Synthesis of 1-Aminonaphthalene-2-carbonitrile Derivatives by the Reaction of 2-Vinylbenzonitriles with 2-Lithioacetonitrile

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Abstract: A new and simple method for the preparation of 1-aminonaphthalene-2-carbonitrile derivatives has been developed. When 2-(1-arylethenyl)benzonitriles are treated with 2-lithioacetonitrile, 1-amino-4-aryl-3,4-dihydronaphthalene-2-carbonitriles are obtained in good yields. The reaction of 2-(1-aryl-2-methoxyethenyl)benzonitriles with 2-lithioacetonitrile leads to the formation of 1-amino-4-arylnaphthalene-2-carbonitriles in fair-to-good yields.

Key words: arenes, carbanions, nitriles, ring closure, tandem reaction

In previous papers, we reported a new short-step general synthesis of 4-aryl-3,4-dihydroisoquinoline derivatives based on the reaction of 2-(1-arylethenyl)benzonitriles with organolithiums.1 Subsequently, we decided to examine the reaction of 2-(1-arylethenyl)benzonitriles 1 with 2-lithioacetonitrile, and found that it gave 1-amino-4-aryl-3,4-dihydronaphthalene-2-carbonitriles 2. On the other hand, it was noted that the reaction using 2-(1-aryl-2-methoxyethenyl)benzonitriles 3 in place of 1 afforded 1-aminonaphthalene-2-carbonitriles 4. In this paper we wish to describe the results of these studies. Compounds having an enamino nitrile moiety have already proven to be useful precursors for the synthesis of a variety of heterocycles,2 some of which have been reported to be of biological importance. However, only a few general synthetic methods of 1-aminonaphthalene-2-carbonitrile derivatives have been developed.3,4

The preparation of 1-amino-4-aryl-3,4-dihydronaphthalene-2-carbonitriles 2 was carried out as shown in Scheme 1. Thus, treatment of 2-(1-arylethenyl)benzonitriles 1 with two molar amounts of 2-lithioacetonitrile, generated by treatment of acetonitrile with butyllithium in THF at –78 °C, at the same temperature followed by raising reaction temperature to 0 °C, resulted in the efficient production of the desired products 2, after aqueous work-up. Scheme 1 also shows the yields of the products, which are generally good independent of the 3-aryl substituents and the 4-methoxy group of the starting nitriles 1.

It was envisioned that the use of 2-(1-aryl-2-methoxyethenyl)benzonitriles 3 in the place of 1 would be capable of affording 1-amino-4-arylnaphthalene-2-carbonitriles 4.

Scheme 1:

As expected, subjecting 3 to the reaction with two molar amounts of 2-lithioacetonitrile under the same conditions as described for the preparation of 2 gave the desired products 4, but the yields were somewhat lower than those of 2, as illustrated in Scheme 2. When lithium enolates of tert-butyl acetate and N,N-dimethylacetamide were used, the starting nitrile was recovered almost quantitatively in each case.

Scheme 2:

The mechanistic rationale, depicted in Scheme 3, begins with coupling of the first molecule of 2-lithioacetonitrile with the nitrile of 2-vinylbenzonitrile derivatives 1 and 3 to give the adduct 5. Abstraction of a hydrogen α to the nitrile of this adduct by the second molecule of 2-lithioacetonitrile gives the dianionic intermediate 6, which undergoes an intramolecular ring closure to give the benzylic anion intermediate 7. The intermediate 7 (X = H) gives 2 through successive tautomerization via the intermediate 8, and protonation (or in the inverse order). On the other hand, the intermediate 8 (X = OMe) loses methoxide after the tautomerization (or in the inverse order) to

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provide 4 as the result of protonation. Although the possibility of anion-promoted electrocyclic reaction of the enamide form of the intermediate 5 for the present ring closure cannot be excluded, the mechanism depicted in Scheme 3 may explain the necessity of two molar amounts of 2-lithioacetonitrile for the satisfactory production of the desired products 2 and 4. It is noteworthy that no products arising from the addition of imino anion of the adduct 5 to the β-carbon atom of the vinyl moiety were isolated.

