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DABCO-based ionic liquids: introduction of two metal-free catalysts for one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidines†

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Straightforward methods for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives are described through three-component condensation of aromatic aldehydes, malononitrile, and 3-amino-1,2,4-triazole or 6-amino-1,3-dimethyluracil. In both procedures two affordable and metal-free DABCO-based ionic liquids are employed as catalysts and the obtained outcomes are compared with each other. All reactions are performed under mild conditions during acceptable reaction times in good to high yields. After ensuring the efficiency of the catalysts in both reactions, four new derivatives are synthesized and their structures are characterized by FT-IR, ^{1}H NMR and ^{13}C NMR. Simplicity, easy work-up procedures and recoverability of the catalysts are other advantages of these methods.

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Introduction

Since the first synthesized ionic liquid (IL) introduced in 1914,[1] ILs have caused a drastic change in synthetic chemistry. Nowadays, ILs are known as environmentally benign and convenient catalysts or dual solvent-catalysts to improve and facilitate organic reactions by omitting traditional solvents.[2–4] Functionalized ILs, so-called "task-specific ionic liquids", have been designed for use in particular reactions. Hence, versatile ILs with acidic and basic functional groups have been synthesized through metathesis of halide salts or quaternization of appropriate amines and utilized to accelerate different organic transformations.[5]

1,4-Diazabicyclo[2.2.2]octane (DABCO) as a cage-like tertiary amine with weak alkalescence is an adequate alternative to former linear tertiary amines, imidazole and pyrimidine derivatives which have been employed to prepare various ILs. The cage-like structure of DABCO leads to an increase in the energy barrier of nitrogen inversion, which is about 7 kcal mol^{-1} for a trialkylamine. As a result, the lone pair of nitrogen in DABCO is precisely localized and makes DABCO more attuned for quaternization. In recent decades, this feature of DABCO has been applied for the synthesis of different DABCO-based ILs[6–28] as far as they are classified in a distinct category.

Due to them having three nitrogens in their structure, compounds which have a 1,2,4-triazole moiety possess a wide array of pharmaceutical and therapeutic activities such as anti-inflammatory,[29] antiviral,[30] antimicrobial,[31–34] antitumor[35] anticonvulsant,[30] analgesic,[36] antihypotensive,[37] antiparasitic, fungicidal, insecticidal, herbicidal and plant growth regulatory activities.[38–41] Many drugs with the triazole moiety are manufactured, including ribavarin (or tribavirin, an antiviral medication for treating RSV infection, hepatitis C, and viral hemorrhagic fever), alprazolam (or Xanax, an anxiolytic medication used to treat anxiety disorders) and letrozole (an anticancer medication for treatment of local or metastatic breast cancer) (Fig. 1(a)). Moreover, triazolopyrimidines are an attractive purine analogue because of their structure which is constructed from two five- and six-fused rings containing nitrogens like purine (Fig. 1(b)).

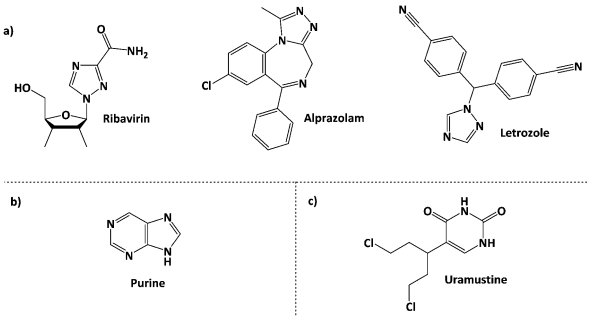

Fig. 1 The structures of (a) some triazole-containing drugs, (b) purine, and (c) uramustine.

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Many nitrogen-containing, biologically important compounds, containing uracil as a structural block, have been recently reported such as pyrazolopyridines,[42] pyramidopyrimidines,[43] pyridopurines,[44] pyrazolopyrimidines[45] and xanthine derivatives.[46] This considerable interest is correlated with a vast range of biological activities such as antitumor,[47] antihypertensive,[48] hepatoprotective,[48] cardiotonic[49] and antifolate activities.[50] Besides, uracil derivatives like uramustine (Fig. 1(c)) have been utilized as chemotherapy drugs by damaging DNA, because cancer cells take up uracil to make nucleic acids during their cycles of cell division.

Results and discussion

In recent years, our research group has pursued the goal of developing more efficient organic processes. For this reason, new DABCO-based ILs were synthesized and used as catalysts and dual catalyst-solvents in various organic transformations.[19–21,25–28] In continuation of these studies, we were interested in investigating the catalytic activity of $[H_2\text{-DABCO}][H_2PO_4]_2$ and $[H_2\text{-DABCO}][ClO_4]_2$, as two DABCO-based ILs, in the synthesis of diverse structurally functionalized 1,2,4-triazolo[4,3-*a*]pyrimidines and pyrido[2,3-*d*]-pyrimidines and in comparing the effect of anion exchange in the activity of these ILs.

At first, to select the best conditions for the reactions, the syntheses of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]-pyrimidine derivatives of 4-chlorobenzaldehyde were chosen as models and the effects of various amounts of the catalysts, different solvents and temperatures on reaction times and yields were investigated.

Despite using aprotic and protic solvents in the synthesis of 5-amino-7-(4-chlorophenyl)-7,8-dihydro[1,2,4]triazolo[4,3-*a*]-pyrimidine-6-carbonitrile (**4a**), the reaction was completed in the absence of solvent for both catalysts (Table 1, entries 5 and 6). An increase of the catalyst amounts led to an increase in reaction times and decrease in yields, so the best conditions could be achieved when 0.016 mmol of the catalysts was used under solvent-free conditions at 100 °C (Table 1, entry 5). On the other hand, using ethanol as a solvent in the synthesis of 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido-[2,3-*d*]pyrimidine-6-carbonitrile (**6b**) led to reaction completion (Table 1, entries 14–17); however, the amounts of the catalysts were not the same and $[H_2\text{-DABCO}][ClO_4]_2$ could complete the reaction in smaller amounts (Table 1, entries 14 and 15). The best conditions for both reactions, extracted from Table 1, are portrayed in Scheme 1.

Furthermore, to investigate the efficiency of these methods, different aliphatic and aromatic aldehydes with electron-withdrawing and -donating functional groups were employed to synthesize other structurally functionalized derivatives of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine. Despite the successful reaction of aromatic aldehydes, these methods could not realize the preparation of corresponding derivatives of aliphatic aldehydes. The obtained results are compiled in Table 2. According to this table, all reactions gave products in good to high yields in decent reaction times.

