KIMIKA 17 (2) 71–74 (2001)
Printed in the Philippines

Aqueous Diels-Alder as an Alternative Approach to the Anthraquinone Backbone

Susan D.R. Arco*, Jonathan T. Miranda, and Ma. Edna B. Vitalicia

Institute of Chemistry
University of the Philippines
Diliman, Quezon City 1101, PHILIPPINES

Aqueous Diels-Alder conditions were used to effectively and efficiently synthesize some *tetra*hydroanthraquinones. Similar control reactions carried out in organic environments prove that aqueous media is more advantageous in terms of yield. Both sonication and thermal activation were implemented. Details of solvent and temperature optimization as well as derivatization method of the Diels-Alder adducts are also presented.

Keywords: aqueous Diels-Alder reaction; *tetra*hydroanthraquinone; anthraquinone; anthraquinone derivatives

INTRODUCTION

The Diels-Alder (DA) reaction is one of the most important methodologies of synthetic organic chemistry [1]. Its versatility and effectiveness make it the usual and preferred choice in the construction of six-membered and polycyclic ring systems [2]. The reaction is believed to occur via a concerted process wherein six π electrons are involved: the four π electrons come from the reactant called the diene and the other two π electrons come from the dienophile [3].

Thus, the DA reaction involves a diene-dienophile reactant system. The concertedness of the reaction implies a small change in the charge separation during the change from the initial state to the activated complex or transition state. This would mean that the rate of DA reactions are almost unaffected by the solvent [4]. However, independent studies of Grieco and Breslow involving DA reactions in aqueous media prove that water enhances the rate of reaction dramatically [5–8] and accelerations up to 13,000 compared to organic solvents have been achieved using water as a medium [9].

The enormous rate enhancing effect of water on DA reaction has obtained much attention and researchers have taken advantage of this effect in the synthesis of various novel compounds [10, 11] some natural products [12, 13] and some antifungal agents [1].

It has been found out that ultrasonic irradiation enhances the rate of DA reactions too. The use of ultrasonic irradiation to promote DA reactions has attracted chemists and the technique is undergoing continuous expansion [2]. In fact ultrasound promoted DA was successfully employed by some research groups [14].

The preceding discourse shows that indeed the Diels-Alder methodology has received much attention. In the light of these discoveries, we conducted our own research. Herein is presented our work that attempts to show that uncatalyzed DA reactions in aqueous media are feasible in synthesizing key intermediates toward anthraquinone dye precursors. The overall strategies are outlined in Figs. 1 and 2.

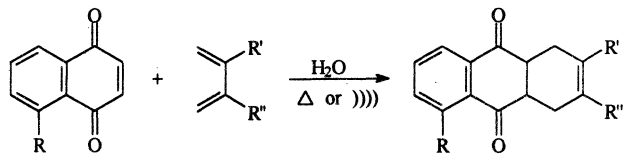


Fig. 1. General strategy employed for the uncatalyzed DA reaction to afford the tetrahydroanthraquinone adducts in water.

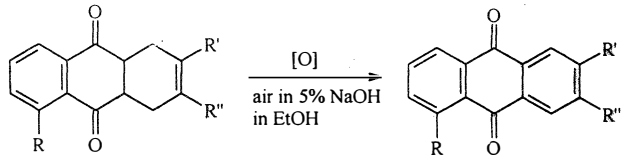


Fig. 2. Air oxidation of the adducts to afford the aromatized 9,10-anthraquinone backbone.

EXPERIMENTAL

General procedure. IR spectra were recorded on a Perkin Elmer 1330 spectrophotometer using KBr as reference. Ultraviolet-visible spectra were recorded in a Shimadzu UV/Vis spectrophotometer. NMR spectra were recorded using JEOL Lambda 400 NMR spectrometer. Chemical shifts are in ppm relative to TMS standard. Sonication was carried out using Branson 5200 ultrasonic bath cleaner. Reactions were monitored visually or by thin layer chromatography (TLC) using either UV illumination or by immersion in 10% H_2SO_4 in EtOH and warming on a hot plate. Uncorrected melting points were determined using Thomas Hoover or Fischer Johns Melting Point apparatus. The solvents used were either AR or HPLC grade. The water used was deionized distilled water. Isoprene (Across), 2,3-dimethylbutadiene (Across), pinacol (Across), and anthraquinone (Across) were used without further purification. Naphthoquinone (Across) was purified by sublimation with steam.