Scheme 3

In conclusion, we have developed a new method for preparing 1-aminonaphthalene-2-carbonitrile derivatives. The present procedure may find some value in organic synthesis, because it has some advantages over the previously reported methods; simple manipulations as well as ready availability of the starting materials.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer. The 1H NMR spectra were recorded in CDCl3 using TMS as an internal reference using a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The 13C NMR spectra were recorded in CDCl3 using TMS as an internal reference on a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EL, 70 eV) were measured using a JEOL AUTOMASS 20 spectrometer. TLC was carried out on a Merck Kieselgel 60 PF254. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

2-(2-(1-Phenylethenyl)benzonitrile (1a).1 2-benzoylbenzonitrile,1,6 2-bromo-3-methylbenzonitrule,7 2-bromo-4-methylbenzophene none,7 2-[1-(4-methoxyphenyl)ethyl]benzonitrile (1d),6 2-bromomethyl[1-naphthyl]methylene7 were prepared by reported methods. All other chemicals used in this study were commercially available.

2-(2-Methoxy-1-phenylethenyl)benzonitrile (3a)10

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (3.4 g, 9.9 mmol) in 1,2-dimethoxyethane (DME, 70 mL) at 0 °C under argon was added dropwise BuLi (1.6 M in hexane; 6.2 mL, 9.9 mmol). After 4 min, the resulting ylide was treated with a solution of 2-benzoylbenzonitrile (1.6 g, 7.5 mmol) in DME (15 mL) and stirring was continued for an additional 10 min at the same temperature. H2O (30 mL) was added and the mixture was extracted with Et2O (2 × 30 mL). The combined extracts were washed with H2O (20 mL) and brine (20 mL), dried (Na2SO4), and evaporated. The residue was purified by column chromatography on silica gel (hexane–Et2O, 2:1) to give 3a: Yield: 1.3 g (73%); yellow oil; mixture of stereoisomers (E/Z = 1:1); Rf = 0.36 (hexane–Et2O, 2:1).

IR (neat): 2225, 1634 cm–1. 1H NMR (270 MHz): δ = 3.82 and 3.84 (2 s, 3 H), 6.49 (s, 0.5 H), 6.69 (s, 0.5 H), 7.11 (dd, J = 7.9, 1.6 Hz, 1 H), 7.20–7.40 (m, 6 H), 7.45–7.60 (m, 1 H), 7.72 (d, J = 8.6 Hz, 0.5 H) and 7.76 (d, J = 7.9 Hz, 0.5 H).

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2-[(1-Naphthyl)ethyl]benzonitrile

This compound was prepared by treating 2-(1-naphthoyl)benzonitrile with methylenetriphenylphosphorane under conditions for the preparation of 1a reported by us. 1 Yield: 57%; yellow viscous oil; \( R_f = 0.52 \) (THF–hexane, 1:4).

IR (neat): 2224 cm\(^{-1}\).

1H NMR (500 MHz): \( \delta = 5.84 \) (s, 1 H), 6.12 (s, 1 H), 7.18 (dd, \( J = 7.8 \) Hz, 1 H), 7.34 (ddd, \( J = 7.8, 1.4, 1.0 \) Hz, 1 H), 7.37–7.46 (m, 4 H), 7.49 (dd, \( J = 7.8, 7.3 \) Hz, 1 H), 7.74 (dd, \( J = 7.8, 1.4 \) Hz, 1 H), 7.80 (d, \( J = 8.7 \) Hz, 1 H), 8.77 (d, \( J = 8.2 \) Hz, 2 H).

Anal. Calcld for C_{30}H_{28}N: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.58; H, 5.36; N, 5.20.

2-[2-Methoxy-1-(naphthyl)ethyl]benzonitrile (3e)

This compound was prepared by treating 2-(1-naphthoyl)benzonitrile with (methoxymethylene)triphenylphosphorane as described for the preparation of 3a. Yield: 72%; mixture of stereoisomers (~1:1); colorless viscous oil; \( R_f = 0.31 \) (THF–hexane, 1:4).

