1,3-Dipolar cycloaddition of phthalazinium ylides to 5-arylidene-2-spirocyclohexane-1,3-dioxane-4,6-diones

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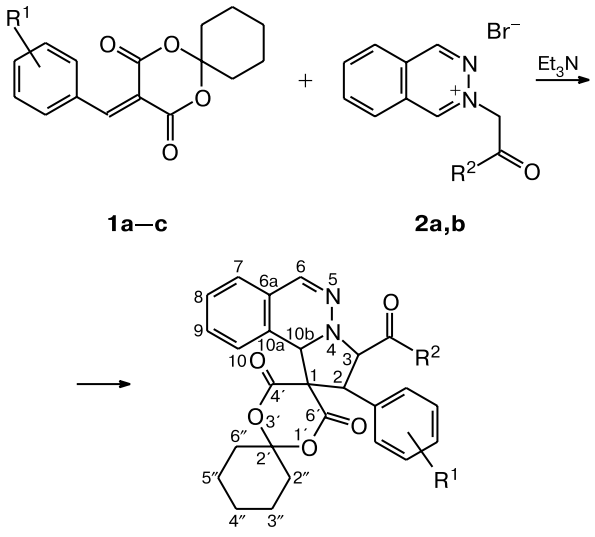
Tetrahydrospiropyrrolo[2,1-*a*]phthalazines were synthesized by the reaction of 5-arylidene-2-spirocyclohexane-1,3-dioxane-4,6-diones with phthalazinium ylides. One of the reaction products, *viz.*, 3-ethoxycarbonyl-2-(4-methoxyphenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione, was studied by X-ray diffraction. The spectroscopic characteristics of the reaction products are discussed.

Key words: 1,3-dipolar cycloaddition, phthalazinium ylides, 5-arylidene-2-spirocyclohexane-1,3-dioxane-4,6-diones, X-ray diffraction analysis.

The 1,3-dipolar cycloaddition reaction is a convenient method for the synthesis of fused heterocyclic systems.[1] The reactions of quinolinium,[2] isoquinolinium,[3] and phthalazinium[4,5] ylides with simple electron-deficient olefins have been well studied. The field of application of these reactions is limited by the presence of a rather activated double bond and the absence of shielding groups around this bond in the molecule serving as a dipolarophile. In some cases, the cycloaddition products are unstable or can undergo further transformations.[6]

Examples of the reactions of azahetaryl ylides with methylidenes are scarce.[7,8] In the present study, we demonstrated that 2-ethoxycarbonylmethylphthalazinium ylide adds to 5-arylidene-2-spirocyclohexane-1,3-dioxane-4,6-diones in high yield. One of the reaction products, *viz.*, 3-ethoxycarbonyl-2-(4-methoxyphenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione, was studied by X-ray diffraction.

Scheme 1



3a—d

1	R^1	2	R^2	3	R^1	R^2
a	4-OMe	**a**	OEt	**a**	4-OMe	OEt
b	3,4-$(OMe)_2$	**b**	4-$MeOC_6H_4$	**b**	3,4-$(OMe)_2$	OEt
c	4-NO_2			**c**	4-NO_2	OEt
				d	4-OMe	4-$MeOC_6H_4$

Results and Discussion

Treatment of arylidenes **1a—c** and phthalazinium bromides **2a,b** with an excess of Et_3N in MeCN afforded the corresponding tetrahydrospiropyrrolo[2,1-*a*]phthalazines **3a—d** (Scheme 1).

Arylidenemalononitriles are known[9] to be involved in 1,3-cycloaddition reactions with quinolinium and isoquinolinium ylides yielding the corresponding tetrahydropyrrolo[1,2-*a*]quinolines and tetrahydropyrrolo[2,1-*a*]iso-

