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One-pot, three-component synthesis of highly substituted pyridines and 1,4-dihydropyridines by using nanocrystalline magnesium oxide

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Abstract. One pot, three component synthesis of 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydropyridines are from readily accessible starting materials is described. Simply heating of an ethanolic solution of structurally diverse aldehydes with various thiols and malononitrile in the presence of nanocrystalline magnesium oxide provides the highly substituted pyridine derivatives in moderate to high yields, each representing a privileged medicinal scaffold with their structural motif. After completion of the reaction, the catalyst can be recovered efficiently and reused with constintent activity.

Keywords. Multicomponent reactions (MCRs); pyridines; 1,4-dihydropyridines; aldehydes; thiols; malononitrile; nanocrystalline magnesium oxide.

1. Introduction

One-pot multicomponent coupling reactions (MCRs), where several organic moieties are coupled in one step, for carbon-carbon and carbon–heteroatom bond formation is an attractive synthetic strategy for the synthesis of small–molecule libraries with several degrees of structural diversities.[1] The pyridine moiety has been found in a wide variety of both naturally occurring and synthetic bioactive compounds, and are often with considerable complexity.[2] The highly substituted pyridine derivatives, like 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines have significant and diverse medicinal utility. Essentially, these compounds serve as high-potency agonists for the human adenosine receptors and act as potential therapeutic agents for the treatment of Creutzfeldt–Jacob disease, Parkinson's disease, hypoxia, asthma, cancer, kidney disease and prion disease.[3] In addition, they serve as potassium channel openers with applications in treating urinary incontinence and exhibit anti-bacterial, anti-biofilm and anti-infective properties.[4]

Thus, the synthesis of highly substituted pyridine derivatives has attracted much attension, and a number of methods have been developed to prepare these compounds using a variety of protocols. Those include Vilsmeier reactions of tertiary alcohols,[5] Diels–Alder reactions of 3-siloxy-1-aza-1,3-butadienes and 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones with different types of acetylenic compounds,[6] Ni/Ru-catalysed cycloadditions of alkynes and nitriles,[7] [4 + 2] cycloadditions of oximinosulfonates,[8] reaction of imines with enamines or carbonyl compounds,[9] condensation of α,β-unsaturated esters or nitriles with thiols,[10] and transformation of ketene dithioacetals to pyridine derivatives.[11]

A few MCR methods are also reported for synthesis of diverse substituted pyridines, such as three-component condensations of aldehyde, malononitrile and thiol using various bases Et_3N, DABCO[12] and basic ionic liquid [bmIm]OH,[13] and microwave irradiation of aldehyde, β-ketoester and ammonium nitrate using bentonite clay.[14] One-pot, three-component condensation of aldehydes, *o*-picolylamines and isocyanides produced the 1H-imidazol-4-yl-pyridines in the presence of Lewis acid in methanol.[15] Recently Zhu *et al* reported the one-pot MCRs of aromatic aldehydes, 3-cyanoacetyl indoles and ammonium acetate under microwave irradiation in the synthesis of *bis*(3′-indolyl)pyridine derivatives.[16]

Nanocrystalline metal oxides have found excellent applications as active adsorbents for gases, for destruction of hazardous chemicals,[17] and as catalysts for various organic transformations.[18] Their high reactivity is due to high surface areas combined

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with unusually reactive morphologies. In continuation of our work on the application of nanomaterials in organic methodologies, here we report an effective three-component condensation of aldehydes, malononitrile and thiols to afford 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines **P** and the corresponding 1,4-dihydropyridines **DP** in moderate to high yields by using nanocrystalline magnesium oxide (NAP-MgO) catalyst (schemes 1 and 2).

2. Experimental

2.1 *General remarks*

Nanocrystalline MgO samples were obtained from NanoScale Materials Inc., (formally Nantek, Inc.) Manhattan, Kansas, USA. All catalysts were calcined at 400°C for 4 h before use. All chemicals were purchased from Aldrich Chemicals or S.D Fine Chemicals Pvt. Ltd. India, and used as received. ACME silica gel (60–120 mesh) was used for column chromatography, while thin layer chromatography was performed on Merck make precoated silica gel 60-F_{254} plates. Melting points were measured in open capillary tubes and are uncorrected. The IR spectra of all compounds were recorded with a NEXUS 670 FTIR spectrometer (Necolet Corporation Ltd, USA) using KBr pellet method. The IR values are reported in reciprocal centimeters (cm^{-1}). The ^1H, ^{13}C NMR spectra were recorded in DMSO-d_6 with a Varian-Gemini 200 MHz or Bruker-Avance 300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), using TMS ($\delta = 0$) as an internal standard. The mass spectra were recorded with a QSTAR XL high resolution mass spectrometer (Applied Biosystems, Foster city, USA).

