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SELECTIVE FORMATION OF DIELS-ALDER ADDUCTS IN AQUEOUS MEDIA USING CHIRAL BENZIMIDAZOLES: INVESTIGATION THROUGH CHIRAL HPLC

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ABSTRACT

Reactions between anthrone and alkyl/aryl maleimide catalyzed by benzimidazole derived chiral Bronsted bases led to the formation of an unexpected Diels-Alder (D-A) adduct instead of Michael adduct in aqueous ethanol. An excellent yield was observed within a short period of time. Chiral HPLC analysis at different reaction times was used to confirm the formation of the unexpected Diels-Alder (D-A) adduct.

KEYWORDS: Diels-Alder, Bronsted base, Michael adduct, chiral HPLC.

1. INTRODUCTION

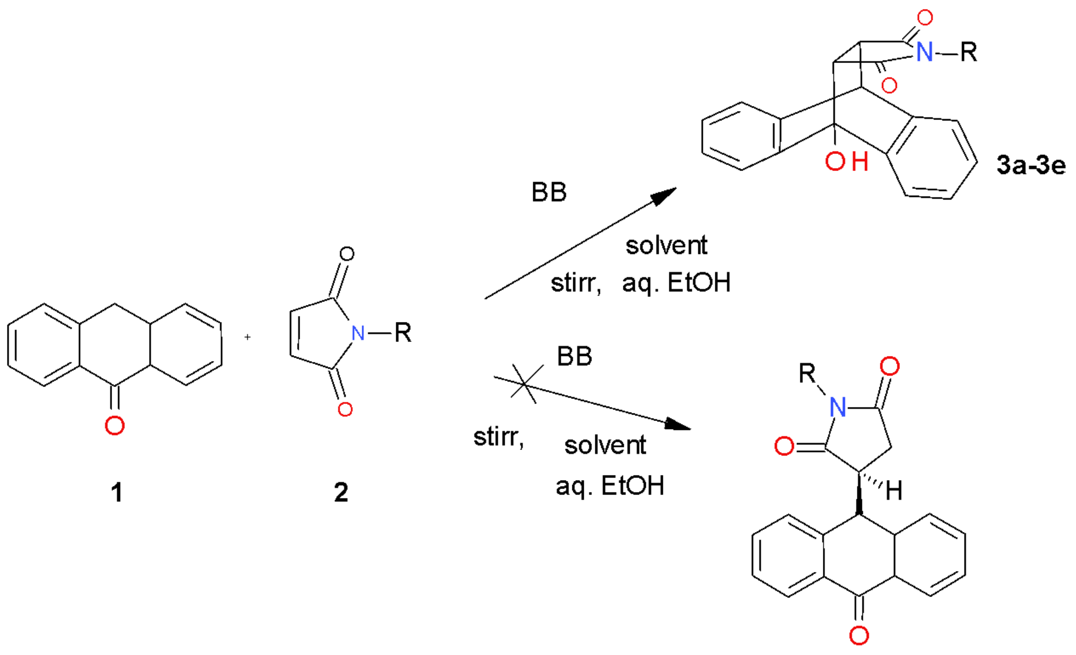
In recent times, there has been a major emphasis on the use of water or water-mixed solvents instead of conventional organic solvents to carry out various organic transformations.[1-4] There are many latent advantages of using water-mixed solvents such as environmentally benign protocol, safety, low cost and energy. In the view of this development,[4+2] cycloadditions have also been performed using water mixed protic solvents. Rickborn *et. al.*[5-7] studied base catalysed reaction between anthrone and maleimides in polar protic system. In the course of the reaction, the authors observed that initially major amount of Diels-Alder (D-A) adduct.[8-10] along with some minor amount of Michael adduct was formed. When the reaction was analyzed after several hours Michael adduct was the only product isolated, owing to the conversion of kinetically favored D-A adduct to thermodynamically favored Michael adduct.

