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Synthesis of Spiropyrazoline [5.3′] 4′-Chromanones

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ABSTRACT: *Synthesis of a series of novel 1,3-diphenyl-4-aryl spiropyrazolines [5.3'] 4'-chromanones has been accomplished in good yields by regioselective 1,3-dipolar cycloaddition of diphenylnitrilimine to 3-arylidene-4-chromanones. X-ray crystal structure analysis of one of the products* **4a** *confirms the structure and the regiochemistry of cycloaddition.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:327–332, 1998

INTRODUCTION

In recent years, we have witnessed a significant increase in the utilization of 1,3-dipolar cycloaddition reactions as a useful methodology for the synthesis of novel heterocycles [1]. The regio and stereoselection in these types of reactions have resulted in elegant applications in the synthesis of natural products [2]. As a part of our endeavour to explore the synthetic potentiality of this reaction in the construction of spiroheterocyclic compounds [3], and also study their biological applications, we have undertaken a systematic study of the reaction of the versatile 1,3-dipolar compound diphenylnitrilimine (DPNI) with various 3-arylidene-4-chromanones. Apart from a few examples of 1,3-dipolar cycloaddition reactions to coumarin and chromanones [4,5], there appears to be no instance of arylidene chromanones having been used as dipolarophilic partners in 1,3-dipolar cycloaddition reactions. Chromanone heterocycles have drawn much attention owing to their important pharmacological properties [6].

In the present study, we discuss 1,3-dipolar cycloaddition reactions of DPNI with various arylidene chromanones. The frontier molecular orbital method has been used to evaluate the regiochemistry of cycloaddition.

RESULTS AND DISCUSSION

1,3-Dipolar cycloaddition reactions of DPNI with 3-arylidene-4-chromanones have resulted in the formation of novel spiroheterocycles in good yields (Scheme 1). The addition is highly regiospecific to give a single product exclusively in each of the cases that we have studied. The 3-arylidene-4-chromanones were prepared by the acid catalyzed reaction of 4-chromanones with various benzaldehydes, and

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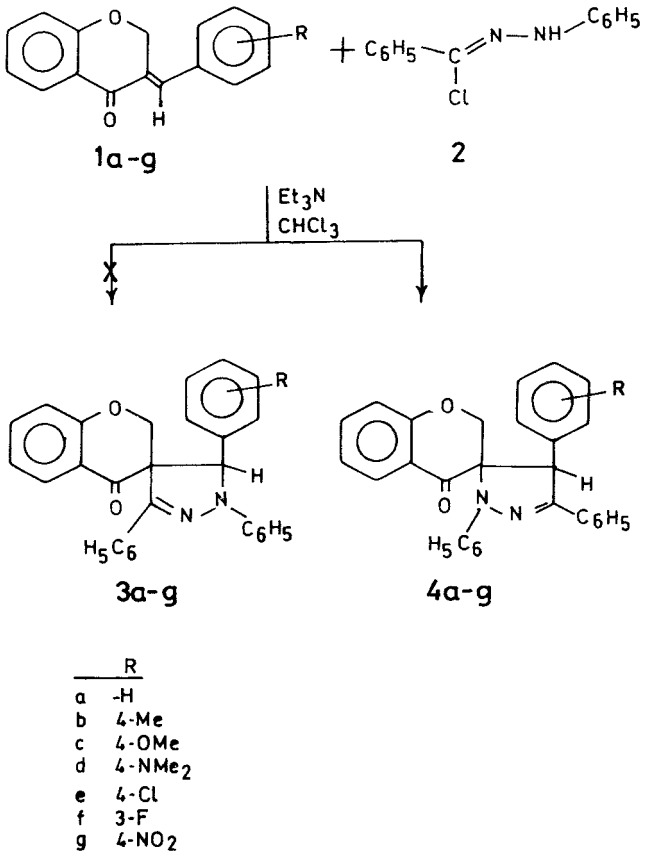

