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Electron Deficient Dienes I. Normal and Inverse Electron Demand Diels-Alder Reactions of the Same Carbon Skeleton.

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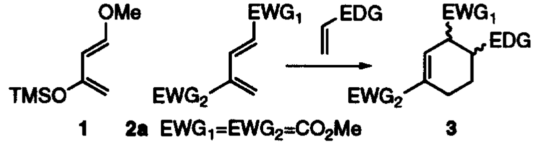
Abstract: The synthesis of compound **11**, which features a diene moiety bearing electron withdrawing groups at the 1 and 3 positions, and its completely regioselective inverse electron demand Diels-Alder reactions with 1,1-diethoxyethylene, ethyl vinyl ether and styrene are described. *Endo* addition is preferred. The direct synthetic precursor of **11**, in which one of the electron withdrawing groups (a ketone) is protected, participates in normal electron demand Diels-Alder reactions with 1,4-naphthoquinone and *N*-phenylmaleimide, but is unreactive towards 1,1-diethoxyethylene.

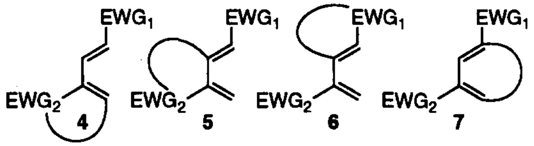
1,3-Disubstituted 1,3-butadienes such as Danishefsky's diene **1**[1] have enjoyed widespread use in synthesis owing to their ready and regiochemically predictable participation in the normal electron demand Diels-Alder reaction and the useful functionality that they impart to their adducts.[2] However, members of this family of dienes in which both substituents are electron withdrawing in nature, i.e. **2**, are rare. By analogy to their electron rich counterparts, regioselective reactions with electron rich dienophiles to give multifunctional adducts like **3** might be expected. In 1981, Hall described the synthesis and facile polymerization of dienes **2a**-**2d** in a 1,4 sense,[3] but their Diels-Alder chemistry was not investigated. More recently, Padwa reported the preparation of the bis(sulfone) **2e** which dimerized readily in its pure form,[4] but reacted with several electron rich dienophiles when generated *in situ*.[4,5] Although the direct adducts were not observed due to subsequent reactions, complete regiochemical control in these cycloadditions can be inferred. We are aware of very few other examples.[6] Padwa's results in particular led us to initiate work directed toward the development of electron deficient dienes **2** as precursors to multifunctional carbocycles *via* the inverse electron demand (IED) Diels-Alder reaction. At present, the field of IED Diels-Alder chemistry is dominated by systems incorporating heteroatoms in either or both the diene and dienophile.[7] Of the known purely carbon-containing diene systems, 2-pyrones appear to be the most useful from a synthetic point of view,[8] particularly in light of recent reports of enantioselectivity by the groups of Markó[9] and Posner.[10] Cyclopentadienones[11] and thiophene 1,1-dioxides[12] also have their place, among others, but are of more limited synthetic utility. In any event, there is ample room for expansion in this relatively untapped niche of Diels-Alder chemistry and we now report our preliminary results.



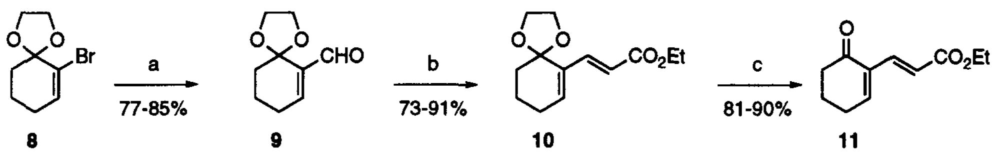
1

3

2a EWG$_1$=EWG$_2$=CO$_2$Me
2b EWG$_1$=CO$_2$Me, EWG$_2$=CN
2c EWG$_1$=CN, EWG$_2$=CO$_2$Me
2d EWG$_1$=EWG$_2$=CN
2e EWG$_1$=EWG$_2$=SO$_2$Ph

