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Protic ionic liquids: a lucid, rational tool for synthesis of phthalazinediones, quinoxalines and benzopyrans

A. G. Mulik[1] · D. R. Chandam[2] · D. R. Patil[2] · P. P. Patil[2] · G. N. Mulik[1] · S. T. Salunkhe[1] · M. B. Deshmukh[2]

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Abstract Protic ionic liquids (PILs), which are easily produced through the combination of a Brønsted acid and Brønsted base, such as [Mim]Ac and 1,4-diazabicyclo[2.2.2]octane (DABCO):AcOH:H_2O (1:1:3), were found to be lucid, tunable tool for synthesis of various heterocyclic motifs such as phthalazinediones, quinoxalines and benzopyrans. These PILs were found to be efficient for synthesis of diverse heterocyclic derivatives, along with demonstrating noteworthy aspects such as high yields, isolation of pure products without column chromatography and recyclable reaction media.

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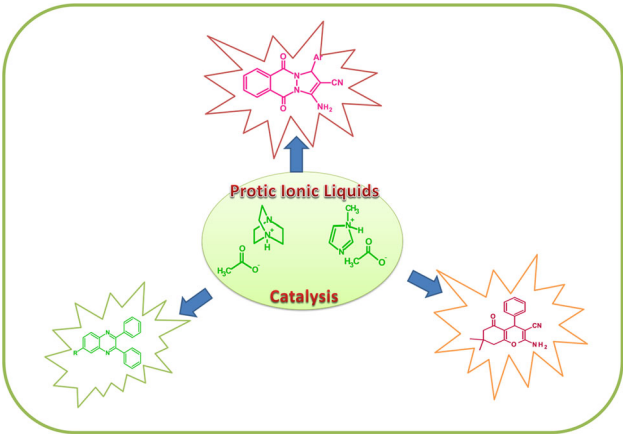
✉ A. G. Mulik
abhi_mulik1@rediffmail.com

[1] PG Department of Chemistry, Balwant College, Vita 415311, Maharashtra, India

[2] Heterocyclic Laboratory, Department of Chemistry, Shivaji University, Kolhapur 416004, Maharashtra, India

Graphical abstract



Keywords Ionic liquids · Phthalazinediones · Benzopyran · Quinoxaline

Introduction

To synthesize diverse range of organic molecules under a single catalytic umbrella is a cornerstone of contemporary synthetic chemistry. With respect to this, protic ionic liquids (PILs) were found to be a tunable solvent–catalyst system for various organic transformations, such as synthesis of substituted 1,2,4-triazoles [1], the Diels–Alder reaction [2], formation of diphenylmethyl ethers [3] and synthesis of oxoisoindolines [4]. PILs, liquid acid–base salts that can readily be prepared and recycled, perfectly answer this constraint. Proton transfer from the acid to the base creates proton-donor as well as proton-acceptor sites, establishing hydrogen-bonded networks that distinguish PILs from other ILs [5]. Having unanimous properties such as negligible vapour pressure, thermal stability and reusability makes them an impressive alternative for conventionally used toxic organic solvents [6].

Heterocyclic moieties such as phthalazinediones, quinoxalines and benzopyrans have a wide range of applications (Fig. 1). Several derivatives of quinoxaline (e.g.-HBY-097 and s-2720) display interesting activity against HIV, as non-nucleosidic inhibitors of reverse transcriptase (RT) (Fig. 1) [7, 8]. In addition, they are well known for their applications as dyes [9], electroluminescent material [10], organic semiconductors [11, 12], building blocks for the synthesis of anion receptors [13], cavitands [14, 15], dehydroannulenes [16], DNA cleaving agents [17, 18], and also as pesticides [19]. Phthalazine derivatives are an important structural motif, as they have been reported to possess anticonvulsant [20], cardiotonic [21] and vasorelaxant [22] activities. Besides these, they are endowed with anti-inflammatory, analgesic, antihypoxic and antipyretic properties [23]. Pyran framework are usually found in a variety of important natural compounds including carbohydrates, alkaloids, polyether antibiotics, pheromones and iridoids [24].

