

Preliminary Communication

Qiang Zhang*, Huaixin Wei, Jihang Li, Xin Zhao and Jun Luo

One-pot synthesis of benzopyrans catalyzed by silica supported dual acidic ionic liquid under solvent-free conditions

<https://doi.org/10.1515/hc-2017-0163>

Received July 26, 2017; accepted September 14, 2017; previously published online November 8, 2017

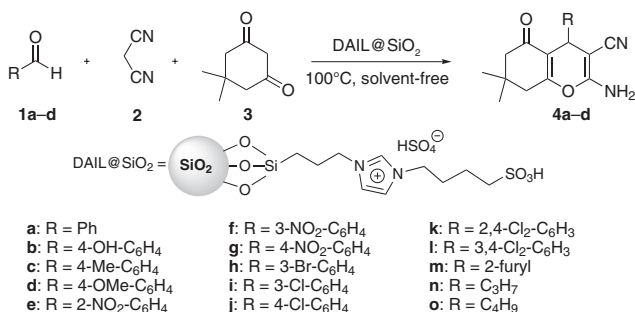
Abstract: A mild and efficient method was developed for the preparation of tetrahydrobenzo[*b*]pyrans through a one-pot three-component condensation of aldehydes, malononitrile and dimedone in the presence of silica supported dual acidic ionic liquid (DAIL@SiO₂) as a powerful catalyst under solvent-free conditions. This procedure is characterized by mild reaction conditions, simple workup and environmental friendliness. Moreover, the catalyst could be recycled for five times with only a slight loss of catalytic activity.

Keywords: benzopyrans; one-pot; solvent-free; supported ionic liquid.

Multicomponent reactions (MCRs) are highly efficient approaches to access complex structures in a simple synthetic operation from three or more reactants. High atom economy, great efficiency and procedural convenience in the construction of heterocycles are the advantages of MCRs [1–3]. Tetrahydrobenzo[*b*]pyrans are an important class of heterocyclic compounds, as they form the essential kernel structure of emerging drugs with diverse bioactivity, such as inhibitors of tyrosinase and agents with anti-influenza, anticancer and anti-anaphylactin activity [4, 5]. Additionally, substituted 4*H*-pyrans can be employed as pigments, agrochemicals and photoactive materials [6, 7]. These

compounds can be prepared by multicomponent condensation of dimedone with aldehyde and malononitrile in the presence of various catalysts including tetra-methyl ammonium hydroxide [8], RE(PFO)₃ [9], iodine [10], NaBr [11], Na₂SeO₄ [12], solid acids [13, 14], ion-exchange resins [15], magnetic nanocatalysts [16, 17], 1,4-diazabicyclo[2.2.2]octane based ionic liquids [18] and metal complexes [19]. Many of the reported methods suffer from limitations such as prolonged reaction times [10, 12], use of volatile organic solvents [9, 10, 14, 15], use of microwave or ultrasonic irradiation [11, 16] and poor catalyst recyclability [8, 10–12]. Moreover, most of them are practical with aromatic aldehydes only [13, 15–19] as the reactions with aliphatic aldehydes furnish low yields [9].

Ionic liquids (ILs), as eco-friendly reaction media or catalysts, have attracted increasing attention due to their low vapor pressure, high thermal stability, excellent solubility, and ease of recovery and reuse [20, 21]. A concept of supported ionic liquid catalysis (SILC) has been proposed, which combines the benefits of ILs and heterogeneous catalysts, providing high designability, high ‘solubility’ of catalytic site and ease of handling, separation and recycling [22]. Recently, we have prepared some supported ionic liquid catalysts [23–25], which are effective in the synthesis of amidoalkyl naphthols and benzoxanthenes through the MCRs. In continuation of our work, herein we report a mild and efficient procedure for one-pot three-component

