One-Pot, Three-Component Synthesis of a Library of New Pyrrolo[1,2-*a*]quinoline Derivatives

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Abstract: The synthesis of a library of pyrrolo[1,2-*a*]quinoline derivatives **4**–**33** was performed by an efficient one-pot, three-component reaction from quinolines **1a**–**c**, 2-bromoacetophenones **2** and non-symmetrical acetylenic dipolarophiles **3a**–**c** in 1,2-epoxypropane as both reaction medium and HBr scavenger. As this approach was unsuccessful in the case of DMAD, a different method was used for the synthesis of pyrrolo[1,2-*a*]quinolines **35**–**44**. The structural features of the cycloadducts **19** and **44** were investigated by X-ray analysis.

Key words: 1,3-dipolar cycloaddition, *N*-ylide, pyrrolo[1,2-*a*]quinoline, multicomponent reaction

In the last decade, interest in pyrrolo[1,2-*a*]quinolines has been constant and, as a result, various new syntheses and reconsiderations of previously known synthetic pathways have been reported.[1] The pyrrolo[1,2-*a*]quinoline derivatives were found to possess interesting biological[2] and physical properties.[3] For example, gephyrotoxin, a substituted perhydropyrrolo[1,2-*a*]quinoline isolated by Daly and coworkers in 1977 from secretions of the frog *dendrobates histrionicus*,[4] was studied for its biological activity and has been a target for total synthesis.[5]

Generally, for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives, two main routes are available: the first starting from quinoline and its derivatives and the second starting from pyrrole derivatives substituted at the nitrogen atom with an aryl group. Additionally, examples of the syntheses of pyrrolo[1,2-*a*]quinolines based on rearrangement reactions or starting from acyclic compounds are reported in the literature.[6]

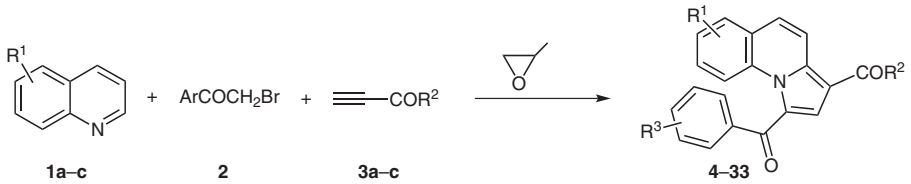
One of the most important methods for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives involves the 1,3-dipolar cycloaddition reactions of heterocyclic *N*-ylides with electron-deficient alkynes or alkenes.[7] Herein, we describe the synthesis of a library of pyrrolo[1,2-*a*]quinolines via 1,3-dipolar cycloaddition reactions in an efficient one-pot, three-component synthesis based on a consecutive quaternization, 1,3-dipolar cycloaddition and aromatization sequence.

Sequential transformations, multicomponent processes and one-pot reactions provide opportunities for the syntheses of heterocycles.[8] These synthetic pathways involve reactions with at least three starting materials in one-pot, which offers straightforward one-step transformations.

The key components of the multi-stage process are quinolines **1**, bromoacetophenones **2**, non-symmetrical electron-deficient alkynes **3** and 1,2-epoxypropane, which acts both as solvent and proton scavenger.

Usually, the synthesis of pyrrolo[1,2-*a*]quinolines via quinolinium *N*-ylides requires the preparation and separation of quinolinium salts in the first step. Subsequently, quinolinium salts are converted into pyrrolo[1,2-*a*]quinolines by treatment with a base, which generates the corresponding quinolinium *N*-ylide in the presence of an acetylenic dipolarophile.

In the multicomponent pathway, the reaction mechanism implies the intermediate formation of the quinolinum salt from the corresponding quinoline and 2-bromoacetophenone. In the next step, the bromide ion from the salts attacks the oxirane ring of 1,2-epoxypropane, resulting in ring-opening and generation of the *N*-ylide by the alkoxide. The *N*-ylide reacts with the activated alkyne **3** to give the corresponding dihydropyrroloquinoline. Finally, the pyrroloquinolines **4**–**33** are obtained by dehydrogenation of the dihydropyrroloquinoline intermediate (Scheme 1).



Scheme 1

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The reaction conditions are mild, involving only mixing of the components under stirring at room temperature for 30 hours, followed by partial evaporation of the solvent and subsequent precipitation by the addition of methanol.[9] The compounds **4–33** (Table 1) were obtained with yields in the 50–70% range. The substituents of the new pyrrolo[1,2-*a*]quinoline compounds **4–33** are given in Table 1.

