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LETTERS

Reactivity of Hindered 1,1-Dimethylbutadienes Towards α, β-Unsaturated Enones.

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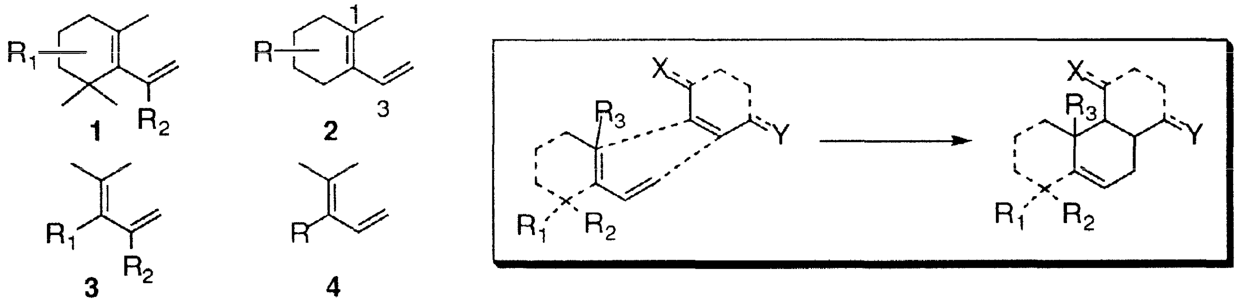
Abstract: The reactivity of several hindered 1,1-dimethylbutadienes towards α,β-unsaturated enones were studied and compared. Computational and experimental results suggest that substituents at C-2 and C-3 of the dienes significantly effect the reactivities. A synthetic application of this reaction is also described. © 1998 Elsevier Science Ltd. All rights reserved.

The Diels–Alder cycloaddition reaction is a powerful transformation in organic synthesis. However, 1,1-dialkyl substituted dienes (**1-4**) have found limited synthetic utility in this important cycloaddition reaction (**Figure 1**).[2] The rate of these reactions is usually slow because steric interactions cause the S-*trans* conformer to predominate. Thus, highly reactive dienophiles[3-5] or drastic reaction conditions[3] are required in many cases for dienes such as **1** and **2**. The reactivities of 1,1-dimethylbutadienes such as **3** towards α,β-unsaturated aldehydes and other reactive dienophiles under Lewis-acid conditions[6-8] have been reported. However, their reactivity towards simple mono-functionalized α,β-unsaturated enones are not well known. As a part of our ongoing research effort in exploring less-reactive dienes and dienophiles,[9] we studied the reactivity of 1,1-dialkyl substituted butadienes represented by structures **3** and **4** towards mono-functionalized α,β-unsaturated enones, and found that substituents at C-2 and C-3 of dienes **3** play a role in these reactions. We report here the results of our initial investigation and a synthetic application of these reactions.

Figure 1



Our study showed that although the BF_3-Et_2O promoted cycloaddition reaction of 2-carbethoxy-1,1,3-trimethyl-1,3-butadiene (**5**)[6,7] with crowded 2-bromocinnamaldehyde (**6**) provided the hetero Diels–Alder adduct **7**[10] in 45% yield, reaction with the much smaller propiolaldehyde also gave adduct **8** as the only product in 75% yield under the same conditions ($SnCl_4$ provided **8** in 63% yield).[11] While **5** was not reactive towards methylpropiolate under these conditions (not shown in **Scheme 1**), the reaction of **5** with 2 eq of methyl vinyl ketone (MVK) in CH_2Cl_2 in the presence of 2.5 eq of BF_3-Et_2O at -20 °C afforded the cycloadduct **9** in 65%