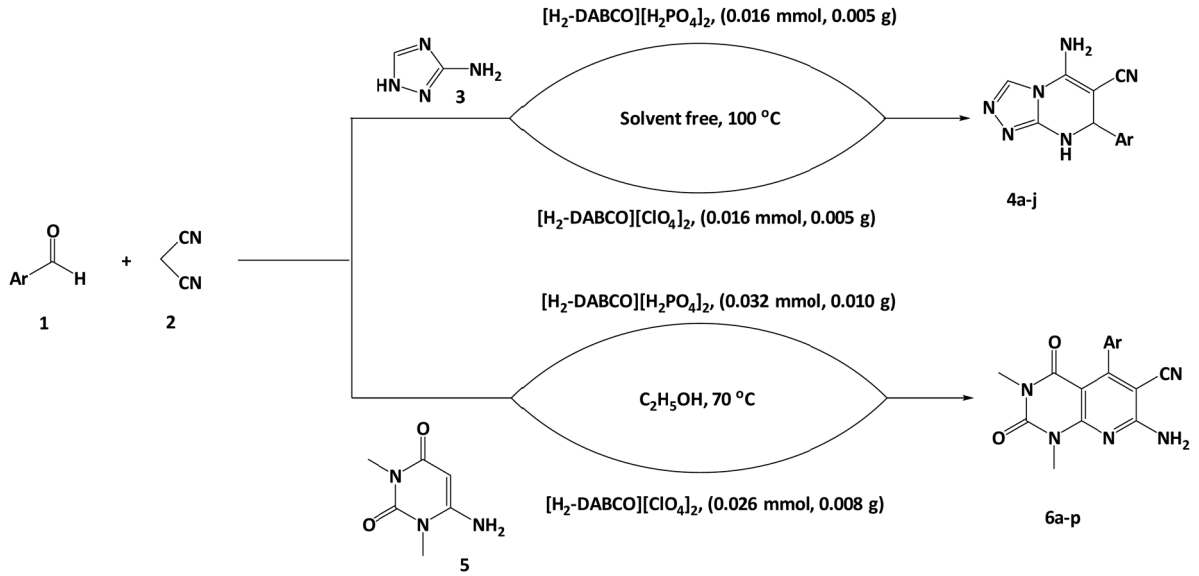
In this step, it is necessary to provide a comparative table to show the utility of these methods *vs.* former procedures used for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido-[2,3-*d*]pyrimidine derivatives. For this reason, the syntheses of **4a** and **6b** are selected as models and the comparisons are carried out in terms of catalyst amounts, reaction times and yields, and turnover frequencies (TOFs) (Table 3).

Although it seems that the described methods are time-consuming, they are cost-saving and efficient due to the smaller amounts of the catalysts; the calculated TOFs support this claim.

Table 1 Optimization of the amounts of the catalysts, temperature and solvent in the synthesis of 5-amino-7-(4-chlorophenyl)-7,8-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carbonitrile (**4a**, entries 1–6) and 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-6-carbonitrile (**6b**, entries 7–17)

	Catalyst amount (mmol)		Solvent		Temp. (°C)		Time (min)		Conversion (isolated yield %)	
Entry	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]
1	0.016		EtOH		70		75	90	Not completed	
2	0.016		H_2O		70		60	80	Not completed	
3	0.016		H_2O : EtOH (1 : 1)		70		65	70	Not completed	
4	0.016		MeCN		70		70	70	Not completed	
5	0.016		—		100		40	50	100 (95)	100 (96)
6	0.026		—		100		80	80	100 (90)	100 (93)
7	0.032		H_2O		70		60	80	Trace	
8	0.026	0.032	H_2O		70	80	70	80	Trace	
9	0.016	0.032	H_2O		70	90	70	90	Trace	
10	0.032		H_2O : EtOH (2 : 1)		70		80	70	Trace	
11	0.032		H_2O : EtOH (1 : 1)		r.t.		100	100	Not completed	
12	0.032		MeCN		70		95	90	Not completed	
13	0.032		—		100		100	100	Not completed	
14	0.032		EtOH		70		40	50	100 (95)	100 (90)
15	0.026		EtOH		70		55	50	100 (90)	100 (95)
16	0.016		EtOH		70		65	60	100 (93)	
17	0.026		EtOH		r.t.		110	100	Not completed	

[a] A: $[H_2\text{-DABCO}][H_2PO_4]_2$. [b] B: $[H_2\text{-DABCO}][ClO_4]_2$.



Scheme 1 Synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives using $[H_2\text{-DABCO}][H_2PO_4]_2$ and $[H_2\text{-DABCO}][ClO_4]_2$ as the catalysts.

Once again, the syntheses of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives of 4-chlorobenzaldehyde were chosen as the models to investigate the reusability of the catalysts. After completion of the reactions, water was poured into the reaction mixtures (for the synthesis of pyrido[2,3-*d*]pyrimidine derivative, it was added after filtering off the solvent) in order to separate the catalysts. Afterwards the reaction mixtures were filtered off and the filtrates were evaporated under vacuum at 70 °C. The obtained white precipitates were washed with diethyl ether and reused three times for both catalysts. The achieved results, presented in Fig. 2 and 3, show the least variation in reaction times and yields after three runs.

The postulated mechanisms for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives are depicted in Scheme 2, based on previous literature.[26,28] To begin with, carbonyl group of aldehyde is activated through hydrogen bonding with ILs to obtain intermediate a. The structures delimited in dashed lines show how carbonyl group is activated by hydrogen bonding. After that, the mechanism pathway divides into three routes. In route 1, intermediate b, produced from malononitrile 2, attacks the activated carbonyl group to change into intermediate c. Activated by ILs, intermediate c is attacked by 6-amino-1,3-dimethyluracil 5, which leads to intermediate d. A hydrogen shift takes place in intermediate d to convert to intermediate e. In this step, intermediate e is able to undergo an intra-cyclization to produce intermediate f. Two steps of hydrogen shift (in intermediate f) and aromatization (in intermediate g) lead to the product (**6a–p**). In general, product (**4a–j**) is produced from routes 2 and 3, but at the beginning, they differ in the formation of intermediates c and j. In route 2, intermediate b makes for activated carbonyl group to convert into intermediate c, whereas in route 3 the reaction starts with preparation of an imine (intermediate j) through the attack of amino group of 3-amino-1,2,4-triazole 3 to intermediate a. When intermediate c is attacked by 3-amino-1,2,4-triazole 3 or intermediate j takes part in a reaction with intermediate b, intermediate h can be produced. ILs exchange hydrogen in intermediate h to lead to an intra-cyclization (intermediate i). Finally, a hydrogen shift in intermediate i leads to the product (**4a–j**).

