New Synthesis of Isoquinoline Derivatives by Reactions of 2-(2-Methoxyethenyl)benzonitriles with Organolithiums and Lithium Dialkylamides

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A simple and efficient synthesis of 1-alkyl(or aryl)isoquinoline and isoquinolin-1-amine derivatives based on intramolecular cyclization of 2-(2-methoxyethenyl)benzonitriles initiated by the addition of alkyl(or aryl)lithiums and lithium dialkylamides to the nitrile carbons, respectively, is described.

Recently, we have described a new and efficient synthesis of 2,4-disubstituted quinolines via a sequence of addition and intramolecular ring closure between *o*-isocyano-β-methoxystyrene derivatives and organolithiums.[1] In this paper, we wish to describe the results of our extensive investigation of this quinoline synthesis, which provide a convenient method to prepare 1-alkyl(or aryl)isoquinoline **2** and isoquinolin-1-amine derivatives **3** by reactions of 2-(2-methoxyethenyl)benzonitriles (*o*-cyano-β-methoxystyrenes) **1** with alkyl(or aryl)lithiums and lithium dialkylamides. Over recent years, development of new methods for the preparation of isoquinolines,[2] including isoquinolin-1-amines,[3] has attracted much attention due to their biological activities.[4]

The starting nitriles **1** were readily prepared by treatment of the respective 2-acylbenzonitriles, which were commercially available or readily available by the literature methods,[5–8] with (methoxymethylene)triphenylphosphoran in 1,2-dimethoxyethane (DME) at 0 °C.

We first investigated reactions of 2-(2-methoxy-1-phenylethenyl)benzonitrile (**1a**) (a mixture of *E* and *Z* isomers; ca. 1:1) with alkyl(or aryl)lithiums, and found that these reactions resulted in the formation of 1-alkyl(or aryl)-4-phenylisoquinolines **2a–2e** in good yields, as shown in Scheme 1. Thus, 2 equiv. of the organolithiums[9] were added to a solution of **1a** in DME at −78 °C. After 10 min the mixture was warmed to room temperature and stirring was continued for an additional 1 h at the same temperature. The attack of organolithiums on the nitrile carbon of **1a** followed by ring closure proceeded smoothly. After usual aqueous workup and purification using preparative TLC on silica gel the desired isoquinolines were obtained. A similar sequence between 4-methoxy-2-(2-methoxy-1-phenylethenyl)benzonitrile (**1b**) (a mixture of *E* and *Z* isomers; ca. 2:1) and phenyllithium also proceed and the desired isoquinoline derivative **2f** could be obtained but in rather diminished yield.

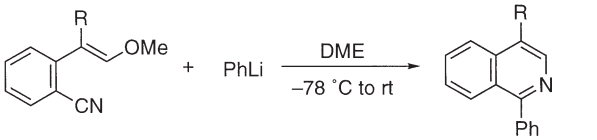
Conducting reactions of 2-(2-methoxyethenyl)benzonitrile (*E*-**1c**) and 2-(2-methoxy-1-methylethenyl)benzonitrile (*E*-**1d**) with phenyllithium, 1-phenylisoquinoline (**2g**) and 4-methyl-1-phenylisoquinoline (**2h**) could be prepared in moderate to fair yields, as shown in Scheme 2. The corresponding *Z*-isomers of these starting nitriles proved to be less reactive to phenyllithium in the present sequence giving poorer results than those using *E*-isomers, as shown in Scheme 3.

Subsequently, we discovered that the same addition/intramolecular ring closure sequence could be carried out using lithium dialkylamides in the place of alkyl(or aryl)lithiums to afford *N*,*N*-diakylisoquinolin-1-amines **3**. Thus, according to the procedure mentioned above for the preparation of 1-alkyl(or aryl)isoquinolines **2**, 2-(2-methoxy-1-phenylethenyl)benzonitriles **1a** and **1b** were allowed to react with lithium dialkylamides in THF (instead of DME) to afford **3** in fair yields generally, as illustrated in Scheme 4. The reaction using 4-methoxy-2-(2-methoxy-1-phenylethenyl)benzonitrile (**1b**) also proved to give a rather diminished yield of the desired product **3g**. It should be noted that attempts to obtain the expected isoquinolineamines from the reactions of **1c** and **1d** with lithium piperidide were un-

