Pergamon

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Tetrahedron Letters 44 (2003) 4733–4736

TETRAHEDRON LETTERS

Synthesis of 3-methoxyquinolines via cyclization of 1-isocyano-2-(2-lithio-2-methoxyethenyl)benzenes

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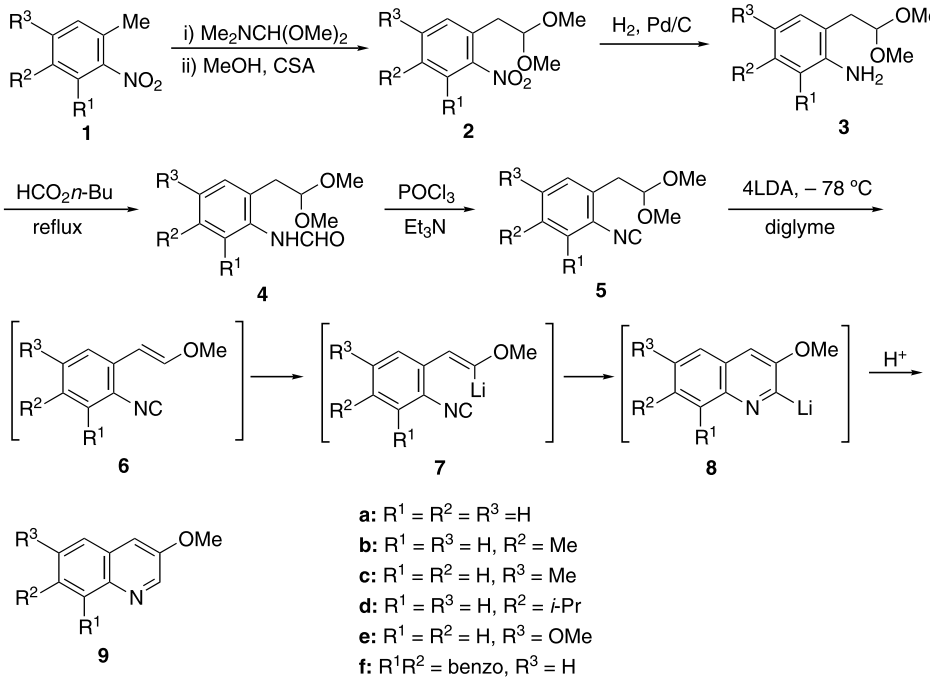
Received 3 March 2003; revised 7 April 2003; accepted 18 April 2003

Abstract—2-(2-Isocyanophenyl)acetaldehyde dimethyl acetals were treated with excess LDA to generate 1-isocyano-2-(2-lithio-2-methoxyethenyl)benzenes, which cyclized intramolecularly to afford 3-methoxyquinolines in good to excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

There is a large number of general preparative methods of quinolines available in the literature[1] because of their useful biological properties.[2] However, few reports on the general synthesis of 3-methoxyquinolines have been reported[3] in spite of their potential importance in organic and medicinal chemistries, though Akula et al.[3a] synthesized 3-methoxy-2-methylquinoline using the Friedlander quinoline synthesis and, more recently, Cherng synthesized 3-methoxyquinoline by nucleophilic substitution of 3-bromoquinoline with sodium methox-



Scheme 1.

Keywords: isocyanides; lithiation; quinolines.

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doi:10.1016/S0040-4039(03)01040-2

Table 1. Preparation of 3-methoxyquinoline derivatives **9** from 2-nitrotoluenes **1**

Entry	**1**	**2** (Yield/%)[a]	**3** (Yield/%)[a]	**4** (Yield/%)[a]	**5** (Yield/%)[a]	**9** (Yield/%)[a]
1	**1a**	**2a** (74)[b]	**3a** (97)[b]	**4a** (94)	**5a** (97)	**9a**[d] (79)
2	**1b**	**2b** (73)	**3b** (82)	**4b** (82)	**5b** (93)	**9b** (72)
3	**1c**	**2c** (53)	**3c** (88)	**4c** (99)	**5c** (90)	**9c** (63)
4	**1d**	**2d** (72)	**3d** (93)	**4d** (86)	**5d** (94)	**9d** (71)
5	**1e**	**2e** (60)	**3e** (91)	**4e** (87)	**5e** (96)	**9e** (47)
6	**1f**	**2f** (75)	**3f** (91)	**4f** (68)[c]	**5f** (82)	**9e** (97)

[a] Isolated yields.
[b] See Ref. 4.
[c] Hexyl formate was used.
[d] Refs. 3b and 3c.

ide.[3b] We decided to investigate the possibility of developing an efficient general method for preparing 3-methoxyquinoline derivatives from readily available starting materials. We found that 2-(2-isocyanophenyl)acetaldehyde dimethyl acetals **5** were treated with excess LDA to give 3-methoxyquinolines **9** via cyclization of 1-isocyano-2-(2-lithio-2-methoxyethenyl)-benzenes **7**. In this letter, the results of our preliminary investigation, which offer the first general construction of the 3-methoxyquinoline system, are reported.