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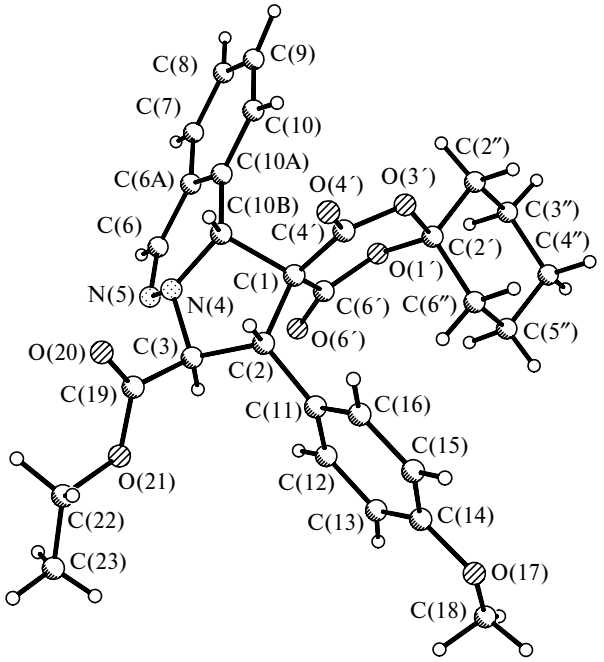

Fig. 1. Molecular structure of compound **3a**.

quinolines. However, methylidenes of Meldrum's acid are inert with respect to the above-mentioned ylides. Evidently, the volume of the 1,3-dioxane-4,6-dione fragment is larger than that of two nitrile groups, and the reaction centers in the β-dicarbonyl compound are substantially shielded by the oxygen atoms. A comparison of the structures of cycloaddition adducts of isoquinolinium ylides[10] and phthalazinium ylides[11,12] shows that the angle between the planes of the tetrahydropyrrole and phthalazine fragments is much larger than the analogous angle in the isoquinoline derivative. The phthalazine fragment is arranged in such a way as to minimize steric hindrance. Apparently, this is responsible for high reactivity of carbonylmethylphthalazinium ylides with respect to such dipolarophiles. In addition, phthalazinium ylides

Table 1. Selected bond lengths (*d*) in compound **3a**

Bond	*d*/Å	Bond	*d*/Å
C(1)—C(6′)	1.504(2)	C(7)—C(8)	1.371(3)
C(1)—C(4′)	1.517(2)	C(8)—C(9)	1.384(3)
C(1)—C(2)	1.556(2)	C(9)—C(10)	1.383(2)
C(1)—C(10B)	1.593(2)	C(10)—C(10A)	1.386(2)
C(2)—C(11)	1.507(2)	C(10A)—C(10B)	1.498(2)
C(2)—C(3)	1.551(2)	C(19)—O(20)	1.195(2)
C(3)—N(4)	1.462(2)	C(19)—O(21)	1.310(2)
C(3)—C(19)	1.512(2)	C(4′)—O(4′)	1.193(2)
N(4)—N(5)	1.390(2)	C(4′)—O(3′)	1.345(2)
N(4)—C(10B)	1.464(2)	O(3′)—C(2′)	1.433(2)
N(5)—C(6)	1.282(2)	C(2′)—O(1′)	1.435(2)
C(6)—C(6A)	1.444(2)	O(1′)—C(6′)	1.349(2)
C(6A)—C(10A)	1.396(2)	C(6′)—O(6′)	1.194(2)
C(6A)—C(7)	1.397(2)		

are more basic,[13] which also can lead to an increase in the reactivity of the dipole.

Noteworthy is the influence of the substituent at position 2 of phthalazinium ylide. The presence of the 4-methoxyphenacyl group in bromide **2b** instead of the 2-ethoxycarbonyl group in **2a** leads to a substantial decrease in the yield of adduct **3d** compared to **3a** and results in the formation of a considerable amount of resinous substances. In the case of benzhydryloxycarbonylmethylphthalazinium bromide, the cycloaddition product was not isolated at all.

The synthesis was carried out in acetonitrile at 40—45 °C for 2 h. The ylides were generated *in situ* by the addition of Et_3N to a solution of compounds **1** and **2**. An increase in the reaction time and temperature did not lead to an increase in the yield.

