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OPPI BRIEF

Facile and Efficient Synthesis of Bicyclic *ortho*-Aminocarbonitrile Derivatives Using Nanostructured Diphosphate $Na_2CaP_2O_7$

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One of the most helpful strategies for the synthesis of the title compounds[1] is that of multicomponent reactions (MCRs). In MCRs three or more reactants form products such that all or most of the initial atoms are present in the final product. This has clear benefits in terms of cost, efficiency and environmental stewardship.[2–4] There are some literature methods for the synthesis of *ortho*-aminocarbonitrile derivatives, and these include using such reagents as *N*-butylpyridinium tetrafluoroborate $[BPy]BF_4$,[5] ammonium acetate,[6] imidazole,[7] ethanediamine,[8] β-1-imidazol-2,3,4,6-tetraacetyl-D-glucopyranosyl bromide ($[Bmim\text{-}G]^+[Br]^-$),[9] *ortho*-benzenedisulfonimide (OBS) or triethylammonium acetate (TEAA),[10] and 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIm][BF_4]$)[11] as catalysts. Although all of the above synthetic methods have advantages, they also suffer from some limitations such as long reaction times, low yields, and extensive work-up. We would now like to report our method for the synthesis of *ortho*-aminocarbonitrile derivatives by condensation of aldehydes (1 equiv.) and malononitrile (2 equiv.) with cyclohexanone (1 equiv) utilizing the nanostructured diphosphate $Na_2CaP_2O_7$[12–18] as catalyst (Scheme 1).

This was done in continuation of our previous studies.[19–31] In order to obtain the best conditions for our reaction, we optimized the parameters as listed in Table 1. We found that the best conditions for this reaction constituted reflux in ethanol in the presence of 30 mol% of nanostructured diphosphate $Na_2CaP_2O_7$. To illustrate the effect of nanostructured diphosphate $Na_2CaP_2O_7$ in promoting the formation of the bicyclic *ortho*-aminocarbonitriles, the model reaction was performed under the optimized reaction conditions but in the absence of catalyst. No significant product formation was observed even after 240 min (Entry 7).

In order to explore the extent of this reaction, we investigated the use of several aldehydes as substrates. Moreover, the scope and efficiency of the reaction were explored for cyclopentanone (entries **4l-4m**). The results are listed in Table 2.

The recyclability of the nanocatalyst in the reaction among benzaldehyde, malononitrile and cyclohexanone was evaluated in the presence of 30 mol % nanocatalyst. After

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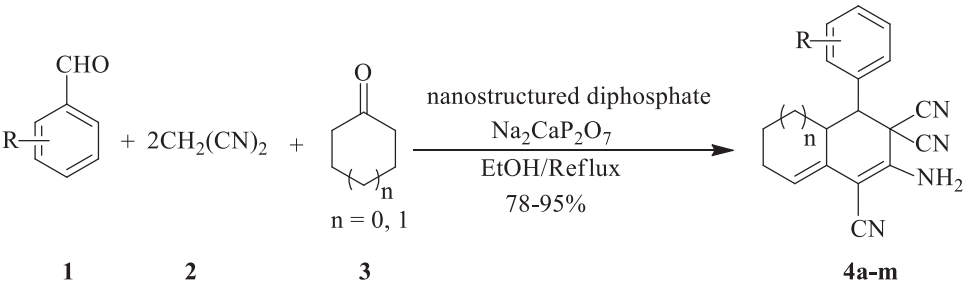
Supplemental data for this article can be accessed here.



Scheme 1. Synthesis of bicyclic *ortho*-aminocarbonitrile derivatives.

Table 1. Optimizing reaction conditions.[a]

Entry	Amount of $Na_2CaP_2O_7$ (mol %)	Conditions	Time (h)	Temperature (°C)	Yield (%)
1	30	Reflux/EtOH	4	80	92
2	30	Reflux/H_2O	4	100	70
3	30	Reflux/MeOH	4	65	68
4	30	Solvent-free	5	80	55
5	20	Solvent-free	6.5	80	45
6	20	Reflux/EtOH	6	80	82
7	-[b]	Reflux/EtOH	4	80	-[c]

[a]Reaction conditions: benzaldehyde (1 mmol), malononitrile (0.14 g, 2 mmol) and cyclohexanone (1 mmol) in 5 ml ethanol.
[b]In the absence of catalyst.
[c]No product **4a** observed.