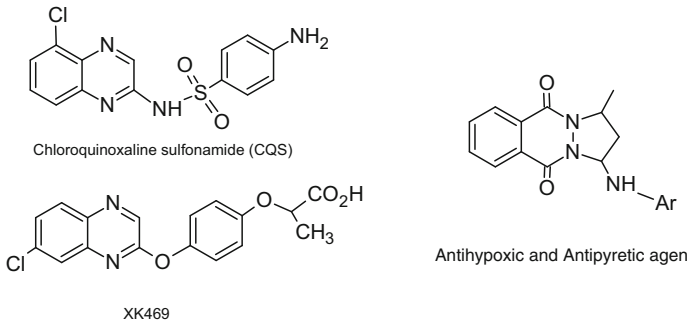


Fig. 1 Bioactive quinoxalines and phthalazinediones

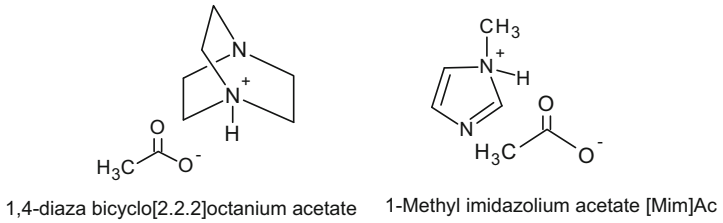


Fig. 2 Protic ionic liquids (PILs) used

Thus, synthesis of all these structural units under one catalytic umbrella of protic ionic liquids has been demonstrated in this report.

1,4-diaza bicyclo[2.2.2]octanium acetate and 1-methylimidazolium acetate ([Mim]Ac) (Fig. 2) PILs were found to be a proficient solvent–catalyst system for various one-pot organic transformations, depicted by the successful synthesis of phthalazinediones, quinoxalines and benzopyrans.

Result and discussion

The first reaction we examined was one-pot, three-component syntheses of phthalazinediones by condensation reactions of phthalhydrazide, malononitrile and various aryl aldehydes. Very few catalytic systems, such as *p*-TSA in [bmim]Br [25], triethylamine using ultrasound [26] and recently using mild basic ionic liquids [27], have been reported to be effective for the synthesis of these vital moieties. However, most of these systems suffer from drawbacks such as use of hazardous organic solvents, longer reaction time, resolute toxicity of the catalyst, etc. Thus, there is an immense need for the development of a newer synthetic route for their synthesis.

To show the efficacy of PILs and in continuation of our work in ILs [28], we initially investigated the synthesis of phthalazinediones by the reaction of

Table 1 Synthesis of 1H-pyrazolo[1,2-b]phthalazinediones promoted by different DABCO and Imidazolium salts of weak acids

Entry	Catalyst[a]	Time (min)	Yield (%)[b]
1	DABCO[c]	55	80
2	DABCO–PhCOOH–$3H_2O$	20	85
3	DABCO–Cinnamic acid–$3H_2O$	3 h	15
4	DABCO–Hippuric acid–$3H_2O$	3 h	00
5	DABCO–AcOH–$3H_2O$[d]	<5	95
6	DABCO–AcOH–$5H_2O$	15	70
7	DABCO–AcOH–$7H_2O$	40	70
8	First run	<5[e]/10[f]	95[e]/90[f]
9	Second run	5/10	92/88
10	Third run	5/10	91/85
11	Acetic acid	2 h	00
12	1-methylimidazole-AcOH (1:1)	10	90

Reaction run at the 1.0 mmol scale with respect to each component of phthalhydrazide, malononitrile and aldehyde

[a] 1.0 equiv used based on DABCO

[b] Isolated yield

[c] Reaction carried out at 80 °C using water as co-solvent and 20 mol % of DABCO