SCHEME 1

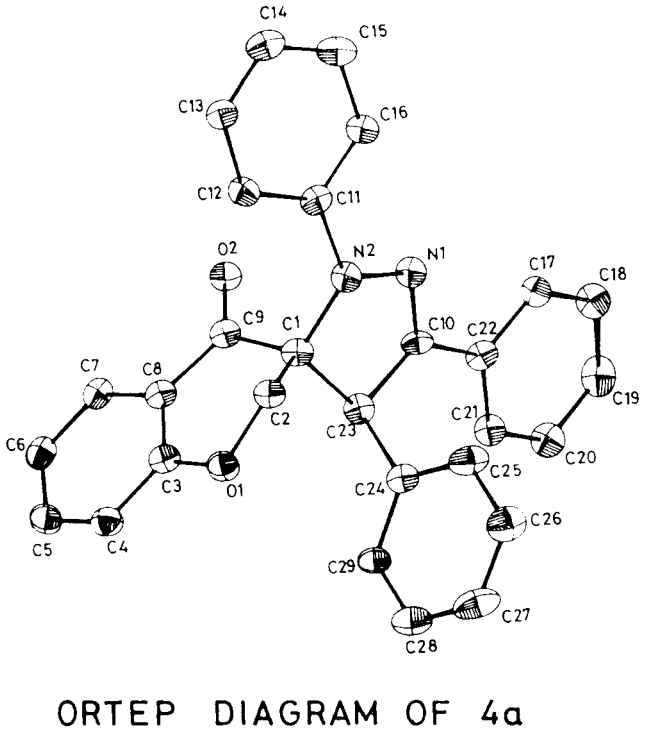

FIGURE 1

the products were assigned the *E* configuration on the basis of their NMR spectra, in accordance with a literature report [7]. The arylidene proton signal is observed at around δ 7.85 in all cases (Table 1), more deshielded than in the *Z* isomer, which is reported to resonate around δ 6.90 [7].

Reactions of 3-arylidene-4-chromanones (**1a–g**) with DPNI (generated in situ from N-phenyl benzhydrazidoyl 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. The reaction has yielded a series of novel 1,3-diphenyl-4-aryl spiropyrazolines [5.3] 4′-chromanones by the regioselective cycloaddition of the 1,3-dipolar compound across the exocyclic double bond of the arylidene chromanone in each case. The reaction time for these reactions varied, depending on the substituent on the benzene ring of the benzylidene moiety (Table 2). The structure of each product (**4a–g**) and the regiochemistry of cycloaddition has been confirmed by spectroscopic data and by X-ray structure analysis of the cycloadduct in the case of **4a.** Thus, the carbonyl absorption in the IR spectrum of the product **4a** exhibited a peak at 1696 cm^{-1} showing an increase of 28 cm^{-1} from the normal value observed for benzylidene chromanone, indicating the loss of conjugation of the carbonyl group. The PMR spectrum of the product exhibited a singlet at δ 4.85 due to the benzylic proton, a doublet at δ 4.29 and 4.89 due to the O–CH_2 protons, a multiplet in the range δ 6.9–7.58, and a doublet of a doublet at δ 8.01 due to aromatic protons. The singlet at δ 4.85 clearly shows the regiochemistry of the dipolar cycloaddition that gave exclusively the 5-substituted pyrazoline (**4a**). We could not find even a trace of the other regioisomer (**3a–g**) in all the cases that we have studied. ^{13}C NMR spectra of the products showed peaks for three sp^3 carbons, one sp^2 carbon, one carbonyl carbon, and aromatic carbons that confirmed the proposed structures.

Finally, X-ray crystal analysis (Figure 1) confirmed the structure of **4a** with the proposed regiochemistry. Identical results were obtained with other derivatives of benzylidene chromanones in the cycloaddition with DPNI, irrespective of the substituent present in the arylidene moiety.