2-(2-Isocyanophenyl)acetaldehyde dimethyl acetals **5** were prepared from commercially available *o*-nitrotoluene derivatives by a five-step sequence as shown in Scheme 1. Thus, 2-(2-nitrophenyl)acetaldehyde dimethyl acetals **2** were synthesized according to the procedure reported by Fukuyama et al.[4] These nitro compounds **2** were hydrogenated (1 atm) over 10% Pd on activated carbon. The resulting amino compounds **3** were then formylated with butyl formate (or hexyl formate for **3f**) at reflux temperature to form formamides **4**, dehydration of which by treatment with $POCl_3/Et_3N$ afforded the isocyano acetals **5**.[5] These results are summarized in Table 1.

The preparation of 3-methoxyquinolines **9** from 2-(2-isocyanophenyl)acetaldehyde dimethyl acetals **5** is also illustrated in Scheme 1 and the yields are summarized in Table 1 as well. Isocyano acetals **5** were treated with 4 equiv. of LDA in diglyme at −78°C. The action of LDA upon **5** generated the corresponding benzylanions, from which elimination of methoxide gave *o*-isocyano-β-methoxystyrenes **6**. These isocyano styrenes **6** were lithiated with additional molar(s) of LDA to generate 1-isocyano-2-(2-lithio-2-methoxyethenyl)-benzenes **7**, which underwent an intramolecular cyclization to provide 3-methoxyquinolines **9**. The use of less than 4 equiv. of LDA in the reaction with 2-(2-isocyanophenyl)acetaldehyde dimethyl acetals (**5a**) resulted in decrease of the yield of the desired 3-methoxyquinoline (**9a**), and 1-isocyano-2-(*E*)-(2-methoxyethenyl)benzene (**6a**) were obtained. 2-(1-Isocyanonaphthalen-2-yl)acetaldehyde dimethyl acetal (**5f**), derived similarly from 2-methyl-1-nitronaphthalene, was allowed to react with LDA under the same conditions to give the corresponding desired product, 3-methoxybenzo[*h*]quinoline (**9f**), in excellent yield (entry 6).

A representative experimental procedure for the preparation of 3-methoxyquinoline derivatives **9** from 2-(2-isocyanophenyl)acetaldehyde dimethyl acetals **5** is illustrated for the preparation of 3-methoxyquinoline (**9a**). To a stirred solution of LDA (14 mmol; generated from diisopropylamine and butyllithium by the standard method) in diglyme (8.0 mL) at −78°C under argon was added dropwise isocyano acetal **5a** (0.65 g, 3.4 mmol). After stirring for 1 h at the same temperature, the reaction was quenched by adding aqueous saturated NH_4Cl, and the mixture was extracted with Et_2O twice (20 mL each). The combined extracts were washed with water three times and with brine once, and dried over anhydrous K_2CO_3. After evaporation of the solvent the residue was purified by preparative TLC on silica gel (EtOAc–hexane 1:3) to give **9a**[3b,c] (0.43 g, 79%).[5]

In summary, we have demonstrated that the present reaction sequence provides the first general preparative method of 3-methoxyquinolines. Studies on the synthesis of methoxypyridine-fused heterocyclic compounds, such as naphthyridine and azaindole derivatives, utilizing the present procedure are now under way in our laboratory.

Acknowledgements

The authors thank Mrs. Miyuki Tanmatsu of this department for obtaining the mass spectra and performing combustion analyses.

