Reaction Behavior of Cumulene in Diels–Alder and Friedel–Crafts Reactions

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Diels–Alder and Friedel–Crafts reactions of [3]cumulene **1** were investigated. Although the Diels–Alder reaction with cyclopentadiene selectively occurred on the C2, 3 double bond to give tetrasubstituted allenyl products, the Friedel–Crafts addition of electron-rich heteroaromatics and subsequent protonation cleanly occurred on the C3, 4 double bond to afford tetrasubstituted conjugated dienes.

Cumulenes have received a lot of attention due to their unique structural, physical,[1] and chemical properties, which are derived from their cumulated polyene systems. Cumulenes are also found as partial structures of natural products. One of the most prominent examples is the neocarzinostatin chromophore in which the biradical species generated by a Bergman-type cycloaromatization of the eneyne[3]cumulene plays a key role in its potent anti-tumor activity.[2] Although the double bonds should display a remarkable reactivity toward a wide variety of reagents, their reactivity has yet to be fully investigated. Most reports have focused on the reactivity of the symmetrically substituted cumulenes and the variety of the reaction tested is limited.[3] This remarkable reactivity and the need to further study cumulenes has prompted us to survey the reaction behavior of cumulenes.

2-Methyl-5,5′-diphenylpenta-2,3,4-trienal (**1**),[4] a stable [3]-cumulene derivative, should show a unique reactivity on the distinct double bonds, which possess different electronic and steric properties, due to the electron-withdrawing nature of the formyl group and steric bulkiness of diphenyl moiety. The Diels–Alder (DA) and Friedel–Crafts reactions of **1** gave allene **2** and diene **3**, respectively (Figure 1). The details of the reaction behavior of **1** during these reactions are described herein.

We initially tested the DA reaction of **1** with cyclopentadiene as depicted in Table 1. The thermal DA reaction while heating at 150 °C in toluene proceeded at the C2, 3 double bond of **1** to give tetrasubstituted allenyl products **2** with an *exo* selectively (entry 1).[5] To increase the reactivity and selectivity, Lewis-acid catalysts were screened. An equivalent amount of Yb(OTf)$_3$ improved the yield of **2** in CH$_2$Cl$_2$ (entry 2). A unique solvent effect was observed in SnCl$_4$-catalyzed reactions. Although SnCl$_4$ in CH$_2$Cl$_2$ was ineffective (entry 3), the reaction in THF gave the best yield (entry 4). Other Lewis acids, AlCl$_3$, Me$_3$Al, and TMSOTf, also facilitated the DA reaction, but these catalysts gave the product in diminished yields (entries 5–8). The structures of the *endo*- and *exo*-isomers were determined by NOE experiments as shown in Table 1.

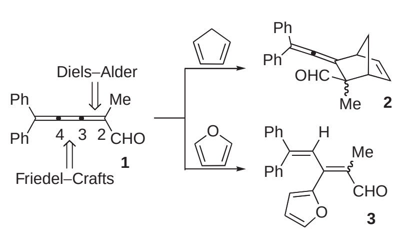
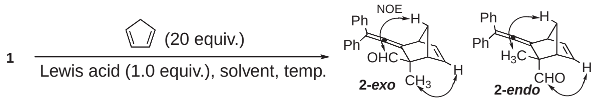


Figure 1. Reaction behavior of cumulene **1**.