The compositions and structures of compounds **3a—d** were confirmed by elemental analysis and ^1H and ^{13}C NMR spectroscopy. The structure of product **3a** was additionally established by X-ray diffraction analysis (Fig. 1, Tables 1 and 2). In all cases, the cycloaddition

Table 2. Selected bond angles (ω) in compound **3a**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(6′)—C(1)—C(4′)	114.86(11)	N(5)—N(4)—C(3)	112.20(12)	O(3′)—C(4′)—C(1)	118.43(11)
C(6′)—C(1)—C(2)	114.02(11)	N(5)—N(4)—C(10B)	122.97(12)	C(4′)—O(3′)—C(2′)	121.41(11)
C(4′)—C(1)—C(2)	111.16(11)	C(3)—N(4)—C(10B)	109.72(11)	O(3′)—C(2′)—O(1′)	110.48(11)
C(6′)—C(1)—C(10B)	108.51(10)	C(6)—N(5)—N(4)	117.72(13)	O(3′)—C(2′)—C(6″)	110.30(13)
C(4′)—C(1)—C(10B)	108.85(10)	N(4)—C(10B)—C(10A)	113.07(12)	O(1′)—C(2′)—C(6″)	109.69(13)
C(2)—C(1)—C(10B)	97.96(10)	N(4)—C(10B)—C(1)	103.92(11)	O(3′)—C(2′)—C(2″)	107.21(13)
C(11)—C(2)—C(3)	117.25(12)	C(10A)—C(10B)—C(1)	118.12(11)	O(1′)—C(2′)—C(2″)	106.11(14)
C(11)—C(2)—C(1)	116.06(11)	O(20)—C(19)—O(21)	123.56(15)	C(6″)—C(2′)—C(2″)	112.94(16)
C(3)—C(2)—C(1)	104.37(11)	O(20)—C(19)—C(3)	124.81(15)	C(6′)—O(1′)—C(2′)	118.29(10)
N(4)—C(3)—C(19)	111.07(13)	O(21)—C(19)—C(3)	111.62(14)	O(6′)—C(6′)—O(1′)	119.05(12)
N(4)—C(3)—C(2)	105.55(11)	O(4′)—C(4′)—O(3′)	118.60(12)	O(6′)—C(6′)—C(1)	123.53(12)
C(19)—C(3)—C(2)	110.16(12)	O(4′)—C(4′)—C(1)	122.73(13)	O(1′)—C(6′)—C(1)	117.02(11)

occurs strictly stereospecifically to give one of eight possible isomers. The ^{1}H NMR spectra of compounds **3** always have two doublets for the protons H(2) and H(3) ($^2J_{H,H}$ = 10.8 Hz) and a singlet for the proton at the C(10b) atom.

According to the X-ray diffraction data for compound **3a**, the central five-membered ring C(1)C(2)C(3)N(4)C(10B) adopts an envelope conformation with the C(1) atom deviating from the plane through the other four atoms of the ring by 0.67 Å (the folding angle along the C(2)...C(10B) line is 40.7°). The benzene fragment and the 2-ethoxycarbonyl group at the C(2) and C(3) atoms, respectively, are in the *trans* positions with respect to the planar fragment of the ring (the C(11)—C(2)—C(3)—C(19) dihedral angle is 85.9°). The N(4) atom has a tetrahedral configuration (the deviation from the plane of the substituents is 0.33 Å). The six-membered ring N(4)N(5)C(6)C(6A)C(10A)C(10B) adopts a flattened sofa conformation with the N(4) and N(5) atoms deviating from the plane through the other atoms of the ring by 0.29 and 0.10 Å, respectively. The C(2′)C(2″)C(3″)C(4″)C(5″)C(6″) ring adopts a usual chair conformation, and the C(1)C(4′)O(3′)C(2′)O(1′)C(6′) ring assumes a distorted half-chair conformation with the C(2′) atom deviating from the plane through the other atoms by 0.46 Å.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument. The course of the reactions was monitored and the purities of the reaction products were checked on Silufol UV-254 plates. Column chromatography was performed on silica gel Davisil (Aldrich, 200—425 mesh, 60 Å). Commercial solvents and reagents (reagent grade) were used without additional purification. 5-Arylidene-2-spirocyclohexane-1,3-dioxane-4,6-diones **1a—c** [14] and carbonylmethylphthalazinium bromides **2a,b** [15] were synthesized according to known procedures.

Synthesis of tetrahydrospiropyrrolo[2,1-*a*]phthalazines 3a—d (general procedure). Triethylamine (4.03 mmol, 0.57 mL) was added with stirring to a solution of bromide **2a,b** (3.36 mmol) and compound **1a—c** (3.36 mmol) in MeCN (130 mL) at 40 °C for 30 min. The reaction mixture was stirred at 40—45 °C for 1.5 h. The solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt—benzene, 2 : 1, as the eluent) and then crystallized from an acetone—water mixture.