It is notable that if intermediate c were attacked with N^2, the corresponding product would be 7. However, according to the spectral data for new compound **4j**, the observed doublet peaks at 8.79 and 5.31 related to NH and CH, respectively, show a coupling (J = 2 Hz) between them in pyrimidine ring. This proves that aliphatic CH and NH are neighbors in the ring. The same result was observed in the spectral data for compound **4i**. The spectra of new compounds are presented in ESI† and correlated with previous literature.[51]

Experimental

Materials

All aldehydes, malononitrile, 6-amino-1,3-dimethyluracil, and 3-amino-1,2,4-triazole were purchased from Merck chemical company (Munich) and were used without further purification. The purity of them was monitored by thin layer chromatography (TLC). DABCO (CAS: 280-57-9, M_W: 112.17 g mol^{-1}, assay ≥99% w/w), phosphoric acid (CAS: 7664-38-2, M_W: 98.00 g mol^{-1}, concentration ≥85% v/v) and perchloric acid (CAS: 7601-90-3, M_W: 100.46 g mol^{-1}, assay ≥70% v/v) were purchased from Sigma-Aldrich (Mumbai). Both assays were reported by the manufacturer and were not examined more. All solvents were obtained from Merck (Munich) and were kept sealed in airtight bottles to minimize the absorption of atmospheric moisture. Moreover, they were distilled before being used.

Table 2 Preparation of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives using $[H_2\text{-DABCO}][H_2PO_4]_2$ (A) and $[H_2\text{-DABCO}][ClO_4]_2$ (B) as the catalysts

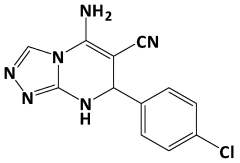
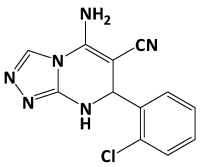
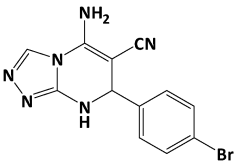
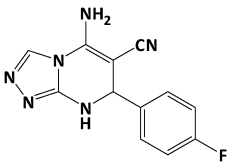
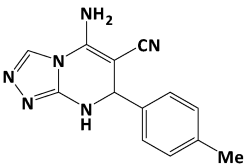
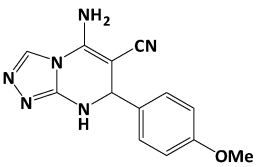
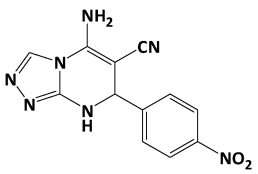
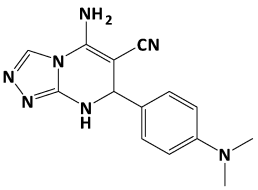
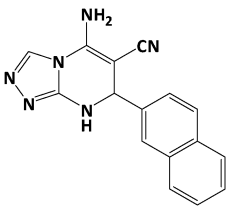
Entry	Aldehyde	Product		Time (min) A	Time (min) B	Yield[a] (%) A	Yield[a] (%) B	MP (°C) Found	MP (°C) Rep.	Ref.
1	4-ClC_6H_4CHO		4a	40	50	95	96	258–259	257–258	51
2	2-ClC_6H_4CHO		4b	35	25	90	90	265–268	263–266	51
3	4-BrC_6H_4CHO		4c	45	50	96	95	260–262	264–266	51
4	4-FC_6H_4CHO		4d	30	40	95	96	251–253	252–254	51
5	4-MeC_6H_4CHO		4e	50	45	92	93	244–246	245–246	51
6	4-$OMeC_6H_4CHO$		4f	75	60	90	93	215–220	218–219	51
7	4-$NO_2C_6H_4CHO$		4g	55	60	90	90	243–246	245–247	51
8	4-$Me_2NC_6H_4CHO$		4h	50	60	90	90	244–248	242–245	51
9	2-Naphthaldehyde		4i	70	60	93	95	280–284	—	New

Table 2 (*continued*)

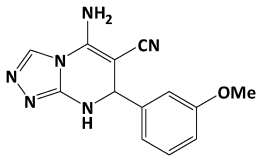
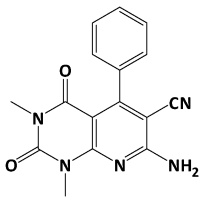
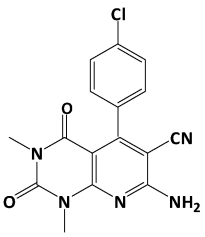
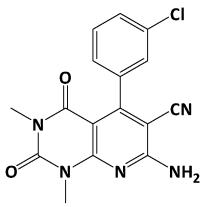
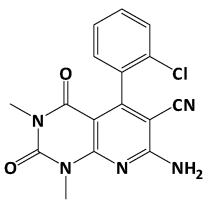
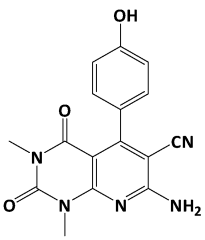
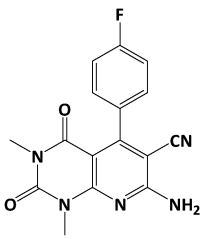
Entry	Aldehyde	Product		Time (min) A	Time (min) B	Yield[a] (%) A	Yield[a] (%) B	MP (°C) Found	MP (°C) Rep.	Ref.
10	3-$MeOC_6H_4CHO$		4j	55	50	95	90	218–221	—	New
11	C_6H_4CHO		6a	45	55	93	90	307–308	>300	52
12	4-ClC_6H_4CHO		6b	40	50	95	95	311–315	>300	53
13	3-ClC_6H_4CHO		6c	40	50	93	90	301–304	>300	53
14	2-ClC_6H_4CHO		6d	40	45	91	93	300–304	>300	53
15	4-OHC_6H_4CHO		6e	70	75	89	90	297–302	>300	54
16	4-FC_6H_4CHO		6f	50	65	95	96	300–302	>300	53

Table 2 (*continued*)