2.2 *Typical procedure for the synthesis of pyridines and 1,4-dihydropyridines*

To a stirred solution of the aldehyde (1·0 mmol) and malononitrile (2·1 mmol) in 5 ml of ethanol, was added NAP–MgO (0·1 g) at room temperature. The resulting mixture was heated to 50°C, the thiol (1·1 mmol) was added and the reaction mixture was refluxed. After completion of the reaction (monitored by TLC), the mixture was brought to room temperature, centrifuged to separate the catalyst and the catalyst was washed with ethyl acetate (3 × 5 mL). The centrifugate was concentrated under reduced pressure to afford the crude product, which after chromatography on silica gel (60–120 mesh) using hexane/ethyl acetate in varying proportions as eluent afforded the respective pyridine or 1,4-dihydropyridine. The products were characterized on the basis of spectral data and the data of known products were also compared with the literature data.[12,13] The physical and spectral data of the new products are given below.

2.2a *2-Amino-4-furan-2-yl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile* (**P9**): Yellow solid; Melting point 190–192°C; IR (KBr): 3410, 3319, 3215, 2213, 1626, 1578, 1538, 1515, 1477, 1265, 749, 687 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 6·71 (*t*, J = 3·8 Hz, 1H), 6·91 (*s*, *br*, 2H), 7·43–7·58 (*m*, 6H), 7·82 (*s*, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 82·7, 89·4, 112·8, 115·5, 115·6, 116·4, 127·1, 129·4, 129·6, 134·8, 143·9, 145·0, 146·5, 160·2, 167·3; Mass (ESI): *m/z* 341 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{17}H_{10}N_4ONaS$: 341·0473; Found: 341·0487.

2.2b *2-Amino-4-phenyl-6-para-tolylsulfanyl-pyridine-3,5-dicarbonitrile* (**P10**): Colourless solid; Melting point 246–249°C; IR (KBr): 3450, 3322, 3208, 2214, 1618, 1547, 1524, 1490, 1264, 808, 704 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2·43 (*s*, 3H), 6·58 (*s*, *br*, 2H), 7·24 (*d*, J = 8·2 Hz, 2H), 7·43 (*d*, J = 8·2 Hz, 2H), 7·51–7·58 (*m*, 5H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20·8, 86·9, 93·1, 114·9, 115·2, 123·4, 128·3, 128·6, 130·0, 130·2, 133·9, 134·8, 139·5, 158·5, 159·6, 166·5; Mass (ESI): *m/z* 365 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{20}H_{14}N_4NaS$: 365·0836; Found: 365.0848.

2.2c *2-Amino-4-(4-methoxy-phenyl)-6-para-tolylsulfanyl-pyridine-3,5-dicarbonitrile* (**P11**): Pale yellow solid; Melting point 230–233°C; IR (KBr) ν 3463, 3323, 3215, 2221, 1632, 1603, 1545, 1508, 1258, 1179, 1028, 811 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2·38 (*s*, 3H), 3·85 (*s*, 3H), 6·74 (*s*, *br*, 2H), 7·0 (*d*, J = 7·5 Hz, 2H), 7·19 (*d*, J = 8·2 Hz, 2H), 7·37 (*d*, J = 7·5 Hz, 2H), 7·43 (*d*, J = 8·2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20·9, 55·3, 86·8, 93·2, 113·8, 114·1, 115·3, 115·5, 123·5, 125·8, 128·1, 130·1, 130·2, 131·3, 134·9, 139·5, 158·3, 159·8, 160·8, 166·6; Mass (ESI): *m/z* 395 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{21}H_{16}N_4ONaS$: 395·0942; Found: 395·0944.

2.2d *2-Amino-6-(furan-2-ylmethylsulfanyl)-4-(4-methoxy-phenyl)-pyridine-3,5-dicarbonitrile* (**P15**): Pale yellow solid; Melting point 217–218°C; IR (KBr): 3459, 3324, 3209, 2363, 2214, 1616, 1541, 1506, 1459, 1247, 1170, 1016, 826, 743 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 3·88 (*s*, 3H), 4·51 (*s*, 2H), 6·29 (*t*, *J* = 2·2, 2·9 Hz, 1H), 6·44 (*d*, *J* = 2·9 Hz, 1H), 7·04 (*d*, *J* = 8·8 Hz, 2H), 7·37–7·62 (*m*, 5H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 25·9, 55·2, 85·9, 93·4, 108·9, 110·7, 113·6, 114·0, 115·3, 125·7, 130·1, 142·7, 149·8, 158·1, 159·6, 160·7, 165·4; Mass (ESI): *m/z* 369 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{19}H_{14}N_4ONaS$: 369·0786; Found: 369·0776.

