Tandem Synthesis of Bicyclic *ortho*-Aminocarbonitrile Derivatives in Ionic Liquids

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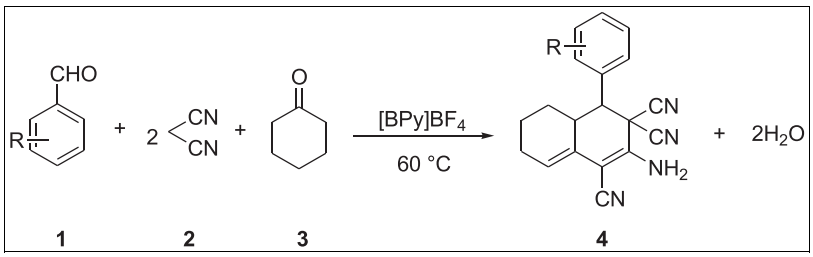

An efficient synthesis of 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitriles via the tandem four-component condensation of one equivalent of aromatic aldehyde, cyclohexanone, and two equivalents of malononitrile in ionic liquids was undertaken. Up to four new bonds and one new ring were formed in one-pot with water as the only by-product in this multi-component procedure.

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INTRODUCTION

Creation of molecular functionality and diversity[1] from common starting materials while combining economic[2,3] and environmental[4] aspects constitutes a great challenge in modern organic chemistry[5]. In these contexts, multi-component reactions (MCRs) in ionic liquids must be competent to come close to reaching this ideal goal. MCRs meet the economic desires, for they can avoid time-consuming and costly processes for purification of various precursors and tedious steps of protection and deprotection of functional groups[6].

Ionic liquids are regarded as substitutes for traditional solvent in syntheses because of their non-volatility, non-flammability, stability, and ease of recyclability[7]. Therefore, MCRs in ionic liquids have emerged as a powerful tool in organic chemistry[8].

ortho-aminocarbonitriles are widely used in organic synthesis for the preparation of various heterocyclic compounds[9]. Numerous preparations of them have been investigated during the past few years[10–13]. However, most methods have their limitations such as requirement of organic solvents (MeOH, HOAc)[10,11,14], using catalyst (Et_3N[10], morpholine[11], 1,2-diamine[14]), and complex substrate[10–13]. To obtain these potential units of *ortho*-aminocarbonitriles in high yields as well as in a green media, we would like to report an efficient and green method to synthesize 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitriles via four-component of one equivalents of aromatic aldehyde, cyclohexanone, and two equivalents of malononitrile in ionic liquids [BPy]BF_4 (Scheme 1).

RESULTS AND DISCUSSION

Malononitrile is one of the most versatile reagents to be used in MCRs because of the high reactivity of both the methylene and the cyano groups[15]. Traditionally, it is a very useful method to extend carbon chains and to prepare heterocyclic compounds that have medical and industrial utility[16]. From this perspective, we used malononitrile (**2**, 2.0 mmol) as the active reagent to react with aromatic aldehyde (**1e**, 1.0 mmol) and cyclohexanone (**3**, 1.0 mmol) to optimize the reaction conditions at first. A summary of the optimization experiment is provided in Table 1.

It was found that the reaction could not run smoothly in organic solvent and water except in the presence of ionic liquid (Table 1, Entries **1–8**). No reaction was carried out in lower polar $CHCl_3$ (Table 1, Entry **1**). In the solvents with higher polarity, the reaction cannot afford expected product (Table 1, DMF entry **2**, and H_2O entry **3**). In the medium polar solvent such as EtOH (Table 1, entry **4**), the reaction can be carried out, but the yield of product was lower than that in ionic liquid (Table 1, Entries **4–7**). It showed that the polarity of solvent has great effect on the reaction process and yield. The importance of ionic liquids may be attributed to its appropriate dissolution and excellent ionic conductivity. The influence of different cations or anions on the yield was further studied. As revealed in Table 1, [BPy]BF_4 appeared to be the best media for this reaction (Table 1, Entries **5–8**). Finally, it was also realized that the process was efficiently facilitated at 60°C (Table 1, Entries **10–13**). However, elevating the temperature did not enhance the yields of

