Synthesis of Novel Phenanthroline Derivatives by 3+2 Dipolar Cycloadition Reaction

Ramona Danac,* Alexandru Rotaru, Gabi Drochioiu and Ioan Druta

Al. I. Cuza University of Iasi, 11 Carol I, Iasi-6600, Romania

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Eleven new 1,10-phenanthroline derivatives have been prepared by 3+2 dipolar cycloaddition reactions of 1,10-phenanthrolinium-ylides **7-12** *in situ* generated from corresponded salts, with dimethyl acetylenedicarboxylate and ethyl propiolate.

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Introduction.

The aim of this paper is to present the synthesis of some new phenanthroline derivatives by a 3+2 dipolar cycloaddition of some 1,10-phenanthrolinium-ylides with activated symmetrical or nonsymmetrical alkynes. Thus, we started from the observation that the non-stable monosubstituted heteroaromatic N-ylides obtained *in situ* by deprotonation of the corresponding cycloimmonium salts undergo 1,3-dipolar cycloaddition with activated symmetrical or nonsymmetrical olefins and alkynes resulting in the formation of a new heterocycle of five members [1-7]. These reactions are very important due to the possibility of preparing new heterocycles, which can difficult to obtain by other reactions.

Some reactions of 1,10-phenanthrolinium-ylides with dimethyl acetylenedicarboxylate and ethyl propiolate to yield novel pyrrolo[1,2-*a*][1,10]phenanthroline derivatives were investigated.

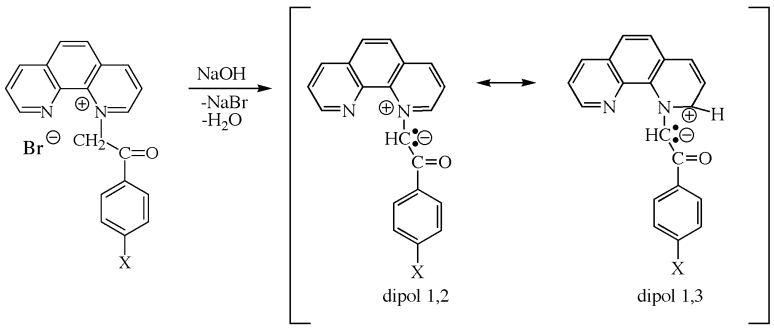
Results and Discussion.

The pyrrolo[1,2-*a*][1,10]phenanthroline derivatives were synthesized by the 3+2 dipolar cycloaddition of 1,10-phenanthrolinium-ylides **7-12** with dimethyl acetylenedicarboxylate or ethyl propiolate. 1,10-Phenanthrolinium salts **1-6** were synthesized by reaction of 1,10-phenanthroline with reactive halide derivatives, as previously reported [8]. Ylides **7-12** were obtained *in situ* by the reaction between the salts **1-6** suspended in different organic solvents, and an aqueous solution of 0.2 *N* sodium hydroxide (NaOH).

Ylides **7-12** are characterized by a zwitterionic structure and, therefore, can be dipole 1,3 reagents in the 3+2 dipolar cycloaddition reactions (Figure 1).

1,10-Phenanthrolinium-ylides **7-12** react with dimethyl acetylenedicarboxylate to afford cycloadducts **13-18**. As it is shown in Figure 2, ylides obtained *in situ*, probably form non-isolating intermediate cycloadducts of type **13-18**, which due to the tendency of stabilization may suffer a dehydrogenation process. Working in ambient conditions, an oxidative dehydrogenation process may also occur. Finally, isolating slowly fluorescent cycloadducts **19-24** were obtained; they possess a system of conjugated double bonds.

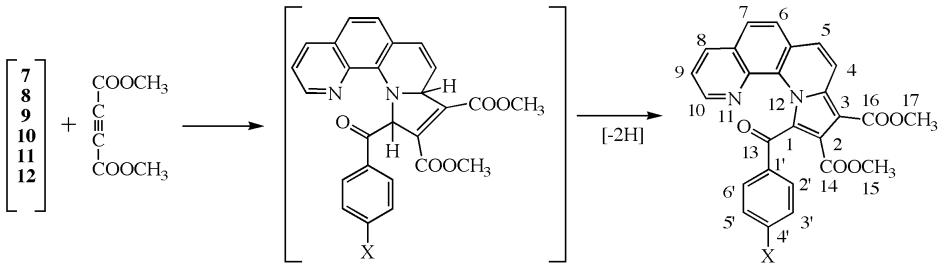
According to the theories referring to the orbital, steric and electronic factors, the cycloaddition reactions of cycloimmonium ylides with activated and non-symmetrical alkynes could follow, theoretically, two pathways with formation of regioisomers A or B (Figure 3) [3,9]. Nevertheless, spectral analyses shows evidence for regioisomer A only. This fact is in agreement with the electronic