Inspired by this observation, numerous synthetic protocols were developed for the formation of C-C and C-hetero bonds exploiting Michael reaction in aqueous media as a solvent. Both acidic and basic catalysis have been employed, using various nucleophiles ranging from neutral amines, alcohols, thiols and carbanions. Taking cue from these reports, we attempted enantioselective [4+2] cycloadditions between anthrone and maleimides, mediated by a chiral Bronsted base (BB) (**Scheme 1**). Contrary to the literature reports [5-7], the only product observed in our study was the D-A adduct reported herein.

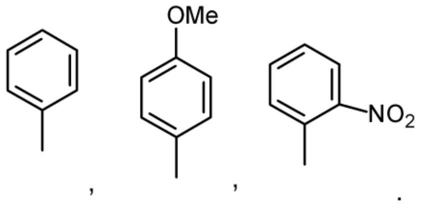
2. RESULTS AND DISCUSSION

In the earlier literature reports, rate enhancements in most of the [4+2] cycloadditions have frequently been observed using aqueous mixtures such as salt solutions or mixtures of water with an organic solvent[5-7], Accordingly, a well-organized and adaptable method of increasing the solubility of the reactants, which does not require any alteration of the solute is to use an organic co-solvent such as DMSO, lower alcohols or acetone with water. Hence, for the present study 50:50 mixture of water:ethanol system (volume:volume) was selected as a solvent of choice.

Conventionally, D-A reactions have been carried out using various achiral and chiral Bronsted bases in which the most challenging task is the selection of a chiral BB. Generally, this selection is based on the ease of preparation of the chiral BB, accessibility of the commonly available non-racemic precursors from the chiral pool and the cost factor.[8,10] Different nitrogen-containing compounds have been used for the preparation of new chiral BBs. The most prominent ones are, imidazoles, guanidines, amidines, and tertiary amines.[8-12] Prompted by the literature reports, we used chiral benzimidazoles as BB of choice. These could easily be prepared from an enantiomerically enriched α-hydroxy acid and *O*-phenylenediamine. We have used three different heterocyclic chiral bases, namely, (R, R)-(-)-Bis-benzimidazolyl-1,2-ethanediol; (S)-(-)-2-(α-hydroxyethyl)-benzimidazole[8], and (S)-(+)-2-(α-hydroxybenzyl)-benzimidazole in this study.[8-12] Typically, the reaction of 0.5 mmol of anthrone was performed using 0.5 mmol of maleimide in 20 mL aq. ethanol (50:50; v/v) **(Scheme 1).**



Where R=CH_3-, CH_3-CH_2-,



Scheme 1: Reaction between anthrone and maleimides.

After 15 minutes of reaction progress, an aliquot of the reaction mixture was taken out for reaction monitoring purpose and analyzed using proton NMR studies. The ^{1}H NMR clearly depicted the formation of D-A adducts at our hands and no Michael adduct was observed. Determining the ratio of D-A adduct to Michael adduct might be difficult using ^{1}H NMR and would result in erroneous predictions. Hence, it was thought to perform the highly sensitive chiral HPLC technique to estimate the correct amount of D-A or Michael adduct present, even in traces. Once the reaction started, the formation of the product was analysed using chiral HPLC, after 15 minutes (**Figure 1 B**). "We observed only two peaks in the HPLC chromatograms whose t_R were corresponding to the already reported D-A adduct obtained by the chiral base mediated cycloaddition reaction in $CHCl_3$ (**Figure 1 A**)."[8] The reaction procedded for an additional 16 hours and the reaction mixture was analysed by chiral HPLC (**Figure 1 C**) and ^{1}H NMR. Interestingly, we only observed an unexpected racemic D-A adduct instead of the desired Michael adduct following the present protocol.

