Indian Journal of Chemistry
Vol. 60B, October 2021, pp. 1378-1384

A convenient metal free approach towards the synthesis of dihydropyrimidones mediated by achiral nicotinic acid without solvent

Mohinuddin Khan Imon[a], Koteswara R Kamma[b], M N Islam[a] & Harendra N Roy*[a]

[a] Department of Chemistry, University of Rajshahi, Rajshahi, Bangladesh

[b] Department of Chemistry,University of Science and Technology (UST), Deajon 305-330, Korea

E-mail: hnroy01@yahoo.com; mohinuddinru14@gmail.com; kamma@krict.re.kr

Received 17 April 2021; accepted (revised) 9 September 2021

A very simple arrangement of Biginelli's condensation reaction of 1,3-dicarbonyl compound, aromatic / aliphatic aldehyde and urea / thiourea has been performed in a convenient way by using nicotinic acid without any solvent and under ambient conditions. This approach of pyrimidone synthesis is simple, versatile, metal-free, high yielding and environmentally benign.

Keywords: Dihydropyrimidones, nicotinic acid, solvent-free, N-heterocycles, metal-free

Dihydropyrimidone and its derivatives have drawn immense interest in the recent years owing to their promising biological activities as cardiovascular[1] and antihypertensive agents[2], calcium channel blockers[3,4] anti-HIV agent[5–7] and anti-cancer agents[8]. Moreover, dihydropyrimidones popularly show antibacterial[9], antifungal[10], antiviral[11], as well as anti-inflammatory[12] properties. Many alkaloids, such as batzelladine[13], have been isolated from marine sources and exhibit significant biological properties due to the presence of dihydropyrimidones as the core unit. As a result, the synthesis of such N-heterocycle core units is a hot topic right now. Biginelli published a simple procedure in 1893 that involved the synthesis of ethyl acetoacetate, benzaldehyde, and urea in one pot under strong acidic conditions[14]. However, there are two significant disadvantages to this procedure: the use of strong inorganic acid and the low yield (20-60%) obtained for substituted aromatic or aliphatic aldehyde.

A major goal of modern organic synthesis is to perform efficient chemical transformations coupling three or more components in a single vessel using a catalytic process while avoiding stoichiometric amounts of toxic reagents, massive amounts of solvents, and costly purification techniques. Therefore, Biginelli's reaction for the synthesis of dihydropyrimidones/thiones has received renewed interest and several improved approaches have been recently developed. Some of the methods involving strong Lewis acids such as BF_3 [15], $InCl_3$ [16], $Ln(OTf)_3$ [17], $Yb(OTf)_3$ [17], $FeCl_3$ [18], in a solvent such as CH_3CN, CH_2Cl_2 or THF and protic acids such as HCl and additives (LiBr) [19] have already been reported. Additionally, others catalytic process also involved with use of nano-materials[20], nano-composite[21], polymer[22], zeolites[23] and most recently ionic liquids[24–26].

It is true, many of these catalysts and solvents which were used in the aforementioned literatures are not at all acceptable in the context of green synthesis. As a result, there are numerous opportunities for renovation toward milder conditions, substituent variance in all three components, and improved yields. Organocatalysts[27–30] have recently emerged as a powerful method for various chemical transformations, with high regio- and chemoselectivity[31–33]. Furthermore, organocatalyst has been found to be moisture tolerant, easy to handle, stoichiometric, and environmentally friendly, and it is true, in a few multicomponent condensation reactions it has been exploited to date. We previously discovered that L-proline, amino alcohol, and 3-picolinic acid are effective organocatalysts for condensing three and four component coupling reactions[34–36]. Observing the efficacy of this organocatalyst, we wish to report here a remarkable catalytic activity of nicotinic acid to a one-pot three component condensation of 1, 3-dicarbonyl compound, aldehyde and urea or thiourea to dihydropyrimidin-2(1*H*)-ones or thiones.

Experimental Section

Materials and methods

The melting points were determined on a capillary melting point apparatus and were matched with the literature values. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on FT-IR 8400 Perkin-Elmer 883 grating spectrometers. ^{1}H NMR spectra were taken on AC-Bruker 400 MHz spectrometer in DMSO and contained TMS as internal standard. All *J* values are given in Hz, chemical shifts in *δ*-units, and the necessary spectra were given as supporting file. Progress of the reactions were monitored by TLC.