1. X=NO_2
2. X=Cl
3. X=Br
4. X=OCH_3
5. X=CH_3
6. X=H

7. X=NO_2
8. X=Cl
9. X=Br
10. X=OCH_3
11. X=CH_3
12. X=H

Figure 1. Zwitterionic structure of phenanthrolinium-ylides



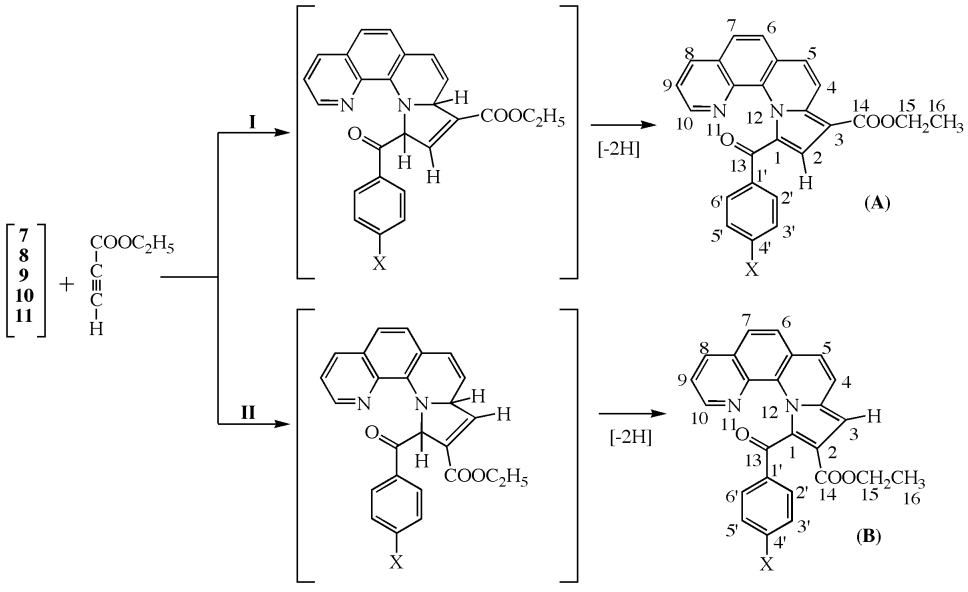
13. X=NO_2
14. X=Cl
15. X=Br
16. X=OCH_3
17. X=CH_3
18. X=H

19. X=NO_2
20. X=Cl
21. X=Br
22. X=OCH_3
23. X=CH_3
24. X=H

Figure 2. Reaction between cycloimmonium ylides and dimethyl acetylenedicarboxylate

effects within the ethyl propiolate molecule. Thus, we supposed that the reactions between 1,10-phenanthroliniumylides 7-12 and ethyl propiolate follow route I to give fluorescent cycloadducts 25-29 A. According to this statement, the cycloaddition reaction described above is regioselective.

absorbed at different frequencies. The presence of two absorption bands showed that the two esteric groups are not situated in the same plane. The group which absorbs at higher wave numbers (C=O ester 14), between 1720-1740 cm^{-1}, is probably not conjugated with the double bonds of the pyrrolo[1,2-*a*][1,10]phenanthroline cycle due to steric



25. X=NO_2
26. X=Cl
27. X=Br
28. X=OCH_3
29. X=CH_3

Figure. 3. Reaction between cycloimmonium ylides and ethyl propiolate.