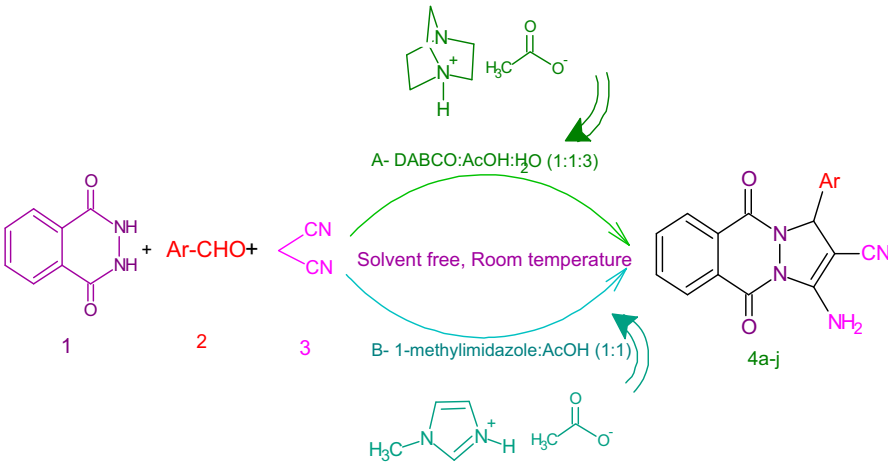
[d] 2.0 equivalent used based on DABCO

[e] Yield and time when DABCO PIL is used

[f] Yield and time when imidazolium PIL is used

phthalhydrazide, benzaldehyde and malononitrile using 1,4-diazabicyclo[2.2.2]octane (DABCO) in aqueous media at 80 °C, which afforded an 80 % yield within 1 h (Table 1, entry 1). When the same reaction was carried out using salt of DABCO and acetic acid with water in proportion (1:1:3) [41], respectively, it afforded a 95 % yield within 5 min (Scheme 1; Method A). Furthermore, the product was analyzed without purifying with column chromatography and was found to be correct. Water was deliberately added to the mixture to make it viscous. The reaction was so rapid and efficient that as soon as the third component was added to the reaction mixture, completion of reaction was confirmed within 5 min, affording an excellent yield (95 %). Enthused with these astonishing results, we tried various proportions of DABCO, acetic acid and water (Table 1, entries 5–7) and found that 1:1:3 was the most efficient and rapid proportion, possibly due to its viscosity. Besides this, we also tried the salts of DABCO with various weak acids such as cinnamic acid, hippuric acid, benzoic acid (Table 1, entries 2–4). Salt of DABCO with benzoic acid showed efficacy over cinnamic acid and hippuric acid salts and afforded an 80 % yield after 20 min.

With these optimized reaction conditions, to check the substrate scope of the protocol, we reacted various aryl aldehydes with electron-donating and withdrawing substituents. Interestingly, all the aldehydes participated well in the reaction and



Scheme 1 Synthesis of 1H-pyrazolo[1,2-b]phthalazinediones using ionic liquids **a** DABCO:AcOH:H_2O (1:1:3) and **b** 1-methylimidazole:AcOH as catalyst at ambient temperature under solvent-free conditions

there was no subsequent effect of the substituents on the reaction time and yield (Table 2).

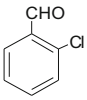
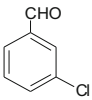
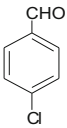
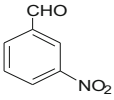
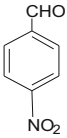
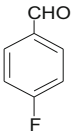
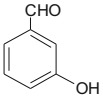
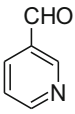
Encouraged by these results with DABCO-based PILs, we decided to pursue the concerns for synthesis of phthalazinediones using imidazolium based PILs. Thus, we carried out a model reaction of phthalhydrazide, malononitrile and benzaldehyde (Scheme 1) using imidazolium salt with acetic acid [Mim]Ac obtained using literature method [40]. To our surprise, like DABCO-based PILs, imidazolium-based PIL [Mim]Ac also proved to be rapid and efficient catalyst, since the reaction was completed within 10 min. In order to prove the catalytic activity of [Mim]Ac, we also carried out the reaction in only acetic acid, which afforded no yield (Table 1, entry 11).

With the optimistic reaction conditions in hand, we reacted a variety of structurally diverse aromatic aldehydes to understand scope and versatility of imidazolium-based, PILs-promoted synthesis of 1H-pyrazolo[1,2-b]phthalazine-diones (Scheme 1). It was observed that all the aldehydes reacted with the same efficiency attributing to yields and time (Table 2).

Recyclability and recovery of a catalyst is an important aspect from a commercial point of view. Thus, we studied the recyclability of the DABCO–AcOH–H_2O and [Mim]Ac solvent–catalyst system. After completion of the reaction, 5 ml water was added to the reaction mixture to separate the product, which was then filtered and recrystallized. Removal of extra water from the filtrate under reduced pressure recovered the catalyst system (95 %), which was washed with toluene and reused for three times, showing no significant loss of activity (Table 1, entries 8–10; Fig. 3).