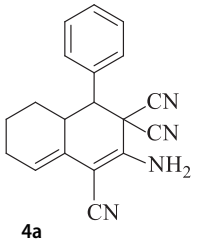
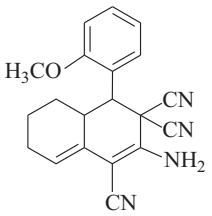
Table 2. Synthesis of bicyclic *ortho*-aminocarbonitrile derivatives.

					mp (°C)	
Entry	Products (4a-m)	n	Yield[a] (%)	Time (min)	Found	Lit.
4a	R = 4H	1	92	240	255-257	255-257[5]
4b	R = 4-Br	1	89	300	264-266	265-268[5]
4c	R = 2-Cl	1	84	420	266-268	271-272[5]
4d	R = 4-Cl	1	78	300	251-253	248-250[5]
4e	R = 2,4-Cl	1	88	360	261-263	257-260[5]
4f	R = 4-OMe	1	90	390	254-256	261-262[5]
4g	R = 2-OMe	1	95	360	262-264	264-265[5]
4h	R = 3,4-OMe	1	80	420	251-253	254-255[5]
4i	R = 4-NO_2	1	90	390	265-267	264-266[10]
4j	R = 2-Br	1	83	320	239-241	245-248[5]
4k	R = 4-F	1	89	300	262-264	265-267[5]
4l	R = 4-OMe	0	90	420	214-216	215-217[11]
4m	R = 4-F	0	90	360	220-222	219-221[11]

completing the reaction, the catalyst was separated from the reaction mixture easily by filtration and washed with acetone, calcinated at 500 °C for 1h and re-used in the same reaction. The nanocatalyst could be re-used at least 6 times without significant loss in activity.

In order to demonstrate the effectiveness of the present method in comparison with previously reported results in the literature, we have compared some of the results for the preparation of bicyclic *ortho*-aminocarbonitrile derivatives in Table 3. They show that nanostructured diphosphate $Na_2CaP_2O_7$ is the most efficient catalyst with respect to the reaction time and yields of the products.

Table 3. Comparison of methods.

Compounds	Conditions	Time (min)	Yield (%)
 **4a**	Present work	240	92
	$[BPy]BF_4$/solvent-free/60 ^0C[5]	300	83
	Ammonium acetate/EtOH-H_2O/50-60 ^0C[6]	120	90
	Ethanediamine/MeOH/rt[8]	1440	86
	$[Bmim\text{-}G]^+[Br]^-$/solvent-free/rt[9]	240	83
	OBS/EtOH/reflux[10]	360	93
 **4g**	Present work	360	95
	$[BPy]BF_4$/solvent-free/60 ^0C[5]	300	87
	Ammonium acetate/EtOH-H_2O/50-60 ^0C[6]	120	92
	$[Bmim\text{-}G]^+[Br]^-$/solvent-free/rt[9]	300	89
	OBS/EtOH/reflux[10]	360	86

In conclusion, a facile, efficient, multicomponent reaction is presented for the synthesis of the title compounds in the presence of nanostructured diphosphate $Na_2CaP_2O_7$. The main benefits include use of a catalyst that is known to be safe and non-volatile, affordable, easy to separate and convenient to recycle.

Experimental section

All reagents were obtained from commercial sources. ^1H and ^{13}C NMR spectra were determined on a Bruker DRX-400 Avance spectrometer in $CDCl_3$ or DMSO-d_6, and shifts are given in ppm downfield from tetramethylsilane (TMS) as an internal standard. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. Melting points were determined by an Electrothermal 9200 apparatus and are uncorrected. The catalyst was prepared according to the method previously described.[14] Data on the recycling experiments are available from the corresponding author upon request.

General procedure for the synthesis of compounds 4a-k using nanostructured diphosphate $NaCaP_2O_7$

$Na_2CaP_2O_7$ was added to a mixture of the aldehyde (1 mmol), malononitrile (0.14 g, 2 mmol) and cyclohexanone (1 mmol) in a 10 mL flask; ethanol (2 mL) was added and the mixture was brought to reflux using an oil bath for heating. The progress of reaction was controlled by TLC (silica gel; hexane-ethyl acetate, 4:1). After completing the reaction, 2 ml acetone was added to the reaction mixture. After stirring (1 min), the nanocatalyst was easily filtered off. The filtered reaction mixture was poured onto crushed ice to precipitate the product, which was filtered off and dried to give pure material.

Spectroscopic data of representative compounds

2-Amino-4a,5,6,7-tetrahydro-4-phenyl-4H-naphthalene-1,3,3-tricarbonitrile (4a)

IR (KBr): 3417, 3342, 3240, 2927, 2869, 2202, 1605, 1600, 1442, 1407, 1272, 1097, 879 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.84-0.90 (m, 1H, CH), 1.45-1.48 (m, 2H, CH_2), 1.67-1.73 (m, 1H, CH), 2.02-2.08 (m, 1H), 2.17-2.21 (m, 1H), 2.73-2.89 (m, 1H), 3.53 (d, 1H), 5.73 (s, 1H), 7.35 (s, 2H), 7.43-7.59 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.96, 24.83, 26.97, 33.84, 42.82, 50.55, 81.57, 112.32, 112.52, 116.11, 120.34, 128.56, 128.81, 128.90, 134.59, 143.52.

Anal. Calcd. for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.61. Found: C, 75.89; H, 5.48; N, 18.99.

2-Amino-4a,5,6,7-tetrahydro-4-(4-bromophenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4b)

IR (KBr): 3419, 3343, 3234, 2920, 2856, 2200, 1641, 1589, 1492, 1483, 1407, 1263, 1074, 1010, 819 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.80-0.90 (m, 1H), 1.44-1.47 (m, 2H), 1.67-1.69 (m, 1H), 2.06-2.21 (m, 2H), 2.73-2.80 (m, 1H), 3.62 (d, 1H), 5.73 (s, 1H), 7.27-7.33 (m, 2H), 7.38 (s, 2H), 7.49 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.88, 24.78, 26.76, 33.83, 42.23, 55.79, 81.47, 111.78, 112.56, 116.03, 120.55, 120.59, 122.15, 128.03, 130.05, 243.76, 157.75.