Spectral methods and elemental analysis were used to prove the structure of compounds 19-24 and 25-29. The ir spectra for compounds 19-24 showed absorption bands between 1635 cm^{-1} and 1680 cm^{-1} which are characteristic for ketonic carbonyl groups. The esteric carbonyl groups

reasons. The band which appears at lower wave numbers (1695-1705 cm^{-1}) was assigned to an esteric carbonyl group (C=O ester 16). This band was found at lower wave numbers due to the conjugation of the esteric carbonyl group 16 with the double bonds of the pyrrolic cycle. In

addition, the conjugation is extended to the phenanthroline cycle, which is situated in the same plain with the pyrrolic cycle and the esteric group 16. The ir spectra of the compounds 25-29 confirmed the structure of type A of these products. The esteric carbonyl group absorbs at 1675-1700 cm^{-1} similarly with esteric carbonyl group 16 in compounds 19-24. If the compound structures were of type B, the esteric carbonyl group would absorb at higher wave numbers. The ketone bands were found in the range of wave numbers of 1640-1650 cm^{-1}.

The structure of compounds 19-24 and 25-29 was also investigated by ^{1}H nmr spectroscopy. In the case of the compounds 19-24, the two singlets δ =3.90-3.92 ppm for the 17-H protons and δ =3.35-3.46 ppm for the 15-H protons, respectively, correspond to the methyl protons. We have established that the doublet which appears at δ =8.46-8.58 ppm may be assigned to 4-H proton. The presence of the methoxycarbonyl group in the neighbourhood of 4-H explained the appearance of this signal at weak field. As for the compounds 25-29, a clear singlet of the 2-H proton in the aromatic region δ =7.54-7.57 ppm was found. The 15-H and 16-H protons gave a quartet at δ =4.39-4.43 ppm and a triplet at δ =1.41-1.44 ppm, respectively. The supplementary evidence for structures of type 24-29 A was given by NOE experiment for the compound 26: irradiation of 15-H produced enhancement with 6% at 4-H shift. The signals of the phenanthroline protons were assigned according to the literature available data [10-12]. Also, ^{13}C nmr spectra for 23 and 26 compounds were carried out and they confirmed the proposed structures [13].

The new pyrrolo[1,2-*a*][1,10]phenanthroline compounds were tested from the biological point of view and proved to be effective antibacterial and antifungal agents [14].

Table I

^{1}H nmr (δ, ppm) and ir (ν, cm^{-1}) Spectra of Compounds 19-23

Compd.	**19**	**20**	**21**	**22**	**23**	**24**
1H, 4-H	^{d}8.58	^{d}8.55	^{d}8.54	^{d}8.51	^{d}8.46	^{d}8.54
1H, 5-H	^{d}7.85	^{d}7.72	^{d}7.72	^{d}7.68	^{d}7.12	^{d}7.70
1H, 6-H	^{d}7.85	^{d}7.84	^{d}7.85	^{d}7.80	^{d}7.74	^{d}7.81
1H, 7-H	^{d}7.90	^{d}7.87	^{d}7.88	^{d}7.83	^{d}7.77	^{d}7.85
1H, 8-H	^{dd}8.01	^{dd}8.05	^{dd}8.04	^{dd}8.04	^{dd}8.01	^{dd}8.02
1H, 9-H	^{dd} 7.37	^{dd} 7.35	^{dd} 7.35	^{dd} 7.32	^{dd} 7.32	^{dd} 7.33
1H, 10-H	^{dd} 8.23	^{dd} 8.18	^{dd} 8.18	^{dd} 8.15	^{dd} 8.11	^{dd} 8.16
2H, 2'-, 6'-H	^{d} 8.24	^{d} 8.04	^{d} 7.98	^{d} 8.08	^{d} 7.99	^{d} 8.11
2H, 3'-, 5'-H	^{d} 8.32	^{d} 7.47	^{d} 7.63	^{d} 6.97	^{d} 7.28	^{d} 7.47
3H, 15-H	^{s}3.46	^{s}3.43	^{s}3.43	^{s}3.42	^{s}3.38	^{s}3.35
3H, 17-H	^{s}3.92	^{s}3.90	^{s}3.91	^{s}3.90	^{s}3.89	^{s}3.90
3H, OCH_3	-	-	-	^{s}3.90	-	-
3H, CH_3	-	-	-	-	^{s}2.44	-
1H, 4'-H	-	-	-	-	-	^{dd}7.55
$\nu_{C=O}$ ketonic	1650	1645	1645	1648	1645	1645
$\nu_{C=O}$ esteric 14	1698	1705	1700	1695	1705	1705
$\nu_{C=O}$ esteric 16	1748	1755	1755	1740	1735	1745

