NEW PYRROLO[2,1-a]PHTHALAZINE DERIVATIVES BY 1,3-DIPOLAR CYCLOADDITION REACTIONS

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The esters of pyrrolo[2,1-a]phthalazine-1,2-dicarboxylic acid 13a-c were obtained from phthalazinium bromide 9, esters of acetylenedicarboxylic acid, triethylamine and tetrakis-pyridinocobalt(II) dichromate (TPCD) as oxidant. The synthesis of pyrrolo[2,1-a]phthalazine-1-carboxylic esters from 9, acetylenemonocarboxylic acid esters and triethylamine was performed in the absence of TPCD. Structure proof for the new compounds is based on H-, C-NMR, COSY and Hetcor experiments.

INTRODUCTION

1,3-Dipolar cycloadditions are powerful tools for the synthesis of simple and highly fused heterocyclic compounds because their ability to create sets of bonds in a single operation. Among a variety of 1,3-dipoles, heteroaromatic N-ylides are some of the most important dipoles in the construction of N-heterocycles, raising at the same time interesting regio- and stereoselectivity problems.1-13

The 1,3-dipolar cycloaddition reactions between heteroaromatic N-ylides 1 and acetylenic dipolarophiles 2 give the primary cycloadducts 3 which rearrange to pyrrolines 4 and/or 5. Usually, in the reaction conditions, intermediates 4 and 5 are too unstable due to their tendency to dehydrogenation with the formation of fused pyrroles 6 (Scheme 1).

Pyrrolo[2,1-a]phthalazine derivatives have also been found to possess biological activity and interesting optical properties.14-18

Herein we describe the synthesis of new pyrrolo[2,1-a]phthalazines 13a-e by 1,3-dipolar cycloaddition reactions between phthalazinium N-ylide 10 and activated alkynes.
RESULTS AND DISCUSSION

The starting material, 2-[2-(3-nitrophenyl-2-oxoethyl)phthalazinium bromide 9 was prepared by N-alkylation of phthalazine 7 with 2-bromo-3'-nitroacetophenone 8 (Scheme 2). The structure of the phthalazinium bromide 9 was confirmed by elemental analysis and NMR spectroscopy. In the $^1$H-NMR spectrum of compound 9, recorded in CDCl$_3$+TFA, the protons H-1 ($\delta = 10.57$ ppm) and H-2 ($\delta = 9.69$ ppm) are strongly deshielded due to the vicinity of the two nitrogen atoms (they are grafted on double bond C-N). In the dilute solution the signals for H-1 and H-4 appear as two triplets with a coupling constant of ca. 0.9 Hz. The multiplicity of H-1 could be explained by long range coupling of H-1 with H-4 and H-5, respectively. Similarly, the proton H-4 is coupled with H-1 and H-8, respectively. These long range couplings were put in evidence by HH decoupling experiments.

The phthalazinium $N$-ylide 10, being unstable, was generated in situ by deprotonation of the cycloimmonium bromide 9 with triethylamine. Treatment of phthalazinium bromide 9 with dimethyl acetylenedicarboxilate (DMAD) in the presence of an excess of triethylamine gave the 1,10b-dihydrophthalazine derivative 12a (Scheme 2). The reaction was performed in methylene chloride at room temperature for ca. 15 min. Similar results were obtained when DMAD was replaced by diethyl and diisopropyl acetylenedicarboxylate, respectively.

The structure of dihydroderivative 12a was assigned by $^1$H- and $^{13}$C-NMR spectroscopy. The protons H-1 ($\delta = 4.53$ ppm) and H-10b ($\delta = 5.35$ ppm) appeared in the $^1$H-NMR spectrum as two doublets with $J = 12.9$ Hz. The large value of the vicinal coupling constant between H-1 and H-10b indicates a cis configuration.