IR (neat): 2224, 1639 cm\(^{-1}\).

1H NMR (500 MHz): \( \delta = 3.77 \) (s, 1.5 H), 3.89 (s, 1.5 H), 6.55 (s, 0.5 H), 7.04 (dd, \( J = 8.2, 0.9 \) Hz, 0.5 H), 7.07 (s, 0.5 H), 7.10 (dd, \( J = 7.8, 0.9 \) Hz, 0.5 H), 7.21–7.27 (m, 1 H), 7.32 (dd, \( J = 7.8, 1.4 \) Hz, 0.5 H), 7.35–7.52 (m, 4.5 H), 7.68 (dd, \( J = 7.8, 1.4 \) Hz, 0.5 H), 7.72 (J = 7.8, 0.9 Hz, 0.5 H), 7.81–7.89 (m, 3 H).

Anal. Calcld for C_{29}H_{25}NO: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.07; H, 5.51; N, 4.72.

2-Benzoyl-4-methoxybenzonitrile\(^{10}\)

This compound was prepared from 2-bromo-5-methoxybenzophenone\(^{12}\) and CuCN under the conditions reported by Fried- man et al.\(^{11}\) Yield: 40%; white solid; mp 130–131 °C (hexane–THF). IR (KBr): 2226, 1665 cm\(^{-1}\).

1H NMR (270 MHz): \( \delta = 3.89 \) (s, 3 H), 7.05–7.15 (m, 2 H), 7.50 (dd, \( J = 7.9, 7.3 \) Hz, 2 H), 7.65 (tt, \( J = 7.3, 1.3 \) Hz, 1 H), 7.74 (d, \( J = 9.2 \) Hz, 1 H), 7.83 (dd, \( J = 7.9, 1.3 \) Hz, 2 H).

Anal. Calcld for C_{18}H_{14}NO: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.04; H, 4.65; N, 5.84.

4-Methoxy-2-(1-phenylethenyl)benzonitrile (1f)

This compound was prepared by treating 4-methoxy-2-benzoylbenzonitrile\(^{10}\) with methylenetriphenylphosphorane under conditions for the preparation of 1a reported by us. 1 Yield: 53%; yellow oil; \( R_f = 0.43 \) (THF–hexane, 1:4).

IR (neat): 2222 cm\(^{-1}\).

1H NMR (500 MHz): \( \delta = 3.84 \) (s, 3 H), 5.48 (s, 1 H), 5.86 (s, 1 H), 6.84 (d, \( J = 2.3 \) Hz, 1 H), 6.92 (dd, \( J = 8.7, 2.3 \) Hz, 1 H), 7.27–7.35 (m, 5 H), 7.63 (d, \( J = 8.7 \) Hz, 1 H).

Anal. Calcld for C_{27}H_{21}NO: C, 76.98; H, 5.70; N, 5.28. Found: C, 76.96; H, 5.99; N, 5.21.
1-Amino-4-phenyl-3,4-dihydropthalene-2-carbonitrile (2a); Typical Procedure

To a stirred solution of MeCN (0.21 g, 5.2 mmol) in THF (10 mL) at −78 °C was added n-BuLi (1.6 M in hexane; 3.3 mL, 5.3 mmol). After 15 min, a solution of 1a (0.54 g, 2.6 mmol) in THF (5 mL) was added and the mixture was gradually raised to 0 °C. The resulting mixture was quenched with sat. aq NH₄Cl (15 mL) and extracted with Et₂O (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄), and evaporated. The residue was subjected to column chromatography on silica gel to give 2a. Yield: 0.50 g (77%); light-gray solid; mp 182–184 °C (hexane–CH₂Cl₂).

