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(2E)-4-Methoxy-2,4-pentadienamides as New Dienes in the Diels-Alder Reaction¹

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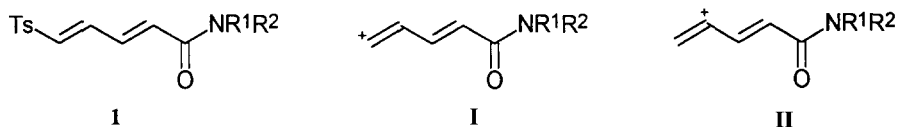
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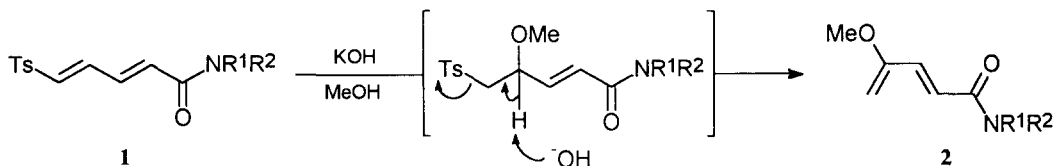
Abstract: (2E)-4-Methoxy-2,4-pentadienamides have been stereoselectively prepared by treatment of (2E,4E)-5-tosyl-2,4-pentadienamides with 1M methanolic potassium hydroxide in good yields. They behave as new electron-rich dienes in Diels-Alder reactions to give stereoselectively highly functionalized adducts **3** mainly with *endo*-selectivity and, after hydrolysis, only their corresponding cyclohexanone derivatives **4**. Semi-empirical calculations corroborate their reactivity.

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The use of substituted dienes in the Diels-Alder reaction increased the potential of this methodology to the synthesis of multi-functionalized 6-membered rings.² Dienes bearing electron-attracting and electron-donating groups are interesting substrates and have received much less attention.³ Recently, we described the preparation of the new dienic sulfones (2E,4E)-5-tosyl-2,4-pentadienamides **1** by iodosulfonylation-dehydroiodination of (2E)-2,4-pentadienamides and their application to the stereoselective synthesis of (2E,4E)-2,4-dienamides such as sarmentine and an *Achillea* amide.⁴ Compounds **1** react at the δ -position with nucleophiles acting thus as δ -acyldienyl cation equivalents of type I. We have found that these δ -tosyl dienamides **1** can also act as γ -acyldienyl cation equivalents of type II and can be transformed into (2E)-4-methoxy-2,4-pentadienamides (**2**, Scheme 1). These new dienes bearing an electron-releasing and an electron-withdrawing group should be adequate for the synthesis of highly functionalized Diels-Alder adducts.



Reaction of (2E,4E)-5-tosyl-2,4-pentadienamides⁵ **1** with 1M methanolic potassium hydroxide for 3h at room temperature produced (2E)-4-methoxy-2,4-pentadienamides **2**⁶ in good yields resulting from the Michael addition of the methoxide anion to the vinylic sulfone moiety followed by dehydrosulfinylation⁷ (Scheme 1 and Table 1). The obtained dienes were pure enough for subsequent and immediate Diels-Alder reactions although they could be stored in the freezer for few days without appreciable decomposition.



Scheme 1

Table 1. Preparation of 4-Methoxydienamides **2**.^a

No.	R ¹	R ²	yield ^b (%)	R _f ^c
2a		(CH ₂) ₄	85	0.15
2b		(CH ₂) ₅	93	0.45
2c	H	Bu ⁱ	86	0.42
2d	H	(<i>S</i>)-PhCHCH ₃	89	0.27 ^c

^a All compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS) ^b Crude yield (>90% pure by 300 MHz ¹H NMR). ^c Hexane/AcOEt 1:1. ^c [α]_D²² = -54.4 (c, 1.6; CHCl₃).

