Novel cycloaddition reactions of o-benzoquinones and related chemistry[+]

VIJAY NAIR*, SASI KUMAR, GOPINATHAN ANILKUMAR,
G ANILKUMAR, K V RADHAKRISHNAN, J SOMARAJAN NAIR,
DAVIS MALIAKAL, K C SHEELA, BINI MATHEW,
P M TREESA, A U VINOD, JAYA PRABHAKARAN,
V SHEEBA and ABRAHAM THOMAS
Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum
695019, India
e-mail: gvn@csrrltrd. ren.nic.in

Abstract. o-Benzoquinone is a unique conjugated 1,2-dione that can exhibit diverse cycloaddition modes, participating either as carbodiene, heterodiene, dienophile or heterodienophile. With electron-rich dienes, benzodioxins are formed in excellent yields. Pentafulvenes including 6-vinylfulvenes normally give rise to bicyclo[2.2.2] adducts. Exceptions are observed with cycloalkylfulvenes where the fulvenes undergo rearrangement to cyclopentadiene derivatives prior to cycloaddition, resulting in benzodioxins. o-Benzoquinones participate as dipolarophiles on treatment with nitrile oxides and carbonyl ylides yielding highly oxygenated novel spiro compounds. Triphenylphosphine catalyzed addition of DMAD to o-benzoquinones afforded another class of novel spirolactones. The bicyclo[2.2.2] octene diones derived from o-benzoquinones undergo a number of synthetically useful transformations.

Keywords. o-Benzoquinones; cycloaddition reactions; benzodioxins; bicyclo [2.2.2]octene diones.
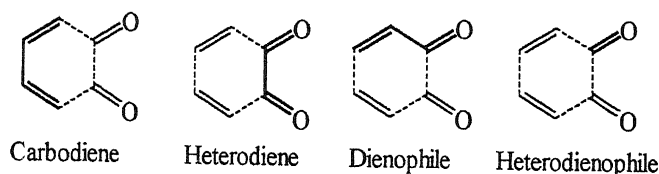
1. Introduction

Quinones are important organic compounds endowed with rich and fascinating chemistry, many of them being valuable therapeutic agents. They are versatile intermediates in organic synthesis and in the dye industry and they play a vital role in electron transport in the respiratory and photosynthetic elements of biological systems as well as a number of redox processes in Nature [1,2]. The Diels-Alder reaction involving quinones has been the subject of extensive investigations, largely due to the potential offered by such reactions in natural products syntheses [3]. Much of this cycloaddition chemistry has centred around p-quinones. In contrast, however, the reactivity profile of o-quinones has received only marginal attention presumably due to the instability and inaccessibility of these compounds. Not surprisingly, a large amount of the cycloaddition chemistry of o-quinones has involved the readily available and

stable *o*-chloranil and *o*-bromanil. Potentially *o*-quinones can serve as carbodienes, heterodienes and dienophiles; the following representations of *o*-benzoquinone

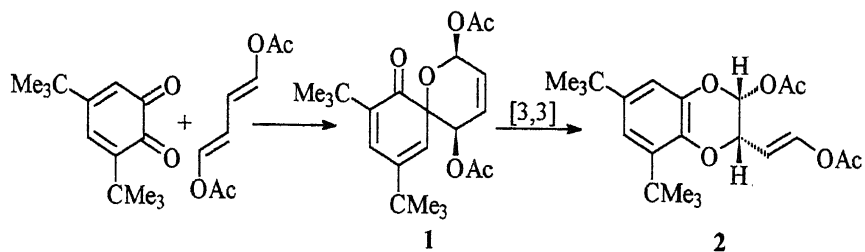Carbodiene   Heterodiene   Dienophile   Heterodienophile

Scheme 1.

emphasize its propensity for different modes of cycloaddition (scheme 1).

Although there are isolated reports on the diverse reactivity patterns of *o*-quinones, there has been no systematic investigations in this area. Therefore we have thoroughly investigated the cycloadditions and related chemistry of *o*-quinones. These studies have uncovered much novel chemistry and the results are highlighted in this review against a historical background.

