Room Temperature, Endo-Specific 1-Aza-1,3-butadiene Diels–Alder Reactions: Acceleration of the $LUMO_{diene}$-Controlled [4 + 2] Cycloaddition Reactions through Noncomplementary Azadiene Substitution

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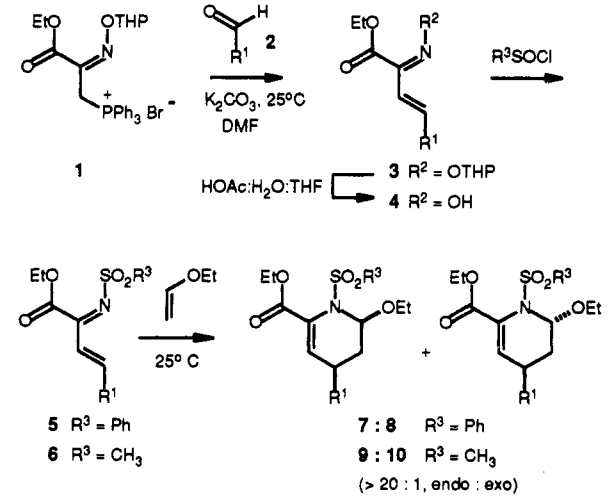
Summary: A preparation of *N*-sulfonyl-2-(ethoxycarbonyl)-1-aza-1,3-butadienes **5–6** is described and is based on the use of the stabilized Wittig reagent **1** and implementation of a subsequent room temperature, in situ homolytic oxime *O*-sulfinyl → *N*-sulfonyl rearrangement. The 4π participation of the electron-deficient 1-aza-1,3-butadienes **5–6** in room temperature, endo-specific $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions is described and represents a demonstration of the acceleration of the Diels–Alder reaction of 1-aza-1,3-butadienes achieved through noncomplementary azadiene substitution.

Simple α,β-unsaturated imines have been shown to participate in Diels–Alder reactions preferentially through their enamine tautomer and in instances where tautomerization is not accessible, [2 + 2] cycloaddition usually intervenes.[2] Consequently, the Diels–Alder 4π participation of 1-aza-1,3-butadienes is rarely observed and typically suffers low conversions, competitive imine addition, and/or imine tautomerization precluding productive [4 + 2] cycloaddition.[2] In a recent effort we detailed the general, 4π participation of stable *N*-(phenylsulfonyl)-1-aza-1,3-butadienes in regiospecific and endo-specific inverse electron demand Diels–Alder reactions suitable for the diastereoselective preparation of 1,2,3,4-tetrahydropyridines.[3] Further, complementary substitution of the 1-aza-1,3-butadienes with a C-3 electron-withdrawing substituent was shown to predictably accelerate the diene participation in the [4 + 2] cycloaddition reaction. Herein, we describe a general approach to the preparation of *N*-(phenylsulfonyl)- or *N*-(methylsulfonyl)-2-(ethoxycarbonyl)-1-aza-1,3-butadienes based on the use of a stabilized Wittig reagent **1**[4] and detail studies which demonstrate that the *noncomplementary*[5,6] addition of a C-2 electron-withdrawing substituent (CO_2Et) to the *N*-sulfonyl-1-aza-1,3-butadienes predictably accelerates their 4π participation in $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions, maintains the expected cycloaddition regioselectivity, maintains or enhances the cycloaddition endo diastereoselectivity (≥95%), and that the reactions display characteristics consistent with a concerted $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction.

The 4-substituted *N*-(phenylsulfonyl)- and *N*-(methylsulfonyl)-2-(ethoxycarbonyl)-1-aza-1,3-butadienes **5–6** were prepared through Wittig reaction (25 °C, DMF) of the stabilized phosphorane generated in situ (K_2CO_3) from the phosphonium salt **1**[4] with aldehydes (25 °C, DMF, 20–40 h, 94–72%) followed by acid-catalyzed removal of the