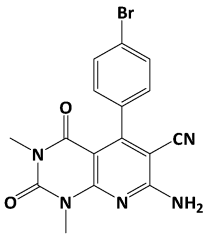
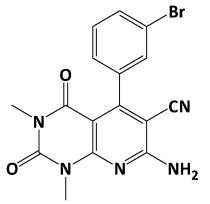
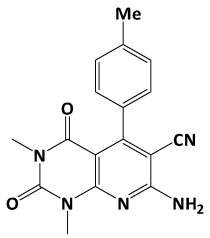
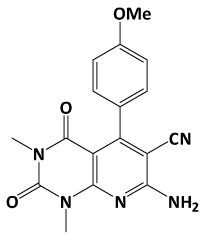
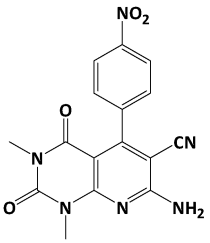
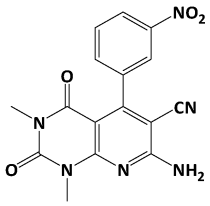
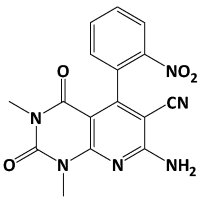
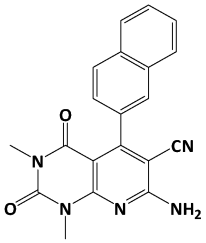
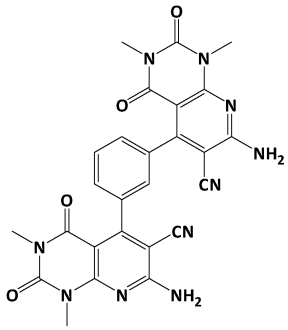
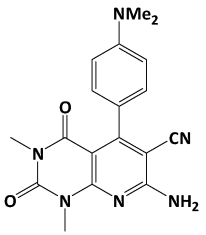
Entry	Aldehyde	Product		Time (min) A	Time (min) B	Yield[a] (%) A	Yield[a] (%) B	MP (°C) Found	MP (°C) Rep.	Ref.
17	4-BrC_6H_4CHO		6g	65	80	95	96	303–307	>300	55
18	3-BrC_6H_4CHO		6h	50	75	90	92	304–310	>300	53
19	4-MeC_6H_4CHO		6i	35	45	92	95	302–307	>300	52
20	4-$OMeC_6H_4CHO$		6j	70	75	85	93	300–303	>300	52
21	4-$NO_2C_6H_4CHO$		6k	60	70	87	92	307 (Dec.)[b]	>300	55
22	3-$NO_2C_6H_4CHO$		6l	95	100	92	93	298–300	>300	53
23	2-$NO_2C_6H_4CHO$		6m	75	80	90	93	303 (Dec.)	>300	54

Table 2 (*continued*)

Entry	Aldehyde	Product		Time (min) A	Time (min) B	Yield[a] (%) A	Yield[a] (%) B	MP (°C) Found	MP (°C) Rep.	Ref.
24	2-Naphthaldehyde		6n	80	90	89	90	310–315	>300	56
25	3-$CHOC_6H_4CHO$		6o	30	30	93	92	>300	—	New
26	4-$NMe_2C_6H_4CHO$		6p	90	90	90	90	>300	—	New

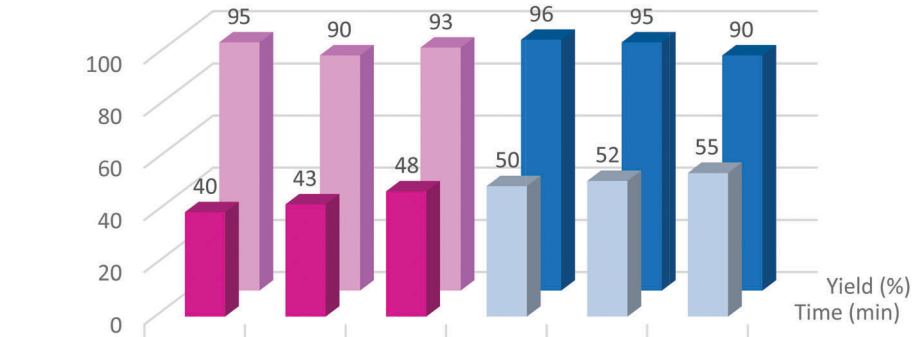
[a] Isolated yields. [b] Decomposition.

Table 3 Comparison of the activity of $[H_2\text{-DABCO}][H_2PO_4]_2$ and $[H_2\text{-DABCO}][ClO_4]_2$ with those of other reported catalysts in the synthesis of 5-amino-7-(4-chlorophenyl)-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carbonitrile (**4a**, entries 1–6) and 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**6b**, entries 7–17)

Entry	Catalyst	Amount (mol)	Conditions	Time (min)	Yield (%)	TOF (min^{-1})	Ref.
1	NaOH	2×10^{-4}	Reflux/EtOH	30	82	13666.67	51
2	NaOH	2×10^{-4}	US/H_2O	60	88	7333.35	51
3	Boric acid	0.2	CTAB and H_2O/60 °C	20	95	23.75	57
4	1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	1	Reflux/EtOH	15	90	6	58
5	$[H_2\text{-DABCO}][H_2PO_4]_2$	16×10^{-6}	Solvent-free/100 °C	40	95	148437.5	This work
6	$[H_2\text{-DABCO}][ClO_4]_2$	16×10^{-6}	Solvent-free/100 °C	50	96	120 000	This work
7	Triethylbenzylammonium chloride (TEBAC)	66×10^{-5}	H_2O/90 °C	720	96	202.02	55
8	Nano-MgO	25×10^{-5}	H_2O/80 °C	15	90	24 000	53
9	SBA-15-Pr-SO_3H	0.02 g	Solvent-free/60 °C	20	80	—	59
10	Urea	0.1	H_2O : EtOH (1 : 1)/r.t.	55	92	16.73	54
11	Triethanolamine (TEOA)	0.2	H_2O/80 °C	120	92	3.83	60
12	Electrolysis	—	EtOH/KBr	20	71	—	61
13	Electrolysis	—	EtOH/NaBr	20	90	—	62
14	Al-HMS-20	0.03 g	EtOH/r.t.	720	92	—	63
15	$[C_4(DABCO)_2]\cdot 2OH$	0.1	Grinding/r.t.	7	94	134.29	56
16	$[H_2\text{-DABCO}][H_2PO_4]_2$	32×10^{-6}	EtOH/70 °C	40	95	74218.75	This work
17	$[H_2\text{-DABCO}][ClO_4]_2$	26×10^{-6}	EtOH/70 °C	50	95	73076.92	This work

