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PYRROLO[1,2-*a*]QUINOLINE DERIVATIVES *via* 1,3-DIPOLAR CYCLOADDITION OF QUINOLINIUM *N*-YLIDES

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The new pyrrolo[1,2-*a*]quinoline derivatives **4** were obtained by 1,3-dipolar cycloaddition of the corresponding quinolinium *N*-ylides generated *in situ* in an efficient one pot three component procedure starting from substituted quinolines, 2-bromoacetophenones and ethyl propiolate in 1,2-epoxypropane. The new compounds were characterized by IR and NMR spectroscopy.

INTRODUCTION

The chemistry of *N*-bridgehead heterocycles such as indolizines,[1] azaindolizines[2] and benzoindolizines[3] is of actuality due to their applications. Among these compounds the pyrrolo[1,2-*a*]quinoline derivatives constantly raised the interest because of their potential biological activity[4] and physical properties[5] which determined studies regarding their synthesis and properties.[6] Moreover, the isolation of gephyrotoxin a natural alkaloid with pyrrolo[1,2-*a*]quinoline skeleton, conducted to numerous studies regarding its biological activity and its total synthesis.[7]

One of the most facile synthetic methods for pyrrolo[1,2-*a*]quinolines is the 1,3-dipolar cycloaddition of the quinolinium *N*-ylides to acetylenic or olefinic dipolarophiles.[8]

The current paper describes the synthesis and characterization of new pyrrolo[1,2-*a*]quinolines obtained by one-pot three components synthesis starting from the substituted quinolines **1**, the bromoacetophenones **2** and ethyl propiolate **3**.

RESULTS AND DISCUSSION

Multi-component reactions are of much interest because open new possibilities in the synthetic chemistry. Moreover, multi-component processes and one-pot reactions provided useful tools for synthesis of azoles, azines or condensed *N*-heterocycles.[9] Usually, the synthesis of pyrrolo[1,2-*a*]quinolines by 1,3-dipolar cycloaddition of the quinolinium *N*-ylides implies the preparation and separation of quinolinium salts which in the second step by reaction with a suitable base afford the corresponding quinolinium *N*-ylides. In presence of the suitable dipolarophiles the pyrrolo[1,2-*a*]quinolines are obtained by 1,3-dipolar cycloaddition reaction. In order to simplify the synthesis, an alternative one-pot three-component reaction towards such type of compounds seems to be promising.

The starting materials for synthesis of the pyrrolo[1,2-*a*]quinolines **4** were the corresponding substituted quinolines **1**, substituted 2-bromoacephenones **2** and ethyl propiolate **3**. The synthesis of pyrrolo[1,2-*a*]quinolines **4** was

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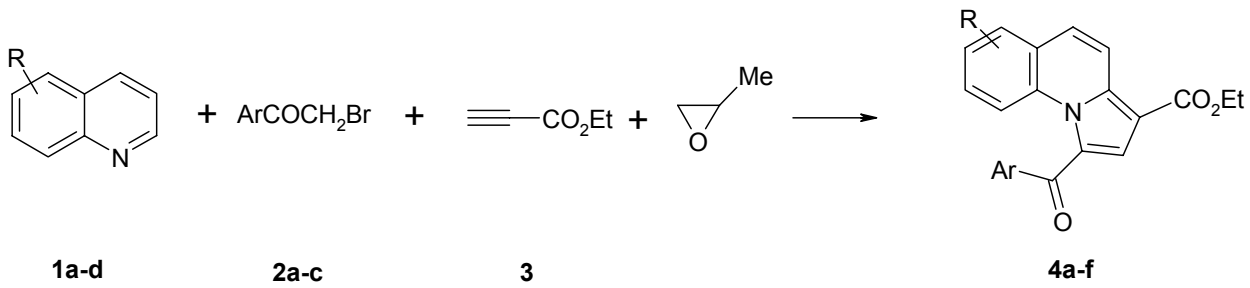
performed in propeneoxide under stirring at room temperature for 40 hours. The pyrrolo[1,2-*a*]quinolines **4** were obtained in yields ranging in the interval 51-54%.

