Cyclobutenone as a Highly Reactive Dienophile: Expanding Upon Diels−Alder Paradigms

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Abstract: Cyclobutenone was employed as a dienophile in Diels−Alder cycloadditions, provide diverse and complex cycloadducts in good yields. Experimental outcomes indicated cyclobutenone to be more reactive than either cyclopentenone or cyclohexenone. In addition, cycloadducts bearing a strained cyclobutanone moiety were able to undergo regioselective ring expansions to produce corresponding cyclopentanones, lactones, and lactams, which are otherwise difficultly obtained by direct Diels−Alder reactions.

The power of the Diels−Alder cycloaddition reaction in organic synthesis is widely appreciated.[1] The six-membered rings created through Diels−Alder technology can be substructures of relatively simple targets or may be of value in building molecules of considerable complexity. Indeed, the Diels−Alder reaction has proven to be a valuable resource in reaching many natural products of novel architecture.[2]
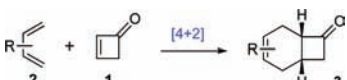
Access to higher levels of complexity might well be facilitated if the dienophilic double bond in a Diels−Alder reaction is already housed in an existing ring. However, under strictly thermal conditions, parent cyclenones such as cyclohexenone and cyclopentenone are relatively unreactive unless the diene contains strategically placed activating groups.[3] While both of these dienophiles are known to undergo Lewis acid catalyzed Diels−Alder cycloaddition with less activated dienes, such applications require substrates which are stable to Lewis acids.

Remarkably, although cycloadditions of substituted cyclobutenones have been reported,[4] we were unable to find a report of a Diels−Alder reaction of the parent cyclobutenone (**1**, Table 1). We anticipated that perhaps the ring strain of **1** might well serve to enhance its dienophilicity relative to corresponding cyclopentenones or cyclohexenones. Moreover, we could foresee that the products of such Diels−Alder reactions (cf. **3**) could well represent particularly useful platforms for further elaborations (vide infra).

Sieja[5] had actually described a preparation of cyclobutenone **1**, following a very harsh Hunsdiecker-type decarboxylation−bromination of 3-oxo-cyclobutanecarboxylic acid[6] and subsequent elimination. We developed a modified version of the Sieja protocol in which a much milder Hunsdiecker-type decarboxylation−bromination was utilized, leading to gram-scale quantities of **1**.[7a,b] Cyclobutenone (**1**) was found to be prone to polymerization when stored in the neat state, even at very low temperatures. Accordingly, it was stored as a solution in chloroform.

Activated acyclic dienes **2a**−**c** were explored and found to be quite reactive in Diels−Alder reactions with **1** (Table 1). Dienes **2a**, **b**, and **d** gave rise, predominantly, to *endo* products (entries 1, 2, 4). Not

Table 1. Diels−Alder Reaction of Various Dienes with Cyclobutenone

entry	diene	reaction condition	product	yield[a] (%)
1[b]	**2a** (OMe, TBSO)	CHCl$_3$, 0 °C, 12 h	**3a**	90%
2	**2b** (NMe$_2$, TBSO)	CHCl$_3$, -40 °C, 2.5 h	**3b**	78%
3	**2c** (TBSO)	CHCl$_3$, 45 °C, 12 h	**3c**	55%
4[c]	**2d**	CHCl$_3$, RT, 1 h	**3d**	80%
5	**2e** (Ph, Ph)	CHCl$_3$, 45 °C, 12 h	**3e**	62%
6	**2f**	CHCl$_3$, 45 °C, 12 h	**3f**	82%
7	**2g**	ZnCl$_2$, CHCl$_3$/CH$_3$CN(1:1) 45 °C, 12 h	**3g**	81%
8[d]	**2h**	ZnCl$_2$, CHCl$_3$/CH$_3$CN(1:1) 45 °C, 12 h	**3h**	68%
9	**2i**	ZnCl$_2$, CHCl$_3$/CH$_3$CN(1:1) 45 °C, 24 h	**3i**	60%
10	**2j**	ZnCl$_2$, CHCl$_3$/CH$_3$CN(1:1) 45 °C, 24 h	**3j**	46%

[a] Isolated yield. [b] A mixture of cycloadducts (*endo/exo* = 4:1) was isolated in 90% combined yield. When the reaction was conducted at −30 °C for 48 h, the *endo/exo* ratio was increased to 13:1 (52% yield based on 60% conversion). [c] The minor adduct was isolated in 8% yield. [d] Cycloadduct **3h** was isolated in 40% yield in the absence of ZnCl$_2$.

surprisingly, dienes **2c**, **2e**, and **2f** require higher temperatures (45 °C) and longer reaction times to produce cycloadducts (entries 3, 5−6). The structure of **3e** was confirmed by X-ray crystallographic analysis.[7c]

