Efficient Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives via a Sequential Michael Addition/Enolate−Nitrile Coupling Route and Its Application to Facile Preparation of 9-Amino Analogues of Arylnaphthofuranone Lignans

Kazuhiro Kobayashi,* Tomokazu Uneda, Keiichiro Takada, Hiroto Tanaka, Tomohide Kitamura, Osamu Morikawa, and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Tottori 680, Japan

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The reaction of 2-(α-lithioalkyl)benzonitriles, generated *in situ* by treatment of 2-alkylbenzonitriles with LDA in diglyme, with α,*β*-unsaturated carboxylates and nitriles produced 1-amino-3,4-dihydro-2-naphthalenecarboxylates and carbonitriles in 54−98% yields through Michael addition of the lithio nitriles to α,*β*-unsaturated carboxylic acid derivatives, followed by zinc iodide-promoted intramolecular enolate−nitrile coupling of the resulting enolate intermediates. The dihydronaphthalenecarboxylic acid derivatives were converted to the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives in 43−99% yields on dehydrogenation with palladium on activated carbon in refluxing *p*-cymene. Subsequently, we showed that, by using a similar reaction sequence, 9-amino analogues of arylnaphthofuranone lignan derivatives {9-amino-4-arylnaphtho[2,3-*c*]furan-1(3*H*)-ones} could also be prepared from 2-(arylmethyl)benzonitriles and furan-2(5*H*)-one in good overall yields (59−61%).

2-Aminobenzoic acids are important precursors for the generation of benzynes, which are efficient intermediates for the synthesis of a variety of polycyclic compounds.[1] 2-Aminobenzoic acid derivatives are also known as useful starting materials for the synthesis of heterocyclic compounds.[2] The synthetic utility of 1(or 3)-amino-2-naphthalenecarboxylic acid derivatives, which are the benzo-analogues of 2-aminobenzoic acid derivatives, is also well documented.[3] A survey of the literature, nevertheless, reveals that few general methods for the preparation of this class of molecules have been developed.[4] This background prompted us to concentrate on development of simple methods for their preparation, and we previously reported the general synthesis of *tert*-butyl 3-amino-2-naphthalenecarboxylates by an electrocyclic reaction of *o*-quinonedimethides generated from *tert*-butyl (*Z*)-3-amino-3-(benzocyclobuten-2-yl)propenoates.[5] In this paper we wish to describe a new efficient method for the general preparation of 1-amino-2-naphthalenecarboxylates and nitriles, which is based on the tandem Michael addition/enolate−nitrile coupling reaction between α-lithio derivatives of 2-alkylbenzonitriles and α,*β*-unsaturated carboxylic acid derivatives. Although lithiation of 2-methylbenzonitrile using LDA in THF/HMPA has been reported by Kaiser and his co-workers,[6] no synthetic application of the lithiated 2-methylbenzonitrile has been achieved. To our knowledge, the present report is the first example of the practical use of 2-(α-lithioalkyl)-benzonitriles in organic synthesis.[7] We also report that 9-amino analogues of arylnaphthofuranone lignans {9-amino-4-arylnaphtho[2,3-*c*]furan-1(3*H*)-ones} can be simply constructed by applying this reaction sequence. This is the first construction of this system.

Results and Discussion

General Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives 6 and 9. The starting materials 2-methylbenzonitrile (**1a**) and 2,5-dimethylbenzonitrile (**1d**) were commercially available, and compounds **1b**,[8] **1c**,[9] and **1e** were easily prepared as follows. 2-Benzylbenzonitrile (**1b**) was prepared from the corresponding aldehyde,[10] which was alternatively obtainable by reduction of commercially available 2-benzylbenzoic acid with lithium aluminum hydride (LAH) and subsequent oxidation of the resulting alcohol with PCC, by the derivatization to its oximes followed by dehydration with

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(2) For a review on early work, see: Taylor, E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles*; Interscience: New York, 1970; p 79. For recent reports, see Groundwater, P. W.; Solomons, K. R. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 173. Besson, T.; Emayan, K.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1419 and references therein.

