Heteroatom Chemistry
Volume 10, Number 4, 1999

A Regioselective 1,3-Dipolar Cycloaddition of 2-Arylidene-1-tetralones with DPNI

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Received 13 November 1998; revised 20 January 1999

ABSTRACT: *Synthesis of a series of novel 1,3-diphenyl-4-arylspiropyrazolines[5.2^1]-1^1-tetralones has been accomplished in good yield by regioselective 1,3-dipolar cycloaddition of diphenylnitrilimine with (E)-2-arylidene-1-tetralones. X-ray crystal structure analysis of one of the products* **4b** *confirms the structure and the regiochemistry of cycloaddition.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 331–336, 1999

INTRODUCTION

1,3-Dipolar cycloaddition offers a versatile route for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds [1]. The 1,3-dipolar cycloaddition reaction has been applied to the synthesis of natural products such as sugar derivatives [2], β-lactams [3], aminoacids [4], and alkaloids [5]. Pyrazoline derivatives have a broad spectrum of biological activity (e.g., as anti-inflammatory, analgetics, anti-implantation agents, and herbicides), and their synthesis has attracted much attention [6]. Tetralone derivatives have been utilized for the synthesis of benzophenanthridine antitumor alkaloids [7a] and ring B of tetracyclins [7b]. As a part of our ongoing research program in the construction of novel pyrazoline derivatives [8–10], 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 2-arylidene-1-tetralones. The Frontier molecular orbital (FMO) method has been used to study the regiochemistry of cycloaddition.

RESULTS AND DISCUSSION

In an attempt to evaluate the effect of the presence of the 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 2-arylidene-1-tetralones, 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 required dipolarophiles were prepared by the base catalyzed condensation of 1-tetralone with aromatic aldehydes [11], and each product was assigned the *E* configuration, based on the relative

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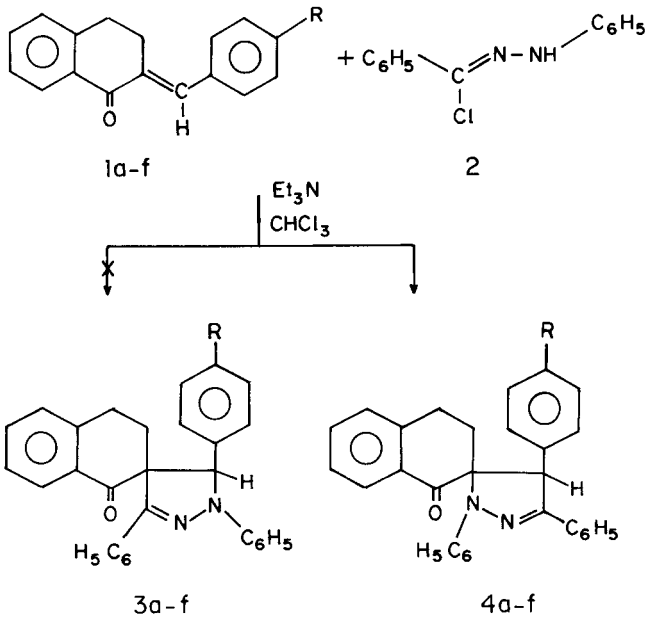
Contract Grant Sponsors: University Grants Commission, New Delhi and University of Madras
Contract Grant Sponsors: Financial support from CSIR, UGC-SAP
 CCC 1042-7163/99/040331-06



R
a -H
b -Me
c -OMe
d -NMe_2
e -Cl
f -NO_2

SCHEME 1

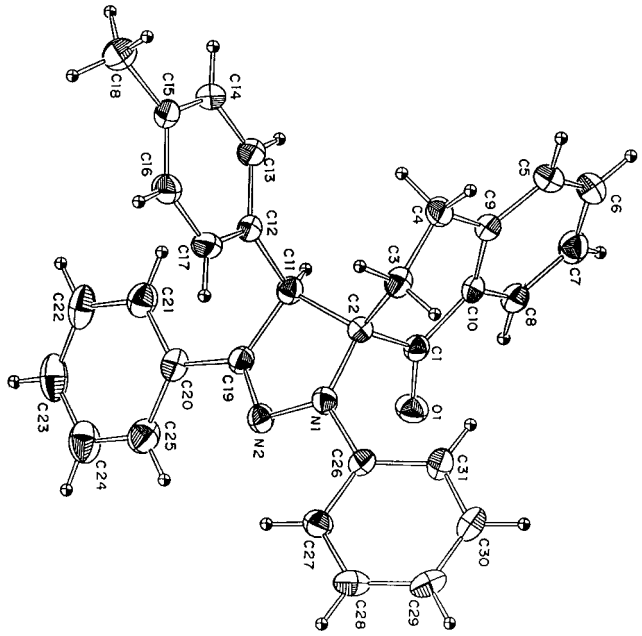
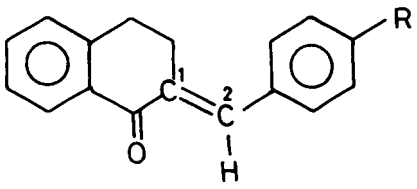