MOLECULAR ORBITAL CALCULATIONS

We have examined the frontier molecular orbital (FMO) interaction to study the electronic effects on

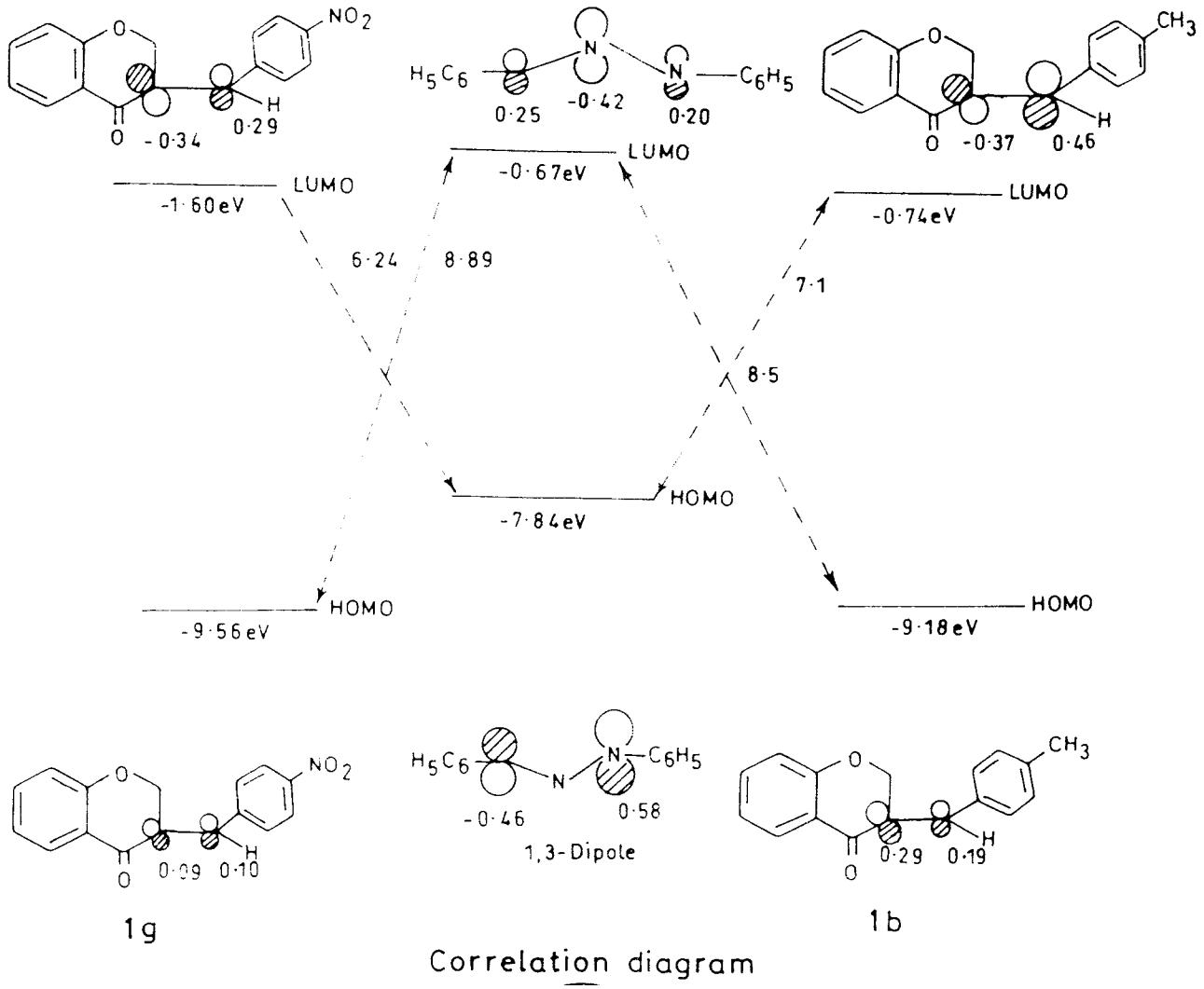

FIGURE 2

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 [13].