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5. All new compounds gave satisfactory spectral and analytical data. **5a**: a pale yellow liquid; R_f 0.57 (EtOAc–hexane 1:3); IR (neat) 2120 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.08 (2H, d, $J=5.6$ Hz), 3.38 (6H, s), 4.60 (1H, t, $J=5.6$ Hz), 7.2–7.4 (4H, m); MS m/z 191 (M^+, 0.09), 190 (0.57), 160 (36), 145 (42), 117 (100). Calcd for $C_{11}H_{13}NO_2$: M, 191.0946. Found: m/z 191.0933. **5b**: a pale yellow liquid; R_f 0.62 (EtOAc–hexane, 1:3); IR (neat) 2119 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.02 (2H, d, $J=5.3$ Hz), 3.37 (6H, s), 4.57 (1H, t, $J=5.3$ Hz), 7.14 (1H, d, $J=8.2$ Hz), 7.17 (1H, s), 7.23 (1H, d, $J=8.2$ Hz); MS m/z 205 (M^+, 0.90), 204 (1.1), 174 (59), 130 (81), 103 (100). Calcd for $C_{12}H_{15}NO_2$: M, 205.1103. Found: m/z 205.1086. **5c**: a pale yellow liquid; R_f 0.60 (EtOAc–hexane, 1:3); IR (neat) 2118 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.03 (2H, d, $J=5.6$ Hz), 3.37 (6H, s), 4.60 (1H, t, $J=5.6$ Hz), 7.05 (1H, dd, $J=7.9$, 1.3 Hz), 7.14 (1H, s), 7.24 (1H, d, $J=7.9$ Hz); MS m/z 205 (M^+, 1.0), 204 (1.4), 174 (75), 130 (100). Calcd for $C_{12}H_{15}NO_2$: M, 205.1103. Found: m/z 205.1125. **5d**: a pale yellow liquid; R_f 0.62 (EtOAc–hexane, 1:3); IR (neat) 2119 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24 (6H, d, $J=7.0$ Hz), 2.88 (1H, septet, $J=7.0$ Hz), 3.03 (2H, d, $J=5.5$ Hz), 3.37 (6H, s), 4.59 (1H, t, $J=5.5$ Hz), 7.19 (1H, dd, $J=7.7$, 1.6 Hz), 7.21 (1H, s), 7.26 (1H, d, $J=7.7$ Hz); MS m/z 233 (M^+, 0.72), 232 (2.5), 202 (100). Calcd for $C_{14}H_{19}NO_2$: M, 233.1416. Found: m/z 233.1398. **5e**: a pale yellow liquid; R_f 0.53 (EtOAc–hexane, 1:2); IR (neat) 2118 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.03 (2H, d, $J=5.3$ Hz), 3.38 (6H, s), 3.81 (3H, s), 4.59 (1H, t, $J=5.3$ Hz), 6.75 (1H, dd, $J=8.6$, 1.6 Hz), 6.85 (1H, d, $J=1.6$ Hz), 7.29 (1H, d, $J=8.6$ Hz); MS m/z 221 (M^+, 8.7), 205 (100). Calcd for $C_{12}H_{15}NO_3$: M, 221.1052. Found: m/z 221.1053. **5f**: a pale yellow solid; mp 71–72°C (hexane–Et_2O); IR (KBr disk) 2113 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.28 (2H, d, $J=5.3$ Hz), 3.40 (6H, s), 4.68 (1H, t, $J=5.3$ Hz), 7.45 (1H, d, $J=8.3$ Hz), 7.56 (1H, ddd, $J=8.2$, 7.3, 1.0 Hz), 7.66 (1H, ddd, $J=8.2$, 7.3, 1.3 Hz), 7.83 (1H, d, $J=8.3$ Hz), 7.86 (1H, $J=8.2$ Hz), 8.17 (1H, dd, $J=8.2$, 1.0 Hz); MS m/z 241 (M^+, 9.9), 210 (100). Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.44; H, 6.40; N, 5.90. **9b**: colorless crystals; mp 82–85°C (hexane–CH_2Cl_2); IR (KBr disk) 1608 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.54 (3H, s), 3.94 (3H, s), 7.3–7.4 (2H, m), 7.63 (1H, d, $J=8.6$ Hz), 7.82 (1H, s), 8.63 (1H, d, $J=3.0$ Hz); MS m/z 173 (M^+, 99), 130 (100). Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.27; H, 6.46; N, 8.34. **9c**: a pale yellow liquid; R_f 0.37 (EtOAc–hexane, 1:3); IR (neat) 1608 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.52 (3H, s), 3.94 (3H, s), 7.29 (1H, d, $J=3.0$ Hz), 7.38 (1H, dd, $J=8.6$, 2.0 Hz), 7.49 (1H, s), 7.92 (1H, d, $J=8.6$ Hz), 8.60 (1H, d, $J=3.0$ Hz); MS m/z 173 (M^+, 60), 130 (100). Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.40; H, 6.70; N, 7.88. **9d**: a pale yellow liquid; R_f 0.62 (EtOAc–hexane, 1:3); IR (neat) 1607 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.35 (6H, d, $J=6.9$ Hz), 3.09 (1H, septet, $J=6.9$ Hz), 3.93 (3H, s), 7.35 (1H, d, $J=3.0$ Hz), 7.42 (1H, dd, $J=8.2$, 1.6 Hz), 7.66 (1H, d, $J=8.2$ Hz), 7.87 (1H, s), 8.64 (1H, d, $J=3.0$ Hz); MS m/z 201 (M^+, 44), 186 (100). Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.79; H, 7.69; N, 7.09. **9e**: a pale yellow solid; mp 85–86°C (hexane); IR (KBr disk) 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.92 (3H, s), 3.94 (3H, s), 7.01 (1H, d, $J=2.6$ Hz), 7.20 (1H, dd, $J=9.2$, 1.3 Hz), 7.30 (1H, d, $J=3.0$ Hz), 7.92 (1H, d, $J=9.2$ Hz), 8.51

(1H, d, $J=3.0$ Hz); MS m/z 189 (M^+, 100). Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.69; H, 5.84; N, 7.11. **9f**: a white solid; mp 149–150°C (hexane–Et_2O); IR (KBr disk) 1596 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.99 (3H, s), 7.49 (1H, d, $J=3.0$ Hz), 7.55–7.75 (3H, m), 7.80 (1H, d, $J=8.6$ Hz), 7.88 (1H, dd, $J=7.6$, 1.3 Hz), 8.75 (1H, d, $J=2.6$ Hz), 9.17 (1H, dd, $J=8.2$, 1.0 Hz); MS m/z 209 (M^+, 100). Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.51; H, 5.22; N, 6.48.