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Natural dolomitic limestone catalyzed synthesis of benzimidazoles, dihydropyrimidinones and highly substituted pyridines under ultrasound irradiation

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Abstract

In this paper, for the first time, naturally occurring dolomitic limestone is employed as a heterogeneous green catalyst for the synthesis of medicinally valuable N-heterocycles, 2-aryl-1-arylmethyl-1H-benzo[d]imidazoles, dihydropyrimidinones/ thiones and 2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines in good to excellent isolated yields *via* a rapid construction of C-N, C-C and C-S bond formations in 1:1 ratio of ethanol:H_2O under ultrasound irradiation. Dolomitic limestone is characterized by X-ray diffraction (XRD), FT-IR, Raman and SEM with EDAX analyses. Further, the catalyst is environmentally benevolent, non-toxic, most abundant, easy to handle low catalyst loading and is reused 7 times without significant loss of catalytic activity. Hence, the catalyst is greener alternative for the synthesis of aforementioned N-heterocycles as compared with the existing reported catalysts.

Keywords

Natural dolomitic limestone; ultrasound irradiation; benzimidazoles; dihydropyrimidinones; highly substituted pyridines

Introduction

Nitrogen heterocycles are recognized as ‘privileged medicinal scaffolds’ because these compounds are found in a wide variety of bioactive natural products and pharmaceutical compounds [1]. Among them, benzimidazoles, dihydropyrimidinones and pyridines are emerged as promising and valuable structural units in many pharmaceutical lead compounds (Figure 1) [2]. Hence, there is a continuing interest in the development of green and sustainable synthetic routes for the synthesis of aforesaid nitrogen heterocycles.

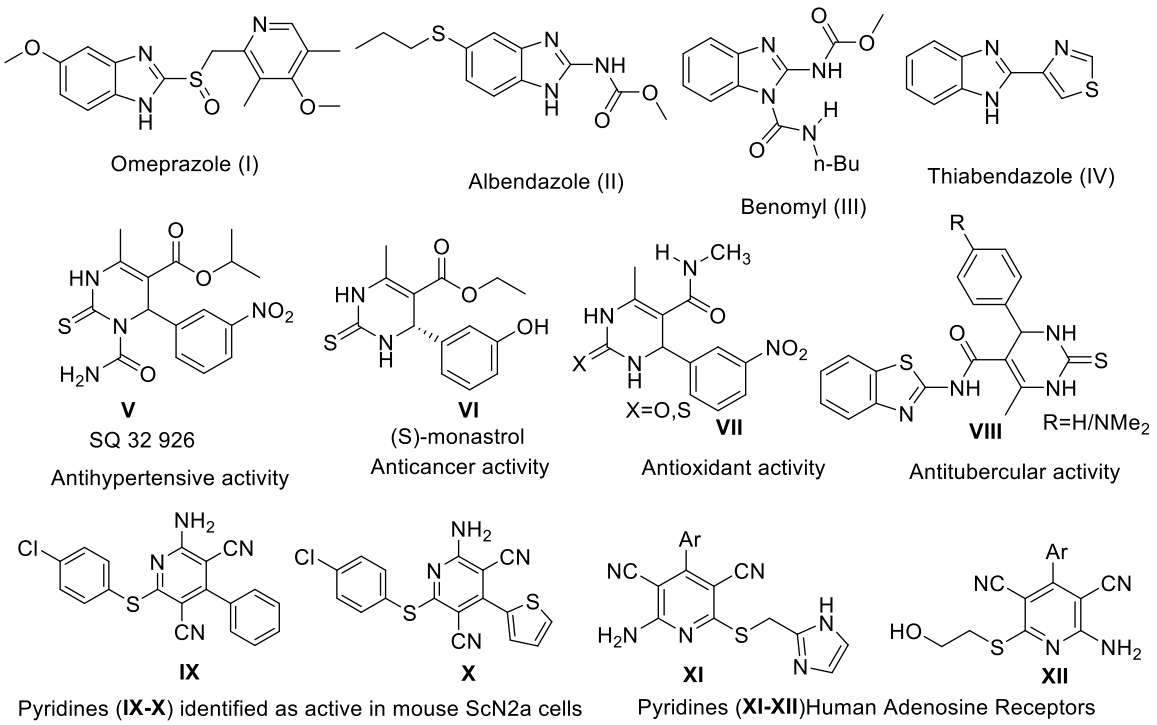


Figure 1. Benzimidazoles (I-IV) Dihydropyrimidinones/thiones (V-VIII) and 2-amino-4-aryl-3,5-dicarbonitrile-6-thio-pyridines (IX-XII) as "Medicinally Privileged Structures."

Benzimidazoles are important class of N-heterocycles due to their potential biological applications in both biology and medicinal chemistry [3]. These compounds used in the treatment of diseases like obesity, ischemia-reperfusion injury, hypertension, *etc.* [4]. In addition, these compounds are important intermediates in a variety of organic reactions and key elements of many functional materials [5]. Because of their potential utility, a huge number of synthetic protocols have been developed for the preparation of benzimidazole derivatives. The most common method for the preparation of benzimidazoles is the reaction between *o*-phenylenediamines and carboxylic acids [6]. Another general synthetic route employed for the synthesis of benzimidazoles derivatives is the condensation reaction of *o*-phenylenediamine with aldehydes in the presence of a wide variety of catalysts such as metal salts, metal

triflates, CAN, DBSA, p-TSA, $BF_3.OEt_2$, Montmorillonite K-10 clay, ionic liquids and nanoporous materials [7].

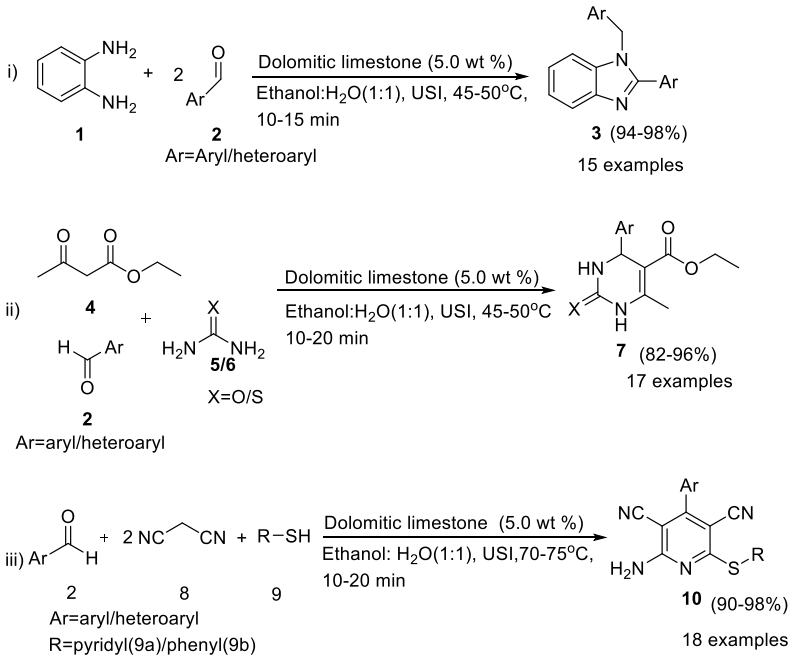
Dihydropyrimidinones (Biginelli products) occupy an important position in the fields of natural products and synthetic organic chemistry [8] because of their potential biological applications of anti-cancer, anthelmintic, anti-hypertensive, anti-inflammatory, antifungal, anti-viral, antibacterial, anti-oxidant and anti-topoisomerase activities [9]. Owing to their broad based utility in various fields, a wide variety of Brønsted acids and Lewis acids are employed as efficient catalysts for the Biginelli reaction [10]. In addition, some transition metal based catalysts and a few non acidic inorganic salts like are utilized as catalysts for the Biginelli reaction [11,12]. Further, very limited base catalysts such as t-$(CH_3)_3COK$, Ph_3P and L-proline are reported for the Biginelli reaction [13]. Moreover, improving already known MCRs also is of substantial interest in current organic synthesis.