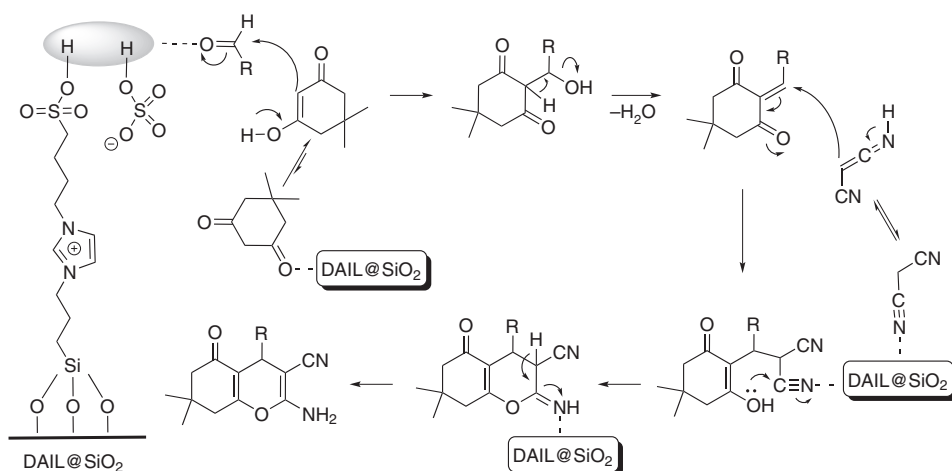


Scheme 1 The DAIL@SiO₂ catalyzed synthesis of tetrahydrobenzo[*b*]pyrans 4.

*Corresponding author: Qiang Zhang, School of Chemistry, Biology and Material Engineering, Suzhou University of Science and Technology, Suzhou 215009, China, e-mail: zhangqiang005@gmail.com

Huaixin Wei, Jihang Li and Xin Zhao: School of Chemistry, Biology and Material Engineering, Suzhou University of Science and Technology, Suzhou 215009, China

Jun Luo: School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China



Scheme 2 Plausible mechanism for the synthesis of tetrahydrobenzo[*b*]pyrans.

synthesis of the tetrahydrobenzo[*b*]pyrans using silica-supported dual acidic ionic liquid DAIL@SiO₂ as a recoverable catalyst under solvent-free conditions (Scheme 1).

Under optimal conditions, a model reaction of benzaldehyde (2 mmol), malononitrile (2.2 mmol) and dimedone (2 mmol) in the presence of DAIL@SiO₂ was preformed under solvent-free conditions at 100°C to give product **4a** in 86% yield. Under similar conditions, products **4b–o** were obtained in the yields ranging from 51% to 91%. In the absence of the catalyst, only a trace amount of product could be detected. The optimum amount of DAIL@SiO₂ was 60 mg, and no improvement was observed by increasing the amount of the catalyst to 80 mg or 100 mg. Lower temperatures (40–90°C) decelerated the reaction rate significantly and led to lower yields. A higher temperature (110°C) did not provide a higher yield due to the increased formation of by-products [26, 27].

A simple recovery and reuse of catalyst is highly preferable in terms of green synthetic process. The recyclability of the DAIL@SiO₂ was investigated using a three-component reaction of 3-nitrobenzaldehyde (2 mmol), malononitrile (2.2 mmol) and dimedone (2 mmol) under solvent-free conditions at 100°C. When the reaction was completed, acetone was added to dissolve the product. The catalyst was simply filtered off and washed with acetone. After being dried, it was subjected to the next run. The catalyst DAIL@SiO₂ could be recycled five times with only a slight loss of catalytic activity.

Aromatic aldehydes with electron-donating or electron-withdrawing groups undergo smoothly the transformation under the optimized reaction conditions. It was shown that the aromatic aldehydes with electron-withdrawing groups react faster than the aromatic aldehydes with electron-donating groups, as expected

[16–18]. Successful synthesis of the 2-furanyl substituted tetrahydrobenzo[*b*]pyran derivative **4m** and two alkyl-substituted analogs **4n** and **4o** in acceptable yields can also be noted (Scheme 1). As already mentioned, the reported methods provide alkyl substituted benzopyrans in low yields [4, 5, 9].

A possible reaction mechanism for the synthesis of tetrahydrobenzo[*b*]pyrans is given in Scheme 2. This synthetic scheme is self-explanatory and fully compatible with other literature reports on the use of acidic catalysts in the synthesis of these products.

Silica supported dicationic acidic ionic liquid DAIL@SiO₂ catalyzes synthesis of benzopyrans in a one-pot three-component reaction under solvent-free conditions. The procedure is equally effective with aliphatic and aromatic aldehydes. The advantages of this method are high catalytic activity, short reaction time, simple work-up and environmental friendliness.

Experimental

Melting points were determined on a Perkin-Elmer differential scanning calorimeter and are uncorrected. ¹H NMR spectra were recorded on a Bruker AVANCE III spectrometer (500 MHz, DMSO-*d*₆). The DAIL@SiO₂ catalyst was synthesized according to our previous report [23]. All commercially available chemicals and solvents were used without further purification.