FIGURE 1 Ortep diagram of **4b**.

chemical shift value of olefinic protons at about δ = 7.85, in accordance with ^{1}H NMR literature data [12]. Reactions of 2-arylidene-1-tetralone 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 by TLC and mass spectral studies.

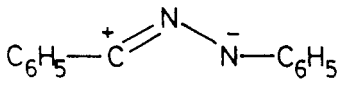
TABLE 1 Computed Data for **1a–f**



1a–f

	HOMO Energy (eV)		*LUMO Energy (eV)*		*LUMO Coefficients*			
					C_1		*C_2*	
Substrate	*AM1*	*PM3*	*AM1*	*PM3*	*AM1*	*PM3*	*AM1*	*PM3*
1a	−9.28	−9.52	−0.59	−0.58	−0.32	−0.26	+0.42	+0.35
1b	−9.09	−9.17	−0.58	−0.61	−0.32	−0.35	+0.42	+0.42
1c	−8.86	−8.95	−0.56	−0.59	−0.32	−0.34	+0.43	+0.42
1d	−8.46	−9.29	−0.51	−0.66	−0.31	−0.36	+0.42	+0.43
1e	−9.29	−9.21	−0.75	−0.76	−0.35	−0.37	+0.42	+0.41
1f	−9.83	−9.94	−1.43	−1.49	−0.31	−0.32	+0.25	+0.25

TABLE 2 Computed Data for 1,3-Dipole



1,3-dipole

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

The reaction has yielded a series of novel 1,3-diphenyl-4-aryl spiropyrazolines [5.2[1]]-1[1]-tetralone by the regioselective cycloaddition of the 1,3-dipole across the exocyclic double bond of the 2-arylidene-1-tetralone in each case. 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 **4b.** Thus, the carbonyl absorption in the IR spectrum of the product **4a** exhibited a peak at 1687 cm^{-1} showing an increase of 26 cm^{-1} from the benzylidenetetralone, indicating the loss of conjugation of the carbonyl group. The PMR spectrum of the product exhibited a multiplet at δ 2.16, 2.60, 2.78, and 2.95 due to the four methylene protons, a singlet at δ 4.74 due to the benzylic proton, a multiplet in the range δ 6.88–7.56, and a doublet at δ 8.14 due to aromatic protons. The ^{13}C NMR spectrum of the product showed peaks for four sp^3 carbons, one sp^2 carbon, 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 spiro quaternary carbon atoms = 76.00–76.68 (singlet). These chemical shift values are in good agreement with the literature value [9,10], 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 **4b** (Figure 1).

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

MOLECULAR ORBITAL CALCULATION

We have examined the FMO interaction to study the electronic effects on the dipolarophile by both the electron-withdrawing and electron-releasing substituent and to explain the regiochemistry of cycloaddition. The dipolarophilic activity of double bonds depends to a large extent on the effect of substituents [13]. According to the FMO theory of reactivity, the majority of chemical reactions takes place at the position and in the orientation where a maximum overlap of HOMO and LUMO of the reactants is possible [14,15]. Accordingly, bond formation will take place between those atoms having the highest (or smallest) coefficients in the interacting pair of HOMO and LUMO. The computations were performed using the all-valence semiempirical molecular orbital methods AM1 [16] and PM3 [17,18] included in the GAUSSIAN 94 package (version D.3) [19].

