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Synthesis of Spiropyrazolines

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ABSTRACT: *Synthesis of a series of novel 1,3,2′-triphenyl-4-aryl spiropyrazolines [5.4′]-2′-butenolides has been accomplished in good yield by regioselective 1,3-dipolar cycloaddition of diphenylnitrilimine with (E)-3-arylidenebutenolides. X-ray crystal structure analysis of one of the products* **4a** *confirms the structure of the product and the regiochemistry of cycloaddition.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:517–522, 1998

INTRODUCTION

In recent years, we have witnessed a significant increase in the utilization of 1,3-dipolar cycloaddition reaction as a useful methodology for the synthesis of novel heterocycles [1]. The regio- and stereoselection in these types of reactions have resulted in an elegant application in the synthesis of natural products [2]. Many pyrazoline derivatives have an important biological activity (e.g., as anti-inflammatory, analgetics, and herbicides), and their synthesis has attracted much attention [3]. Butenolide heterocycles have drawn much attention owing to their important pharmacological properties [4]. As part of our endeavor to explore the synthetic potentiality in the construction of novel pyrazoline derivatives [5,6] and also to study their biological applications, we have undertaken a systematic study of the reactions of the versatile 1,3-dipole diphenylnitrilimine (DPNI) with various 3-arylidenebutenolides.

In the present study, we discuss 1,3-dipolar cycloaddition reactions of DPNI with 3-arylidenebutenolides. The Frontier Molecular Orbital method has been used to study the regiochemistry of cycloaddition.

RESULTS AND DISCUSSION

In an attempt to evaluate the effect of the presence of electron-donating and electron-withdrawing groups in direct conjugation with the double bond of the dipolarophile on the regioselectivity in the cycloaddition reactions, we have studied the reactions of DPNI with α-arylidene-γ-phenyl-$\Delta^{\beta\gamma}$ butenolides, resulting in the formation of novel spiropyrazolines in good yields (Scheme 1). The addition is highly regioselective to give a single product exclusively in each of the cases that we have studied.

The 3-arylidenebutenolides were prepared by the condensation of β-benzoylpropionic acid with aromatic aldehydes in the presence of acetic anhydride and sodium acetate by the Perkin Erlenmeyer reaction [7], and the products were assigned the *E* configuration on the basis of their NMR spectra, in accordance with a literature report [8,9]. Reactions of 3-arylidenebutenolides with DPNI (generated in situ from N-phenylbenzhydrazidoyl chloride in chloroform solution in the presence of triethylamine at room temperature) led to the formation of 1:1 adducts as a single product in each case, as evidenced

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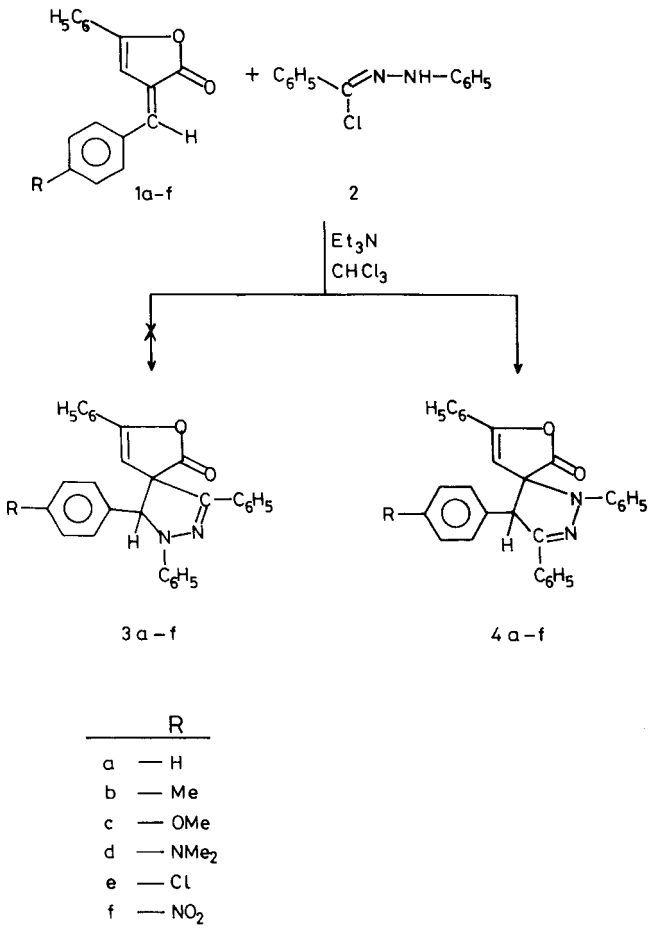
by TLC and mass spectral studies. The reaction has yielded a series of novel 1,3,2′-triphenyl-4-aryl spiropyrazolines [5.4′]-2′-butenolides by the regioselective cycloaddition of the 1,3-dipole across the exocyclic double bond of the 3-arylidenebutenolides in each case. The reaction time for these reactions varied, depending on the substituent on the benzene ring of the benzylidene moiety (Table 4). The structure of each product (**4a–f**) and the regiochemistry of cycloaddition has been confirmed by spectroscopic data and by X-ray structure analysis of the cycloadduct **4a**. Thus, the carbonyl absorption in the IR spectrum of the product **4a** exhibited a peak at 1795 cm^{-1} showing an increase of 32 cm^{-1} from the benzylidenebutenolides, indicating the loss of conjugation of the carbonyl group. The PMR spectrum of the product exhibited a singlet at δ 5.08 due to the benzylic proton, a singlet at δ 5.31 due to the olefinic proton, and a multiplet in the range δ 7.11–7.68 due to aromatic protons. ^{13}C NMR spectra of the product showed peaks for two sp^3 carbons, three sp^2 carbons, one carbonyl carbon, and aromatic carbons that confirmed the proposed structures. The regiochemistry of the cycloadducts (**4a–f**) was established by ^{13}C NMR spectroscopy. The chemical shift values for the spiro quaternary carbon atom = 78.22–78.37 (singlet). These chemical shift values are in good agreement with the literature value [6], wherein the nitrogen terminal of the 1,3-dipole is attached to the spiro quaternary carbon atom. The structure and the regiochemistry of cycloaddition was further corroborated by X-ray crystal analysis of the product **4a** (Figure 1).

