Pergamon

Tetrahedron Letters, Vol. 37, No. 20, pp. 3595-3598, 1996
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0040-4039/96 $15.00 + 0.00

S0040-4039(96)00631-4

(2*E*)-4-Methoxy-2,4-pentadienamides as New Dienes in the Diels-Alder Reaction[1]

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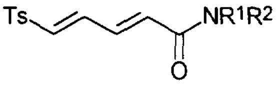
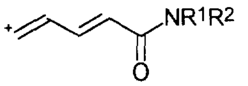
Abstract: (2*E*)-4-Methoxy-2,4-pentadienamides have been stereoselectively prepared by treatment of (2*E*,4*E*)-5-tosyl-2,4-pentadienamides with 1M methanolic potassium hydroxide in good yields. They behave as new electron-rich dienes in Diels-Alder reactions to give stereoselectively highly functionalized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

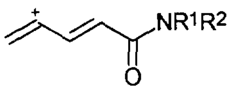
The use of substituted dienes in the Diels-Alder reaction increased the potential of this methodology to the synthesis of multi-functionalized 6-membered rings.[2] Dienes bearing electron-attracting and electron-donating groups are interesting substrates and have received much less attention.[3] Recently, we described the preparation of the new dienic sulfones (2*E*,4*E*)-5-tosyl-2,4-pentadienamides **1** by iodosulfonylation-dehydroiodination of (2*E*)-2,4-pentadienamides and their application to the stereoselective synthesis of (2*E*,4*E*)-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 (2*E*)-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.



1

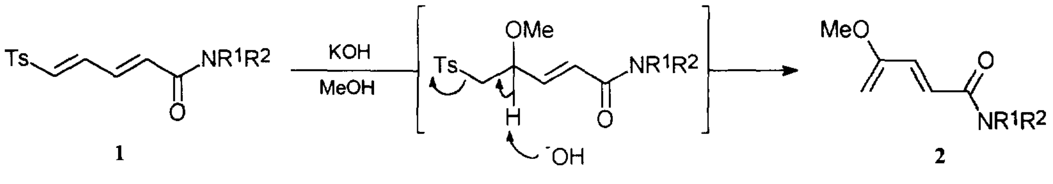


I



II

Reaction of (2*E*,4*E*)-5-tosyl-2,4-pentadienamides[5] **1** with 1M methanolic potassium hydroxide for 3h at room temperature produced (2*E*)-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 dehydrosulfinylation[7] (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	(*S*)-PhCHCH$_3$	89	0.27[c]

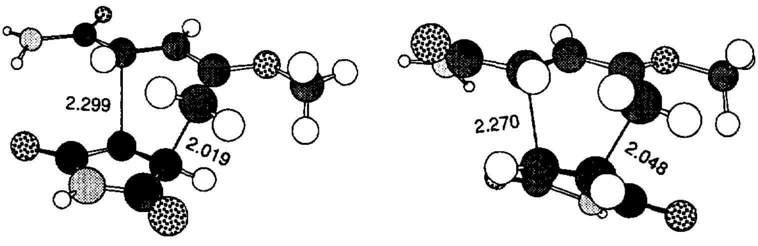
[a] All compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR and MS) [b] Crude yield (>90% pure by 300 MHz ^1H NMR). [c] Hexane/AcOEt 1:1. [c] $[\alpha]_D^{22}$ = -54.4 (*c*, 1.6; $CHCl_3$).

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 obtained[9] (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 [$AlCl_3$, Et_2AlCl, $BF_3{\cdot}Et_2O$, $ZnCl_2$, $Eu(tfd)_3$] 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 method[10-13] 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 (2*E*)-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).

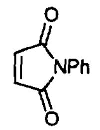
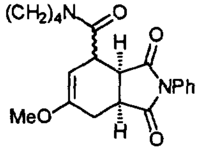
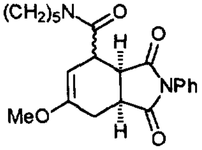
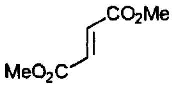
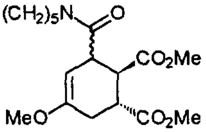
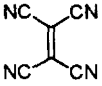
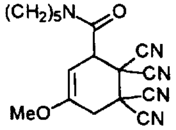
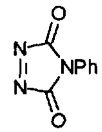
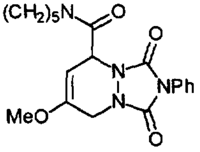
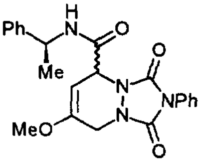
This value is subjected to the usual uncertainties in AM1 predictions as is shown in earlier Diels-Alder reaction analyses,[14] where AM1 underestimates the relative stability of the sterically most crowded transition state by 1.4-3.4 kcal/mol when compared to the available experimental data and *ab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



$\Delta H_f(exo)$ = -61.0 kcal/mol $\Delta H_f(endo)$ = -62.0 ± 1.7 kcal/mol

Figure 1. Computer plot of the AM1 transition states (lengths in Å) for the *exo* and *endo* cycloaddition of (2*E*)-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	product[a] no.	product[a] *endo*/*exo* ratio[b]	product[a] 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

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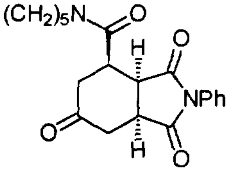
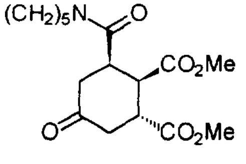
[a] All compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR and MS)[b]. Determined by ^1H NMR (300 MHz). [c] Isolated yield after column chromatography: Neutral alumina (entries 1, 2, and 4), deactivated silica gel (entry 5) or florisil® (entries 3, 6, and 7). [d] In a sealed tube. [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 (ΔH_f = -136.2 kcal/mol) to be 1.4 kcal/mol more stable than the *endo* (ΔH_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.

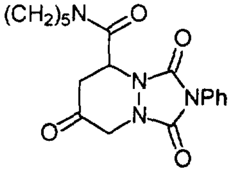
Final hydrolysis of the obtained cycloadducts furnished stereoselectively cyclohexanone derivatives **4**. In the case of adduct **3ba** obtained as a 0.86:1 *endo*/*exo* ratio (Table 1, entry 3), after treatment with 10% H_2SO_4 in THF for 4d, only *cis*-**4ba** was obtained in 67% isolated yield referred 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 hydrolized with conc. HCl in CH_2Cl_2 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.



4ba



4bb



4bd

In summary, (2*E*)-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 (Na_2SO_4) and evaporated (15 Torr) to yield compounds **2** (see Table 1) which were pure enough for subsequent use.[17]

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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.
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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.

(*Received in UK* 6 *March* 1996; *revised* 28 *March* 1996; *accepted* 3 *April* 1996)