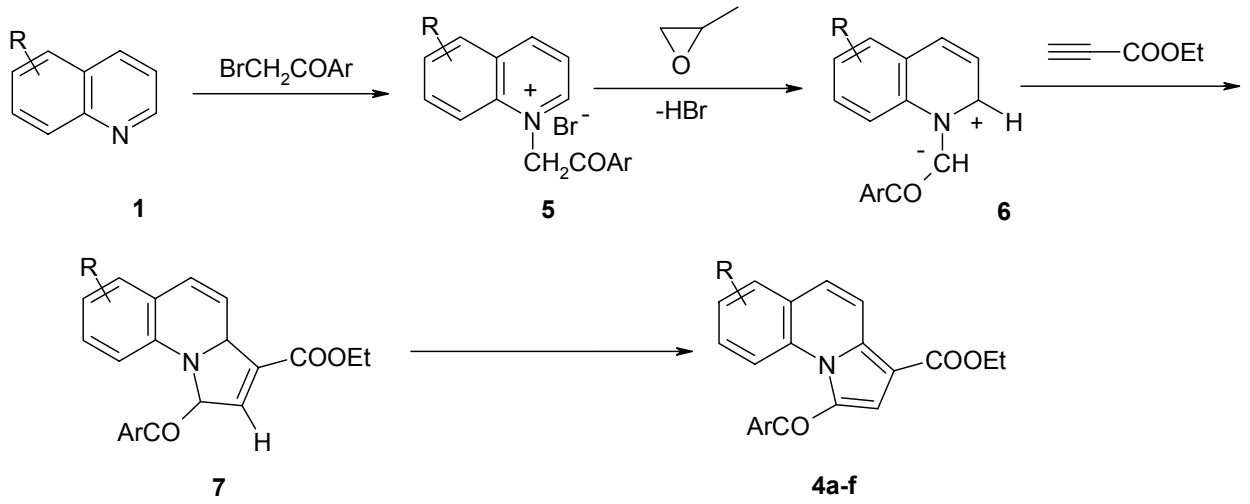


1a-d **2a-c** **3** **4a-f**

1a: R=H; **1b**: R=4-Me; **1c**: R=6-Me; **1d**: R=6-OMe
4a: R=H; Ar=4-$NO_2C_6H_4$; **4b**: R= H; Ar = 3,4-di$MeOC_6H_3$ **4c**: R=5-Me; Ar=4-$NO_2C_6H_4$;
4d: R=7-Me; Ar=4-$NO_2C_6H_4$; **4e**: R=7-OMe; Ar = 3-$NO_2C_6H_4$ **4f**: R=7-OMe; Ar=4-$NO_2C_6H_4$.

Scheme 1

The scheme of the synthesis involves a sequence of steps starting with the quaternization of substituted quinolines **1** with 2-bromoacetophenones **2** towards the quinolinum bromides **5**. Then, the quinolinium *N*-ylides **6** are generated *in situ* by the action of 1,2-epoxypropane on the quinolinium bromides. The 1,3-dipolar cycloaddition between *N*-ylide and ethyl propiolate afforded the hydrogenated cycloadducts **7** which suffer dehydrogenation *in situ* to give the pyrrolo[1,2-*a*]quinolines **4**.



Scheme 2

The structures of the new compounds were studied by IR and NMR spectroscopy.

The IR spectra of the compounds present the characteristic bands of the main functional groups. A characteristic for these spectra are the carbonyl bands. Compounds **4** present these bands at 1630-1638 cm^{-1} for the carbonyl groups in the COAr. The carbonyl group in the carboethoxy groups is observed as strong bands at around 1700 cm^{-1}. Another characteristic band is the C-O stretch band in the methoxy or carboethoxy groups which is found at about 1230 cm^{-1}. The two NO_2 vibrations in the corresponding compounds could be observed at around 1340 and 1540 cm^{-1}.