General procedure for the synthesis of benzopyrans **4a–o**

A mixture of aldehyde (2 mmol), malononitrile (2.2 mmol) dimedone (2 mmol) and DAIL@SiO₂ (60 mg) was stirred under solvent-free conditions for several hours at 100°C. After completion of the reaction

as indicated by TLC analysis (ethyl acetate/*n*-hexane, 1:3), acetone (15 mL) was added to the mixture and the solid catalyst was separated by filtration, washed with acetone and dried under reduced pressure. Pure benzopyran product was obtained by concentration of the mixture, followed by crystallization of the residue from 95% ethanol.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a) Yield 86% of white solid; mp 230–231°C, lit mp 227–229°C [13].

2-Amino-7,7-dimethyl-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b) Yield 87% of white solid; mp 203–205°C, lit mp 204–205°C [8]; ¹H NMR: δ 9.25 (s, 1H), 6.91–6.94 (m, 4H), 6.66 (d, *J* = 8 Hz, 2H), 4.07 (s, 1H), 2.49 (s, 2H), 2.24 (d, *J* = 16 Hz, 1H), 2.09 (d, *J* = 16 Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H).

2-Amino-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c) Yield 84% of white solid; mp 218–219°C, lit mp 217–219°C [4]; ¹H NMR: δ 7.09 (d, *J* = 8 Hz, 2H), 7.02 (d, *J* = 8 Hz, 2H), 6.97 (s, 2H), 4.13 (s, 1H), 2.52 (s, 2H), 2.23–2.26 (m, 4H), 2.09 (d, *J* = 8 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H).

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d) Yield 82% of white solid; mp 192–194°C, lit mp 195–196°C [5].

2-Amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e) Yield 90% of pale yellow solid; mp 222–223°C, lit mp 223–224°C [13].

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f) Yield 87% of pale yellow solid; mp 213–214°C, lit mp 214–216°C [4]; ¹H NMR: δ 8.08 (d, *J* = 8 Hz, 1H), 7.98 (s, 1H), 7.61–7.69 (m, 2H), 7.18 (s, 2H), 4.42 (s, 1H), 2.56 (s, 2H), 2.27 (d, *J* = 16 Hz, 1H), 2.12 (d, *J* = 16 Hz, 1H), 1.05 (s, 3H), 0.96 (s, 3H).

2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g) Yield 91% of pale yellow solid; mp 178–179°C, lit mp 179–182°C [16].

2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h) Yield 89% of white solid; mp 229–230°C, lit mp 227–228°C [5]; ¹H NMR: δ 7.40 (m, 1H), 7.31 (s, 1H), 7.27 (t, *J* = 8 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 7.10 (s, 2H), 4.21 (s, 1H), 2.53 (s, 2H), 2.16 (d, *J* = 16 Hz, 1H), 2.13 (d, *J* = 16 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H).

2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4i) Yield 83% of white solid; mp 231–232°C, lit mp 230–232°C [8].

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j) Yield 86% of white solid; mp 215–217°C, lit mp 215–217°C [8].

2-Amino-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k) Yield 88% of white solid; mp 191–193°C, lit mp 192–194°C [16].

2-Amino-4-(3,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l) Yield 90% of white solid; mp 226–227°C, lit mp 225–227°C [28].

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4m) Yield 85% of gray white solid; mp 218–220°C, lit mp 219–221°C [16]; ¹H NMR: δ 7.48–7.45 (m, 1H), 7.02 (s, 2H), 6.31 (m, 1H), 6.04 (d, *J* = 4 Hz, 1H), 4.33 (s, 1H), 2.45 (s, 2H), 2.32 (d, *J* = 16 Hz, 1H), 2.15 (d, *J* = 16 Hz, 1H), 1.05 (s, 3H), 0.99 (s, 3H).

2-Amino-7,7-dimethyl-5-oxo-4-propyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4n) Yield 56% of white solid; mp 170–172°C, lit mp 172–174°C [9]; ¹H NMR: δ 6.89 (s, 2H), 3.16 (t, *J* = 4.5 Hz, 1H), 2.44 (d, *J* = 17 Hz, 1H), 2.35 (d, *J* = 17 Hz, 1H), 2.28 (d, *J* = 16 Hz, 1H), 2.19 (d, *J* = 16 Hz, 1H), 1.13–1.48 (m, 4H), 1.03 (s, 3H), 1.00 (s, 3H), 0.84 (t, *J* = 7.5 Hz, 3H).