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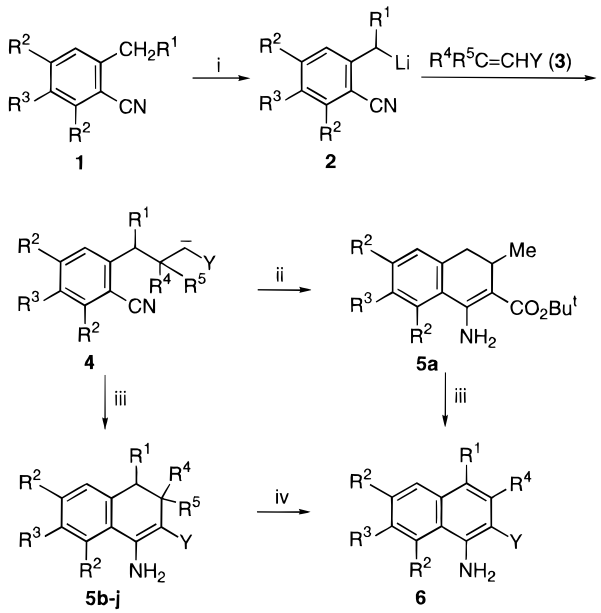
Scheme 1



Reagents and conditions: i, 2LDA, THF, -78 °C; ii, -78 °C to r.t.; iii, ZnI_2, -78 °C to r.t.; iv, 10% Pd/C, *p*-cycmene, reflux.

triphenylphosphine−carbon tetrachloride. Lithiation of **1a** with LDA in diethylene glycol dimethyl ether (diglyme) produced 2-(lithiomethyl)benzonitrile (*vide infra*) which, on treatment with iodomethane, afforded 2-ethylbenzonitrile (**1c**) in a good yield. 2,3,4-Trimethoxy-6-methylbenzonitrile (**1e**) was obtained from 2,3,4-trimethoxy-6-methylbenzaldehyde[11] by a method similar to that described for **1b**. This aldehyde was also available from 3,4,5-trimethoxytoluene by methoxycarbonylation using reaction of its 2-lithio derivative with methyl chloroformate and subsequent reduction with LAH, followed by oxidation of the resulting benzyl alcohol with PCC.

The sequence for our preparation of the aminonaphthalenecarboxylates and nitriles **6** is outlined in Scheme 1. Addition of one of the 2-alkylbenzonitriles **1** to a solution of LDA (2 equiv) in diglyme at −78 °C resulted immediately in deep-red coloration which, on treatment with one of the α,*β*-unsaturated carboxylic acid derivatives **3** (1 equiv), turned yellow, suggesting that addition of the anion to **3** had taken place to form an intermediate **4**. Zinc iodide (2 equiv) was added at this temperature to promote the enolate−nitrile coupling, and the mixture was then allowed to reach room temperature. After stirring for 1−2 h, the usual workup gave, after purification by preparative TLC on silica gel or recrystallization, 1-amino-2,3-dihydronaphthalenecarboxylic acid derivatives **5**. With 1 equiv of LDA the reaction sequence did not proceed in a satisfactory manner and gave only an intractable mixture of products and the starting materials. When this reaction sequence was carried out in the absence of zinc iodide, the coupling reaction, even with heating, occurred extremely slowly. Moreover, quenching the reaction mixture after 2 h at reflux temperature gave the protonation product of **4** along with a minor amount of the desired **5**, which were inseparable by means of preparative TLC. In the case of using *tert*-butyl 2-butenoate (**3a**), however, the coupling reaction proceeded cleanly without the catalyst at room temperature to give a good yield of the desired product **5a** (entry a in Table 1). It can be reasonably assumed that the addition of zinc iodide generates the corresponding zinc enolates[12] and that bivalent zinc ion is responsible for the success of the coupling reaction.[13] Although other Lewis acids, such as magnesium bromide and boron trifluoride diethyl etherate, were examined, they proved to be ineffective in this cyclization. When the reaction sequence was carried out in THF, even the addition of the carbanion to **3** did not proceed in a satisfactory manner and an intractable mixture of products was obtained. A variety of 2-alkylbenzonitriles **1** and α,*β*-unsaturated carboxylic acid derivatives **3** was tested in this reaction sequence, and the formation of the products **5**, along with the reaction conditions, are summarized in Table 1. The results show that most of these reactions proceeded smoothly to afford the corresponding products **5** in good yields. The reaction between 2-methylbenzonitrile (**1a**) and ethyl 3-methyl-2-butenoate (**3f**) also took place smoothly to provide the expected product **5f** in a fair yield as shown in entry f. The lithium derivatives from α-substituted 2-methylbenzonitriles, such as 2-benzylbenzonitrile (**1b**) and 2-ethylbenzonitrile (**1c**), reacted with 2-butenenitrile (**3d**) to provide the corresponding products **5g** and **5h** as inseparable mixtures of two diastereomers (entries g and h, respectively). The product **5h** from **1c** and **3d** was obtained in somewhat lower yield (entry h). A similar lowering in the yield of the product **5j** was observed in the corresponding reaction sequence between 3,4,5-trimethoxy-6-methylbenzonitrile (**1e**) and **3b** (entry j). We attribute these lower yields to the instability of the corresponding α-lithiated derivatives of **1c** and **1e**. The intermediates **4** from α,*β*-unsaturated nitriles were found to cyclize more readily than those from α,*β*-unsaturated carboxylates (see the Experimental Section).

