Synthesis of 2,4-Disubstituted Quinolines by Reactions of *o*-Isocyano-β-methoxystyrene Derivatives with Organolithiums

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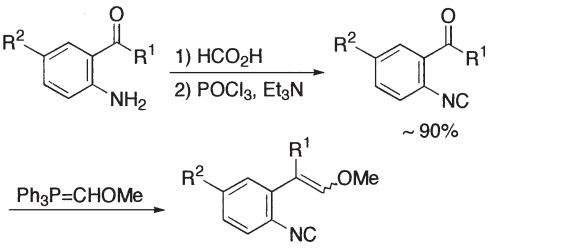
Alkyl(or aryl)lithiums reacted efficiently with *o*-isocyano-β-methoxystyrene derivatives, prepared in three steps from *o*-aminophenyl ketones, to afford the corresponding 2,4-disubstituted quinolines in satisfactory yields.

Quinolines are important because of their occurrence in nature,[1] their biological properties,[2] and their utilities as intermediates for the design of biologically active compounds.[3] Especially 2-alkylated derivatives have been reported to exhibit notable biological activities.[4] Thus, a large number of general methods for the preparation of substituted quinolines have recently been reported.[5,6] In this paper we wish to describe the results of our investigation, which offer a simple and general method for preparing 2,4-disubstituted quinolines by reactions of *o*-isocyano-β-methoxystyrene derivatives with alkyl(or aryl)-lithiums.

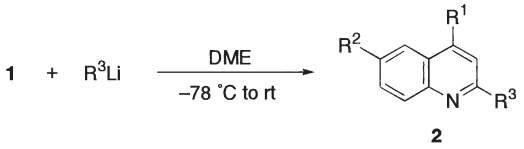
o-Isocyano-β-methoxystyrene derivatives **1** were prepared in three steps from *o*-aminophenyl ketones as shown in Scheme 1. Thus, formylation of *o*-aminophenyl ketones with formic acid afforded the corresponding formamides which were dehydrated by treatment with phosphoryl chloride/triethylamine to afford *o*-isocyanophenyl ketones. Wittig reaction of these isocyano ketones with (methoxymethyl)triphenylphosphonium ylide gave *o*-isocyano-β-methoxystyrene derivatives **1**, as a mixture of stereoisomers in each case.[7]



1a R^1 = Ph, R^2 = H 72% (*E*:*Z* = ~1:1)
1b R^1 = Ph, R^2 = Cl 67% (*E*:*Z* = ~1:1)
1c R^1 = Me, R^2 = H 70% (*E*:*Z* = ~7:3)

Scheme 1.

o-Isocyano-β-methoxystyrene derivatives **1** were treated with alkyl(or aryl)lithiums (1.5 eq) at −78 °C in 1,2-dimethoxyethane (DME) and the mixtures were allowed to warm to room temperature. Usual aqueous workup, followed by purification using preparative TLC on silica gel, gave 2,4-disubstituted quinoline derivatives **2**. The results summarized in Table 1 demonstrate that the good yields of the desired products were obtained in general (entries 1–9), though somewhat poorer results were obtained by using *o*-isocyano-β-methoxy-α-methylstyrene (**1c**) (entries 10 and 11). When the reactions were conducted in



Scheme 2.

Table 1. Preparation of 2,4-disubstituted quinolines **2** according to Scheme 2

Entry	**1**	R^3 in R^3Li	**2** (Yield/%)[a]
1	**1a**	*n*-Bu	**2a** (79)
2	**1a**	*sec*-Bu	**2b** (84)
3	**1a**	*tert*-Bu	**2c** (89)
4	**1a**	Ph	**2d**[b] (91)
5	**1a**	*p*-Tol	**2e**[c] (88)
6	**1a**	2-thienyl	**2f**[d] (74)
7	**1a**	2-furyl	**2g**[d] (75)
8	**1b**	*tert*-Bu	**2h** (87)
9	**1b**	Ph	**2i**[e] (85)
10	**1c**	*tert*-Bu	**2j**[f] (58)
11	**1c**	Ph	**2k**[g] (55)

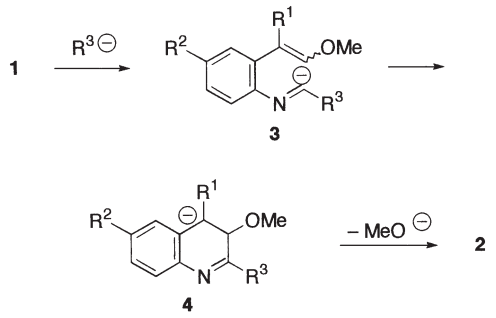
[a]Isolated yields after purification by preparative TLC on silica gel. [b]Ref. 8. [c]Ref. 9. [d]Ref. 10. [e]Ref. 11. [f]Ref. 12. [g]Ref. 13.

THF, rather diminished yields of the desired products were obtained. This is probably attributable to the lability of THF to alkyl(or aryl)lithiums.

