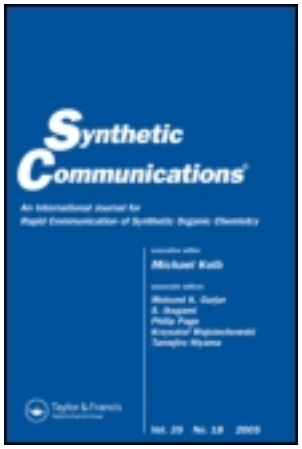

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FACILE SYNTHESIS OF SOME NEW PYRIMIDOQUINOLINES

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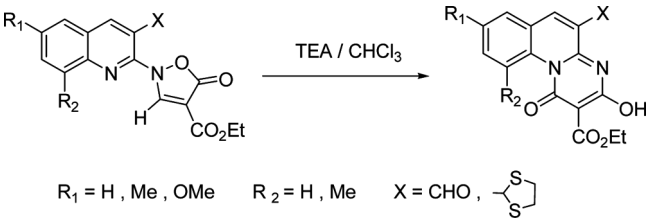
GRAPHICAL ABSTRACT



Abstract *The reaction of ethyl 5-oxo-2,5-dihydroisoxzole-4-carboxylate with derivatives of 2-chloroquinoline afforded the desired* N*-quinolinyl isoxazolones. Their reactions with triethylamine in chloroform produced the corresponding pyrimidoquinoline derivatives, through intramolecular cyclization.*

Keywords Pyrimidoquinolines; *N*-quinolinyl isoxazolones; rearrangements; triethylamine

INTRODUCTION

The development of new methods for the synthesis of nitrogen-containing heterocycles is of extreme importance in organic chemistry. In past years, the syntheses of imidazoles,[1,2] pyrimidines,[3] imidazopyridines,[4,5] and pyrimido- and pyrazoloquinolines[6] starting from isoxazoline-5-ones have been reported. Of these compounds, pyrimidoquinolines are important because of their biological properties, which are known to depend mainly on the nature and position of substituents and include anticancer,[7] antimalarial,[8] antimicrobial,[9] anti-oxidant and anti-inflammatory activities.[10,11]

Here we report the synthesis of pyrimidoquinolines by rearrangement of *N*-quinolinyl isoxazol-5(2H)-ones, substituted on nitrogen with 2-chloroquinoline derivatives, under mild base-catalyzed conditions.

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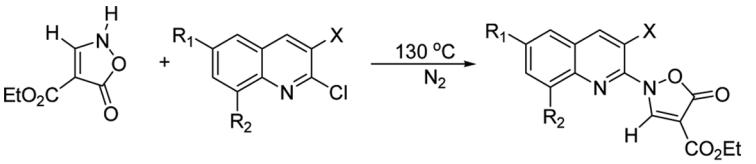
RESULTS AND DISCUSSION

N-Arylation of ethyl 5-oxo-2,5-dihydroisoxzole-4-carboxylate with derivatives of 2-chloroquinoline afforded the desired *N*-quinolinyl isoxazolones in good yields (Scheme 1). While the formation (**2a–e**) appears trivial, the reaction generally proceeded best in the absence of solvent by heating the required reagents under nitrogen atmosphere at 130 °C.

The compounds **2a–e** were prepared in 75–84% yield, and their structures were confirmed by their spectral data and microanalyses.

The rearrangement of *N*-quinolinyl isoxazolones (**2a–e**) by mild base triethylamine led to synthesis of new pyrimidoquinoline derivatives **3a–e** (Scheme 2). This structure exists in the form of tautomers **3** ⇌ **4**.

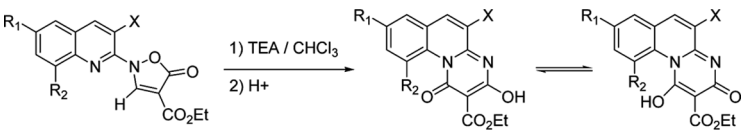
The pyrimidoquinolines **3a–e** were formed in 70–80% yields, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, Fourier transform–infrared (FT-IR) spectra and microanalyses. It is interesting that the rearrangements could be achieved in good yield by triethylamine in chloroform under reflux conditions by



1a-e **2a-e**

a: R_1 = H R_2 = H X = CHO
b: R_1 = H R_2 = H X = S,S
c : R_1 = Me R_2 = H X = CHO
d: R_1 = H R_2 = Me X = CHO
e: R_1 = OMe R_2 = H X = CHO

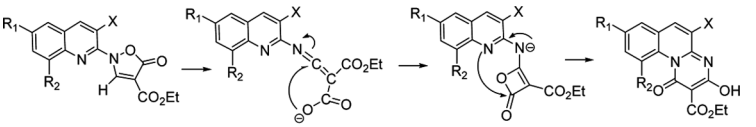
Scheme 1.