General procedure for the preparation of dihydropyrimidinones derivatives

Pure aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea/thio-urea (1.2 mmol), and nicotinic acid (5-10 mol percent) were thoroughly mixed and stirred at RT for 30 minutes with an effective $CaCl_2$ guard tube protecting the reaction vessel. After 30 minutes of stirring at RT, there were no discernible changes found in the TLC. The reaction mixture was then steadily heated to 100−105°C, and the reaction progress was detected after a few minutes by the appearance of solid over the reaction mixture. Stirring was continued at about 1hour till the completion of the reaction. After that, crushed ice was added to the reaction mixture, scratched, and the product was filtered. The isolated product is sufficiently pure, as shown by the ^{1}H NMR spectroscopy. To obtain analytic grade sample, the isolated product was recrystallized from ethanol.

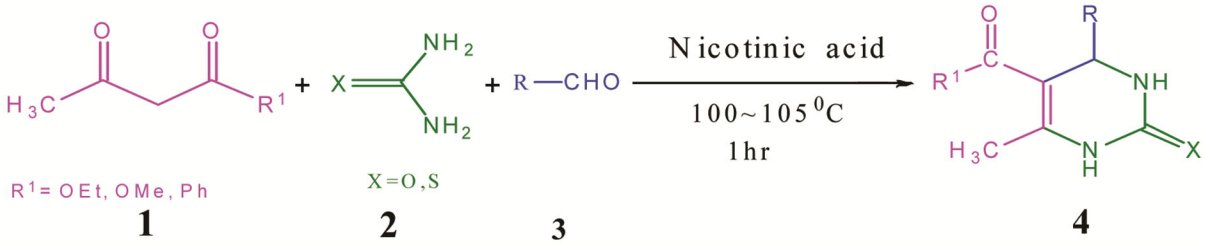
Ethyl-4-(4-(dimethylamino)-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 4j:

The product was prepared by following the general procedure as mentioned. Isolated yield 85%. Yellow solid. m.p.256-258°C (lit. 257-258°C) [16]. ^{1}H NMR (400 MHz,): δ 9.08 (s, 1H, N-*H*), 7.58 (s, 1H, N-*H*), 7.04 (d, 2H, *J*= 4Hz, Ar-*H*), 6.65 (d, 2H, *J*= 2Hz, Ar-*H*), 5.05 (s, 1H, -C*H*), 4.01 (q, 2H, *J*= 5Hz, -CH_2), 2.84(s, 6H, -CH_3), 2.23(s, 3H, -CH_3),1.10 (s, 3H, *J*= 7Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6, 18.2, 53.8, 59.6, 100.4, 112.7, 127.4, 133.1, 148.0, 150.2, 152.8, 165.9.

All other data are provided in the supporting information file.

Results and Discussion

Initially, a solution of a β-dicarbonyl compound, an aldehyde and a urea / thiourea in ethanol solvent was refluxed sequentially in the presence of L-cystine, *o*-aminobenzoic acid, aspartic acid, L-glutamic acid, and 2-picolinic acid, as in a standard general experimental protocol (Scheme I). All are the trial catalytic reactions and hence for a succinct representation, percentages of catalyst loading, yields, reaction time and reaction temperature are given in the Table I.



Scheme I

Table I — Effects of catalysts, solvents, and reaction temperature

Entry	Catalyst	Catalyst loading (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	L-Cystine	5	EtOH	RT, reflux (80)	>48	No
2	o-Amino benzoic acid	5	EtOH	RT, reflux (80)	>48	10
3	Aspartic acid	5	EtOH	RT, reflux (80)	>48	15
4	L-Glutamic acid	5,10	EtOH	RT, reflux (80)	48	25
5	2-Picolinic acid	5,10	EtOH	RT, reflux (80)	>48	50
6	Nicotinic acid	5	Without solvent	100-105	1	90
7	Nicotinic acid	10	Without solvent	100-105	1	Not more than 90
8	Without catalyst	–	,,	100-105	4-5	30

Reaction conditions: aldehyde(1.0mmol), urea (1.5mmol) and *β*-keto ester(1.0mmol) and without catalyst.