A typical procedure is illustrated by the preparation of 2-butyl-4-phenylquinoline (**2a**). To a stirred solution of isocyanostyrene **1a** (0.12 g, 0.51 mmol) in 1,2-dimethoxyethane (2.5 mL) at −78 °C under argon was added dropwise butyllithium (0.77 mmol; 1.6 M in hexane solution). After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. Saturated aqueous ammonium chloride (15 mL) was added and the mixture was extracted with diethyl ether three times (15 mL each). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by preparative TLC on silica gel (1 : 3 EtOAc–hexane) to give **2a** (0.11 g, 79%) as a pale-yellow viscous oil.[14]

The pathway to quinoline derivatives **2** is outlined in Scheme 3. The α-addition of a nucleophile to the isocyano carbon of **1** resulted in formation of the imidoyl anion intermediate **3**. This anion attacks to the α-carbon atom of the methoxyvinyl moiety of **3** to afford the benzyl anion intermediate **4**, which, after a loss of methoxide, provides **2**.

In conclusion, we have demonstrated that the reactions of *o*-isocyano-β-methoxystyrene derivatives with alkyl(or aryl)-lithiums provide a new method to prepare 2,4-disubstituted



Scheme 3.

quinolines. This method is useful because of its efficiency, the ready availability of the starting materials and the ease of operation. Work on investigating the reactions using other nucleophiles for preparing 2-functionalized quinolines is currently progress in our laboratory.

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7 **1a**: a pale-yellow viscous oil; *Rf* 0.66 (1 : 3 EtOAc–hexane); IR (neat) 2123, 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.81 (1.5H, s), 3.83 (1.5H, s), 6.38 (0.5H, s), 6.69 (0.5H, s), 7.05–7.5 (9H, m); MS m/z 235 (M^+, 97) 165 (100). **1b**: a pale-yellow viscous oil; *Rf* 0.61 (1 : 3 EtOAc–hexane); IR (neat) 2123, 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.82 (1.5H, s), 3.84 (1.5H, s), 6.40 (0.5H, s), 6.69 (0.5H, s), 7.10 (1H, dd, $J = 7.9$, 1.6 Hz), 7.2–7.4 (7H, m); MS m/z 269 (M^+, 100). **1c**: a pale-yellow oil; *Rf* 0.31 (1 : 10 EtOAc–hexane); IR (neat) 2124, 1666 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.91 (2.1H, d, $J = 1.3$ Hz), 2.00 (0.9H, d, $J = 1.3$ Hz), 3.63 (2.1H, s), 3.73 (0.9H, s), 6.13 (0.7H, q, $J = 1.3$ Hz), 6.23 (0.3H, q, $J = 1.3$ Hz), 7.15–7.4 (4H, m); MS m/z 173 (M^+, 60), 130 (100).

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14 All new compounds gave satisfactory spectral and analytical data. **2a**; *Rf* 0.67; IR (neat) 1592 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, t, $J = 7.3$ Hz), 1.47 (2H, sextet, $J = 7.3$ Hz), 1.75–1.9 (2H, m), 3.01 (2H, t, $J = 7.9$ Hz), 7.24 (1H, s), 7.43 (1H, td, $J = 8.2$, 1.3 Hz), 7.5–7.6 (5H, m), 7.68 (1H, td, $J = 8.2$, 1.3 Hz), 7.86 (1H, dd, $J = 8.2$, 1.3 Hz), 8.11 (1H, dd, $J = 8.2$, 1.3 Hz); MS m/z 261 (M^+, 1.1), 246 (6.9), 232 (19), 219 (100). Found: C, 87.09; H, 7.20; N, 5.36. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. **2b**: a pale-yellow viscous oil; *Rf* 0.74 (1 : 3 EtOAc–hexane); IR (neat) 1592 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.3$ Hz), 1.40 (3H, d, $J = 6.9$ Hz), 1.65–2.0 (2H, m), 2.95–3.15 (1H, m), 7.23 (1H, s), 7.43 (1H, td, $J = 8.2$, 1.3 Hz), 7.5–7.55 (5H, m), 7.68 (1H, td, $J = 8.2$, 1.3 Hz), 7.86 (1H, dd, $J = 8.2$, 1.3 Hz), 8.12 (1H, dd, $J = 8.2$, 1.3 Hz); MS m/z (%) 261 (M^+, 3.3), 246 (45), 233 (100). Found: C, 87.07; H, 7.29; N, 5.20. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. **2c**: a pale-yellow solid; mp 85–88 °C (hexane); IR (KBr disk) 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (9H, s), 7.42 (1H, td, $J = 8.2$, 1.3 Hz), 7.44 (1H, s), 7.45–7.55 (5H, m), 7.66 (1H, td, $J = 8.2$, 1.3 Hz), 7.84 (1H, dd, $J = 8.2$, 1.3 Hz), 8.12 (1H, dd, $J = 8.2$, 1.3 Hz); MS m/z 261 (M^+, 43), 246 (100). Found: C, 87.48; H, 7.09; N, 5.27. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. **2h**: a pale-yellow viscous oil; *Rf* 0.81 (1 : 3 hexane-AcOEt); IR (neat) 1590 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.48 (9H, s), 7.4–7.6 (6H, m including s at δ 7.45), 7.60 (1H, dd, $J = 8.9$, 2.3 Hz), 7.80 (1H, $J = 2.3$ Hz), 8.05 (1H, d, $J = 8.9$ Hz); MS m/z 295 (M^+, 37), 280 (100). Found: C, 76.96; H, 5.95; N, 4.55. Calcd for $C_{19}H_{18}NCl$: C, 77.15; H, 6.13; N, 4.74.