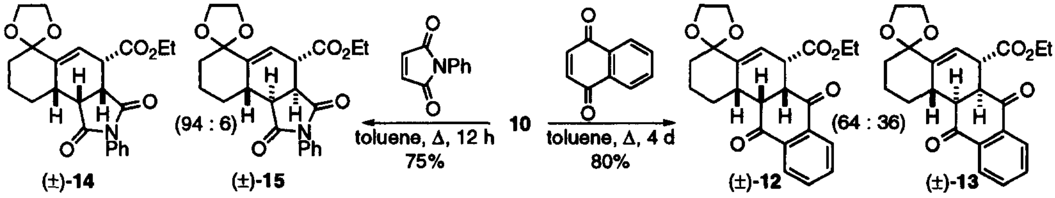


The reported instability of **2a**-**2e** led us to direct our initial efforts towards cycloalkane-annelated dienes which we hoped would exhibit sufficient kinetic stability to be isolated pure. There are four modes of annelating a ring to **2** such that the *s-cis* conformation can still be attained easily, as depicted by structures **4**-**7**. The first of these was chosen for initial study. Protected 2-bromo-2-cyclohexenone **8**, which was prepared in 76% overall yield from 2-cyclohexen-1-one over two steps,[13] was treated with butyllithium and then DMF to afford aldehyde **9** in 77-85% yield (Scheme 1). Wadsworth-Horner-Emmons reaction then gave the "protected diene" **10**[15] (73-91%). No trace of the corresponding *Z* isomer could detected by nmr. Finally, removal of the 1,3-dioxolane protecting group provided the first of our targeted dienes **11**[15] (81-90%). This sequence is quick, reliable and can be performed on a multigram scale. Diene **11** is indeed relatively stable and can be stored at -20 °C under nitrogen for at least two weeks without significant decomposition, but is best used when freshly prepared. Diene **10** is stable for months under the same conditions.



Scheme 1. Reagents and conditions: a) *n*-BuLi, THF, -78 °C, then DMF; b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; c) $(COOH)_2$, H_2O / THF.

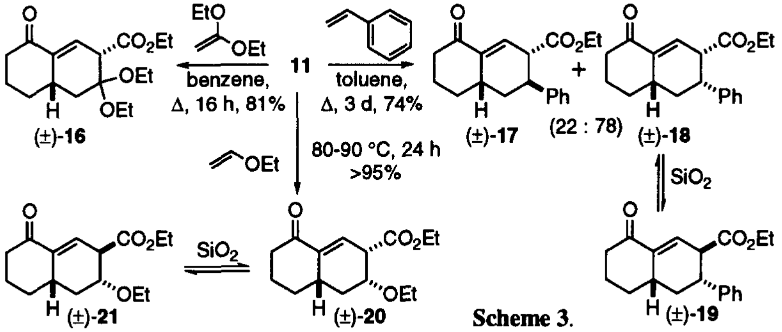
The presence or absence of the 1,3-dioxolane protecting group in **10** and **11** has a profound effect on the behavior of the diene moiety in the Diels-Alder reaction. The protected diene **10** participates in normal electron demand Diels-Alder reactions whereas the more electron deficient diene **11** reacts in an inverse electron demand sense. For example, reaction of **10** with 2.9 equivalents of 1,4-naphthoquinone in toluene for 4 days under a nitrogen atmosphere (Scheme 2) gave a mixture of the *endo* adduct **12**[15] and the *exo* adduct **13**.[15] The crude ratio of **12**:**13** was estimated to be 65:35 by integration of the crude ^1H nmr spectrum. Column chromatography afforded pure samples in 51% and 29% yields. Thus the combined yield was 80% and the product ratio 64:36. The structures were confirmed by X-ray crystallography[14] after a variety of nmr experiments failed to provide unequivocal structural proof. No products arising from aromatization, epimerization of the ester group or migration of the double bond into conjugation with the ester were observed. No starting material was recovered which may suggest that decomposition of the starting diene **10** under the reaction conditions accounts for the incomplete mass balance.



Scheme 2.