2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines have gained considerable attention due to their wide range biological activities [14]. The most common synthetic route for the preparation of 2-amino-4-aryl-3,5-dicarbonitrile-6-thio-pyridines is the condensation reaction of an aldehydes, malononitrile and thiols in the presence of a variety of catalysts [15]. Though the reported methods are efficient to provide desired benzimidazoles, dihydropyrimidinones/thiones and 2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines there are still some drawbacks include the use of expensive catalysts, preparation of catalyst, long reaction times, a limited substrate scope, complicated work-up process and the products require chromatographic purification etc.

Natural dolomitic limestone has not been utilized as heterogeneous catalyst for the synthesis of Biginelli products and poly substituted pyridines to the best of our knowledge. Dolomitic limestone is an irregular combination of calcium and

magnesium carbonate mineral. It is water insoluble, inexpensive, nontoxic and more abundant in nature. Further, dolomite was used as a heterogeneous green catalyst in a very few organic transformations such as Knoevenagel, Michael and Henry reactions and trans esterification reaction for biodiesel production [16, 17]. To the best of our knowledge, there are no reports on natural dolomitic limestone catalyzed synthesis of aforesaid N-heterocycles in a mixture of EtOH : H_2O (1:1 ratio) under ultrasonic irradiation.

In this paper, for the first time, a natural dolomitic limestone is used as catalyst for the synthesis of benzimidazoles (3), dihydropyrimidinones/thiones (7) and 2-amino-4-aryl-3,5-dicarbonitrile-6-thio-pyridines (10) *via* a C-N, C-C and C-S bond forming reactions in 1:1 ratio of EtOH : H_2O under ultrasonic irradiation **(Scheme 1).** All the reactions proceeded well by loading of lower amount of natural dolomitic limestone (5.0 wt%) to provide the corresponding N-heterocycles (3,7 & 10) in good to excellent yields.



Scheme 1. Dolomitic limestone catalyzed synthesis of i) benzimidazoles (3), ii) dihydropyrimidinones/thiones (7) and ii) 2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines (10) under ultrasound irradiation.

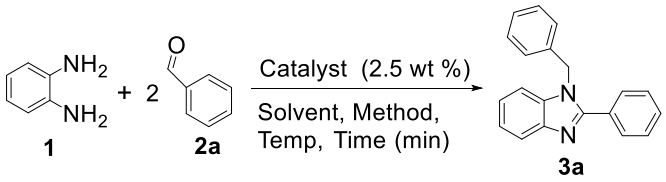
Results and Discussion

In the present study, we aimed to develop an environmentally benign procedure for the synthesis of benzimidazoles (3), dihydropyrimidinones/thiones (6) and 2-amino-4-aryl-3,5-dicarbonitrile-6-thio-pyridines (9). At first, for this purpose, *o*-phenylenediamine (1) and benzaldehyde (2a) were chosen as model substrates to optimize the reaction conditions for the synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a).

Initially, a control experiment was conducted by using model substrates, 1 and 2a in H_2O in the absence of catalyst under ultra sound irradiation for 180 min at 25-30°C. It was found that the reaction did not proceed in the absence of catalyst (Table 1, entry 1). To achieve the target compound **3a**, the same reaction was repeated by employing various catalysts (2.5 wt%), like Fe_2O_3, Al_2O_3, KF-Alumina, dolomitic limestone, triethyl amine, pyridine and DABCO in different solvents such as water, ethanol, i-PrOH, acetone and EtOH : H_2O (1:1) (Table 1, entries 2-8) under ultra sound irradiation at 45-50°C. From this study, it was observed that the dolomitic limestone was the best option, which gave the target compound 4a in high yield (85%) in 1:1 ratio of EtOH : H_2O under ultra sound irradiation for 30 min at 45-50°C (Table 1, entry 5). The other catalysts, Fe_2O_3, Al_2O_3, KF-Alumina, triethyl amine, pyridine and DABCO provided moderate to low yields of product 3a (Table 1, entries 2-4 & 6-8). Further, the same reaction was performed under conventional stirring in the presence of various catalysts and solvents at reflux temperature as mentioned in the Table 1. The study revealed that the dolomitic limestone in a mixture of EtOH and H_2O (1:1) afforded a moderate yield (70%) of product 3a, whereas the other catalysts in various solvents provided the lower yields under conventional reaction conditions. From above observations, it is concluded that the ultrasound irradiation method is

better than the conventional method in giving the maximum yield of **3a** (Table 1). Next, the amount of dolomitic limestone was varied (2.5, 5.0, 7.5, 10.0 and 12.5 wt%) to improve the yield of **3a** (Table 2). The study revealed that the 5.0 wt % of dolomitic limestone was the best option to get the highest yield of product 3a (98%) in a short reaction time (10 min) (Table 2, entry 2). Further, it was also mentioned that the same yields were obtained when increase in the amount of loading of catalyst i.e. 7.5, 10.0 and 12.5 wt% (Table 2, entries 4-5).

Table 1: Optimization of reaction conditions[a]



Entry	Catalyst (2.5 wt %)	Solvent	Product	Conventional Method[b]		Ultrasound Irradiation Method[c]	
				Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
1	No catalyst	H_2O	**3a**	180	-	60	-
2	Fe_2O_3	H_2O	**3a**	60	10	30	15
		Acetone		60	-	30	-
		Isopropanol		60	10	30	20
		EtOH		60	15	30	20
		EtOH : H_2O (1:1)		60	20	30	25
3	Al_2O_3	H_2O	**3a**	60	20	30	20
		Acetone		60	-	30	-
		Isopropanol		60	15	30	20
		EtOH		60	25	30	25
		EtOH : H_2O (1:1)		60	30	30	40
4	KF-Alumina	H_2O	**3a**	60	30	30	30
		Acetone		60	-	30	-
		Isopropanol		60	25	30	30
		EtOH		60	40	30	35
		EtOH : H_2O (1:1)		60	50	30	40
5	Dolomitic limestone	H_2O	**3a**	60	55	30	65
		Acetone		60	-	30	-
		Isopropanol		60	35	30	45
		EtOH		60	60	30	75
		EtOH : H_2O (1:1)		60	70	30	85
6	Et_3N	H_2O	**3a**	60	10	30	10

		Acetone		60	-	30	-
		Isopropanol		60	20	30	25
		EtOH		60	30	30	30
		EtOH : H_2O (1:1)		60	40	30	50
7	Pyridine	H_2O	**3a**	60	-	30	-
		Acetone		60	-	30	-
		Isopropanol		60	5	30	5
		EtOH		60	10	30	10
		EtOH : H_2O (1:1)		60	5	30	5
8	DABCO	H_2O	**3a**	60	15	30	20
		Acetone		60	-	30	-
		Isopropanol		60	25	30	30
		EtOH		60	35	30	45
		EtOH : H_2O (1:1)		60	45	30	50

[a]Reaction conditions: *o*-phenylenediamine (1), benzaldehyde (2) (1.0 mmol), catalyst (2.5 wt %), solvent (3.0 mL); [b]Conventional method performed by stirring at reflux temperature; [c]Ultrasound irradiation (USI) method performed at 45-50°C [d]Isolated yield.