Only L-Glutamic acid and 2-Picolinic acid yielded a poor conversion (detected in TLC) after 12 hours of reflux in ethanol, but the isolated yield was not inspiring. Then we tried the same reaction with 2-picolinic acid without the solvent, but there was no noticeable improvement in yield with this process. Such difficulties could be caused by the catalyst molecule's ability to form intramolecular H-bonds. Whatever the conversion, the result of the 2-picolinic acid catalyzation (entry 5) reaction has inspired us to use nicotinic acid in a multi-component reaction. Nicotinic acid produced complete transformation of the starting materials after a four-hour reflux in ethanol, as evidenced by standard TLC monitoring. However, after isolating the sample, the yield observed is not as high as we had hoped during TLC testing. It is possible that certain products were soluble in ethanol, making product recovery difficult. We decided to perform the same reaction without the use of any solvent in order to achieve a higher yield.

To achieve this, the requisite reactants were added one by one into a vessel, and the catalyst (5-10 mol%) was added after one minute of mechanical mixing. To our delight, reactants were fully transformed into the products after one hour of heating (100-105°C) in an oil bath. By adding ice cold water to the reaction mixture, the product was seen to float on top of the water and was therefore easily collected by the filtration process. For a few cases, ethanol re-crystallization was done instead of chromatographic separation to obtain NMR grade samples. By this developed technique, 29 different dihydropyrimidine-2(1H)-ones / thiones were tailored and structures were established by various physico-chemical methods. All these data firmly supported the formation of dihydropyrimidones and completely agreed with the given structures (Table II and Table III).

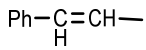
After establishing optimal conditions, we explored the generality to three aliphatic aldehydes (entry 25, 26 and 27) to this multicomponent reaction and obtained desired amounts of yields (80-82%). To test the efficacy for other nucleophiles methyl acetoacetate

Table II — Synthesis of dihydropyrimidinones catalyzed by Nicotinic acid without any solvent

Entry	R	R^1	X	Product	Reaction time (min)	Yield (%)
1	Ph	OEt	O	**4a**	50	82
2	3-(NO_2)-C_6H_4	OEt	O	**4b**	45	80
3	3-(OMe)-C_6H_4	OEt	O	**4c**	60	83
4	3-(OH)-4-(OMe)-C_6H_3	OEt	O	**4d**	60	85
5	2-(Cl)- C_6H_4	OEt	O	**4e**	48	85
6	4-(Cl)- C_6H_4	OEt	O	**4f**	46	85
7	4-($NHCOCH_3$)- C_6H_4	OEt	O	**4g**	50	85
8	3-(Br)- C_6H_4	OEt	O	**4h**	48	83
9	2-(OH)-5(Br)- C_6H_3	OEt	O	**4i**	55	83
10	4(N-Di-CH_3)- C_6H_3	OEt	O	**4j**	60	85
11	4-(F)- C_6H_4	OEt	O	**4k**	52	82
12	4-(CN)- C_6H_4	OEt	O	**4l**	48	82
13		OEt	O	**4m**	58	84
14		OEt	O	**4n**	53	85
15		OEt	O	**4o**	60	82
16		OEt	O	**4p**	58	80
17	Ph-	OEt	S	**4q**	50	80
18	4-(NO_2)-C_6H_4-	OEt	S	**4r**	45	85
19	3-(OH)-C_6H_4-	OEt	S	**4s**	54	82
20	3-(OH)-4-(OMe)-C_6H_3-	OEt	S	**4t**	58	82
21	4-(Cl)- C_6H_4	OEt	S	**4u**	52	85

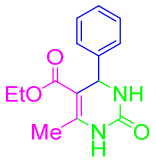
(contd.)

Table II — Synthesis of dihydropyrimidinones catalyzed by Nicotinic acid without any solvent (*contd.*)

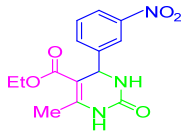
Entry	R	R^1	X	Product	Reaction time (min)	Yield (%)
22	4(N-Di-CH_3)- C_6H_3	OEt	S	**4v**	50	82
23	2-(OH)-5(Br)- C_6H_3	OEt	S	**4w**	55	85
24		OEt	S	**4x**	53	85
25		OEt	O	**4y**	55	81
26		OMe	O	**4z**	52	86
27	n-Bu-	OMe	O	**4ab**	50	8o
28	n-Hex-	OMe	O	**4ac**	52	82
29	4-(NO_2)-C_6H_4	Ph	O	**4ad**	48	84