2. Reactions of *o*-benzoquinones with acyclic dienes and trienes
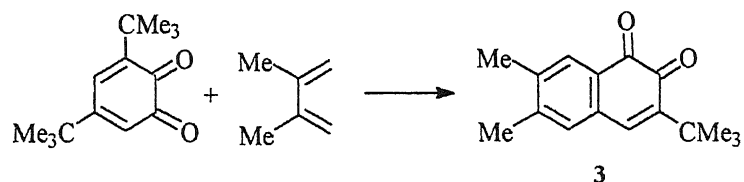
Diels-Alder reactions of acyclic dienes with *o*-benzoquinone and mono-, di-, and tri-substituted *o*-benzoquinones have been studied by Ansell and his co-workers[4]. In these reactions the quinone always functions as a dienophile with the addition occurring preferentially to the more electron deficient C=C bond. The reactions of monomethyl-, methoxy-, chloro- and acetamido-*o*-benzoquinones were comparable to those of benzoquinone itself; in all cases addition occurred at the less hindered double bond. During the course of his work on the synthesis of various elemanolide sesquiter-penoids, Danishefsky has observed some unusual solvent effects in the cycloaddition process involving *o*-quinones and acyclic dienes[5]. The synthesis of quassinoid skeleton employing cycloaddition strategy based on *o*-quinones has been reported by Weller and coworkers[6]. The dienophilic activity of *o*-benzoquinones has been utilised in the asymmetric synthesis of tanshindiol[7].

We found that electron-rich dienes undergo hetero Diels–Alder reaction with substituted *o*-benzoquinones to give benzodioxin adducts[8,9]. The reaction proceeds by a two-step mechanism; the initial [4 + 2] adduct **1** is positioned for [3,3] sigmatropic rearrangement leading to the benzodioxin **2**.
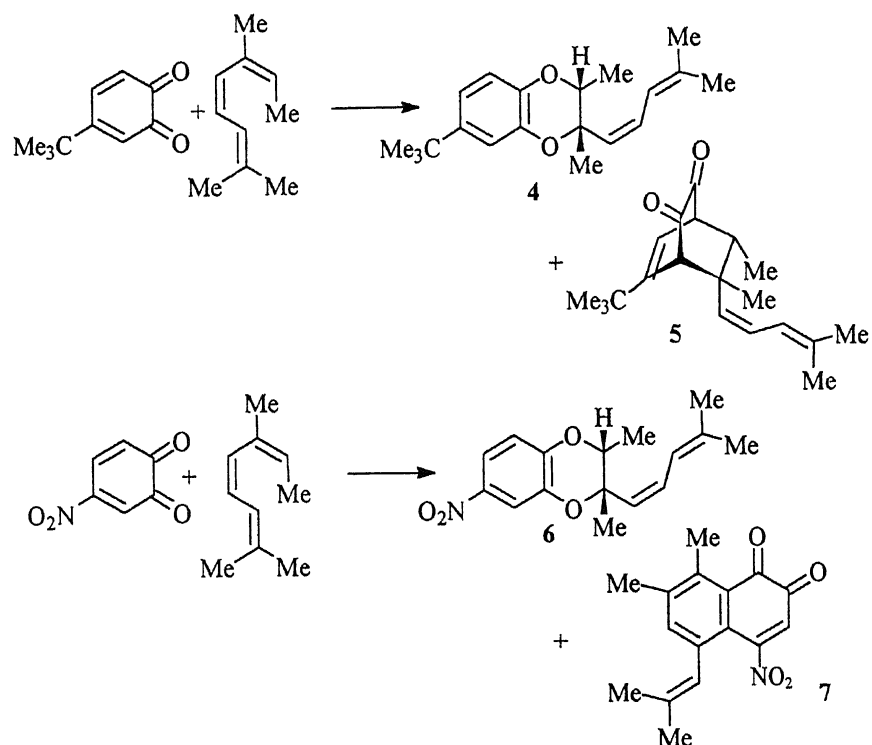

Scheme 2.

2,3-Dimethylbutadiene, however, undergoes normal Diels-Alder reaction leading to naphthoquinones, presumably by the aromatization of the primary adducts.

Scheme 3.