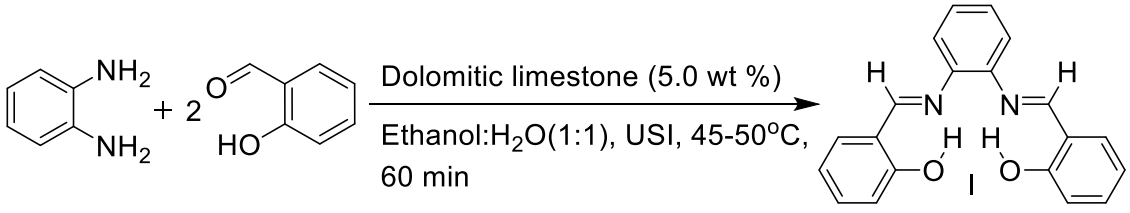
Table 2. Load of catalyst[a]

Entry	Dolomitic limestone (wt %)	Solvent	Method[b]	Time (min)	Product	Yield[b] (%)
1	2.5	EtOH : H_2O (1:1)	USI	30	3a	85
2	5.0	EtOH : H_2O (1:1)	USI	10	3a	98
3	7.5	EtOH : H_2O (1:1)	USI	10	3a	98
4	10.0	EtOH : H_2O (1:1)	USI	10	3a	98
5	12.5	EtOH : H_2O (1:1)	USI	10	3a	98

[a]Reaction conditions: *o*-phenylenediamine (1), benzaldehyde (2) (1.0 mmol), dolomitic limestone (2.5 to 12.5 wt %), (EtOH : H_2O (1:1) (3.0 mL), ultrasound irradiation at 45–50°C, 10 min; [b]Isolated yield.

To demonstrate the generality and substrate scope of the present method, a variety of aromatic aldehydes were employed under the optimized reaction conditions **Table 3**. *o*-phenylenediamine (1) reacts with the parent benzaldehyde (2a) to obtain the corresponding product 3a in 98% yield (entry 1, Table 3). Benzaldehyde with a range of functional groups such as activating groups (4-Me (2b), 4-t-butyl(2c), 2,4-dimethyl (2d), 4-OMe(2e), 3,4-dimethoxy (2f), 3,4,5-trimethoxy (2g), 4-OH-3-OMe (2j), 4-OH-3-OC_2H_5 (2k)) (entries 2-7&10,11, Table 3), deactivating group (4-NO_2, (2l)) (entry 12, Table 3) and halo groups, (4-F (2m), 4-Cl (2n) and 4-Br (2o) (entries 13-15, Table 3)

at different positions provided good to excellent isolated yields of the corresponding products (3a-3g, 3k-3o) that ranged from 94 to 98 %. Further, hetero-aromatic aldehydes such as furan-2-aldehyde (2p) and thiophene-2-aldehyde (2q) produced the corresponding products 3p and 3q in good isolated yields (entries 16-17, Table 3). But, the salicylaldehyde (2h) underwent the reaction with *o*-phenylenediamine (1) afforded the 2,2'-((1E,1'E)-(1,2-phenylenebis(azanylylidene))bis (methanylylidene))diphenol(3h) (diimide I) under the optimized reaction conditions (Scheme 2). The formation of diimide (I) was confirmed by ^{1}H NMR spectral studies (Fig. 2). In ^{1}H NMR (DMSO-d_6) spectra, the two hydroxyl protons of diimide (I) appeared as broad singlet at the strong downfield region i.e. δ 13.19. The sharp singlet at δ 8.66 indicated the presence of two imine,–N=C**H**- protons of diimde (I). This clearly indicated that the reaction was stopped at the diimide (I) stage. This is due to the intra molecular hydrogen bonding between the *ortho* hydroxyl group of hydrogen and the imine group of nitrogen through a cyclic six membered ring transition state. Similarly, the reaction between 3-ethoxysalicylaldehyde (2i) and *o*-phenylenediamine (1) also stopped at the intermediate, 6,6'-((1E,1'E)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))bis(2-ethoxyphenol)(3i) stage only (See ESI, Fig. S13). Most of the synthesized compounds are known and identified easily by comparison of their melting points and spectroscopic data with those reported.



Scheme 2. Unexpected formation of diimide (I) from salicylaldehyde.

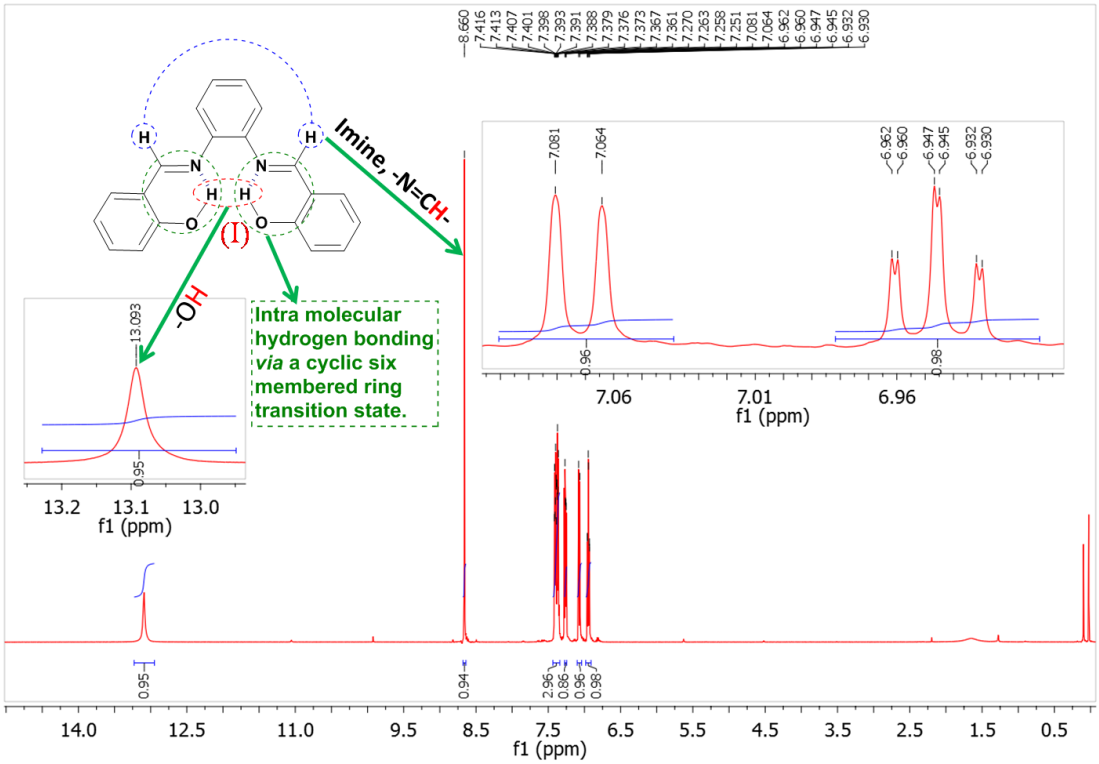
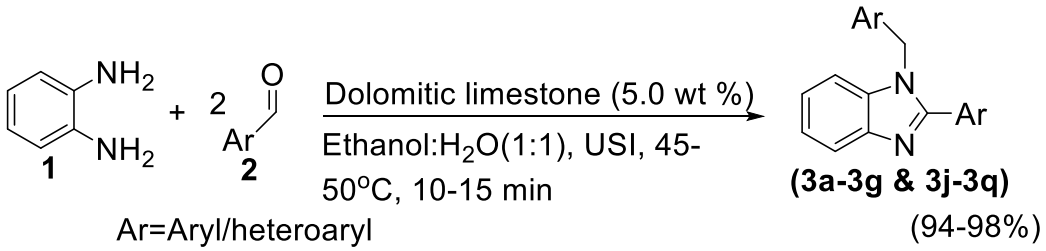