Table 1. DA reaction with cyclopentadiene



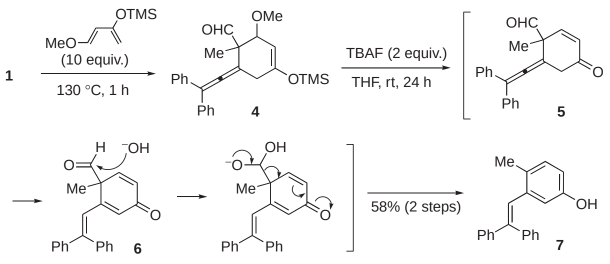
Entry	Lewis acid	Solvent	Temp.	Time/h	Yield[b]/%	Ratio[c] (*exo*:*endo*)
1	—	toluene	150 °C	6	43	2.0:1.0
2	Yb(OTf)$_3$	CH$_2$Cl$_2$	60 °C	48	63	1.0:1.0
3	SnCl$_4$	CH$_2$Cl$_2$	−78 °C → rt	15	—[d]	—
4	SnCl$_4$	THF	−78 °C → rt	15	88	2.0:1.0
5	AlCl$_3$	THF	−78 °C → rt	20	43	1.9:1.0
6	Me$_3$Al	THF	−78 °C → rt	24	18	1.8:1.0
7	TMSOTf	THF	−78 °C	2	16	1.6:1.0
8	TMSOTf[a]	THF	−78 °C → rt	23	45	1.1:1.0

[a]TMSOTf (0.3 equiv.) was used. [b]Combined yield. [c]Determined by ^{1}H NMR. [d]Only **1** decomposed.

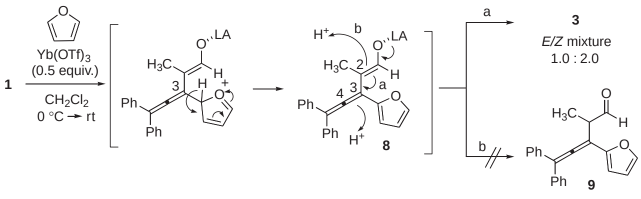
The reactivity of **1** was further investigated with Danishefsky's diene. Although the DA reaction proceeded smoothly on the C2, 3 double bond to afford unstable allenyl cycloadduct **4**, further treatment of TBAF afforded trisubstituted benzene derivative **7** as a major product. This unexpected aromatization might occur via allene **5** to diene **6** isomerization and successive deformylation of **6** by nucleophilic attack of hydroxide ion[6] (Scheme 1).

None of the DA reactions gave products on the C3, 4 or C4, 5 double bonds. These observations indicate that cumulene **1** has a sufficient reactivity toward DA reactions and is an excellent dienophile with a reactive C2, 3 double bond due to the presence of the electron-withdrawing formyl group.

These promising results inspired us to focus our survey on the reactivity of **1** with electron-rich heteroaromatics. Although the reaction conditions are quite similar to the DA reactions, the Friedel–Crafts reaction proceeded smoothly by treating **1** and furan with 50 mol % of Yb(OTf)$_3$.[7] This reaction yielded the corresponding tetrasubstituted conjugated dienes **3** as an E/Z mixture in 93% yield (Scheme 2).[8] Allene derivative **9**, which

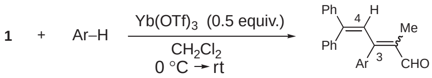


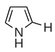
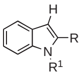
Scheme 1. DA reaction with Danishefsky's diene.



Scheme 2. Friedel–Crafts reactions of **1** with furan.

Table 2. Friedel–Crafts reactions of **1** with nitrogen-containing electron-rich aromatics



Entry	Ar–H (equiv.)	Time/h	Product	Yield[a]/%	Ratio[b] (E:Z)
1	 **10** (20)	24	**15**	70	1.0:1.5
2	**11**: $R^1 = R^2 = H$ (2.0)	12	**16**	70	1.0:3.0
3	 **12**: $R^1 = Me, R^2 = H$ (2.0)	24	**17**	73	1.0:2.3
4	**13**: $R^1 = H, R^2 = Me$ (2.0)	10	**18**	76	1.0:4.0
5	**14**: $R^1 = R^2 = Me$ (1.0)	6	**19**	78	1.0:8.0

[a]Combined yield. [b]Determined by ^{1}H NMR.