4-*tert*-butyl- and 4-nitro-*o*-benzoquinones afforded two types of products on reaction with alloocimene.
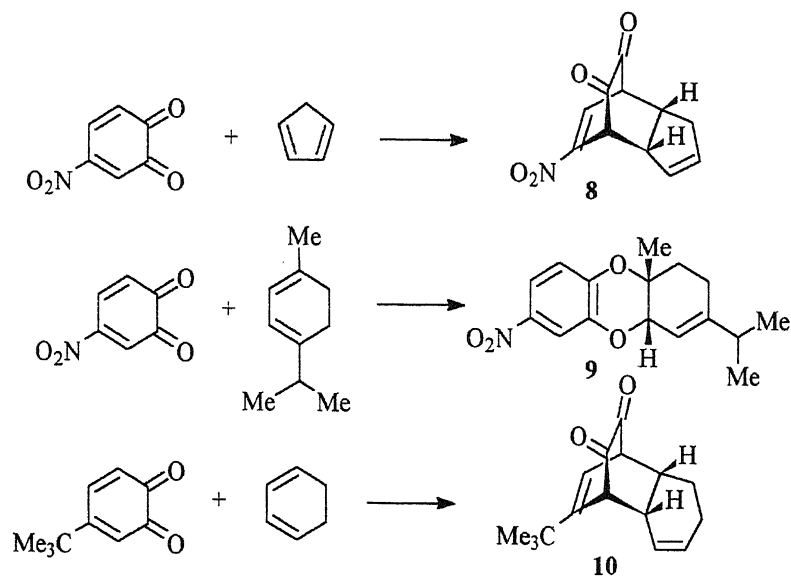

Scheme 4.

3. Reactions of *o*-benzoquinones with carbocyclic dienes

Diels-Alder reactions, between a number of alkyl-, aryl-, alkoxy and chloro substituted *o*-benzoquinones and cyclopentadiene are reported. The quinone reacts both as diene and dienophile and the interconversion of the two types of products *via* a Cope rearrangement has been discussed. Cycloaddition to *o*-benzoquinones bearing strong electron withdrawing substituents in the 3 or 4 position has been reported to occur at the more electron deficient olefinic bond[10]. *o*-Chloranil reacts with tetracyclone to

yield a cyclopenta[b][1,4] benzodioxin whereas *o*-benzoquinone itself afforded the ethanoindene trione along with the benzodioxin [11].

For the first time we have observed that 4-nitro-*o*-benzoquinone undergoes two different modes of cycloaddition with cyclopentadiene and α-terpinene; the quinone participates as a carbodiene with cyclopentadiene whereas it functions as a heterodiene with α-terpinene [12]. The bicyclo[2.2.2] octene dione adduct was isolated from the reaction of 4-*tert*-butyl-*o*-benzoquinone with cyclohexadiene.
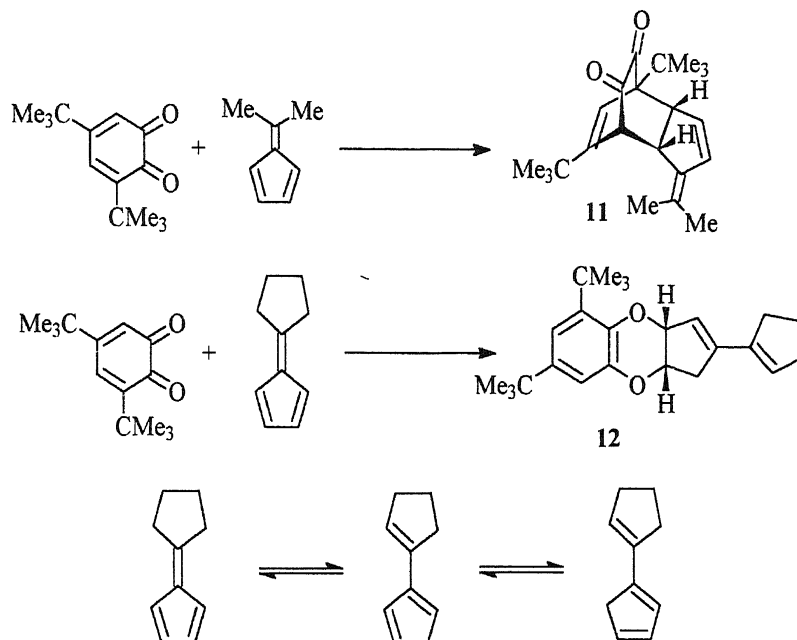

Scheme 5.

