RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 19111

Multicomponent diversity-oriented synthesis of symmetrical and unsymmetrical 1,4-dihydropyridines in recyclable glycine nitrate ($GlyNO_3$) ionic liquid: a mechanistic insight using Q-TOF, ESI-MS/MS†‡

Rajesh Kumar,[ab] Nitin H. Andhare,[c] Amit Shard,[a] Richa[a] and Arun Kumar Sinha*[abc]

Received 24th February 2014
Accepted 28th March 2014

DOI: 10.1039/c4ra02169j

www.rsc.org/advances

Multicomponent reactions are compelling strategies for generating a chemically diverse set of multifunctionalized heterocyclic motifs with high atom economy, rendering the transformations green. These strategies can further become more prolific if catalyst recyclability, compatibility and exploration of precise mechanistic pathways are considered. To this end, an inexpensive and recyclable glycine nitrate ($GlyNO_3$) ionic liquid has been efficiently employed to obtain diversely substituted symmetrical and unsymmetrical 1,4-dihydropyridines with up to 93% yields *via* three and four components, respectively. The catalyst recyclability and compatibility to obtain both symmetrical and unsymmetrical 1,4 DHPs under identical reaction conditions are added benefits to its practical utility. Furthermore, progress of the reaction was monitored by Q-TOF, direct infusion electrospray ionization mass spectrometry (ESI-MS), and key cationic intermediates involved in the reaction have been further identified by a tandem MS experiment (Q-TOF, ESI-MS/MS), which served as the proof of concept to the mechanistic model. This is the first report which revealed that the Hantzsch reaction predominantly follows the diketone pathway among four competing reaction pathways.

Introduction

The creation of multiple carbon–carbon or carbon–hetero bonds in a one-pot reaction helps in minimizing the waste of time and energy. These benefits are broadly encompassed under the periphery of green chemistry and are generally accomplished by using the multicomponent reaction (MCRs),[1] which have been used for the preparation of structurally diverse, drug-like compounds.[2] As a result, they have emerged as significant tool in organic synthesis.[3]

One prominent MCR that produces an interesting class of nitrogen-based heterocycles is the venerable Hantzsch reaction, which provides 1,4-dihydropyridines (1,4-DHPs) as privileged pharmacophores.[4] DHP derivatives exhibit a wide range of pharmacological properties.[5] Initially, these molecules were recognized as calcium channel modulators but were later developed as cardiovascular and antihypertensive drugs, which includes amlodipine, felodipine, nicardipine and nifedipine[6] (Fig. 1). Beside this, these structural motifs are also credited with such versatile biological properties as anticonvulsant,[7] radioprotective,[8] selective antagonism of adenosine-A3 receptors,[9] anticancer,[10] HIV protease inhibition,[11] and the treatment of Alzheimer's disease.[12]

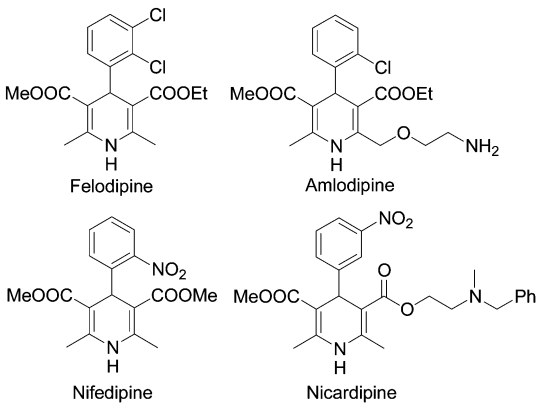


Fig. 1 1,4 DHPs used as clinical drugs.

[a]*Natural Plant Products Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur-176061, H.P., India*

[b]*Academy of Scientific and Innovative Research (AcSIR), New Delhi, India*

[c]*Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, BS10/1, Sector 10, Janakipuram Extension, Sitapur Road, Lucknow-226031, U.P., India. E-mail: aksinha08@rediffmail.com*

† Some part of work carried out at CSIR-IHBT, Palampur (H.P.).

‡ Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR data and spectra of symmetrical and unsymmetrical 1,4-DHPs. See DOI: 10.1039/c4ra02169j

Conventionally, 1,4-DHPs accessed through Hantzsch reaction, reduction of pyridines, addition to pyridines, or cycloaddition[13] suffer from the limitations, including low to moderate yields besides requiring harsh conditions and longer reaction times. As a result, several modifications have been developed for the classical Hantzsch approach.[14] However, despite their potential usefulness, many of these methods still involve expensive and toxic catalysts, cumbersome product isolation procedures and incompatibility with certain functional groups. Thus, these methods are not aligned with the principles of green chemistry. Hence, the challenge for a sustainable environment calls for more general and viable routes, which would be of great relevance to both synthetic and medicinal chemists.

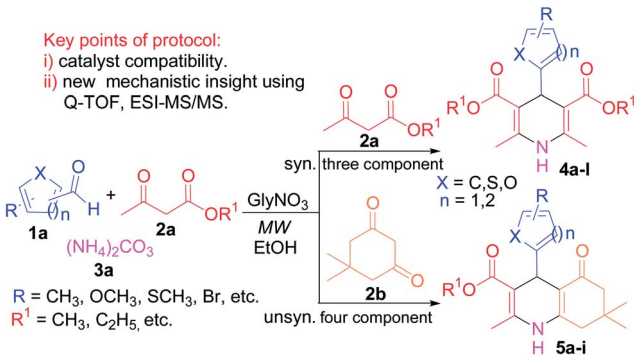
In this context, ionic liquids (ILs) is being hailed as the green solvent of the future, which increases the portfolio of environmentally benign organic synthesis due to their particular properties such as undetectable vapour pressure, ease of recovery and reuse.[15] Thus far, ILs with cations derived from imidazolium- and guanidinium-based ILs have been used as catalysts for the Hantzsch reaction.[16] Although these ILs help to reduce the risk of air pollution, concerns are being raised over their potential toxicity to aquatic environments and inaccessible biodegradability.[17]

Therefore, the development of bio-degradable ILs based on amino acids and their derivatives to replace the above cations is another promising approach because these compounds are the most abundant natural source of quaternary nitrogen precursors.[18] Moreover, low cost, easy preparation, and their properties to act as both anions and cations are added advantage in these amino acid ionic liquids[18b,e,19] (AAILs).

As a continuation of our ongoing endeavours in developing novel and practical multicomponent reactions to synthesize useful heterocyclic compounds,[20] we herein present the catalytic efficiency of glycine nitrate ($GlyNO_3$) ionic liquid under microwave (MW) irradiation for the multicomponent synthesis of aromatic/heterocyclic symmetrical and unsymmetrical 1,4-DHPs under identical reaction conditions (Scheme 1). Furthermore, a detailed Q-TOF-, ESI-MS- and ESI-MS/MS-based mechanistic study revealed that the reaction predominately follows the diketone pathway among four competing pathways.

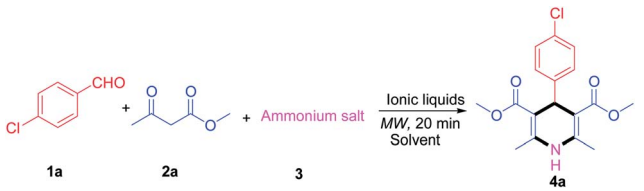
Results and discussion

After an initial survey of reaction conditions, a mixture of 4-chlorobenzaldehyde (**1a**, 0.5 mmol), methylacetoacetate (**2a**, 2 equiv.), ammonium acetate (**3a**, 2 equiv.) and $GlyNO_3$ (0.4 equiv.) as a catalyst was irradiated under focused monomode microwave (CEM, $P = 100$ W, 90 °C) for 20 min in EtOH (0.5 mL), producing 1,4-dihydropyridines **4a** in 45% yield (Table 1, entry **1**). To further increase the yield of **4a**, various sources of ammonium salt were screened (Table 1, entries **2–5**), wherein the satisfactory yield of **4a** up to 73% was obtained with ammonium carbonate (Table 1, entry **5**). Thereafter, the effect of the amount of catalyst (Table 1, entries **6–7**) was considered, and a yield of 82% was obtained with 0.5 equiv. $GlyNO_3$ (Table 1, entry **6**).



Scheme 1 Synthesis of symmetrical and unsymmetrical 1,4-dihydropyridines in $GlyNO_3$ ionic liquid *via* three- and four-component reactions.