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Scheme 1

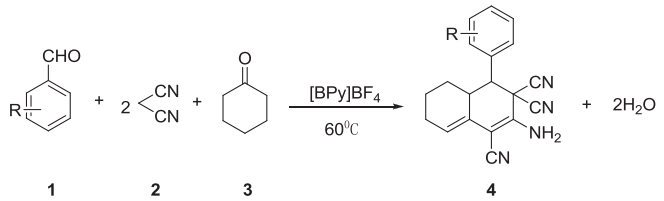


Table 1

Synthesis of **4e** under different conditions.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[d]
1	$CHCl_3$	60	12	Nr[e]
2	DMF	60	12	Np[f]
3	H_2O	60	12	Np[f]
4	EtOH	60	12	30
5	[BMIM]Br[b]	60	12	60
6	[BMIM]BF_4	60	12	56
7	[BPy]Br[c]	60	12	62
8	[BPy]BF_4	60	12	95
9	[BPy]BF_4	60	8	92
10	[BPy]BF_4	60	4	92
11	[BPy]BF_4	RT	4	Nr[e]
12	[BPy]BF_4	40	4	45
13	[BPy]BF_4	50	4	72
14	[BPy]BF_4	70	4	91

[a]Reactions were performed in 1:2:1 (4-cyanobenzaldehyde: malononitrile: benzaldehyde: cyclohexanone) in different conditions.
[b]BMIM = 1-butyl-3-methylimidazolium.
[c]BPy = 1-butylpyridiniumtetra.
[d]Isolated yields.
[e]No reaction.
[f]Not product **4e**.

4e (Table 1, Entry **14**). Therefore, reaction temperature of 60°C in ionic liquid [BPy]BF_4 were identified as the optimum condition.

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes under the optimal condition (Table 2). It showed that this reaction can afford moderate to high yield, and the product can be separated easily. However, the yields of **4** were not sensitive to the electronic properties of the aromatic rings in the presence of electron-withdrawing groups (such as halide, cyano) or electron-donating groups (such as alkyl group).

The possible reaction mechanism was proposed in Scheme 2. We presume that the reaction proceeds via initial formation of **I** through Knoevenagel condensation of aryl aldehyde and malononitrile. Meanwhile, cyclohexanone condensed with another malononitrile to give the other product of Knoevenagel condensation **II**. Then, **II** lost a hydrogen atom under the action of ionic liquids. Subsequently, the Michael addition between **III** and **I** produces intermediate **IV**, followed by intramolecular cyclization to form **V**. The isomerization of **V** gives the final product **4**.

In summary, an efficient method is exploited for the synthesis of 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitriles from four-component condensation in [BPy]BF_4. The features of this multi-component procedure include mild reaction conditions, high yields, one-pot, operational simplicity, and the formation of up to four new bonds and one new ring in one-pot with water as the only by-product. In addition, there are several modifiable and coordinate sites in this interesting type of framework, so the subsequent step of the combinatorial development process, namely, structural optimization, should be possible.

EXPERIMENTAL

General Information. IR spectra were recorded with a Bruker Varian FTIR-Tensor-27 spectrophotometer (Germany) using KBr optics. ^{1}H-NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Mass was determined by using a Bruker TOF-MS high resolution mass spectrometer (Germany). Ionic liquid [BPy]BF_4 was prepared in our lab.

General procedure for the preparation of 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitriles 4. A mixture of aromatic aldehyde (1.0 mmol), malononitrile (2.0 mmol) and cyclohexanone (1.0 mmol), and ionic liquid of [BPy]BF_4 (2 mL) was stirred at 60°C until complete consumption of the starting material as monitored by TLC. After completion of the reaction, the mixture was cooled down to RT and added water (40 mL), then the crude solid was filtered and washed with 95% EtOH. The solid residue was then recrystallized (95% EtOH/DMF, 1:4) to provide the pure product **4**.