The ^{1}H-NMR spectra are in agreement with the structure of compounds **4**. The multiplicity of the signals depends on the nature and position of the substituents attached to the quinoline system. A characteristic of the ^{1}H-NMR spectra is the signal of the hydrogen H-2 which appears as a singlet in the range of 7.57-7.62 ppm. Also H-4 is the most deshielded proton in the quinoline ring due to its vicinity with the carboethoxy moiety. This is a proof for the regioselectivity of the reaction. In the

case of unsubstituted and 7-susbtituted compounds it appears as a doublet with J = 9.3 Hz. By comparison with pyrroloquinolines **4a,b** the presence of the methyl group or methoxy group attached at position 5 or position 7 in the quinoline ring influences the chemical shift and also the multiplicity of the ^{1}H-NMR signals. For example the presence of the methoxy group at position 7 influences the multiplicity and chemical shifts of the protons H-6 and H-8 which are in *ortho* position in respect with the methoxy group. H-6 and H-8 appear as a multiplet at 7.20-7.32 ppm, whereas in the unsubstituted compounds **4a** and **4b** appear as two multiplets in the range 7.43-7.57 ppm.

The signals in the ^{13}C-NMR spectra were solved in respect with chemical shifts and by HETCOR experiments. The most characteristic feature is the chemical shift of carbon C-3 which appears at 107.4-108.4 ppm in compounds **4.** The carbon C-2 in the compounds **4** appears at about 128.9-131.4 ppm. Due to the MeO group attached at the carbon C-7 in the compounds **4e,f**, the carbons C-6 and C-8 are shielded (ca. 118 ppm). For example in the compound **4d** with a methyl group at carbon C-7 instead of methoxy, C-6 and C-8 appear in the range 128-130 ppm. The carbon C-7 in the compounds **4e,f** appears at 157.1-157.4 ppm strongly deshielded by the OMe group directly attached to it.

It is interstingly to note that the pyrrolo[1,2-a]quinolines **4** exhibit strongly fluorescence in solution and the quantitative determination is under study.

EXPERIMENTAL

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. Supplementary evidence was given by HETCOR and COSY experiments.

General procedure for synthesis of pyrrolo[1,2-a]quinolines 4

5 Mmol of quinoline **1a-d**, 5 mmol of phenacyl bromide **2a-c** and 7 mmol of ethyl propiolate in 40 mL propyleneoxid were stirred at room temperature for 40 hours. The solvent was partly removed by evaporation, 10 mL of methanol was added and the mixture was left over night at room temperature. The solid was filtered, washed with a MeOH:Et_2O 1:1 mixture and recrystallized from $CHCl_3$/MeOH.

Ethyl 1-(4-nitrobenzoyl)-pyrrolo[1,2-a]quinoline-3-carboxylate (**4a**). Yellow crystals with mp 187-9ºC; Yield 50%. Anal. Calcd. $C_{22}H_{16}N_2O_5$: C 68.04; H 4.15; N 7.21. Found: C 68.38; H 4.29; N 7.49. FT-IR (cm^{-1}): 1340, 1543, 1638, 1704, 2983.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.1 Hz, $MeCH_2$); 4.38 (q, 2H, J = 7.1 Hz, CH_2); 7.51-7.56 (m, 1H, H-7); 7.59-7.65 (m, 1H, H-8); 7.61 (s, 1H, H-2); 7.77 (d, 1H, J = 9.3 Hz, H-5); 7.85 (dd, 1H, J = 7.8, 1.5 Hz, H-6); 8.10 (d, 1H, J = 8.6 Hz, H-9); 8.23 (d, 2H, J = 8.9 Hz, H-2', H-6').8.36 (d, 1H, J = 9.3 Hz, H-4); 8.41 (d, 2H, J = 8.9 Hz, H-3', H-5').

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.6 ($MeCH_2$); 60.5 (CH_2O); 108.5 (C-3); 117.6 (C-4); 120.3 (C-9); 123.8 (C-3', C-5'); 125.9 (C-7); 129.0 (C-8); 129.1 (C-6); 130.1 (C-5); 130.8 (C-2); 130.9 (C-2', C-6'); 125.2, 127.5, 133.2, 141.2 (C-1, C-3a, C-5a, C-9a); 143.9 (C-1'); 150.2 (C-4'); 163.7 (COO); 182.1 (COAr).