Table 1 Optimization study for the synthesis of 1,4-dihydropyridins[a]



S. No	Ammonium salt	Solvent	Ionic liquid	Yield[b] (%)
1	NH_4OAc	EtOH	$GlyNO_3$	45
2	NH_4BF_4	EtOH	$GlyNO_3$	30
3	NH_4Cl	EtOH	$GlyNO_3$	20
4	NH_4HCO_3	EtOH	$GlyNO_3$	70
5	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	73
6[c]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	82
7[d]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	80
8[e]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	87
9	$(NH_4)_2CO_3$	H_2O	$GlyNO_3$	19
10	$(NH_4)_2CO_3$	DCM	$GlyNO_3$	34
11	$(NH_4)_2CO_3$	DMSO	$GlyNO_3$	20
12	$(NH_4)_2CO_3$	PEG 400	$GlyNO_3$	30
13	$(NH_4)_2CO_3$	EtOH–H_2O	$GlyNO_3$	40
14	$(NH_4)_2CO_3$	EtOH	$GlySO_4$	66
15	$(NH_4)_2CO_3$	EtOH	GlyTFA	40
16	$(NH_4)_2CO_3$	EtOH	GlyOAC	59
17	$(NH_4)_2CO_3$	EtOH	GlyCl	57
18	$(NH_4)_2CO_3$	—	$GlyNO_3$	29
19	$(NH_4)_2CO_3$	EtOH	—	26
20[f]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	55
21	$(NH_4)_2CO_3$	EtOH	Glycine	65
22	$(NH_4)_2CO_3$	EtOH	HNO_3	20

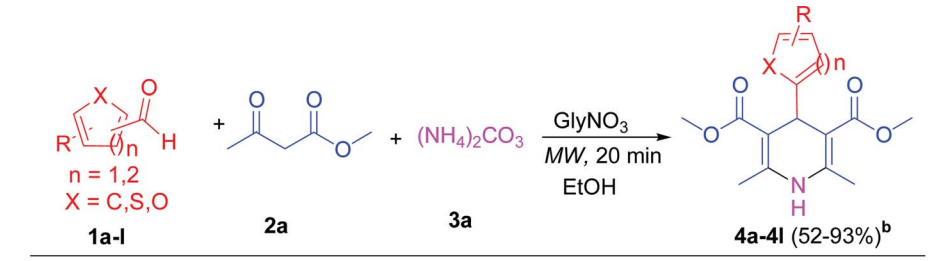
[a] Experimental conditions: 0.5 mmol of 4-chlorobenzaldehyde, methylacetoacetate (2 equiv.), $(NH_4)_2CO_3$ (2 equiv.), $GlyNO_3$ (0.5 equiv.) in 1 mL of EtOH under MW at $P = 100$ W, 90 °C for 20 min. [b] Isolated yield (after recrystallization in water and methanol). [c] $GlyNO_3$ (0.5 equiv.). [d] $GlyNO_3$ (0.6 equiv.). [e] EtOH (1 mL). [f] Reflux for 5 h. For entries **1–7**, EtOH = 0.5 mL; entries **8–22**, solvent = 1 mL.

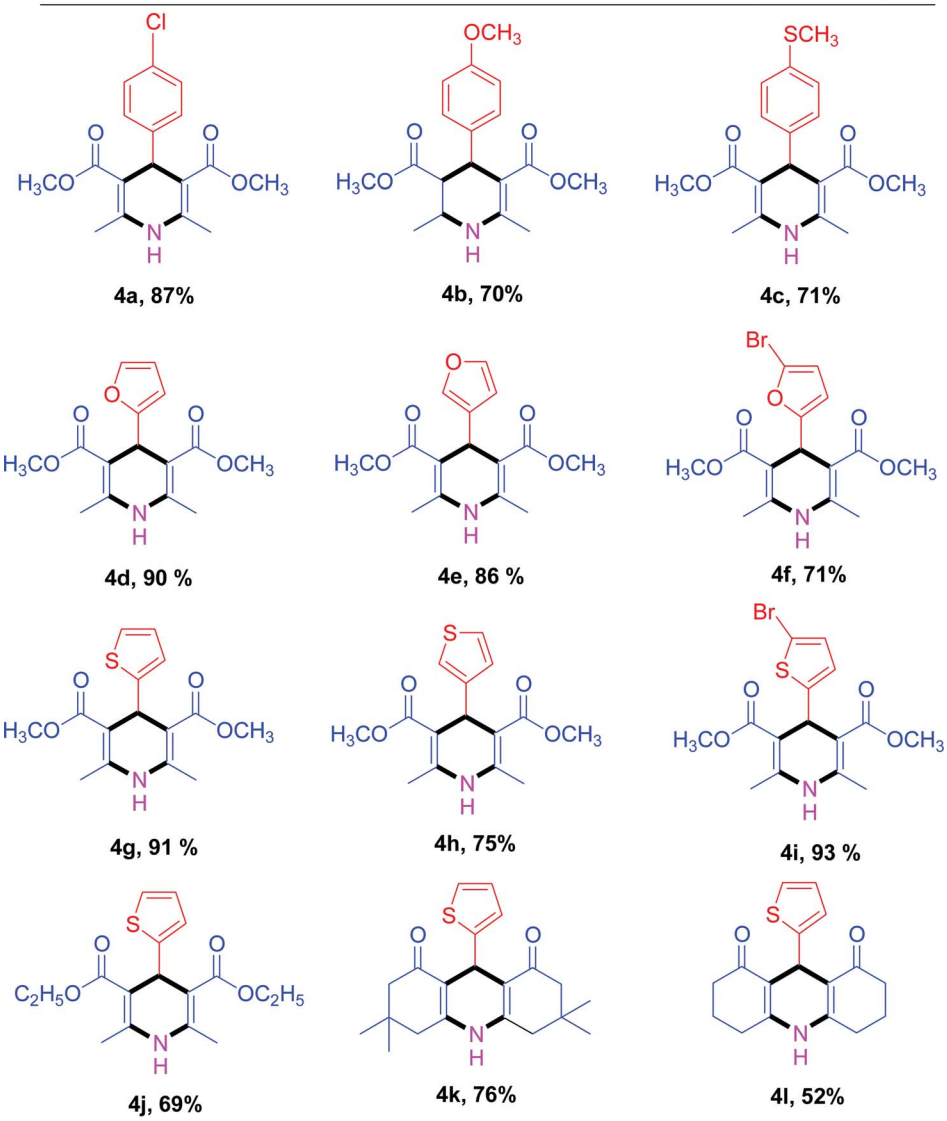
A further increase in the amount of catalyst could not exert any positive influence on the yields of **4a** (Table 1, entry **7**). Gratifyingly, the yield was improved to 87% with the increased in volume of EtOH up to 1 mL (Table 1, entry **8**). A further

increase in the volume of EtOH fails to enhance the yields of **4a**. Thereafter, the effects of different solvents and co-solvents (Table 1, entries **9–13**), and catalysts (Table 1, entries **14–17**) were studied, but inferior yields were obtained compared with Table 1, entry **8**.

Control experiments in the absence of solvents and catalysts (Table 1, entries **18–19**) produced **4a** in low yield, demonstrating the crucial role of solvents and catalysts. The reaction under conventional conditions by refluxing the reaction mixture for 5 h failed to improve the yield of **4a** (Table 1, entry **20**). Surprisingly, an experiment with glycine (Table 1, entry **21**) and HNO_3 (Table 1, entry **22**) resulted in a drastic decrease in the yield of **4a**, which emphasized the importance of $GlyNO_3$ IL in catalysis.