Yield refers to pure products characterized by m.p and spectral data (IR, ^{1}H and ^{13}C)

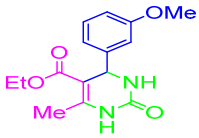
Table III — Structure of synthesized dihydropyrimidinones/ thiones



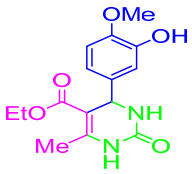
4a (50 min, 82%) m.p.202-204°C Lit. 204-206°C [16]



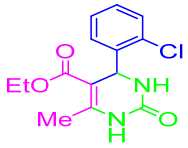
4b (45min, 80%) m.p.226-227°C Lit.227-228°C [33]



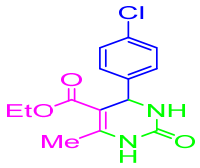
4c (60 min,83 %) m.p.206-208°C Lit.207-208°C [16]



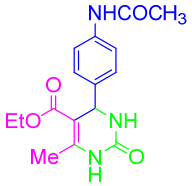
4d (60 min,85%) m.p.184-185°C



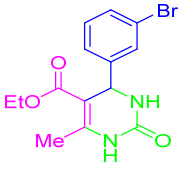
4e (48 min, 85%) m.p.221-223°C Lit.222-224°C [33]



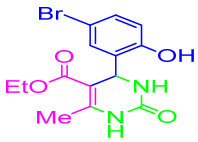
4f (46min,85 %) m.p.234-236°C Lit.233-234°C [42]



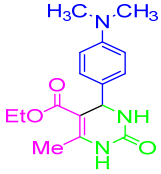
4g (50 min, 85%) m.p.280-282°C Lit.185-187°C [33]



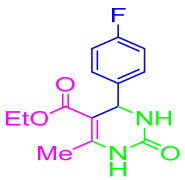
4h (48 min, 83%) m.p.183-185°C



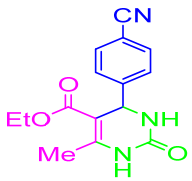
4i (55 min, 83%) m.p.290-291°C Lit.291-292°C [17]



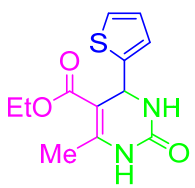
4j (60 min,85%) m.p.256-258°C Lit.257-258°C [41]



4k (52 min, 82%) m.p.181-183°C Lit.180-181°C [42]

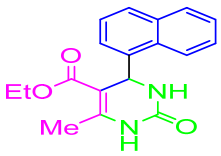


4l (48min,82%) m.p.233-235°C

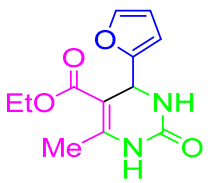


4m (58 min, 84% m.p.214-217°C Lit.215-217°C [21]

4n (53min, 85%) m.p.245-247°C



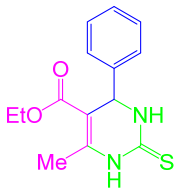
4o (60 min,82%) m.p.248-250°C Lit.203-204°C [16]



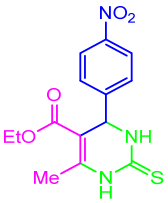
4p (58 min, 82%) m.p.202-204°C

(*contd.*)

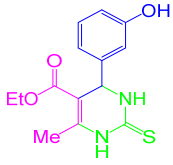
Table III — Structure of synthesized dihydropyrimidinones/ thiones



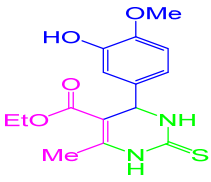
4q
(50 min, 80%)
m.p.205-208°C
Lit.208-209°C [44]



4r
(45 min, 85%)
m.p.210-212°C
Lit.212-214°C [16]

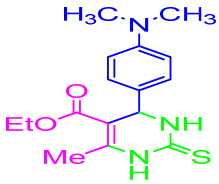


4s
(54 min, 82%)
m.p.210-212°C
Lit.212-214°C [1]