3-Ethoxycarbonyl-2-(4-methoxyphenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione (3a). The yield was 72%. Colorless crystals, m.p. 174—176 °C. Found (%): C, 67.11; H, 5.87; N, 5.34. $C_{29}H_{30}N_2O_7$. Calculated (%): C, 67.17; H, 5.83; N, 5.40. ^{1}H NMR (DMSO-d_6), δ: 0.48—0.86 (m, 2 H, CH_2); 1.09 (t, 3 H, Me, *J* = 7.0 Hz); 1.13—1.29 and 1.32—1.65 (both m, 4 H each, 4 CH_2); 3.72 (s, 3 H, OMe); 4.11 (q, 2 H, OCH_2, *J* = 6.8 Hz); 4.30 and 5.07 (both d, 1 H each, CH, *J* = 10.6 Hz); 5.86 (s, 1 H, NCH); 6.88—7.03 and 7.15—7.26 (both m, 3 H each, H arom.); 7.26—7.38 (m, 1 H, H arom.); 7.38—7.50 (m, 2 H, H arom.). ^{13}C NMR (DMSO-d_6), δ: 14.1 (C(23)); 21.5 (C(4″)); 21.6 (C(3″), C(5″)); 22.3 (C(2″), C(6″)); 35.6 (C(1)); 55.2 (OMe); 61.2, 67.4, 72.1, 72.7 (C(2), C(3), C(10b), C(22)); 102.3 (C(2′)); 106.1, 112.1, 121.3, 124.1, 124.8, 124.9, 125.4, 126.4, 130.2, 130.9, 149.0 (C(6), C(6a), C(7), C(8), C(9), C(10), C(10a), C(11), C(12), C(13), C(14), C(15), C(16)); 166.1 (C(4′), C(6′)); 171.1 (C(O)OEt).

3-Ethoxycarbonyl-2-(3,4-dimethoxyphenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione (3b). The yield was 80%. Colorless crystals, m.p. 180—181 °C. Found (%): C, 65.64; H, 5.93; N, 5.03. $C_{30}H_{32}N_2O_8$. Calculated (%): C, 65.68; H, 5.88; N, 5.11. ^{1}H NMR (DMSO-d_6), δ: 0.48—0.88 (m, 2 H, CH_2); 1.11 (t, 3 H, Me, *J* = 7.0 Hz); 1.13—1.29 and 1.35—1.68 (both m, 4 H each, 4 CH_2); 3.71 (br.s, 6 H, 2 OMe); 4.12 (q, 2 H, OCH_2, *J* = 6.8 Hz); 4.30 and 5.10 (both d, 1 H each, CH, *J* = 10.6 Hz); 5.85 (s, 1 H, NCH); 6.80—7.05 and 7.18—7.55 (both m, 4 H each, H arom.). ^{13}C NMR (DMSO-d_6), δ: 14.0 (Me); 21.5 (C(4″)); 21.8 (C(3″), C(5″)); 22.6 (C(2″), C(6″)); 35.8 (C(1)); 53.5, 55.6 (2 OMe); 61.2, 67.8, 72.3, 72.7 (C(2), OCH_2, C(3), C(10b)); 106.3, 112.3, 121.4, 124.3, 124.5, 124.7, 125.1, 126.3, 127.5, 130.0, 130.9, 149.0, 149.4 (C(6), C(6a), C(7), C(8), C(9), C(10), C(10a), C(2′), C arom.); 166.1 (C(4′), C(6′)); 170.9 (C(O)OEt).