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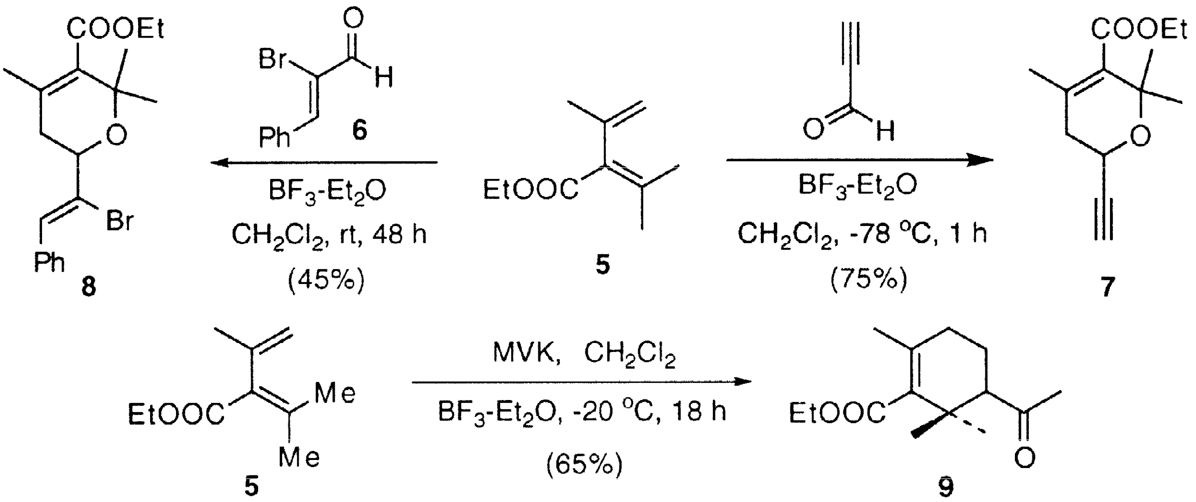
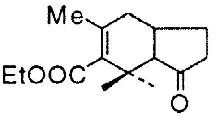
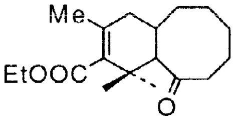
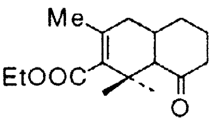
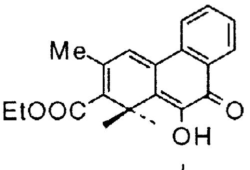
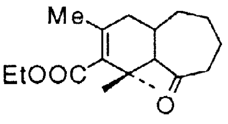
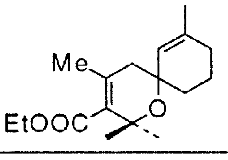
yield (**Scheme 1**). This result prompted us to examine cycloaddition reactions of **5** with other α,β-unsaturated enones, not only because of the synthetic potential presented by these cycloadducts (**Figure 1**), but also because mechanistically, neither the hindered 1,1-dimethylbutadiene **5** nor dienophiles with one electron withdrawing group can be considered reactive components in a Diels–Alder reaction.

Scheme 1



Reactions of the diene **5** with various α,β-unsaturated enones are summarized in **Table 1**. These reactions were carried out at room temperature, and with the exception of 2-cyclohexen-1-one (entry 2), reaction time was more than 24 h. Reactions of **5** with 2-cyclopenten-1-one and 2-cyclohexen-1-one appeared to provide the best yields (entries 1 and 2), while larger cyclic enones (entries 3 and 4) were less reactive. The reaction of **5** with 2-cycloocten-1-one afforded the cycloadduct **13** in <10% yield even when 10 eq of BF_3-Et_2O was added. Reaction with the more reactive 1,2-naphthoquinone, however, provided the interesting tricyclic compound **14** in 40% yield (entry 5), whereas a hindered β,β'-disubstituted enone such as 3-methyl-2-cyclohexen-1-one underwent cycloaddition again in favor of the hetero cycloadduct **15** with 45% yield (entry 6). We attempted reaction of **5** with 2-cyclohexen-1-one in toluene under the thermal condition (sand bath temperature 200 °C, in a sealed tube), but it did not provide any meaningful cycloadduct after 48 h.

