, which can be targeted to side chain modified calixarenes following the method of Sartori \(et\ al.\)\(^3\). Thus, this article describes the synthesis and characterization of 4-alkyl-2-([5-substituted-2-hydroxyphenyl]iminomethyl)benzenols \(1\) by the conventional as well as microwave irradiation methods.

The aldehydes, 2-hydroxy-5-substituted benzaldehydes \(2\) have been prepared from the corresponding 4-substituted phenols by Reimer-Tiemann reaction in moderate yield. The amines, 2-hydroxy-5-alkylanilines \(3\) have been prepared by the reduction of the respective nitro compounds \(4\) using zinc and formic acid, slightly modifying the reported procedure.\(^4\) The nitro compounds, in turn, have been obtained from 4-substituted phenols by nitration. The condensation of \(2\) with \(3\) has been effected in presence of ethanol in less than an hour and the yields are good. As the microwave induced condensation of aldehydes and amines have already been reported\(^5\) under solvent free conditions, the microwave-assisted condensation of the present reaction has also been explored in this work. An intimate mixture of the aldehyde \(2\) and amine \(3\) without any solvent or catalyst has been irradiated in a domestic microwave oven. The reaction gets completed in just three minutes with excellent yield of the Schiff bases \(1\) (Scheme 1).

The yield and the physical constants of the synthesized compounds by the conventional and
microwave irradiation methods are given in Table I. All the imines show the characteristic bands at 1630 for C=N stretching and at 3420 cm⁻¹ for hydroxyl groups in their IR spectra. The NMR spectral details of compounds I are presented in Table II and they have all been characterized using H-H COSY, C-H COSY, DEPT and NOESY experiments.

A closer look at the ¹H NMR spectrum of 1a shows two doublets at δ 6.95 and 6.97 (J = 8.4 Hz), two doublets of doublets at 7.23 and 7.44 (J = 8.4, 2.1 Hz) and two doublets at 7.12 and 7.41 (J = 2.1 Hz). From H-H-COSY experiment, it is noticed that the doublet of doublets at δ 7.23 has cross peaks with the doublets at 6.95 and 7.41. The doublet of doublets at δ 7.44 has H-H-COSY correlation with signals at 6.97 and 7.12. The signals at δ 6.95, 7.23 and 7.41 have been assigned to Hₐ, Hₐ and Hₐ and the signals at
δ 6.97, 7.44 and 7.12 to Hx, Hy and Hz respectively (Figure 1). Hc, the hydrogen ortho to CH=N moiety has been deshielded than the other hydrogens. This can be the case only when the rotation of the C-aryl ring is restricted and the ring is in plane with CH=N moiety, thereby experiencing the −M effect of this group. The hydrogen bonding between the ortho hydroxyl of C-aryl ring and the imino nitrogen could have been the reason for this restriction (Figure 1). By this way, of the two hydroxyl hydrogens, the one that appears at around δ 5 (Hm) may be assigned to the ortho hydroxyl hydrogen of N-aryl ring and that around 12 (Hn) to the ortho hydroxyl hydrogen of C-aryl ring, the latter being hydrogen bonded. The azomethine hydrogen in its NOESY spectrum forms a relatively intense cross peak with Hc, thereby adding evidence to the above assigned structure. All other compounds have more or less the same NMR characteristics.

All the imines have either t-butyl or isopropyl group in one of the aromatic rings and show a prominent M-15 peak, being the base peak in most cases. This could be explained by the loss of a methyl group from t-butyl or isopropyl group, the resultant cation being stabilized by resonance. When both the rings have t-butyl or isopropyl groups, only one of the alkyl groups loses methyl group and there is no M-30 peak. In those cases, it can be assumed that the methyl from the alkyl group of N-aryl ring is removed during fragmentation and not from C-aryl ring, as the inductive effect favours the former fragmentation and not the latter.

Experimental Section

General Procedure. p-Cresol was purified by distillation prior to use and the other phenols reported are purchased from Acros Chemicals and used as such. Domestic microwave oven (LG, 1300 W, 28 L capacity) was used to carry out MW irradiation. Melting points were uncorrected. IR spectra were recorded in a Jasco FT-IR spectrometer as KBr pellets. 1H, 13C, H-H COSY, C-H COSY, DEPT and NOESY NMR experiments were carried out in a Bruker 300-MHz NMR instrument, using TMS as internal standard and CDCl3 as solvent. Mass spectra were recorded in Finnigan GC-MS instrument.

Preparation of aldehydes. General procedure. The aldehydes 2 were prepared by Reimer-Tiemann reaction by reacting 0.1 mole of p-substituted phenols in 50 mL of alcohol and 30 g of sodium hydroxide in 100 mL water with 0.2 mole of chloroform at 70°C. The crude mixture was purified through silica column.

Preparation of nitro compounds. General procedure. 0.05 mole of the p-substituted phenols were added to 30 mL of concentrated nitric acid (50% nitric acid in the case of p-cresol) at 0°C during one hr with constant stirring. The stirring was continued further one hr. After completion of the reaction, the mixture was poured into ice water and separated by column chromatography to get the 2-nitro derivatives 4.

Reduction of nitro compounds. General procedure. A mixture of 0.01 mole of the nitro compounds 4, 10 mL of methanol and 5 mL of formic acid was added with 0.04 mole of zinc dust slowly during 15 min. The stirring was continued for a further period of 5 min. The reaction mixture was then filtered, extracted with ether, washed with sodium bicarbonate solution, dried and evaporated to give amines 3.

Preparation of imines. By conventional method. Aldehyde 2 (0.01 mole) was mixed with 0.01 mole of the amine 3 and refluxed with 50 mL alcohol for 1 hr. After completion of the reaction, the solvent was concentrated and cooled. The product was filtered off and recrystallised from alcohol to give pure imines 1.

By microwave irradiation. A mixture of 0.01 mole of the aldehyde and 0.01 mole of the amine was ground well and placed in the microwave oven for the period of time specified in Table I. The progress of the reaction was monitored by TLC. After the completion of reaction, the product was recrystallised from alcohol.
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