The spectral data of new products are given in the succeeding text. ***2-amino-4-(4-chlorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (4a).*** Melting point 288–289°C; IR (KBr) *v*: 3421, 3343, 3252, 3229, 3034, 2946, 2865, 2212, 1645, 1605, 1493, 1447, 1430, 1414, 1391, 1350, 1339, 1278, 1212, 1162, 1094, 1037, 1015, 956, 918, 882, 838, 805, 782, 753, and 727 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.81–0.90 (m, 1H, CH_2), 1.44–1.47 (m, 2H, CH_2), 1.68–1.70 (m, 1H, CH_2), 2.05–2.21 (m, 2H, CH_2), 2.77–2.83 (m, 1H, CH_2), 3.66 (d, J = 12.8 Hz, 1H, CH), 5.73 (s, 1H, CH=), 7.40 (s, 2H, NH_2), and 7.48–7.62 (m, 4H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.3, 133.8, 133.6, 128.6, 120.5, 116.1, 112.4, 112.2, 81.6, 49.7, 42.5, 33.7, 26.9, 24.8, and 20.9; HRMS: Calcd for $C_{19}H_{15}ClN_4$ $[M+Na]^+$ found (expected): 357.0914 (357.0883).

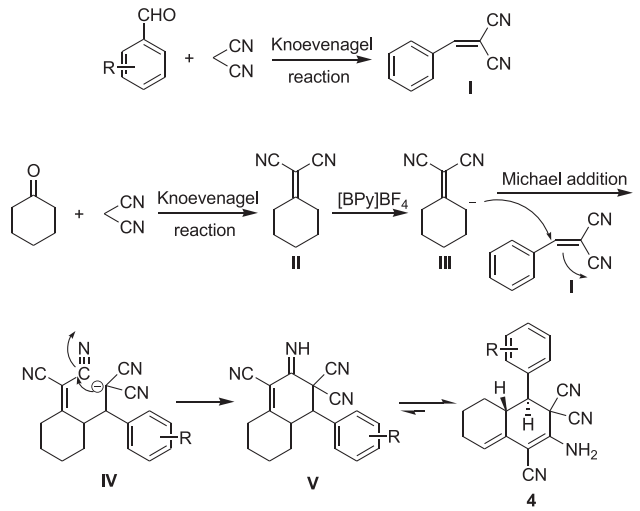
Table 2

Synthesis of **4** under optimum different conditions.[a]

Entry	R	Products	Time/h	Yield/%[b]	Mp/°C	
					Found	Report
1	4-Cl	**4a**	4	89	248–250	
2	4-Br	**4b**	4	87	265–268	273–274[12]
3	4-I	**4c**	4	91	212–214	
4	H	**4d**	5	83	255–257	254–255[11]
5	4-CN	**4e**	4	92	239–241	270–272[13]
6	4-F	**4f**	4	85	265–267	261–263[12]
7	3-Br	**4g**	5	88	250–253	
8	3-F	**4h**	5	82	260–262	
9	3,4,5-$(CH_3O)_3$	**4i**	4	83	234–236	
10	4-CH_3O	**4j**	4	89	261–262	
11	2-Br	**4k**	5	87	245–248	
12	3,4-$(CH_3O)_2$	**4l**	5	85	254–255	265–268[13]
13	2,4-$(Cl)_2$	**4m**	5	84	257–260	
14	2-Cl	**4n**	5	89	271–272	
15	2-CH_3O	**4o**	5	88	264–265	

[a]All reactions were performed in 2 mL $[BPy]BF_4$, **2** (2.0 mmol) and **3** (1.0 mmol) at 60°C.
[b]Isolated yields.