2.2e *2-Amino-4-(2,6-dichloro-phenyl)-6-para-tolyl-sulfanyl-1,4-dihydro-pyridine-3,5-dicarbonitrile* (**DP3**): Colourless solid; Melting point 313–315°C; IR (KBr): 3443, 3353, 2204, 2168, 1643, 1487, 1246, 1035, 811, 772 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2·38 (*s*, 3H), 5·4 (*s*, *br*, 2H), 5·65 (*s*, 1H), 7·17–7·51 (*m*, 7H), 8·57 (*s*, *br*, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20·6, 34·8, 52·1, 86·9, 117·4, 119·7, 125·5, 128·6, 130·1, 130·4, 131·4, 135·1, 138·8, 143·4, 151·4; Mass (ESI): *m/z* 435 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{20}H_{14}N_4NaSCl_2$: 435·0213; Found: 435·0226.

2.2f *2-Amino-4-(2-chloro-6-fluoro-phenyl)-6-para-tolylsulfanyl-1,4-dihydro-pyridine-3,5-dicarbonitrile* (**DP6**): Yellow solid; Melting point 277–279°C; IR (KBr) ν 3465, 3362, 2205, 2169, 1643, 1599, 1488, 1449, 1243, 892, 778 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2·36 (*s*, 3H), 5·22 (*d*, *J* = 2·1 Hz, 1H), 5·4 (*s*, *br*, 2H), 6·98–7·53 (*m*, 7H), 8·65 (*s*, *br*, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20·6, 35·5, 52·4, 87·4, 115·2, 115·5, 117·6, 119·9, 126·1, 130·4, 130·8, 138·5, 142·9, 151·1; Mass (ESI): *m/z* 419 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{20}H_{14}N_4FNaSCl$: 419·0509; Found: 419·0518.

2.2g *2-Amino-4-(2,6-dimethoxy-phenyl)-6-para-tolylsulfanyl-pyridine-3,5-dicarbonitrile* (**P17**): Colourless solid; Melting point 202–203°C; IR (KBr) ν 3440, 3343, 3220, 2212, 2180, 1630, 1593, 1541, 1465, 1253, 1106, 1021, 768 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2·42 (*s*, 3H), 3·85 (*s*, 6H), 6·62 (*s*, *br*, 2H), 6·7 (*d*, *J* = 8·8 Hz, 2H), 7·24 (*d*, *J* = 8·1 Hz, 2H), 7·45 (*d*, *J* = 8·1 Hz, 2H), 7·66 (*s*, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20·8, 56·0, 88·8, 94·8, 104·5, 110·8, 114·7, 114·9, 123·2, 130·0, 132·2, 135·0, 139·5, 153·9, 156·6, 159·5, 165·8; Mass (ESI): *m/z* 425 $(M + Na)^+$; HRMS (ESI): Anal. Calcd. for $C_{22}H_{18}N_4O_2NaS$: 425·1048; Found: 425·1037.

3. Results and discussion

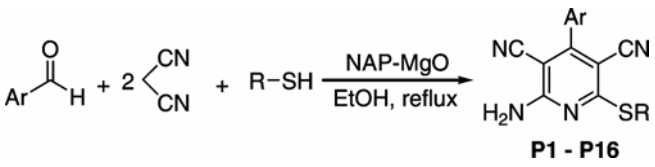
In order to understand the relationship between structure and reactivity, various forms of magnesium oxide crystals CM-MgO (commercial MgO, SSA: 30 m^2/g), NA–MgO (NanoActive MgO, conventionally prepared MgO, SSA: 250 m^2/g), NAP–MgO (NanoActive Plus MgO, aerogel prepared MgO, SSA: 590 m^2/g) were initially evaluated for the three-component condensation of benzaldehyde, malononitrile, and thiophenol at reflux temperature of ethanol. All these MgO crystals catalysed the reaction, but best result was obtained with NAP–MgO (table 1).