^{d}-doublet; ^{s}-singlet; ^{dd}-doublet of doublet

Table II

^{1}H nmr (δ, ppm) and ir (ν, cm^{-1}) Spectra of Compounds **24-29**

Compd.	**24**	**25**	**26**	**27**	**28**
1H, 4-H	^{d}8.62	^{d}8.55	^{d}8.58	^{d}8.56	^{d}8.57
1H, 5-H	^{d}7,57	^{d}7.68	^{d}7.72	^{d}7.68	^{d}7.70
1H, 6-H	^{d}7.80	^{d}7.76	^{d}7.80	^{d}7.77	^{d}7.79
1H, 7-H	^{d}7.94	^{d}7.84	^{d}7.88	^{d}7.85	^{d}7.87
1H, 8-H	^{dd}8.26	^{dd}8.24	^{dd}8.21	^{dd}8.17	^{dd}8.19
1H, 9-H	^{dd}7.45	^{dd}7.34	^{dd}7.38	^{dd}7.32	^{dd}7.35
1H, 10-H	^{dd}8.29	^{dd}8.19	^{dd}8.25	^{dd}8.22	^{dd}8.24
2H, 2'-, 6'-H	^{d}8.33	^{d}8.20	^{d}8.11	^{d}8.15	^{d}8.22
2H, 3'-, 5'-H	^{d}8.39	^{d}7.52	^{d}7.71	^{d}7.30	^{d}7.06
3H, OCH_3	-	-	-	-	^{s}3.94
3H, CH_3	-	-	-	^{s}2.50	-
1H, 2-H	^{s}7.56	^{s}7.54	^{s}7.55	^{s}7.56	^{s}7.57
2H, 15-H	^{q}4.43	^{q}4.40	^{q}4.42	^{q}4.39	^{q}4.41
3H, 16-H	^{t}1.43	^{t}1.41	^{t}1.44	^{t}1.41	^{t}1.42
$\nu_{C=O}$ ketonic	1649	1645	1645	1648	1645
$\nu_{C=O}$ esteric	1690	1700	1695	1690	1675

^{d}-doublet; ^{s}-singlet; ^{dd}-doublet of doublets; ^{q}-quartet; ^{t}-triplet

Table III

Coupling Constants (J, Hz) of Compounds **19-29**

Compd.	$J_{4,5}$	$J_{6,7}$	$J_{8,9}$	$J_{8,10}$	$J_{9,10}$	$J_{2',3'}$	$J_{15,16}$	$J_{4',5'}$	$J_{4',6'}$
19	9.45	8.55	3.30	1.06	7.00	7.55	-	-	-
20	8.50	7.85	3.40	1.10	7.20	7.40	-	-	-
21	8.70	7.90	3.60	1.10	7.30	7.61	-	-	-
22	9.21	8.57	4.22	1.49	8.10	8.76	-	-	-
23	9.20	8.53	3.20	1.10	7.93	8.12	-	-	-
24	9.25	8.59	4.31	1.51	8.19	7.70	-	7.81	1.3
25	9.30	8.40	8.03	1.10	4.50	8.70	7.11	-	-
26	9.16	8.54	7.80	1.25	4.15	7.95	7.00	-	-
27	9.15	8.58	8.10	1.30	4.37	8.39	7.20	-	-
28	9.17	8.56	8.10	1.35	4.20	8.83	7.12	-	-
29	9.12	8.56	8.19	1.46	4.13	8.04	7.12	-	-

EXPERIMENTAL

The ^{1}H nmr spectra were run on BRUKER-300 spectrometer and were recorded in ppm downfield from an internal standard TMS in deuteriochloroform. The coupling constants are given in hertz (Hz). The ir (potassium bromide) spectra were recorded with a SPECORD-71 spectrometer. The ir and ^{1}H nmr spectra of the adducts 13-23 derived from 1,10-phenanthrolinium salts are given in Table I, Table II, and Table III. Melting points were measured on a MEL-TEMP capillary apparatus and are uncorrected.

General Procedure.