Figure 2. ^{1}H NMR spectrum of 2,2'-((1E,1'E)-(1,2-phenylenebis(azanylylidene))bis (methanylylidene))diphenol(3h) (Diimide I).

Table 3. Dolomitic limestone Synthesis of 2-aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles (3).[a]



S.No.	Ar	Products	Yield[c] (%)	Mp (°C)	
				Found	Reported
1	Phenyl (2a)	3a	98	128-131	133-134 [7b]
2	4-methylphenyl(2b)	3b	98	127-128	128-129 [7b]
3	4-t-butylphenyl (2c)	3c	94	124-125	122-126 [7d]
4	2,4-dimethylphenyl (2d)	3d	96	120-122	119-123 [7d]
5	4-methoxyphenyl (2e)	3e	98	157-159	158-160 [7b]
6	3,4-dimethoxyphenyl (2f)	3f	95	167-169	171-173 [7c]
7	3,4,5-trimethoxyphenyl (2g)	3g	94	261-262	262-263 [7a]
8[b]	2-hydroxyphenyl (2h)	3h	98	247-248	-

9[b]	2-hydroxy-3-ethoxyphenyl (2i)	3i	96	235-237	-
10	4-hydroxy-3-methoxyphenyl (2j)	3j	96	181-183	184–186 [7c]
11	4-hydroxy-3-ethoxyphenyl (2k)	3k	97	228-230	-
12	4-nitroyphenyl (2l)	3l	98	190-192	189-191 [7b]
13	4-fluorophenyl (2m)	3m	98	108-109	110-112 [7b]
14	4-chlorophenyl (2n)	3n	98	138-140	137-139 [7b])
15	4-bromophenyl (2o)	3o	96	158-160	160-162 [7b]
16	2-furanyl (2p)	3p	95	90-92	88-89 [7b]
17	2-Thienyl (2q)	3q	96	149-150	150-152 [7b]

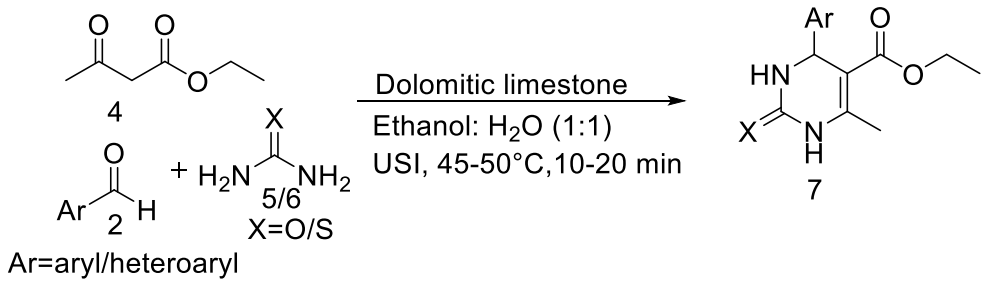
[a]Reaction conditions: *o*-phenylenediamine (1.0 mmol), benzaldehydes (2.0 mmol), dolomitic limestone (5.0 wt %), (EtOH : H_2O (1:1) (3.0 mL); [b]The reaction stopped at diimide(I) stage; [c]Isolated yield.

Encouraged by above results, the present dolomitic limestone catalyzed methodology was extended for the preparation of dihydropyrimidinones (6) from the reaction of benzaldehyde (2), ethyl acetoacetate (4) and urea/thiourea (5) under optimized reaction conditions. To check the feasibility, the reaction of benzaldehyde (1a, 1.0 mmol), ethyl acetoacetate (4) (1.0 mmol) and urea (5) (1.0 mmol) and dolomitic limestone (5.0 wt%) under similar conditions resulted in a 96 % yield of 6a.

To exploit the substrate scope and generality of the present method, various substituted benzaldehydes (2) were examined and the obtained results summarized in Table 5. The parent benzaldehyde (2a) reacts with ethylacetoacetate (4) and urea (5) to obtain the corresponding dihydropyrimidinone (7a) in 97% yield (entry 1, Table 4). Benzaldehyde with electron-donating groups such as 4-Me (2b), 4-OMe (2e), 3,4-diOMe (3f), 3-OH (2r) and 2-OH(2h) at different positions on the ring react with ethylacetoacetate (4) and urea (5) to produce the products, 7b, 7c, 7d, 7e and 7f in good isolated yields that ranged from 92 to 96 (entries 2-6, Table 4) Benzaldehyde with electron-accepting groups such as 4-NO_2 (2l) at *para* position on the ring

showed good reactivity with ethylacetoacetate (4) and urea (5) to afford the corresponding product, 7g in excellent isolated yields (94%) (entry 7, Table 4). Halo groups at different positions on the ring of benzaldehyde with (4-F(2m), 4-Cl(2n) and 3-Br(2s)) underwent reaction with ethylacetoacetate (4) and urea (5) to provide the corresponding products (7h, 7i and 7j) in good isolated yields that ranged from 93 to 96% (entries 8-10, Table 4). Further, hetero aromatic aldehydes such as furan-2-aldehyde (2p) and thiophene-2-aldehyde (2q) showed good reactivity and afforded the good yields of products, 7k (90%) and 7l (92%), respectively (entries 11-12, Table 4). From this study, it was concluded that the optimized reaction conditions are suitable for mono substituted (both electron-rich and electron-deficient), di substituted benzaldehydes and heteroaromatic aldehydes. The reaction of aromatic aldehydes with ethyl acetoacetate and thiourea was also examined. Benzaldehyde (2a) underwent the reaction with ethylacetoacetate (4) and thiourea (6) to produce the product 7m in excellent isolated yield (96%) (entry 13, Table 4). Benzaldehyde electron-releasing groups such as 4-Me (2b) and 4-OMe (2c) displayed excellent reactivity with ethylacetoacetate (4) and thiourea (6) to produce the corresponding products, 7n (95%) and 7o (95%) in excellent yields (entries 14 & 15, Table 4).. Benzaldehyde with electron-withdrawing groups such as 4-NO_2 (2f) and 4-Cl (2i) at *para* position reacted well with ethylacetoacetate (4) and thiourea (6) to give the corresponding products 7p and 7q in good isolated yields (95 and 96 %) (entries 16 & 17, Table 4). Most of the synthesized compounds are known and identified easily by comparison of their melting points and spectroscopic data with those reported.

