A one-pot four-component synthesis of pyrrolo[1,2-*a*]quinolines

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A facile one-pot, four-component reaction for the synthesis of pyrrolo[1,2-*a*]quinolines is described. Knoevenagel condensation reaction of malononitrile and aromatic aldehydes gave 2-arylmethylidenemalononitriles which on treatment with quinoline and cyclohexyl isocyanide under solvent-free conditions afforded 1-(cyclohexylamino)-2-arylpyrrolo[1,2-*a*]quinoline-3-carbonitriles in good yields.

Keywords: four-component reactions, pyrrolo[1,2-*a*]quinolines, 2-arylmethylidenemalononitriles, cyclohexyl isocyanide

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity. Pyrrolo[1,2-*a*]quinolines (benzo analogues of indolizines), tricyclic-fused 6 : 6 : 5 systems, have attracted much synthetic attention. The interest in these heterocycles stems from the occurrence of some saturated and partially saturated derivatives in many biologically active compounds.[1–3] For example, gephyrotoxin (Fig. 1), a natural alkaloid with a saturated pyrrolo[1,2-*a*]quinoline skeleton, has shown activity as a muscarinic antagonist.[4,5] In addition, some pyrroloquinolines have been used as pesticides, light-sensitive and photographic materials and in electroluminescent devices.[6–11]

One of the most powerful methods for the synthesis of pyrrolo[1,2-*a*]quinolines is 1,3-dipolar cycloaddition of quinolinium *N*-methylides with different dipolarophiles such as active alkenes and alkynes.[3,12] Recently, various metal-catalysed cyclisations have been developed.[13–15]

In 2003, Mironov *et al*.[16] defined a new three-component reaction between isoquinoline, *gem*-dicyanoalkenes and isocyanides. They assigned 1,10b-dihydropyrrolo[2,1-*a*] isoquinoline-2,2(3*H*)-dicarbonitriles as the structures of the isolated products. In 2011, Li and coworkers[17] developed this reaction to phenanthridine and reported the synthesis of 2,3-dihydropyrrolo[1,2-*f*]phenanthridines. Recently, four-component versions of this reaction have been developed for the preparation of pyrrolo[1,2-*a*][1,10]phenanthrolines,[18,19] 2-Aryl-1-(cyclohexylimino)-1,2-dihydropyrrolo[1,2-*a*]quinoline-3,3(3a*H*)-dicarbonitriles,[20] and 2-aryl-3-(cyclohexylimino)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitriles.[21]

Due to the unique properties of pyrrolo[1,2-*a*]quinolines, the development of synthetic methods which enable facile access to these useful entities are desirable. As part of our studies on the development of efficient and facile methods for the preparation of biologically active heterocyclic compounds from readily available building blocks,[22–25] we now report an efficient four-component synthesis of 2-aryl-1-(cyclohexylamino)-pyrrolo[1,2-*a*]quinoline-3-carbonitriles. Thus, heating a mixture of an aldehyde **1** and malononitrile **2** at 70 °C for 40 min under solvent-free conditions gave 2-arylmethylidenemalononitriles **6**. After nearly complete conversion to **6** as was indicated by TLC monitoring, quinoline **3** and cyclohexyl isocyanide **4** were added to the reaction mixture and stirring was continued at 70 °C for 35 min under solvent-free conditions to afford 1-(cyclohexylamino)-2-arylpyrrolo[1,2-*a*]quinoline-3-carbonitriles **5a**–**f** in 78–94% yields (Schemes 1 and 2).

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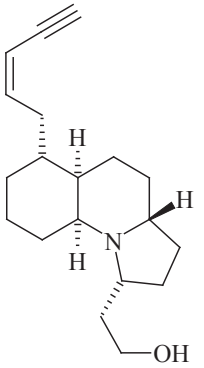
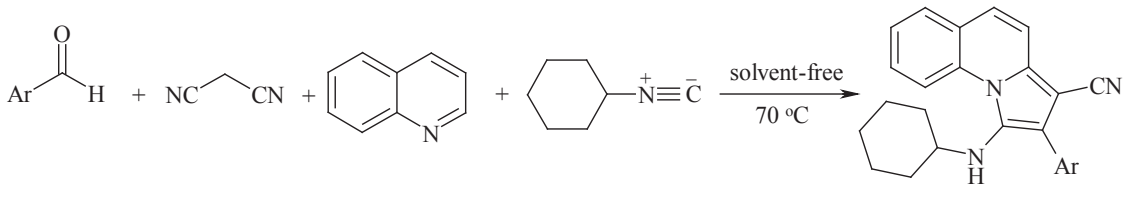


Fig. 1 Structure of gephyrotoxin.