Scheme I



Scheme II

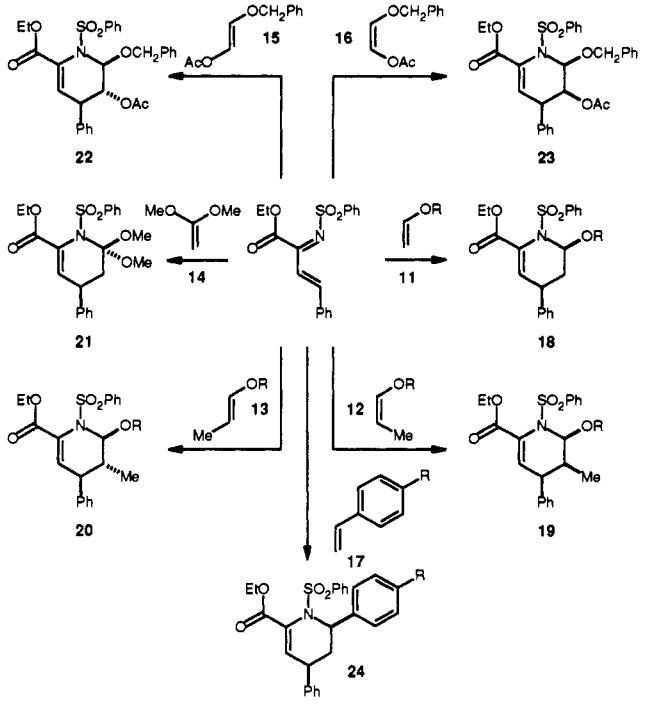


Table I

2 R^1	3 (% yield)	4 (% yield)	5 or 6 (% yield)	7:8 or 9:10 (% yield)
C_6H_5	**3a** (94)	**4a** (82)	**5a** (69)	**7a:8a** >20:1 (80)
			6a (64)	**9a:10a** >20:1 (61)
$(CH_2)_5CH_3$	**3b** (89)	**4b** (55)	**5b** (64)	**7b:8b** >20:1 (55)
			6b (59)	**9b:10b** >20:1 (53)
CH_3	**3c** (72)	**4c** (72)	**5c** (45)	**7c:8c** >20:1 (51)
			6c (56)	**9c:10c** >20:1 (59)

(1) Alfred P. Sloan fellow, 1985–1989.
(2) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
(3) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517.
(4) Phosphonium salt **1** was prepared from ethyl 3-bromopyruvate by the following sequence: (1) NH_2OH·HCl, CH_3OH–$CHCl_3$, 23 °C, 18 h, 92%, (2) DHP, PPTS, CH_2Cl_2, 23 °C, 20 h, 94%, (3) Ph_3P, THF–C_6H_6, 80 °C, 18 h, 91%. For the related preparation and Wittig reactions of $EtO_2CC(NOCH_3)CH_2PPh_3^+Br^-$, see: Bicknell, A. J.; Burton, G.; Elder, J. S. *Tetrahedron Lett.* **1988**, *29*, 3361.
(5) For a brief discussion of complementary versus noncomplementary substitution, see: Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373, 5793.
(6) (a) Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481. Teng, M.; Fowler, F. W., submitted. (b) Kim, J.-B.; Hall, H. K., Jr. *Macromolecules* **1988**, *21*, 1547.

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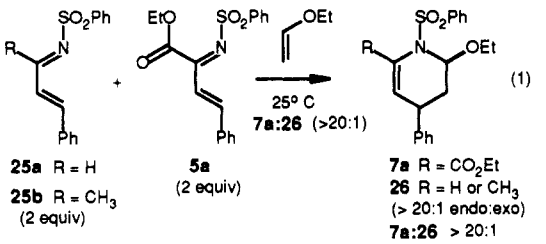
Table II

dienophile	conditions	product, endo:exo (% yield)
11a, R = Et	25 °C, 24 h, CH_2Cl_2	**7a** >20:1 (80)
11b, R = CH_2Ph	25 °C, 15 h, CH_2Cl_2	**18** >20:1 (84)
12a, R = Et	25 °C, 120 h, CH_2Cl_2	**19a** >20:1 (49)
	25 °C, 96 h, CH_2Cl_2, 6.2 kbar	>20:1 (54)
12b, R = CH_2Ph	25 °C, 104 h, CH_2Cl_2, 6.2 kbar	**19b** >20:1 (50)
13, R = Et	25 °C, 36 h, CH_2Cl_2, 6.2 kbar	**20** >20:1 (65)
14	25 °C, 1 h, CH_2Cl_2	**21** (58)
15	25 °C, 97 h, CH_2Cl_2, 6.2 kbar	**22** >20:1 (50)
16	25 °C, 97 h, CH_2Cl_2, 6.2 kbar	**23** >20:1 (68)
17a, R = H	25 °C, 96 h, CH_2Cl_2	**24a** – (0)
	80 °C, 7 d, toluene	– (0)
	25 °C, 67 h, CH_2Cl_2, 6.2 kbar	>20:1 (37)
17b, R = OCH_3	25 °C, 72 h, CH_2Cl_2	**24b** >20:1 (12)
	80 °C, 48 h, toluene	>20:1 (46)
	25 °C, 67 h, CH_2Cl_2, 6.2 kbar	>20:1 (85)