Table 4 Dolomitic limestone catalyzed synthesis of Dihydropyrimidinone/thione derivatives.[a]



S.No.	Ar	X	Products	Yield[b] (%)	Mp (°C)	
					Found	Reported
1	Phenyl(2a)	O	7a	97	207-209	209–210 [11e]
2	4-methylphenyl (2b)	O	7b	96	213-214	215-216 [10b]
3	4-methoxyphenyl (2e)	O	7c	96	200-201	199-202 [11c]
4	3,4-dimethoxyphenyl (2f)	O	7d	94	213–215	212–214 [11g]
5	3-hydroxyphenyl (2r)	O	7e	95	162-164	163-165 [10b]
6	2-hydroxyphenyl (2h)	O	7f	92	198-200	199–201 [11d]
7	4-nitroyphenyl (2l)	O	7g	94	210-211	209–212 [11c]
8	4-fluorophenyl (2m)	O	7h	95	176-179	175-177 [10a]
9	4-chlorophenyl (2n)	O	7i	96	208-210	209–211 [11c]
10	3-bromophenyl (2s)	O	7j	93	184-185	185-186 [11b]
11	2-furanyl (2p)	O	7k	90	204-206	203–205 [11c]
12	2-Thienyl (2q)	O	7l	92	216-218	215-217 [10b]
13	Phenyl (2a)	S	7m	96	211-212	208-210 [10b]
14	4-methylphenyl (2b)	S	7n	95	189-190	192-194 [10b]
15	4-methoxyphenyl (2e)	S	7o	95	148-150	150-152 [10b]
16	4-nitroyphenyl (2l)	S	7p	94	113-114	109-111 [10b]
17	4-chlorophenyl (2n)	S	7q	95	190-191	192-194 [10b]

[a]Reaction conditions: Benzaldehydes (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea/thiourea(1.0 mmol), dolomitic limestone(5.0 wt%), ethanol: H_2O (1:1). [b] Isolated yield.

To expand the scope of this method, we applied the optimized reaction conditions for the synthesis of 2-amino-4-aryl/heteroaryl-6-(pyridin-2-yl/phenylthio)pyridine-3,5-

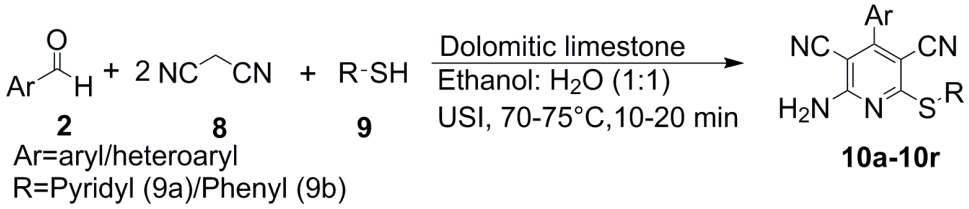
dicarbonitriles (10) from the reaction of aldehydes (2), malononitrile (8) and thiols (9). With regard to this, the reaction of benzaldehyde (2a, 1.0 mmol), malononitrile (8, 2.0 mmol) and 2-mercaptopyridine (9a, 1.0 mmol) and dolomitic limestone (5.0 wt%) under similar conditions resulted in a 70 % yield of 10a. Further, it was also found that the yield of the product (10a) was significantly improved (98%) by increasing the temperature 50 to 75°C within a short period of time (10 min).

The optimized procedure was successfully applied for the synthesis of series of highly substituted pyridines (10b-10r, Table 5) by utilizing a range of benzaldehydes (2), malononitrile (8) and thiols (9) as starting materials. The parent benzaldehyde (2a) underwent the reaction with malononitrile (8) and 2-mercaptopyridine (9a) to obtain the corresponding product (10a) in 97% yield (entry 1, Table 5). Benzaldehyde containing a range of functional groups such as strong electron-releasing groups (4-OMe (2e), 3,4,5-trimethoxy (2g) and 3-OH (2r), strong electron-withdrawing group (4-NO_2, (2l)) and halo groups, (4-F (2m), 4-Cl (2n) and 3,4-difluoro (2t) at different positions on the aromatic ring showed good reactivity with malononitrile (8) and 2-mercaptopyridine (9a) and afforded the corresponding products (10b-10h) that ranged from 92 to 96 % (entries 2-8, Table 5). Further, the pyridine-2-aldehyde (2u) also produced the corresponding product 10i in good isolated yield (93%) (entry 9, Table 5). In similar way, the parent benzaldehyde (2a) underwent reaction with malononitrile (8) and thiophenol (9b) to produce the corresponding product (10j) in 98% yield (entry 10, Table 5). Benzaldehyde substituted with various functional groups such as electron-donating groups (4-Me (2b), 4-OMe (2e) and 3,4,5-trimethoxy (2g), strong electron-accepting group (4-NO_2, (2l)) and halo groups, (4-F (2m), 4-Cl (2n) and 3-Br (2s) at different positions on the aromatic ring displayed good reactivity with malononitrile (8) and thiophenol (9b) and obtained the corresponding products (10k-10q) in good isolated yields ranging from 94 to 98 %

(entries 11-17, Table 5). Further, the pyridine-2-aldehyde (2u) also provided the corresponding product 10i in good isolated yield (94%) (entry 18, Table 5).

From above observation, it was worthy to mention that the all reactions proceeded well irrespective of the substituents present on aryl/heteroaryl aldehydes and afforded the highly substituted pyridines (10) in excellent isolated yields that ranged from 91 to 96 %. Most of the synthesized compounds are known and identified easily by comparison of their melting points and spectroscopic data with those reported.

Table 5. Dolomitic limestone catalyzed synthesis of 2-amino-4-aryl/heteroaryl-6-(pyridin-2-yl/phenylthio)pyridine-3,5-dicarbonitriles(10).[a]



2 **8** **9**

Ar=aryl/heteroaryl
R=Pyridyl (9a)/Phenyl (9b)

10a-10r

S.No.	Ar	R	Products	Yield[b] (%)	Mp (°C)	
					Found	Reported
1	Phenyl (2a)	Pyridyl (9a)	10a	97	222-223	224-227 [15i]
2	4-methoxyphenyl (2e)	Pyridyl (9a)	10b	96	248-249	250-253 [15i]
3	3,4,5-trimethoxyphenyl (2g)	Pyridyl (9a)	10c	92	267-269	265-268 [15i]
4	3-hydroxyphenyl (2r)	Pyridyl (9a)	10d	94	223-224	222-226 [15i]
5	4-nitroyphenyl (2l)	Pyridyl (9a)	10e	96	241-243	245-248 [15i]
6	4-fluorophenyl (2m)	Pyridyl (9a)	10f	95	248-250	246-249 [15i]
7	4-bromophenyl (2o)	Pyridyl (9a)	10g	94	257-258	260-263 [15i]
8	3,4-difluorophenyl (2t)	Pyridyl (9a)	10h	90	252-253	251-254 [15i]
9	Pyridyl (2u)	Pyridyl (9a)	10i	93	230-231	233-235 [15i]
10	Phenyl (2a)	Phenyl (9b)	10j	98	210-212	215-216[15b]
11	4-methylphenyl(2b)	Phenyl (9b)	10k	98	206-207	208-210 [15h]
12	4-methoxyphenyl (2e)	Phenyl (9b)	10l	97	234-235	236-238 [15c]
13	3,4,5-trimethoxyphenyl (2g)	Phenyl (9b)	10m	94	240-241	238-239 [15b]

14	4-nitroyphenyl (2l)	Phenyl (9b)	10n	95	280-282	286-287 [15b]
15	4-fluorophenyl (2m)	Phenyl (9b)	10o	96	127-128	224-225 [15h]
16	4-chlorophenyl (2n)	Phenyl (9b)	10p	96	220-221	222-223 [15h]
17	3-bromophenyl (2s)	Phenyl (9b)	10q	94	250-253	256-258 [15d]
18	Pyridyl(2u)	Phenyl (9b)	10r	94	300-302	305-306 [15b]

[a]Reaction conditions: Aldehydes (1.0 mmol), malononitrile (2.0 mmol), thiols (1.0 mmol), dolomitic limestone (5.0 wt%), ethanol: H_2O (1:1), 70-75°C. [b] Isolated yield.