Scheme 2



2-amino-4a,5,6,7-tetrahydro-4-(4-iodophenyl)naphthalene-1,3,3 (4H)-tricarbonitrile (4c). Melting point 268–269°C; IR (KBr) *v*: 3425, 3345, 3250, 3005, 2922, 2863, 2830, 2209, 1645, 1597, 1485, 1447, 1431, 1407, 1392, 1349, 1302, 1277, 1211, 1162, 1102, 1041, 1007, 953, 917, 864, 831, 804, 779, and 750 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.80–0.90 (m, 1H, CH_2), 1.41–1.49 (m, 2H, CH_2), 1.65–1.71 (m, 1H, CH_2), 2.09–2.23 (m, 2H, CH_2), 2.75–2.82 (m, 1H, CH_2), 3.60 (d, J = 12.4 Hz, 1H, CH), 5.72 (s, 1H, CH=), 7.23 (d, J = 8.0 Hz, 1H, ArH), 7.39–7.41 (m, 3H, NH_2 + ArH) and 7.82–7.88 (m, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.3, 137.4, 134.4, 131.1, 128.6, 120.5, 116.1, 112.4, 112.2, 95.7, 81.6, 49.9, 42.6, 33.6, 26.9, 24.8, and 20.9; HRMS: Calcd for $C_{19}H_{15}IN_4$ $[M + Na]^+$ found (expected): 449.0263 (449.0239).

2-amino-4-(3-bromophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3 (4H)-tricarbonitrile (4g). Melting point 250–253°C; IR (KBr) *v*: 3447, 3357, 3204, 3035, 2948, 2918, 2854, 2840, 2217, 1632, 1619, 1594, 1568, 1473, 1433, 1390, 1269, 1212, 1201, 1164, 1097, 1023, 950, 922, 868, 813, 777, 746, and 686 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.82–0.92 (m, 1H, CH_2), 1.40–1.54 (m, 2H, CH_2), 1.66–1.70 (m, 1H, CH_2), 1.99–2.06 (m, 1H, CH_2), 2.17–2.23 (m, 1H, CH_2), 2.81–2.84 (m, 1H, CH_2), 3.65 (d, J = 12.8 Hz, 1H, CH), 5.73 (s, 1H, CH=), 7.41 (s, 2H, NH_2), 7.45–7.50 (m, 1H, ArH), and 762–7.79 (m, 3H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.3, 137.4, 134.7, 130.7, 128.5, 126.2, 120.5, 116.1, 112.7, 112.3, 112.2, 81.6, 49.9, 42.6, 33.7, 26.9, 24.8, and 20.9; HRMS: Calcd for $C_{19}H_{15}BrN_4$ $[M + H]^+$ found (expected): 379.0543 (379.0559).

2-amino-4-(3-fluorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (4h). Melting point 273–275°C; IR (KBr) *v*: 3420, 3341, 3255, 3232, 3031, 2935, 2866, 2830, 2211, 1650, 1601, 1498, 1454, 1430, 1392, 1350, 1339, 1274, 1212, 1160, 1103, 1038, 954, 882, 866, 838, 808, 787, 731, 714, and 698 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.80–0.90 (m, 1H, CH_2), 1.40–1.51 (m, 2H, CH_2), 1.66–1.70 (m, 1H, CH_2), 2.00–2.21 (m, 2H, CH_2), 2.78–2.84 (m, 1H, CH_2), 3.54 (d, J = 12.8 Hz, 1H, CH), 5.73 (s, 1H, CH═), 7.38 (s, 2H, NH_2), 7.43 (s, 2H, ArH), and 7.49–7.61 (m, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.3, 128.6, 123.1, 120.5, 116.1, 112.4, 112.2, 81.6, 49.9, 42.6, 33.5, 26.9, 24.8, and 20.9.