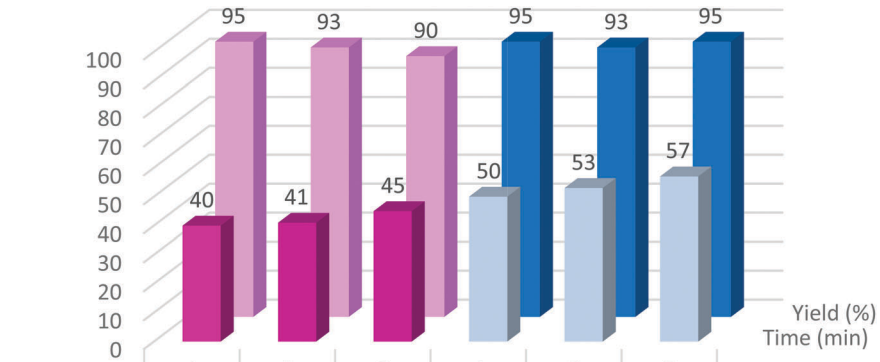
Characterization techniques

Products were characterized by their physical constants, comparison with authentic samples and IR and NMR spectroscopy. The purity determination of the substrate and reaction monitoring were accomplished by TLC on silica-gel Polygram SILG/UV 254 plates. Melting points were measured by an Electrothermal IA9100 melting point apparatus in capillary tubes. The starting



	1	2	3	4	5	6
Time (min)	40	43	48	50	52	55
Yield (%)	95	90	93	96	95	90

Fig. 2 The reusability of $[H_2\text{-DABCO}][H_2PO_4]_2$ (runs 1–3, the columns in purple) and $[H_2\text{-DABCO}][ClO_4]_2$ (runs 4–6, the columns in blue) in the synthesis of 5-amino-7-(4-chlorophenyl)-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carbonitrile (**4a**).



	1	2	3	4	5	6
Time (min)	40	41	45	50	53	57
Yield (%)	95	93	90	95	93	95

Fig. 3 The reusability of $[H_2\text{-DABCO}][H_2PO_4]_2$ (runs 1–3, the columns in purple) and $[H_2\text{-DABCO}][ClO_4]_2$ (runs 4–6, the columns in blue) in the synthesis of 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**6b**).

temperature of the approximate melting range was input *via* the keyboard and the melting point range was observed visually. FT-IR spectra were recorded with a PerkinElmer Spectrum BX series and KBr pellets were used for solid samples. Mass spectra were obtained with an Agilent Technologies 5975C spectrometer *via* a mass selective detector (MSD) operating at an ionization potential of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AV-400 using TMS (0.00 ppm) as internal standard and DMSO-d_6 as solvent.

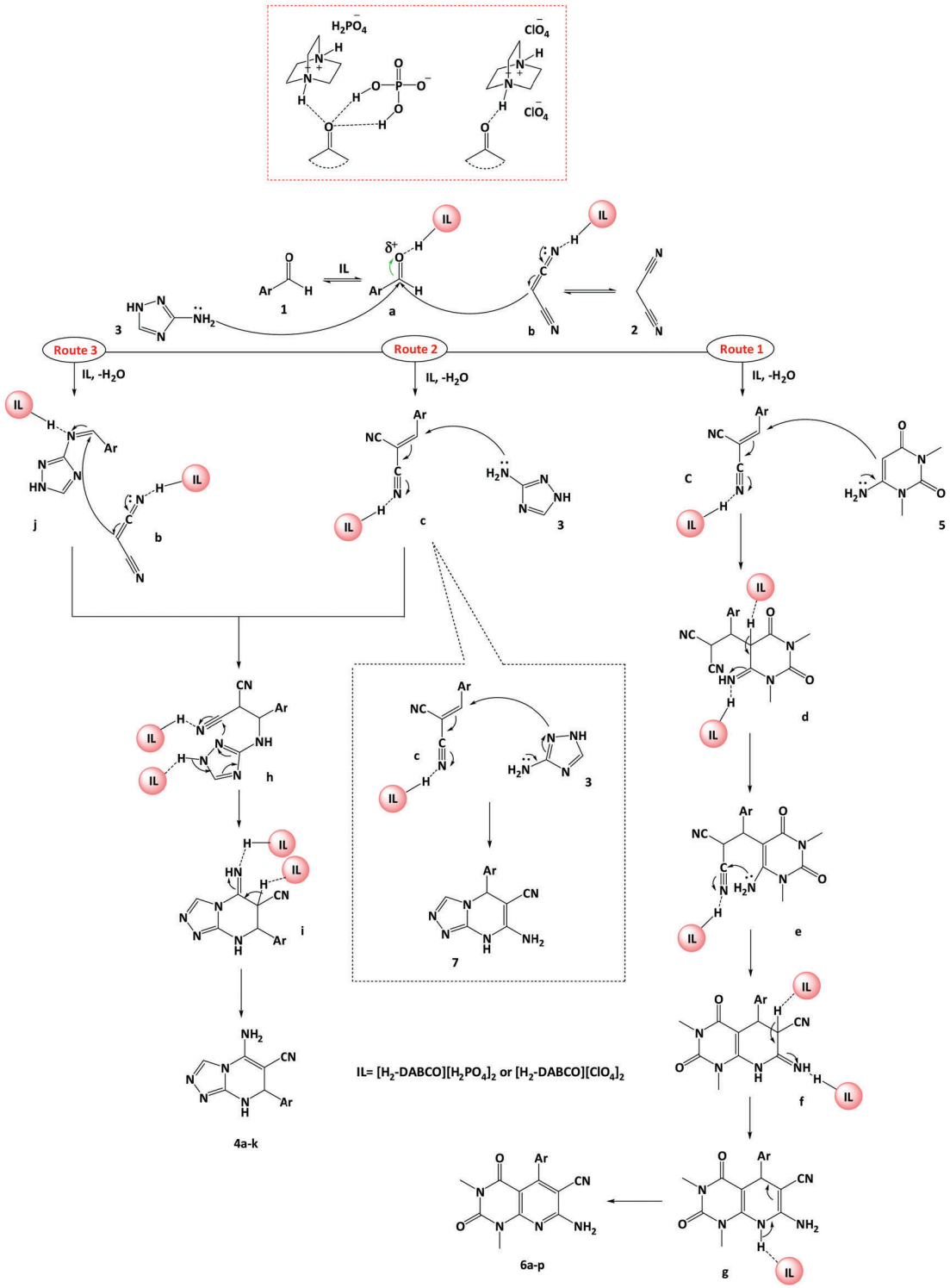
Preparation of 1,4-diazabicyclo[2.2.2]octane-1,4-diium dihydrogen phosphate {$[H_2\text{-DABCO}][H_2PO_4]_2$}