2a-e **3a-e** **4a-e**

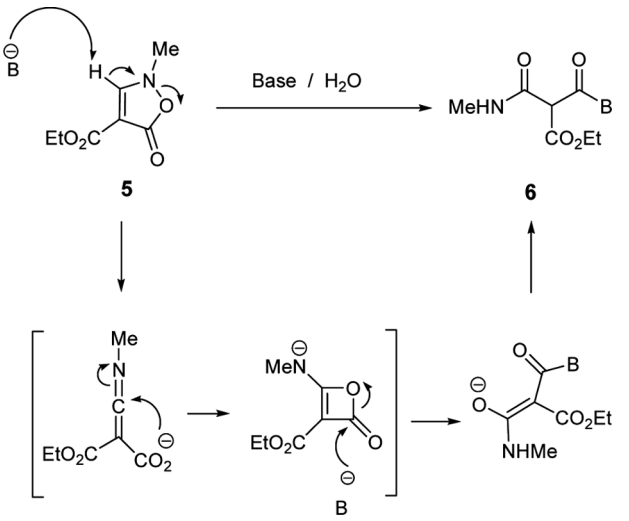
a: R_1 = H R_2 = H X = CHO
b: R_1 = H R_2 = H X = S,S
c : R_1 = Me R_2 = H X = CHO
d: R_1 = H R_2 = Me X = CHO
e: R_1 = OMe R_2 = H X = CHO

Scheme 2.



a: R_1 = H R_2 = H X = CHO
b: R_1 = H R_2 = H X =
c : R_1 = Me R_2 = H X = CHO
d: R_1 = H R_2 = Me X = CHO
e: R_1 = OMe R_2 = H X = CHO

Scheme 3.



Scheme 4.

removing a vinyl hydrogen atom as shown in Scheme 3. There was no considerable ester hydrolysis.

The rearrangement of a 2-methylisoxazolin-5-ones (**5**), unsubstituted at C-3, has shown[12,13] that the system afforded ring-opened product **6**. The mechanism suggested, for which good evidence has been presented, is shown in Scheme 4.

An adaptation of this scheme in the present context leads to the pathway shown in Scheme 3.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with a Bruker spectrometer at 300 and 75.5 MHz, respectively. The spectra were measured in $CDCl_3$ or $CDCl_3$ + dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Thermonicolet (Nexus 670) FT-IR spectrometer, using sodium chloride cells and measured as KBr disks. Mass spectra were recorded on

a Varian Matt 311 spectrometer, and relative abundances of fragments are quoted in parentheses after the m/z values. Microanalyses were performed on a Leco Analyzer 932. Melting points were determined on a digital melting-point apparatus (Electrothermal) and remain uncorrected.

Ethyl 2-(3-Formylquinolin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2a)

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate[14] (100 mg, 0.64 mmol) and 2-chloro-3-formylquinoline[15] (122 mg, 0.64 mmol) were heated neat under nitrogen in 130 °C for 15 min. The resulting product was recrystallized from ethanol to afford the ethyl 2-(3-formylquinolin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (159 mg, 80%) as a pale yellow solid, mp 188–190 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (t, $J = 7.2$ Hz, 3H, CH_3), 4.43 (q, $J = 7.2$ Hz, 2H, CH_2), 7.68 (td, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 7.93 (td, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 8.01 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 8.05 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 8.93 (s, 1H, ArH), 9.62 (s, 1H, H-isoxazolone ring), 10.68 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 14.37, 61.33, 96.62, 121.21, 126.57, 128.31, 128.43, 129.68, 134.15, 142.16, 144.41, 147.78, 148.73, 160.81, 164.01, 187.47; FT-IR (KBr, cm^{-1}): 1808, 1708, 1691, 1560, 1494, 1440, 1208, 1031, 787, 776. Anal. calcd. for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.69; H, 3.66; N, 9.01.