The position of the double bond in the pyrroline moiety resulted from the chemical shifts of the three carbonyl groups. Thus, the large difference between the two carbonyl ester groups ($\delta = 164.0$ ppm and 172.6 ppm) shows that they are grafted on a Csp$^2$ ($\delta = 164.0$ ppm) and a Csp$^3$ ($\delta = 172.6$ ppm), respectively. Also, the shielding of the ketone group ($\delta = 186.2$ ppm) is a good evidence for conjugation with a double bond of the pyrroline ring. This value is close with to those of the corresponding of aromatic compounds 13a, which were found to be 184.4 ppm.

The formation of dihydroderivatives 12 may be explained by the regio- and stereoselective prototropic rearrangement of the primary cycloadducts 11 in the presence of an excess of triethylamine. The isolation
New pyrrolo[2,1-a]phthalazine derivatives and characterization of such primary cycloadducts in the phthalazine series was recently reported.\textsuperscript{6,9} The aromatization of dihydroderivative 12a to pyrrolophthalazine 13a was performed, in good yields, by action of tetrakis-pyridinoCo(II)dichromate (TPCD). This reagent was used recently for aromatization of cycloadducts obtained by reaction between heteroaromatics N-ylides and activated olefines.\textsuperscript{19-21}

Pyrrolo[2,1-a]phthalazine derivatives 12a-c were also obtained by the “one pot” synthesis from phthalazinium bromide 9, esters of acetylenedicarboxylic acid, triethylamine and TPCD, in DMF, at 90 °C.

The 1,3-dipolar cycloaddition between N-ylide 10 and non-symmetrical acetylenic dipolarophiles such as ethyl or isopropyl propiolate is regiospecific. The reaction of N-ylide 10 with ethyl or isopropyl propiolate in methylene chloride at room temperature produced directly the aromatic pyrrolophthalazine 13d,e (Scheme 3). The regioselectivity in the cycloaddition of 10 with activated non-symmetrical acetylenes can be satisfactorily explained by strong polarization of the dipolarophile triple bond.

From the above results it can be concluded that the intermediates in the 1,3-dipolar cycloaddition of phthalazinium N-ylides with activated non-symmetrical alkynes are less stable than in the case of activated symmetrical acetylenes.

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The new pyrrolophthalazine derivatives were characterized by elemental analysis and NMR spectroscopy.

In the \textsuperscript{1}H-NMR spectra of compounds 13a-e the signal of H-10 (δ = 8.84-9.84) is deshielded in comparison with the protons of the phthalazine moiety which appeared in the range 7.68-7.90 ppm. The high chemical shift for proton H-10 can be explained by deshielding and this is a consequence of the presence of carboalkoxy groups in the position 1 of the pyrrole ring. Also, the proton H-6 (δ = 8.46-8.77) is deshielded because is grafted on a double C-N bond. It is interesting to note that the signal for the proton H-6 appeared as a doublet with J ≈ 0.8 Hz when \textsuperscript{1}H-NMR spectra of the compounds 13 were recorded in dilute solution. The multiplicity of H-6 can be explained by presence of a long range coupling between protons H-6 and H-10. This coupling was confirmed by HH decoupling experiments.

CONCLUSIONS

The 1,3-dipolar cycloaddition between N-ylide 10 with diesters of acetylenedicarboxylic acid, performed in dichloromethane, gave dihydroderivatives 12 which were subsequently aromatized with TPCD to 13a-c. In the same reaction conditions, 10 and esters of acetylenemonocarboxylic acid gave directly pyrrolophthalazine derivatives 13d,e.

The pyrrolophthalazine 13a-c were obtained in ‘one pot' reactions from phthalazinium bromide 9, diesters of acetylenedicarboxylic acid, triethylamine and TPCD.

EXPERIMENTAL PART

Melting points were determined on a Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for \textsuperscript{1}H and 75 MHz for \textsuperscript{13}C.