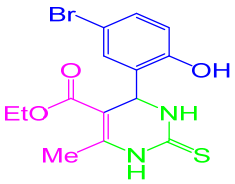


4t
(58min, 82%)
m.p.288-291°C

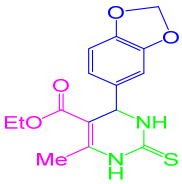
4u
(52 min,85 %)
m.p.181-183°C
Lit.180-181°C [44]



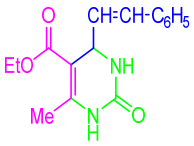
4v
(50 min, 82%)
m.p.212-214°C
Lit.211-213°C [41]



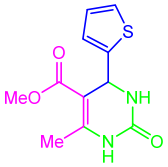
4w
(55 min, 85%)
m.p.290-292°C



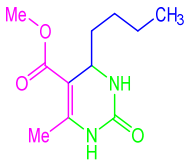
4x
(53 min, 85%)
m.p.253-255°C



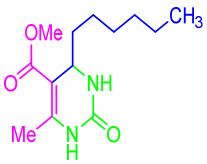
4y
(55 min, 81%)
m.p.175-178°C
Lit.176-178°C [33]



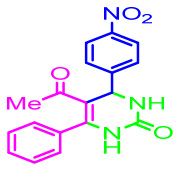
4z
(52 min, 86%)
m.p.157-159°C



4ab
(50 min, 80%)
m.p.171-173°C
Lit.172-175°C [43]

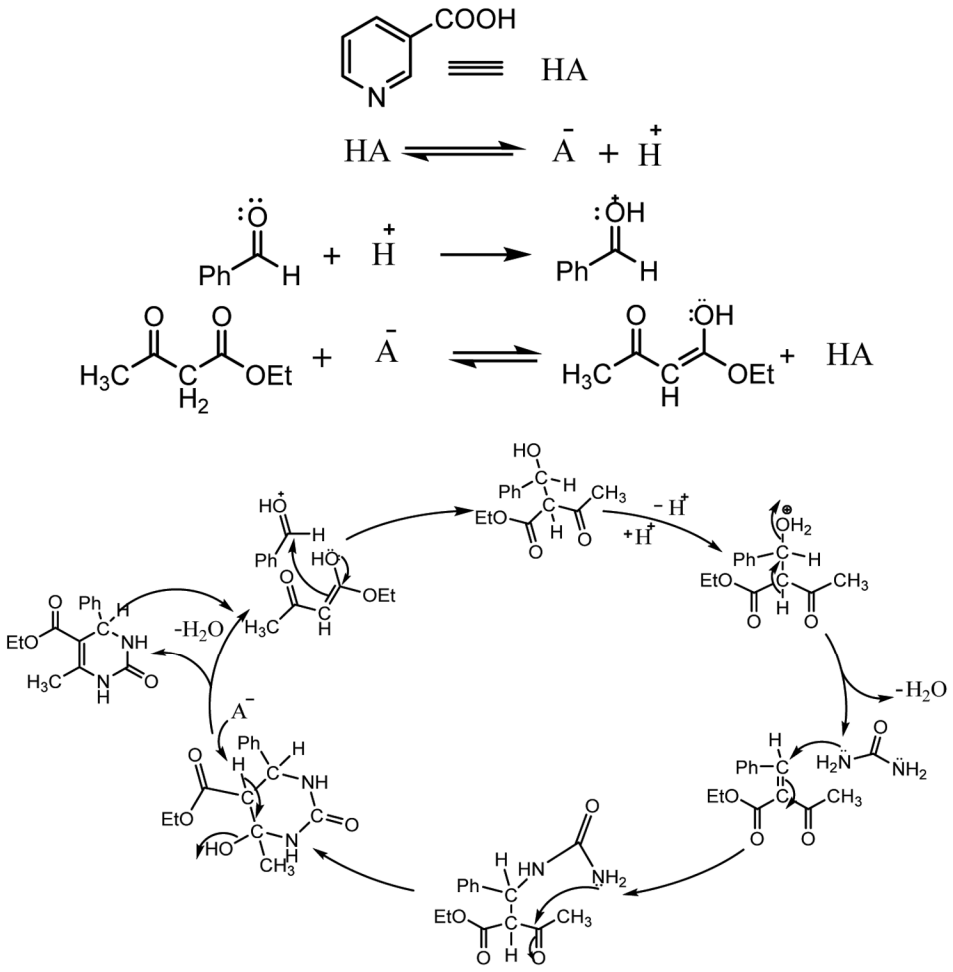


4ac
(52 min, 82%)
m.p.148-150°C
Lit.146-149°C [43]