Compounds **5** thus obtained, except for **5f**, could be easily converted to the corresponding 1-amino-2-naphthalenecarboxylates and carbonitriles **6** on dehydrogenation with 10% Pd/C in refluxing *p*-cymene. The yields of the products obtained are also listed in Table 1. As can be seen in Table 1, the yields are generally good. It should be noted that the dihydronaphthalenecarboxylate **5a** underwent elimination of isobutene under these conditions to give 3-methyl-1-amino-2-naphthalenecarboxylic acid (**6a**) (entry a). The reactions were complete in 5−12 h. We found a clear difference in the rates of the dehydrogenation of the carbonitriles and the carboxylates; dehydrogenation of the former was rather faster than that of the latter (see the Experimental Section).

The addition−cyclization procedure with 2-(dimethoxymethyl)benzonitrile **7** and crotononitrile (**1d**) also provided the expected product **8** in 45% yield, treatment of which with *p*-toluenesulfonic acid in benzene at room temperature for 10 min resulted in the formation of 3-methoxy-1-amino-2-naphthalenecarbonitrile (**9**) in 64% yield. Scheme 2 shows the outline of this reaction sequence.

Preparation of 9-Amino-4-arylnaphtho[2,3-*c*]furan-1(3*H*)-ones 11. There has been continued interest

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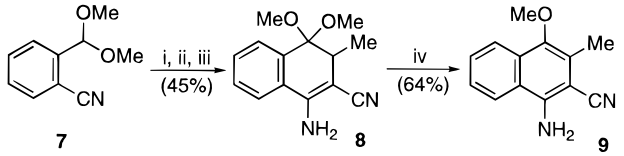
Table 1. Preparation of 2-Amino-3-naphthalenecarboxylic Acid Derivatives 5 and 6

entry	1	3	conditions	5 (Yield/%[b])	6 (Yield/%[b])
a	**1a** ($R^1 = R^2 = R^3 = H$)	**3a** (R^4 = Me, R^5 = H, Y = $COOBu^t$)	A	**5a** (78)	**6a**[c] (43)
b	**1a**	**3b** (R^4 = Me, R^5 = H, Y = COOEt)	B	**5b** (98)	**6b** (90)
c	**1a**	**3c** (R^4 = Ph, R^5 = H, Y = COOEt)	B	**5c** (81)	**6c** (99)
d	**1a**	**3d** (R^4 = Me, R^5 = H, Y = CN)	B	**5d** (89)	**6d** (85)
e	**1a**	**3e** (R^4 = Ph, R^5 = H, Y = CN)	B	**5e** (73)	**6e** (85)
f	**1a**	**3f** ($R^4 = R^5$ = Me, Y = COOEt)	B	**5f** (60)	–
g	**1b** (R^1 = Ph, $R^2 = R^3$ = H)	**3d**	B	**5g** (94)[d,f]	**6g** (75)
h	**1c** (R^1 = Me, $R^2 = R^3$ = H)	**3d**	B	**5h** (55)[e,f]	**6h** (78)
i	**1d** ($R^1 = R^2$ = H, R^3 = Me)	**3d**	B	**5i** (70)	**6i** (83)
j	**1e** (R^1 = H, $R^2 = R^3$ = OMe)	**3b**	B	**5j** (54)	**6j** (82)

[a] After addition of 3 to a solution of lithiated 2-alkylbenzonitrile, A: −78 °C to rt; B: 2 equiv of ZnI_2, −78 °C to rt. [b] Yields of products after preparative TLC on silica gel or recrystallization. [c] 1-Amino-3-methyl-2-naphthalenecarboxylic acid. [d] Obtained as a ca. 3:1 mixture of diastereomers. [e] Obtained as a ca. 1:1 mixture of diastereomers. [f] The ratio was based on the ^{1}H NMR spectrum. The stereochemistry of each diastereomer was not determined.

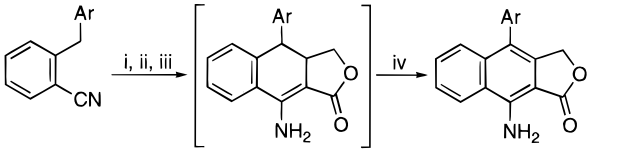
Scheme 2



7 8 9

Reagents and conditions: i, 2LDA, THF, -78 °C; ii, **3d**, -78 °C; iii, ZnI_2, -78 °C to r.t.; iv, *p*-TsOH, benzene, r.t.