2-amino-4a,5,6,7-tetrahydro-4-(3,4,5-trimethoxyphenyl) naphthalene-1,3,3(4H)-tricarbonitrile (4i). Melting point 245–256°C; IR (KBr) *v*: 3447, 3358, 3253, 3005, 2939, 2872, 2836, 2201, 1640, 1593, 1509, 1469, 1456, 1429, 1349, 1334, 1306, 1275, 1253, 1130, 1008, 967, 845, 804, 756, and 698 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.85–0.95 (m, 1H, CH_2), 1.47–1.59 (m, 2H, CH_2), 1.68–1.72 (m, 1H, CH_2), 2.01–2.23 (m, 2H, CH_2), 2.78–2.85 (m, 1H, CH_2), 3.45 (d, J = 12.4 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.73 (s, 1H, CH), 6.83 (s, 1H, ArH), 6.89 (s, 1H, ArH), and 7.34 (s, 2H, NH_2); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 153.1, 152.4, 143.6, 137.8, 130.2, 128.9, 120.3, 116.2, 112.9, 112.4, 104.2, 81.5, 60.1, 56.0, 51.1, 42.9, 34.0, 26.9, 24.9, and 21.0; HRMS: Calcd for $C_{22}H_{22}N_4O_3$ $[M+H]^+$ found (expected): 391.1822 (391.1771).

2-amino-4a,5,6,7-tetrahydro-4-(4-dimethoxyphenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4j). Melting point 261–262°C; IR (KBr) *v*: 3420, 3341, 3252, 3015, 2947, 2868, 2832, 2213, 1650, 1599, 1516, 1474, 1458, 1431, 1391, 1339, 1309, 1287, 1255, 1213, 1181, 1120, 1029, 953, 917, 882, 839, 806, 795, 765, and 729 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.79–0.89 (m, 1H, CH_2), 1.44–1.50 (m, 2H, CH_2), 1.66–1.70 (m, 1H, CH_2), 2.04–2.22 (m, 2H, CH_2), 2.72–2.79 (m, 1H, CH_2), 3.47 (d, J = 12.4 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 5.71 (s, 1H, CH═), 6.96–7.07 (m, 2H, ArH), 7.35(s, 3H, NH_2 + ArH), and 7.50 (d, J = 8.0 Hz, 1H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 159.5, 155.5, 143.6, 133.6, 129.0, 126.4, 120.2, 118.6, 115.4, 112.6, 112.5, 81.6, 55.1, 50.0, 43.2, 34.0, 27.0, 24.9, 21.0; HRMS: Calcd for $C_{20}H_{18}N_4O$ $[M+H]^+$ found (expected): 331.1506 (331.1560).

2-amino-4-(2-bromophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3 (4H)-tricarbonitrile (4k). Melting point 294–296°C; IR (KBr) *v*: 3425, 3346, 3251, 3224, 3005, 2922, 2863, 2830, 2209, 1645, 1603, 1486, 1447, 1431, 1407, 1392, 1349, 1302, 1277, 1211, 1162, 1121, 1062, 1041, 1007, 953, 917, 831, 804, 779, and 750 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.77–0.87 (m, 1H, CH_2), 1.34–1.46 (m, 2H, CH_2), 1.65–1.69 (m, 1H, CH_2), 2.09–2.21 (m, 2H, CH_2), 2.85–2.91 (m, 1H, CH_2), 3.87 (d, J = 12.4 Hz, 1H, CH), 5.77 (s, 1H, CH═), 7.41–7.43 (m, 1H, ArH), 7.47 (s, 2H, NH_2), 7.58 (t, J = 7.6 Hz, 1H, ArH), and 7.75–7.81 (m, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.5, 133.5, 133.4, 130.9, 129.2, 128.5, 128.4, 126.5, 120.9, 115.9, 112.2, 111.5, 81.5, 49.3, 41.6, 34.7, 26.8, 24.7, and 20.8; HRMS: Calcd for $C_{19}H_{15}BrN_4$ $[M+H]^+$ found (expected): 379.0594 (379.0559).