Ethyl 2-[3-(1,3-Dithiolan-2-yl)quinolin-2-yl]-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2b)

Using the corresponding quinoline[15] (170 mg, 0.64 mmol) by the same procedure gave **2b** (185 mg, 75%) as a pale yellow solid, mp 175–176 °C. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, $J = 7.2$ Hz, 3H, CH_3), 3.98 (s, 4H, CH_2CH_2), 4.41 (q, $J = 7.2$ Hz, 2H, CH_2), 6.39 (s, 1H, CH), 7.62 (t, $J = 8.2$ Hz, 1H, ArH), 7.78 (t, $J = 8.2$ Hz, 1H, ArH), 7.91 (d, $J = 8.4$ Hz, 1H, ArH), 7.97 (d, $J = 8.4$ Hz, 1H, ArH), 8.85 (s, 1H, ArH), 9.41 (s, 1H, H-isoxazolone ring); ^{13}C NMR ($CDCl_3$): δ 14.42, 39.43, 50.39, 61.08, 95.72, 127.71, 127.83, 128.01, 128.32, 130.56, 131.32, 139.36, 144.29, 145.47, 150.11, 161.12, 164.62; FT-IR (KBr, cm^{-1}): 1784, 1691, 1557, 1491, 1224, 1024, 777; MS m/z (%) 389 [($M^+ + 1$), 4], 388 (M^+, 3), 344 (18), 316 (100), 272 (72), 244 (58), 211 (42), 169 (60), 128 (25). Anal. calcd. for $C_{18}H_{16}N_2O_4S_2$: C, 55.65; H, 4.15; N, 7.21; S, 16.51. Found: C, 55.75; H, 4.03; N, 7.31; S, 16.62.

Ethyl 2-(3-Formyl-6-methylquinolin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2c)

Using the corresponding quinoline[15] (100 mg, 0.48 mmol) by the same procedure gave **2c** (126 mg, 80%) as a pale yellow solid, mp 199–201 °C. ^{1}H NMR ($CDCl_3$) δ: 1.41 (t, $J = 7.2$ Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.41 (q, $J = 7.2$ Hz, 2H, CH_2), 7.75 (d, $J = 8.4$ Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.91 (d, $J = 8.4$ Hz, 1H, ArH), 8.81 (s, 1H, ArH), 9.57 (s, 1H, H-isoxazolone ring), 10.63 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ: 14.38, 21.63, 61.27, 96.28, 121.19, 126.68, 128.08, 128.34, 136.58, 138.83, 141.22, 143.88, 146.34, 148.73, 160.87, 164.17, 187.62; FT-IR

(KBr, cm^{-1}): 1801, 1699, 1553, 1500, 1444, 1335, 1213, 1160, 1027, 950, 780; MS m/z (%) 327 [($M^+ + 1$), 51], 326 (M^+, 13), 253 (36), 237 (71), 211 (100), 209 (98), 183 (78), 142 (72), 115 (40). Anal. calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.71; H, 4.22; N, 8.66.

Ethyl 2-(3-Formyl-8-methylquinolin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2d)

Using the corresponding quinoline[15] (100 mg, 0.48 mmol) by the same procedure gave **2d** (119 mg, 75%) as a pale yellow solid, mp 178–180 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, $J = 6.9$ Hz, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.43 (q, $J = 6.9$ Hz, 2H, CH_2), 7.55 (t, $J = 7.8$ Hz, 1H, ArH), 7.76 (d, $J = 7.8$ Hz, 1H, ArH), 7.84 (d, $J = 7.8$ Hz, 1H, ArH), 8.87 (s, 1H, ArH), 9.55 (s, 1H, H-isoxazolone ring), 10.66 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 14.37, 17.68, 61.34, 99.40, 120.78, 126.67, 127.52, 128.11, 134.22, 136.81, 142.42, 143.29, 146.77, 148.32, 161.01, 163.99, 187.61; FT-IR (KBr, cm^{-1}): 1801, 1704, 1681, 1611, 1589, 1561, 1455, 1490, 1468, 1434, 1367, 1218, 1028, 947, 781. Anal. calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.69; H, 4.29; N, 8.27.