Scheme 3



1b (Ar=C_6H_5)
1f (Ar=3,4-$(MeO)_2C_6H_3$)

10

11a (Ar=C_6H_5) (61%)
11b (Ar=3,4-$(MeO)_2C_6H_3$) (59%)

Reagents and conditions: i, 2LDA, THF, -78 °C; ii, furan-2(5*H*)-one, -78 °C; iii, ZnI_2, reflux; iv, 10% Pd/C, *p*-TsOH, reflux.

in the development of new methods for the synthesis of arylnaphthofuranone lignans.[14] We have recently described the use of a tandem Michael addition/condensation sequence between *o*-aroylbenzyllithiums and furan-2(5*H*)-one for the preparation of arylnaphthofuranone derivatives, including some natural lignans.[14a] We have now established conditions for efficient preparation of 9-amino-4-arylnaphtho[2,3-*c*]furan-1(3*H*)-ones **11**, 9-amino analogues of arylnaphthofuranone lignans, from 2-(arylmethyl)benzonitriles (**1b** and **1f**) and furan-2(5*H*)-one as an application of the present Michael addition/nitrile−enolate coupling sequence as outlined in Scheme 3.

In our first attempt, the reaction of 2-(phenylmethyl)-benzonitrile (**1b**) with furan-2(5*H*)-one under the same reaction conditions described for the preparation of the aminodihydronaphthalenecarboxylic acid derivatives **5** using zinc iodide was investigated, and we found that the reaction resulted in the formation of the primary Michael addition product along with a minor amount of the desired dihydronaphthofuranone **10a**. Conversion of the primary adduct to **10a** was achieved by heating the reaction mixture after addition of ZnI_2 at reflux temperature for 3 h; the ^{1}H NMR of the crude product revealed that **10a** was produced in a reasonable yield. However, its purification by preparative TLC on silica gel resulted in formation of a mixture of unidentified decomposition products as well as **10a** and the dehydrogenated product **11a**. Fortunately, this problem was circumvented by carrying out dehydrogenation of **10a** without any purification. Dehydrogenation of the crude **10a** with 10% Pd on activated carbon in refluxing *p*-cymene proceeded smoothly to give the desired product **11a** in 61% overall yield from the starting nitrile **1b**. Similarly, 2-[(3,4-dimethoxyphenyl)methyl]benzonitrile (**1f**) and furan-2(5*H*)-one gave the corresponding aminonaphthofuranone **11b** without purification of the initial product **10b** in 59% overall yield.

In summary, the results described above have shown that the present Michael addition/enolate−nitrile coupling sequence provides an efficient general method for the preparation of 1-amino-2-naphthalenecarboxylic acid derivatives. The methodology has been applied to the first construction of the 9-amino-4-arylnaphtho[2,3-*c*]-furan-1(3*H*)-one system.

Experimental Section

***tert*-Butyl 1-Amino-3,4-dihydro-3-methyl-2-naphthalenecarboxylate (5a). Method A.** 2-Methylbenzonitrile (**1a**) (1.0 mmol, 0.12 g) was added dropwise to a stirred solution of LDA (2.0 mmol) in diglyme (5 mL) at −78 °C, resulting in the production of a deep-red solution, to which was added dropwise with a syringe *tert*-butyl crotonate (**2a**) (1 mmol, 0.28 g). After the characteristic red color turned into yellow, the resulting mixture was allowed to warm up to room temperature, poured into aqueous NH_4Cl (10 mL), and extracted with Et_2O (10 mL). The aqueous layer was further extracted with Et_2O (2 × 10 mL). The combined ether layers were washed first with water and then with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was recrystallized from hexane to give the title compound **5a** (0.20 g, 78%) as a pale yellow solid: mp 99−102 °C; IR (KBr disk) 3466, 3317, 1654, 1615 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.84 (3H, d, J = 6.7 Hz), 1.50 (9H, s), 2.50 (1H, d, J = 13.2 Hz), 2.8−3.2 (2H, m), 6.40 (2H, br s), 7.05−7.45 (4H, m); MS (rel intensity) m/z 259 (M^+, 6.5), 203 (12), 188 (100). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.08; N, 5.30.