Enthused with the above-mentioned gratifying results, we decided to circumvent the concerns of synthesis of quinoxaline by using the same protic ionic liquid 'DABCO–AcOH–H_2O'. Although there are several methods that afford good yields

Table 2 Synthesis of 1H-pyrazolo[1,2-b]phthalazine-dione derivatives in the presence of A: DABCO:CH_3COOH:H_2O (1:1:3) and B: [Mim]Ac PILs as catalyst under solvent-free conditions

Entry	Aldehydes		Time (min)		Yield (%)[c]		Melting point reported. m.p. (°C)/ Lit. m.p (°C) [Ref]
			A	B	A[a]	B[b]	
1		**4a**	5	10	95	90	276/(276–278) [25]
2		**4b**	5	15	94	92	260–262/(259–261) [25]
3		**4c**	5	15	90	87	266/(266–267) [26]
4		**4d**	8	15	87	85	269–270/(270–272) [25]
5		**4e**	5	10	94	90	265/(265–266) [26]
6		**4f**	5	10	92	88	268–270/(269–271) [27]
7		**4g**	5	10	95	90	231/(230–232) [27]
8		**4h**	8	10	90	86	263–265/(263–265) [26]
9		**4i**	5	8	90	87	212 The product was prepared for first time
10		**4j**	5	10	95	92	230–232 The product was prepared for first time

Reaction at 1 mmol of phthalhydrazide, malononitrile and aryl aldehydes at RT (27 °C)

[a] Synthesis using DABCO:AcOH:H_2O in proportions of 1:1:3, respectively

[b] Synthesis using 1-methylimidazole:AcOH in proportions of 1:1, respectively

[c] Isolated yields

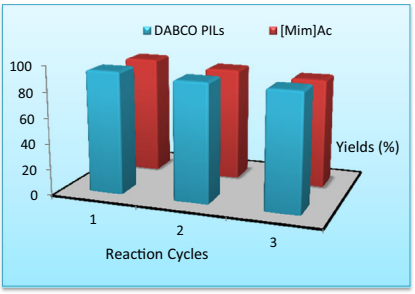


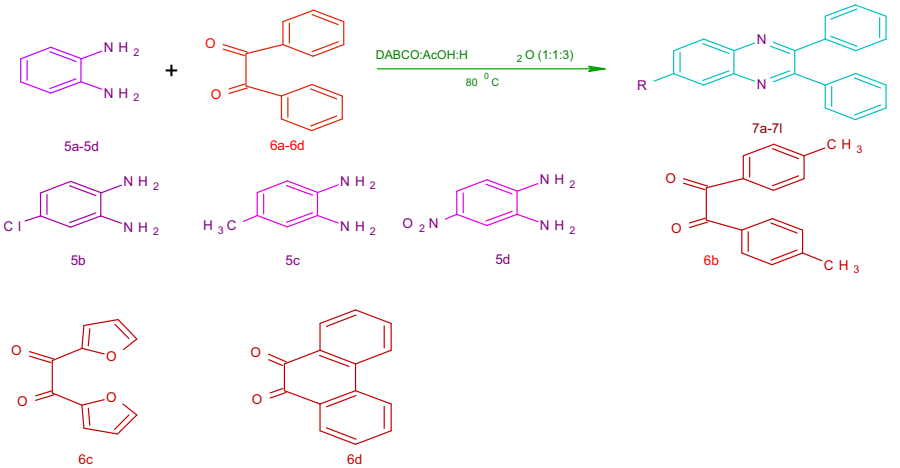
Fig. 3 Recyclability of DABCO:AcOH:H_2O and 1-methylimidazolium acetate [Mim]Ac as catalyst under solvent-free condition using a model reaction of phthalhydrazide, benzaldehyde and malononitrile

Table 3 Synthesis of quinoxaline using DABCO salts with weak acids as catalyst under solvent-free conditions

Entry	Catalyst	Temperature (°C)	Time (min)	Yield (%)[a]
1	DABCO–AcOH–3H_2O	R.T.	2 h	20
2	DABCO–AcOH–3H_2O	80 °C	20 min	85
3	DABCO–PhCOOH–3H_2O	R.T.	1 h	50
4	DABCO–Cinnamic acid–3H_2O	R.T.	2 h	00
5	DABCO–Hippuric acid–3H_2O	R.T.	2 h	00

Reaction carried out at 1 mmol of each component, i.e., orthophenylene diamine and benzil

[a] Isolated yield



Scheme 2 Synthesis of quinoxaline derivatives using DABCO:AcOH:H_2O (1:1:3) as a recyclable solvent–catalyst system