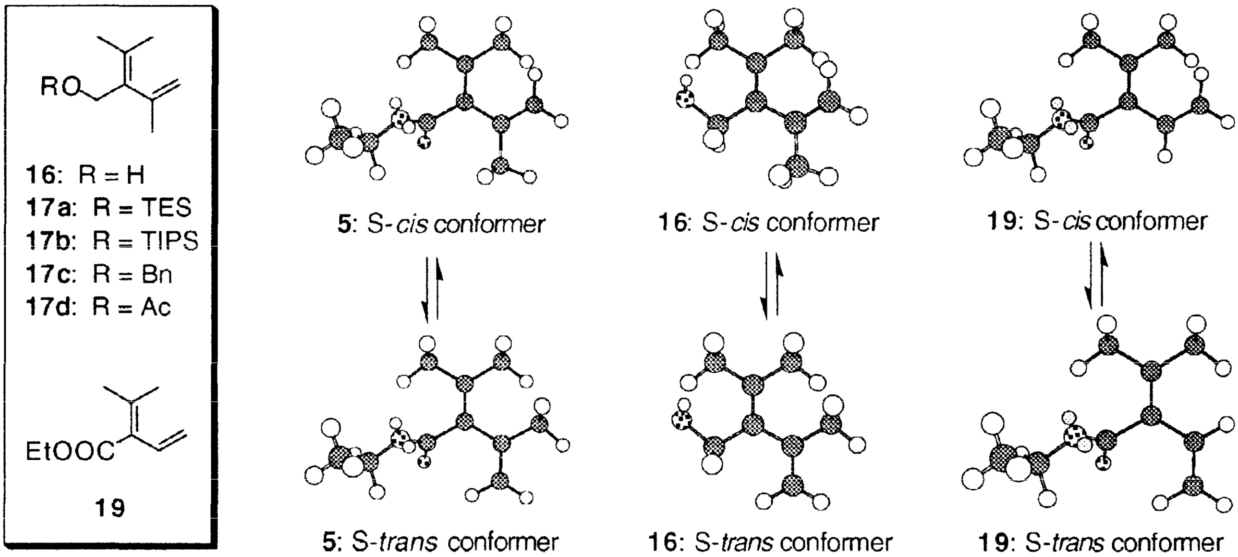
Table 1. Reactions of **5** with α,β-Unsaturated Enones.

Entry[a]	Product	Time	Yield[b]	Entry	Product	Time	Yield
1	 Me EtOOC O **10**	70 h	53%	4	 Me EtOOC O **13**	96 h	<10%[c]
2	 Me EtOOC O **11**	24	60	5	 Me EtOOC O OH **14**	72	40
3	 Me EtOOC O **12**	72	30	6	 Me EtOOC O **15**	72	45

a. The ratio of the diene to enone to BF_3-Et_2O is 1 : 2 : 2.5, except for entry 4, in which 3.5 -10 eq of BF_3-Et_2O was used. Reactions were carried out in CH_2Cl_2 at room temperature. b. Isolated yields. c. GC yield due to an inseparable by-product.

We prepared other 1,1-dimethylbutadienes **16**,[7] **17a-d**,[7] and **19** as shown in **Scheme 2**. However, none of the expected cycloadducts were isolated from reactions of **16**, **17a-d** and **19** with 2-cyclohexen-1-one or 2-cyclopenten-1-one under either Lewis acid promoted or thermal conditions. Initially, it was thought that the lack of reactivity could be solely due to the instability of these dienes under the reaction conditions. *Ab initio* (HF-6-31G**) calculations of the energy difference between S-*cis* and S-*trans* conformers of dienes **5**, **16**, and **19** were carried out using the Spartan Program™. These calculations revealed that the diene **5** has the smallest energy difference between S-*cis* and S-*trans* conformers [$\Delta E = -0.20$ kcal/mol in favor of the S-*trans* conformer], whereas the diene **16** has a $\Delta E = -2.11$ kcal/mol, and the diene **19** has a $\Delta E = -3.52$ kcal/mol in favor of their respective S-*trans* conformers (for illustrations see **Scheme 2**).