Anal. Calcd. for $C_{19}H_{15}BrN_4$: C, 60.17; H, 3.99; N, 14.77. Found: C, 60.44; H, 4.15; N, 15.03.

2-Amino-4a,5,6,7-tetrahydro-4-(2-chlorophenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4c)

IR (KBr): 3440, 3353, 3186, 2943, 2844, 2210, 1625, 1465, 1438, 1388, 1478, 1271, 1035, 776, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.78-0.87 (m, 1H), 1.36-1.46 (m, 2H), 1.66-1.69 (m, 1H), 2.04-2.21 (m, 2H), 2.86-2.89 (m, 1H), 3.89 (d, 1H), 5.77 (s, 1H), 7.42 (s, 2H), 7.48-7.54 (m, 2H), 7.63 (d, 1H), 7.77 (d, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.79, 24.72, 26.09, 34.51, 41.61, 46.45, 81.52, 111.53, 112.22, 115.93, 120.88, 127.84, 128.36, 129.15, 130.13, 130.59, 131.78, 135.10, 143.41.

2-Amino-4a,5,6,7-tetrahydro-4-(2,4-dichlorophenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4e)

IR (KBr): 3440, 3357, 2941, 2916, 2206, 1623, 1589, 1471, 1384, 1265, 1103, 813, 815 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.78-0.87 (m, 1H), 1.39-1.47 (m, 2H), 1.67-1.70 (m, 1H), 2.09-2.22 (m, 2H), 2.87-2.94 (m, 1H), 3.88 (d, 1H), 5.77 (s, 1H), 7.45 (s, 2H), 7.59-7.86 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.67, 24.69, 26.66, 34.07, 41.46, 46.51, 81.62, 111.40, 111.98, 115.88, 121.06, 128.13, 129.08, 129.63, 131.70, 132.55, 133.85, 134.59, 143.03.

2-Amino-4a,5,6,7-tetrahydro-4-(3,4-dimethoxyphenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4h)

IR (KBr): 3434, 3330, 3226, 2943, 2831, 2208, 1650, 1595, 1508, 1463, 1259, 1143, 1018, 815, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.85-0.88 (m, 1H), 1.50-1.53 (m, 2H), 1.67-1.69 (m, 1H), 2.01-2.20 (m, 2H), 2.73-2.88 (m, 1H), 3.43 (t, 1H), 3.73-3.78 (d, 6H), 5.72 (s, 1H), 6.96 (s, 1H), 7.09-7.14 (m, 2H), 7.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.99, 24.85, 26.91, 30.71, 35.71, 43.05, 50.38, 50.84, 55.58, 81.59, 110.30, 11.26, 111.90, 112.47, 116.15, 119.22, 120.26, 124.66, 126.85, 128.93, 143.53, 162.25.

2-Amino-4a,5,6,7-tetrahydro-4-(4-nitrophenyl)naphthalene-1,3,3(4H)-tricarbonitrile (4i)

IR (KBr): 3429, 3350, 3222, 2931, 2842, 2202, 1637, 1600, 1514, 1342, 1274, 862, 721 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.81-0.90 (m, 1H), 1.39-1.48 (m, 2H), 1.66-1.70 (m, 1H), 2.08-2.22 (m, 2H), 2.87-2.89 (m, 1H), 3.80 (d, 1H), 5.75 (s, 1H), 7.40 (s, 2H), 7.66 (s, 1H), 7.83 (s, 1H), 7.97-7.99 (m, 2H).

5-Amino-1,2,7,7a-tetrahydro-7-(4-methoxyphenyl)indene-4,6,6-tricarbonitrile (4l)

IR (KBr): 3423, 3332, 3242, 2968, 2936, 2846, 2208, 1650, 1612, 1585, 1452, 1393, 1275, 1020, 841, 803, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26-1.34 (m, 1H), 2.02-2.09 (m, 1H), 2.43-2.48 (m, 2H), 3.14 (d, 1H), 3.35-3.43 (m, 1H), 3.84 (s, 3H), 5.07 (s, 2H), 5.83 (d, 1H), 6.89 (d, 2H), 7.40 (d, 2H).

5-Amino-1,2,7,7a-tetrahydro-7-(4-fluorophenyl)indene-4,6,6-tricarbonitrile (4m)

IR (KBr): 3420, 3336, 3244, 2948, 2850, 2210, 1650, 1610, 1590, 1458, 1310, 1281, 1010, 844, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23-1.36 (m, 1H), 2.01-2.08 (m, 1H), 2.40-2.49 (m, 2H), 3.18 (d, 1H), 3.36-3.43 (m, 1H), 5.09 (s, 2H), 5.85 (d, 1H), 7.15(d, 2H), 7.45 (d, 2H).

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