We have taken two classes of dipolarophiles, one with an electron-withdrawing group (**1g**) and the other with an electron-donating group (**1b**), for calculation of atomic coefficients of the olefinic carbons. The FMO energy levels of the molecules at optimized geometries obtained using the all valence semi-empirical molecular orbital method AM_1 [14] are shown in Figure 2.

From the correlation diagram, it is seen that the energy gap between the LUMO of the dipolarophile and the HOMO of the dipolar compound is significantly smaller than that of the LUMO of the dipolar compound 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 in 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 (**1b, 1g**) reveal that LUMO coefficients of the olefinic carbons are comparable in magnitude. In the case of **1g**, it is seen that the atomic coefficient of the olefinic carbon of the dipolarophile bearing the *p*-nitro substituted benzene ring is comparable

TABLE 1 Characterization of 3-Arylidene-4-chromanones

Substrate	mp (°C) Found	mp (°C) Reported	^{1}H NMR ($CDCl_3$/TMS) δ,J (Hz)	IR (KBr) (cm-1) $\nu_{c=O}$
1a	111–112	113 [8]	5.34 (d, 2H, J = 1.8), 6.95–7.62 (m, 8H), 7.89 (s, 1H), 8.04 (dd, 1H, J = 7.9, 1.8)	1668
1b	118–119	118–119 [8]	2.32 (s, 3H), 5.31 (d, 2H, J = 1.8), 6.92–7.62 (m, 7H), 7.81 (s, 1H), 7.97 (dd, 1H, J = 7.8, 1.7)	1669
1c	134–135	133–134 [8]	3.83 (s, 3H), 5.35 (d, 2H, J = 1.7), 6.69–7.6 (m, 7H), 7.81 (s, 1H), 7.99 (dd, 1H, J = 7.9, 1.7)	1667
1d	150–151	149–150 [9]	3.01 (s, 6H), 5.38 (d, 2H, J = 1.8), 6.66–7.6 (m, 7H), 7.79 (s, 1H), 7.95 (dd, 1H, J = 7.9, 1.6)	1667
1e	169–171	—	5.31 (d, 2H, J = 1.8), 6.88–7.61 (m, 7H), 7.8 (s, 1H), 8.01 (dd, 1H, J = 7.9, 1.8)	1667
1f	100–101	—	5.32 (d, 2H, J = 1.8), 6.92–7.6 (m, 7H), 7.81 (s, 1H), 8.02 (dd, 1H, J = 7.9, 1.8)	1667
1g	216–218	—	5.28 (d, 2H, J = 1.8), 6.9–7.61 (m, 5H), 7.89 (s, 1H), 8.02 (dd, 1H, J = 7.9, 1.8), 8.31 (d, 2H, J = 8.1)	1668

TABLE 2 Spiropyrazolines **4a–g** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)	IR (KBr) (cm^{-1}) $\nu_{c=O}$	IR (KBr) (cm^{-1}) $\nu_{c=N}$	MS (70 eV m/z) (M^+)	Molecular Formula	Analysis Calcd/Found C	H	N
4a	36	79	191–192	1696	1601	430	$C_{29}H_{22}N_2O_2$	80.90	5.15	6.51
								80.81	5.21	6.42
4b	48	75	151–152	1696	1599	444	$C_{30}H_{24}N_2O_2$	81.05	5.45	6.31
								81.22	5.39	6.42
4c	60	70	173–175	1693	1603	460	$C_{30}H_{24}N_2O_3$	78.23	5.26	6.09
								78.07	5.28	6.01
4d	60	71	167–169	1694	1600	473	$C_{31}H_{27}N_3O_2$	78.61	5.75	8.90
								78.80	5.69	8.78
4e	48	74	157–159	1693	1599	464	$C_{29}H_{21}N_2O_2Cl$	74.98	4.56	6.03
								74.81	4.47	6.15
4f	48	72	216–218	1693	1599	448	$C_{29}H_{21}N_2O_2F$	77.65	4.72	6.25
								77.85	4.68	6.37
4g	40	72	97–99	1697	1600	475	$C_{29}H_{21}N_3O_4$	73.24	4.45	8.85
								73.40	4.41	9.01