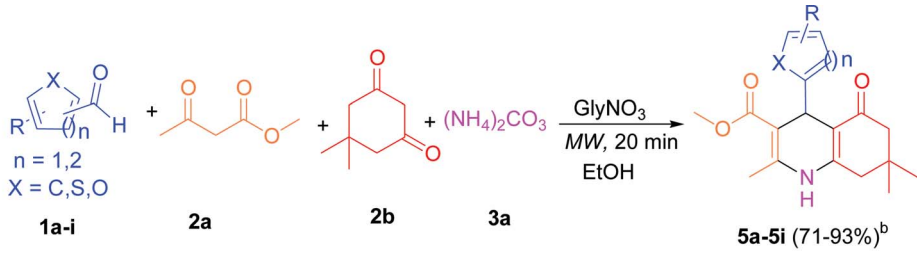
Table 2 Substrate scope of $GlyNO_3$-catalyzed synthesis of symmetrical 1,4-dihydropyridines[a]

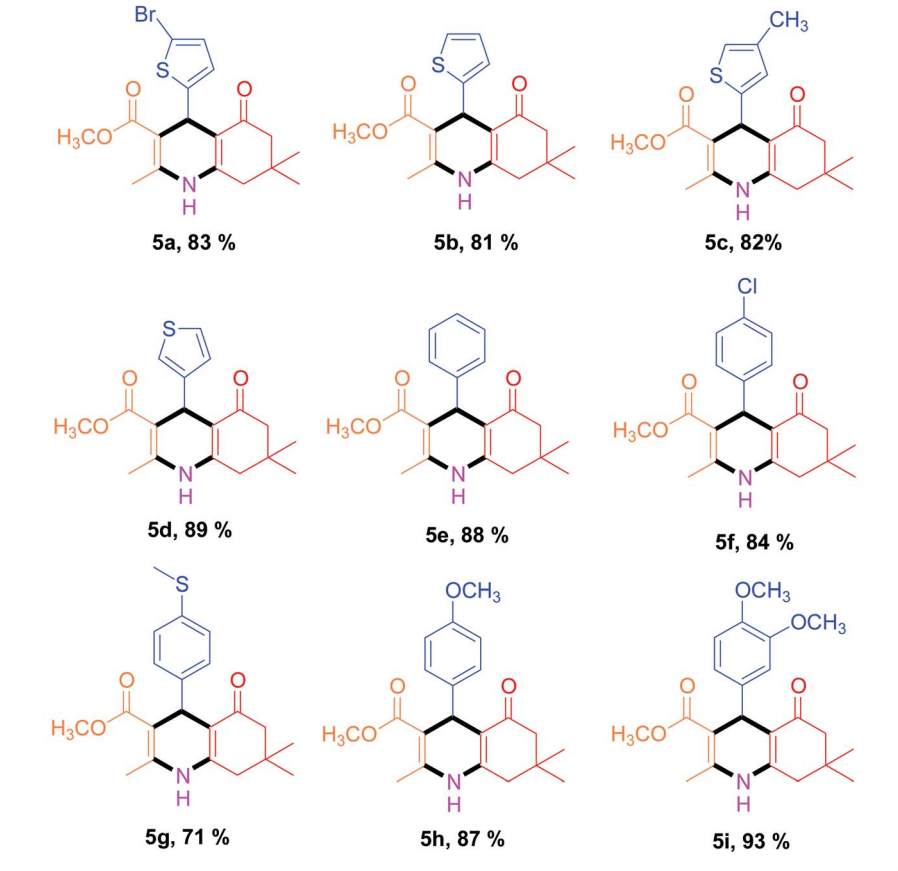




[a] Experimental conditions: 0.5 mmol of substituted benzaldehyde, methylacetoacetate (2 equiv.), $(NH_4)_2CO_3$ (2 equiv.), $GlyNO_3$ (0.5 equiv.) in 1 mL of EtOH under MW at $P = 100$ W, 90 °C for 20 min. [b] Isolated yield (after recrystallization in water and methanol).

Table 3 Substrate scope of $GlyNO_3$-catalyzed synthesis of unsymmetrical 1,4-dihydropyridines[a]





[a] Experimental conditions: 0.5 mmol of substituted benzaldehyde, **2a** (1 equiv.), **3a** (1 equiv.), $(NH_4)_2CO_3$ (2 equiv.), $GlyNO_3$ (0.5 equiv.) in 1 mL of EtOH under MW at $P = 100$ W, 90 °C, for 20 min. [b] Isolated yield (after recrystallization in water and methanol).

With the optimized reaction conditions in hand for the synthesis of symmetrica1 1,4-DHPs (Table 1, entry **8**), the generality and scope of this one-pot, three-component Hantzsch reaction was then explored. For this, a wide range of substituted benzaldehyde compounds, including heterocyclic moieties (**1a–i**), methylacetoacetate (**2a**), and ammonium carbonate (**3a**), were irradiated under focused MW ($P = 100$ W, 90 °C) for 20 min, which produced the corresponding 1,4-DHPs **4a** in good-to-excellent yields (Table 2, entries **4a–i**). During the substrate scope study, it was observed that the catalyst exhibited remarkable activity for heterocyclic-substituted benzaldehydes, particularly for thiophene containing moiety (Table 2, entries **4d–i**). Therefore, we further extended our substrate scope by using various dicarbonyl compounds in conjunction with thiophene-2-carboxaldehyde and ammonium carbonate, which afforded the desired compound in good yield (Table 2, entries **4j–l**).

After the successful synthesis of three-component symmetrical 1,4-DHPs, our goal was to synthesize four-component unsymmetrical 1,4-DHPs, also known as polyhydroquinoline, which enjoys the status of being privileged motifs in terms of their diverse biological profiles, compared with symmetrical 1,4-DHPs.[21]

Recently, these motifs have been recognized as lead molecules in antidiabetic drug discovery.[22] There are a plethora of reagents and catalyst reported in the literature for the synthesis of unsymmetrical 1,4-DHPs.[23] However, some of these suffer from limitations such as the usage of precious metal catalysts,

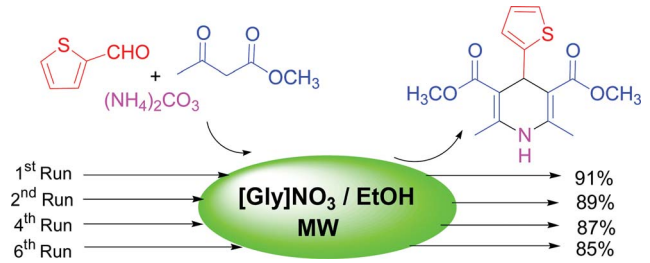
longer reaction time (6–11 h), two-step synthesis, cumbersome product isolation, selectivity and recyclability issues.

In addition, Rajesh *et al.*[23x] have recently reported hydromagnesite as a heterogeneous solid-based catalyst for the synthesis of 1,4-DHPs. Despite promising results, this methodology has limited substrate scope due to the non-involvement of any heterocyclic benzaldehydes.

To the best of our knowledge, only a small number of reports exist in literature in which the synthesis of unsymmetrical and symmetrical 1,4-DHPs is carried out under identical reaction conditions; these suffer from limitations such as longer reaction times, poor substrate scopes and tedious synthesis of catalysts.[24] Considering the sheer importance of unsymmetrical 1,4-DHPs, we were also interested in investigating whether our catalytic system could efficiently result in the synthesis of unsymmetrical 1,4-DHPs by overcoming the existing lacunae of reported protocols.[23]

We were pleased to observe that the mixture of 5-bromothiophene-2-carboxaldehyde (**1a**), methylacetoacetate (**2a**), 5,5-dimethyl-1,3-cyclohexanedione (**2b**) and ammonium carbonate (**3a**) successfully condensed in one pot under similar reaction conditions[25] providing **5a** in 83% yield. Thereafter, various substituted aromatic or heterocyclic benzaldehydes (**1a–i**) were condensed with **2a**, **2b** and **3a** to produce unsymmetrical 1,4-DHPs (Table 3, **5b–i**) in excellent yields.

From an economical point of view, the recyclability of $GlyNO_3$ was also considered. The IL retained high reactivity for up to six cycles (Scheme 2).



Scheme 2 Recyclability study of catalyst for the synthesis of 1,4-dihydropyridines.

Mechanistic study

Mechanistically, it was presumed that there are four plausible pathways[26] for the synthesis of symmetrical 1,4-DHPs (Fig. 2). These are (i) enamine (ii) diketone, (iii) dienamine and (iv) imine pathways (Fig. 2 and see ESI‡).

