3-ACETYL-PYRROLO[2,1-*a*]PHTHALAZINES BY ONE-POT REACTION

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*Pirolo[2,1-a]ftalazinele **6** au fost obținute prin reacția de cicloaditie 1,3-dipolară dintre acetil ftalaziniu-metilida **3** și diferiți dipolarofili acetilenici care dau varietate structurală seriei de compuși. Metoda one-pot de sinteză a pirolo[2,1-a]ftalazinelor **6** ilustrează conceptul de chimie verde sau chimie sustenabilă.*

*The pyrrolo[2,1-a]phthalazines **6** were obtained by 1,3-dipolar cycloaddition of the corresponding acetylphtalazinium methanide **3** with acetylenic dipolarophiles. The structural variety was achieved by varying the dipolarophiles. The one-pot reaction fits well to the concept of sustainable chemistry.*

Keywords: pyrrolo[2,1-a]phthalazines, 1,3-dipolar cycloaddition, ylides, one-pot reaction

1. Introduction

Pyrrolo[2,1-*a*]phtalazines are N-bridgehead heterocyclic compounds that have been reported during the time to posses interesting properties such as optical properties [1,2] and biological activity [3-5].

Synthetic routes towards pyrrolo[2,1-*a*]phthalazines were reported during the time [6-17], among them the 1,3-dipolar cycloaddition of the phtalazinium *N*-ylides being one of the most versatile [11-17]. In the classic procedure the 1,3-dipolar cycloaddition reaction is conducted as a two stage process in which the phthalazinium salts are prepared in the first step following to react with acetylenic or olefinic dipolarophiles in the second step, in the presence of a base which has the role to generate the corresponding ylide *in situ*. In order to simplify the synthetic strategy a one-pot synthetic strategy was empolyed. Furthermore, the

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one-pot reactions are of present interest due to their simplicity and advantages in the context of green chemistry [18].

3. Experimental

Melting points were determined on a Boëtius hot plate and they are not corrected. The IR spectra were recorded on FT-IR Bruker Vertex 70. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C.

*General procedure for obtaining the phtahalazinium chloride **2***

5 mmoles phthalazine **1** and 5 mmoles of chloroacetone were suspended in ethyl acetate and kept under stirring for 8 hours. The precipitate was collected by vacuum filtration and used further without purification.

N-acetonyl-phthalazinium chloride (**2**). Light brown crystals with M.p. 169-172 ^{o}C; Yield 94%; Anal. Calcd.$C_{11}H_{11}ClN_2O$: N 12.58. Found: N 13.17; ATR-IR (cm^{-1}): 1725, 2936, 3067. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.45 (s, 1H, H-1), 9.96 (s, 1H, H-4), 8.66-8.57 (m, 2H, H-5, H-8), 8.34-8.29 (m, 1H, H-6), 8.22-8.16 (m, 1H, H-7), 6.35 (s, 2H, CH_2), 2.39 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.8 (COMe), 154.4, 153.3 (C-1, C-4), 139.7,136.3, 131.2, 128.5 (C-5, C-6, C-7, C-8); 127.6, 127.4 (C-4a, C-8a), 71.2 (CH_2), 27.8 (Me) ppm.

*General procedure for obtaining the compounds **6***

5 mmoles **l** phthalazinium chloride **2**, 7 mmoles acetylenic dipolarophile **4** were kept under stirring at reflux for 16 hours in 15 mL 1,2-epoxybutane. After the solvent was partially removed by evaporation, 10 mL of methanol were added, and the mixture was left over night at room temperature. The solid was filtered, washed with a small quantity of cold ethanol and then crystallized from a suitable solvent.

Methyl 3-acetyl-pyrrolo[2,1-*a*]phthalazine-1-carboxylate (**6a**). Colorless crystals crystallized from acetonitrile with M.p. 198-200 ^{o}C; Yield 65%; Anal. Calcd.$C_{15}H_{12}N_2O_3$: C 67.16; H 4.51; N 10.44. Found: C 67.49; H 4.88; N 10.68; ATR-IR (cm^{-1}): 1649, 1701, 2951, 3116. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.75-9.72 (m, 1H, H-10), 8.69 (s, 1H, H-6), 7.97 (s, H-2); 7.88-7.83 (m, 2H, H-7, H-9), 7.73-7.68 (m, 1H, H-8), 3.95 (s, 3H, MeO), 2.75 (s, 3H, MeCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.7 (COMe), 164.6 (COOMe), 146.2 (C-6), 133.0 (C-9), 129.7, 127.6, 127.5 (C-7, C-8, C-10), 123.0. (C-2), 129.5, 128.2, 126.7, 121.8 (C-3, C-6a, C-10a, C-10b), 108.1 (C-1), 51.9 (MeO), 29.7 (MeCO) ppm.