Ethyl 2-(3-Formyl-6-methoxyquinolin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2e)

Using the corresponding quinoline[15] (100 mg, 0.45 mmol) by the same procedure gave **2e** (129 mg, 84%) as a pale yellow solid, mp 162–164 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, $J = 6.9$ Hz, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.41 (q, $J = 6.9$ Hz, 2H, CH_2), 7.24 (s, 1H, ArH), 7.56 (d, $J = 9$ Hz, 1H, ArH), 7.92 (d, $J = 9$ Hz, 1H, ArH), 8.79 (s, 1H, ArH), 9.53 (s, 1H, H-isoxazolone ring), 10.64 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 14.37, 55.87, 61.23, 96.16, 106.31, 121.46, 127.38, 128.02, 129.84, 140.04, 142.89, 143.90, 148.83, 159.17, 160.93, 164.25, 187.64; FT-IR (KBr, cm^{-1}): 1781, 1715, 1695, 1619, 1567, 1504, 1464, 1371, 1348, 1229, 1017, 835, 775. Anal. calcd. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.51; H, 4.21; N, 8.43.

Ethyl 5-Formyl-3-hydroxy-1-oxo-1H-pyrimido[1,2-a]quinoline-2-carboxylate (3a)

The isoxazolone (100 mg, 0.32 mmol) was refluxed in chloroform with triethylamine (0.5 mL) for 4 h. The solvent was removed, the residue was dissolved in water (2 mL), and the solution was acidified to pH 2 with concentrated HCl. The yellow precipitate was filtered to give the compound **3a** (80 mg, 80%), mp 169–171 °C. ^{1}H NMR ($CDCl_3$): δ 1.52 (t, $J = 7.2$ Hz, 3H, CH_3), 4.57 (q, $J = 7.2$ Hz, 2H, CH_2), 7.64 (t, $J = 7.5$ Hz, 1H, ArH), 7.83 (ddd, $J_1 = 9$ Hz, $J_2 = 7.5$ Hz, $J_3 = 1.5$ Hz, 1H, ArH), 7.93 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz, 1H, ArH), 8.61 (s, 1H, ArH), 9.52 (d, $J = 9$ Hz, 1H, ArH), 10.86 (s, 1H, CHO), 13.91 (s, 1H, OH, exchanged by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.35, 62.63, 90.34, 122.25, 123.33, 125.72, 127.61, 131.45, 133.46, 136.64, 141.84, 153.14, 159.87, 171.3, 171.68, 188.82; FT-IR

(KBr, cm^{-1}): 3451, 3060, 1698, 1620, 1576, 1525, 1488, 1333, 1213, 1093, 807. Anal. calcd. for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.77; H, 3.52; N, 8.88.

Ethyl 3-Hydroxy-5-(1,3-oxathiolan-2-yl)-1-oxo-1H-pyrimido[1,2-a]quinoline-2-carboxylate (3b)

This compound was prepared by the same procedure as described for compound **3a**, using the corresponding isoxazolone **2b** (100 mg, 0.26 mmol), to give **3b** as a pale yellow solid (70 mg, 70%), mp 173–175 °C. ^{1}H NMR ($CDCl_3$): δ 1.51 (t, $J = 7.2$ Hz, 3H, CH_3), 3.61 (s, 4H, CH_2CH_2), 4.54 (q, $J = 7.2$ Hz, 2H, CH_2), 6.31 (s, 1H, CH), 7.55 (t, $J = 7.8$ Hz, 1H, ArH), 7.65 (ddd, $J_1 = 9$ Hz, $J_2 = 7.8$ Hz, $J_3 = 1.5$ Hz, 1H, ArH), 7.75 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz, 1H, ArH), 8.43 (s, 1H, ArH), 9.42 (d, $J = 9$ Hz, 1H, ArH), 13.75 (s, 1H, OH, exchanged by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.41, 39.05, 50.17, 62.41, 89.97, 121.79, 124.04, 126.97, 128.9, 130.35, 134.07, 134.36, 136.8, 152.58, 160.45, 170.87, 171.82; FT-IR (KBr, cm^{-1}): 3500, 1716, 1627, 1578, 1521, 1483, 1342, 1222, 805, 758; MS m/z (%) 389 [($M^+ + 1$), 2], 388 (M^+, 1), 373 (6), 343 (7), 316 (100), 271 (81), 211 (37), 168 (42), 129 (39), 115 (12). Anal. calcd. for $C_{18}H_{16}N_2O_4S_2$: C, 55.65; H, 4.15; N, 7.21; S, 16.51. Found: C, 55.55; H, 4.32; N, 7.33; S, 16.42.