In order to investigate the scope of the above optimized protocol, a variety of structurally different aldehydes with different thiols and malononitrile were employed for the three component condensation and the results are depicted in tables 2 and 3. As summarized in table 2, for the synthesis of substituted pyridines, it was found that aromatic as well as heterocyclic aldehydes underwent this reaction to

Table 1. One-pot synthesis of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **P1** with various catalysts[a].

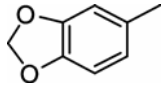
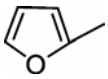
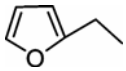
Entry	Catalyst	Time (h)	Yield (%)[b]
1	NAP–MgO	2, 2[c]	64, 58[c]
2	NA–MgO	4	59
3	CM–MgO	9	55
4	Sil–NAP–MgO	4	50
5	None	12	–

[a]Reaction conditions: Benzaldehyde (1·0 mmol), malononitrile (2·1 mmol), thiophenol (1·1 mmol), catalyst (0·1 g), ethanol (5 mL) at reflux temperature
[b]Isolated yield; [c]Fourth cycle



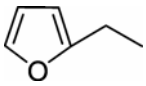
Scheme 1. One-pot synthesis of substituted pyridines catalysed by NAP–MgO.

Table 2. One-pot synthesis of substituted pyridines catalysed by NAP–MgO[a].

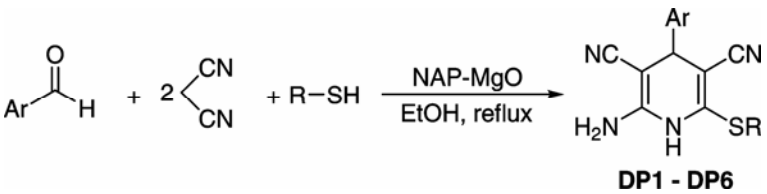
Entry	Ar	R	Time (h)	Product **P**[b]	Yield (%)[c]
1.	C_6H_5	C_6H_5	2	**P1**	64
2.	4-MeO–C_6H_4	C_6H_5	6	**P2**	61
3.	4-Me–C_6H_4	C_6H_5	6	**P3**	59
4.	4-NO_2–C_6H_4	C_6H_5	2	**P4**	52
5.	4-Cl–C_6H_4	C_6H_5	2	**P5**	49
6.	4-OH–C_6H_4	C_6H_5	7	**P6**	64
7.	4-HOOC–C_6H_4	C_6H_5	2	**P7**	50
8.		C_6H_5	9	**P8**	48
9.		C_6H_5	4	**P9**	69
10.	C_6H_5	4-Me–C_6H_4	4	**P10**	65
11.	4-MeO–C_6H_4	4-Me–C_6H_4	8	**P11**	59
12.	C_6H_5	4-Cl–C_6H_4	5	**P12**	50
13.	C_6H_5	C_6H_5–CH_2	4	**P13**	44
14.	4-Me-C_6H_4	C_6H_5–CH_2	7	**P14**	41
15.	4-MeO–C_6H_4		8	**P15**	56
16.	4-Cl–C_4H_4		6	**P16**	52

[a]Reaction conditions: Aldehyde (1 mmol), malononitrile (2·1 mmol), thiophenol (1·1 mmol), NAP–MgO (0·1 g), ethanol (5 mL) at reflux temperature
[b]All the products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy
[c]Isolated yield

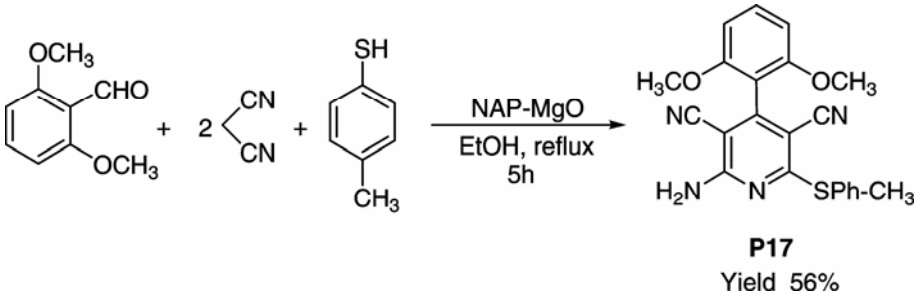
Table 3. One-pot synthesis of substituted 1,4-dihydropyridines catalysed by NAP–MgO[a].