3-Ethoxycarbonyl-2-(4-nitrophenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione (3c). The yield was 85%. Pale-yellow crystals, m.p. 183—184 °C. Found (%): C, 63.01; H, 5.15; N, 7.80. $C_{28}H_{27}N_3O_8$. Calculated (%): C, 63.03; H, 5.10; N, 7.88. ^{1}H NMR (DMSO-d_6), δ: 0.51—0.86 (m, 2 H, CH_2); 1.21 (t, 3 H, Me, *J* = 7.0 Hz); 1.15—1.32 and 1.38—1.71 (both m, 4 H each, 4 CH_2); 4.18 (q, 2 H, OCH_2, *J* = 6.8 Hz); 4.42 and 5.11 (both d, 1 H each, CH, *J* = 10.8 Hz); 5.86 (s, 1 H, NCH); 6.90—7.05, 7.10—7.32, and 7.32—7.56 (all m, 3 H each, H arom.). ^{13}C NMR (DMSO-d_6), δ: 14.0 (Me); 21.5 (C(4″)); 21.6 (C(3″), C(5″)); 22.6 (C(2″), C(6″)); 36.9 (C(1)); 64.1, 67.6, 72.6, 72.9 (C(2), OCH_2, C(3), C(10b)); 106.4, 112.1, 121.5, 123.3, 124.1, 124.9, 125.3, 125.5, 127.5, 130.0, 142.9, 147.4 (C(6), C(6a), C(7), C(8), C(9), C(10), C(10a), C(2′), C arom.); 166.1 (C(4′), C(6′)); 167.2 (C(O)OEt).

3-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-2′,2′-pentamethylene-1,2,3,10b-tetrahydrospiro[pyrrolo[2,1-*a*]phthalazine-1,5′-[1,3]dioxane]-4′,6′-dione (3d). The yield was 35%. Colorless crystals, m.p. 196—197 °C. Found (%): C, 70.46; H, 5.68; N, 4.84. $C_{34}H_{32}N_2O_7$. Calculated (%): C, 70.33; H, 5.56; N, 4.82. ^{1}H NMR ($CDCl_3$), δ: 0.72—0.98 (m, 2 H, CH_2); 1.09—1.34 and 1.34—1.68 (both m, 4 H each, 4 CH_2); 3.68 and 3.84 (both s, 3 H each, OMe); 4.61 (d, 1 H, CH, *J* = 10.0 Hz); 5.88 (s, 1 H, NCH); 5.97 (d, 1 H, CH, *J* = 10.0 Hz); 6.87 (d, 2 H, H arom., *J* = 8.0 Hz); 6.98—7.15 (m, 2 H, H arom.); 7.24 (d, 2 H, H arom., *J* = 8.0 Hz); 7.30—7.52 (m, 5 H, H arom.); 8.14 (m, 2 H, H arom.). ^{13}C NMR (DMSO-d_6), δ: 21.4 (C(4″)); 21.8 (C(3″), C(5″)); 22.8 (C(2″), C(6″)); 35.8 (C(1)); 55.2 ($C_6H_4O\underline{Me}$); 55.6 ($C(O)C_6H_4O\underline{Me}$); 68.4, 72.2, 72.6 (C(2), C(3), C(10b)); 105.8, 114.0, 124.3, 125.3, 125.6, 125.9, 126.4, 128.8, 130.1, 130.3, 130.9, 131.6, 159.4, 163.7 (C(6), C(6a), C(7), C(8), C(9), C(10), C(10a), C(2′), C arom.); 165.6 (C(4′), C(6′)); 167.2 (C(O)Ar).

X-ray diffraction study of compound 3a. Colorless crystals were grown from a solution in DMSO-d_6. The crystals

($C_{29}H_{30}N_2O_7$) are monoclinic, space group $P2_1/c$, at 293 K a = 11.583(2) Å, b = 11.275(2) Å, c = 20.702(4) Å, β = 95.12(3)°, V = 2693.1(9) Å^3, Z = 4, M = 518.55, d_{calc} = 1.279 g cm^{-3}. The intensities of 6497 independent reflections were measured on an automated Siemens P3/PC diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, ω scanning technique, $2\theta_{max}$ = 56°). The structure was solved by direct methods and refined by the full-matrix least-squares method against F^2_{hkl} with anisotropic displacement parameters for all nonhydrogen atoms. The hydrogen atoms were located from difference electron density maps and refined isotropically. The final R factors were as follows: R_1 = 0.0445 (based on F for 3938 observed reflections with $I > 2\sigma(I)$), wR_2 = 0.1231 (based on F^2 for all independent reflections), 463 parameters were refined. All calculations were carried out on a PC with the use of the SHELXTL program package.[16]

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