An Efficient General Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives Based on a Tandem Conjugate Addition-Enolate Nitrile Coupling Sequence

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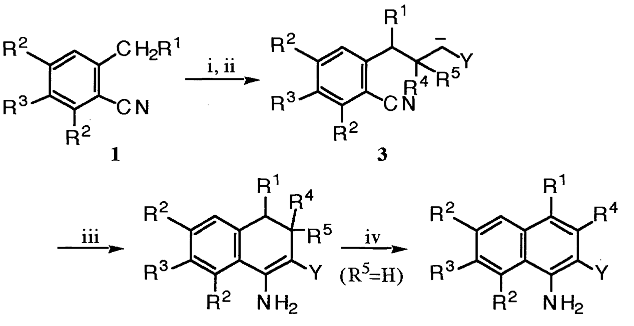
Reaction of *o*-(α-lithioalkyl)benzonitriles with α,ß-unsaturated carboxylic acid derivatives produced 1-amino-3,4-dihydro-2-naphthalenecarboxylic acid derivatives through the tandem conjugate addition-enolate nitrile coupling sequence, which in turn were converted into 1-amino-2-naphthalenecarboxylic acid derivatives on dehydrogenation with palladium on activated carbon.

Although the synthetic efficiency of 1(or 3)-amino-2-naphthalenecarboxylic acid derivatives, the benzo-analogues of 2-aminobenzoic acid derivatives, is well recognized,[1,2] little work on the general method for preparing this group of molecules has been reported.[3] This prompted us to investigate simple methods for their preparation, and we have previously reported the facile general synthesis of 3-amino-2-naphthalenecarboxylates.[2] In this paper we wish to describe a new method for the preparation of 1-amino-2-naphthalenecarboxylic acid derivatives **5** utilizing the conjugate addition of lithium anions generated from *o*-alkylbenzonitriles to α,ß-unsaturated carboxylic acid derivatives followed by zinc iodide catalyzed enolate nitrile coupling reaction (Scheme 1). To our knowledge, this is the first example of practical use of *o*-(α-lithioalkyl)benzonitriles in organic synthesis.[4]



1a: $R^1=R^2=R^3=H$
1b: $R^1=Ph, R^2=R^3=H$
1c: $R^1=Me, R^2=R^3=H$
1d: $R^1=R^2=H, R^3=Me$
1e: $R^1=H, R^2=R^3=OMe$

2a: $R^4=Me, R^5=H, Y=COOEt$
2b: $R^4=Me, R^5=H, Y=COOBu^t$
2c: $R^4=Ph, R^5=H, Y=COOEt$
2d: $R^4=Me, R^5=H, Y=CN$
2e: $R^4=Ph, R^5=H, Y=CN$
2f: $R^4=R^5=Me, Y=COOEt$

Reagents and conditions: i, LDA, diglyme, -78 °C; ii, $R^4R^5C=CHY$ (**2**), -78 °C; iii, ZnI_2, -78 °C to r.t.; iv. 10% Pd/C, *p*-cymene,reflux.

Scheme 1.

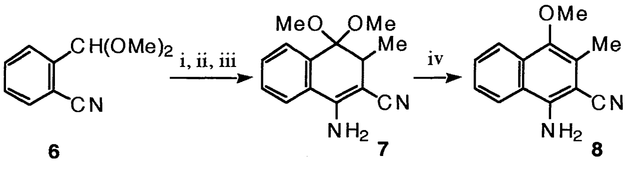
Table 1. Preparation of 1-amino-2-naphthalenecarboxylic acid derivatives **4** and **5**

Entry	1	2	Conditions[a]	Yield/%[b]	
				4	5
a	**1a**	**2a**	A	**4a** (98)	**5a** (90)
b	**1a**	**2b**	B	**4b** (78)	**5b**[g] (43)
c	**1a**	**2c**	A	**4c** (81)	**5c** (99)
d	**1a**	**2d**	A	**4d** (89)	**5d**[h] (85)
e	**1a**	**2e**	A	**4e** (73)	**5e** (85)
f	**1a**	**2f**	A	**4f** (60)	—
g	**1b**[c]	**2d**	A	**4g** (94)[f]	**5g** (75)
h	**1c**[d]	**2d**	A	**4h** (55)[f]	**5h** (78)
i	**1d**	**2d**	A	**4i** (70)	**5i** (83)
j	**1e**[e]	**2a**	A	**4j** (54)	**5j** (82)

[a] After additon of **2** to a solution of lithiated *o*-alkylbenzonitrile, A: 2 eq. of ZnI_2, -78 °C to r.t. for 2 h; B: -78 °C to r. t. [b] Isolated yields. [c] Ref. 5. [d] Ref. 6. [e] Prepared from the corresponding aldehyde (Ref. 7) by the derivatization to its oxime followed by dehydration with PPh_3-CCl_4. [f] A mixture of diastereomers. [g] 1-Amino-3-methyl-2-naphthalenecarboxylic acid. [h] Ref. 3a.

Addition of one of *o*-alkylbenzonitriles **1** to a solution of LDA (2 eq.) in diethyleneglycol dimethyl ether (diglyme) at -78 °C resulted in an immediate deep red coloration, which on treatment with each of α,ß-unsaturated carboxylic acid derivatives **2** (1 eq.) became yellow indicative of addition of the anion of **1** to **2** and of formation of a intermediate **3**. Treatment of **3** with zinc iodide (2 eq.) promoted the enolate nitrile coupling reaction and led to the formation of the corresponding cyclization product **4** after the usual workup procedure. Dehydrogenation of **4** with 10% Pd/C afforded 1-amino-2-naphthalenecarboxylic acid derivatives **5**. The reaction took place in refluxing *p*-cymene.