Entry	Ar	R	Time (h)	Product **DP**[b]	Yield (%)[c]
1.	2,6-Cl–C_6H_3	C_6H_5	5	**DP1**	87
2.	2,6-Cl–C_6H_3	4-Cl-C_6H_4	4	**DP2**	80
3.	2,6-Cl–C_6H_3	4-Me-C_6H_4	4	**DP3**	84
4.	2,6-Cl–C_6H_3		3	**DP4**	71
5.	2-Cl-6-F-C_6H_3	C_6H_5	2	**DP5**	69
6.	2-Cl-6-F-C_6H_3	4-Me-C_6H_4	2	**DP5**	85

[a]Reaction conditions: Aldehyde (1 mmol), malononitrile (2·1 mmol), thiophenol (1·1 mmol), NAP–MgO (0·1 g), ethanol (5 mL) at reflux temperature
[b]All the products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy
[c]Isolated yield



Scheme 2. One-pot synthesis of substituted 1,4-dihydropyridines catalysed by NAP–MgO.



Scheme 3. One-pot synthesis of substituted pyridine **P17** catalysed by NAP–MgO.

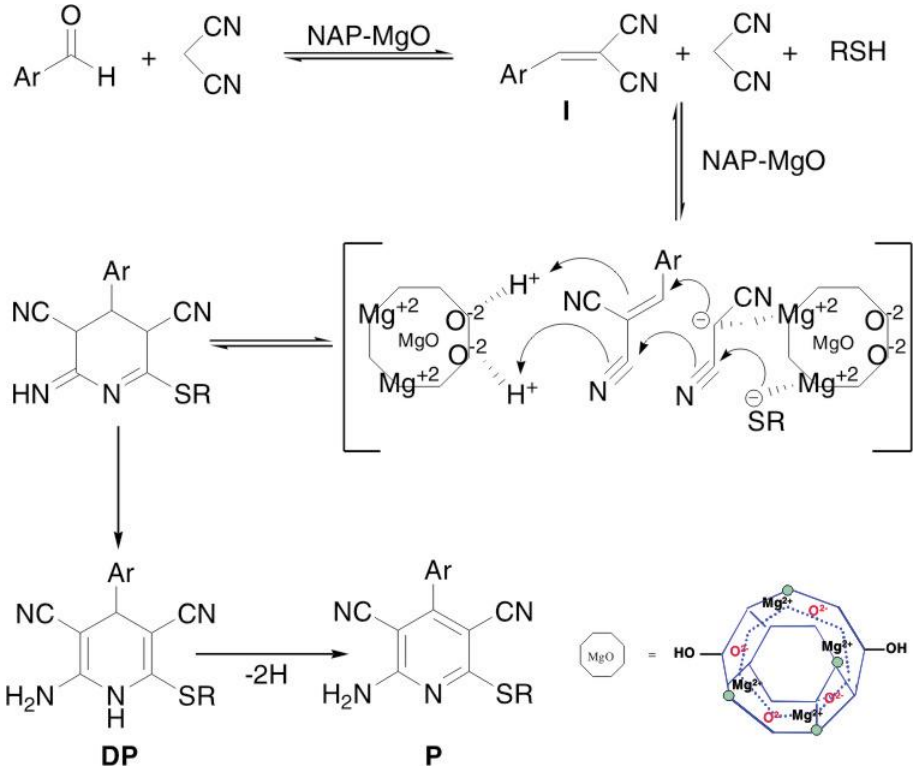
afford their corresponding pyridine products in moderate yields. The substrates bearing electron-donating (methyl, methoxy, methylenedioxy, hydroxy) or electron-withdrawing (nitro, carboxy, chloro) groups on the aromatic ring showed similar results. Using furfural, malononitrile and thiophenol the pyridine derivative **P9** (table 2, entry 9) was obtained in good yield. In contrast to the findings of Evdokimov *et al*,[12] with aliphatic aldehydes, unidentified constituents were isolated instead of the pyridine product.[13] Whereas, aliphatic cyclohexanethiol with 4-chlorobenzaldehyde gave the corresponding pyridine **P16** (table 2, entry 16) in 52% of isolated yield. The other thiols such as 4-methyl benzene thiol, 4-chloro benzene thiol and furyl methanethiol reacted with different aromatic aldehydes to afford their corresponding pyridine derivatives in good yields (table 2, entries 10–12 and 15), and with benzylthiol afforded the pyridine product in moderate yields (table 2, entries 13 and 14).