Ethyl 3-acetyl-pyrrolo[2,1-*a*]phthalazine-1-carboxylate (**6b**). Colorless crystals crystallized from acetonitrile with M.p. 145-146 ^{o}C ; Yield 62 %; Anal. Calcd.$C_{16}H_{14}N_2O_3$: C 68.08; H 5.00; N 9.92. Found: C 68.44; H 5.32; N 9.67; ATR-IR (cm^{-1}): 1649, 1705, 2948, 3117. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.78-

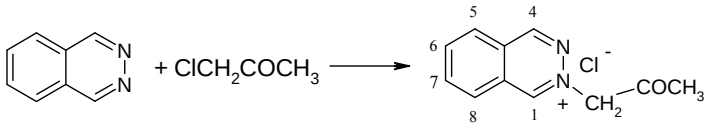
9.74 (m, 1H, H-10), 8.69 (s, 1H, H-6), 7.99 (s, H-2), 7.88-7.83 (m, 2H, H-7, H-9), 7.73-7.68 (m, 1H, H-8), 4.42 (q, 2H, J = 7.1 Hz, CH_2), 2.75 (s, 3H, MeCO), 1.46 (t, 3H, J = 7.1 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ : 187.8 (COMe), 164.2 (COOMe), 146.2 (C-6), 132.9 (C-9), 129.6, 127.6, 127.5 (C-7, C-8, C-10), 123.0. (C-2), 129.5, 128.3, 126.8, 121.7 (C-3, C-6a, C-10a, C-10b), 108.6 (C-1), 60.8 (CH_2), 29.7 (MeCO), 14.5 (Me) ppm.

Dimethyl 3-acetyl-pyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**6c**). Colorless crystals crystallized from ethanol with M.p. 148-151 ^{o}C; Yield 71%; Anal. Calcd.$C_{17}H_{14}N_2O_5$: C 64.40; H 4.32; N 8.58. Found: C 62.82; H 4.70; N 8.91; ATR-IR (cm^{-1}): 1656, 1704,1730, 2934, 3118.^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.43-9.40 (m, 1H, H-10), 8.62 (s, 1H, H-6), 7.86-7.80 (m, 2H, H-7, H-9), 7.72-7.66 (m, 1H, H-8), 4.01, 3.95 (2s, 6H, 2MeO), 2.80 (s, 3H, MeCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ : 188.7 (COMe), 166.5, 163.8 (2COOMe), 146.6 (C-6), 133.4 (C-9), 129.8, 127.8, 126.9 (C-7, C-8, C-10), 127.5, 127.4, 126.7, 126.5, 121.5 (C-2, C-3, C-6a, C-10a, C-10b), 106.6 (C-1), 52.9, 52.3 (2MeOO), 31.5 (MeCO) ppm.

Diethyl 3-acetyl-pyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**6b**). Colorless crystals crystallized from ethanol with M.p. 138-141 ^{o}C; Yield 76%; Anal. Calcd.$C_{19}H_{18}N_2O_3$: C 64.40; H 5.12; N 7.91. Found: C 64.67; H 5.12; N 8.17; ATR-IR (cm^{-1}): 1662, 1705, 1736, 2954, 3117. ^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.44-9.40 (m, 1H, H-10), 8.59 (s, 1H, H-6), 7.82-7.77 (m, 2H, H-7, H-9), 7.69-7.64 (m, 1H, H-8), 4.46, 4.38 (2q, 4H, J = 7.1 Hz, $2CH_2$), 2.78 (s, 3H, MeCO), 1.44,1.39 (2t, 6H, J = 7.1 Hz, $2CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ : 188.7 (COMe), 165.9.163.5 (2COOEt), 146.5 (C-6), 133.3 (C-9), 129.7, 127.8, 126.9 (C-7, C-8, C-10), 127.5, 127.3, 127.0, 126.6, 121.5 (C-2, C-3, C-6a, C-10a, C-10b), 106.8 (C-1), 61.8, 61.3 (2 CH_2), 31.5 (MeCO), 14.2, 14.1 (Me) ppm.

2. Results and discussion

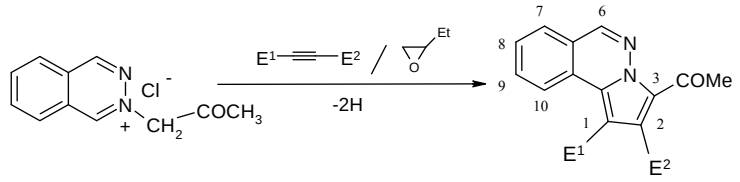
Our previuos results in obtaining pyrroloazines and the proven efficiency of the one-pot reactions [19-29] led us to expand our studies in order to achieve the structural variety leading to libraries of compounds. Thus, starting from the corresponding phthalazinium chloride **2** obtained in a previous step according to Scheme 1, the new pyrrolo[2,1-*a*]phthalazines **6** were obtained by the one-pot 1,3-dipolar cycloaddition reaction with acetylenic dipolarophiles (Scheme 2).