Q-TOF electrospray ionization mass spectrometry (ESI-MS) is the preferred technique for studying reaction intermediates because of its ability to "fish" ionic or ionized intermediates

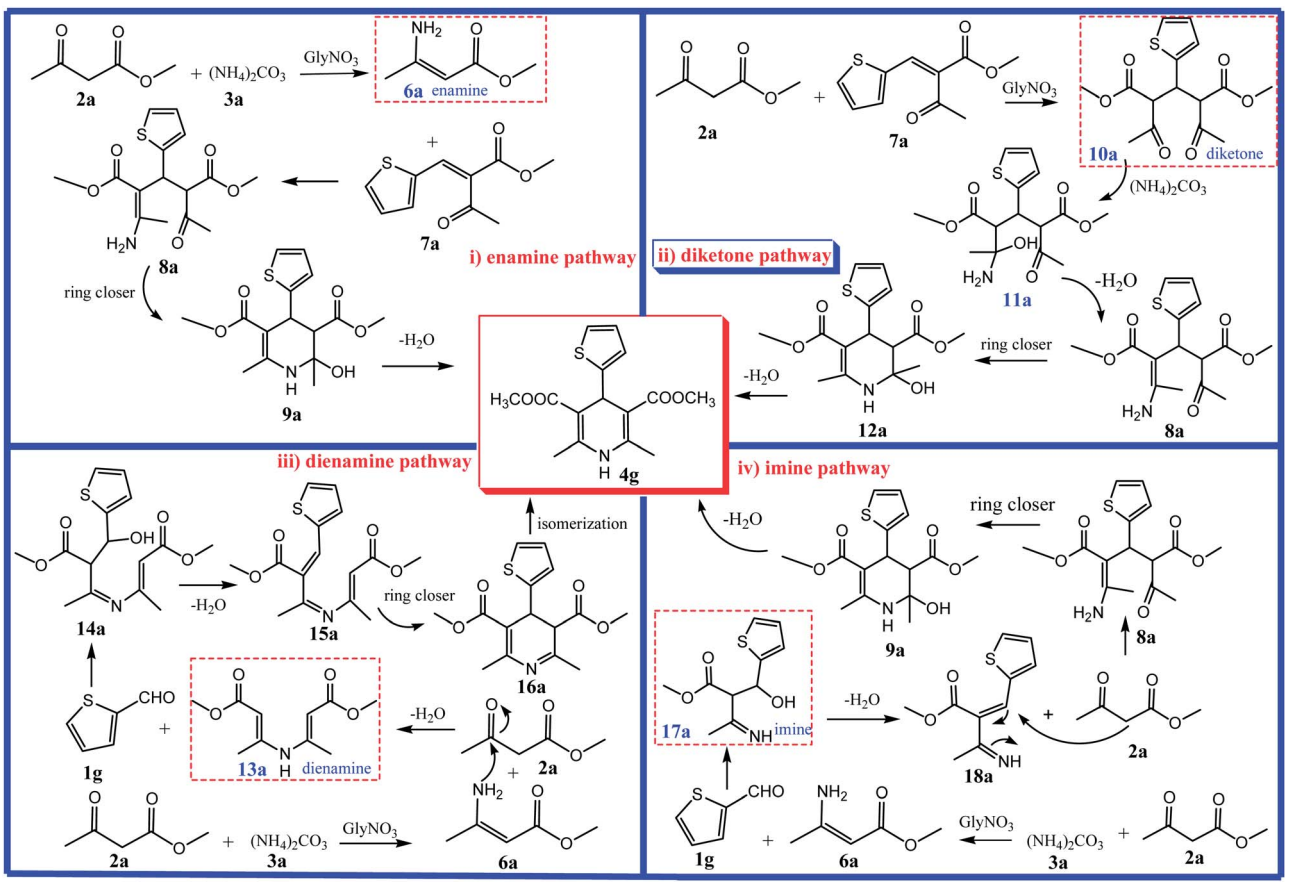


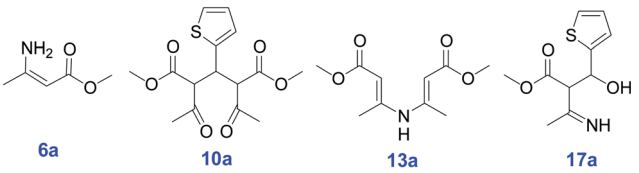
Fig. 2 Various plausible pathways for the synthesis of 1,4-dihydropyridines.

directly from reaction solutions into the gas phase with high speed and sensitivity[27] to prove the feasibility of precise pathways among four competing mechanisms involved in the synthesis of 1,4-dihydropyridines. Moreover, its tandem version, ESI-MS/MS, is rapidly becoming the technique of choice for solution-phase mechanistic studies in chemistry.[28]

Therefore, we performed Q-TOF ESI (+ve) MS studies on aliquots of samples withdrawn after 10 min from the $GlyNO_3$-catalyzed reaction of **1g**, **2a** and **3a** (Scheme 3)[29] at capillary voltage (3100 V), cone voltage (25 V), dissolution temp. (200 °C) and source temp. (80 °C).

The total ion chromatogram (TIC) revealed the presence of ions at m/z 308.26 (m_1), 325.29 (m_2), 344.31 (m_3), 327.31 (m_4), 224.15 (m_5),[30] 211.16 (m_6), 179.09 (m_7), and 117.13 (m_8), which corresponds to $[\mathbf{4g} + H]^+$, $[\mathbf{4g} + NH_3 + H]^+$, $[\mathbf{11a} + H]^+$, $[\mathbf{10a} + H]^+$, $[\mathbf{19a} + H]^+$, $[\mathbf{7a} + H]^+$, $[\mathbf{7a} - OMe]^+$ and $[\mathbf{2a} + H]^+$, respectively. The presence of characteristic peaks $m_3 = [\mathbf{11a} + H]^+$, $m_4 = [\mathbf{10a} + H]^+$ and $m_6 = [\mathbf{7a} + H]^+$ in Fig. 3 revealed the possibility of diketone pathways (Fig. 2), and the absence of key intermediate **6a** (enamine), **13a** (dienamine) and **17a** (imine) (Scheme 4) in the TIC (Fig. 3) ruled out the possibility of enamine, dienamine and imine pathways.

Scheme 3 The one-pot, three-component Hantzsch reaction.



Scheme 4 Key intermediates of four plausible pathways.

For further structure elucidation in the context of diketone pathways and product formation, tandem MS/MS experiments were carried out for a few selected ions observed in the TIC (Fig. 3) at m/z 308.17 = m_1, 325.29 = m_2, 344.31 = m_3 and 327.31 = m_4. The MS/MS or MS^2 spectra derived from the ion of m/z 308.17 = m_1 showed peak m/z at 276.14 and 224.15 assigned as $[\mathbf{4g} - OCH_3]^+$ and $[\mathbf{4g} - C_4H_3S + H]^+$ (Fig. 4), respectively, confirmed the product formation.

In the case of m_2, the MS^2 spectra (Fig. 5) exhibited the parent ion $m_2 = [\mathbf{4g} + NH_3 + H]^+$ and daughter ion with m/z at 308.17 and 224.28 corresponded to $[\mathbf{4g} - NH_3 + H]^+$ and $[\mathbf{4g} - C_4H_3S + H]^+$, respectively, confirming the ammoniated adduct of desired product, *i.e.* **4g** (Scheme 3).

To further confirm the presence of the intermediate (m_3) in the context of diketone pathways, the MS^2 experiment was carried out of $m_3 = [\mathbf{11a} + H]^+$ ion (Fig. 6). The MS/MS spectra revealed the presence of the ion with m/z 327.34, 309.31, 295.29 and 211.21, which were diagnosed as $[\mathbf{11a} - NH_2]^+$, $[\mathbf{11a} - NH_2 - H_2O]^+$, $[\mathbf{11a} - NH_2 - H_2O - CH_3]^+$ and $[\mathbf{11a} - NH_2 - H_2O - CH_3 - C_4H_4O_2]^+$, respectively, confirmed the fragments of m_3 and their involvement in diketone pathways.

Most importantly, the key intermediate involved in diketone pathway $m_4 = [\mathbf{10a} + H]^+$ was also ascertained by the MS^2

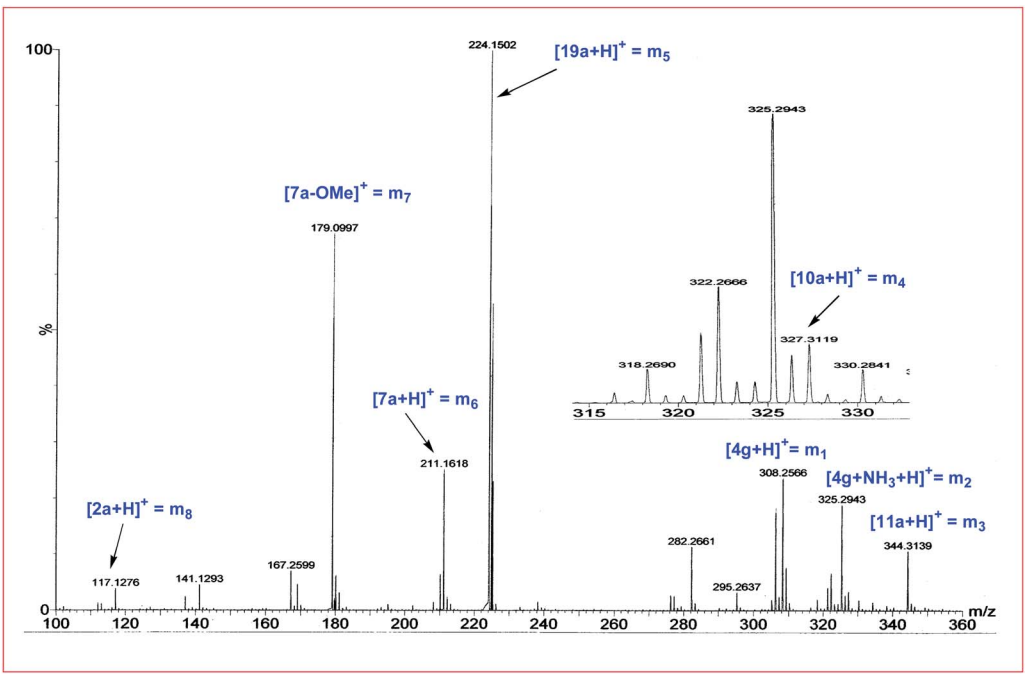


Fig. 3 TIC of Q-TOF, ESI(+) MS of sample withdrawn after 10 min for three-component Hantzsch reaction of **1g**, **2a** and **3a** catalyzed by $GlyNO_3$.