A mixture of DABCO (0.909 g, 8.1 mmol) in dry dichloromethane (50 mL) was charged into a 100 mL round-bottomed flask and was stirred in an ice-bath for 1 min. Then, a stoichiometric amount of phosphoric acid (85% v/v, 1 mL, 1.84 g) was added dropwise to this mixture during a period of 25 min. After the addition, the flask, fitted with a reflux condenser, was immersed in a recirculating heated water-bath for 24 h. After that, the obtained ionic liquid was washed with diethyl ether repeatedly (3 × 15) to remove non-ionic residues and then dried under vacuum to give $[H_2\text{-DABCO}][H_2PO_4]_2$ as a white solid in 97% yield (2.417 g) (Fig. 4(a)). The purity of the product was determined by melting point, and mass, FT-IR, ^{1}H NMR and ^{13}C NMR spectra.[26]

Spectral data for $[H_2\text{-DABCO}][H_2PO_4]_2$: white solid; m.p. 98 °C; MS: m/z = 308 (M^+); FT-IR (KBr, cm^{-1}) ν_{max}: 3421, 2823, 2380, 1638, 1115, 1053, 961; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.54 (s, 6H), 6.70 (s, 1H, NH), 10.90 (s, 1H, H_2PO_4); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 43.4.

Preparation of 1,4-diazabicyclo[2.2.2]octane-1,4-diium perchlorate {$[H_2\text{-DABCO}][ClO_4]_2$}

After dissolving DABCO (0.673 g, 6 mmol) in 50 mL dry dichloromethane in a 100 mL round-bottomed flask, the mixture was stirred in an ice-bath for 1 min. Then a stoichiometric amount of perchloric acid (70%, 1 mL, 12 mmol) was added dropwise to the mixture in 5 parts (5 × 0.2 mL) within 25 min. After completion of the addition, the mixture was stirred at room temperature for 20 h. At this point, the solvent was decanted and the obtained white solid was



Scheme 2 The presumed mechanism for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives using $[H_2\text{-DABCO}][H_2PO_4]_2$ and $[H_2\text{-DABCO}][ClO_4]_2$ as the catalysts.

repeatedly washed with diethyl ether (3 × 15 mL) to remove non-ionic residues. At last, the obtained IL was dried under vacuum to afford $[H_2\text{-DABCO}][ClO_4]_2$ in 95% yield (1.78 g) (Fig. 4(b)). For being certain about the purity of the product, it was checked by melting point, and mass, FT-IR, ^{1}H NMR and ^{13}C NMR spectra.[64]

Spectral data for $[H_2\text{-DABCO}][ClO_4]_2$: white solid; m.p. 55 °C; MS: m/z = 313 (M^+); FT-IR (KBr, cm^{-1}) ν_{max}: 3470, 1150, 1082, 798, 623; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.35 (s, 6H), 5.42 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 43.4.

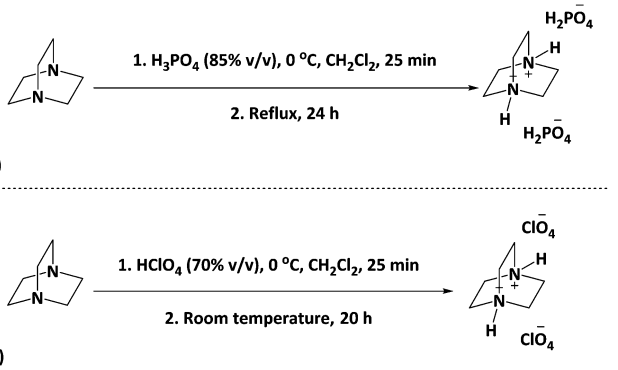


Fig. 4 The preparation of $[H_2\text{-DABCO}][H_2PO_4]_2$ (a) and $[H_2\text{-DABCO}][ClO_4]_2$ (b).

General procedure for preparation of 1,2,4-triazolo[4,3-*a*]pyrimidines

To a mixture of aromatic aldehyde **1** (1 mmol), malononitrile **2** (1 mmol) and 3-amino-1,2,4-triazole **3** (1 mmol) in a 25 mL round-bottom flask, $[H_2\text{-DABCO}][H_2PO_4]_2$ (0.005 g, 0.016 mmol, Method A) or $[H_2\text{-DABCO}][ClO_4]_2$ (0.005 g, 0.016 mmol, Method B) was added. Then the mixture was stirred magnetically under solvent-free conditions at 100 °C for the appropriate time. Meanwhile, the reaction process was carefully monitored by TLC (*n*-hexane : ethyl acetate; 8 : 2). After completion of the reaction, 5 mL water was poured into the reaction medium and then filtered off so as to separate the catalyst. Finally, the obtained precipitate was recrystallized from ethanol to afford the required product (**4a–j**).

5-Amino-7-(naphthalen-2-yl)-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carbonitrile (4i)

White powder; m.p. 280–284 °C; IR (KBr, ν, cm^{-1}): 3360, 3256, 3183, 2189, 1657, 1629, 1526; ^1H NMR (400 MHz, DMSO-d_6): 8.88 (d, J = 2.4 Hz, 1H, NH), 7.90–7.97 (m, 3H, N=CH–N and CH–Ph), 7.77 (d, J = 10.8 Hz, 2H, CH–Ph), 7.50–7.55 (m, 3H, CH–Ph), 7.31 (d, J = 2.8 Hz, 2H, NH_2), 5.56 (d, J = 2 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): 153.9, 151.9, 147.0, 140.3, 132.6, 132.5, 128.7, 127.9, 127.6, 127.5, 126.5, 126.2, 124.6, 124.4, 119.0, 54.3.

5-Amino-7-(3-methoxyphenyl)-7,8-dihydro[1,2,4]triazolo[4,3-*a*]-pyrimidine-6-carbonitrile (4j)

White powder; m.p. 218–221 °C; IR (KBr, ν, cm^{-1}): 3427, 3245, 3098, 2192, 1678, 1623, 1515; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.79 (d, J = 2.4 Hz, 1H, NH), 7.72 (s, 1H, N=CH–N), 7.31 (t, J = 8 Hz, 1H, CH–Ph), 7.23 (d, J = 2.4 Hz, 2H, NH_2), 6.82–6.91 (m, 3H, CH–Ph), 5.31 (d, J = 2 Hz, 1H, CH), 3.74 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 159.3, 151.8, 144.7, 130.6, 129.9, 120.2, 118.0, 112.0, 55.0, 53.7.