Full characterisation involving IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis demonstrated the identity of the isolated products. The IR spectrum of **5a** showed the stretching bands for the amine and nitrile functionalities at 3325 and 2210 cm^{-1}, respectively. The mass spectrum of **5a** displayed the molecular ion [M$^+$] peak at *m/z* = 365, which was consistent with the 1 : 1 : 1 : 1 adduct of benzaldehyde, malononitrile, quinoline and cyclohexyl isocyanide with the loss of H_2O and HCN molecules. The ^{1}H NMR spectrum of **5a** consisted of multiplet signals for the eleven protons of the cyclohexyl ring at δ 0.84–1.75 and δ 2.66–2.85 [CH(CH$_2$)$_5$]. A broadened doublet was seen for the amine NH group (δ 3.95, *J* = 8.1 Hz) because of coupling with the adjacent CH group along with characteristic signals with appropriate chemical shifts and coupling constants for the eleven aromatic H-atoms. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 21 distinct resonances in agreement with the assigned structure.

Single-crystal X-ray analysis of **5a** confirmed conclusively its structure, and by analogy, those of the other isolated products. An ORTEP diagram of **5a** is shown in Fig. 2. Selected X-ray crystallographic data for compound **5a** are summarised in Table 1.

A mechanistic rationalisation for this reaction is provided in Scheme 2. The first step is the formation of dicyanostyrene **6** by the Knoevenagel condensation reaction of aromatic aldehyde **1** and malononitrile **2**. The electrophilic carbon atom of dicyanostyrene may undergo nucleophilic addition of isocyanide **4** leading to the highly reactive zwitterionic intermediate **7**. 1,3-Dipolar cycloaddition reaction of the zwitterion with quinoline **3** as dipolarophile gives the 1,2-dihydropyrrolo[1,2-*a*]quinoline intermediate **8**. Subsequent elimination of hydrogen cyanide and tautomerisation affords the pyrrolo[1,2-*a*]quinoline **5**.

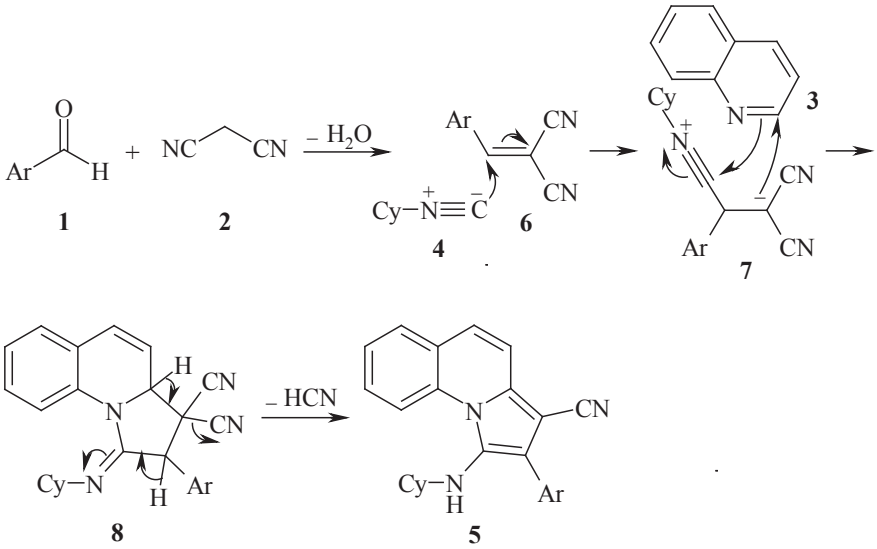


1 **2** **3** **4** **5**

5	Ar	Yield of **5** (%)[a]
5a	Ph	94
5b	3-ClC_6H_4	83
5c	4-BrC_6H_4	90
5d	4-MeC_6H_4	80
5e	4-$MeOC_6H_4$	78
5f	4-ClC_6H_4	88

[a]Yields of isolated products.

Scheme 1 Reaction between aldehydes, malononitrile, quinoline, and cyclohexyl isocyanide.



Scheme 2 Proposed mechanism for the formation of pyrrolo[1,2-*a*]quinolines **5**.