2-Amino-4-butyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4o) Yield 51% of white solid; mp 166–168°C, lit mp 165–167°C [9].

Acknowledgments: This work was financially supported by the Natural Science Foundation of Jiangsu Province (China) (No. BK20150282), the Natural Science Foundation of the Higher Education Institutions of Jiangsu Province (No. 17KJD430005) and the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions. The authors would like to thank the Excellent Innovation Team at the Science and Technology of Education Department of Jiangsu Province for discussions.

References

- [1] Dömling, A.; Wang, W.; Wang, K. Chemistry and biology of multi-component reaction. *Chem. Rev.* **2012**, *112*, 3083–3135.
- [2] Cioc, R. C.; Ruijter, E.; Orru, R. V. A. Multicomponent reactions: advanced tools for sustainable organic synthesis. *Green Chem.* **2014**, *16*, 2958–2975.
- [3] Fan, L.; Yao, C. C.; Shu, M. M. Three-component synthesis of new *o*-hydroxyphenyl substituted pyrazolo[3,4-*b*]pyridines promoted by FeCl₃. *Heterocycl. Commun.* **2016**, *22*, 63–67.
- [4] Pandit, K. S.; Chavan, P. V.; Desai, U. V.; Kulkarni, M. A.; Wadgaonkar, P. P. Tris-hydroxymethylaminomethane (THAM): a novel organocatalyst for an environmentally benign synthesis of medicinally important tetrahydrobenzo[*b*]pyrans and pyran-annulated heterocycles. *New J. Chem.* **2015**, *39*, 4452–4463.
- [5] Brahmachari, G.; Banerjee, B. Facile and one-pot access to diverse and densely functionalized 2-amino-3-cyano-4H-pyrans and pyran-annulated heterocyclic scaffolds via an eco-friendly multi-component reaction at room temperature using urea as a novel organo-catalyst. *ACS Sustainable Chem. Eng.* **2014**, *2*, 411–422.
- [6] Armesto, D.; Horspool, W. M.; Martin, N. Synthesis of cyclo-tutenes by the novel photochemical ring contraction of 4-substituted 2-amino-3,5-dicyano-6-phenyl-4H-pyrans. *J. Org. Chem.* **1989**, *54*, 3069–3072.

