Generation and Cycloaddition of o-Quinodimethane in Aqueous Medium

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Received: 9 March 2001; in revised form 24 April 2001 / Accepted: 24 April 2001 / Published: 30 April 2001

Abstract: o-Quinodimethane can be generated from $\alpha,\alpha'$-dihalo-o-xylenes using zinc in aqueous solution. In the presence of activated dienophiles cycloadducts can be obtained directly. Catalysis with tris-triphenylphosphine ruthenium(II) dichloride reduces side reactions such as reduction and polymerisation and improves the yield. This is the first example of an organometallic cyclisation in aqueous medium using dihalo compounds.

Keywords: Dehalogenation, zinc, Diels-Alder reaction, Ru catalysis, aqueous solvent

Introduction

o-Quinodimethanes (o-xylylenes) are reactive intermediates widely used for the synthesis of polycyclic compounds via inter- or intramolecular Diels-Alder reactions [1]. Because of their high reactivity and thermal instability they must be generated in situ by various methods: dehalogenation of $\alpha,\alpha'$-dihalo-o-xylenes, thermal or photochemical extrusion of stable molecules or ring opening of benzocyclobutenes. The unsubstituted parent compound, generated at low temperature, has been proven to exist in a singlet ground state [2]. To our knowledge, all synthetic or mechanistic work in
this field has been performed in organic solvents under anhydrous conditions. Recent progress in aqueous Diels-Alder cycloadditions and organometallic reactions [3], especially the successful Wurtz coupling of benzylic halides [4] and their Barbier addition to carbonyl compounds [5], prompted us to study the behaviour of \( \alpha,\alpha'-\text{dihalo-o-xylene} \) (1) under similar conditions in the hope to obtain benzocyclobutene (2) or, in the presence of dienophiles, cycloadducts of o-quinodimethane.

**Results and Discussion**

The reaction of the dibromo compound 1a with zinc dust in saturated aqueous ammonium chloride was complete in a few minutes at r.t. and produced a polymeric material 3 containing 67 % of C-C coupled methylene groups and 28 % of methyl groups as a result of reduction; only trace amounts of o-xylene and dimeric or trimeric coupling products, but no 2 at all could be detected by GC/MS (Table 1, entry 1). These results agree rather well with those obtained by Alder under anhydrous conditions in DMF [6]. The reaction of the dichloride 1b was much slower (1 h), but gave a very similar product composition (entry 2). Use of metal catalysts such as CuCl, CuI, AgNO₃ and Pb(OAc)₂, which had an important influence on the reactivity of benzylic monohalides [4], brought no significant change.

More promising results were obtained in the presence of dimethyl fumarate (solubilized with CH₃CN): 22 % of the trans-cycloadduct 6 was produced with the dibromide and 53 % with the dichloride. In both cases, polymerisation to 3 and reduction of the dienophile to dimethyl succinate were important side reactions (entries 3 and 4). In an attempt to obtain a cleaner reaction and better yield, different temperatures, acidic, neutral and basic salt solutions and several water soluble or unsoluble cosolvents were tried without positive results. Other metals were also tested in different solvent systems: Mg, Al, Mn and Ti gave no cycloadduct at all and In, Sn, Fe and Bi produced only modest yields (15 -30 %). Similarly, 15 different transition metal ions and the triphenylphosphine complexes of Ni, Pd and Ru were examined as catalysts in the Zn-promoted reaction. Cu and Fe were found to increase the amount of the polymer 3 and Co, Ni, Pd and Au catalyzed the reduction of 1b. The only improvement of the cycloaddition reaction was observed with tris-triphenylphosphine ruthenium(II) dichloride; using 5 mg of this catalyst, the yield of 6 raised to 40 % for the dibromide and 84 % for the dichloride (entries 5 and 6); in the latter case, all side reactions were reduced to a
few percent. The use of the preformed catalyst was essential, because addition of ruthenium(III) chloride and triphenylphosphine had no effect (entry 7).