Table 1 One-Pot, Three-Component Synthesis of Pyrrolo[1,2-*a*]quinolines **4–33**

Product	R^1	R^2	R^3	Mp (°C)
4	H	OEt	H	166–167
5	H	OEt	4-F	160–161
6	H	OEt	4-Cl	146–147
7	H	OEt	4-Br	180–181
8	H	OEt	3-MeO	132–133
9	H	OEt	4-MeO	152–153
10	H	OEt	3-NO_2	210–211
11	H	OEt	4-Ph	164–165
12	H	Me	4-Me	174–176
13	H	Me	4-Cl	193–195
14	H	Ph	H	144–145
15	H	Ph	4-F	154–155
16	H	Ph	2-NO_2	174–176
17	H	Ph	3-NO_2	183–184
18	7-Me	OEt	H	143–144
19	7-Me	OEt	4-Me	173–175
20	7-Me	OEt	4-F	173–174
21	7-Me	OEt	4-Cl	182–183
22	7-Me	OEt	3-Br	184–185
23	7-Me	OEt	4-Br	199–200
24	7-Me	OEt	3-MeO	187–188
25	7-Me	OEt	4-MeO	159–161
26	7-Me	OEt	2-NO_2	216–217
27	7-Me	OEt	3-NO_2	231–232
28	5-Me	OEt	4-Me	171–172
29	5-Me	OEt	4-Cl	149–150
30	5-Me	OEt	3-Br	177–178
31	5-Me	OEt	4-MeO	157–159
32	5-Me	OEt	3-NO_2	227–228
33	5-Me	OEt	4-CN	184–186

The structures of the new pyrroloquinolines were assigned by elemental analysis, IR and NMR spectroscopy. The characteristic IR spectral features of compounds **4–33** are the carbonyl bands observed in the range 1630–1740 cm^{-1}. Additionally, the ester C–O vibration could be observed at 1080 cm^{-1} and 1230 cm^{-1} for compounds **4–11** and **18–33**. In the ^1H NMR spectra of compounds **4–33**, the general characteristic feature is the chemical shifts of atoms H-2, H-4 and H-9, which appear strongly deshielded due to the spatial vicinity of the carbonyl groups attached to the positions 1 and 3 of the pyrrole ring. The H-2 proton appears as a singlet with $\delta = 7.21–7.77$ ppm. The ^{13}C NMR spectra contain all the expected signals. Additionally, the regioselectivity of the cycloaddition reaction and the stereochemistry of cycloadducts **4–33** were determined by X-ray analysis of compound **19** as a representative compound (see below).

Interestingly, under the same reaction conditions the three-component method for the synthesis of pyrrolo[1,2-*a*]quinolines **35–43** gave very poor yields in the case of dimethyl acetylenedicarboxylate (DMAD). Most probably due to its high reactivity, DMAD reacts faster with the nitrogen atom from the quinoline instead of acting as a dipolarophile in the further 1,3-dipolar cycloaddition. Because of this competition, the reaction leading to the formation of the pyrroloquinolines is inhibited, and only traces of these compounds were observed.

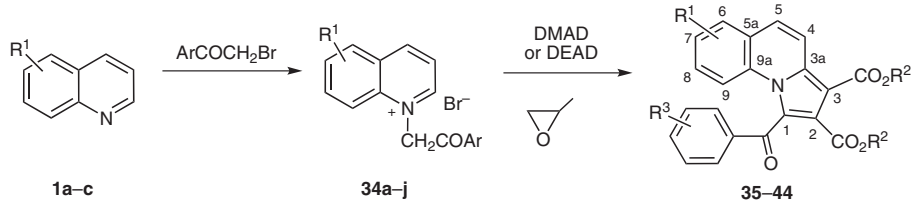
However, compounds **35–43** were obtained starting from the corresponding quinolinium salts **34a–j**, which were obtained separately by reaction of the substituted quinolines **1** and bromoacetophenones **2**. The reaction of the salts with DMAD in epoxypropane medium led to the formation of the corresponding pyrroloquinolines by a simple one-pot reaction (Scheme 2).[10] Similar results were obtained in the case of compound **44** when the dipolarophile DMAD was replaced by diethyl acetylenedicarboxylate (DEAD). The pyrroloquinolines **35–44** (Table 2) were obtained in yields of 48–58%.