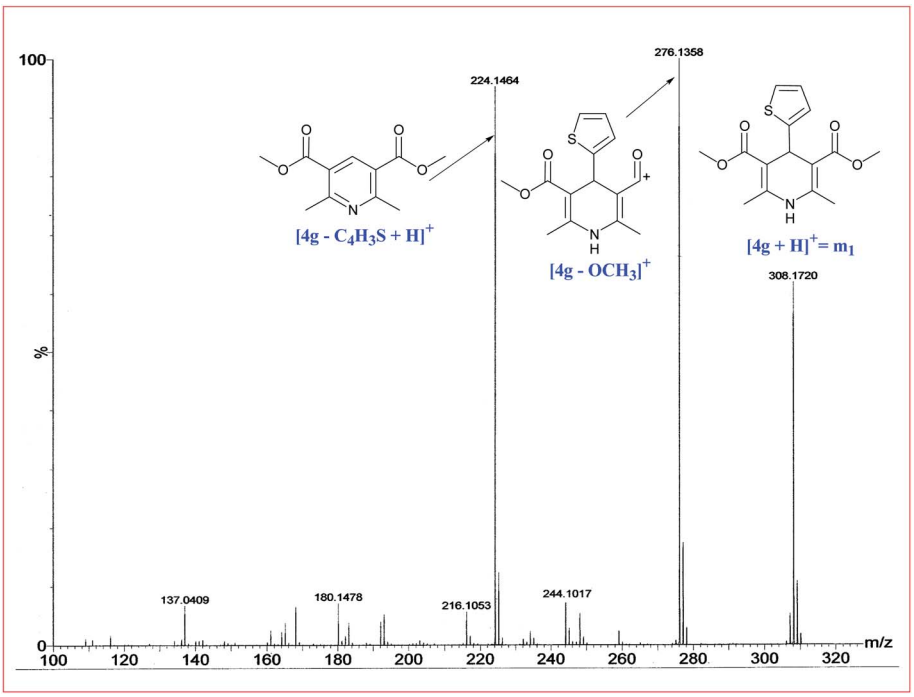


Fig. 4 On line Q-TOF, ESI(+) MS/MS of peak $m_1 = 308.17$ as shown in Fig. 2.

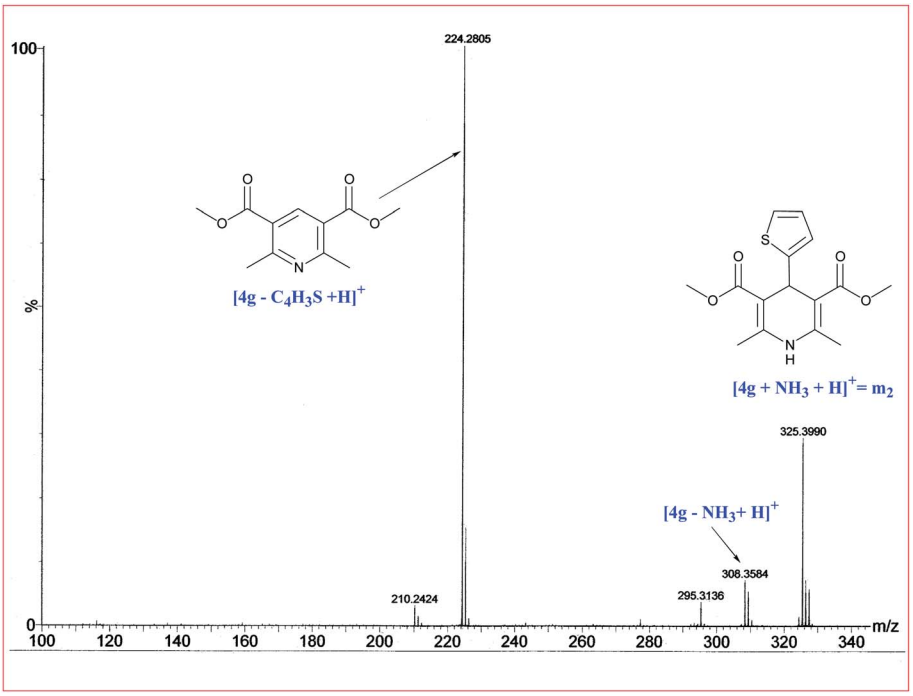


Fig. 5 On line Q-TOF, ESI(+) MS/MS of peak $m_2 = 325.29$, as shown in Fig. 2.

experiment. The MS^2 spectra (Fig. 7) exhibited the parent ion m_4 = [**10a** + H]$^+$ and daughter ions with m/z 295.18, 243.21 and 211.13 correspond to [**10a** − OCH_3]$^+$, [**10a** − C_4H_3S]$^+$ and [**10a** − $C_5H_7O_3$]$^+$, respectively, confirmed the fragments of ion m_4 and their involvement in diketone pathways.

On the basis of the Q-TOF, ESI-MS/MS studies, it is determined that $GlyNO_3$ IL-catalyzed three-component Hantzsch reaction follows the diketone pathway among four competing mechanistic pathways (Fig. 2).

On the other hand, the possibility of enamine pathways cannot be ignored because of the observation of peak m_6 = [**7a** + H]$^+$

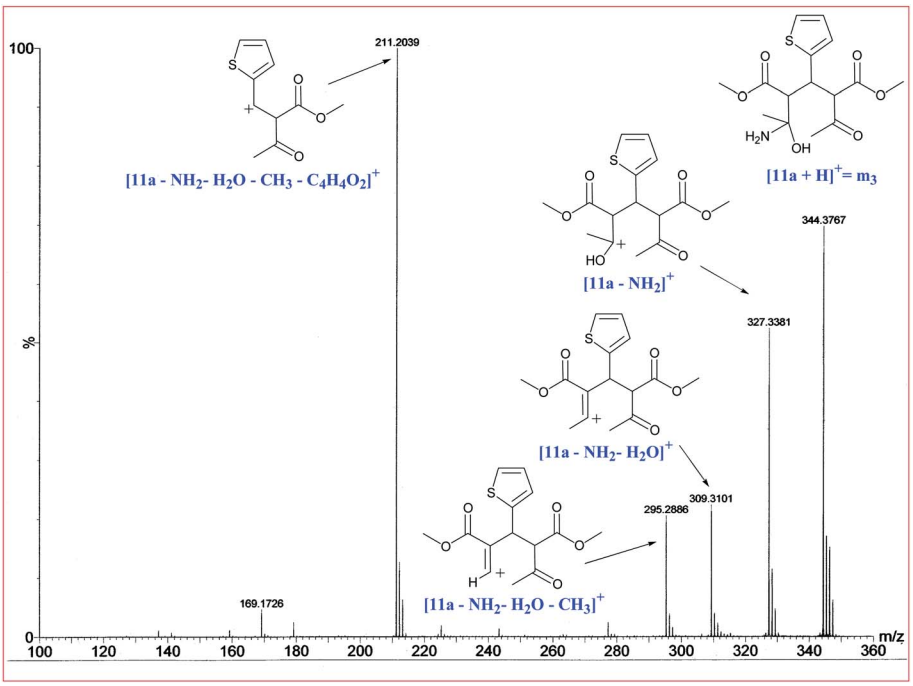


Fig. 6 On line Q-TOF, ESI(+) MS/MS of peak $m_3 = 344.31$, as shown in Fig. 2.