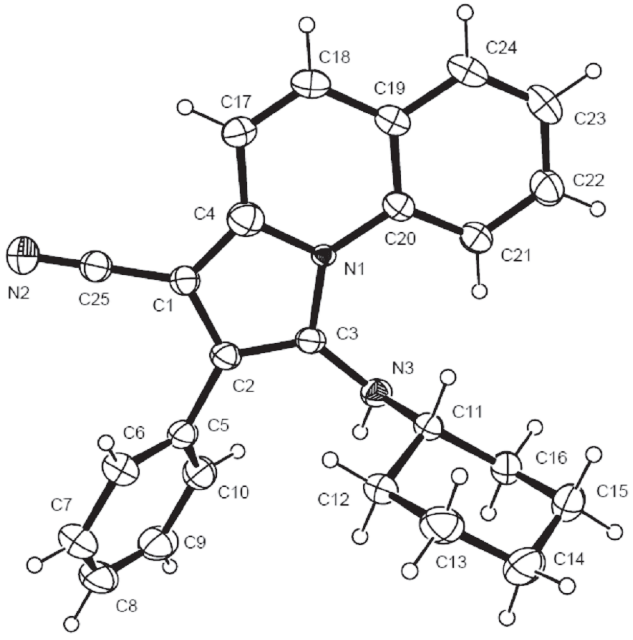


Fig. 2 ORTEP diagram of the molecular structure of **5a**.

Table 1 Crystallographic data and refinement parameters for **5a**.

Empirical formula	$C_{25}H_{23}N_3$
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	7.0339(3)
b/Å	15.2876(7)
c/Å	18.4356(9)
β/°	96.537(4)
V/Å^3	1969.52(9)
Z	4
D_c/g cm^{-3}	1.232
μ/mm^{-1}	0.073
Observed reflections	2564
T/K	295(2)
R^1, wR^2 [I>2σ (I)]	0.040, 0.111
R^1, wR^2 [all data]	0.063, 0.142

In summary, we have developed a facile one-pot and four-component reaction between malononitrile, aromatic aldehydes, quinoline and cyclohexyl isocyanide for the preparation of pyrrolo[1,2-*a*]quinolones of potential synthetic and pharmacological interest. Solvent-free conditions, good to excellent yields of the products, use of simple and readily available starting materials, and fairly short reaction times are the main advantages of this method.

Experimental

All the chemicals were obtained from Merck (Germany), and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-rapid analyser. Mass spectra were recorded on an Agilent Technologies (HP) 5973 mass spectrometer operating at an ionisation potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured using Bruker DPX-250 Avance (at 250.1 and 62.9 MHz) and Bruker DRX-300 Avance (at 300.1 MHz) spectrometers using $CDCl_3$ solvent with TMS as an internal standard. X-ray crystallography was performed on a Bruker SMART diffractometer equipped with a CCD area detector with graphite monochromatised Mo-Kα radiation. Chromatography columns were prepared from Merck silica gel 60 mesh.

Synthesis of **5a–f***; general procedure*

A mixture of the appropriate aldehyde (**1**, 1.0 mmol) and malononitrile (**2**, 1.2 mmol) was stirred at 70 °C for 40 min. After complete conversion to the 2-arylmethylidenemalononitrile, as was indicated by TLC monitoring, the mixture was allowed to cool to ambient temperature. Then quinoline (**3**, 1.0 mmol) was added, followed by addition of cyclohexyl isocyanide (**4**, 1.0 mmol) and stirred at 70 °C for 35 min. After cooling to room temperature, the product was purified by column chromatography using 10 : 1 *n*-hexane-EtOAc as eluent.

*1-(Cyclohexylamino)-2-phenylpyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5a**): Pale yellow crystals; yield: 0.34 g (94%), m.p. 153–155 °C. IR (KBr) (ν_{max}/cm^{-1}): 3325 (NH), 2210 (CN), 1603, 1546, 1497, 1448, 1414, 1346, 1075, 793, 743, 692. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.84–1.75 [m, 10H, CH(CH_2)$_5$], 2.66–2.85 (br m, 1H, CH), 3.95 (d, *J*=8.1 Hz, 1H, NH), 7.28 (d, *J*=9.1 Hz, 1H, ArH), 7.42–7.61 (m, 8H, 8ArH), 7.72 (d, *J*=7.7 Hz, 1H, ArH), 9.47 (d, *J*=8.6 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.8, 25.5, 33.0, 56.6, 83.9, 116.4, 116.7, 117.9, 122.2, 123.3, 124.7, 125.3, 127.6, 127.7, 128.6, 129.1, 129.2, 132.6, 132.9, 133.7, 134.8. EI-MS: *m/z* (%)=365 (M$^+$, 53), 282 (100), 255 (21), 128 (64), 97 (14), 84 (79), 69 (24), 55 (42). Anal. calcd for $C_{25}H_{23}N_3$ (365.48): C, 82.16; H, 6.34; N, 11.50; found: C, 82.05; H, 6.42, N, 11.39%.