Aqueous Diels-Alder Reaction

2,3-Dimethyl-1,4,4a,9a-tetrahydroanthraquinone (R=H, R'=CH_3, R"=CH_3). A mixture of naphthoquinone (0.10 g, 0.6 mmol), 2,3-dimethylbutadiene (1 mL, 9.0 mmol) and 15 mL deionized distilled water was heated for 15 min at 80°C in an air-tight reaction vessel. The resulting mixture was cooled in a refrigerator for 12 h after which the white solid mass formed was filtered *in vacuo*. The white solid mass was then recrystallized in ethanol to afford the product (98%) as white crystals; mp 147-149°C; λ_{max} UV/Vis: EtOH 293, 252 and 223 nm; IR (pellet): 3610 (w), 3490 (w), 3395 (w), 3360 (w), 3320, 3300, 1945, 1900, 1655 (s), 1600, 1530, 1320, 1140, 895, 850, 810, 605, 415; ^{1}H NMR (*acetone*-D_6): 7.993 (dddd, *J*=5.6, 3.2, 1.6 Hz, 2H, 5-H and 8-H), 7.843 (dddd, *J*=5.6, 3.2, 1.6 Hz, 2H, 6-H and 7-H), 2.394 (dt, 2H, 1-H and 4-H or 1'-H and 4'-H), 2.112 (dt, 2H, 1-H and 4-H or 1'-H and 4'-H), 2.054 (m, 2H, 4a-H and 9a-H), 1.628 (s, 6H, 2-CH_3 and 3-CH_3).

2-Methyl-1,4,4a,9a-tetrahydroanthraquinone (R=H, R'=CH_3, R"=H). A 20 mL vial was charged with naphthoquinone (70 mg, 0.44 mmol) and 15 mL water. After flushing with nitrogen for several seconds, isoprene (0.70 mL, 7.0 mmol) was hastily introduced and the vial was immediately capped. After ultrasonic irradiation for 8 hours at an average temperature of 45°C, the resulting emulsion was allowed to settle. The excess unreacted isoprene was evaporated and the mixture was extracted with ether (2 × 10 mL). The combined ether extracts were dried ($MgSO_4$) and the solvent evaporated. The very slightly yellow residue was chromatographed (10 g silica gel; eluent, 2:1 Pet Ether-EtOAc) affording the product (94%) as white short needles; mp 76–77°C; λ_{max} UV/Vis: EtOH 303, 297, 251 and 222 nm; IR (pellet): 3390 (w), 3090 (w), 3040, 2990, 2930, 2900, 2860, 2840, 1695 (s), 1605, 1465, 1297, 1262, 1090, 980, 933, 800, 773, 743, 720; ^{1}H NMR ($CDCl_3$): 8.000 (dddd, *J*=7.6, 3.2, 0.9 Hz, 2H, 5-H and 8-H), 7.891 (dddd, *J*=7.6, 3.2, 0.9 Hz, 2H, 6-H and 7-H), 5.409 (m, 1H, 3-H), 3.514 (m, 1H, 4a-H), 3.405 (m, 1H, 9a-H), 2.430 (m, 2H, 4-H and 4'-H), 2.384 (m, 2H, 1-H and 1'-H), 1.673 (s, 3H, 2-CH_3).

Aromatization of Adducts

Typical Procedure. A 50 mL three-necked flask equipped with a reflux condenser and inlet tube were charged with 50 mg of adduct, 25 mL 95% ethanol and 5 mL 1 M KOH solution. The resulting greenish solution was bubbled with air for 24 h after which 75 mL of water was added. The yellow anthraquinone thus formed was filtered and washed with 10 mL water, then with 1 mL ethanol and finally with 0.5 mL ether.

2,3-Dimethylanthraquinone (R=H, R'=CH_3, R"=CH_3); (96%); mp 209-210°C; λ_{max} UV/Vis: EtOH 329.6, 259.6 and 204.6 nm; IR (pellet): 3080, 3075, 2940, 2915, 2875, 1680, 1605, 1340, 1305, 1237, 965, 710, 620; ^{1}H NMR ($CDCl_3$): 8.272 (dddd, *J*=5.6, 3.6, 0.8 Hz, 2H, 5-H and 8-H), 8.022 (dddd, *J*=5.6, 3.6, 0.8 Hz, 2H, 6-H and 7-H), 7.764 (s, 2H, 1-H and 4-H), 2.421(s, 6H, 2-CH_3 and 3-CH_3).