When *o,o′*-disubstituted aldehydes were used in this process, 1,4-dihydropyridines were obtained in high yields (table 3). The difference in the product profile may be due to steric hinderance of *o,o′*-disubstituted biaryl systems.[12,13] In this system, 2,6-dichloro-benzaldehyde and 2-Cl,6-F-benzaldehyde was combined with various thiols to afford 1,4-dihydropyridines **DP1–DP6** in good to high yields. In contrast, 2,6-dimethoxy benzaldehyde gave the substituted pyridine **P17** instead of the predicted 1,4-dihydropyridine (scheme 3). This may be due to the difference in the electronic and steric properties of 2,6-dimethoxy benzaldehyde compared to 2,6-dihalo aldehydes and also the possibility of hydrogen bonding between halogens of 2,6-dihalo aldehydes and hydrogen of pyridine ring.

We also explored different active methylene group containing nitriles such as ethyl cyanoacetate and 2-phenyl acetonitrile for the synthesis of pyridines. When the reaction was conducted with ethyl cyanoacetate, benzaldehyde and thiophenol, only 6% of the pyridine derivative was isolated. However, there was no reaction with phenyl acetonitrile.

It is noteworthy that there was no reaction without NAP–MgO catalyst (table 1, entry 5), which indicated that the catalyst is essential for the reaction. The proposed mechanism is, in the first step of this reaction, malononitrile is activated by O^{2-}/O^{-} (Lewis base) and aldehyde is activated by Mg^{2+}/Mg^{+} (Lewis acid) of NAP–MgO. This involves the Knoevenagel reaction which forms the corresponding Knoevenagel product **I** (scheme 4). The second molecule of malononitrile then undergoes Michael addition to **I**, simultaneously thiol activation by Mg^{2+}/Mg^{+} of NAP–MgO, and the thiolate addition to CN of the adduct. Then cyclization takes place to form 1,4-dihydropyridine, which upon aromatization and aerobic oxidation under the reaction conditions, leads to pyridine product.[13] Presumably, the reactions of *o,o′*-dihalo substituted aldehydes were restricted to 1,4-dihydropyridines only, as further aromatization did not occur, possibly, this is due to steric hinderance at the 4-position by two ortho substituents at the aromatic ring.[12,13]

To understand the relationship between structure and reactivity of the catalyst in this three-component reaction, it is important to know the structure and nature of the reactive sites of NAP–MgO. The catalyst NAP–MgO has a single crystallite, three-dimensional polyhedral structure, with high surface concentrations of edges/corners and various exposed crystal planes (such as 002, 001, 111). This leads to inherently high surface reactivity per unit area. Besides this, the NAP–MgO has Lewis acid sites Mg^{2+}, Lewis basic sites O^{2-} and O^{-}, lattice-bound and isolated Bronsted hydroxyls and anionic and cationic vacancies.[19] Thus, NAP–MgO displays the highest activity compared to NA–MgO and CM–



Scheme 4. The plausible mechanism for one-pot synthesis of substituted pyridines **P** and dihydropyridines **DP** catalysed by NAP–MgO.

MgO. Generally, this three-component reaction is known to be driven by base catalysts,[12] and accordingly, the surface –OH and O^{2-} sites of these oxide crystals are expected to trigger these reactions. The poorer result with the Sil–NAP–MgO[19] devoid of free –OH, was established the role of –OH (table 1, entry 4). Although both NAP–MgO and NA–MgO possess defined shapes and the same average concentrations of surface –OH groups, a possible rationale for this higher reactivity towards pyridines by the NAP–MgO is that the presence of more surface Lewis acid sites (20%), along with –OH groups present on the edge and corner sites on the NAP–MgO, which are stretched in three-dimensional space, are therefore more isolated and accessible to the reactants. Thus, NAP–MgO displays highest activity compared to NA–MgO and CM–MgO. This three-component reaction proceeds via dual activation of substrates by NAP–MgO. The Lewis base moiety (O^{2-}/O^{-}) of the catalyst activates the malononitrile and the Lewis acid moiety (Mg^{2+}/Mg^{+}) activates the aldehyde and thiol (scheme 4).[20]

The NAP–MgO was reused for four cycles with consistent activity (table 1, entry 1). After completion of the reaction, the catalyst was centrifuged and washed with ethyl acetate for three times. The recovered catalyst was activated at 250°C for 1 h under nitrogen atmosphere, before reuse.

4. Conclusion

In conclusion, we have demonstrated that nanocrystalline MgO is an effective catalyst for the MCRs of structurally diverse aldehydes with various thiols and malononitrile, resulting in the formation of substituted pyridines and 1,4-dihydropyridines in moderate to high yields. The catalyst can be recovered, and reused atleast up to four cycles for the synthesis of pyridine derivatives.

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