IR (KBr): 3464, 3356, 3258, 2174, 1661, 1649 cm⁻¹.
1H NMR (500 MHz): δ = 2.74 (d, J = 7.8 Hz, 2 H), 4.13 (t, J = 7.8 Hz, 1 H), 4.65 (br s, 2 H), 6.96 (dd, J = 7.3 Hz, 1 H), 7.15 (dd, J = 7.3, 1.4 Hz, 2 H), 7.25–7.36 (m, 5 H), 7.46 (dd, J = 7.8, 1.4 Hz, 1 H).
13C NMR (125 MHz): δ = 100.91, 120.80, 121.64, 123.43, 125.40, 125.60, 126.16 (2 C), 127.24, 127.72, 129.04, 129.24, 129.50, 130.64, 131.41, 134.19, 137.51, 140.57, 151.59.
MS: m/z (%) = 296 (100, [M⁺]).


1-Amino-6-methoxy-4-phenyl-3,4-dihydropthalene-2-carbonitrile (2f)

Pale-yellow solid; mp 115–117 °C (hexane–CH₂Cl₂).

IR (KBr): 3449, 3373, 3256, 2170, 1647, 1609 cm⁻¹.
1H NMR (500 MHz): δ = 2.70 (dd, J = 15.1, 7.8 Hz, 1 H), 2.72 (dd, J = 15.1, 7.3 Hz, 1 H), 3.73 (s, 3 H), 4.09 (dd, J = 8.7, 7.3 Hz, 1 H), 4.65 (br s, 2 H), 6.92 (dd, J = 7.8 Hz, 1 H), 6.94 (dd, J = 7.3, 1.4 Hz, 1 H), 6.97 (s, 1 H), 7.08 (d, J = 7.3 Hz, 1 H), 7.20 (dd, J = 7.8, 7.3 Hz, 1 H), 7.28–7.34 (m, 2 H), 7.45 (dd, J = 7.3, 1.8 Hz, 1 H).
MS: m/z (%) = 276 (100, [M⁺]).

Anal. Calcd for C₁₇H₁₁N₂O: C, 78.24; H, 5.84; N, 10.14. Found; C, 78.15; H, 6.05; N, 9.93.

1-Amino-4-(1-naphthyl)-3,4-dihydropthalene-2-carbonitrile (2g)

Pale-yellow solid; mp 181–182 °C (hexane–CH₂Cl₂).

IR (KBr): 3464, 3356, 3258, 2174, 1655, 1647, 1604 cm⁻¹.
1H NMR (500 MHz): δ = 2.85 (dd, J = 15.3, 6.7 Hz, 1 H), 2.96 (dd, J = 15.3, 8.6 Hz, 1 H), 4.71 (br s, 2 H), 4.97 (dd, J = 8.6, 6.7 Hz, 1 H), 6.89 (d, J = 7.3 Hz, 1 H), 7.03 (d, J = 7.3 Hz, 1 H), 7.25–7.38 (m, 3 H), 7.50–7.53 (m, 3 H), 7.78 (d, J = 8.6 Hz, 1 H), 7.91–8.03 (m, 2 H).
13C NMR (125 MHz): δ = 29.78, 39.89, 75.08, 120.37, 121.99, 123.43, 125.40, 125.60, 126.16 (2 C), 127.14, 127.72, 129.04, 129.24, 129.50, 130.64, 131.41, 137.51, 140.57, 151.59.
MS: m/z (%) = 296 (100, [M⁺]).


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Anal. Calcd for C_{18}H_{14}N_{2}: C, 83.69; H, 5.46; N, 10.84. Found: C, 85.67; H, 4.67; N, 9.46.

1-Amino-4-(1-naphthyl)naphthalene-2-carbonitrile (4e)
Pale-yellow solid; mp 165–167 °C (dec.) (hexane–CH_{2}Cl_{2}).

1H NMR (500 MHz): δ = 8.7 Hz, 2 H), 7.29–7.59 (m, 9 H), 7.91–7.96 (m, 3 H).

MS: m/z (%) = 294 (100, [M+]).
Anal. Calcd for C_{18}H_{14}N_{2}: C, 83.69; H, 5.46; N, 10.84. Found: C, 85.67; H, 4.67; N, 9.46.

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References