tetrahydropyranyl (THP) group (HOAc–H_2O–THF, 3:1:1, 55 °C, 37–53 h), *O*-phenylsulfinyl or *O*-methylsulfinyl formation (PhSOCl or CH_3SOCl, Et_3N, 0 °C, CCl_4 or Et_2O, 0.5–1.0 h), and subsequent in situ homolytic rearrangement (25 °C, 1–3 h)[3,7] to provide **5–6**, Scheme I and Table I.[8] The results of the [4 + 2] cycloaddition reaction of **5–6** with ethyl vinyl ether (25 °C, CH_2Cl_2, 0.2–0.5 M, 17–26 h) *conducted at room temperature* are detailed in Table I, and the comparative results of the reaction of **5a** with a range of dienophiles are summarized in Scheme II and Table II. The assigned stereochemistry of the [4 + 2] cycloadducts was derived initially from diagnostic ^1H NMR chemical shifts and coupling constants,[9a] was supported by 2D NOE experiments,[9a] and was unambiguously established with the single-crystal X-ray structure determinations of **7a** and **19a**[9b] coupled with chemical correlation (**20**).

The [4 + 2] cycloaddition reactions of **5–6** with vinyl ethers were determined to proceed predominantly if not exclusively (≥95%) through an endo transition state, the endo diastereoselectivity proved independent of the steric bulk of the *N*-sulfonyl substituent (R^3 = Ph = CH_3) and may be attributed to a strong, stabilizing secondary orbital interaction between the diene C-2/dienophile OR.[10] In addition, the [4 + 2] cycloaddition reactions were found to proceed with full preservation of the dienophile olefin geometry in the reaction products, Scheme II, to exhibit little solvent dependency on the [4 + 2] cycloaddition rate [k_{rel} (ethyl vinyl ether): CH_3CN and CH_2Cl_2 (2), C_6H_6 (1) for **7a**], and the noncomplementary C-2 addition of an electron-withdrawing group (CO_2Et) to the *N*-(phenylsulfonyl)-1-aza-1,3-butadiene was determined to substantially accelerate the rate of [4 + 2] cycloaddition,[10] eq 1 [k(**5a**)/k(**25**) > 20].[11a] Further consistent with the characteristics of a concerted Diels–Alder reaction, trans-1,2-disubstituted dienophiles were found to react more rapidly than the cis-1,2-disubstituted dienophiles with **5a** [(k-(*E*)/k(*Z*) = 9.2 (1 atm), 5.6 (6.2 kbar) for 1-ethoxypropene)],[11b] the cis-1,2-disubstituted dienophiles exhibited a preferential pressure-induced rate acceleration, and even the [4 + 2] cycloaddition reactions of the cis-1,2-disubstituted dienophiles were found to proceed predominantly (≥95%) through an endo transition state despite the increased destabilizing steric interactions (e.g. **19a**). Remarkably, the azadiene **5a** proved sufficiently reactive to undergo intermolecular [4 + 2] cycloaddition with a full range of dienophiles including the relatively unreactive olefins **17** (R = OCH_3 > H, Scheme II),[12] suggesting a broad and general scope for the 1-aza-1,3-butadiene Diels–Alder reactions. Applications of the [4 + 2] cycloaddition reactions of the *N*-sulfonyl-1-aza-1,3-butadienes are in progress as are additional studies to define their full [4 + 2] cycloaddition scope and the results of such studies will be reported in due course.



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Supplementary Material Available: Full experimental details for the preparation of **1**, representative experimentals for the preparation of **3–6**, full physical and spectroscopic characterization of **3–7**, **9**, **18–24**, a summary of computational studies (ref 10), and a summary of the X-ray structure determinations of **7a** and **19a** (55 pages); structure factors for **7a** and **19a** (18 pages). Ordering information is given on any current masthead page.