Ethyl 5-Formyl-3-hydroxy-8-methyl-1-oxo-1H-pyrimido[1,2-a]quinoline-2-carboxylate (3c)

This compound was prepared by the same procedure as described for compound **3a**, using the corresponding isoxazolone **2c** (100 mg, 0.31 mmol), to give **3c** as a pale yellow solid (75 mg, 75%), mp 182–184 °C. ^{1}H NMR ($CDCl_3$): δ 1.51 (t, $J = 7.2$ Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.56 (q, $J = 7.2$ Hz, 2H, CH_2), 7.63 (dd, $J_1 = 9$ Hz, $J_2 = 2.1$ Hz, 1H, ArH), 7.69 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.43 (d, $J = 9$ Hz, 1H, ArH), 10.85 (s, 1H, CHO), 13.87 (s, 1H, OH, exchanged by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.38, 20.76, 62.6, 90.27, 122.06, 123.14, 125.58, 130.69, 134.74, 134.96, 137.89, 141.8, 152.95, 159.92, 171.12, 171.74, 188.99; FT-IR (KBr, cm^{-1}): 3421, 1718, 1697, 1616, 1579, 1518, 1334, 1099; MS m/z (%) 327 [($M^+ + 1$), 100], 326 (M^+, 90), 309 (19), 253 (55), 210 (23), 205 (13), 142 (11). Anal. calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.45; H, 4.55; N, 8.66.

Ethyl 5-Formyl-3-hydroxy-10-methyl-1-oxo-1H-pyrimido[1,2-a]quinoline-2-carboxylate (3d)

This compound was prepared by the same procedure as described for compound **3a**, using the corresponding isoxazolone **2d** (100 mg, 0.31 mmol), to give **3d** as a pale orange solid (71 mg, 71%), mp 229–231 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1.33 (t, $J = 7.5$ Hz, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.30 (q, $J = 7.5$ Hz, 2H, CH_2), 7.30 (t, $J = 7.5$ Hz, 1H, ArH), 7.55 (d, $J = 6.9$ Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.69 (d, $J = 7.5$ Hz, 1H, ArH), 8.45 (s, 1H, CHO), 11.62 (s, 1H, OH, exchanged by D_2O addition); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 14.32, 17.99, 61.31, 98.06, 113.90, 124.92, 125.10, 126.78, 132.38, 135.64, 139.41, 143.23, 148.20, 148.27, 160.40, 163.82, 184.32; FT-IR (KBr, cm^{-1}): 3448, 1693, 1675, 1627, 1615,

1568, 1330, 1283, 1254, 826, 746, 604. Anal. calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.66; H, 4.21; N, 8.73.

Ethyl 5-Formyl-3-hydroxy-8-methoxy-1-oxo-1H-pyrimido[1,2-a]quinoline-2-carboxylate (3e)

This compound was prepared by the same procedure as described for compound **3a**, using the corresponding isoxazolone **2e** (100 mg, 0.3 mmol), to give **3e** as a pale green solid (79 mg, 79%), mp 166–168 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, $J = 7.2$ Hz, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.28 (q, $J = 7.2$ Hz, 2H, CH_2), 7.39 (d, $J = 9$ Hz, 1H, ArH), 7.70 (s, 1H, ArH), 8.61 (s, 1H, ArH), 9.39 (d, $J = 9$ Hz, 1H, ArH), 10.59 (s, 1H, CHO), 12.82 (s, 1H, OH, exchanged by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.57, 56.17, 61.31, 93.99, 113.01, 121.62, 123.24, 125.14, 126.06, 130.97, 140.83, 150.73, 157.47, 160.54, 165.35, 166.95, 189.89; FT-IR (KBr, cm^{-1}): 3481, 1729, 1694, 1615, 1582, 1526, 1469, 1439, 1336, 1247, 1226, 1099, 1039, 827. Anal. calcd. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.42; H, 4.09; N, 8.25.

CONCLUSION

This study shows a new and facile synthetic pathway to the pyrimidoquinoline system, allowing large substitution patterns. Furthermore, starting from a suitable substrate, the synthesis of other heterocyclic compounds is possible, which may have pharmaceutical applications.

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