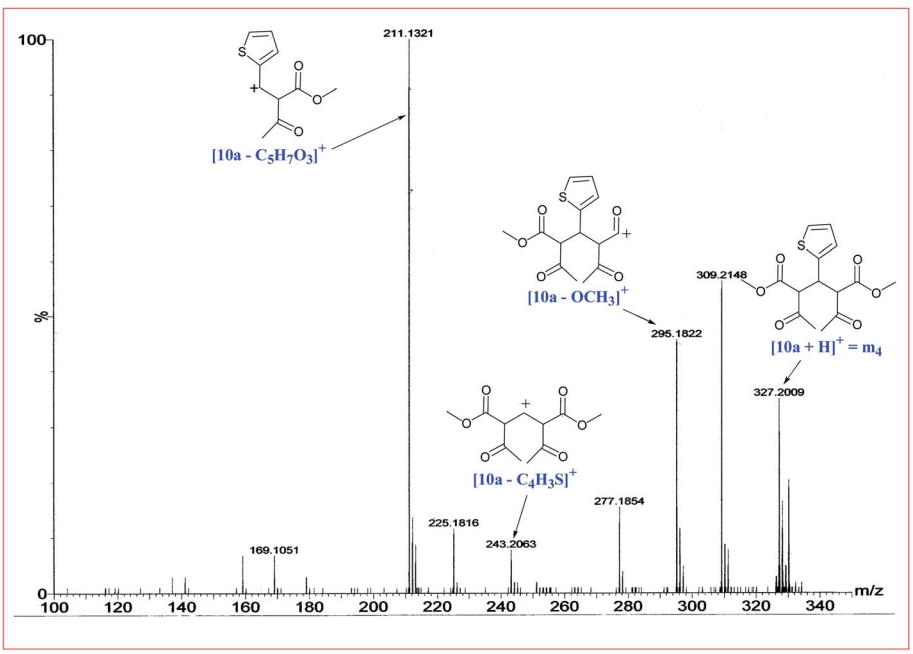
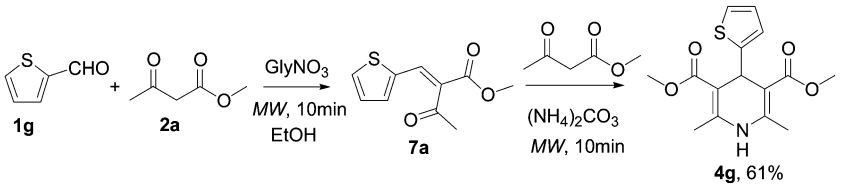


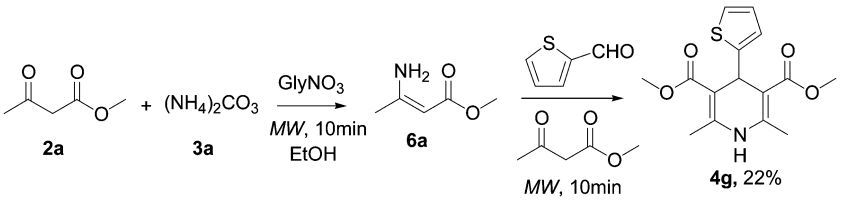
Fig. 7 On line Q-TOF, ESI(+) MS/MS of peak $m_4 = 327.31$, as shown in Fig. 2.

(Fig. 3) during the analysis of aliquots of samples withdrawn after 10 min, which is also one of the intermediates of enamine pathways (Fig. 2). Therefore, two control experiments or experiments to validate our perception regarding diketone pathways were carried out in sequential one-pot two-step ways (Schemes 5 and 6). The results revealed that 61% of the product yield (Scheme 5) was obtained *via* diketone pathways, compared with a 22% yield *via* enamine pathways (Scheme 6).

Finally, on the basis of control experiments and the Q-TOF, ESI-MS/MS studies, we can say that the most predominant pathway for the synthesis of symmetrical 1,4-DHPs is diketone, rather than enamine, dienamine and imine. This is the first report that proved the participation of diketone pathways in the synthesis of symmetrical 1,4-DHPs by using the Q-TOF, ESI-MS/MS studies.



Scheme 5 Sequential one-pot, two-step synthesis of 1,4-DHP *via* diketone pathway.



Scheme 6 Sequential one-pot, two-step synthesis of 1,4-DHP *via* enamine pathway.

Conclusion

In summary, an operationally simple and highly efficient one-pot multicomponent reaction for the synthesis of symmetrical and unsymmetrical 1,4 DHPs has been developed, which could have great importance for synthetic and medicinal chemistry. The methodology is practical, recyclable and economical, in addition to being flexible, because it also allows heterocyclic benzaldehydes to participate in the synthesis of both symmetrical and unsymmetrical 1,4 DHPs under identical reaction conditions. Furthermore, mechanistic studies using Q-TOF, ESI-MS/MS revealed that the synthesis of symmetrical 1,4 DHPs predominately follows the diketone pathway among four competing reaction pathways. Finally, we anticipate that this catalytic system will find applications in both academia and industry. The Q-TOF, ESI-MS/MS-based studies may also helpful to reveal the mechanistic details of numerous other reactions. The mechanistic study related to unsymmetrical 1,4 DHPs is currently under investigation.

Experimental section

General procedure for the synthesis of symmetrical 1,4-dihydropyridins from substituted benzaldehydes (Table 2, 4a–l)

Substituted benzaldehyde (0.5 mmol), dicarbonyl compound (2 equiv.), ammonium carbonate (2 equiv.) and glycine nitrate (0.5 equiv.) were taken in 1 mL ethanol in a round-bottomed flask and the reaction mixture was subjected to microwave irradiation by using a CEM monomode microwave at $P = 100$ W, 90 °C for 20 min. After completion, the crude reaction mixture was filtered to obtain $GlyNO_3$. The filtrate was vacuum evaporated and then recrystallized from water–methanol, which gave an isolated yield of **4a–l** in the range of 52–93% yields. Products were identified and confirmed by their ^1H, ^{13}C NMR spectra and HRMS values.

General procedure for the synthesis of unsymmetrical 1,4-dihydropyridins from substituted benzaldehydes (Table 3, 5a–i)

Substituted benzaldehyde (0.5 mmol), methylacetoacetate (1 equiv.), 5,5-dimethyl-1,3-cyclohexanedione (1 equiv.), ammonium carbonate (2 equiv.) and glycine nitrate (0.5 equiv.) were taken in 1 mL ethanol in a round-bottomed flask, and the reaction mixture was subjected to microwave irradiation by using a CEM monomode microwave at $P = 100$ W, 90 °C for 20 min. After completion, the crude reaction mixture was filtered to obtain $GlyNO_3$. The filtrate was vacuum evaporated and then recrystallized from water–methanol, which gave an isolated yield of **5a–i** in the range of 52–93% yields. Products were identified and confirmed by their ^1H, ^{13}C NMR spectra and HRMS values.

Acknowledgements

RK, NHA and AS are indebted to CSIR and UGC, New Delhi, for the award of research fellowships. The authors gratefully acknowledge Director(s) CDRI, Lucknow and IHBT, Palampur for their kind cooperation and encouragement. This work was supported by Council of Scientific and Industrial Research (project CSC-0108 and ORIGIN). Thanks to Mr Shiv Kumar and Pawan Kumar for providing spectral data. CDRI Communication No. 8644.

References

1 (*a*) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486; (*b*) J. D. Sunderhaus and S. F. Martin, *Chem. –Eur. J.*, 2009, **15**, 1300–1308; (*c*) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463–472; (*d*) N. Ismabery and R. Lavila, *Chem. –Eur. J.*, 2008, **14**, 8444–8454; (*e*) D. M. D. Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, 2007, **36**, 1095–1108; (*f*) B. Jang, F. Shi and S.-T. Tu, *Curr. Org. Chem.*, 2010, **14**, 357–378; (*g*) B. Jiang, T. Rajale, W. Wever, S.-J. Tu and G. Li, *Chem. –Asian J.*,

2010, **5**, 2318–2335; (*h*) A. Domling, *Chem. Rev.*, 2006, **106**, 17–89; (*i*) J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133–1144; (*j*) D. J. Ramon and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602–1634; (*k*) N. Isambert and R. Lavilla, *Chem. –Eur. J.*, 2008, **14**, 8444–8454; (*l*) Y. Gu, *Green Chem.*, 2012, **14**, 2091–2128.

2 (*a*) U. A. Domling and W. Horl, *Endeavour*, 1994, **18**, 115–122; (*b*) L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304–322; (*c*) R. V. A. Orru and M. D. Greef, *Synthesis*, 2003, 1471–1499.