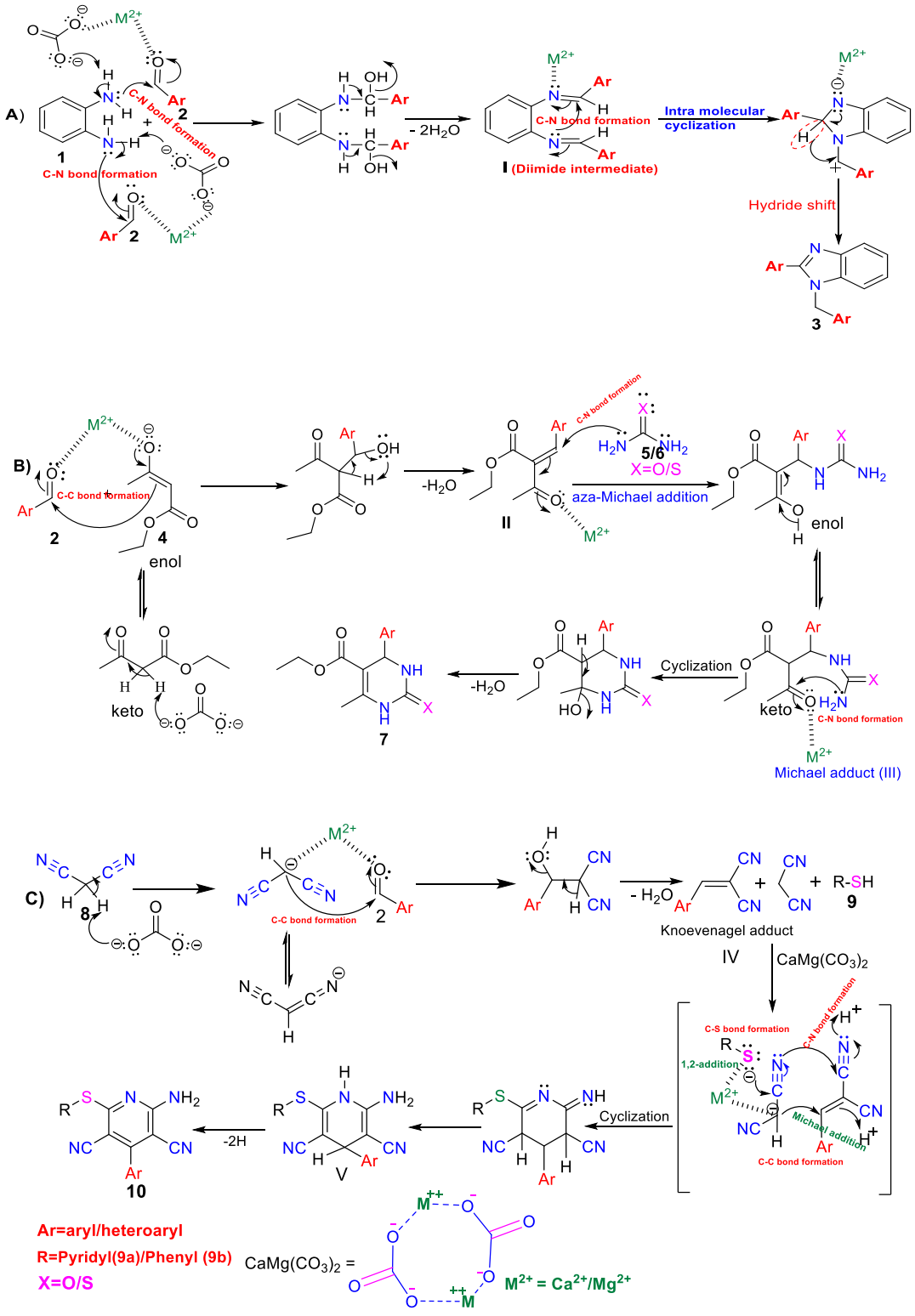
The mechanism for the formation of 2**-**aryl-1-arylmethyl-1H-benzo[d]imidazoles (**3**), dihydropyrimidinones/thiones (**7**) and 2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines (**10**) as shown in scheme 2.

A) At first, *o*-phenylenediamine (**1**) reacts with the carbonyl group of aldehyde (**2**) that activated by the dolomitic limestone to form the diimide (**I**). Further, the diimide (**I**) undergoes cyclization followed by hydride transfer to produce the 1,2-disubtituted benzimidazoles (**3**) (scheme 2A).

B) The mechanism starts with the condensation reaction of aldehyde (2) with ethyl acetoacetate (4) in the presence of dolomitic limestone to form enone intermediate (II).Then the 1,4-nucleophilic addition of urea/thiourea (5/6) with enone intermediate (II) which is activated by dolomitic limestone to give Michael adduct (III). Further, the Michael adduct (III) undergoes the intra molecular 1, 2-nucleophilic addition followed by dehydration to obtain the desired product (7) (Scheme 2B).

C) The mechanism begins with the dolomitic limestone catalyzed condensation reaction of an aldehyde (2) with malononitrile (8) to obtain the Knoevenagal adduct (IV) Next, simultaneous 1,4-addition (Michael addition) between Knoevenagal adduct (IV) and the another molecule of malononitrile (8) and 1,2- addition between thiolate ion of thiol (9) and the nitrile group of malononitrile followed by cyclization to afford 1,4-dihydropyridine (V) in the presence of dolomitic limestone. Further, 1,4-

dihydropyridine (V) undergoes oxidation in the presence of atmospheric air to obtain the desired product (10) (Scheme 2C).



Scheme 2. Plausible pathway for the formation of A) 2-aryl-1-arylmethyl-1H-benzo[d]imidazoles (3), B) dihydropyrimidinones/thiones (7) and C) 2-amino-4-

aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines (10) using dolomitic limestone as heterogeneous green catalyst.

The catalyst (dolomitic limestone) was also tested for its reusability in the preparation of 3k using 1a and 2k. After completion of the reaction, the catalyst was separated by centrifugation. The separated catalyst was washed with ethyl acetate twice (5 mL) followed by water, dried under vacuum and then reused for another 6 times. The study revealed that the catalyst was successfully reused 7 times without significant loss of catalytic activity and the obtained isolated yields of the product 3k were 98%, 98%, 97%, 97%, 96%, 95%, and 93%, respectively.