4ad
(48 min, 84%)
m.p.253-256°C
Lit.255-258°C [42]

(entry 26, 27 and 28) and acetyl acetophenone (entry 29) were used and received good yields. In our developed method only 5~10 mol% nicotinic acid is sufficient to push the reaction forward. Higher catalyst loading did not bring any extra benefits in improving the reaction yield. We attempted to recover the used nicotinic acid in one of our trial reactions, and we were successful in isolating the catalyst to its original amount using a 5% $NaHCO_3$ extraction. Furthermore, when it was re-used in the same reaction, it produced excellent conversion with no problems, implying that this method could ensure Nicotinic acid reusability. Moreover, this mild technique tolerates a wide range of functional varieties, including Cl, F, Br, -NO_2, -OH, -O-, -S-, O-CH_2-O and -OMe, and in each run, we were able to achieve the expected products with high yields without any side products. Piperastrol and Monastrol[37], two biologically active and well-known molecules, were prepared with ease and in high yields using our standardized process. Thiourea also produces excellent yield of thio-derivatives, many of which have recently been shown to be biologically active molecules. Presumably, the reaction followed the usual mechanism dictated by Lewis acid base principles[38–40], and it is possible that, due to the presence of opposing functionalities in nicotinic acid, it is serving a dual role in the condensation process.



Scheme II — Plausible mechanism of the reactions

Mechanism is possibly very straight forward, and it is terminated by the subsequent proton addition, subtraction and expulsion of water during the whole domino process. Plausible reaction mechanism is given in Scheme II.

Conclusions

The present procedure for the synthesis of dihydropyrimidones by the nicotinic acid catalyzed condensation reaction of 1,3-dicarbonyl compound, aldehyde and urea / thiourea provides an efficient, metal-free and much improved modification of Biginelli's reaction. In addition, because of its simplicity and milder reaction conditions, the process can accommodate a wide range of substituents in all three components, which is uncommon in other organo-catalyzed methods. Thus, this procedure has offered an easy access to substituted dihydropyrimidones and a few examples of thiones with various substitution patterns with attractive yields. Moreover, in this study, we used nicotinic acid for the first time to perform pyrimidinone synthesis, which is a significant accomplishment for our protocol. As a result, we would expect that our protocol will be competitive with the established methodologies.

Conflicts of interest

The authors declare no conflict of interest.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgments

The authors gratefully acknowledge the UGC for research grants, and the Department of Chemistry, University of Rajshahi, Bangladesh for the facilities

provided and the Green Chemistry Laboratory, KRICT for providing spectral data.