3 (*a*) A. Pinto, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 3291–3295; (*b*) M. R. M. Huettl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*c*) L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967–1983; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136; (*e*) P. Arya, R. Joseph and D. T. H. Chou, *Chem. Biol.*, 2002, **9**, 145–156.

4 J.-P. Wan and Y. Liu, *RSC Adv.*, 2012, **2**, 9763–9777.

5 (*a*) A. Hilgeroth and H. Lilie, *Eur. J. Med. Chem.*, 2003, **38**, 495–499; (*b*) C. Avendano and J. C. Menendez, *Curr. Med. Chem.*, 2002, **9**, 159–193; (*c*) C. Avendano and J. C. Menendez, *Med. Chem. Rev.–Online*, 2004, **1**, 419–444; (*d*) A. Boumendjel, H. B. Cortay, D. Trompier, T. Perrotton and A. D. Pietro, *Med. Res. Rev.*, 2005, **25**, 453–472; (*e*) I. O. Donkor, X. Zhou, J. Schmidt, K. C. Agrawal and V. Kishore, *Bioorg. Med. Chem.*, 1998, **6**, 563–566; (*f*) K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Mereland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806–811.

6 (*a*) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. MaCarthy, R. Zhang and S. Mereland, *J. Med. Chem.*, 1995, **38**, 119–129; (*b*) C. O. Kappe, W. M. F. Fabian and M. A. Semones, *Tetrahedron*, 1997, **53**, 2803–2816; (*c*) K. Aouam and A. Berdeaux, *Therapie*, 2003, **58**, 333–339; (*d*) A. Hilgeroth, *Mini-Rev. Med. Chem.*, 2002, **2**, 235–247.

7 K. K. Borowicz, M. Gasior, Z. Kleinrok and S. J. Czuczwar, *Eur. J. Pharmacol.*, 1997, **323**, 45–51.

8 I. O. Donkor, X. Zhou, J. Schmidt, K. C. Agrawal and V. Kishore, *Bioorg. Med. Chem.*, 1998, **6**, 563–568.

9 H. Li, S. Moro, N. Forsyth, N. Melman, X.-D. Ji and K. A. Jacobson, *J. Med. Chem.*, 1999, **42**, 706–721.

10 (*a*) S. R. M. D. Morshed, K. Hashimoto, Y. Murotani, M. Kawase, A. Shah, K. Satoh, H. Kikuchi, H. Nishikawa, J. Maki and H. Sakagami, *Anticancer Res.*, 2005, **25**, 2033–2038; (*b*) H. A. S. Abbas, W. A. El Sayed and N. M. Fathy, *Eur. J. Med. Chem.*, 2010, **45**, 973–982; (*c*) X. Zhou, L. Zhang, E. Tseng, E. Scott- Ramsay, J. J. Schentag, R. A. Coburn and M. E. Morris, *Drug Metab. Dispos.*, 2005, **33**, 321–328; (*d*) L. Bazargan, S. Fouladdel, A. Shafiee, M. Amini, S. M. Ghaffari and E. Azizi, *Cell Biol. Toxicol.*, 2008, **24**, 165–174.

11 (*a*) A. Hilgeroth, *Mini-Rev. Med. Chem.*, 2002, **2**, 235; (*b*) A. Hilgeroth and H. Lilie, *Eur. J. Med. Chem.*, 2003, **38**, 495–503; (*c*) A. Hilgeroth, M. Wiese and A. Billich, *J. Med. Chem.*, 1999, **42**, 4729–4732.

12 J. Marco-Counntelles, R. Leon, C. de los Rios, A. Guglietta, J. Terencio, M. G. Lopez, A. G. Garcia and M. Villarroya, *J. Med. Chem.*, 2006, **49**, 7607–7610.

13 (*a*) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1–42; (*b*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223–243; (*c*) A. Sausins and G. Duburs, *Heterocycles*, 1988, **27**, 269–289.

14 (*a*) N. Koukabi, E. Kolvari, A. Khazaei, M. A. Zolfigol, B. S. Shaghasemi and H. R. Khavasi, *Chem. Commun.*, 2011, **47**, 9230–9232; (*b*) R. Ananthakrishnan and S. Gazi, *Catal. Sci. Technol.*, 2012, **2**, 1463–1471; (*c*) L. Shen, S. Cao, J. Wu, J. Zhang, H. Li, N. Liu and X. Qian, *Green Chem.*, 2009, **11**, 1414–1420; (*d*) M. M. -Aghayan, R. Boukherroub, M. Nemati and M. Rahimifard, *Tetrahedron Lett.*, 2012, **53**, 2473–2475; (*e*) A. Debache, R. Boulcina, A. Belfaitah, S. Rhouti and B. Carboni, *Synlett*, 2008, 509–512; (*f*) S. Thakrar, A. Bavishi, D. Bhavsar, S. Parekh, H. Vala, A. Radadiya, M. Parmar and M. Savant, *Synth. Commun.*, 2012, **42**, 3269–3278; (*g*) S. Rostamnia and K. Lamei, *Chin. Chem. Lett.*, 2012, **23**, 930–932; (*h*) A. Kuraitheerthakumaran, S. Pazhamalai and M. Gopalakrishnan, *Chin. Chem. Lett.*, 2011, **22**, 1199–1202; (*i*) A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati and B. Carboni, *Tetrahedron Lett.*, 2009, **50**, 5248–5250; (*j*) F. Tamaddon, Z. Razmi and A. A. Jafari, *Tetrahedron Lett.*, 2010, **51**, 1187–1189; (*k*) R. S. Varma and D. Kumar, *Tetrahedron Lett.*, 1999, **40**, 21–24; (*l*) H. Salehi and Q.-X. Guo, *Synth. Commun.*, 2004, **34**, 4349–4357; (*m*) M. Kidwai, S. Saxena, R. Mohan and R. Venkataramanan, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1845–1846; (*n*) G. Sabitha, G. S. K. K. Reddy, C. S. Reddy and J. S. Yadav, *Tetrahedron Lett.*, 2003, **44**, 4129–4131; (*o*) A. Dondoni, A. Massi, E. Minghini and V. Bertolasi, *Tetrahedron Lett.*, 2004, **60**, 2311–2326; (*p*) R. K. Vohra, C. Bruneau and J.-L. Renaud, *Adv. Synth. Catal.*, 2006, **348**, 2571–2574; (*q*) N. Koukabi, E. Kolvari, M. A. Zolfigol, A. Khazaei, B. S. Shaghasemi and B. Fasahati, *Adv. Synth. Catal.*, 2012, **354**, 2001–2008.

15 (*a*) R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792–793; (*b*) J. P. Hallett and T. Welton, *Chem. Rev.*, 2011, **111**, 3508–3576; (*c*) P. Hapiot and C. Lagrost, *Chem. Rev.*, 2008, **108**, 2238–2264; (*d*) T. L. Greaves and C. J. Drummond, *Chem. Rev.*, 2008, **108**, 206–237; (*e*) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667–3692.

16 (*a*) J.-C. Legeay, J. J. V. Eynde and J. P. Bazureau, *Tetrahedron*, 2005, **61**, 12386–12397; (*b*) L. Ming, G. W. -Si, W. L. -Rong, L. Y. Feng and Y. H. Zheng, *J. Mol. Catal. A: Chem.*, 2006, **258**, 133–138; (*c*) A. Shaabani, A. H. Rezayan and A. Rahmati, *Chem. Mon.*, 2006, **137**, 77–81; (*d*) J. S. Yadav, B. V. S. Reddy, A. K. Basak and A. V. Narsaish, *Green Chem.*, 2003, **5**, 60–63.

17 (*a*) K. S. Egorova and V. P. Ananikov, *ChemSusChem*, 2014, **7**, 336–360; (*b*) R. P. Swatloski, J. D. Holbrey and R. D. Rogers, *Green Chem.*, 2003, **5**, 361–363; (*c*) N. Gathergood, M. T. Garcia and P. J. Scammells, *Green Chem.*, 2004, **6**, 166–176; (*d*) G.-H. Tao, L. He, W.-S. Liu, L. Xu, W. Xiong, T. Wang and Y. Kou, *Green Chem.*, 2006, **8**, 639–646.