General procedure for preparation of pyrido[2,3-*d*]pyrimidines

5 mL ethanol was poured into a 25 mL round-bottom flask containing aldehyde **1** (1 mmol), malononitrile **2** (1 mmol), 6-amino-1,3-dimethyluracil **5** (1 mmol) and $[H_2\text{-DABCO}][H_2PO_4]_2$ (0.010 g, 0.032 mmol, Method A) or $[H_2\text{-DABCO}][ClO_4]_2$ (0.008 g, 0.026 mmol, Method B). The mixture was stirred magnetically at 70 °C to dissolve all components. However, the precipitate of product appeared in the reaction medium after a short time. Besides, the reaction progress was traced to completion by TLC (*n*-hexane : ethyl acetate; 2 : 8). After completion of the reaction, the mixture was filtered off and the obtained residue was washed with water to remove the catalyst. Finally, the crude product was recrystallized from ethanol if necessary (**6a–p**).

5,5′-(1,3-Phenylene)bis(7-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile) (6o)

White powder; m.p. >300 °C; IR (KBr, ν, cm^{-1}): 3445, 3346, 3240, 3035, 2959, 2222, 1704, 1663, 1624, 1566; ^1H NMR (400 MHz, DMSO-d_6): 8.59 (s, 1H, CH–Ph), 8.08 (dt, J_1 = 8 Hz, J_2 = 1.6 Hz, J_3 = 1.2 Hz, 1H, CH–Ph), 7.77 (s, 2H, NH_2), 7.72 (t, J = 8 Hz, 1H, CH–Ph), 7.59 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, J_3 = 1.2 Hz, 1H, CH–Ph), 3.50 (s, 6H, Me), 3.07 (s, 6H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): 160.7, 160.2, 160.1, 158.5, 157.3, 153.6, 150.7, 138.4, 133.3, 130.8, 129.8, 129.2, 115.5, 114.1, 113.1, 98.5, 88.0, 82.1, 29.6, 27.7.

7-Amino-5-(4-(dimethylamino)phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (6p)

Orange powder; m.p. >300 °C; IR (KBr, ν, cm^{-1}): 3395, 3352, 3233, 2918, 2202, 1660, 1613, 1564; ^1H NMR (400 MHz, DMSO-d_6): 7.82 (dd, J_1 = 9.2 Hz, J_2 = 2 Hz, 2H, CH–Ph), 6.84 (dd, J_1 = 9.2 Hz, J_2 = 2 Hz, 2H, CH–Ph), 6.78 (s, 2H, NH_2), 3.23 (s, 3H, C–Me), 3.10 (s, 6H, NMe_2), 3.07 (s, 3H, C–Me); ^{13}C NMR (100 MHz, DMSO-d_6): 161.3, 158.8, 154.2, 151.5, 133.5, 118.7, 116.2, 115.5, 111.7, 74.8, 68.5, 29.2, 27.0.

Conclusions

In this paper, the syntheses of 1,2,4-triazolo[4,3-*a*]pyrimidine and pyrido[2,3-*d*]pyrimidine derivatives are investigated in the presence of $[H_2\text{-DABCO}][H_2PO_4]_2$ and $[H_2\text{-DABCO}][ClO_4]_2$ as efficient catalysts. All products are prepared in good reaction times and excellent yields without any by-products. The work-up procedures are simple and obtained products are purified without need of column chromatography. Above all, small amounts of catalysts are used in both procedures, which indicate them as affordable and cost-saving procedures. Finally, the reusability of both catalysts is investigated and the catalysts show utility in recycling during 3 runs.

Conflicts of interest

There are no conflicts to declare.