4. Cycloaddition reactions of *o*-benzoquinones with pentafulvenes

The cycloadditions of *o*-quinones and fulvenes present a very interesting situation. In such cases, either the quinone or the fulvene can function as the diene or the dienophile. In addition, such systems offer the prospect of higher order cycloadditions. Friedrichsen has shown that simple *o*-benzoquinone and methyl substituted *o*-benzoquinones react with symmetric fulvenes to give the dicarbonyl compounds. *o*-Chloranil reacts with 6,6-diphenyl- and 6,6-*bis*(p-methoxy)phenyl fulvene forming [4 + 4] cycloadducts of the benzodioxin type [13]. The reaction of 6,6-dimethylfulvene with *o*-chloranil, however, afforded a mixture of the [6 + 4] adduct along with the dimeric product, the latter presumably arising from a second [4 + 2]cycloaddition to the primary adduct. Similar results were obtained in the cycloaddition of *o*-chloranil with 6,6-pentamethylene-fulvene [14].
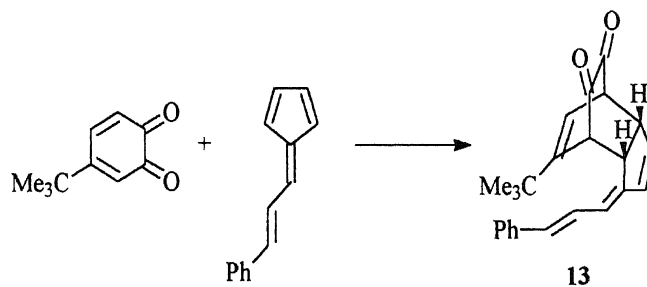
Our investigations have uncovered remarkable reactivity differences in the cycloaddition reaction of fulvenes with *o*-benzoquinones [15-18]. 6,6-Dialkyl substituted fulvenes afforded the bicyclo[2.2.2] adducts with sterically hindered *o*-benzoquinones. The reaction of *o*-quinone with 6,6-tetramethylenefulvene, however, afforded a novel product, the structure of which was found to be **12** from spectral data and ultimately by single crystal X-ray determination.

Scheme 6.

The formation of benzodioxin adduct can be best explained by invoking the isomerization of 6,6-tetramethylenefulvene to the cyclopent-1-enyl cyclopentadiene. The latter then undergoes cycloaddition to the quinone to afford the product. The MMX calculations showed that there is a difference in the heat of formation to the tune of 4·9 kcal/mole between the fulvene and the cyclopent-1-enyl cyclopentadiene. The heat of formation as well as the MMX energy is higher for the unisomerized fulvene. It may be recalled that a similar reactivity pattern was observed with the acylic triene-*trans, trans*-2,6-dimethyl-2,4,6-octatriene (alloocimene). The same reactivity profile was displayed by 4-*tert*-butyl-*o*-benzoquinone. Although we favour the mechanistic rationale given for the formation of the benzodioxin adducts, a stepwise addition mechanism also cannot be ruled out. Other fulvenes like 6-phenyl-, 6-methoxy phenyl-, 6-methyl-6-phenyl-, 6,6-diphenyl-, 6-furyl etc. afforded the bicyclo[2.2.2] adducts in high yields.
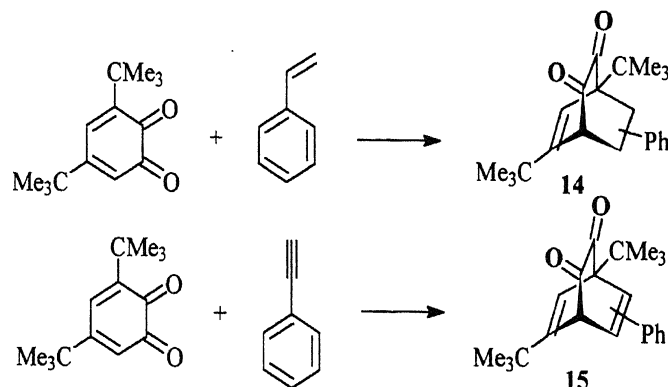
Reactions of *o*-benzoquinones with 6-vinyl fulvenes afforded exclusively the bicyclo[2.2.2]octenediones[19]. An example is given in the following scheme.