The yields of the products **4** and **5** along with the reaction conditions are summarized in Table 1. A variety of *o*-alkylbenzonitriles **1** and α,ß-unsaturated carboxylic acid derivatives **2** could be used in the present transformation to give products **4** and **5** in moderate to high yields. Without using zinc iodide, even under heating, we could not effect cyclization of **3** to **4**, except for the case of Entry b, in which the cyclization reaction proceeded smoothly without the catalyst at room temperature. When **1c** and **1e** were used, the yields of the products **4h** and **4j**, respectively, were lower than those in the other cases (Entries h and j). These results may be attributable to the instabilities of



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

Scheme 2.

the corresponding carbanions of **1c** and **1e**.

The cyclization procedure with *o*-(dimethoxymethyl)-benzonitrile **6** and crotononitrile (**2d**) also provided the expected product **7**, which in turn was smoothly converted into **8** on treatment with *p*-toluenesulfonic acid.

We have therefore shown that the present procedure provides an efficient synthetic method of 1-amino-2-naphthalenecarboxylic acid derivatives. The method has some advantages over the previous methods:[3] high generality and simple manipulations as well as the ready availability of the starting materials. Further synthetic applications of this methodology are currently being explored.

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8 All new compounds provided CHN combustion analytical and spectroscopic data consistent with their structure. Selected data are as follows [^1H and ^{13}C NMR (270 MHz, $CDCl_3$), IR (KBr disk or neat)]. **4a**: mp 88-91 °C (hexane); ν 3448, 3322, 1652, 1616 cm^{-1}; δ_H 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); δ_C 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. Found: C, 72.46; H, 7.35; N, 6.12%. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.40; N, 6.06%. **4c**: mp 109-112 °C (hexane); ν 3442, 3318, 1656, 1618 cm^{-1}; δ_H 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). Found: C, 77.81; H, 6.49; N, 4.93%. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%. **4d**: mp 108-110 °C (hexane); ν 3463, 3363, 3254, 2178, 1636 cm^{-1}; δ_H 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); δ_C 19.4, 27.8, 36.6, 82.1, 120.2, 122.0, 126.9, 128.7, 128.9, 130.2, 137.4, 151.6. Found: C, 78.51; H, 6.64; N, 15.00%. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.56; N, 15.20%. **4f**: *Rf* 0.60 (1:3, EtOAc-hexane); ν 3468, 3330, 1653, 1614 cm^{-1}; δ_H 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). Found: C, 73.70; H, 7.88; N, 5.59%. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71%. **4g**: a mixture of diastereomers (ca. 1:3); *Rf* 0.27 (1:3, EtOAc-hexane); ν 3466, 3363, 3255, 2178, 1636 cm^{-1}; δ_H 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). Found: C, 83.00; H, 6.09; N, 10.85%. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.20; N, 10.76%. **4j**: *Rf* 0.20 (1:3, EtOAc-hexane); ν 3467, 3307, 1651, 1601 cm^{-1}; δ_H 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, *J*=13.4, 5.4 Hz), 3.86, 3.87, and 3.89 (combined 9H, 3s), 4.15-4.25 (2H, m), 8.68 (2H, br. s), 6.54 (1H, s). Found: C, 63.77; H, 7.36; N, 4.24%. Calcd for $C_{17}H_{13}NO_5$: C, 63.54; H, 7.21; N, 4.36%. **5b**: *Rf* 0.47 (1:3 EtOAc-hexane); ν 3443, 3369, 3232, 1631 cm^{-1}; δ_H 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). Found: C, 71.35; H, 5.40; N, 7.09%. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96 %. **5c**: *Rf* 0.55 (1:3 EtOAc-hexane); IR (neat) 3487, 3369, 1684, 1602 cm^{-1}; δ_H 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 (8H, m); δ_C 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. Found: C, 78.19; H, 5.71; N, 5.00%. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. **5e**: mp 214 °C (CH_2Cl_2); ν 3459, 3373, 3246, 2201, 1645 cm^{-1}; δ_H 5.25 (2H, br. s), 7.24 (1H, s), 7.4-7.65 (7H, m), 7.75-7.85 (2H, m). Found: C, 83.53; H, 4.86; N, 11.40%. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47%. **5h**: mp 189-191 °C (hexane); ν 3460, 3375, 3249, 2204, 1645 cm^{-1}; δ_H 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). Found: C, 79.58; H, 6.20; N, 14.34%. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27%. **5i**: mp 163-166 °C (hexane-Et_2O); ν 3454, 3373, 3250, 2197, 1651 cm^{-1}; δ_H 2.51 (6H, s), 5.01 (2H, br. s), 7.37 (1H, d, *J*=8.4 Hz), 7.50 (1H, s), 7.57 (1H, d, *J*=8.4 Hz); δ_C 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. Found: C, 79.69; H, 6.21; N, 14.16%. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27%. **8**: *Rf* 0.22 (1:3 EtOAc-hexane); ν 3462, 3374, 2201, 1648 cm^{-1}; 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). Found: C, 73.45; H, 5.81; N, 13.44%. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20 %.