Ethyl 1-(3,4-dimethoxybenzoyl)-pyrrolo[1,2-a]quinoline-3-carboxylate (**4b**). Yellow crystals with mp 176-8ºC; Yield 52%. Anal. Calcd. $C_{24}H_{21}NO_5$: C 71.45; H 5.25; N 3.47. Found: C 71.77; H 5.09; N 3.69. FT-IR (cm^{-1}): 1236, 1631, 1707, 2996.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, 3H, J = 7.1 Hz, $MeCH_2$); 3.98, 4.00 (s, 6H, 2MeO); 4.38 (q, 2H, J = 7.1 Hz, CH_2); 6.99 (d, J = 8.4 Hz, H-5'); 7.43-7.48 (m, 1H, H-7); 7.51-7.58 (m, 1H, H-8); 7.62 (s, 1H, H-2); 7.64 (d, 1H, J = 9.3 Hz, H-5); 7.67 (d, 1H, J = 1.9 Hz, H-2'); 7.75-7.80 (m, 2H, H-6, H-6'); 7.98 (d, 1H, J = 8.6 Hz, H-9); 8.32 (d, 1H, J = 9.3 Hz, H-4);

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 ($MeCH_2$); 56.1, 56.2 (2 MeO); 60.1 (CH_2O); 107.6 (C-3); 110.1 (C-5'); 112.1 (C-2'); 117.8 (C-4); 120.0 (C-9); 125.3 (C-7); 125.4 (C-6'); 125.1, 128.3, 133.2, 139.7 (C-1, C-3a, C-5a, C-9a); 128.0 (C-5); 128.7 (C-8); 128.9 (C-2, C-6); 131.2 (C-1'); 149.3, 153.6 (C-3', C-4'); 164.1 (COO); 184.4 (COAr).

Ethyl 1-(4-nitrobenzoyl)-5-methyl-pyrrolo[1,2-a]quinoline-3-carboxylate (**4c**). Yellow crystals with mp 186-7 ºC; Yield 50 %. Anal. Calcd. $C_{23}H_{18}N_2O_5$: C 68.65; H 4.41; N 6.96. Found: C 68.91; H 4.09; N 7.14. FT-IR (cm^{-1}): 1346, 1521, 1633, 1701, 2976.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.1 Hz, Me); 2.73 (d, 3H, J = 1.1 Hz, 5-Me); 4.37 (q, 2H, J = 7.1 Hz, CH_2); 7.57 (s, 1H, H-2); 7.54-7.66 (m, 2H, H-7, H-8); 7.98-8.01 (m, 1H, H-6); 8.12-8.16 (m, 1H, H-9); 8.20-24 (m, 3H, H-4, H-3', H-5'); 8.41 (d, 2H, J = 8.8 Hz, H-2', H-6').

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 ($MeCH_2$); 19.6 (5-Me); 60.2 (OCH_2); 107.4 (C-3); 117.2 (C-4); 120.6 (C-9); 123.6 (C-3', C-5'); 125.1 (C-6); 125.4 (C-5); 125.7 (C-7); 127.1, 132.9, 137.8, 141.3 (C-1, C-3a, C-5a, C-9a); 128.6 (C-8); 131.1 (C-2); 130.7 (C-2', C-6'); 144.1 (C-1'); 150.0 (C-4'); 163.7 (COOEt). 181.7 (COAr).

Ethyl 1-(4-nitrobenzoyl)-7-methyl-pyrrolo[1,2-a]quinoline-3-carboxylate (**4d**). Orange crystals with mp 203-4 ºC; Yield 51 %. Anal. Calcd. $C_{23}H_{18}N_2O_5$: C 68.65; H 4.41; N 6.96. Found: C 68.86; H 4.74; N 7.24. FT-IR (cm^{-1}): 1349, 1520, 1638, 1704, 2987.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.1 Hz, $MeCH_2$); 2.52 (s, 3H, 7-Me); 4.37 (q, 2H, J = 7.1 Hz, CH_2); 7.44 (dd, 1H, J = 8.8, 2.1 Hz, H-8); 7.60 (s, 1H, H-2); 7.63 (d, 1H, J = 2.1 Hz, H-6); 7.71 (d, 1H, J = 9.3 Hz, H-5); 8.00 (d, 1H, J = 8.8 Hz, H-9); 8.20 (d, 2H, J = 8.8 Hz, H-2', H-6'); 8.33 (d, 1H, J = 9.3 Hz, H-4); 8.41 (d, 2H, J = 8.8 Hz, H-3', H-5').