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References

1 P. Walden, *Bull. Acad. Imp. Sci. St.-Petersbourg*, 1914, 1800.
2 J. Gui, X. Cong, D. Liu, X. Zhang, Z. Hu and Z. Sun, *Catal. Commun.*, 2004, **5**, 473.
3 D. M. Du and X. Chen, *Chin. J. Org. Chem.*, 2003, **23**, 331.
4 A. Davoodnia, S. Allameh, A. R. Fakhari and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, 2010, **21**, 550.
5 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
6 X. Liang, Sh. Gao, J. Yang and M. He, *Catal. Lett.*, 2008, **125**, 396.
7 Z.-Z. Yang, L.-N. He, X.-Y. Dou and S. Chanfreau, *Tetrahedron Lett.*, 2010, **51**, 2931.
8 Z.-Z. Yang, L.-N. He, S.-Y. Peng and A.-H. Liu, *Green Chem.*, 2010, **12**, 1850.
9 D.-Z. Xu, Y. Liu, S. Shi and Y. Wang, *Tetrahedron: Asymmetry*, 2010, **21**, 2530.
10 A. Mulik, D. Chandam, P. Patil, D. Patil, S. Jagdale and M. Deshmukh, *J. Mol. Liq.*, 2013, **179**, 104.
11 S. Keithellakpam and W. S. Laitonjam, *Chin. Chem. Lett.*, 2014, **25**, 767.
12 A. Ying, Z. Li, J. Yang, S. Liu, S. Xu, H. Yan and C. Wu, *J. Org. Chem.*, 2014, **79**, 6510.
13 A. Ying, Y. Ni, S. Xu, S. Liu, J. Yang and R. Li, *Ind. Eng. Chem. Res.*, 2014, **53**, 5678.
14 M. K. Munshi, S. M. Gade, V. H. Rane and A. A. Kelkar, *RSC Adv.*, 2014, **4**, 32127.
15 A. R. Hajipoura and F. Mohammadsaleh, *Tetrahedron Lett.*, 2014, **55**, 3459.
16 F. Shirini, M. Abedini, M. Seddighi, O. G. Jolodar, M. Safarpoor, N. Langroodi and S. Zamani, *RSC Adv.*, 2014, **4**, 63526.
17 H.-L. Hou, F.-L. Qiu, A.-G. Ying and S.-L. Xu, *Chin. Chem. Lett.*, 2015, **26**, 377.
18 F. Shirini, M. Abedini, N. Mahmoodi, M. Biglari and M. S. N. Langrudi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2015, **190**, 1912.
19 F. Shirini, M. S. N. Langarudi and O. Goli-Jolodar, *Dyes Pigm.*, 2015, **123**, 186.
20 F. Shirini, M. S. N. Langarudi, M. Seddighi and O. G. Jolodar, *Res. Chem. Intermed.*, 2015, **41**, 8483.
21 O. Goli-Jolodar, F. Shirini and M. Seddighi, *J. Mol. Liq.*, 2016, **224**, 1092.
22 S. Keithellakpam and W. S. Laitonjam, *Indian J. Chem.*, 2016, **55B**, 110.
23 L. Z. Fekri, M. Nikpassand and R. Maleki, *J. Mol. Liq.*, 2016, **222**, 77.
24 T. Lohar, A. Kumbhar, M. Barge and R. Salunkhe, *J. Mol. Liq.*, 2016, **224**, 1102.
25 N. Seyyedi, F. Shirini and M. S. N. Langarudi, *RSC Adv.*, 2016, **6**, 44630.
26 F. Shirini, M. S. N. Langarudi and N. Daneshvar, *J. Mol. Liq.*, 2017, **234**, 268–278.
27 N. Seyyedi, F. Shirini, M. S. N. Langarudi and S. Jashnani, *J. Iran. Chem. Soc.*, 2017, **14**, 1859.
28 F. Shirini, M. S. N. Langarudi, N. Daneshvar, M. Mashhadinezhad and N. Nabinia, *J. Mol. Liq.*, 2017, **243**, 302.
29 B. Tozkoparan, N. Gokhan, G. Aktay, E. Yesilada and M. Ertan, *Eur. J. Med. Chem.*, 2000, **34**, 743.
30 M. kritsanida, A. Mouroutsou, P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, C. Pannecouque and M. Witvouw, *E. De. Clercq, II Farmaco*, 2002, **57**, 253.
31 B. S. Holla, R. Gonsalves and S. Shenoy, *II Farmaco*, 1998, **53**, 574.
32 S. Ersan, S. Nacak and R. Berkem, *II Farmaco*, 1998, **53**, 773.
33 H. Yuksek, A. Demirbs, A. Ikizler, C. B. Johansson, C. Celik and A. A. Ikizler, *Arzneim. Forsch.*, 1997, **47**, 405.
34 A. A. Ikizler, F. Ucar, N. Demirbas, I. Yasa, A. Ikizler and T. Genzer, *Indian J. Heterocycl. Chem.*, 1999, **61**, 271.
35 N. Demirbs and A. Ugurluoglu-Demirbas, *Bioorg. Med. Chem.*, 2002, **10**, 3723.
36 G. Turan-Zitouni, Z. A. Kaplancikli, K. Erol and F. S. Killic, *II Farmaco*, 1999, **54**, 218.
37 H. Emilsson, H. Salender and J. Gaarder, *Eur. J. Med. Chem. Chim. Ther.*, 1985, **21**, 333.
38 M. Moreno-Manas, Y. Arredondo, R. Pleixats, M. Teixido, M. M. Haga, C. Palacin, J. M. Castello and J. A. Oritizz, *J. Heterocycl. Chem.*, 1992, **29**, 1557.
39 L. Czollner, G. Sxilagli and J. Janaky, *Arch. Pharm.*, 1990, **323**, 225.
40 C. H. Chu, X. W. Sun, L. Sun, Z. Y. Zhang, Z. C. Li and R. A. Liao, *J. Chin. Chem. Soc.*, 1999, **46**, 229.
41 A. Er-Rhaimini and R. Mornet, *Indian J. Heterocycl. Chem.*, 1992, **29**, 1561.
42 J. Quiroga, S. Cruz, B. Insuasty and R. Abonia, *J. Heterocycl. Chem.*, 2001, **38**, 53.
43 A. J. Thakur, P. Saikia, D. Prajapati and J. S. Sandhu, *Synlett*, 2001, 1299.
44 M. J. Perez-Perez, E. M. Pretago, M. L. Jimeno and M. J. Camarasa, *Synlett*, 2002, 155.
45 P. Bhuyan, R. C. Boruah and J. S. Sandhu, *J. Org. Chem.*, 1990, **55**, 568.
46 C. E. Muller, U. Geis, J. Hipp, U. Schobert, W. Frobenius, M. Pawlowski, F. Suzuki and J. Sandoval-Ramirez, *J. Med. Chem.*, 1997, **40**, 4396.
47 E. M. Grivaky, S. Lee, C. W. Siyal, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, 1980, **23**, 327.
48 S. Furuya and T. Ohtaki, *Pyridopyrimidine derivatives, their production and use, Eur. Pat. Appl.*, EP, 608565, 1994.
49 D. Heber, C. Heers and U. Ravens, *Pharmazie*, 1993, **48**, 537.
50 J. I. DeGraw, P. H. Christie, W. T. Clowell and F. M. Sirotnak, *J. Med. Chem.*, 1992, **35**, 320.
51 K. Ablajan, W. Kamil, A. Tuoheti and S. Wan-Fu, *Molecules*, 2012, **17**, 1860.
52 S. Abdolmohammadi and S. Balalaie, *Int. J. Org. Chem.*, 2012, **2**, 7.
53 A. Mossafaii-Rad and M. Mokhtary, *Int. Nano. Lett.*, 2015, **5**, 109.
54 R. S. Dongre and R. S. Selokar, *Am. J. PharmTech Res.*, 2016, **6**, 471.
55 D. Shi, L. Niu, J. Shi, X. Wang and S. Ji, *J. Heterocycl. Chem.*, 2007, **44**, 1083.
56 O. G. Jolodar, F. Shirini and M. Seddighi, *Chin. J. Catal.*, 2017, **38**, 1245.

57 M. Singh, S. Fatma, P. Ankit, S. B. Singh and J. Singh, *Tetrahedron Lett.*, 2014, **55**, 525.
58 H. Alluri, H. Gonthina, R. K. Ganta, M. Ch and V. Rao, *B. Der Pharma Chemica*, 2015, **7**, 515.
59 G. M. Ziarani, N. H. Nasab, M. Rahimifard and A. A. Soorki, *J. Saudi Chem. Soc.*, 2015, **19**, 676.
60 P. Bhattacharyya, S. Paul and A. R. Das, *RSC Adv.*, 2013, **3**, 3203.
61 R. Kazemi-rad, J. Azizian and H. Kefayati, *J. Serb. Chem. Soc.*, 2016, **81**, 29.
62 A. Upadhyay, L. K. Sharma, V. K. Singh and R. K. P. Singh, *Tetrahedron Lett.*, 2016, **57**, 5599.
63 B. Sabour, M. H. Peyrovi and M. Hajimohammadi, *Res. Chem. Intermed.*, 2015, **41**, 1343.
64 F. Shirini, M. S. N. Langarudi, N. Daneshvar, N. Jamasbi and M. Irankhah-Khanghah, *J. Mol. Struct.*, 2018, **1161**, 366.