The structural assignments were made by elemental analysis, IR and NMR spectroscopy. The stereochemistry for this series was confirmed by X-ray analysis of the representative compound **44** (see below).

The reaction pathway used in the case of DMAD (Scheme 2) could also be successfully applied in the case of compounds **4–33**. Thus, starting from the salts of type **34** and non-symmetrical acetylenic dipolarophiles in propenoxide medium, the pyrroloquinolines could be obtained in yields differing by ±3–5% from those obtained using the one-pot, three-component method.

The X-ray structures of the representative compounds **19**[11] and **44**[12] are shown in Figure 1 and Figure 2 respectively. Thermal ellipsoids are drawn at the 50% probability level in each case and the rings of the tricyclic system have been labeled for reference.

Given the paucity of explicit X-ray structural information on the pyrrolo[1,2-*a*]quinoline system, and finding evi-



Scheme 2

Table 2 Two-Step Synthesis of Pyrrolo[1,2-*a*]quinolines **35**–**44**

Product	R^1	R^2	R^3	Mp (°C)
35	H	Me	4-F	210–211
36	H	Me	4-Br	196–198
37	H	Me	3-NO_2	191–193
38	H	Me	3,4-(MeO)-	245–247
39	7-Me	Me	3-Br	192–194
40	7-Me	Me	3-NO_2	190–191
41	7-Me	Me	3,4-(MeO)-	198–199
42	5-Me	Me	4-F	211–212
43	5-Me	Me	3,4-(MeO)-	214–216
44	7-Me	Et	3,4-(MeO)-	167–168

dence of unusual features in the representative molecules **19** and **44**, we were prompted to examine their molecular conformations in some detail. Molecular strain, leading to significant deviations from planarity of the tricyclic systems in both **19** and **44**, is evident. This originates from intramolecular repulsion reflected in significantly short contact distances between the carbonyl group C15=O16 and atom C12 in both molecules [C12···C15, 3.210(2) Å and C12···O16, 2.977(2) Å in **19**, with corresponding values of 3.085(2) and 2.947(2) Å in **44**]. More strikingly, this steric strain results in carbonyl atom C15 being displaced by ~0.50 Å above the plane of the pyrrole ring A in both molecules, simultaneously inducing helical distortion of the entire tricyclic system. One measure of this distortion is the sequence of interplanar angles A^B, B^C, A^C (see Figure 1 and Figure 2), whose values are 6.6, 7.4 and 13.9°, respectively, in **19**, and are somewhat larger than those in **44**, which are 1.9, 5.4 and 6.2° (all e.s.d.s ≤0.1°). In both molecules, two C–H···O hydrogen bonds determine the orientations of the carbonyl bond vectors relative to the mean plane of the tricyclic system.

The distortions described above are virtually absent in 1-aminopyrrolo[1,2-*a*]quinoline-2-carbonitrile,[13a] in which the substituent at position C2 in the figures below is NH_2, the interplanar angles having values of only 0.8, 0.9 and 1.7° (e.s.d.s ≤0.1°) and the nitrogen atom being practically coplanar with the pyrrole ring (deviation ~0.05 Å). A small degree of helicity arises in 1-*n*-butylpyrrolo[1,2-*a*]quinolin-3-yl acetate,[13b] the three interplanar angles of the tricyclic system having values 2.4, 2.9 and 5.0° (e.s.d.s ~0.2°). Finally, a somewhat larger helical distortion occurs in *N*-[3,5-bis(trifluoromethyl)benzyl]-5-phenylpyrrolo[1,2-*a*]quinoline-4-carboxamide[2a] (interplanar angles: 4.3, 3.3 and 7.2°, e.s.d.s ~0.2°). Here, however, the only substituents on the pyrrole ring are hydrogen atoms, and the helicity originates from steric interactions remote from that site (i.e. on ring B, between a phenyl group at-