The [4+2] cycloaddition reaction between compounds **2** and different dienophiles was carried out under thermal conditions to give the corresponding cycloadducts **3** and are summarized in Table 2. The reaction with *N*-phenylmaleimide and dimethyl fumarate took place with *endo* selectivity affording mainly *cis*-adducts **3aa**, **3ba**, and **3bb** (Table 2, entries 1, 2, and 4). In the case of compound **3ba**, when the reaction was carried out under toluene reflux for 6d, a *ca.* 1:1 *endo/exo* mixture was obtained⁹ (Table 2, entry 3).

Intermolecular Diels-Alder reaction of **2** with electron-rich dienophiles such as enamines or vinyl ethers failed. Several attempts with dienophiles bearing one or two electron-releasing groups at the same olefinic carbon such as acrylic systems (methyl vinyl ketone, 1-chloroacrylonitrile and 1-bromoacrolein) also failed, probably due to the low reactivity of the dienophile or to steric reasons in the case of disubstituted olefins. The use of different Lewis acids [AlCl₃, Et₂AlCl, BF₃·Et₂O, ZnCl₂, Eu(tfd)₃] produced mainly hydrolysis of the vinyl methyl ether moiety to the corresponding (*E*)-2-oxo-2-pentenamides. In the case of the reaction of monoalkylated amide **2c** with *N*-phenylmaleimide, only complex mixtures of adducts were obtained. When chiral diene **2d**, derived from (*S*)-phenylethylamine, was allowed to react with 4-phenyl-1,2,4-triazoline-3,5-dione as dienophile for **1d** and at 50°C in a sealed tube the process showed a lack of diastereoselectivity with the isolation of a mixture of diastereomeric cycloadducts **3da** in a *ca.* 1:1 molar ratio (Table 2, entry 7).

According to calculations using the AM1 semi-empirical method¹⁰⁻¹³ for **2b**, the energy for the all *s-cis* conformation is -48.77 kcal/mol and for the *s-trans* is -48.33 kcal/mol (Scheme 1), and the energies corresponding to the frontier orbitals are typical for electron-rich dienes (E_{HOMO} = -9.49466 eV, E_{LUMO} = -0.30949 eV). Moreover, calculations on the model reaction between (*2E*)-4-methoxy-2,4-pentadienamide and maleimide were used to locate the *endo/exo* transition structures (Figure 1), showing that the *exo* transition state (ΔH_f = -61.0 kcal/mol) should be slightly favored over the *endo* (ΔH_f = -60.3 kcal/mol).

This value is subjected to the usual uncertainties in AM1 predictions as is shown in earlier Diels-Alder reaction analyses,¹⁴ where AM1 underestimates the relative stability of the sterically most crowded transition state by 1.4-3.4 kcal/mol when compared to the available experimental data and *ab initio* calculations. Assuming similar errors for the currently studied reaction, we would estimate the *endo* transition state to be

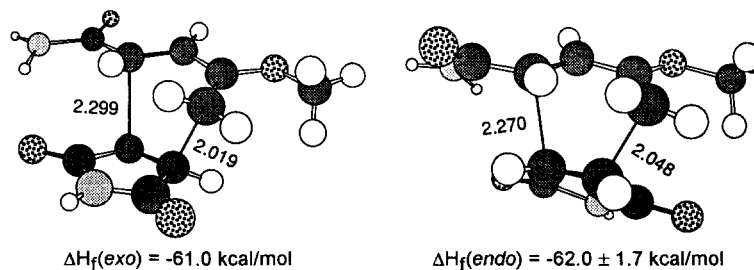
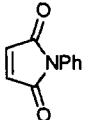
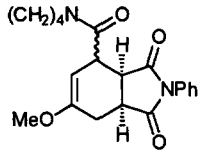
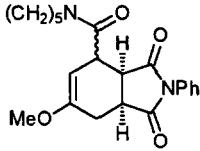
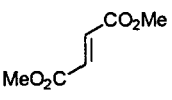
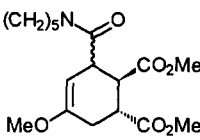
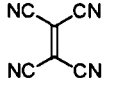
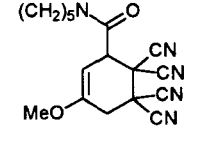
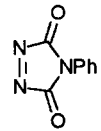
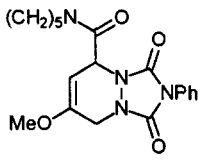
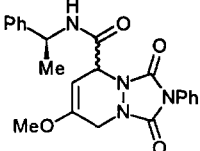