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 ($MeCH_2$); 21.0 (7-Me); 60.2 (OCH_2); 108.4 (C-3); 117.4 (C-4); 120.0 (C-9); 123.6 (C-3', C-5'); 125.2, 127.2, 131.3, 135.8, 140.9 (C-1, C-3a, C-5a, C-9a, C-7); 128.5 (C-6); 129.9 (C-5); 130.4 (C-8); 130.6 (C-2); 130.8 (C-2', C-6'); 144.0 (C-1'); 150.4 (C-4'); 163.7 (COO); 181.9 (COAr).

Ethyl 1-(3-nitrobenzoyl)-7-methoxy-pyrrolo[1,2-a]quinoline-3-carboxylate (**4e**). Yellow crystals with mp 244-5ºC; Yield 54%. Anal. Calcd. $C_{23}H_{18}N_2O_6$: C 66.03; H 4.34; N 6.70. Found: C 66.21; H 4.22; N 6.89. FT-IR (cm^{-1}): 1234, 1343, 1524,1631, 1704, 2996.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (t, 3H, *J* = 7.1 Hz, $MeCH_2$); 3.98 (s, 3H, 7-MeO); 4.45 (q, 2H, *J* = 7.1 Hz, CH_2); 7.26-7.32 (m, 2H, H-6 , H-8); 7.74 (s, 1H, H-2); 7.82 (t, 1H, *J* = 7.9 Hz, H-5'); 7.85 (d, 1H, *J* = 9.3 Hz, H-5); 7.99 (d, 1H, *J* = 8.9 Hz, H-9); 8.29 (d, 1H, *J* = 9.3 Hz, H-4); 8.38-8.41 (m, 1H, H-6'); 8.56-8.59 (m, 1H, H-4'); 8.90 (t, 1H, *J* = 1.9 Hz, H-2'). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1 ($MeCH_2$); 55.9 (7-OMe); 62.1 (CH_2O); 108.3 (C-3); 117.6, 119.3 (C-6, C-8); 118.0 (C-4); 121.7 (C-9); 125.0 (C-2'); 126.7 (C-4'); 126.7, 127.8, 127.9, 139.3 (C-1, C-3a, C-5a, C-9a); 127.7 (C-5); 130.1 (C-5'); 131.4 (C-2); 135.5 (C-6'); 141.4 (C-1'); 148.3 (C-3'); 157.4 (C-7); 165.9 (COO); 183.0 (COAr).

Ethyl 1-(4-nitrobenzoyl)-7-methoxy-pyrrolo[1,2-a]quinoline-3-carboxylate (**4f**). Orange crystals with mp 231-2 ºC; Yield 51 %. Anal. Calcd. $C_{23}H_{18}N_2O_6$: C 66.03; H 4.34; N 6.70. Found: C 66.21; H 4.22; N 6.89. N 7.17. FT-IR (cm^{-1}): 1234, 1348, 1529 1630, 1707, 2989.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, 3H, *J* = 7.1 Hz, $MeCH_2$); 3.94 (s, 3H, 7-MeO); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 7.20-7.25 (m, 2H, H-6, H-8); 7.58 (s, 1H, H-2); 7.71 (d, 1H, *J* = 9.3 Hz, H-5); 8.07 (d, 1H, *J* = 8.8 Hz, H-9); 8.21 (d, 2H, *J* = 6.8 Hz, H-2', H-6'); 8.34 (d, 1H, *J* = 9.3 Hz, H-4); 8.40 (d, 2H, *J* = 6.8 Hz, H-3', H-5').

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.6 ($MeCH_2$); 55.8 (7-OMe); 60.4 (CH_2O); 108.3 (C-3); 109.3, 118.4 (C-6, C-8); 118.0 (C-4); 121.8 (C-9); 123.7 (C-3', C-5'); 126.6, 127.1, 127.9, 140.5 (C-1, C-3a, C-5a, C-9a,); 129.8 (C-5); 130.6 (C-2); 130.8 (C-2', C-6'); 144.0 (C-1'); 150.1 (C-4'); 157.1 (C-7); 163.8 (COO); 182.0 (COAr).

CONCLUSIONS

In conclusion, the synthesis of the pyrrolo[1,2-a]quinolines **4a-f** was carried out by a simple one-pot three component method and the structure of the new compounds was assigned on the basis of NMR spectroscopy. The regioselectivity of cycloaddition was deduced on the basis of ^{1}H-NMR data.

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