A sample of cycloimmonium salt 1-6 (1 mmol, 0.42 g salt 1, 0.41 g salt 2, 0.45 g salt 3, 0.40 g salt 4, 0.39 g salt 5, 0.37 g salt 6), was treated with dimethyl acetylenedicarboxylate (1.56 g, 1.1 mmol) or ethyl propiolate (1.07 g, 1.1 mmol) in 15 mL of a mixture of solvent (water, methanol and acetonitril) and were stirred together at room temperature. Then 7 mL 0.2 *N* aqueous NaOH was added drop wise and the resulting solution stirred for 2-3 h. At the beginning, the solution became red-orange in color due to the formation of ylides and then, the yellow-orange product

crystallized quickly. The adduct was collected by filtration to give yellow or orange microcrystals that were washed with 10 mL of the appropriate mixture of solvents. The product was purified by recrystallization (19-24) or by column chromatography (25-29).

1-(*p*-Nitrobenzoyl)-2,3-dimethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (19).

For this procedure the mixture of solvents contained 5 mL water, 5 mL methanol and 5 mL acetonitrile. The product was recrystallized from benzene: chloroform (1:1, v/v) mixture when orange crystals were obtained (0.29 g). Yield 62%, mp 337-339 ºC.

Anal. Calcd. for $C_{26}H_{17}N_3O_7$: C, 64.10; H, 3.54; N, 8.69. Found: C, 64.30; H, 3.50; N, 8.68.

1-(*p*-Chlorobenzoyl)-2,3-dimethoxycarbonylpyrrolo[1,2-*a*]-[1,10]phenanthroline (20).

For this procedure the mixture of solvents contained 10 mL water and 5 mL methanol. The crude product was recrystallized from ethanol: chloroform (1:1, v/v) mixture and yellow crystals were obtained (0.28 g). Yield 60%, mp 311-313 ºC.

Anal. Calcd. for $C_{26}H_{17}ClN_2O_5$: C, 66.04; H, 3.62; N, 5.92. Found: C, 66.08; H, 3.48; N, 5.88.

1-(*p*-Bromobenzoyl)-2,3-dimethoxycarbonylpyrrolo[1,2-*a*]-[1,10]phenanthroline (21).

For this procedure the mixture of solvents contained 5 mL water and 10 mL methanol. The product was recrystallized from benzene: chloroform (1:1, v/v) mixture and yellow-orange powder was obtained (0.27 g). Yield 54%, mp 319-321 ºC.

Anal. Calcd. for $C_{26}H_{17}BrN_2O_5$: C, 60.36; H, 3.31; N, 5.42. Found: C, 60.40; H, 3.28; N, 5.38.

1-(*p*-Methoxybenzoyl)-2,3-dimethoxycarbonylpyrrolo[1,2-*a*]-[1,10]phenanthroline (22).

For this procedure the mixture of solvents contained 5 mL water, 5 mL methanol and 5 mL acetonitrile. The crude product was recrystallized from ethanol: chloroform (1:1, v/v) mixture and an orange powder was obtained (0.23 g). Yield 51%, mp 282-284 ºC.

Anal. Calcd. for $C_{27}H_{20}N_2O_6$: C, 69.22; H, 4.30; N, 5.98. Found: C, 69.28; H, 4.24; N, 5.80.

1-(*p*-Methylbenzoyl)-2,3-dimethoxycarbonylpyrrolo[1,2-*a*]-[1,10]-phenanthroline (23).

For this procedure the mixture of solvents contained 7 mL water and 8 mL methanol. The crude compound was recrystallized from benzene: chloroform (1:1, v/v) mixture and an orange powder was obtained (0.26 g). Yield 58%, mp 268-270 ºC. ^{13}C nmr: 21.71 (1C, CH_3), 51.59 (1C, 15-C), 52.1 (1C, 17-C), 103.74 (1C, 3-C), 120.14 (1C, 2-C), 122.44 (1C, 9-C), 125.24 (1C, 1-C), 125.25 (1C, 5a-C), 125.77 (1C, 4-C), 125.98 (1C, 5-C), 126.54 (1C, 6-C), 126.55 (1C, 7-C), 128.76 (2C, 3'-C, 5'-C), 128.97 (1C, 7a-C), 129.86 (2C, 2'-C, 6'-C), 131.19 (1C, 11b-C), 135.27 (1C, 3a-C), 135.87 (1C, 8-C), 137.07 (1C, 4'-C), 137.35 (1C, 1'-C), , 142.76 (1C, 11a-C), 145.69 (1C, 10-C), 163.93 (1C, 14-C), 165.90 (1C, 16-C), 184.27 (1C, 13-C).