Catalyst characterization

Dolomitic limestone was collected from Vemula Mandal, Pulivendula, YSR Kadapa District, Andhra Pradesh, India. Dolomitic limestone was ground into a fine powder and then sieved in a 200-mesh sieve. A finely powdered sample was used for XRD, IR, Raman and SEM and EDAX analyses.

The chemical composition of the finely powdered natural dolomitic limestone was determined by adopting standard quantitative analysis [18a] and the obtained results summarized in Table 6. The study revealed that the carbonate content of the dolomitic limestone was greater than 92%.

Table 6. Chemical composition of dolomitic limestone (%).

Total carbonates ($CaCO_3$+ $MgCO_3$)	92.13%
LOI (Loss of Ignition)	38.90%
CaO	41.84%
MgO	9.90%
SiO_2	7.3%
Al_2O_3	0.94%
Fe_2O_3	0.30%
SO_3	0.24%
Na_2O	0.28%
K_2O	0.05%

Powder X-ray diffraction (XRD) analysis of natural dolomitic limestone was shown in Figure 2. The diffraction peaks at 2θ = 23.16, 29.51, 31.05, 36.02, 38.07, 39.40, 43.04, 47.16, 47.50, 48.52, 56.58, 57.61, 60.86 and 64.80° were attributed to the (012), (104), (006), (015), (110), (113), (021), (024), (018), (116), (211), (122), (214) and (030) planes of natural dolomitic Limestone [JCPDS files Card 5–586(calcite) and 11–78 (dolomite)][81e,18f].

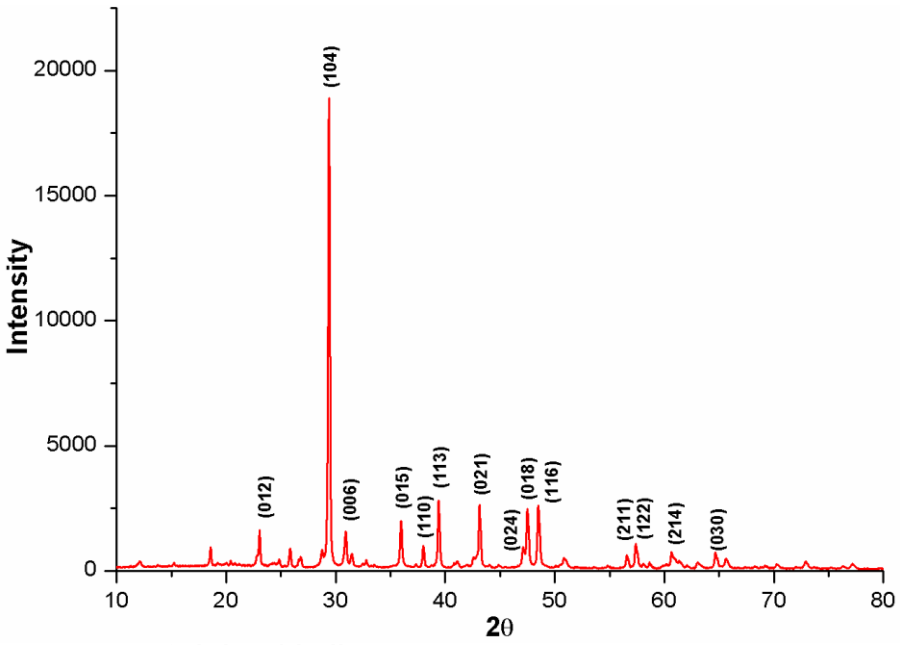


Figure 2. XRD pattern of dolomitic limestone.

The FT IR spectrum of natural dolomitic limestone was shown in Figure 3. In the IR spectrum, the two distinct vibrational modes of carbonates i.e. the out-of-plane bending vibration was observed at 875 cm^{-1} (v_2) and the in-plane bending vibration was found at 729 cm^{-1} (v_4). The bands at 1086 cm^{-1} and 1424 cm^{-1} were ascribed to symmetric stretching vibration (v_1) and asymmetric stretching vibration (v_3) of carbonates, respectively. The combination bands of carbonates, (v_1+v_4)and (v_1+v_3)were observed at 1798 and 2524 cm^{-1}, respectively.

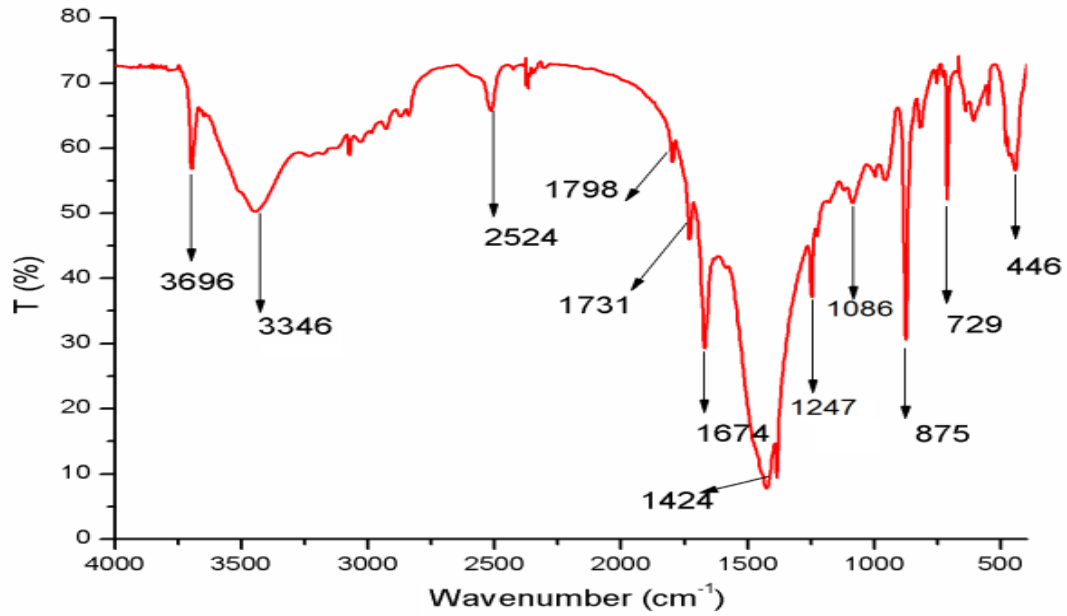


Figure 3. FT IR spectrum of dolomitic limestone

The Raman spectrum of natural dolomitic limestone was shown in Figure 4. The band at 1092 cm^{-1} was ascribed to the symmetric stretching vibration (v_1) of carbonates (CO_3^{2-}). The peaks at 714 and 1435 cm^{-1}were attributed to symmetric bending (v_4) and asymmetric stretching vibration (v_3) of carbonate. The weak combination band (v_1 + v_4) was observed at 1750 cm^{-1}. The bands at 152 and 278 cm^{-1} were ascribed to the external vibrations of the carbonate

group. The observed Raman and infrared vibrational bands of dolomitic limestone were in good agreement with the reported values [18b-f]. The minor shift in band positions might be due to the presence of trace metal contents and impurities in natural dolomitic limestone.