Identical results were obtained with other derivatives of butenolides in the cycloaddition with DPNI, irrespective of the substituent present in the arylidene moiety.

Molecular Orbital Calculation

We have examined the Frontier Molecular Orbital (FMO) interaction to study the electronic effects on the dipolarophile by the substituent and to explain the regioselectivity of cycloaddition. The dipolarophilic activity of double bonds depends, to a large extent, on the effect of substituents [10]. The computations were performed using the all-valence semiempirical molecular orbital methods AM1 [11] and PM3 [12,13] included in the GAUSSIAN 94 package (version D.3) [14].

From Tables 1 and 2, it is clear that the energy gap between the LUMO of the dipolarophile and the HOMO of the dipole is significantly smaller than that



SCHEME 1

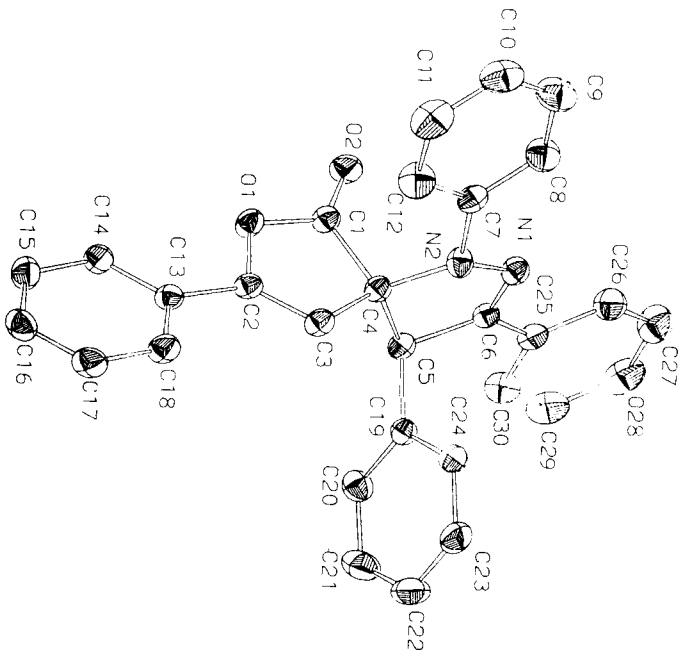
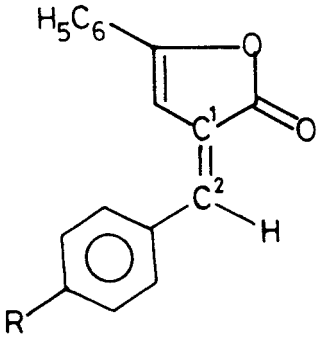


FIGURE 1 Ortep diagram of **4a**.