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

TABLE 3 Characterization of 2-Arylidene-1-tetralones

Substrate	Mp (°C)		^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	IR (KBr) (cm^{-1}) $\nu_{c=o}$
	Found	Reported		
1a	104–105	107 [11]	2.90–3.08 (m, 4H), 7.21–7.47 (m, 8H), 7.87 (s, 1H), 8.14 (d, 1H, J = 8.1)	1661
1b	127–128	—	2.92–3.09 (m, 4H), 2.33 (s, 3H), 7.23–7.50 (m, 7H), 7.82 (s, 1H), 8.12 (d, 1H, J = 8.0)	1661
1c	113–115	—	2.92–3.14 (m, 4H), 3.83 (s, 3H), 6.88–7.49 (m, 7H), 7.85 (s, 1H), 8.12 (d, 1H, J = 7.9)	1667
1d	155–157	—	2.90–3.09 (m, 4H), 2.96 (s, 6H), 6.70 (d, 2H, J = 8.1), 7.21–7.47 (m, 5H), 7.86 (s, 1H), 8.06 (d, 1H, J = 8.1)	1653
1e	147–149	—	2.91–3.08 (m, 4H), 7.30–7.46 (m, 7H), 7.79 (s, 1H), 8.13 (d, 1H, J = 8.0)	1668
1f	190–192	—	2.92–3.08 (m, 4H), 7.30–7.62 (m, 5H), 7.84 (s, 1H), 8.10 (d, 1H, J = 8.0), 8.27 (d, 2H, J = 8.3)	1665

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

Product	Reaction Time (*h*)	Yield[a] (°C)	Mp (°C)	IR (KBr) (cm^{-1})	MS (70 eV m/z) (M^+)	Molecular formula	Analysis Calcd/Found C	H	N
4a	24	84	171–172	1687	428	$C_{30}H_{24}N_2O$	84.08	5.65	6.54
							83.73	5.71	6.47
4b	30	82	185–186	1690	442	$C_{31}H_{26}N_2O$	84.12	5.93	6.33
							84.59	5.99	6.24
4c	36	79	187–189	1688	458	$C_{31}H_{26}N_2O_2$	81.19	5.72	6.11
							80.89	5.64	6.20
4d	48	71	134–136	1685	471	$C_{32}H_{29}N_3O$	81.49	6.20	8.91
							81.23	6.30	8.79
4e	36	75	158–160	1684	462	$C_{30}H_{23}N_2OCl$	77.90	5.02	6.06
							77.59	5.11	6.17
4f	36	76	251–253	1684	473	$C_{30}H_{23}N_3O_3$	76.08	4.90	8.88
							76.19	4.96	8.80

[a]Yield of pure, isolated product.

TABLE 5 Spiropyrazolines **4a–f** Prepared

Product	^1H NMR ($CDCl_3$/TMS δ), *J* (*Hz*)	^{13}C NMR ($CDCl_3$/TMS) ppm
4a	2.16 (m, 1H), 2.60 (m, 1H), 2.78 (m, 1H), 2.95 (m, 1H), 4.74 (s, 1H), 6.88–7.56 (m, 18H), 8.14 (d, 1H, $J = 7.8$)	26.30, 27.13, 60.85, 76.50, 118.77, 121.48, 126.47, 127.41, 128.32, 128.43, 128.53, 128.90, 129.05, 129.41, 130.02, 132.40, 132.13, 134.54, 135.93, 143.23, 143.50, 148.30, 194.06
4b	2.15 (m, 1H), 2.31 (s, 3H), 2.65 (m, 1H), 2.80 (m, 1H), 2.96 (m, 1H), 4.71 (s, 1H), 6.88–7.61 (m, 17H), 8.14 (d, 1H, $J = 7.8$)	21.10, 26.01, 26.80, 60.18, 76.06, 118.29, 120.96, 126.12, 127.00, 127.90, 128.03, 128.50, 128.72, 128.99, 129.49, 130.02, 131.86, 132.45, 134.16, 137.91, 142.92, 143.21, 148.04, 193.77
4c	2.14 (m, 1H), 2.61 (m, 1H), 2.79 (m, 1H), 2.94 (m, 1H), 3.72 (s, 3H), 4.70 (s, 1H), 6.79–7.56 (m, 17H), 8.12 (d, 1H, $J = 7.8$)	25.95, 27.77, 55.08, 59.83, 76.00, 114.14, 118.23, 120.94, 126.14, 127.00, 127.39, 127.91, 128.04, 128.50, 128.73, 128.96, 130.04, 130.69, 131.83, 134.18, 142.91, 143.20, 148.05, 159.29, 193.82
4d	2.13 (m, 1H), 2.63 (m, 1H), 2.82 (m, 1H), 2.93 (m, 1H), 2.98 (s, 6H), 4.70 (s, 1H), 6.68 (d, 2H, $J = 8.1$), 6.90–7.58 (m, 15H), 8.13 (d, 1H, $J = 7.9$)	26.12, 26.91, 40.11, 60.10, 76.09, 111.59, 118.15, 123.56, 126.26, 126.95, 128.15, 128.53, 128.71, 129.26, 130.23, 130.99, 132.05, 134.05, 137.88, 142.89, 143.39, 148.31, 150.02, 194.15
4e	2.12 (m, 1H), 2.62 (m, 1H), 2.76 (m, 1H), 2.90 (m, 1H), 4.70 (s, 1H), 6.89–7.53 (m, 17H), 8.12 (d, 1H, $J = 7.9$)	26.04, 26.85, 59.59, 76.30, 118.70, 121.44, 126.04, 127.18, 128.18, 128.56, 128.76, 129.09, 129.92, 130.92, 131.48, 134.07, 134.18, 134.32, 142.62, 143.07, 147.73, 193.30
4f	2.15 (m, 1H), 2.63 (m, 1H), 2.79 (m, 1H), 2.96 (m, 1H), 4.82 (s, 1H), 7.00–7.59 (m, 15H), 8.11 (d, 1H, $J = 7.8$), 8.20 (d, 2H, $J = 7.9$)	26.21, 27.08, 59.47, 76.68, 119.37, 122.13, 124.13, 125.97, 127.44, 128.40, 128.53, 128.67, 128.81, 129.29, 129.82, 130.58, 131.11, 134.54, 142.27, 142.94, 143.24, 147.37, 147.72, 192.70