2-[2-(3-nitrophenyl)-2-oxoethyl]phthalazinium bromide (9)

\begin{center}
1.3 g (10 mmol) Phthalazine and 2.7 g (11 mmol) 2-bromo-3'-nitroacetophenone in 80 mL of acetone were stirred at room temperature for 5-6 hrs. The precipitate was collected on the filter paper and washed with acetone. The crude product was in 94% yield. The phthalazinium bromide 9 was purified by recrystallization from methanol, giving white crystals with m.p. 254-7°C.
\end{center}
The product was recrystallized from acetonitrile and white crystals with m.p. 121-2°C were obtained. Under stirring, triethylamine (5.5 mmol) and tetrakispyridine cobalt(II)-dichromate (TPCD) (2 g, 3.2 mmol) were added to the reaction mixture. The reaction mixture was stirred at 80-90°C for 5 hrs. and then cooled at room temperature and poured into a 5% aqueous HCl solution (100 mL). The solid product was filtered, washed with water and purified either by recrystallization or column chromatography on neutral Al₂O₃, using CH₂Cl₂ as eluent.

Compound 13a was also obtained from 12a as it follows: 2.5 mmol of dihydroderivative 12a and 1 g of TPCD in 15 mL of DMF were stirred at 90°C for 5 hrs. The reaction mixture was treated as above to give the pyrrolophthalazine 13a, in 74% yield.

**Dimethyl 3-(3-nitrobenzoyl)-pyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (13a)**

The product was recrystallized from acetonitrile and white crystals with m.p. 180-2°C were obtained. Yield 78%. Required for C₂H₂N₂O₃: C, 60.75; H, 3.13; N, 9.70. Found: C, 61.22; H, 3.88; N, 9.97. ¹H-NMR (CDCl₃; δ, ppm; J, Hz): 7.67 (s, 2H, CH₂); 7.85-7.87 (m, 1H, H-8); 7.90-7.93 (m, 2H, H-7, H-9); 8.14-8.17 (m, 1H, H-4); 3.90-3.93 (2s, 6H, 2 Me); 4.52 (d, 1H, 12.9, H-10b); 7.35 (s, 1H, H-6); 7.43 (s, 1H, H-5); 7.84 (t, 1H, 8.0, H-5'); 8.41-8.49 (m, 3H, H-6, H-7, H-4'); 8.53-8.61 (m, 1H, H-6'); 7.25-7.27 (m, 1H, H-7); 7.39-7.46 (m, 2H, H-9); 7.52-7.57 (m, 1H, H-10, H-8); 7.74 (t, 1H, 8.1, H-5'); 8.34 (bd, 1H, 8.1, H-6'); 8.46-8.50 (m, 1H, H-4'); 8.85 (bs, 1H, H-2'). ¹³C-NMR (CDCl₃; δ, ppm): 51.5, 52.3 (2 OMe); 53.0 (C-1); 62.0 (C-10b); 102.3 (C-2); 123.4 (C-2'); 124.6, 126.5, 126.8 (C-2, C-3, C-6a, C-10a, C-10b); 124.2 (C-2'); 127.5 (C-4'); 128.4, 130.6 (C-6a, C-10a), 128.4, 130.2, 130.6 (C-4', C-5'); 132.0 (C-10); 132.0 (C-8); 134.7 (C-6'); 134.9 (C-6'); 136.2 (C-1'); 142.7 (C-6); 148.7 (C-3'); 151.8 (C-2'); 164.0 (2-COOC); 172.6 (1-COO); 186.2 (COAr).