2-amino-4-(2,4-dichlorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (4m). Melting point 280–282°C; IR (KBr) *v*: 3448, 3361, 3072, 3032, 2949, 2921, 2861, 2836, 2217, 1632, 1592, 1561, 1470, 1453, 1433, 1389, 1350, 1301, 1269, 1211, 1197, 1167, 1099, 1045, 971, 952, 907, 885, 846, 824, 812, 794, and 763 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.77–0.86 (m, 1H, CH_2), 1.35–1.53 (m, 2H, CH_2), 1.66–1.70 (m, 1H, CH_2), 2.09–2.23 (m, 2H, CH_2), 2.84–2.97 (m, 1H, CH_2), 3.88 (d, J = 12.4 Hz, 1H, CH), 5.77 (s, 1H, CH═), 7.46 (s, 2H, NH_2), and 7.58–7.87 (m, 3H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.0, 134.6, 133.9, 132.6, 131.7, 129.6, 129.2, 128.1, 121.1, 115.9, 112.0, 111.4, 81.6, 46.5, 41.4, 34.1, 26.7, 24.7, and 20.7; HRMS: Calcd for $C_{19}H_{14}Cl_2N_4$ $[M+Na]^+$ found (expected): 391.0522 (391.0494).

2-amino-4-(2-chlorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3 (4H)-tricarbonitrile (4n). Melting point 281–283°C; IR (KBr) *v*: 3448, 3358, 3204, 3073, 2949, 2921, 2856, 2839, 2217, 1632, 1597, 1478, 1447, 1434, 1391, 1340, 1270, 1243, 1212, 1201, 1165, 1056, 1041, 951, 813, 776, and 749 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.77–0.87 (m, 1H, CH_2), 1.35–1.50 (m, 2H, CH_2), 1.65–1.69 (m, 1H, CH_2), 2.04–2.22 (m, 2H, CH_2), 2.84–2.89 (m, 1H, CH_2), 3.89 (d, J = 12.4 Hz, 1H, CH), 5.77 (s, 1H, CH═), 7.45 (s, 2H, NH_2), 7.47–7.54 (m, 2H, ArH), 7.63 (d, J = 8.0 Hz, 1H, ArH), and 7.78 (d, J = 7.6 Hz, 1H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.4, 135.1, 131.8, 130.6, 130.1, 129.1, 128.4, 127.8, 120.9, 115.9, 112.2, 111.5, 81.5, 46.5, 41.6, 34.5, 26.7, 24.7, and 20.8; HRMS: Calcd for $C_{19}H_{15}ClN_4$ $[M+H]^+$ found (expected): 335.1059 (335.1064).

2-amino-4a,5,6,7-tetrahydro-4-(2-methoxyphenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4o). Melting point 280–282°C; IR (KBr) *v*: 3418, 3341, 3258, 3235, 2941, 2924, 2859, 2832, 2211, 1650, 1604, 1569, 1477, 1454, 1429, 1394, 1337, 1299, 1279, 1212, 1159, 1091, 1077, 1038, 996, 888, 846, 796, 745, and 687 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 0.72–0.81 (m, 1H, CH_2), 1.38–1.52 (m, 2H, CH_2), 1.64–1.68 (m, 1H, CH_2), 2.02–2.20 (m, 2H, CH_2), 2.73–2.80 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 3.85 (d, J = 12.4 Hz, 1H, CH), 5.73 (s, 1H, CH═), 7.07–7.15 (m, 2H, ArH), 7.37(s, 2H, NH_2), 7.40–7.44 (m, 1H, ArH), and 7.53 (d, J = 7.2 Hz, 1H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 157.8, 143.8, 130.1, 128.0, 122.2, 120.6, 120.6, 116.0, 112.6, 112.0, 111.8, 81.5, 55.8, 42.3, 42.0, 33.9, 26.8, 24.8, and 20.9; HRMS: Calcd for $C_{20}H_{18}N_4O$ $[M+H]^+$ found (expected): 331.1582 (331.1560).

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REFERENCES AND NOTES

[1] (a) Schreiber, S. L. Science 2000, 287, 1964; (b) Lieby-Muller, F.; Constantieux, T.; Rodriguez, J. J Am Chem Soc 2005, 127, 17176; (c) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. J Am Chem Soc 2009, 131, 1753.

[2] For step economy, see: (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. Pure Appl Chem 2002, 74, 25; (b) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. Pure Appl Chem 2003, 75, 143; (c) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. J Am Chem Soc 2005, 127, 2836.