1a R = H
1b R = OMe

2a R = H, R' = Ph 76%
2b R = H, R' = *n*-Bu 54%
2c R = H, R' = *sec*-Bu 70%
2d R = H, R' = *tert*-Bu 68%
2e R = H, R' = 2-furyl 51%
2f R = OMe, R' = Ph 41%

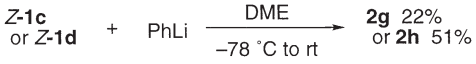
Scheme 1.



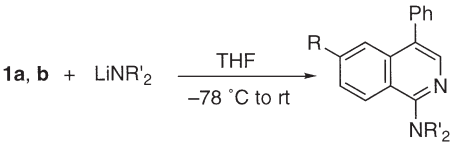
E-**1c** R = H
E-**1d** R = Me

2g R = H 38%
2h R = Me 65%

Scheme 2.

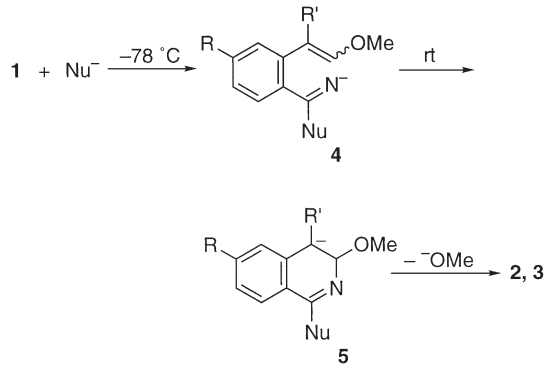


Scheme 3.



3a R = H, R' = Et 59%
3b R = H, R' = *i*-Pr 62%
3c R = H, R'$_2$ = $(CH_2)_4$ 62%
3d R = H, R'$_2$ = $(CH_2)_5$ 65%
3e R = H, R'$_2$ = $(CH_2)_2NMe(CH_2)_2$ 64%
3f R = H, R'$_2$ = $(CH_2)_2O(CH_2)_2$ 67%
3g R = OMe, R'$_2$ = $(CH_2)_5$ 29%

Scheme 4.



Scheme 5.

successful; an intractable mixture of products was obtained in each case.

The pathway to isoquinoline derivatives **2** and **3** is outlined in Scheme 5. Thus, the addition of a nucleophile to the nitrile carbon of **1** at −78 °C results in the formation of the nitrogen anion intermediate **4**. When the reaction temperature is raised to room temperature, the attack of this anion at the α-carbon atom of the methoxyvinyl moiety occurs to give the benzyl anion **5**. Subsequent loss of methoxide gives rise to the isoquinoline derivatives **2** and **3**. It is reasonable that the poorer results were obtained in the cases of using **1b** as the lower stability of the corresponding intermediate benzyl anions due to the methoxy substituent at the benzene nucleus is taken into consideration.

In summary, an efficient procedure for the preparation of isoquinoline derivatives has been developed. It may offer the possibility of accessing compounds of potential biological interest.[10]

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9 The use of less than 2 equiv. of organolithiums resulted in decrease of the yields of the desired products and the starting material **1a** was recovered.

10 All new compounds gave satisfactory apectral and analytical data. Physical data for compounds **2** and **3** follow. **2a**: mp 141 °C (lit.,[11] 131 °C); **2b**: R_f 0.54 (CH_2Cl_2); **2c**: R_f 0.58 (5:1 hexane-AcOEt); **2d**: R_f 0.68 (CH_2Cl_2); **2e**: mp 204–205 °C; **2f**: mp 108 °C; **2g**: mp 100–101 °C; **2h**: mp 77–78 °C (lit.[12] mp 75–76 °C); **3a**: R_f 0.63 (2:1 hexane-AcOEt); **3b**: R_f 0.71 (5:1 hexane-AcOEt); **3c**: mp 104 °C; **3d**: mp 120–121 °C; **3e**: mp 133–134 °C; **3f**: mp 151–152 °C; **3g**: mp 136–137 °C.

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