18 (*a*) W. Bao, Z. Wang and Y. Li, *J.Org. Chem.*, 2003, **68**, 591–593; (*b*) K. Fukumoto and H. Ohno, *Chem. Commun.*, 2006, 3081–3083; K. Fukumoto, M. Yoshizawa and H. Ohno,

J. Am. Chem. Soc., 2005, **127**, 2398–2399; (*c*) L. C. Branco, P. M. P. Gois, N. M. T. Lourenco, V. B. Kurteva and C. A. M. Afonso, *Chem. Commun.*, 2006, 2371–2372; (*d*) G. H. Tao, L. He, N. Sun and Y. Kou, *Chem. Commun.*, 2005, 3562–3564; (*e*) G. H. Tao, L. He, W. S. Liu, L. Xu, W. Xiong, T. Wang and Y. Kou, *Green Chem.*, 2006, **8**, 639–646.

19 (*a*) H. Ohno and K. Fukumoto, *Acc. Chem. Res.*, 2007, **40**, 1122–1129.

20 (*a*) R. Kumar, Richa, N. H. Andhare, A. Shard and A. K. Sinha, *Chem. –Eur. J.*, 2013, **19**, 14798–14803; (*b*) N. Sharma, U. K. Sharma, R. Kumar, Richa and A. K. Sinha, *RSC Adv.*, 2012, **2**, 10648–10651; (*c*) U. K. Sharma, N. Sharma, R. Kumar and A. K. Sinha, *Amino Acids*, 2013, **44**, 1031–1037.

21 One of the main advantage of unsymmetrical 1,4-DHPs is utilization of two different dicarbonyl compounds which results in diversified derivatives of 1,4 DHPs compared to symmetrical 1,4-DHPs where two similar dicarbonyl are utilized. Overall the possibility of discovering new biological entities increased.

22 (*a*) A. Kumar, S. Sharma, V. D. Tripathi, R. A. Maurya, S. P. Srivastava, G. Bhatia, A. K. Tamrakar and A. K. Srivastava, *Bioorg. Med. Chem.*, 2010, **18**, 4138–4148; (*b*) L. E. Hinkel, *J. Chem. Soc., Trans.*, 1920, **117**, 137–140.

23 (*a*) L. Saikia, D. Dutta and D. K. Dutta, *Catal. Commun.*, 2012, **19**, 1–4; (*b*) L.-M. Wang, J. Sheng, L. Zang, J.-W. Han, Z.-Y. Fan, H. Tian and C.-T. Qian, *Tetrahedron*, 2005, **61**, 1539–1543; (*c*) S. K. Kumar and K. N. Singh, *J. Heterocycl. Chem.*, 2010, **47**, 194–197; (*d*) M. Maheswara, V. Siddaiah, G. L. V. Damu and C. V. Rao, *ARKIVOC*, 2006, **2**, 201–206; (*e*) M. Kidwai, R. Chauhan, D. Bhatnagar, A. K. Singh, B. Mishra and S. Dey, *Monatsh. Chem.*, 2012, **143**, 1675–1680; (*f*) D. S. Raghuvanshi and K. N. Singh, *Indian J. Chem.*, 2013, **52B**, 1218–1223; (*g*) K. A. Undale, T. S. Shaikh, D. S. Gaikwad and D. M. Pore, *C. R. Chim.*, 2011, **14**, 511–515; (*h*) J. P. Nirmal, P. V. Dadhaniya, M. P. Patel and R. G. Patel, *Indian J. Chem.*, 2010, **49B**, 587–592; (*i*) A. Rajendran, C. Karthikeyan and K. Rajathi, *Int. J. ChemTech Res.*, 2011, **3**, 810–816; (*j*) E. Rajanarendar, M. N. Reddy and S. Raju, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2011, **50**, 751–755; (*k*) W. H. Correa and J. L. Scott, *Green Chem.*, 2001, **3**, 296–301; (*l*) J. L. Donelson, R. A. Gibas and S. K. De, *J. Mol. Catal. A: Chem.*, 2006, **256**, 309–311; (*m*) A. Kumar and R. A. Maurya, *Tetrahedron Lett.*, 2007, **48**, 3887–3890; (*n*) S. Ko and C.-F. Yao, *Tetrahedron*, 2006, **62**, 7293–7299; (*o*) M. M. Heravi, K. Bakhtiari, N. M. Javadi, F. F. Bamoharram, M. Saeedi and H. A. Oskooie, *J. Mol. Catal. A: Chem.*, 2007, **264**, 50–52; (*p*) J. C. Legeay, J. Y. Goujon, J. J. V. Eynde, L. Toupet and J. P. Bazureau, *J. Comb. Chem.*, 2006, **8**, 829–833; (*q*) S. Ko, M. N. V. Sastry, C. Lin and C.-F. Yao, *Tetrahedron Lett.*, 2005, **46**, 5771–5774; (*r*) M. Tajbakhsh, H. Alinezhsd, M. Norouzi, S. Baghery and M. Akbari, *J. Mol. Liq.*, 2013, **177**, 44–48; (*s*) A. Kumar and R. A. Maurya, *Tetrahedron*, 2007, **63**, 1946–1952; (*t*) N. N. Karade, V. H. Budhewar, S. V. Shinde and W. N. Jadhav, *Lett. Org. Chem.*, 2007, **4**, 16–19; (*u*) G. Song and B. Wang, *Synth. Commun.*, 2005, **35**, 2875–2878; (*v*) S. R. Cherkupally and R. Mekala, *Chem. Pharm. Bull.*, 2008, **56**, 1002–1004; (*w*) X.-L. Zhang, S.-R. Sheng, X.-L. Lu and X.-L. Liu, *ARKIVOC*, 2007, **13**, 79–86; (*x*) U. C. Rajesh, S. Manohar and D. S. Rawat, *Adv. Synth. Catal.*, 2013, **355**, 3170–3178; (*y*) M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshtiha and A. Davoodnia, *Synth. Commun.*, 2010, **40**, 523–529.

24 (*a*) R. F. Affeldf, E. V. Benveutti and D. Russowsky, *New J. Chem.*, 2012, **36**, 1502–15011; (*b*) M. N. Esfahani, S. J. Hoseini, M. Montazerozohori, R. Mehrabi and H. Nasrabadi, *J. Mol. Catal. A: Chem.*, 2014, **382**, 99–105; (*c*) P. P. Ghosh, S. Paul and A. R. Das, *Tetrahedron Lett.*, 2013, **54**, 138–142.

25 The synthesis of four component unsymmetrical 1,4 DHPs carried out under similar reaction condition as adopted for three-component synthesis of symmetrical 1,4 DHPs (Table 1, entry **8**). The difference is only in the utilization of methylacetoacetate and dimedone (1 : 1 equiv.) instead of 2 equiv. of methylacetoacetate.

26 (*a*) A. R. Katritzky, D. L. Ostercamp and T. I. Yousaf, *Tetrahedron*, 1986, **42**, 5729–5738; (*b*) A. Saini, S. Kumar and J. S. Sandhu, *J. Sci. Ind. Res.*, 2008, **67**, 95–111; (*c*) A. R. Katritzky, D. L. Ostercamp and T. I. Yousaf, *Tetrahedron*, 1987, **43**, 5171–5186; (*d*) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, 1955, **77**, 444–447; (*e*) B. Singh and G. Y. Lesher, *J. Heterocycl. Chem.*, 1980, **17**, 1109–1110; (*f*) P. A. Hopes, A. J. Parker and I. Patel, *Org. Process Res. Dev.*, 2006, **10**, 808–813.

27 (*a*) J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong and C. M. Whitehouse, *Science*, 1989, **246**, 64–71; (*b*) D. Schroder, *Acc. Chem. Res.*, 2012, **45**, 1521–1532; (*c*) L. S. Santos, *Eur. J. Org. Chem.*, 2008, 235–253; (*d*) M. Schafer, M. Drayß, A. Springer, P. Zacharias and K. Meerholz, *Eur. J. Org. Chem.*, 2007, 5162–5174; (*e*) J. B. Fenn, Electrospray Wings for Molecular Elephants (Nobel Lecture), *Angew. Chem., Int. Ed.*, 2003, **42**, 3871–3894; (*f*) R. B. Cole, *J. Mass Spectrom.*, 2000, **35**, 763–772.

28 C. Silvestri and J. S. Brodbelt, *Mass Spectrom. Rev.*, 2013, **32**, 247–266.

29 Thiophene-2-carboxaldehyde was taken as model substrate for mechanistic study because of the following reasons: (i) it gave maximum yield of the product, (ii) it had better solubility in EtOH, and (iii) ease in Q-TOF, ESI-MS analysis.

30 The peak $[\mathbf{19a} + H]^+ = m_5$ corresponds to fragmented part of peak **4g** *i.e.* $[\mathbf{4g} - C_4H_3S]^+$ which is further stabilized to 3,5-dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate $[\mathbf{19a} + H]^+$ (see ESI‡).