[a]Yield of pure, isolated product.

in value to that of the cationic carbon of the 1,3-dipolar compound, and the other olefinic carbon of the dipolarophile is comparable to the anionic nitrogen of the dipolar compound, resulting in the overlap between these orbitals leading to the observed regioisomer **4g** in this cycloaddition process.

However, in the case of **1b,** the maximum orbital overlap concept does not explain the regiochemistry of the observed product **4b.** A possible explanation for this mode of cycloaddition is that a steric effect overwhelms the electronic effect [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. Since there is not much difference in the atomic coefficients of the dipolarophile **1b** in its LUMO, the carbon terminal of the 1,3-dipolar compound approaches the less substituted carbon of the dipolarophile from the least hindered side to give the observed regioisomer **4b**.

CRYSTAL DATA FOR COMPOUND **4a**

$C_{29}H_{22}N_2O_2$, M = 430, monoclinic, space group = $P2_1/c$, a = 14.117 (2), b = 13.317 (3), c = 11.888 (4), Å, β = 95.18 (1)°, V = 2225.8 (9) Å^3, Z = 4, Dc = 1.258 g/cm^3, Cu$K\alpha$ radiation, λ = 1.5418 (4) Å, μ = 6.27 cm^{-1}, F (000) = 892. The crystals are pale yellow and needle shaped. A crystal with dimensions of

TABLE 3 ^{1}H and ^{13}C NMR Spectral Data for Spiropyrazolines **4a–g**

Product	*^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)*	*^{13}C NMR ($CDCl_3$/TMS) (ppm)*
4a	4.29 (d, 1H, J = 12.0), 4.85 (s, 1H), 4.89 (d, 1H, J = 12.0), 6.9–7.58 (m, 18H), 8.01 (dd, 1H, J = 7.9. 1.7)	60.39, 68.62, 74.10, 117.85, 188.47, 119.49, 122.05, 122.39, 126.45, 128.26, 128.37, 128.50, 128.69, 128.87, 131.27, 134.16, 136.73, 143.39, 149.13, 160.79, 189.36
4b	2.33 (s, 3H), 4.28 (d, 1H, J = 11.8), 4.86 (s, 1H), 4.88 (d, 1H, J = 11.8), 6.92–7.62 (m, 17H), 8.00 (dd, 1H, J = 7.9, 1.7)	21.23, 60.14, 68.67, 74.04, 117.86, 118.45, 119.38, 121.96, 122.25, 126.42, 128.21, 128.50, 128.65, 129.60, 131.05, 131.34, 136,71, 138.14, 143.47, 149.27, 160.79, 189.40
4c	3.79 (s, 3H), 4.28 (d, 1H, J = 12.0), 4.84 (s, 1H), 4.86 (d, 1H, J = 12.0), 6.84–7.58 (m, 17H), 7.95 (dd, 1H, J = 7.9, 1.7)	55.30, 60.80, 69.02, 74.24, 114.51, 118.11, 120.31, 122.15, 123.10, 126.72, 126.92, 128.07, 128.57, 128.98, 130.81, 131.73, 136.70, 143.86, 149.36, 159.51, 160.92, 189.04
4d	2.98 (s, 6H), 4.37 (d, 1H, J = 12.1), 4.86 (s, 1H), 4.93 (d, 1H, J = 12.1), 6.63–7.62 (m, 17H), 8.00 (dd, 1H, J = 8.0, 1.7)	40.57, 60.32, 69.11, 74.37, 112.63, 118.14, 118.82, 119.53, 121.41, 122.17, 122.34, 126.82, 128.49, 128.75, 128.94, 131.93, 136.88, 143.97, 149.88, 150.48, 161.18, 190.01
4e	4.25 (d, 1H, J = 12.1), 4.86 (s, 1H), 4.91 (d, 1H, J = 12.1), 6.92–7.62 (m, 17H), 8.00 (dd, 1H, J = 7.90, 1.7)	60.14, 68.96, 74.09, 117.81, 118.41, 119.58, 122.04, 122.30, 126.44, 128.19, 128.51, 128.66, 129.59, 131.05, 131.38, 134.92, 136.76, 143.47, 149.31, 160.71, 189.11
4f	4.32 (d, 1H, J = 12.1), 4.89 (s, 1H), 4.90 (d, 1H, J = 12.1), 6.89–7.58 (m, 17H), 7.99 (dd, 1H, J = 7.90, 1.7)	60.01, 69.02, 74.14, 114.11, 117.86, 119.76, 122.20, 122.72, 126.38, 126.92, 128.35, 128.55, 128.72, 130.74, 131.01, 136.85, 143.26, 148.69, 160.71, 163.01, 189.01
4g	4.20 (d, 1H, J = 12.0), 4.87 (d, 1H J = 12.0), 4.95 (s, 1H), 6.87–7.56 (m, 15H), 7.96 (dd, J = 8.1, 1.7), 8.21 (d, 2H, J = 8.3)	59.55, 68.50, 74.56, 117.90, 118.34, 119.81, 122.56, 123.01, 124.09, 126.27, 128.32, 128.52, 128.70, 128.83, 128.99, 130.59, 137.10, 141.80, 143.00, 147.89, 148.03, 160.58, 188.57