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.

Calculation of the atomic coefficients of the dipolarophiles **(1a–f)** by both AM1 and PM3 methods reveals that LUMO coefficients of the olefinic carbons are comparable in magnitude. In the case of the electron-withdrawing substituent present in **1f**, it is seen that the atomic coefficient of the olefinic carbon (C_1) of the dipolarophile is comparable in value to that of the anionic nitrogen of the 1,3-dipole, and the other olefinic carbon (C_2) of the dipolarophile is comparable to the cationic carbon of the dipole, resulting in the overlap between these orbitals consistent with the formation of the observed regioisomer **4f**, whereas, in the case of unsubstituted and electron-releasing substituents **(1a–e),** the atomic coefficient of the olefinic carbon (C_1) of the dipolarophile is comparable in value to that of the cationic carbon of the dipole, and that of the other olefinic carbon (C_2) of the dipolarophile is comparable to that of the anionic nitrogen of the dipole, resulting in the overlap between these orbitals, which would lead to the unobserved regioisomer **(3a–e).**

Thus, the molecular orbital overlap concept does not explain the regiochemistry of the observed product **(4a–e).** A plausible explanation for the observed mode of cycloaddition is that a steric effect dominates the electronic effect [9,10,20]. In the case of nitrilimines, the fact that the C atom is more sensitive to steric requirements than the N atom is well documented. Since 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 least hindered side to give the observed regioisomer **(4a–f).**

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Jeol FX 90Q spectrometer at 90 MHz and a Jeol GX 400 spectrometer at 100.4 MHz, respectively. Mass spectra were recorded on a Finnigan MAT–8230 GC–Mass spectrometer. Elemental analyses were carried out on a CEST 1106 instrument. Column chromatography was performed on silica gel (100–200 mesh).

The starting materials 2-arylidene-1-tetralones [11] and N-phenylbenzhydrazidoyl chloride [21] were prepared according to literature procedures. The physical constants and spectral details of the tetralones are given in Table 3.

Reaction of 2-arylidene-1-tetralones with DPNI; General Procedure

To a solution of 2-arylidene-1-tetralone (3 mmol) and N-phenylbenzhydrazidoyl-chloride (3 mmol) in dry chloroform, triethylamine (3.3 mmol) was added. The reaction mixture was stirred at r.t. until the disappearance of the starting material, as monitored by TLC, was observed. After the reaction was over, the mixture 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 constants, and spectral details for **(4a–f)** are reported in Tables 4 and 5.

ACKNOWLEDGMENTS

The authors acknowledge RSIC, IIT, Madras for some of the spectra reported here and also acknowledge Dr. D. Velmurugan, Department of Crystallography and Bio-Physics, University of Madras, for X-ray crystal analysis.

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