- [7] Saadati-Moshtaghin, H. R.; Zonoz, F. M. Preparation and characterization of magnetite-dihydrogen phosphate as a novel catalyst in the synthesis of tetrahydrobenzo[b]pyrans. *Mater. Chem. Phys.* **2017**, *199*, 159–165.
- [8] Balalaie, S.; Sheikh-Ahmadi, M.; Bararjanian, M. Tetra-methyl ammonium hydroxide: An efficient and versatile catalyst for the one-pot synthesis of tetrahydrobenzo[b]pyran derivatives in aqueous media. *Catal. Commun.* **2007**, *8*, 1724–1728.
- [9] Wang, L. M.; Shao, J. H.; Tian, H.; Wang, Y. H.; Liu, B. Rare earth perfluorooctanoate [RE(PFO)₃] catalyzed one-pot synthesis of benzopyrans derivatives. *J. Fluorine Chem.* **2006**, *127*, 97–100.
- [10] Bhosale, R. S.; Magar, C. V.; Solanke, K. S.; Mane, S. B.; Choudhary, S. S.; Pawar, R. P. Molecular iodine: an efficient catalyst for the synthesis of tetrahydrobenzo[b]pyrans. *Synth. Commun.* **2007**, *37*, 4353–4357.
- [11] Devi, I.; Bhuyan, P. J. Sodium bromide catalyzed one-pot synthesis of tetrahydrobenzo[b]pyrans via a three-component cyclocondensation under microwave irradiation and solvent free conditions. *Tetrahedron Lett.* **2004**, *45*, 8625–8627.
- [12] Hekmatshoar, R.; Majedi, S.; Bakhtiari, K. Sodium selenate catalyzed simple and efficient synthesis of tetrahydro benzo[b]pyran derivatives. *Catal. Commun.* **2008**, *9*, 307–310.
- [13] Shamsi, T.; Amoozadeh, A.; Sajjadi, S. M.; Tabrizian, E. Novel type of SO₃H-functionalized nano-titanium dioxide as a highly efficient and recyclable heterogeneous nanocatalyst for the synthesis of tetrahydrobenzo[b]pyrans. *Appl. Organometal. Chem.* **2017**, *31*, e3636.
- [14] Abdollahi-Alibeik, M.; Nezampour, F. Synthesis of 4H-benzo[b]pyrans in the presence of sulfated MCM-41 nanoparticles as efficient and reusable solid acid catalyst. *React. Kinet. Mech. Catal.* **2013**, *108*, 213–229.
- [15] Keshavarz, M.; Iravani, N.; Azghandi, M. H. A.; Nazari, S. Ion-pair immobilization of L-proline anion onto cationic polymer support and a study of its catalytic activity as an efficient heterogeneous catalyst for the synthesis of 2-amino-4H-chromene derivatives. *Res. Chem. Intermed.* **2016**, *42*, 4591–4604.
- [16] Esmaeilpour, M.; Javidi, J.; Deghani, F.; Dodeji, F. N. A green one-pot three-component synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives using Fe₃O₄@SiO₂-imid-PMA magnetic nanocatalyst under ultrasonic irradiation and reflux conditions. *RSC Adv.* **2015**, *5*, 26625–26633.
- [17] Shahbazi, F.; Amani, K. Synthesis, characterization and heterogeneous catalytic activity of diame-modified silica-coated magnetite-polyoxometalate nanoparticles as a novel magnetically-recoverable nanocatalyst. *Catal. Commun.* **2014**, *55*, 57–64.
- [18] Shirini, F.; Langarudi, M. S. N.; Daneshvar, N. Preparation of a new DABCO-based ionic liquid [H₂-DABCO][H₂PO₄]₂ and its application in the synthesis of tetrahydrobenzo[b]pyran and pyrano[2,3-d]pyrimidinone derivatives. *J. Mol. Liq.* **2017**, *234*, 268–278.
- [19] Rakhtshah, J.; Salehzadeh, S. Multi-wall carbon nanotube supported Co(II) Schiff base complex: an efficient and highly reusable catalyst for the synthesis of 1-amidoalkyl-2-naphthol and tetrahydrobenzo[b]pyran derivatives. *Appl. Organometal. Chem.* **2017**, *31*, e3560.
- [20] Hallett, J. P.; Welton, T. Room-temperature ionic liquids: solvents for synthesis and catalysis. *Chem. Rev.* **2011**, *111*, 3508–3576.
- [21] Mahato, S.; Santra, S.; Chatterjee, R.; Zyryanov, G. V.; Hajra, A.; Majee, A. Bronsted acidic ionic liquid-catalyzed tandem reaction: an efficient approach towards regioselective synthesis of pyrano[3,2-c]coumarins under solvent-free conditions bearing lower E-factors. *Green Chem.* **2017**, *19*, 3282–3295.
- [22] Zhang, S. G.; Zhang, J. H.; Zhang, Y.; Deng, Y. Q. Nanoconfined ionic liquids. *Chem. Rev.* **2017**, *117*, 6755–6833.
- [23] Zhang, Q.; Luo, J.; Wei, Y. Y. A silic gel supported dual acidic ionic liquid: an efficient and recyclable heterogeneous catalyst for the one-pot synthesis of amidoalkyl naphthols. *Green Chem.* **2010**, *12*, 2246–2254.
- [24] Zhang, Q.; Su, H.; Luo, J.; Wei, Y. Y. A magnetic nanoparticle supported dual acidic ionic liquid: a quasi-homogeneous catalyst for the one-pot synthesis of benzoxanthenes. *Green Chem.* **2012**, *14*, 201–208.
- [25] Zhang, Q.; Zhao, X.; Zhu, X.; Li, J. Magnetic nanoparticles supported acidic ionic liquid as a highly active and reusable catalyst for esterification. *Mater. Sci. Forum* **2016**, *852*, 485–488.
- [26] Fang, D.; Yang, J. M.; Liu, Z. L. Eco-friendly synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by ionic liquid in aqueous media. *J. Heterocycl. Chem.* **2011**, *48*, 468–472.
- [27] Li, J. T.; Li, Y. W.; Song, Y. L.; Chen, G. F. Improved synthesis of 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives catalyzed by urea under ultrasound. *Ultrason. Sonochem.* **2012**, *19*, 1–4.
- [28] Zhi, H. Z.; Lü, C. X.; Zhang, Q.; Luo, J. A new PEG-1000-based dicationic ionic liquid exhibiting temperature-dependent phase behavior with toluene and its application in one-pot synthesis of benzopyrans. *Chem. Commun.* **2009**, 2878–2880.