Figure 1. Computer plot of the AM1 transition states (lengths in Å) for the *exo* and *endo* cycloaddition of (*2E*)-4-methoxy-2,4-pentadienamide and maleimide.

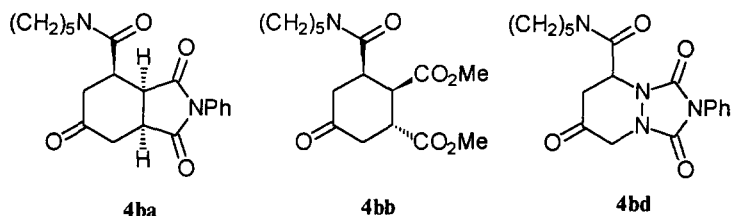
Table 2. Cycloaddition Reaction of 4-Methoxydienamides **2** with Dienophiles.

Entry	diene no.	dienophile	conditions	product ^a			
				structure	no.	<i>endo/exo</i> ratio ^b	yield ^c (%)
1	2a		THF reflux, 3d		3aa	1.5:1	31
2	2b		THF reflux, 1d		3ba	10:1	56
3	2b		PhCH ₃ reflux, 6d		3ba	0.86:1	90
4	2b		PhCH ₃ reflux, 3d		3bb	4:1	40
5	2b		THF r.t., 7d		3bc	-	51
6	2b		THF 50°C, 2d ^d		3bd	-	80
7	2d		THF 50°C, 1d ^d		3da	- ^e	60

^a All compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS)^b. Determined by ¹H NMR (300 MHz). ^c Isolated yield after column chromatography: Neutral alumina (entries 1, 2, and 4), deactivated silica gel (entry 5) or florisil® (entries 3, 6, and 7). ^d In a sealed tube. ^e Diastereomeric mixture *ca.* 1:1.

more stable than the *exo* one with a heat of formation of -62.0 ± 1.7 kcal/mol. The calculated values for the forming C-C bonds are in agreement with a one-step reaction occurring through a concerted pathway that is asynchronous, but with partial formation of both bonds. Lastly, AM1 predicts the *exo* cycloadduct ($\Delta H_f = -136.2$ kcal/mol) to be 1.4 kcal/mol more stable than the *endo* ($\Delta H_f = -134.8$ kcal/mol). The obtained results are in concordance with the experimental findings: the initial formation of the *endo* adduct through the less energetic transition state and the following equilibrium to the most stable *exo* adduct.

Final hydrolysis of the obtained cycloadducts furnished stereoselectively cyclohexanone derivatives **4**. In the case of adduct **3ba** obtained as a 0.86:1 *endo/exo* ratio (Table 1, entry 3), after treatment with 10% H₂SO₄ in THF for 4d, only *cis*-**4ba** was obtained in 67% isolated yield referred to **3ba**. The fumarate *cis/trans*-adduct **3bb** (Table 2, entry 4) gave only *cis*-**4bb** in 85% isolated yield after hydrolysis on alumina. Compound **3bd**, was hydrolyzed with conc. HCl in CH₂Cl₂ for 1d to provide **4bd** in 55% isolated yield, whereas in the case of adduct derived from tetracyanoethylene **3bc**, only extensive decomposition was observed after hydrolysis under different conditions.