2-Methylanthraquinone (R=H, R'=CH_3, R"=H); (96%); mp 182-183°C; λ_{max} UV/Vis: EtOH 327.6, 274.6, 256.2, 205.4 nm; IR (pellet): 3320, 3080, 3040, 2940, 2920, 1680, 1600, 1335, 1300, 1275, 980, 940, 855, 710, 642, 528, 395; ^{1}H NMR ($CDCl_3$): 8.308 (dddd, *J*=5.8, 2.8, 2.0 Hz, 2H, 5-H and 8-H), 7.792 (dddd, *J*=5.8, 2.8, 2 Hz, 2H, 6-H and 7-H), 8.212 (d, *J*=8.0 Hz, 1H, 3-H), 8.109 (d, *J*=1.3.Hz, 1H, 1-H), 7.601 (dd, *J*=8.0, 1.3 Hz, 1H, 4-H), 2 541(s, 3H, 2-CH_3).

RESULTS AND DISCUSSION

Neat reactions (no solvent) carried out for the isoprene-naphthoquinone system proved to be low yielding. It was observed that decomposition of either reactants occurred during the trial run. This was indicated by the coloration of the mixture as the temperature was increased (*i.e.*, greater than 80°C). At a lower temperature (below 80°C) however, coloration of the mixture was minimal. This diene-dienophile system afforded a pinkish crude product after 4 h. TLC analysis reveals approximately 80% yield of product.

A similar neat reaction run for the 2,3-dimethylbutadiene-naphthoquinone system was conducted during the optimization process. This reaction system was observed to be entirely different from the isoprene-naphthoquinone system. Here, no coloration was observed and the reaction proceeded smoothly at 80°C to afford nearly pure product within 2 h.

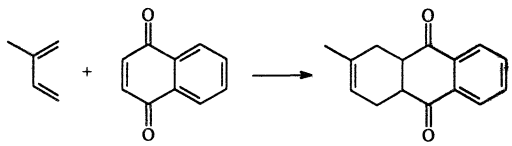
These significant observed differences in reactivities of the two dienes may be attributed to the electron-releasing capacity of the diene substituents. The two methyl groups of 2,3-dimethylbutadiene impart a more electron-releasing effect compared to only one methyl group of isoprene.

Bearing the above observations and consideration in mind, we proceeded in noting the effects of organic solvents (*e.g.*, ethanol and xylene) in the promotion of DA reaction. For isoprene-naphthoquinone system, little or no product at all formed at 80°C for 1.5-h reaction time using ethanol as solvent. On the other hand, minimal coloration of the mixture was observed. The same trend was observed for the reactions with xylene as reaction solvent (Fig. 3).

For the 2,3-dimethylbutadiene-naphthoquinone system, product formation occurred at 80°C after 40 min using ethanol as solvent. However, TLC analysis of the mixture showed that the reaction was not yet complete. This was obvious by visual inspection of the reaction mixture. Xylene as a solvent also promoted the DA reaction of 2,3-dimethylbutadiene-naphthoquinone system although the result was not as good as that with ethanol (Fig. 4).

When we investigated for the effect of water, the results were unprecedented. For both diene-dienophile systems the reaction time was dramatically decreased. We then proceeded in optimizing the following reaction conditions: temperature and amount of water. Based from our previous runs, we set the temperature at 80°C. Since this was observed to be the marginal temperature wherein coloration of reaction mixture begins.

The results of the optimized experiments are found in the experimental section. One of the most dramatic observations in our synthesis was the significant reduction of reaction time



Solvent	Reaction Temp.	Conditions Time	Yield
EtOH	80°C	1.5 h	traces
Xylene	80°C	1.5 h	traces
H_2O	80°C	1.5 h	50%
H_2O	)))) at 45°C	8 h	94%
Neat	80°C	1.5 h	traces

Fig. 3. DA reaction of isoprene-naphthoquinone at different solvents.

when the amount of water was increased. We found out that as we increased the volume of water from 5 mL to 15 mL, the time it took for the reaction of 2,3-dimethylbutadiene-naphthoquinone system to complete was only 15 minutes at 80°C. Not only was the reaction time shorter but also the purity of the product was high as revealed by the product's TLC profile (Table 1).

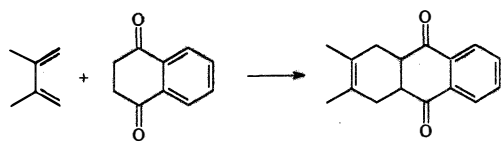
For the isoprene-naphthoquinone system, although increasing the amount of water reduced the reaction time, the effect was not entirely significant. Furthermore, the formation of the pinkish contaminant was not lessened. This contaminant was deemed to be a major factor in the success of the synthesis and we decided to seek an alternative method.