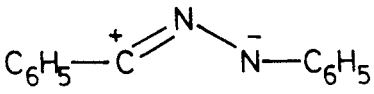
TABLE 1 Computed Data for **1a–f**



1a-f

	HOMO Energy (eV)		*LUMO Energy (eV)*		LUMO Coefficients			
					C_1		C_2	
Substrate	*AM1*	*PM3*	AM1	PM3	AM1	PM3	AM1	PM3
1a	−8.69	−8.84	−1.20	−1.20	−0.35	−0.35	+0.53	+0.53
1b	−8.63	−8.69	−1.18	−1.29	−0.35	−0.36	+0.53	+0.50
1c	−8.55	−8.59	−1.15	−1.25	−0.35	−0.35	+0.53	+0.50
1d	−8.21	−8.35	−1.04	−1.21	−0.30	−0.35	+0.53	+0.50
1e	−8.77	−8.87	−1.34	−1.30	−0.36	−0.36	+0.52	+0.51
1f	−9.10	−9.23	−1.86	−1.83	−0.36	−0.35	+0.41	+0.40

TABLE 2 Computed Data for 1,3-Dipole



1,3-dipole

	HOMO Energy	*LUMO Energy*	*HOMO Coefficients*	
Method	*(eV)*	*(eV)*	C^+	N^-
AM1	−7.84	−0.67	−0.46	+0.58
PM3	−8.19	−0.59	−0.41	+0.60

of the LUMO of the dipole and the HOMO of the dipolarophile, irrespective of the substituent in the dipolarophile. Thus, the major interaction involves the LUMO of the dipolarophile and the HOMO of the dipole.

According to the FMO theory of reactivity, the majority of chemical reactions take place at the position and in the orientation where a maximum overlap of HOMO and LUMO of the reactants is possible [15,16]. Accordingly, bond formation will take place between those atoms having the highest (or smallest) coefficients in the interacting pair of HOMO and LUMO.

Calculation of the atomic coefficients of the dipolarophiles (**1a–f**) by both AM1 and PM3 methods reveal that LUMO coefficients of the olefinic carbons are comparable in magnitude. In all the cases (**1a–f**), it is seen that the atomic coefficient of the olefinic carbon (C_1) of the dipolarophile is comparable in value to that of the cationic carbon of the 1,3-dipole, and the other olefinic carbon (C_2) of the dipolarophile is comparable to the anionic nitrogen of the dipole, resulting in the overlap between these orbitals leading to the unobserved regioisomer (**3a–f**).

Thus, the molecular orbital overlap concept does not explain the regiochemistry of the observed product (**4a–f**). A possible explanation for this mode of cycloaddition is that a steric effect overweighs the electronic effect [6,17]. In the case of nitrilimines, the fact that the C atom is more sensitive to steric requirements than the N atom is well documented. Because there is not much difference in the atomic coefficients of the dipolarophile (**1a–f**) in its LUMO, the carbon terminal of the 1,3-dipole approaches the less substituted carbon of the dipolarophile from the

TABLE 3 Characterization of 3-Arylidenebutenolides

Substrate	Mp(°C) Found	Mp(°C) Reported	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	IR (KBr) (cm^{-1}) $\vartheta_{c=0}$
1a	153–154	153–154 [9]	6.93 (d, 1H, J = 0.8), 7.42 (s, 1H), 7.21–7.82 (m, 10H)	1763
1b	142–143	—	2.31 (s, 3H), 6.90 (d, 1H, J = 0.9), 7.37 (s, 1H), 7.11–7.77 (m, 9H)	1764
1c	170–171	171–172 [9]	3.86 (s, 3H), 6.92 (d, 1H, J = 0.9), 7.35 (s, 1H), 7.01–7.72 (m, 9H)	1765
1d	151–153	—	3.01 (s, 6H), 6.70 (d, 2H, J = 8.7), 6.92 (d, 1H, J = 0.9), 7.37 (s, 1H), 7.01–7.69 (m, 7H)	1757
1e	228–230	—	6.87 (d, 1H, J = 0.9), 7.35 (s, 1H), 7.24–7.76 (m, 9H)	1760
1f	282–284	—	6.91 (d, 1H, J = 0.9), 7.38 (s, 1H), 7.11–7.67 (m, 7H), 8.22 (d, 2H, J = 8.2)	1765

TABLE 4 Spiropyrazolines **4a–f** Prepared

Product	Reaction Time (h)	Yield[a] (%)	Mp (°C)	IR (KBr) (cm^{-1}) $\vartheta_{C=O}$	MS (70 eV m/z) (M^+)	Molecular Formula	Analysis Calcd/Found C	H	N
							81.42	5.01	6.33
4a	36	76	220–222	1795	442	$C_{30}H_{22}N_2O_2$	81.06	4.96	6.39
							81.55	5.30	6.14
4b	48	78	215–216	1793	456	$C_{31}H_{24}N_2O_2$	81.32	5.36	6.19
							78.78	5.12	5.93
4c	72	62	173–175	1794	472	$C_{31}H_{24}N_2O_3$	78.39	5.06	5.96
							79.14	5.61	8.66
4d	60	64	187–189	1792	485	$C_{32}H_{27}N_3O_2$	79.30	5.59	8.59
							75.61	4.45	5.88
4e	48	71	180–182	1792	476	$C_{30}H_{21}N_2O_2Cl$	74.97	4.40	5.95
							73.90	4.34	8.62
4f	60	65	221–223	1795	487	$C_{30}H_{21}N_3O_4$	74.04	4.31	8.49