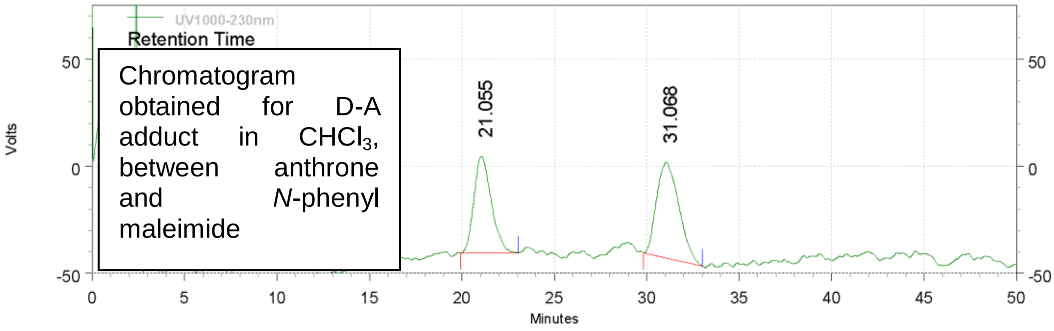


Figure 1 A

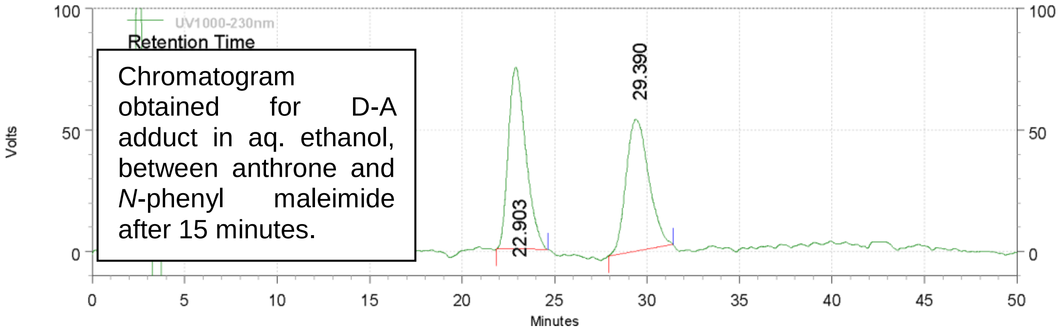


Figure 1 B

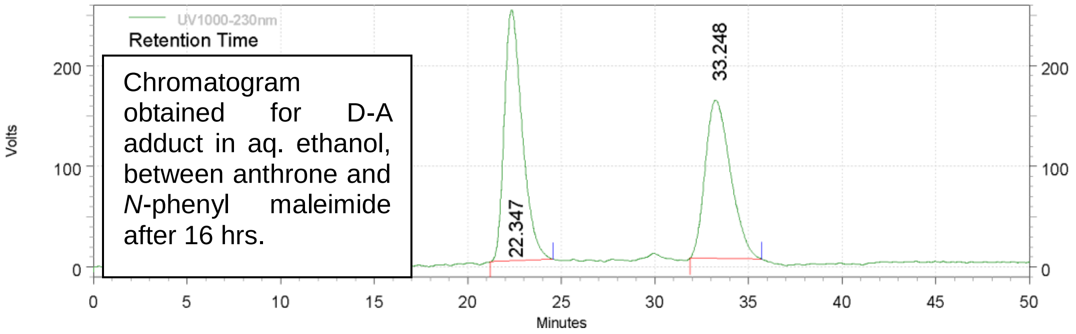


Figure 1 C.

Figure 1: The purity and %ee determined by chiral HPLC; Kromasil-5-cellucoat (4.6 mm i.d.x 250 mm); Mobile phase: hexane:2-propanol::75:25; temperature = 19 °C; UV detection at λ = 230 nm; flow rate = 1.2 ml/min.

Similar results were also obtained using various maleimides (**Scheme 1**) with anthrone in the presence of the chiral BB and all gave D-A adducts as the only product, at our hands.

It is assumed that the hydrogen bonding between water and the dienophile are responsible for the rate enhancement of the D-A reaction.