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Reactions of cyclobutenone with less reactive dienes **2g**−**j** were conducted with Lewis acid activation (ZnCl₂)[8] to produce cycloadducts in moderate to good yields (entries 7−10).[7a]

In our estimation, **1** is quite similar in its Diels−Alder reactivity profile to maleic anhydride. This is remarkable in that vicinal diactivation is a common rate enhancing feature in Diels−Alder cycloadditions. While the magnitude of the effect could not have been predicted in advance, the rate enhancement with **1** must reflect the favorable effects of rehybridization of two particularly strained sp² carbons in the cycloaddition transition state.[9] By contrast, noncatalyzed Diels−Alder reactions of cyclopentenone or cyclohexenone as dienophiles typically require much higher temperatures (180−250 °C).[10] In fact, in our hands, the uncatalyzed reaction of cyclopentadiene with cyclopentenone was only 40% complete after 36 h at 150 °C. The results provided in Table 1 clearly demonstrate that cyclobutenone **1** is a far more reactive dienophile than are the analogous unsubstituted five- and six-membered cycloalkenones.

Given the now enhanced availability of **1** and its powerful dienophilicity, we explored some aspects of the chemistry of adducts **3** with a view to reaching otherwise inaccessible target structures via Diels−Alder logic (Table 2). For instance, treatment of cycloadduct

Table 2. Representative Ring Expansions of Cycloadducts

entry	cycloadduct	conditions[a]	product/ yield (isolated)	dienophilic equivalent
1		A	**4** (60%)	**10**
2	**3f**	B	**5** (70%)	**11**
3		C	**6** (80%)	**12**
4		A	**7** (65%)	
5	**3h**	B	**8** (92%)	
6		C	**9** (92%)	

[a] Key. A: Trimethylsulfoxonium iodide, NaH, DMF, then LiI, THF; B: CF₃CH₂OH, H₂O₂; C: *O*-Mesitylenesulfonyl-hydroxylamine, CH₂Cl₂, 0 °C, then Al₂O₃, PhH/MeOH (3:1).

3f with trimethylsulfoxonium iodide and NaH in DMF (A) afforded the spiroepoxide[11] which, upon exposure to lithium iodide, underwent rearrangement to produce cyclopentanone **4**, apparently as a single regioisomer (entry 1). Thus, methylene insertion had occurred exclusively at the more substituted C−C bond, as consistent with the findings of Markó and co-workers.[11] It is appropriate to note that **4** corresponds to the cycloadduct of a hypothetical Diels−Alder reaction of **2f** and the nonfunctional dienophile, 3-cyclopentenone (**10**).

Correspondingly, **3f** was converted to lactone **5** in 70% yield (entry 2). In this case, oxygen insertion had occurred, as anticipated, at the more substituted C−C bond. It is of note that lactone **5** corresponds to the equivalent of a Diels−Alder reaction between **2f** and butenolide **11**. Once again, butenolide **11** is not a useful dienophile in chemical synthesis. Finally, reaction of **3f** with *O*-mesitylenesulfonyl-hydroxylamine (MSH) in CH₂Cl₂, followed by Al₂O₃-promoted rearrangement (C),[12] afforded lactam **6** in 80% yield as a single isomer (entry 3). Lactam **6** may be seen

as the equivalent of a Diels−Alder reaction between **2f** and 1,5-dihydropyrrol-2-one (**12**), which is, in reality, a nonfunctional dienophile. Similarly, exposure of **3h** to the conditions described afforded cyclopentanone **7**, lactone **8**, and lactam **9** (entries 4−6).

These studies represent a potentially valuable approach to the assembly of complex substructure types by combining Diels−Alder reactions of the now available and highly reactive **1** with a range of dienes to provide cycloadducts of the type **3**, which serve as substrates for appropriate ring expansions.[13]
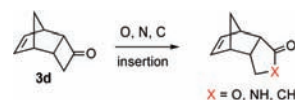
In summary, as a consequence of improved methods for its synthesis and management, the parent cyclobutenone (**1**) has become available as a reagent for chemical synthesis. In thermally driven Diels−Alder cycloadditions, it is far more reactive than Δ² cyclopentenone, which is notably more reactive than Δ² cyclohexenone. For instance, **1** reacts with cyclopentadiene at room temperature with high endo selectivity. Diels−Alder reactions can be readily conducted with other, less reactive diene types (remarkably, with furanoid dienes, high exo selectivity pertains). Ring expansion reactions following Diels−Alder cycloadditions can be used to generate structure types which correspond to cycloadducts of hypothetical but, in reality, nonfunctional dienophiles. In this way, the logic of the Diels−Alder reaction is extendable to reaching hitherto inaccessible structural types.

Supporting Information Available: Experimental procedures, copies of spectral data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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