Ethyl 1-Amino-3,4-dihydro-3-methyl-2-naphthalenecarboxylate (5b). Method B. 2-(Lithiomethyl)benzonitrile (1 mmol) in diglyme (5 mL), generated as above, was treated with ethyl crotonate (**1b**) (1 mmol, 0.14 g) at −78 °C, and then a suspension of ZnI_2 in diglyme (3 mL), prepared *in situ* by the treatment of Zn (2.5 mmol, 0.16 g) with I_2 (2 mmol, 0.51

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g), was added using a syringe at the same temperature. The resulting mixture was allowed to warm up to room temperature and stirring was continued for an additional 2 h before 20 mL of saturated aqueous NH_4Cl was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined ether layers were washed five times with water and then once with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC on SiO_2 to afford the title compound **5b** as a pale yellow solid (0.23 g, 98%): R_f 0.46 (1:5 EtOAc−hexane); mp 88−91 °C (hexane); IR (KBr disk) 3448, 3322, 1652, 1616 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.9 Hz), 1.32 (3H, t, J = 7.3 Hz), 2.56 (1H, d, J = 13.5 Hz), 3.0−3.15 (2H, m), 4.15−4.3 (2H, m), 6.50 (2H, br s), 7.15−7.35 (3H, m), 7.44 (1H, dd, J = 8.9, 2.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.6, 18.7, 26.3, 36.0, 59.0, 99.2, 122.1, 126.5, 129.2, 129.7, 130.6, 138.0, 150.8, 170.3; MS (rel intensity) m/z 231 (M^+, 76), 216 (99), 144 (99), 143 (100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.40; N, 6.06. Found: C, 72.46; H, 7.35; N, 6.12.

Following the above-mentioned procedure (method B) the dihydronaphthalenecarbonitriles **5c−j** were prepared. Formation of the carbonitriles by the ZnI_2-promoted enolate−nitrile coupling was faster than that of the carboxylates, and 1 h stirring proved to be ample.

Ethyl 1-Amino-3,4-dihydro-3-phenyl-2-naphthalenecarboxylate (5c): R_f 0.37 (1:3 EtOAc−hexane); mp 109−112 °C (hexane); IR (KBr disk) 3442, 3318, 1656, 1618 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (3H, t, J = 7.3 Hz), 2.93 (1H, dd, J = 15.2, 1.8 Hz), 3.38 (1H, dd, J = 15.2, 7.3 Hz), 4.0−4.25 (2H, m), 4.27 (1H, dd, J = 7.3, 1.8 Hz), 6.73 (2H, br s), 6.95−7.15 (5H, m), 7.2−7.3 (3H, m), 7.44 (1H, dd, J = 8.7, 1.8 Hz); MS (rel intensity) m/z 293 (M^+, 24), 220 (100). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.81; H, 6.49; N, 4.93.

1-Amino-3,4-dihydro-3-methyl-2-naphthalenecarbonitrile (5d): R_f 0.15 (1:10 EtOAc−hexane); mp 108−110 °C (hexane); IR (KBr disk) 3463, 3363, 3254, 2178, 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 6.3 Hz), 2.58 (1H, dd, J = 14.2, 9.0 Hz), 2.6−2.7 (1H, m), 2.90 (1H, dd, J = 14.2, 4.2 Hz), 4.59 (2H, br s), 7.15−7.4 (4H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.4, 27.8, 36.6, 82.1, 120.2, 122.0, 126.9, 128.7, 128.9, 130.2, 137.4, 151.6; MS (rel intensity) m/z 184 (M^+, 16), 169 (100). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.56; N, 15.20. Found: C, 78.51; H, 6.64; N, 15.00.

1-Amino-3,4-dihydro-3-phenyl-2-naphthalenecarbonitrile (5e): R_f 0.18 (1:3 EtOAc−hexane); mp 165−167 °C (hexane−CH_2Cl_2); IR (KBr disk) 3461, 3364, 3250, 2177, 1634 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.03 (1H, dd, J = 15.2, 6.9 Hz), 3.25 (1H, dd, J = 15.2, 6.9 Hz), 3.83 (1H, t, J = 6.9 Hz), 4.76 (2H, br s), 7.1−7.45 (9H, m); MS (rel intensity) m/z 246 (M^+, 75), 169 (100). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.81; H, 5.60; N, 11.35.

Ethyl 1-Amino-3,4-dihydro-3,3-dimethyl-2-naphthalenecarboxylate (5f): R_f 0.60 (1:3, EtOAc−hexane); IR (neat) 3468, 3330, 1653, 1614 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (6H, s), 1.34 (3H, t, J = 7.3 Hz), 2.65 (2H, s), 4.25 (2H, q, J = 7.3 Hz), 6.31 (2H, br s), 7.15−7.4 (4H, m); MS (rel intensity) m/z 245 (M^+, 21), 230 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.70; H, 7.88; N, 5.59.