Scheme 7.

5. Reactions of *o*-benzoquinones with styrenes and alkynes

o-Benzoquinones participated as carbodienes in their reaction with styrenes and acetylenes yielding bicyclo [2.2.2] adducts. In all cases, mixture of two regioisomers were obtained [20]. Examples are given in the following scheme.
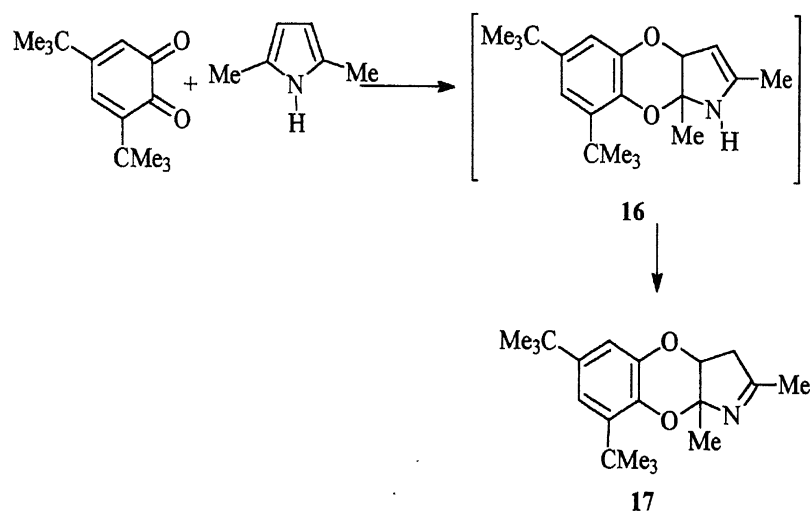
Scheme 8.

6. Reactions of *o*-benzoquinones with heterocyclic dienes

The cycloadditions of *o*-chloranil and *o*-bromanil with furans and isobenzofuran have been reported in detail [21]. *o*-Chloranil gave a dihydrobenzodioxin adduct on treatment with furan in boiling benzene. Similar dihydrobenzodioxin adducts were obtained by reaction between *o*-chloranil and a number of substituted furans.
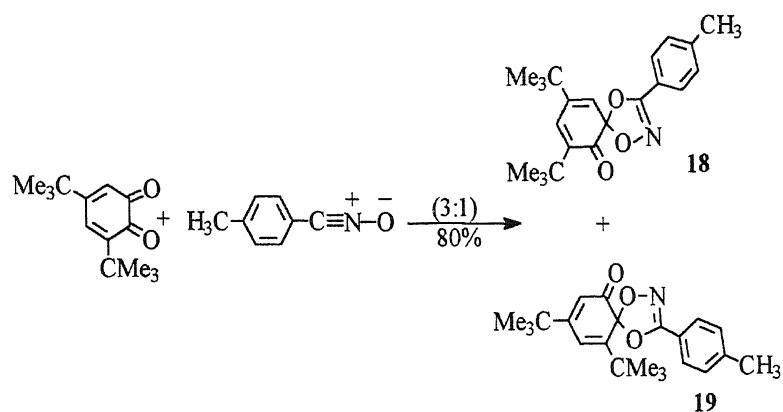
We have recently observed that the reaction of 3,5-di-*tert*-butyl-*o*-benzoquinone with 2,5-dimethylpyrrole at room temperature furnished the pyrroleno[1,4]benzodioxin adduct [22]. Presumably the primary product formed **16**, an enamine, isomerized to the imine under the reaction conditions. Similar adducts were isolated from the reaction of 4-*tert*-butyl-, 3-methoxy and 4-nitro-*o*-benzoquinones.

Scheme 9.