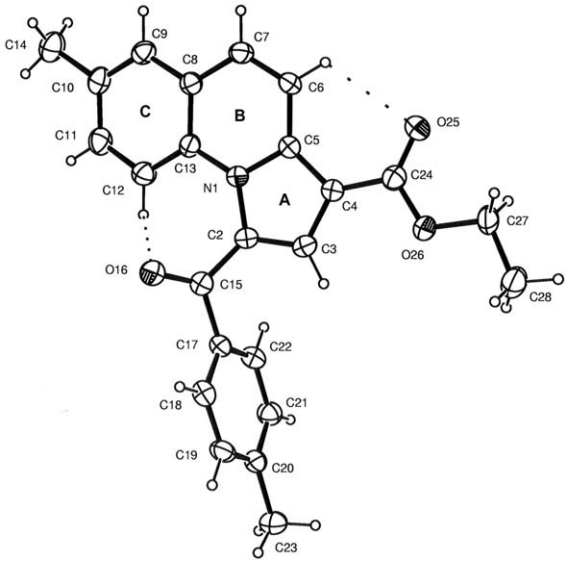


Figure 1 ORTEP plot of **19**

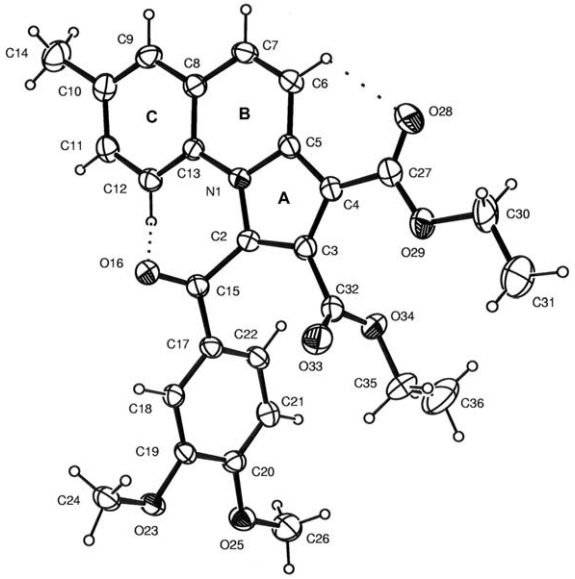


Figure 2 ORTEP plot of **44**

tached at the position corresponding to C7 and a carbonyl group attached to C6).

In conclusion, the three-component reaction of quinolines with 2-bromoacetophenones and non-symmetrical, electron-deficient alkynes in 1,2-epoxypropane is an efficient method for the preparation of a variety of pyrrolo[1,2-*a*]quinolines by sequential quaternization, ylide generation and 1,3-dipolar cycloaddition. Preliminary investigation indicates that this method could be applied to the synthesis of other N-fused heterocyclic systems. A systematic examination of recently determined X-ray structures of molecules containing the pyrrolo[1,2-*a*]quinoline system, including the representative compounds **19** and **44**, revealed that the tricyclic system is susceptible to helical distortion induced by bulky substituents. Maximum distortion was observed when a carbonyl group is attached to atom C2 of the five-membered ring.

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(9) **Synthesis of Pyrrolo[1,2-*a*]quinolines 4–33; General Procedure:** Quinoline **1** (5 mmol), phenacyl bromide **2** (5 mmol) and non-symmetrical acetylene **3** (ethyl propiolate, 3-butyn-2-one or benzoylacetylene; 7 mmol) in 1,2-epoxypropane (40 mL) were stirred at room temperature for 30 h. The solvent was partly removed by evaporation, then methanol (10 mL) was added and the mixture was left overnight at room temperature. The solid was filtered, washed with a mixture of MeOH–Et_2O (1:1) and recrystallised from $CHCl_3$–MeOH. **Ethyl 1-(4-Methylbenzoyl)-7-methyl-pyrrolo[1,2-*a*]quinoline-3-carboxylate (19):** Yellow crystals with mp 173–175 °C were obtained by recrystallization from $CHCl_3$–MeOH. Yield: 54%; Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.91; H, 5.94; N, 3.98. FT-IR: 1617, 1654, 1704, 2976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.1 Hz, 3 H, $MeCH_2$), 2.47 (s, 3 H, MeAr), 2.50 (s, 3 H, 7-Me), 4.39 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.35–7.38 (m, 3 H, H-8, H-3′, H-5′), 7.57 (d, *J* = 2.1 Hz, 1 H, H-6), 7.62 (s, 1 H, H-2), 7.60 (d, *J* = 9.3 Hz, 1 H, H-5), 7.87 (d, *J* = 8.9 Hz, 1 H, H-9), 7.95 (d, *J* = 8.8 Hz, 2 H, H-2′, H-6′), 8.23 (d, *J* = 9.3 Hz, 1 H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 ($MeCH_2$), 20.8, 21.6 (7-Me, MeAr), 59.9 (OCH_2), 107.4 (C-3), 117.6 (C-4), 119.9 (C-9), 125.1, 128.0, 131.4, 135.9, 139.7 (C-1, C-3a, C-5a, C-9a, C-7), 128.3 (C-6), 129.4 (C-5), 128.6 (C-8), 129.1

(C-3′, C-5′), 129.9 (C-2), 130.2 (C-2′, C-6′), 135.1 (C-1′), 143.4 (C-4′), 164.1 (COO), 184.8 (COAr).