1-Amino-3,4-dihydro-3-methyl-4-phenyl-2-naphthalenecarbonitrile (5g): a mixture of diastereomers (ca. 1:3); R_f 0.27 (1:3, EtOAc−hexane); IR (neat) 3466, 3363, 3255, 2178, 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (2.25 H, d, J = 7.3 Hz), 1.14 (0.75 H, d, J = 6.8 Hz), 2.8−2.9 (0.75 H, m), 3.0−3.1 (0.25 H, m), 3.79 (0.75 H, d, J = 7.6 Hz), 4.00 (0.25 H, d, J = 5.9 Hz), 4.67 and 4.75 (2H, 2 br s), 6.9−7.5 (9H, m); MS (rel intensity) m/z 260 (M^+, 28), 245 (100). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.20; N, 10.76. Found: C, 83.00; H, 6.09; N, 10.85.

1-Amino-3,4-dihydro-3,4-dimethyl-2-naphthalenecarbonitrile (5h): a mixture of diastereomers (ca. 1:1); R_f 0.50 (1: 3 EtOAc−hexane); IR (neat) 3465, 3363, 3254, 2178, 1634 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.94 (1.5H, d, J = 6.9 Hz), 1.09 (1.5H, t, J = 7.3 Hz), 1.15 (1.5H, d, J = 7.3 Hz), 1.21 (1.5H, d, J = 6.9 Hz), 2.41 (0.5H, qd, J = 6.9, 2.5 Hz), 2.65−2.75 (1H, m), 2.90 (0.5H, qd, J = 15.2, 6.9 Hz), 4.58 (2H, br s), 7.2−7.4 (4H, m); MS (rel intensity) m/z 198 (M^+, 32), 183 (100). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.65; H, 6.99; N, 14.30.

1-Amino-3,4-dihydro-3,7-dimethyl-2-naphthalenecarbonitrile (5i): R_f 0.25 (1:3 EtOAc−hexane); IR (neat) 3443, 3366, 3254, 2168, 1656 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.17 (3H, d, J = 6.9 Hz), 2.2−2.95 (6H, m including s at 2.33), 4.70 (2H, br s), 7.0−7.2 (3H, m); MS (rel intensity) m/z 198 (M^+, 29), 183 (100). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.57; H, 6.98; N, 14.34.

Ethyl 1-Amino-3,4-dihydro-6,7,8-trimethoxy-3-methyl-2-naphthalenecarboxylate (5j): R_f 0.20 (1:3, EtOAc−hexane); IR (neat) 3467, 3307, 1651, 1601 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.9 Hz), 1.31 (3H, t, J = 7.3 Hz), 2.45 (1H, d, J = 13.4 Hz), 2.93 (1H, d, J = 5.4 Hz), 3.03 (1H, dd, 1H, J = 13.4, 5.4 Hz), 3.86, 3.87, and 3.89 (combined 9H, 3s), 4.15−4.25 (2H, m), 6.54 (1H, s), 8.68 (2H, br s); MS (rel intensity) m/z 321 (M^+, 17), 306 (100). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36%. Found: C, 63.77; H, 7.36; N, 4.24%.

Ethyl 1-Amino-3-methyl-2-naphthalenecarboxylate (6b). General Procedure for Dehydrogenation of 5. The dihydronaphthalenecarboxylate **5b** (0.61 mmol, 0.14 g) was dissolved in dry *p*-cymene (3 mL), and 10% Pd on activated carbon (0.061 mmol, 64 mg) was added. The mixture was heated at reflux temperature for 12 h, the reaction being followed by TLC or taking small aliquots for analysis by ^1H NMR. After cooling and filtration of the catalyst, concentration of the filtrate under reduced pressure gave a residue, which was subjected to preparative TLC on SiO_2 to give **6b** (0.13 g, 90%) as a pale yellow oil: R_f 0.41 (1:5, EtOAc−hexane); IR (neat) 3486, 3366, 1678, 1601 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.40 (3H, t, J = 7.2 Hz), 2.53 (1H, s), 3.0−3.15 (2H, m), 4.36 (2H, q, J = 7.2 Hz), 6.16 (2H, br s), 6.84 (1H, s),7.1−7.85 (4H, m); MS (rel intensity) m/z 229 (M^+, 100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.11 H, 6.29; N, 5.97.

Following the above-mentioned procedure, the aminonaphthalenecarboxylic acid derivatives **6a−e** and **6g−j** were prepared. Heating for 10−12 h was required to complete dehydrogenation to the carboxylates. Dehydrogenation to the carbonitriles was faster than that to the carboxylates and completed after 5−8 h.