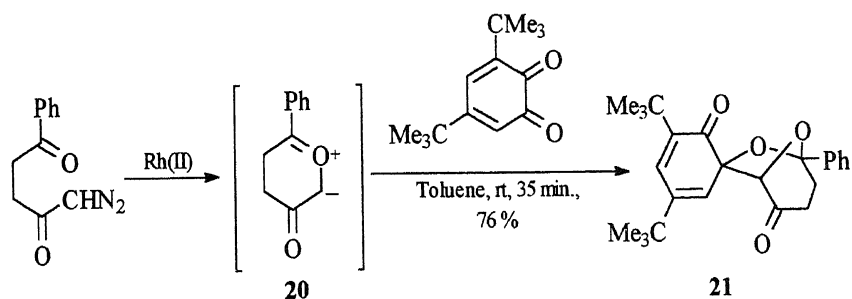## 7. 1,3-Dipolar cycloadditions of o-benzoquinones with nitrile-N-oxides

Subsequent to our investigations on the Diels-Alder reactions of o-benzoquinones, we explored their 1,3-dipolar cycloadditions. The cycloaddition of p-tolyl nitrile oxide with 3,5-di-*tert*-butyl-1,2-benzoquinone afforded a regioisomeric mixture (3:1) of novel spiro-1,3-dioxazoles as illustrated in scheme 10[23]. The reaction was found to be general and proceeded smoothly with a variety of substituted nitrile oxides.

Scheme 10.

8. Dipolar cycloaddition reactions of o-benzoquinones with carbonyl ylides

As a part of our continuing interest in probing the dipolarophilic profile of o-quinones, we have undertaken some work on their reaction with carbonyl ylides. It is noteworthy that although Padwa has studied the reactions of carbonyl ylides with aldehydes[24], as far as we know, no work on the addition of carbonyl ylides to quinones has been reported by anyone. Our studies were initiated with Rh(II) catalyzed cycloaddition of 1-diazo-5-phenyl-2,5-pentanedione to 3,5-di-*tert*-butyl-1,2-benzoquinone[25]. This reaction proceeded smoothly to afford the highly oxygenated novel spiro product as shown below.
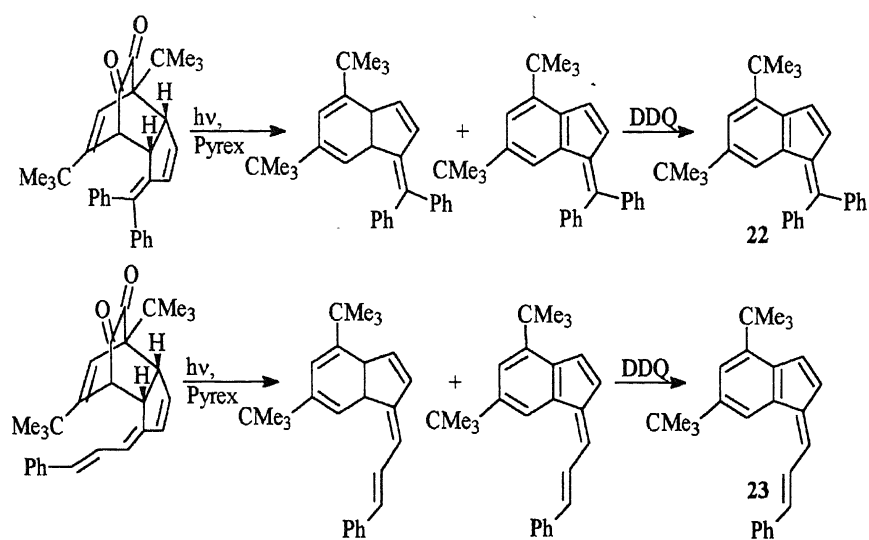

Scheme 11.

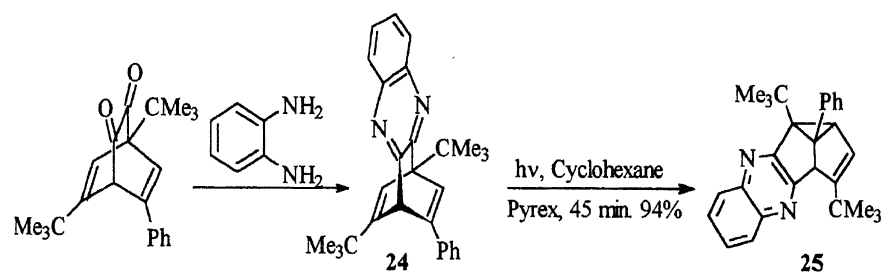This reaction also appears to be general.