**Diisopropyl 3-(3-nitrobenzoyl)-pyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (13c)**

The product was recrystallized from ethanol and white crystals with m.p. 121-3°C were obtained. Yield 80%. Required for C₂H₂N₂O₃: C, 63.80; H, 4.74; N, 8.58. Found: C, 64.12; H, 5.08; N, 8.97. ¹H-NMR (CDCl₃; δ, ppm; J, Hz): 1.15 (t, 3H, 7.1, 1-CO₂CH₂CH₃); 1.43 (t, 3H, 7.1, 2-CO₂CH₂CH₃); 4.15 (q, 2H, 7.1, 1-CO₂CH₂CH₃); 4.49 (q, 2H, 7.1, 2-CO₂CH₂CH₃); 7.67 (t, 1H, 7.9, H-5); 7.68-7.72 (m, 1H, H-8); 8.09-8.19 (m, 1H, H-4); 8.43-8.47 (m, 1H, H-6); 8.48 (s, 1H, H-6); 8.68 (t, 1H, 1.9, H-2); 8.91 (bd, 1H, 8.3, H-10). ¹¹C-NMR (CDCl₃; δ, ppm): 13.8, 14.0 (2 Me); 61.5, 61.8 (2 CH₂O); 108.2 (C-1); 121.3, 121.5, 125.1, 126.5, 126.8 (2-C, C-3, C-6a, C-10a, C-10b); 124.2 (C-2'); 125.1 (C-10); 127.5 (C-4'); 128.3, 129.4 (C-7, C-8); 129.7 (C-5'); 133.6 (C-9); 134.9 (C-6'); 139.1 (C-1'); 147.2 (C-6); 148.3 (C-3'); 163.9, 165.9 (2 COOMe); 184.4 (COAr).

**Ethyl 3-(3-nitrobenzoyl)-pyrrolo[2,1-a]phthalazine-1-carboxylate (13d)**

The product was recrystallized from acetonitrile and white crystals with m.p. 205-7°C were obtained. Yield 77%. Required for C₂H₂N₂O₃: C, 64.78; H, 3.88; N, 10.79. Found: C, 65.12; H, 4.07; N, 11.07. ¹H-NMR (CDCl₃; δ, ppm; J, Hz): 1.41 (t, 3H, 7.1,
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CH₃); 4.43 (q, 2H, 7.1, CH₂); 7.72 (t, 1H, 7.9, H-5'); 7.73 (s, 1H, H-2); 7.76-7.82 (m, 1H, H-8); 7.91-7.97 (m, 2H, H-7, H-9); 8.24-8.27 (m, 1H, H-4'); 8.45-8.49 (m, 1H, H-6'); 13C-NMR (CDCl₃; δ, ppm): 14.4 (Me); 60.9 (CH₂); 109.1 (C-1); 122.2, 126.2, 128.2, 130.9 (C-3, C-6a, C-10a, C -10b); 124.4 (C-2'); 125.2 (C-10); 126.6, 129.7, 130.0 (C-6, C-5', C-7); 127.6, 127.7 (C-2, C-4'); 133.1 (C-9); 135.1 (C-6'); 140.6 (C-6'); 146.7 (C-6); 148.1 (C-3'); 163.4 (COO); 181.9 (COAr).

Isopropyl 3-(3-nitrobenzoyl)-pyrrolo[2,1-a]phthalazine-1-carboxylate (13e)

The product was recrystallized from acetonitrile and white crystals with m.p. 210-2°C were obtained. Yield 78%. Required for C₂₂H₁₇N₃O₅: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.88;  H, 4.57; N, 10.69. 1H-NMR (CDCl₃; δ, ppm; J, Hz): 1.41 (d, 6H, 6.2, 2 Me); 5.31 (sep, 1H, 6.2, CHMe₂); 7.72 (t, 1H, 7.9, H-5'); 7.73 (s, 1H, H-2); 7.75-7.81 (m, 1H, H-8); 7.90-7.97 (m, 2H, H-7, H-9); 8.24-8.27 (m, 1H, H-4'); 8.45-8.49 (m, 1H, H-6'); 8.74 (s, 1H, H-6); 8.74 (t,  1H, 1.9, H-2'); 9.86 (bd, 8.1, 0.9, H-10). 13C-NMR (CDCl₃; δ, ppm): 22.0 (2 Me); 68.4 (CHMe₂); 109.5 (C-1); 122.2, 126.3, 126.8, 130.7 (C-3, C-6a, C-10a, C -10b); 124.4 (C-2'); 125.1 (C-10); 126.6, 129.5, 130.0 (C-6, C-7, C-5'); 127.6, 127.7 (C-2, C-4'); 133.9 (C-9); 135.1 (C-6'); 140.6 (C-6'); 146.6 (C-6); 148.2 (C-3'); 16 3.4 (COO); 182.0 (COAr).

REFERENCES