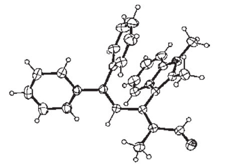


Figure 2. ORTEP view of **19**.

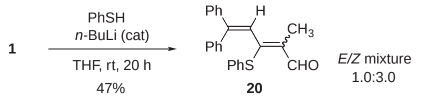
can be generated by the protonation at C2 of enolate **8** (path b), was not detected. This observation clearly shows that the conjugate addition of the aryl group and subsequent protonation of enolate **8** selectively occur at C3 and C4, respectively (path a).

The Friedel–Crafts reaction with nitrogen-containing heteroaromatics, such as pyrrole and indoles, were also investigated (Table 2). In all cases, the reactions proceeded smoothly to give corresponding dienes **15**[8] and **16**–**19**[9] in excellent yields and neither the DA product nor the corresponding allene derivative was detected. With indole derivatives, introducing methyl substituents at the 1 and 2 positions on the indole ring improved the Z-selectivity of the product (entries 4 and 5). X-ray analysis of **19** was used to establish the structures of all the compounds (Figure 2).[10]

To confirm the behavior of **1** toward nucleophiles, the reaction with thiophenol in the presence of catalytic amount of n-BuLi was tested (Scheme 3). Like the Friedel–Crafts reaction, the conjugate addition of the thiolate anion at C3 and subsequent protonation at C4 afforded corresponding conjugated diene **20**.[8]

It is noteworthy that these conjugate addition–protonations can be recognized as a formal 3,4-addition to form tetrasubstituted conjugated dienes. This sharply contrasts the DA reaction, which occurs at the 2, 3 positions of **1** to give tetrasubstituted allene derivatives.

In summary, we have found characteristic DA and conjugate addition reactions of **1**, which have concerted and stepwise reaction pathways. Furthermore, both reactions provide novel and useful routes to highly substituted allene and diene derivatives. Thus, a detailed mechanistic study and further chemical transformations of the reaction products to bioactive tetrasubstituted olefins such as tamoxifen derivative[11] are currently under investigation.



Scheme 3. Conjugate addition of thiophenol to **1**.

This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka, who passed away December 8, 2004.

References and Notes

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5 This *exo* selectivity might originate from the unfavorable *endo* transition state due to the steric repulsion between the methyl substituent of **1** and methylene moiety of cyclopentadiene. Similar *exo* selectivity is known in the DA reaction with methacrolein. For example, see: K. T. Sprott, E. J. Corey, *Org. Lett.* **2003**, *5*, 2465.

6 This hydroxide ion would be derived from the small amount of H_2O contained in 1.0 M solution of TBAF in THF.

7 Similar observations for the different reactivity of dimethylallene-1,3-dicarboxylate in DA and Friedel–Crafts reactions were reported. See: K. Nishide, S. Ichihashi, H. Kimura, T. Katoh, M. Node, *Tetrahedron Lett.* **2001**, *42*, 9237.

8 The configurations of each isomer have not been optimized.

9 Considering that the chemical shift of the Z-isomer aldehyde proton of **19** is shifted to a higher-field compared to the corresponding E-isomer due to the anisotropic shielding of the neighboring indole ring (Figure 2), the major isomer of **16**–**18** should be the Z-isomer.

10 Crystallographic data for **19**: $C_{28}H_{25}NO$, $M_r = 391.51$, triclinic, space group $P\bar{1}$ (#2), $T = 298$ K, $a = 9.9399(10)$ Å, $b = 11.8748(8)$ Å, $c = 9.7921(6)$ Å, $\alpha = 95.791(5)^\circ$, $\beta = 92.372(7)^\circ$, $\gamma = 108.820(6)^\circ$, $V = 1085.07(15)$ Å^3, $Z = 2$, $Dc = 1.198$ g/cm^3, λ (Cu Kα) = 1.54178 Å, $R = 0.0456$, $wR2[F^2] = 0.1798$ for 1816 unique reflections.

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