References

1 Natale N R, Rogers M E, Staples R, Triggle D J & Rutledge A, *J Med Chem*, 42(16) (1999) 3087.
2 Sujatha K, Shanmugam P, Perumal P T, Muralidharan D & Rajendran M, *Bioorg Med Chem Lett*, 16(18) (2006) 4893.
3 Kappe C O, *Tetrahedron*, 49(32) (1993) 6937.
4 Kappe C O, *Accts Chem Res*, 33(12) (2000) 879.
5 Heys L, Moore C G & Murphy P J, *Chem Soc Rev*, 29(1) (2006) 57.
6 Patil A D, Kumar N V, Kokke W C, Bean M F, Freyer A J, Brosse C D & Carte B, *J Org Chem*, 60(5) (1995) 1182.
7 Snider B B, Chen J, Patil A D & Freyer A J, *Tetrahedron Lett*, 37(39) (1996) 6977.
8 Wisén S, Androsavich J, Evans C G, Chang L & Gestwicki J E, *Bioorg Med Chem Lett*, 18(1) (2008) 60.
9 Refat H M & Fadda A A, *Eur J Med Chem*, 70 (2013) 419.
10 Ashok M, Holla B S & Kumari N S, *Eur J Med Chem*, 42(3) (2007) 380.
11 Hurst E W & Hull R, *J Med Chem*, 3(2) (1960) 215.
12 Bahekar S S & Shinde D B, *Bioorg Med Chem Lett*, 14(7) (2004) 1733.
13 Hua H M, Peng J, Dunbar D C, Schinazi R F, de Castro A G, Cuevas C & Hamann M T, *Tetrahedron*, 63(45) (2007) 11179.
14 Biginelli P & Gazz P, *Chim Ital*, 23 (1893) 360.
15 Hu E H, Sidler D R & Dolling U H, *J Org Chem*, 63(10) (1998) 3454.
16 Ranu B C, Hajra A & Jana U, *J Org Chem*, 65 (2000) 6270.
17 Yun M, Qian C, Wang L & Yang M, *J Org Chem*, 65 (2000) 3864.
18 Jun L & Huairang M, *Synlett*, 1 (2000) 63.
19 Maiti G, Kundu P & Guin C, *Tetrahedron Lett*, 44(13) (2003) 2757.
20 Girija D, Naik H B, Kumar B V, Sudhamani C N & Harish K N, *Arabian J Chem*, 12(3) (2019) 420.
21 Safari J & Zarnegar Z, *RSC Adv*, 3(39) (2013) 17962.
22 Sabitha G, Reddy K B, Yadav J S, Shailaja D & Sivudu K S, *Synfacts*, 2 (2006) 0182.
23 Shahid A, Ahmed N S, Saleh T S, Al-Thabaiti S A, Basahel S N, Schwieger W & Mokhtar M, *Catalysts*, 7(3) (2017) 84.
24 Jadhav C K, Nipate A S, Chate A V, Kamble P M, Kadam G A, Dofe V S, Khedkar V M & Gill C H, *J Chinese Chem Soc*, (2021) doi.org/10.1002/jccs.202000468.
25 Sharma N, Sharma U K, Kumar R & Sinha A K, *RSC Adv*, 2(28) (2012) 10648.
26 Zhang Y, Wang B, Zhang X, Huang J & Liu C, *Molecules*, 20(3) (2015) 3811.
27 Suzuki I, Iwata Y & Takeda K, *Tetrahedron Lett*, 49(20) (2008) 3238.
28 da Silva D L, Fernandes S A, Sabino A A & de Fátima Â, *Tetrahedron Lett*, 52(48) (2011) 6328.
29 Jafari-Chermahini M T & Tavakol H, *ChemistrySelect*, 4 (2019) 1895.
30 Hang Z, Zhu J, Lian X, Xu P, Yu H & Han S, *Chem Commun*, 52(1) (2015) 80.
31 Saha S & Moorthy J N, *J Org Chem*, 76(2) (2011) 396.
32 de Graaff C, Ruijter E & Orru R V, *Chem Soc Rev*, 41(10) (2012) 3969.
33 Chen X H, Xu X Y, Liu H, Cun L F & Gong L Z, *J Am Chem Soc*, 128(46) (2006) 14802.
34 Roy H N, Rana M, Munsur A Z A, Lee K I & Sarker A K, *Synthetic Commun*, 46(16) (2016) 1370.
35 Rana M, Rahman A, Razzak A, Roy P K & Roy H N, *J Scientific Res*, 10(1) (2018) 39.
36 Al-Munsur A B Z, Roy H N & Imon M K, *Arabian J Chem*, 12(13) (2020) 8807.
37 Ramos L M, de Leon P, Tobio A Y, dos Santos M R, de Oliveira H C, Gomes A F, Gozzo F C & Neto B A, *J Org Chem*, 77(22) (2012) 10184.
38 Hu E H, Sidler D R & Dolling U H, *J Org Chem*, 63(10) (1998) 3454.
39 Mansoor S S, Shafi S S & Ahmed S Z, *Arabian J Chem*, 9 (2016) S846.
40 Bigi F, Carloni S, Frullanti B, Maggi R & Sartori G, *Tetrahedron Lett*, 40(17) (1999) 3465.
41 Makaev F, Styngach E & Muntyanu V, *Russian J Org Chem*, 43 (2007) 1512.
42 Xie Z-B, Fu L-H, Meng J, Lan J, Hub Z-Y & Le Z-G, *Bioorg Chem*, 101 (2020) 103949.
43 Guo Y, Tang H, Gao Z, Meng X, Yu H, Zhong H, Huang G & Zou C, *ChemistrySelect*, 2 (2017) 8253.
44 Jadhav C K, Nipate A S, Chate A V, Songire V D, Patil A P & Gill C H, *Am Chem Soc Omega*, 4(27) (2019) 22313.