TABLE 4 Selected Bond Lengths and Bond Angles for Compound **4a** (Excluding H atoms)

Bond Lengths (Å)		*Bond Angles (°)*	
C1–N2	1.461	C23–C1–N2	102.0
N2–N1	1.406	C1–N2–N1	110.0
N1–C10	1.279	N2–N1–C10	108.3
C10–C23	1.503	N1–C10–C3	115.4
C23–C1	1.585	C10–C23–C1	99.1
C1–C9	1.522	N1–C10–C22	120.0
C1–C2	1.536	C22–C10–C23	125.0

$0.33 \times 0.15 \times 0.10$ mm was used for X-ray data collection at 293 K on an Enraf-Nonius CAD4 diffractometer, using Cu radiation and a graphite monochromator. The cell parameters were obtained from setting angles from 21 reflections in the range of $8° < \theta < 19°$. A total of 3767 independent reflections for $\theta = 65°$ were measured, out of which 2123 were observed; 2022 reflections were considered for refinement [$I > 2\sigma$ (I)]. The structure was solved by direct methods using the programs SHELXS86 [10]. The structure was refined by the full matrix least-squares method using SHELXL93 [11]. The final R indices are R = 0.079, Rw = 0.21. All of the nonhydrogen atoms were refined anisotopically. All of the hydrogens were located from the difference Fourier map. The maximum shift/e.s.d. was .396. Min and max values in the final difference electron density maps are 0.36 and -0.36 e/Å^3. Atomic scattering factors were taken from international tables [12].

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 100.6 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-arylidene-4-chromanones [7] and N-phenyl benzhydrazidoyl chloride [18] were prepared according to literature procedures. The physical constants and spectral details of the chromanones are given in Table 1.

Reaction of 3-Arylidene-4-chromanones with DPNI; General Procedure

To a solution of a 3-arylidene-4-chromanone (3 mmol) and N-phenyl benzhydrazidoyl 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 from the filtrate under 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 the spectral details for (**4a-g**) are reported in Table 2 and 3. The selected bond lengths and angles for **4a** are found in Table 4.

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