Reaction of **10** with *N*-phenylmaleimide (3.0 eq.) in toluene for 12 h under nitrogen afforded a chromatographically separable 94:6 mixture of two adducts in 75% combined yield. The major product was confirmed as adduct **14**,[15] resulting from *endo* addition, by X-ray crystallography.[14] Since the ^1H and ^{13}C nmr spectra of **13** and the minor product (an oil) exhibited very close similarities (as did those of **12** and **14**), it was assigned to structure **15**[15] by analogy. No starting material was recovered and no other mobile products were formed.

Treatment of **10** with an electron rich dienophile, 1,1-diethoxyethylene, in toluene at reflux for four days resulted in no reaction. On the other hand, electron deficient diene **11** smoothly underwent an IED Diels-Alder reaction with the same dienophile (3.7 eq.) in benzene at reflux for 16 h under N_2 (Scheme 3). Tlc analysis indicated complete consumption of the starting material and the formation of a single mobile product. Column chromatography afforded a 1:1 adduct in 81% yield. The use of 1.2 equivalents of the dienophile resulted in incomplete reaction. That the regiochemistry of the addition had occurred as expected and that the double bond had not migrated was easily established using standard nmr techniques. However, the relative stereochemistry of the two stereogenic centers defied conclusive assignment. Repeated attempts at obtaining crystals of the product, which was originally isolated as an oil, finally succeeded and an X-ray crystal structure determination[14] showed it to be the adduct **16**.[15] The potential epimerization of the ester group, which is part of a vinylogous acetoacetate system, did not occur. No products of follow-on reactions of **16** were observed.



Scheme 3.

Styrene (5.0 eq.) also underwent cycloaddition with **11** in toluene at reflux for 3 d under N_2. The crude ^1H nmr spectrum indicated the presence of two adducts in a 78:22 ratio. Upon chromatography, the minor product was isolated cleanly as an oil in 17% yield, but the major product was now contaminated by a small amount (*ca.* 10% of the mixture) of a new isomer which was not the minor product (combined yield = 57%). Recrystallization of this mixture afforded a pure sample of the major product (50%) and it was identified as **18**,[15] the result of *endo* addition, using X-ray methods.[14] The observable nmr signals of the as yet unisolated new isomer are not consistent with any structure resulting from double bond migrations. Thus it has been tentatively assigned to structure **19**, the -CO_2Et epimer of **18**. This epimerization would appear to be favorable in that it results in a *trans* relationship between the ester and phenyl group. Nmr analysis of the minor product of the reaction showed it to have the same connectivity as **18** and it was assigned as **17**,[15] the product of *exo* addition.

Reaction of **11** with ethyl vinyl ether (10 eq.) in a sealed tube (unlike the other reactions) at 80-90 °C for 24 h gave almost exclusively one adduct in near quantitative yield. Only the slightest traces of other products were observed in the ^1H nmr spectrum of the crude product. The regiochemistry of this adduct was evident from its nmr spectra, but the relative stereochemistry could not be unambiguously assigned despite extensive experiments. Attempted chromatographic purification of the crude product afforded a 13:87 mixture of the initial adduct and a second isomer with 55% combined recovery. Performing the reaction at higher temperature (>120 °C) also led to the formation of varying amounts of the new isomer in the crude mixture. These results are consistent with *endo* addition to give **20**,[15] in which the ester and ethoxy group are *cis*, followed by epimerization of the ester group to give **21**, in which the adjacent substituents are *trans*. *Exo* addition would afford a product analogous to **17**, in which there is a *trans* relationship of the substituents. Epimerization of this to give a *cis* arrangement seems most unlikely.

In summary, dienes **10** and **11** behave in a complementary fashion in the Diels-Alder reaction and this allows the same basic carbon skeleton to participate in cycloadditions with both electron rich and electron poor dienophiles. The latter reacts with complete regioselectivity and *endo* addition is preferred. The multifunctional nature of adducts **16-21** presents abundant opportunities for further elaboration into more complex systems and we anticipate that these and related systems will find application in total synthesis. Work aimed at establishing the full scope and limitations of the Diels-Alder chemistry of **11** and related systems is now in progress.

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14. Full details of the X-ray crystal structure determinations will be published elsewhere.
15. This compound has been fully characterized.

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