1 **2**

Scheme 1

The reaction is carried out in excess of 1,2-epoxibutane which has the role to generate the corresponding ylide from the phthalazinuium salt and also plays the role of reaction medium.

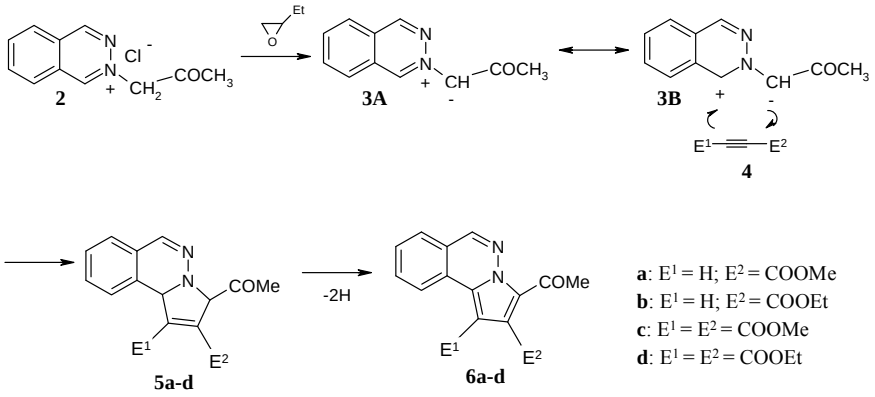


1 **6**

Scheme 2

The mechanism of the reaction (Scheme 3) implies the *in situ* generation of the corresponding phthalazinium *N*-ylide **3** by the action of the epoxide on the chloride salt **1**. The 1,3-dipole **3B** undergoes a 3+2 cycloaddition with acetylenic dipolarophiles **4**. The pyrrolo[2,1-*a*]phthalazines **6** were obtained in good yields by the rearrangement and dehydrogenation of the primary cycloadducts **5** under the reaction conditions. The structural variety is given by the acetylenic dipolarophiles employed.

The new compounds were characterized by IR and NMR spectroscopy. Their NMR spectra are in good agreement with the structure of the compounds. The NMR spectrum of the *N*-acetonyl-phthalazinium chloride present as main characteristic signals the signals of the hydrogens H-1 and H-4 which appear strong deshielded due to their vicinity of the nitrogen atoms. The two hydrogen atoms of the methylene appear deshielded as a singlet at 6.35 ppm. The C-NMR spectrum presents the signals of the carbons C-1 and C-4 which appear strong deshielded due to direct bonding with the nitrogen atoms and the signal of the carbonyl group in the acetyl moiety which appears at 187.8 ppm. The IR spectrum of the salt presents the band of the carbonyl group at 1725 cm^{-1}.



2 **3A** **3B** **4** **5a-d** **6a-d**

a: E^1 = H; E^2 = COOMe
b: E^1 = H; E^2 = COOEt
c: E^1 = E^2 = COOMe
d: E^1 = E^2 = COOEt

Scheme 3

The first evidence of the structure of the compounds **6** was provided by IR spectroscopy. Thus, the common characteristic of the series of compounds is the carbonyl band in the acetyl moiety which appears in the range 1649-1662 cm^{-1}. Also the IR spectra present the carbonyl groups in the carboethoxy or carbomethoxy groups corresponding to the structure of each compound.

The main characteristic of the H-NMR spectra of the compounds are the hydrogen H-6 which appears as a singlet in the range 8.59-8.69 ppm. Also the hydrogen H-10 appears as the most deshielded multiplet in the range 9.72-9.78 ppm for the compounds **6a,b** and 9.40-9.44 for **6c,d** due to the influence of the substituent attached at C-1. The main characteristic for the compounds **6a,b** is the signal of the hydrogen H-2 which appears as a singlet at around 7.98 ppm. The ^{13}C-NMR spectra present the expected signals for the carbonyl groups, a common characteristic of the compounds being the carbonyl in the acetyl moiety which appears in the range 187-188 ppm. Also the carbon atom C-6 appears at around 146 ppm in all the compounds due to its direct bonding with the nitrogen atom in the phthalazine moiety. The carbon C-1 appears at ~108 ppm for the compounds **6a,b** and slightly shielded to 106 ppm in the compounds **6c,d** due to the carboxyl group directly attached to it. The IR and NMR spectroscopy confirm the structure of the new compounds.

4. Conclusions

4 new pyrrolo[2,1-*a*]phthalazines were obtained by *one-pot* procedure starting from the corresponding phthalazinium chloride. Structural variety was conferred by varying the used dipolarophiles. These new compounds were characterized by IR and NMR spectroscopy. The *one-pot* procedure used a more environmental solvent avoiding the use of hazardous solvents such as methylene chloride as in the classical syntheses, being reliable to concepts such as green or sustainable chemistry.

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R E F E R E N C E S

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