Anal. Calcd. for $C_{27}H_{20}N_2O_5$: C, 71.67; H, 4.46; N, 6.19. Found: C, 71.60; H, 4.40; N, 6.10.

1-Benzoyl-2,3-dimethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (24).

For this procedure the mixture of solvents contained 5 mL water and 10 mL acetonitrile. The product was recrystallized from methanol: chloroform (1:1, v/v) mixture and yellow dark crystals were obtained (0.26 g). Yield 61%, mp 264-266 ºC.

Anal. Calcd. for $C_{26}H_{18}N_2O_5$: C, 71.23; H, 4.14; N, 6.39. Found: C, 71.30; H, 4.08; N, 6.30.

1-(*p*-Nitrobenzoyl)-3-ethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (25).

For this procedure the mixture of solvents contained 6 mL water, 3 mL methanol and 6 mL acetonitrile. The crude product was dissolved in 3 mL chloroform and was purified by chromatography on a column of Silica gel, 70-230 mesh, 60 Å, using benzene as an eluent. The weakly fluorescent segment was kept and orange crystals were obtained by evaporation under reduced pressure of the solvent (0.24 g). Yield 55%, mp 231-232 ºC.

Anal. Calcd. for $C_{25}H_{17}N_3O_5$: C, 68.33; H, 3.90; N, 9.56. Found: C, 68.35; H, 3.80; N, 9.51.

1-(*p*-Chlorobenzoyl)-3-ethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (26).

For this procedure the mixture of solvents contained 5 mL water, 5 mL methanol and 5 mL acetonitrile. The crude product was purified by chromatography on a column of silica gel using benzene as eluent. Yellow crystals were obtained (0.22 g). Yield 52%, mp 229-231 ºC. ^{13}C nmr: 14.58 (1C, 16-C), 60.12 (1C, 15-C), 102.66 (1C, 3-C), 118.3 (1C, 2-C), 122.75 (1C, 9-C), 123.98 (1C, 1-C), 125.53 (1C, 5a-C), 125.67 (1C, 4-C), 126.20 (1C, 5-C), 126.72 (2C, 6-C), 126.73 (1C, 7-C), 128.45 (2C, 3'-C, 5'-C), 128.8 (1C, 7a-C), 131.41 (1C, 11b-C), 131.42 (2C, 2'-C, 6'-C), 131.6 (1C, 4'-C), 135.0 (1C, 3a-C), 136.1 (1C, 1'-C), 136.29 (1C, 8-C), 142.8 (1C, 11a-C), 146.05 (1C, 10-C), 165.22 (1C, 14-C), 183.97 (1C, 13-C).

Anal. Calcd. for $C_{25}H_{17}ClN_2O_3$: C, 70.01; H, 4.00; N, 6.53. Found: C, 70.10; H, 3.90; N, 6.48.

1-(*p*-Bromobenzoyl)-3-ethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (27).

For this procedure the mixture of solvents contained 5 mL water and 10 mL methanol. Similarly, it was separated by chromatography. Yellow powder was obtained (0.28 g). Yield 61%, mp 228-229 ºC.

Anal. Calcd. for $C_{25}H_{17}BrN_2O_3$: C, 63.44; H, 3.62; N, 5.92. Found: C, 63.50; H, 3.50; N, 5.82.

1-(*p*-Methoxybenzoyl)-3-ethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (28).

For this procedure the mixture of solvents contained 7 mL water and 8 mL methanol. Orange crystals were obtained after separation by chromatography on silica gel (0.27 g). Yield 65%, mp 216-218 ºC.

Anal. Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.70; H, 4.70; N, 6.59.

1-(*p*-Methylbenzoyl)-3-ethoxycarbonylpyrrolo[1,2-*a*][1,10]-phenanthroline (29).

For this procedure the mixture of solvents contained 7 mL water and 8 mL methanol. The obtained product was chromatographically purified on a column of silica gel using benzene as eluent. Yellow crystals were obtained (0.22 g). Yield 56%, mp 229-231 ºC.

Anal. Calcd. for $C_{26}H_{20}N_2O_3$: C, 76.45; H, 4.94; N, 6.86. Found: C, 76.50; H, 4.85; N, 6.70.

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* Corresponding author: e-mail alramona@yahoo.com or gabidr@uaic.ro

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