Scheme 2



16: R = H
17a: R = TES
17b: R = TIPS
17c: R = Bn
17d: R = Ac

19

5: S-*cis* conformer

16: S-*cis* conformer

19: S-*cis* conformer

5: S-*trans* conformer

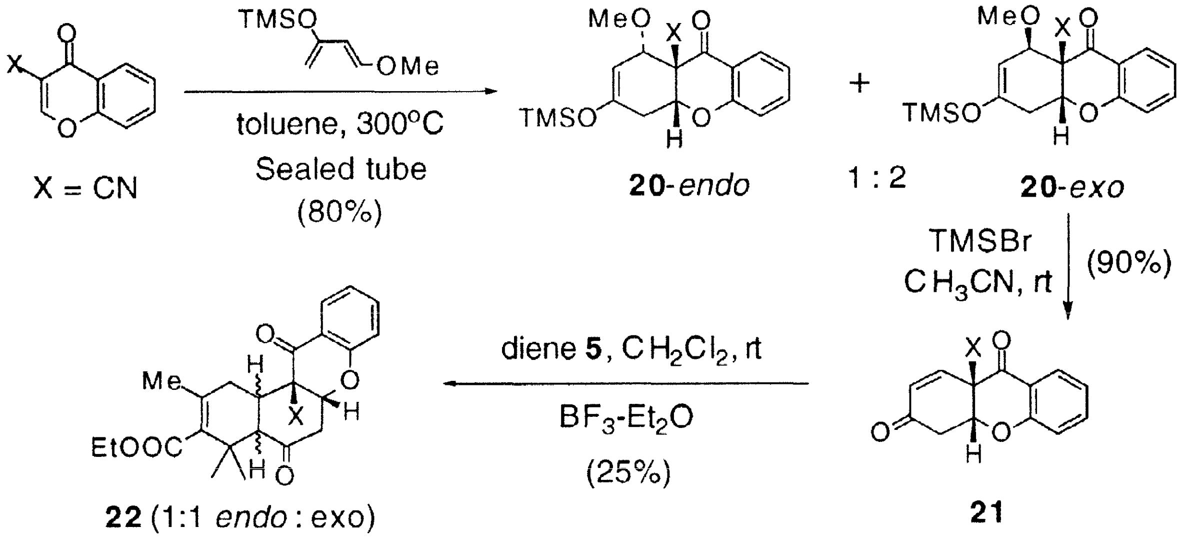
16: S-*trans* conformer

19: S-*trans* conformer

These calculations provided some explanation for our experimental results. The diene **5** is a more reactive diene than **16** and **19**, owing to a more accessible S-*cis* conformation, and therefore, can react with less reactive dienophiles such as α,β-unsaturated enones. Although the exact reasons are not clear, structural differences between **5**, **16**, and **19** suggest that substituents at C-2 and C-3 could play a role in enhancing the S-*cis* conformation of **5**. We are currently exploring this possibility by designing dienes with removable substituents at C-2 and C-3 that may allow such an enhancement of the S-*cis* conformation.

Although compounds **10-15** possess structural features common among natural products, we explored an iterative cycloaddition route as a potential solution for a related synthetic problem in our research. As shown in **Scheme 3**, in conjunction with our recent work on [4+2] cycloaddition reactions of γ-benzopyrones,[9] it is possible to reach the tetracyclic structure **22** via two consecutive [4+2] cycloaddition reactions, second one being between a 1,1-dimethylbutadiene and a cyclic enone. Reaction of 3-cyano-4-benzopyrone with Danishefsky's diene in toluene at 300°C for 96 h provided the desired cycloadduct **20** in 80% yield with an *endo*:*exo* ratio of 1:2 (**Scheme 3**).[9] Hydrolysis of the silyl enol ether proved difficult since the hydrolysis stopped at the stage of isomeric methoxy ketones under most conditions. Only treatment with TMSBr in CH$_3$CN at room temperature proved to be feasible, albeit slow, and afforded the enone **21** in 90% yield. Reaction of diene **5** with enone **21** in the presence of 2.5 eq of BF$_3$-Et$_2$O yielded the tetracycle **22** in 25% yield with an *endo*:*exo* ratio of 1:1 after 120 h at room temperature. Although both starting materials were still present, the reaction conditions did also produce a major product (≥ 40%) derived from aromatization of the enone **21**. However, successful isolation of **22** still suggests that the sequence described here may provide a viable route to the complex tetracyclic structure.

Scheme 3



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