Table 1. Reactions of α,α'-dihalo-o-xylenes (1) and zinc in aqueous mediuma

| Entry | X  | Salt    | Dienophile         | Cosolvent | Catalyst              | Coupling | Reduction | 6  | 7  |
|-------|----|---------|---------------------|-----------|-----------------------|----------|-----------|----|----|
| 1     | Br | NH₄Cl   | -                   | -         | -                     | 65       | 28        | -  | -  |
| 2     | Cl | NH₄Cl   | -                   | -         | -                     | 62       | 25        | -  | -  |
| 3     | Br | NH₄Cl   | Dimethyl fumarate   | MeCN      | -                     | 70       | 4         | 22 | 22 |
| 4     | Cl | NH₄Cl   | Dimethyl fumarate   | MeCN      | -                     | 10       | 36        | 53 | 15 |
| 5     | Br | NH₄Cl   | Dimethyl fumarate   | MeCN      | Ru(PPh₃)₃Cl₂          | 52       | 8         | 40 | 8  |
| 6     | Cl | NH₄Cl   | Dimethyl fumarate   | MeCN      | Ru(PPh₃)₃Cl₂          | 5        | 10        | 84 | 7  |
| 7     | Cl | NH₄Cl   | Dimethyl fumarate   | MeCN      | RuCl₃ + PPh₃c         | 15       | 12        | 48 | 10 |
| 8     | Cl | K₃PO₄   | Methyl acrylate     | MeCN      | Ru(PPh₃)₃Cl₂          | 3        | 12        | 85 | -  |
| 9     | Cl | K₃PO₄   | Acrylonitrile       | MeCN      | Ru(PPh₃)₃Cl₂          | 4        | 13        | 86 | -  |
| 10    | Cl | K₃PO₄   | Methyl vinyl ketone | MeCN      | Ru(PPh₃)₃Cl₂          | 3        | 5         | 92 | 1  |
| 11    | Cl | NH₄Cl   | Dimethyl maleate    | MeCN      | Ru(PPh₃)₃Cl₂          | 46       | 16        | 37 | 5  |
| 12    | Cl | NH₄F    | Methyl crotonate    | -         | Ru(PPh₃)₃Cl₂          | 60       | 5         | 33 | -  |

a General procedure: see Experimental.

b Determined by ¹H-NMR.

c 2 mg of each were employed.

In the following experiments, the dichloride was reacted under standard conditions with other types of dienophiles. Electron deficient terminal olefins such as methyl acrylate, acrylonitrile and methyl vinyl ketone gave even higher yields of cycloaddition when basic conditions were employed to prevent polymerisation (entries 8-10). Somewhat surprisingly, dimethyl maleate produced only 37 % of pure cis-substituted cycloadduct (entry 11), probably due to a less favorable overlap in the endo transition state; in a competition experiment using a mixture of dimethyl fumarate and maleate (1 eq. of each), only the former reacted and produced trans-cycloadduct 6. Methyl crotonate was also less reactive, giving the same 33 % yield in the presence or absence of catalyst, and unactivated olefins like 1-heptene, styrene and cyclohexene did not react at all. The observed differences in the reactivity agree with those found in previously reported demetalating reactions [6-8]. However, the aqueous procedure gives much better yields than the electrochemical generation [7], uses unexpensive starting materials, is experimentally simple and avoids the use of DMF, a solvent which is toxic and difficult to dry.

From the mechanistic point of view, the effect of the ruthenium complex is remarkable but not surprising. Indeed, stable o-xyylene complexes of type 5 bearing aryldialkylphosphine ligands have
been synthesized and characterized by x-ray analysis [9]. Furthermore, oxidative decomposition of the exo-complex in the presence of dimethyl acetylenedicarboxylate has produced a cycloadduct in very low yield [10]. This cycloaddition under oxidative conditions and the inexistence of a stable, isolated complex with triphenylphosphine ligands suggest a similar, but less stable intermediate in our reaction, probably in equilibrium with the free o-quinodimethane 4 (scheme 1). The complexation may prevent the polymerisation of 4, increasing thus its lifetime. Highly reactive dienophiles probably react rapidly with the complex 5 or with free 4. Less reactive olefins need free 4 and have to compete with the polymerisation reaction; for this reason no improvement is observed in the presence of the catalyst. Benzocyclobutene (2) can be excluded as a possible intermediate because it was recovered unchanged in control experiments in the presence or absence of catalyst.

Conclusions

In conclusion, the generation of o-quinodimethane (4) in aqueous medium is a very simple and high yielding alternative for intermolecular cycloadditions to activated dienophiles, especially when catalyzed by the ruthenium complex. The reaction represents the first example of a one-step cyclisation using dihalo compounds and zinc in aqueous medium.

Acknowledgements

This work was supported by CNPq (Brasilia). We thank Ms. Érida M.A. Pequeno for GC/MS analyses.
Experimental

General

In all experiments commercially available reagents and solvents were used without further purification or activation. The cycloadducts obtained in preparative yields (entries 6, 8-10) showed physical and spectroscopic properties in perfect agreement with previously reported data [6-8, 11].

Reaction of α,α'-dihalo-o-xylene (1) with zinc in the presence or absence of dienophiles

To 2 mL of saturated aqueous salt solution (see Table 1) a mixture of 1 (0.5 mmol), dienophile (0.6 mmol), catalyst (5 mg) and 0.5 mL of CH₃CN was added at r.t. Under vigorous stirring zinc dust (1.0 mmol) was added portionwise over a period of 10 min. After 1h, the mixture was hydrolysed with 2 N HCl, extracted with 1 mL of CCl₄ containing 0.05 mmol of cyclohexane as internal quantitative reference. The crude extracts were analysed by ¹H-NMR and GC/MS. In preparative runs, the products were purified by CC and crystallisation.

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Samples Availability: Not available.

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