(7) Hudson, R. F.; Brown, C.; Record, K. A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 822.

(8) All new products exhibited ^1H NMR, ^{13}C NMR, IR, MS, and HRMS or CHN analyses consistent with the assigned structure. All yields are based on pure material isolated by chromatography (SiO_2, Florisil). Consistent with intuitive expectations, the *N*-sulfonylimines **5–6** proved more sensitive to hydrolysis by adventitious water than *N*-sulfonyl azadienes lacking the C-2 ethoxycarbonyl group[3] but may be purified by rapid chromatography with partial but not extensive loss of material.

(9) (a) Characteristic coupling constants (C2-OR axial): $J_{C2\text{-}H_e/C3\text{-}H_e}$ = 2.7–5.0 Hz, $J_{C2\text{-}H_e/C3\text{-}H_{ax}}$ = 2.5–4.4 Hz, $J_{C3\text{-}H_e/C4\text{-}H_e}$ = 1.7–3.3 Hz, $J_{C3\text{-}H_{ax}/C4\text{-}H_e}$ = 8.9–9.3 Hz, $J_{C4\text{-}H/C5\text{-}H}$ = 3.2–3.6 Hz, $J_{C2/H2}$ = 163–158 Hz. The exceptions (**20**, **22**, **24**) may exist in the all-equatorial conformation; for **20**: $J_{C2\text{-}H_{ax}/C3\text{-}H_{ax}}$ = 4.4 Hz, $J_{C3\text{-}H_{ax}/C4\text{-}H_{ax}}$ = 13 Hz, $J_{C4\text{-}H_{ax}/C5\text{-}H}$ = 3.6 Hz, $J_{C2/H2}$ = 156.6 Hz; for **22** $J_{C2/H2}$ = 153.7 Hz; for **24** $J_{C2/H2}$ = 140–145 Hz. (b) The single-crystal X-ray structure determinations of **7a** and **19a** established the C-2/C-4 and C-2/C-3/C-4 cis relative stereochemistry that must arise through endo [4 + 2] cycloaddition and proved consistent with the ^1H NMR spectroscopically assigned structures and stereochemistry. For **7a**: $J_{C2\text{-}H_e/C3\text{-}H_e}$ = 2.5 Hz, $J_{C2\text{-}H_e/C3\text{-}H_{ax}}$ = 4.1 Hz, $J_{C3\text{-}H_e/C4\text{-}H_e}$ = 3.0 Hz, $J_{C3\text{-}H_{ax}/C4\text{-}H_e}$ = 9.3 Hz, $J_{C4\text{-}H_e/C5\text{-}H}$ = 3.6 Hz, $J_{C2/H2}$ = 158.5 Hz; for **19a**: $J_{C2\text{-}H_e/C3\text{-}H_{eq}}$ = 2.8 Hz, $J_{C3\text{-}H_{ax}/C4\text{-}H_{eq}}$ = 8.9 Hz, $J_{C4\text{-}H_{ax}/C5}$ = 3.4 Hz, $J_{C2/H2}$ = 159.9 Hz.

(10) Computational studies (AM1, MNDO, supplementary material) support the diene C-2/dienophile OR secondary orbital interaction derived endo diastereoselectivity (sign and magnitude of diene C-2 (LUMO)/dienophile *O*R (HOMO) coefficient) *and* suggested a predictable rate acceleration with introduction of a *N*-sulfonyl-1-aza-1,3-butadiene C-2(CO_2Et) electron-withdrawing substituent [$\Delta\Delta E$ ($HOMO_{dienophile}/LUMO_{diene}$) = –0.2 eV (AM1)].

(11) (a) No trace of **26** was detected in the reaction mixture of **25**/**5a** with ethyl vinyl ether. (b) The relative rates of [4 + 2] cycloaddition were derived from product distributions obtained from the reaction of a mixture of (*Z*)- and (*E*)-1-ethoxypropene (2.8:1, 10 equiv) with **5a**: 25 °C, 96 h, CH_2Cl_2, 1 atm, **19a**:**20a** (1.0:3.3), 54% and 25 °C, 96 h, CH_2Cl_2, 6.2 kbar, **19a**:**20a** (1.0:2.0), 65%.

(12) Diene **5a** failed to participate in a [4 + 2] cycloaddition reaction with 1-octene, methyl acrylate, and *p*-benzoquinone under reaction conditions detailed herein.