(10) **Synthesis of Pyrrolo[1,2-*a*]quinolines 35–44; General Procedure:** Quaternary salt **34a–j** (5 mmol) and DMAD or DEAD (7 mmol) in 1,2-epoxypropane (40 mL) were stirred at room temperature for 24 h. The solvent was partly removed by evaporation, then methanol (10 mL) was added and the mixture was left overnight at room temperature. The solid was filtered, washed on filter with a mixture of MeOH–Et_2O (1:1) and recrystallised from $CHCl_3$–MeOH.
Dimethyl 1-(3-Bromobenzoyl)-7-methylpyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (39): Yellow crystals with mp 192–194 °C were obtained by recrystallization from MeOH–$CHCl_3$. Yield: 44%. Anal. Calcd for $C_{23}H_{18}BrNO_3$: C, 63.32; H, 4.16; Br, 18.31; N, 3.21. Found: C, 63.44; H, 4.39; Br, 18.66; N, 3.56. FT-IR: 1617, 1654, 1704, 2976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, 7-Me), 3.50, 3.90 (s, 6 H, 2-CO_2Me, 3-CO_2Me), 7.27 (dd, *J* = 8.8, 2.1 Hz, 1 H, H-8), 7.36 (t, *J* = 7.8 Hz, 1 H, H-5′), 7.51 (d, *J* = 8.9 Hz, 1 H, H-9), 7.57 (d, *J* = 2.1 Hz, 1 H, H-6), 7.58 (d, *J* = 9.3 Hz, 1 H, H-5), 7.73–7.77 (m, 1 H, H-4′), 7.84–7.87 (m, 1 H, H-6′), 8.15 (t, *J* = 2.0 Hz, 1 H, H-2′), 8.23 (d, *J* = 9.3 Hz, 1 H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (7-Me), 51.7, 52.8 (CO_2CH_3), 105.5 (C-3), 117.7 (C-4), 118.8 (C-9), 122.7 (C-3′), 125.3, 127.2, 128.8, 131.2, 135.7, 140.3 (C-1, C-3a, C-5a, C-9a, C-7, C-2), 128.4 (C-6), 128.5 (C-2′), 128.9 (C-5), 130.2 (C-5′), 130.4 (C-8), 132.7 (C-2′), 136.5 (C-4′), 139.5 (C-1′), 163.5, 165.1 (2 × COO), 185.7 (COAr).

(11) X-ray crystal data for **19**: $C_{24}H_{21}NO_3$; yellow plate; *M* = 371.42; triclinic; *P(–1)*; *a* = 9.3086 (5) Å, *b* = 10.4631 (5) Å, *c* = 10.9389 (5) Å, α = 91.153 (2)°, β = 112.900(3)°, γ = 104.195 (3)°; *V* = 943.48 (7) $Å^3$; *Z* = 2; *T* = 173 (2) K; F_{000} = 392; *R*1 = 0.0428, *wR*2 = 0.1170. The CCDC deposition number: 718544.

(12) X-ray crystal data for **44**: $C_{28}H_{27}NO_7$; pale-yellow plate; *M* = 489.51; triclinic; *P(–1)*; *a* = 7.5730 (3) Å, *b* = 13.0161 (3) Å, *c* = 13.4416 (6) Å, α = 97.269 (2)°, β = 104.946 (2)°, γ = 102.512 (3)°; *V* = 1226.13 (8) $Å^3$; *Z* = 2; *T* = 173 (2) K; F_{000} = 516; *R*1 = 0.0414, *wR*2 = 0.1132. The CCDC deposition number: 718545.

(13) (a) Tayyari, F.; Wood, D. E.; Fanwick, P. E.; Sammelson, R. E. *Synthesis* **2008**, 279. (b) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783.