Table 4 Synthesis of quinoxaline derivatives using ionic liquid DABCO:AcOH:3H_2O as catalyst at 80 °C under solvent-free conditions

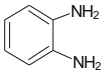
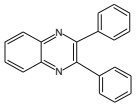
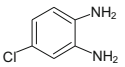
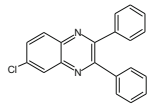
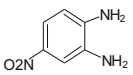
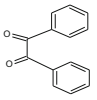
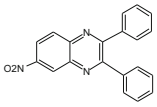
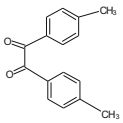
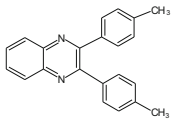
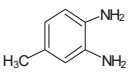
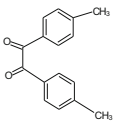
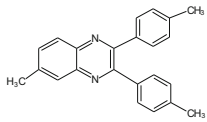
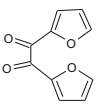
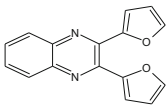
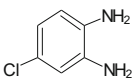
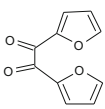
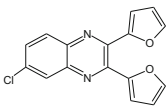
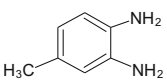
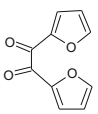
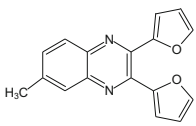
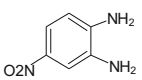
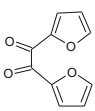
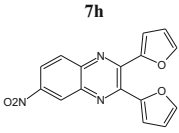
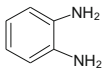
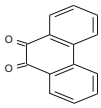
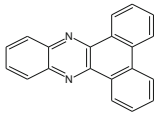
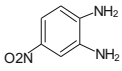
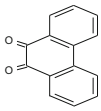
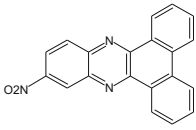
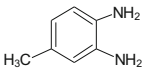
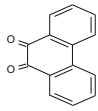
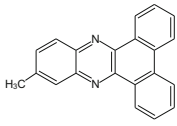
Entry	1,2-diamine	1,2-diketone	Product	Time (min)	Yield[b] (%)	Melting Point Reported. m.p. (^{0}C)/Lit. m.p (^{0}C) [Ref]
1			 **7a**	20	90	126/126-127 [25]
2			 **7b**	30	80	120-121/122-123 [30]
3			 **7c**	20	88	187/187 [30]
4			 **7d**	20	86	145/142-143 [29]
5			 **7e**	25	87	136/137 [25]
6			 **7f**	35	80	131/131-132 [30]
7			 **7g**	40	83	122/122 [30]
8			 **7h**	30	82	119/119-120 [30]
9			 **7i**	45	79	174-175/174-176 [30]

Table 4 continued

Entry	1,2-diamine	1,2-diketone	Product	Time (min)	Yield[b] (%)	Melting Point Reported. m.p. (^{0}C)/Lit. m.p (^{0}C) [Ref]
10			 **7j**	25	90	244/246 [31]
11			 **7k**	40	82	240-242/240-242 [32]
12			 **7l**	20	82	218/218-219 [32]

Reaction carried out at 1 mmol of Each component i.e. 1,2-diamine and 1,2-diketone

[a] Isolated yield

of quinoxaline, some of them suffer from drawbacks such as volatile organic solvents, unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors, and harsh reaction conditions, which limit their use under the aspect of environmentally benign processes [29–36]. Initially, *o*-phenylenediamine and benzil was reacted at room temperature using DABCO acetic acid salt, but this was found to be time consuming and sluggish (Table 3, entry 1). Thus, it was decided to elevate the temperature and we carried out the same reaction at 80 °C, and to our surprise a solid white mass of product was obtained after 20 min. In addition, we also tried the protocol with various salts of DABCO with weak acids such as benzoic acid, cinnamic and hippuric acid, but to no benefit regarding yield and time (Table 3, entries 2–5).

Here again, we investigated the substrate scope by reacting various 1,2-diamine with substituted 1,2-diketones (Scheme 2), and the results are listed in Table 4. All the derivatives were obtained in excellent yields, which depicts our protocol as versatile and convenient for the synthesis of a wide array of quinoxaline derivatives.