9. Synthetic transformations of the bicyclo[2.2.2]adducts

Apart from the novel reactivity profiles uncovered and the new insights gained in the cycloadditions of *o*-quinones, attention may be drawn to the fact that the products obtained themselves are potentially amenable to a number of interesting transformations. Our investigations in this area have revealed a number of synthetically useful processes. For example, the bicyclo [2.2.2] adducts undergo facile photolytic double decarbonylation providing an efficient route to the synthesis of highly substituted benzene and indene derivatives[26,27].
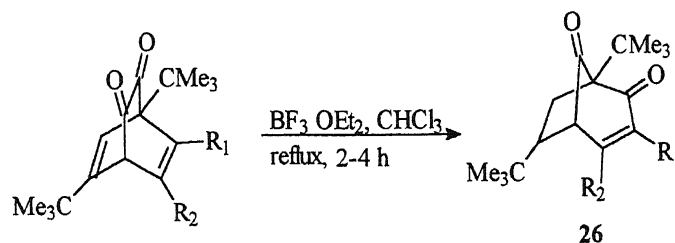
Scheme 12.

The condensation of the bicyclo adducts with 1,2-diamines smoothly affords pyrazinobarrelene derivatives which undergo facile di-π-methane rearrangement as shown in scheme 13[28,29].
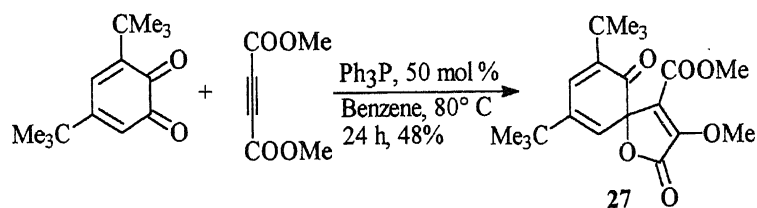
Scheme 13.

Yet another interesting reaction is the Lewis acid catalyzed rearrangement of the bicyclo[2.2.2]adducts leading to a facile entry into bicyclo[3.2.1]systems[30].

Scheme 14.

10. Triphenylphosphine catalyzed addition of DMAD to *o*-benzoquinones

In view of our general interest in the chemistry of quinones we have examined the reaction of dimethyl acetylenedicarboxylate with *ortho*- and *para*- quinones. 3,5-Di-*tert*-butyl-1,2-benzoquinone and DMAD in benzene when treated with 50 mol% of TPP at reflux temperature or 24 h afforded 48% of the γ-spirolactone 27 (scheme 15)[31].

Scheme 15.

This is a general reaction applicable to both *o*- and *p*-quinones.

11. Conclusions

In conclusion, we have uncovered some novel reactivity patterns in the cycloaddition chemistry of *o*-benzoquinones. Particularly noteworthy is the isomerization of 6,6-tetramethylenefulvene and its addition to *o*-quinone. The HOMO-LUMO energy calculations using MNDO program show that the cycloadditions discussed in this article can be explained in terms of inverse electron demand Diels-Alder reactions.

Apart from the fascinating results obtained and the new insights gained on the cycloaddition of *o*-quinones, attention may be drawn to the fact that the products of the cycloadditions themselves are potentially amenable to a number of interesting and possibly useful transformations. Some such reactions are illustrated above. The bicyclo[2.2.2] adducts undergo facile double decarbonylation reaction on photolysis providing an efficient route to the synthesis of highly substituted indenes, benzofulvenes and benzene derivatives that are not easily accessible by conventional methods. The condensation of the bicyclo adducts with 1,2-diamines smoothly affords pyrazinobarrelene derivatives which undergo facile di-π-methane rearrangement. Another interesting reaction is the Lewis acid catalyzed rearrangement of the bicyclo[2.2.2] adducts leading to a facile entry into bicyclo[3.2.1] systems in good yields. A novel spirolactone synthesis involving the TPP catalyzed reactions of DMAD with *o*-benzoquinone is also noteworthy.

Acknowledgements

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