In summary, (*2E*)-4-methoxy-2,4-pentadienamides are appropriate dienes in Diels-Alder reactions with normal-electron demand dienophiles for the synthesis of highly functionalized adducts which can be useful synthetic intermediates.¹⁵ Further studies about the use of these new dienes are now under way.

In a *typical procedure* for the synthesis of dienes **2**, a solution of **1**⁴ (0.3 mmol) in 1M methanolic KOH (5 mL) was stirred for 3 h at rt. The resulting solution was evaporated (15 Torr) and the residue was dissolved in water (10 mL) and extracted with EtOAc (3x10 mL). The organic phase was dried (Na₂SO₄) and evaporated (15 Torr) to yield compounds **2** (see Table 1) which were pure enough for subsequent use.¹⁷

REFERENCES AND NOTES

1. A preliminary account of this work was presented at the 4th International Symposium on Carbanion Chemistry, Fort Collins, CO, USA, August 12-16, 1995.
2. For reviews see for instance: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*, Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5; pp 315-399. (b) Roush, W. In *Comprehensive Organic Synthesis*, Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5; pp 513-550. (c) Carruthers, W. *Cycloadditions Reactions in Organic Synthesis*; Pergamon: New York, 1990.
3. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons: New York, 1990.
4. Bernabeu, M. C.; Chinchilla, R.; Nájera, C. *Tetrahedron Lett.* **1995**, *36*, 3401-3404.
5. Prepared by iododisulfonation of the corresponding (*2E*)-pentadienamides.⁴
6. Spectral NMR data for compound **2b**: δ_{H} (300 MHz) 1.54-1.68 (m, 6H), 3.53-3.65 (m, 4H), 3.66 (s, 3H), 4.41, 4.43 (2d, *J*=2.1 Hz, 2H), 6.71 and 7.04 (2d, *J*=15.0 Hz, 2H); δ_{C} (75 MHz) 24.5, 25.5, 26.6, 43.1, 46.8, 54.8, 91.7, 117.8, 137.8, 157.9 and 165.1.
7. Similar behaviour has been observed in the case of the (*E*)-*N*-isopropyl-3-tosylacrylamide to give *N*-isopropyl-2-methoxyacrylamide.⁸
8. Nájera, C.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 6085-6088.
9. The stereochemistry of compounds **3** could be deduced by one- and two-dimensional ¹H NMR studies, and NOE experiments.
10. Dewar, M. J. S.; Zebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
11. The AM1 method is considered to be the one of choice for studying Diels-Alder reactions since it shows the better agreement with both experimental data and *ab initio* results.¹³
12. Hehre, W. J.; Huang, W. W.; Burke, L. D.; Shusterman, A. J. SPARTAN, Version 4.0.4, Wavefunction, Irvine, 1995.
13. Lehd, M.; Jensen, F. *J. Org. Chem.* **1990**, *55*, 1034-1040 and references cited therein.
14. (a) Ortuño, R. M.; Batllori, R.; Ballesteros, M.; Monsalvatje, M.; Corbera, J.; Sánchez-Ferrando, F.; Font, J. *Tetrahedron Lett.* **1987**, *28*, 3405-3408. (b) Sodupe, M.; Oliva, A.; Bertran, J.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 2488-2490. (c) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129-1131.
15. Cycloaddition adducts of *N*-arylmaleimides and 2-methoxy-1,3-butadiene^{16a} or 2-(trimethylsilylmethyl)-1,3-butadiene have been used as starting products in the synthesis of Gracilins B and C.^{16b}
16. (a) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089-12090. (b) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616-9617.
17. We thank DGICYT (Project PB94-1515) from the Spanish Ministerio de Educación y Ciencia (MEC) and the Universidad de La Rioja (Project 95PYB23MRB) for financial support. R. C. thanks the Universidad de Alicante for a grant.

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