In the light of this consideration we decided to use ultrasonication. It has been found out that the enhancing capability of ultrasound is based on cavitation. Cavitation is the creation of bubbles in a liquid medium, which then collapse, with the liberation of considerable energy. The implosion of the ultrasound generated cavities results in a loci of high pressures (up to 1000 atm) and high temperatures (up to 5000 K). The reputed high pressures induced by ultrasonication could be responsible for the enhanced reactivity [14].

After careful experimentation we found that the time of reaction depended on the amount of water. We had tried the following amounts of water: 1, 2, 3, 5, 10, 15, 20, and 25 mL while keeping the amount of the reactants constant (vide infra). It turned out that the optimum amount of water was 15

Table 1. Effect of volume of water on reaction time for the DA reaction of 2,3-dimethylbutadiene-naphthoquinone system.

Volume of Water (mL)	*Reaction Time* (min)
5	70
10	40
15	15
20	95
25	150 (traces)



Solvent	Reaction Temp.	Conditions Time	Yield
EtOH	80°C	40 min	80%
Xylene	80°C	40 min	50%
H_2O	80°C	40 min	98%
Neat	80°C	2 h	98%

Fig. 4. DA reaction of 2,3-dimethylbutadiene-naphthoquinone at different solvents.

mL. For this particular reaction system, although the reaction time was 8 h, the formation of the pinkish contaminant was eliminated. With the optimized conditions, we then proceeded in synthesizing the *tetra*hydroanthraquinones.

The aromatization of the tetrahydroanthraquinone adducts was quite straightforward. The usual method for dehydrogenating tetrahydroanthraquinones is by air oxidation in 5% ethanolic KOH solution. We had modified the literature procedure by dissolving instead the adduct in ethanol followed by the addition of KOH solution in water. This was done because we found out that the solubility of the adduct is much greater in pure ethanol that in ethanolic KOH solution. Likewise it was much easier to prepare aqueous 1 M KOH that 5% ethanolic KOH. The effectiveness of the revised procedure was quite general that we had used it in generating both the aromatized products.

CONCLUSION

Tetrahydroanthraquinones can be conveniently prepared by the Diels-Alder approach of appropriate diene-dienophile system utilizing water as a reaction medium. Comparison of aqueous DA with those carried out in conventional organic solvents proves that water indeed is a potent medium in the synthesis of anthraquinone dye intermediates since our method afforded high yields of products and of high purity.

ACKNOWLEDGMENT

We thank the Natural Sciences Research Institute (NSRI) of the University of the Philippines, Diliman for funding this research project. We also would like to thank Mr. Marte Villena and Mang Nick for their technical assistance.

REFERENCES

1. Chao, J. L. *Chem. Rev.* 93, 2023 (1993).
2. Pindur, U., Lutz, G., and Otto, C. *Chem. Rev.* 93, 741 (1993).
3. Sauer, J. and Sustmann, R. *Angew. Chem.* (Int. Ed. Engl.). 19, 779 (1980).
4. Otto, S., Bertoncin, F., and Engberts, J. B. F. N. J. *J. Am. Chem. Soc.* 118, 7702 (1996).
5. Rideout, D. C. and Breslow, R. J. *J. Am. Chem. Soc.* 102, 7816 (1980).
6. Grieco, P. A., Yoshida, K., and Garner, P. *J. Org. Chem.* 48, 3137 (1983).
7. Breslow, R. *Acc. Chem. Res.* 24, 159 (1991).
8. Larsen, S. D. and Grieco, P. A. *J. Am. Chem. Soc.* 107, 1768 (1985).
9. Fringuelli, F. and Taticchi, A. *Dienes in the Diels-Alder Reaction.* pp. 1–10 (Wiley, New York, 1990).
10. Lubineau, A. and Queneau, Y. *J. Org. Chem.* 52, 1001 (1987).
11. Lubineau, A. and Queneau, Y. *Tetrahedron Lett.* 26, 2653 (1985).
12. Williams, D. R., Gaston, R. D., and Horton, I. B. *Tetrahedron Lett.* 26, 1391 (1985).
13. Lubineau, A., Auge, J., and Lubin, N. *Tetrahedron Lett.* 32, 7529 (1991).
14. Lee, J. and Snyder, J. K. *J. Am. Chem. Soc.*111, 1522 (1989).