We can't explain the exact mechanism, but a probable mechanism for the formation of quinoxaline and phthalazinedione derivatives has been shown in Fig. 4.

Furthermore, using the same ionic liquid DABCO:AcOH:H_2O (1:1:3), one-pot, three-component synthesis of various benzopyran derivatives was performed (Scheme 3). The reaction proceeds smoothly, affording various derivatives in good to excellent yields (Table 5).

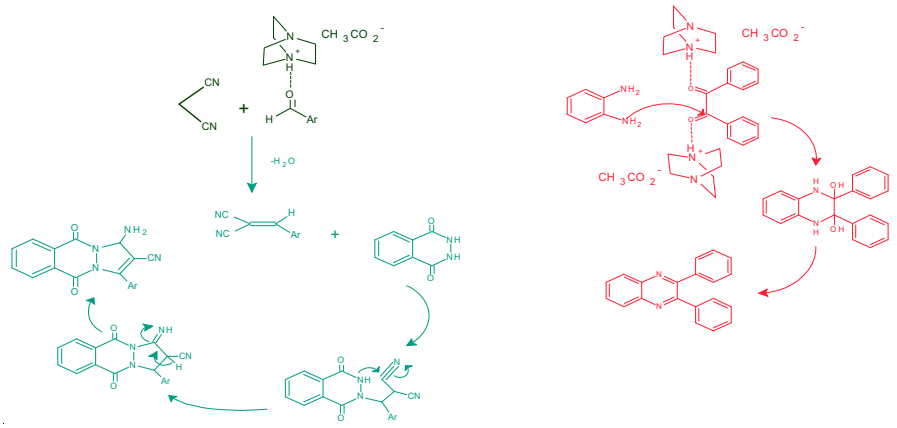
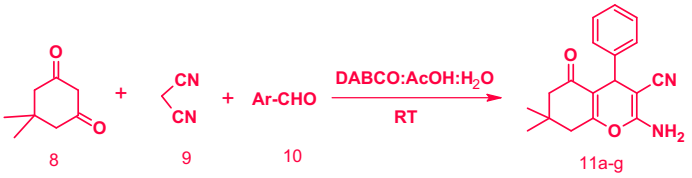


Fig. 4 Suggested mechanism for synthesis of 1H-pyrazolo[1,2-b]phthalazinediones and quinoxalines using DABCO PIL



Scheme 3 Synthesis of tetrahydrobenzo[b]pyran derivatives using DABCO:AcOH:H_2O (1:1:3) as a recyclable solvent–catalyst system

From the results, it is clearly seen that use of PIL as a catalyst offers a sustainable and efficient alternative when the protocol involves hydrophobic substrates like phthalhydrazide and 1,2-diketones.

In conclusion, via this report we suggest that many useful organic structural motifs can be synthesized using a single solvent–catalyst system like PILs. We have successfully demonstrated the use of protic DABCO and imidazolium-based ILs as solvent–catalyst systems for synthesis of phthalazinediones, quinoxalines and benzopyrans. This novel methodology is endowed with fascinating aspects, such as fast conversions within the shortest reaction time, a convenient workup procedure including mere filtration, averting the use of tedious column chromatography, improved yields and high purity of desired products. With these results in hand, we can say PILs act as an efficient dual solvent–catalyst system for various organic transformations.

These inexpensive and readily prepared PILs will provide new opportunities for the study of green synthesis, and green solvents and catalysts, which will upsurge the catalytic tools of the current scientific community.

Table 5 Synthesis of tetrahydrobenzo[b]pyran derivatives using ionic liquid DABCO:AcOH:3H_2O as a catalyst at room temperature

Entry	Aldehydes		Yield[a]	Time (min)	Melting point reported. m.p. (°C)/l m.p (°C) [Ref]
1	C_6H_5	**11a**	90	10	232/233–234 [37]
2	4-$OCH_3C_6H_4$	**11b**	91	8	196-198/197–199 [38]
3	4-$CH_3C_6H_4$	**11c**	90	8	210/209–211 [38]
4	4-$NO_2C_6H_4$	**11d**	87	15	174-176/175–176 [38]
5	4-OHC_6H_4	**11e**	85	15	215/214-215 [39]
6	3-$NO_2C_6H_4$	**11f**	84	15	201-203/201–205 [38]
7	4-ClC_6H_4	**11g**	86	15	212-214/215–218 [37]

Reaction carried out at 1 mmol of each component

[a] Isolated yield

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