*2-(3-Chlorophenyl)-1-(cyclohexylamino)pyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5b**): Pale yellow crystals; yield: 0.33 g (83%), m.p. 197–198 °C. IR (KBr) (ν_{max}/cm^{-1}): 3321 (NH), 2208 (CN), 1599, 1558, 1485, 1446, 1410, 1346, 1072, 888, 791, 745, 678. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.84–1.74 [m, 10H, CH(CH_2)$_5$], 2.68–2.80 (m, 1H, CH), 3.81 (br s, 1H, NH), 7.27 (d, *J*=9.1 Hz, 1H, ArH), 7.35–7.49 (m, 6H, 6ArH), 7.57 (td, *J*=7.6, 1.3 Hz, 1H, ArH), 7.71 (dd, *J*=7.7, 1.1 Hz, 1H, ArH), 9.43 (d, *J*=8.5 Hz, 1H, ArH). ^{13}CNMR (62.9 MHz, $CDCl_3$): δ 24.8, 25.5, 33.0, 56.7, 83.7, 116.2, 116.4, 117.8, 120.9, 123.7, 124.8, 125.2, 127.4, 127.7, 127.9, 128.6, 128.9, 130.3, 132.9, 133.8, 134.5, 134.7, 134.8. EI-MS: *m/z* (%)=401 (M$^+$ ^{37}Cl, 19), 399 (M$^+$ ^{35}Cl, 57), 316 (100), 281 (82), 128 (67), 101 (13), 83 (23), 55 (66). Anal. calcd for $C_{25}H_{22}ClN_3$ (399.92): C, 75.08; H, 5.54; N, 10.51; found: C, 75.15; H, 5.58, N, 10.42%.

*2-(4-Bromophenyl)-1-(cyclohexylamino)pyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5c**): Pale yellow crystals; yield: 0.40 g (90%), m.p. 214–216 °C. IR (KBr) (ν_{max}/cm^{-1}): 3350 (NH), 2202 (CN), 1537, 1491, 1443, 1408, 1349, 1137, 1075, 1008, 801, 754. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.83–1.74 [m, 10H, CH(CH_2)$_5$], 2.68–2.76 (m, 1H, CH), 3.80 (br s, 1H, NH), 7.28 (d, *J*=9.1 Hz, 1H, ArH), 7.37 (d, *J*=8.5 Hz, 2H, 2ArH), 7.44–7.50 (m, 2H, 2ArH), 7.57 (td, *J*=7.7, 1.5 Hz, 1H, ArH), 7.64 (d, *J*=8.5 Hz, 2H, 2ArH), 7.71 (dd, *J*=7.7, 1.3 Hz, 1H, ArH), 9.43 (d, *J*=8.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.8, 25.5, 33.1, 56.7, 83.6, 116.3, 116.5, 117.9, 121.2, 121.8, 123.7, 124.8, 125.3, 127.9, 128.6, 130.7, 131.6, 132.3, 132.7, 133.8, 134.7. EI-MS: *m/z* (%)=445 (M$^+$ ^{81}Br, 48), 443 (M$^+$ ^{79}Br, 47), 362 (100), 360 (97), 281 (80), 242 (9), 128 (76), 101 (15), 83 (21), 55 (76). Anal. calcd for $C_{25}H_{22}BrN_3$ (444.37): C, 67.57; H, 4.99; N, 9.46; found: C, 67.49; H, 5.12, N, 9.40%.