[3] For atom economy, see: (a) Trost, B. M. Science 1991, 254, 1471; (b) Trost, B. M. Angew Chem Int Ed Engl 1995, 34, 259; (c) Trost, B. M. Acc Chem Res 2002, 35, 695.

[4] For a special issue on environmental chemistry, see: Grissom, C. B. Chem Rev 1995, 95, 3.

[5] For asymmetric catalytic domino reactions, see: (a) Tietze, L. F.; Brazel, C. C.; Holsken, S.; Magull, J.; Ringe, A. Angew Chem Int Ed 2008, 47, 5246; (b) Huang, Y.; Waljji, A. M.; Larsen, C. H.; MacMillan, D. W. C. J Am Chem Soc 2005, 127, 15051; (c) Yang, J. W.; Fonseca, H. M. T.; List, B. J Am Chem Soc 2005, 127, 15036; (d) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raab, G. Nature 2006, 441, 861; (e) Lu, M.; Zhu, D.; Lu, Y.; Hou, B.; Tan, B.; Zhong, G. Angew Chem Int Ed 2008, 47, 10187.

[6] (a) Jiang, B.; Tu, S. J.; Kaur, P.; Wever, W.; Li, G. G. J Am Chem Soc, 2009, 131, 11660; (b) Jiang, B.; Li, C.; Shi, F.; Tu, S. J.; Kaur, P.; Wever, W.; Li, G. G. J Org Chem, 2010, 75, 2962; (c) Ivanov, A. S. Chem Soc Rev, 2008, 37, 789; (d) Padwa, A. Chem Soc Rev 2009, 38, 3072; (e) Padwa, A.; Bur, S. K. Tetrahedron 2007, 63, 5341.

[7] (a) Welton, T. Chem Rev 1999, 99, 2071; (b) Wasserscheid, P.; Keim, W. Angew Chem Int Ed 2000, 39, 3772; (c) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. Chem Rev 2002, 102, 3667; (d) Jain, N.; Kumar, A.; Chauhan, S.; Chausan, S. M. S. Tetrahedron 2005, 61, 1015.

[8] (a) Wu, H.; Zhang, P.; Shen, Y.; Zhang, F. R.; Wan, Y.; Shi, D. Q. Synlett 2007, 18, 336; (b) Wu, H.; Wan, Y.; Lu, L. L.; Shen, Y.; Ye, L.; Zhang, F. R. Synthetic Commun 2008, 35, 666; (c) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A. C.; Plaquevent, J. C. Tetrahedron: Asymmetry 2003, 14, 3081.

[9] Taylor, E. C.; Mckillop, A. Adv Org Chem 1970, 7, 415.

[10] El-Sakka, I. A.; El-Kousy, S. M.; Kandil, Z. E. J Praktische Chemie (Leipzig) 1991, 333, 345.

[11] Kurbatov E. S.; Krasnikov V. V.; Mezheritskii V. V. Russ J Org Chem 2006, 42, 460.

[12] Al-Matar, H. M.; Khalil, K. D.; Meier, H.; Kolshorn, H.; Elnagdi, M. H. ARKIVOC 2008, (xvi), 288.

[13] Wang, X. S.; Wu, J. R.; Zhou, J.; Tu, S. J. J Comb Chem 2009, 11, 1011.

[14] Wang, J. F.; Li, Q.; Qi, C.; Liu, Y.; Ge, Z.; Li, R. Org Biomol Chem 2010, 8, 4240.

[15] (a) Freeman, F. Chem Rev 1969, 69, 591; (b) Fatiadi, A. J. Synthesis 1978, 10, 165; (c) Fatiadi, A. J. Synthesis 1978, 10, (4), 241.

[16] (a) Ohashi, M.; Nakatani, K.; Maeda, H.; Mizuno, K. Org Lett 2008, 10, 2741; (b) Alberola, A.; Calvo, L. A.; Ortega, A. G.; Sanudo-Ruiz, M. C.; Yustos, P.; Granda, S. G.; Garcia-Rodriguez, E. J Org Chem 1999, 64, 9493; (c) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. Org Lett 2006, 8, 899.