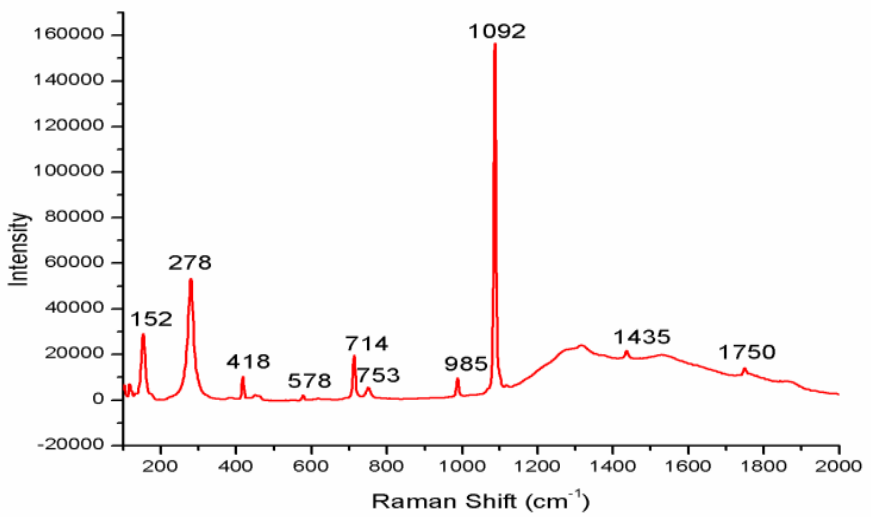


Figure 4. Raman spectrum of dolomitic limestone

SEM micrographs revealed that the morphology of dolomitic limestone was of irregular particulates (Figure 5) with random dispersion. Further, the elemental composition of natural dolomitic limestone was determined by EDAX analysis (Figure 6).

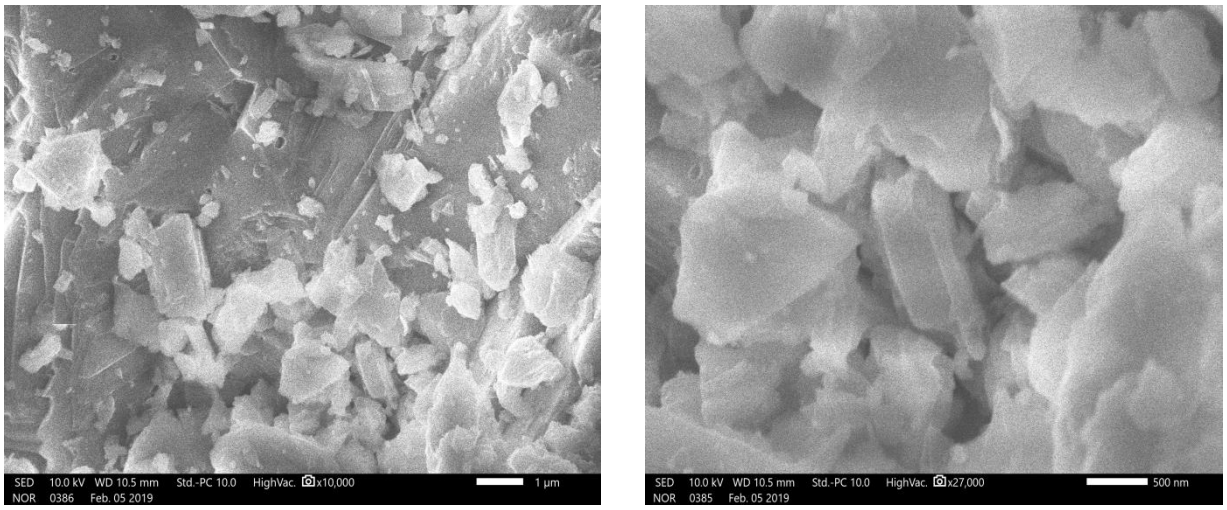
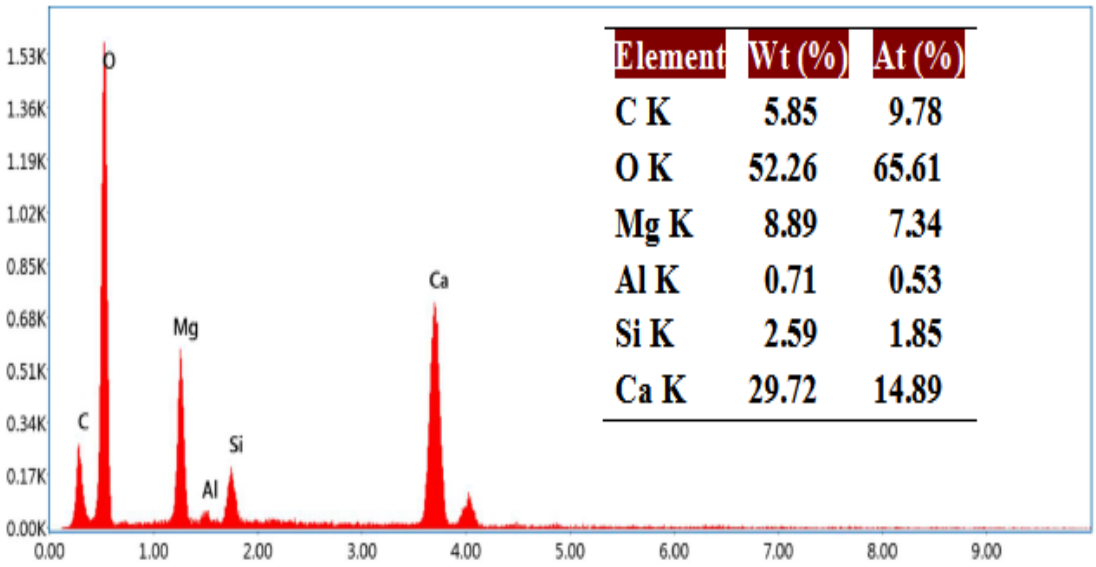


Figure 5. SEM images of dolomitic limestone



Element	Wt (%)	At (%)
C K	5.85	9.78
O K	52.26	65.61
Mg K	8.89	7.34
Al K	0.71	0.53
Si K	2.59	1.85
Ca K	29.72	14.89

Figure 6. EDAX analysis of dolomitic limestone.

Conclusion

An environmentally benign natural dolomitic limestone has been characterized and utilized as a heterogeneous catalyst for the synthesis of 2-aryl-1-arylmethyl-1H-benzo[d]imidazoles, dihydropyrimidinones/thiones and 2-amino-4-aryl-3,5-dicarbonitrile-6-sulfanyl-pyridines 1:1 ratio of ethanol:H_2O under ultrasound irradiation. Notable advantages of this method include clean reaction profile, reasonable substrate scope, simplicity in process and handling, easy and quick isolation of the products in good yields. The products obtained in adequate purity without the use of chromatographic techniques. Besides, the catalyst is non-toxic, most abundant, easy to handle, low catalyst loading and is reused 7 times without significant loss of catalytic activity. Hence, the catalyst is a greener alternative for the synthesis of benzimidazoles, dihydropyrimidinones/thiones and highly substituted pyridines as compared with the existing reported catalysts. Further, the expansion of the catalyst scope and generality for the synthesis of other privileged nitrogen and sulfur based heterocycles is under progress in our laboratory.

Experimental

See Supporting Information File 1 for full experimental data.

Supporting Information

Supporting Information File 1: Experimental procedures, characterization data and copies of ^{1}H & $^{13}CNMR$, Mass and HRMS spectra of some representative compounds (3,7 &10).

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