3. EXPERIMENTAL

General procedure and methods

“All other reagents and solvents are of commercial quality and are used as supplied without further purification, unless otherwise noted. Not all melting points are corrected. The temperatures are recorded in ^{0}C. The infrared spectra were recorded on a Shimadzu FTIR-4200 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 spectrometer (300 MHz). Chemical changes have been reported in parts per million (ppm). The residual solvent peak was used as an internal reference. purity was determined by HPLC analysis in UV1000 HPLC units from the Fisher thermo spectra system”.[8-10]

Typical procedure for the D-A reaction catalyzed by chiral base

Chiral base (R, R) - (-) - Bis-benzimidazolyl-1,2-ethanediol (15% mol), anthrone (194 mg, 1 mmol) and *N*-phenyl maleimide (110 mg, 1 mmol) were added sequentially to a 20 mL aqueous ethanol (1:1 v/v). As soon as room temperature stirring began, a white solid appeared and the reaction was monitored by TLC. After 15 minutes of stirring, an aliquot of the reaction mixture was withdrawn, acidified with HCl, then filtered and washed thoroughly with water. The same work up procedure was also performed after 16 hours of stirring. The products obtained at 15 minutes as well as 16 hours were the same and were characterized; the analytical data matched with the compounds reported.[5-10]

“4-Hydroxy-2-methyl-3a, 4, 9, 9a-tetrahydro-4, 9 [1’, 2’]-benzeno-1H- benz [f] isoindole-1, 3(2H)-dione” (3a):Yield: 0.145 g (96.03%), **melting point:** 218-220^{0}C, **IR (cm^{-1}, KBr):** ν 3413, 3067, 3042, 3007, 2949, 1688, **^{1}H NMR (CDCl$_3$, 300 MHz, ppm):** δ 2.51 (s, 3 H), 3.10 (d, 1H, J = 8.7Hz), 3.31 (dd, 1H, J = 3.6 Hz and 8.25Hz), 4.46 (s, 1H), 4.72 (d, 1H, J = 3.6Hz), 7.15-7.30 (m, 5H), 7.35 (dd, 1H, J = 0.9Hz and 7.2Hz), 7.47 (dd, 1H, J = 0.6Hz, 7.65Hz), 7.67 (dd, 1H, J = 0.6Hz and 7.2Hz), **^{13}C NMR (CDCl$_3$, 75 MHz, ppm):** δ 24.3, 44.5, 47.6, 50.8, 120.8, 120.8, 123.7, 124.4, 126.7, 126.8, 127.1, 127.2, 136.4, 138.9, 140.7, 142.4, 176.5, 176.9.

“4-Hydroxy-2-ethyl-3a, 4, 9, 9a-tetrahydro-4, 9[1’, 2’]-benzeno-1H-benz [f]isoindole-1, 3(2H)-dione” (3b): Yield: 0.148 g (95.07%), **melting point:** 213-215^{0}C,
“4-Hydroxy-2-phenyl-3a, 4, 9, 9a-tetrahydro-4, 9[1’, 2’]-benzeno-1*H*-benz [*f*]isoindole-1, 3(2*H*)-dione” (3c): Yield: 0.175 g (94.28%), **melting point:** 208-210^{0}C.
“4-Hydroxy-2-(4-methoxyphenyl)-3a, 4, 9, 9a-tetrahydro-4, 9[1’, 2’]-benzeno-1*H*-benz [*f*]isoindole-1, 3(2*H*)-dione” (3d): Yield: 0.190 g (95.71%), **melting point:** 250-252^{0}C.

"4-Hydroxy-2-(2-nitrophenyl)-3a, 4, 9, 9a-tetrahydro-4, 9[1', 2']-benzeno-1H-benz[f]isoindole-1, 3(2H)-dione" (3e): Yield: 0.200 g (97.09%) **melting point:** 255-257^{0}C, The IR, ^{1}H NMR and ^{13}C NMR values for **3b-3e** matches with the literature report.[5-10]

4. CONCLUSIONS

We report the formation of an unexpected Diels-Alder adduct instead of the Michael product under mild reaction conditions. The method reported can be used as a green reaction protocol for the formation of D-A adducts, which are typically carried out under harsh anhydrous conditions with numerous restrictions such as harmful organic solvents and tedious workup.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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