*1-(Cyclohexylamino)-2-(4-methylphenyl)pyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5d**): Pale yellow crystals; yield: 0.30 g (80%), m.p. 179–181 °C. IR (KBr) (ν_{max}/cm^{-1}): 3333 (NH), 2199 (CN), 1606, 1538, 1503, 1440, 1406, 1347, 1190, 1079, 803, 746. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.81–1.73 [m, 10H, CH(CH_2)$_5$], 2.42 (s, 3H, CH_3), 2.63–2.82 (br m, 1H, CH), 3.86–3.98 (br s, 1H, NH), 7.23 (d, *J*=9.1 Hz, 1H, ArH), 7.30 (d, *J*=8.0 Hz, 2H, 2ArH), 7.40–7.43 (m, 3H, 3ArH), 7.47 (d, *J*=9.1 Hz, 1H, ArH), 7.54 (td, *J*=7.7, 1.5 Hz, 1H, ArH), 7.69 (dd, *J*=7.7, 1.3 Hz, 1H, ArH), 9.44 (d, *J*=8.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.4, 24.9, 25.6, 33.0, 56.6, 84.0, 116.3, 116.9, 117.9, 122.3, 123.2, 124.6, 125.3, 127.7, 128.5, 129.0, 129.7, 129.8, 132.8, 133.6, 134.8, 137.3. EI-MS: *m/z* (%)=379 (M$^+$, 67), 296 (100), 281 (36), 269 (15), 241 (4), 128 (65), 101 (10), 83 (24), 55 (55). Anal. calcd for $C_{26}H_{25}N_3$ (379.50): C, 82.29; H, 6.64; N, 11.07; found: C, 82.26; H, 6.66, N, 10.97%.

*1-(Cyclohexylamino)-2-(4-methoxyphenyl)pyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5e**): Pale yellow crystals; yield: 0.31 g (78%), m.p. 159–160 °C. IR (KBr) (ν_{max}/cm^{-1}): 3371 (NH), 2196 (CN), 1611, 1567, 1540, 1442, 1284, 1245, 1173, 1142, 1031, 831, 798, 748. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.83–1.73 [m, 10H, CH(CH_2)$_5$], 2.64–2.83 (br m, 1H, CH), 3.76–3.88 (br s, 1H, NH), 3.88 (s, 3H, OCH_3), 7.04 (d, *J*=8.8 Hz, 2H, 2ArH), 7.25 (d, *J*=9.1 Hz, 1H, ArH), 7.40 (d, *J*=8.8 Hz, 2H, 2ArH), 7.41–7.43 (m, 1H, ArH), 7.48 (d, *J*=9.1 Hz, 1H, ArH), 7.52 (td, *J*=7.6, 1.3 Hz, 1H, ArH), 7.69 (d, *J*=7.7 Hz, 1H, ArH), 9.45 (d, *J*=8.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.8, 25.6, 33.0, 55.3, 56.6, 84.0, 114.6, 116.4, 116.8, 117.8, 122.1, 123.1, 124.6, 124.9, 125.3, 127.7, 128.5, 130.3, 132.7, 133.5, 134.8, 159.0. EI-MS: *m/z* (%)=395 (M$^+$, 84), 312 (100), 297 (9), 281 (16), 268 (23), 242 (15), 128 (41), 101 (7), 83 (18), 55 (60). Anal. calcd for $C_{26}H_{25}N_3O$ (395.50): C, 78.96; H, 6.37; N, 10.62; found: C, 78.88; H, 6.29, N, 10.57%.

*2-(4-Chlorophenyl)-1-(cyclohexylamino)pyrrolo[1,2-*a*]quinoline-3-carbonitrile* (**5f**): Pale yellow crystals; yield: 0.35 g (88%), m.p. 206–207 °C. IR (KBr) (ν_{max}/cm^{-1}): 3380 (NH), 2204 (CN), 1601, 1536, 1493, 1443, 1406, 1347, 1137, 1089, 1012, 889, 802, 755. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.82–1.73 [m, 10H, CH(CH_2)$_5$], 2.65–2.79 (m, 1H, CH), 3.80 (d, *J*=7.5 Hz, 1H, NH), 7.27 (d, *J*=9.1 Hz, 1H, ArH), 7.41–7.51 (m, 6H, 6ArH), 7.57 (td, *J*=7.6, 1.5 Hz, CH, ArH), 7.71 (dd, *J*=7.6, 1.1 Hz, 1H, ArH), 9.43 (d, *J*=8.5 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.8, 25.5, 33.1, 56.7, 83.7, 116.3, 116.5, 117.9, 121.2, 123.7, 124.8, 125.3, 127.9, 128.6, 129.3, 130.4, 131.2, 132.8, 133.6, 133.8, 134.7. EI-MS: *m/z* (%)=401 (M$^+$ ^{37}Cl, 7), 399 (M$^+$ ^{35}Cl, 22), 318 (35), 316 (99), 281 (57), 253 (6), 128 (86), 101 (17), 83 (38), 55 (100). Anal. calcd for $C_{25}H_{22}ClN_3$ (399.92): C, 75.08; H, 5.54; N, 10.51; found: C, 74.89; H, 5.57, N, 10.46%.

CCDC 965834 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

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