[a]Yield of pure, isolated product.

least hindered side to give the observed regioisomer (**4a–f**).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a IR-470 Shimadzu instrument. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL FX 90Q at 90 MHz and JEOL GX 400 at 100.4 MHz, respectively. Elemental analyses were carried out on a CEST 1106 instrument. Mass spectra were recorded on a JEOL DX 303HF spectrometer with a JMA DA 5000 data system. Column chromatography was performed on silica gel (100–200 mesh).

The starting materials 3-arylidenebutenolides [7] and N-phenylbenzhydrazidoyl chloride [18] were prepared according to literature procedures. The physical constants and spectral details of the butenolides are given in Table 3.

Reaction of Each 3-Arylidenebutenolide with DPNI: General Procedure

To a solution of the 3-arylidenebutenolide (3 mmol) and N-phenylbenzhydrazidoyl chloride (3 mmol) in dry chloroform, triethylamine (3.3 mmol) was added. The reaction mixture was stirred at room temperature until disappearance of the starting material was observed, as monitored by TLC. After the reaction was over, the solution was filtered to remove triethylamine hydrochloride, and the solvent was evaporated under a vacuum. The resulting crude product was purified by column chromatography (hexane/EtOAc, 9:1) and crystallization from (hexane/benzene, 1:1). The reaction time, physical con-

TABLE 5 ^{1}H and ^{13}C NMR Spectral Data for Spiropyrazolines **4a–f**

Product	*^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)*	*^{13}C NMR ($CDCl_3$/TMS) ppm*
4a	5.08 (s, 1H), 5.31 (s, 1H), 7.11–7.68 (m, 20H)	62.87, 78.29, 102.18, 116.88, 122.42, 125.32, 126.71, 127.43, 128.37, 128.43, 128.78, 128.94, 129.16, 129.23, 130.60, 131.08, 134.67, 144.17, 150.03, 153.73, 175.06
4b	2.33 (s, 3H), 5.03 (s, 1H), 5.35 (s, 1H), 6.95–7.65 (m, 19H)	21.21, 62.21, 78.24, 102.11, 117.32, 122.42, 122.52, 125.12, 126.94, 127.79, 128.31, 128.74, 128.82, 129.17, 129.44, 129.58, 130.47, 131.37, 138.23, 144.29, 150.89, 153.93, 175.37
4c	3.81 (s, 3H), 5.03 (s, 1H), 5.38 (s, 1H), 6.90–7.68 (m, 19H)	55.23, 62.59, 78.31, 102.80, 114.42, 116.44, 121.79, 122.17, 125.39, 126.76, 127.71, 128.32, 128.69, 128.78, 129.11, 129.47, 130.47, 131.42, 144.40, 150.14, 153.42, 159.42, 175.14
4d	2.92 (s, 6H), 4.98 (s, 1H), 5.43 (s, 1H), 6.63 (d, 2H, J = 8.8), 6.99–7.71 (m, 17H)	40.30, 62.43, 78.37, 102.82, 112.64, 116.68, 121.81, 122.10, 125.36, 126.75, 127.66, 128.35, 128.72, 128.76, 129.11, 129.43, 130.42, 131.39, 144.46, 150.12, 150.67, 153.38, 175.29
4e	5.08 (s, 1H), 5.37 (s, 1H), 7.01–7.63 (s, 19H)	61.86, 78.22, 101.53, 117.12, 122.71, 125.33, 126.62, 127.19, 128.51, 128.83, 129.13, 129.17, 129.48, 130.07, 130.78, 133.21, 134.30, 144.02, 149.85, 154.14, 174.65
4f	5.11 (s, 1H), 5.28 (s, 1H), 7.00–7.61 (m, 17H), 8.18 (d, 2H, J = 8.1)	61.73, 78.37, 100.56, 117.59, 123.22, 124.50, 125.39, 126.55, 126.91, 128.69, 128.93, 129.25, 129.43, 129.81, 130.40, 131.07, 142.05, 143.72, 147.84, 149.35, 154.80, 174.21

stants, and the spectral details for (**4a–f**) are reported in Tables 4 and 5.

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