1-Amino-3-methyl-2-naphthalenecarboxylic acid (6a): R_f 0.47 (1:3 EtOAc−hexane); IR (neat) 3443, 3369, 3232, 1631 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.40 (3H, s), 3.68 (2H, br s), 6.60 (1H, s), 7.09 (1H, s), 7.3−7.45 (2H, m), 7.65−7.75 (2H, m); MS (rel intensity) m/z 201 (M^+, 100). Anal. Calcd for $C_{12}H_{11}NO_2$: C,71.63; H, 5.51; N, 6.96. Found: C, 71.35; H, 5.40; N, 7.09.

Ethyl 1-Amino-3-phenyl-2-naphthalenecarboxylate (6c): R_f 0.55 (1:3 EtOAc−hexane); IR (neat) 3487, 3369, 1684, 1602 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.67 (3H, t, J = 7.0 Hz), 3.84 (2H, q, J = 7.0 Hz), 6.10 (2H, br s), 6.99 (1H, s), 7.2−7.9 (9H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.1, 60.3, 119.0, 121.3, 122.5, 125.4, 125.6, 126.4, 127.8, 128.0, 128.3, 128.7, 134.9, 140.0, 140.1, 146.3, 170.0; MS (rel intensity) m/z 291 (M^+, 100). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.19; H, 5.71; N, 5.00.

1-Amino-3-methyl-2-naphthalenecarbonitrile (6d):[4a] mp 146−149 °C (hexane) (lit.[4a] 146−147 °C); IR (KBr disk) 3450, 3384, 3250, 2204, 1643, 1624 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.55 (3H, s), 5.1 (2H, br s), 7.03 (1H, s), 7.3−7.9 (4H, m).

1-Amino-3-phenyl-2-naphthalenecarbonitrile (6e): mp 214 °C (CH_2Cl_2); IR (KBr disk) 3459, 3373, 3246, 2201, 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.25 (2H, br s), 7.24 (1H, s), 7.4−7.65 (7H, m),7.75−7.85 (2H, m); MS (rel intensity) m/z 244 (M^+, 100). Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.53; H, 4.86; N, 11.40.

1-Amino-3-methyl-4-phenyl-2-naphthalenecarbonitrile (6g): R_f 0.47 (1:3 EtOAc−hexane); IR (neat) 3470, 3377, 3254, 2203, 1643 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.30 (3H, s), 5.12 (2H, br s), 7.15−7.25 (2H, m), 7.3−7.5 (6H, m), 7.75−7.85 (1H, m); MS (rel intensity) m/z 258 (M^+, 100). Anal.

Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.51; H, 5.40; N, 10.60.

1-Amino-3,4-dimethyl-2-naphthalenecarbonitrile (6h): mp 189−191 °C (hexane); IR (KBr disk) 3460, 3375, 3249, 2204, 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.48 (3H, s), 2.57 (3H, s), 4.95 (2H, br s), 7.47 (1H, dd, J = 8.3, 6.9 Hz), 7.61 (1H, dd, J = 8.3, 6.9 Hz), 7.80 (1H, d, J = 8.3 Hz), 7.98 (1H, d, J = 8.3 Hz); MS (rel intensity) m/z 196 (M^+, 100). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.58; H, 6.20; N, 14.34.

1-Amino-3,7-dimethyl-2-naphthalenecarbonitrile (6i): mp 163−166 °C (hexane−Et_2O); IR (KBr disk) 3454, 3373, 3250, 2197, 1651 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.51 (6H, s), 5.01 (2H, br s), 6.98 (1H, s), 7.37 (1H, d, J = 8.4 Hz), 7.50 (1H, s), 7.57 (1H, d, J = 8.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 20.8, 21.8, 91.7, 117.8, 118.0, 120.2, 120.4, 128.0, 131.1, 133.8, 134.1, 135.1, 148.1; MS (rel intensity) m/z 196 (M^+, 100). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.69; H, 6.21; N, 14.16.

Ethyl 1-Amino-6,7,8-trimethoxy-3-methyl-2-naphthalenecarboxylate (6j): R_f 0.48 (1:3 EtOAc−hexane); IR (neat) 3473, 3353, 1668, 1601 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.40 (3H, t, J = 7.3 Hz), 2.49 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 4.37 (2H, q, J = 7.3 Hz), 6.66 (1H, s), 6.70 (1H, s), 7.62 (2H, br s); MS (rel intensity) m/z 319 (M^+, 100). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.66; H, 6.88; N, 4.26.

1-Amino-3,4-dihydro-4,4-dimethoxy-3-methyl-2-naphthalenecarbonitrile (8) was prepared following method B described above for the preparation of **5b**−**j**; R_f 0.22 (1:3 EtOAc−hexane); IR (neat) 3466, 3365, 3240, 2180, 1638 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.9 Hz), 2.86 (3H, s), 2.89 (1H, q, J = 6.9 Hz), 3.38 (3H, s), 4.59 (2H, br s), 7.4−7.5 (2H, m), 7.75−7.8 (2H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.48, 36.28, 48.27, 49.51, 82.19, 99.87, 120.10, 122.24, 127.81, 128.26, 128.83, 129.78, 134.74, 149.16; MS (rel intensity) m/z 244 (M^+, 52), 229 (100). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.12; H, 6.62; N, 11.26.

1-Amino-4-methoxy-3-methyl-2-naphthalenecarbonitrile (9). A solution of the foregoing dihydronaphthalenecarbonitrile **8** (0.13 mmol, 32 mg) and *p*-TsOH·H_2O (0.05 mmol, 9.5 mg) in benzene (3 mL) was stirred for 10 min at room temperature under argon. To the resulting mixture was added saturated $NaHCO_3$ (10 mL), and the organic materials were extracted with Et_2O (3 × 10 mL). The combined ether layers were washed first with water and then with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC to give the naphthalenecarbonitrile **9** (15 mg, 64%) as a pale yellow oil: R_f 0.22 (1:3 EtOAc−hexane); IR (neat) 3462, 3374, 2201, 1648 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.52 (3H, s), 3.83 (3H, s), 4.92 (2H, br s), 7.48 (1H, t, J = 8.3 Hz), 7.63 (1H, t, J = 8.3 Hz), 7.78 (1H, d, J = 8.3 Hz), 8.05 (1H, d, J = 8.3 Hz); MS (rel intensity) m/z 212 (M^+, 100). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.45; H, 5.81 N, 13.44.

9-Amino-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (11a). To a stirred solution of LDA (4.0 mmol) in 14 mL of diglyme at −78 °C was added dropwise the nitrile **1b** (0.39 g, 2.0 mmol) in 14 mL of diglyme. The mixture was stirred for 7 min before furan-2(5*H*)-one (0.17 g, 0.2 mmol) was added. Fading of the red color of the carbanion was instantaneous. Then a suspension of ZnI_2, prepared from Zn (0.31 g, 4.5 mmol) and I_2 (1.0 g, 4.0 mmol) in 4 mL of diglyme, was added with a syringe. The mixture was allowed to warm up to room temperature and refluxed for 3 h. A workup similar to that described above for **5b** gave a residue (0.64 g), which was subjected to the next reaction without any purification. Thus, it was dissolved in 31 mL of *p*-cymene, and 10% Pd on activated carbon (0.94 g, 0.88 mmol) was added. The mixture was heated at reflux temperature for 16 h and then cooled. The catalyst was filtered off through a Celite pad and washed with $CHCl_3$. The combined filtrate and washing were concentrated under reduced pressure to give a crude solid, which was further purified by preparative TLC on SiO_2 to give the title aminofuranone **11a** (0.34 g, 61%) as a pale yellow solid: R_f 0.43 (1:2 EtOAc−hexane); mp 188−189 °C (hexane−CH_2Cl_2); IR (KBr disk) 3418, 3324, 1730, 1651, 1637, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.15 (2H, s), 6.15 (2H, br s), 7.3−7.35 (2H, m), 7.4−7.55 (5H, m), 7.65−7.75 (1H, m), 7.9−8.0 (1H, m); MS (rel intensity) m/z 275 (M^+, 100). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.82; H, 4.75; N, 5.09.

9-Amino-4-(3,4-dimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (11b) was prepared from the benzonitrile **1f** and furan-2(5*H*)-one in 59% yield following a procedure similar to that described above for the preparation of **11a**: mp 254−255 °C (hexane−CH_2Cl_2); IR (KBr disk) 3462, 3370, 1731, 1634 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.97 (3H, s), 5.16 (1H, d, J = 14.2 Hz), 5.18 (1H, d, J = 14.2 Hz), 6.14 (2H, br s), 6.84 (1H, d, J = 1.8 Hz), 6.88 (1H, dd, J = 8.0, 1.8 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.45−7.6 (2H, m), 7.75 (1H, dd, J = 7.3, 2.2 Hz), 7.96 (1H, dd, J = 7.3, 2.2 Hz); MS (rel intensity) m/z 335 (M^+, 100). Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.59; H, 5.11; N, 4.19.

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Supporting Information Available: Preparations of nitriles **1b**−**f** and **7**. Physical, spectroscopic (^1H NMR and IR), and analytical data for these nitriles and their precursors (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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