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RESEARCH ARTICLE

Urea as an Ammonia Surrogate in the Hantzsch's Synthesis of Polyhydroquinolines / 1,4-dihydropyridines under Green Reaction Conditions

G. Dhananjaya[1,2], Akula Raghunadh[1], P. Mahesh Kumar[1], S. Pulla Reddy[1], V. Narayana Murthy[1], Venkateswara Rao Anna[2,*] and Manojit Pal[3,*]

[1]*Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, Telangana, India;* [2]*Department of Chemistry, Koneru Lakshmaiah Education Foundation, Vaddeswaram, 522502, Guntur District, Andhra Pradesh, India;* [3]*Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India*

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Abstract: Synthesis of polyhydroquinolines *via* Hantzsch's multicomponent reaction (MCR) involves the use of a hygroscopic and moderately toxic ammonium salt as one of the key reactants. In our effort, we have found urea as an effective ammonia surrogate when the MCR was performed in the presence of sulphonic acid-functionalized Wang resin (Wang-OSO_3H) as a polymeric and recoverable acidic catalyst under green conditions. Urea is relatively less hygroscopic/toxic than the commonly used ammonium salts used in this MCR. The methodology afforded a range of polyhydroquinolines in good yields. Depending on the nature of reaction conditions employed, the MCR afforded Biginelli product or 1,4-DHPs when the use of 1,3-diketone was omitted.

Keywords: Urea, Hantzsch`s reaction, Catalyst, Green reaction.

1. INTRODUCTION

The polyhydroquinolines have emerged as a promising *N*-heterocyclic class of compounds for the identification and development of useful bioactive agents in the area of medicinal and pharmaceutical research. Indeed, remarkable pharmacological properties have been reported for various polyhydroquinoline derivatives including antibacterial/antitubercular [1], antimalarial [2], antiproliferative/cytotoxic [3,4] and antihyperglycemic/lipid modulating activities [5]. For example, compound **A** (Fig. **1**) has been reported to be a cardiomyogenic agent for the inhibition of TGFβ (transforming growth factor-beta) signaling [6]. The coumarin-polyhydroquinoline conjugate **B** (Fig. **1**) has been found to be a potent osteoblastic bone formation promoter *in vitro* and suppressor of ovariectomy induced bone loss *in vivo* [7]. The long chain fatty acid polyhydroquinoline derivative **C** (Fig. **1**) has shown strong activity against the glioma cell line [3]. We were particularly intrigued by the promising antiproliferative/cytotoxic properties of polyhydroquinoline class of compounds. Moreover, in our earlier effort, we have reported structurally similar 1,8-dioxodecahydroacridines [8] **D** (Fig. **2**) as potential inhibitors of sirtuins (that are believed to be useful for the treatment of cancer). In further continuation of this research in the identification of new and potential anticancer agents, we became interested in accessing compounds represented by **E** (Fig. **2**) for their further pharmacological evaluation.

Polyhydroquinolines are generally synthesized *via* the well-known Hantzsch's method involving the reaction of benzaldehyde, dimedone, ethyl acetoacetate and an ammonium salt e.g. ammonium acetate. This multicomponent reaction (MCR) is reported to be catalyzed by a range of catalysts e.g. Lewis or Brønsted acids, [9] organocatalysts, [10] biocatalysts, [11] ionic liquids [12] and nanoparticles [13]. Other conditions such as solvent- and catalyst-free conditions [14] have also been reported especially assisted by microwaves [15], solar thermal energy [16] and grinding [17]. While extensive and outstanding efforts have been devoted to study and establish the efficient or optimized reaction conditions for this MCR little or no effort has been devoted to addressing the issue of handling the ammonium salt, a key reactant in this MCR. The commonly used ammonium acetate (or ammonium chloride) is hygroscopic in nature and hence causes handling as well as storage problems especially during the large scale reaction particularly under humid conditions. Moreover, ammonium acetate (mp 113°C) is recognized as an irritant and reported to be moderately toxic to mammals (e.g. fish) [18]. Ammonium chloride on the other hand is harmful to the eye, skin and respiratory system [19]. In our earlier effort, we also used ammonium chloride for the synthesis of polyhydroquinolines *via* Hantzsch condensation

*Address correspondence to this author at the Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India; Tel/Fax: +91 40 6657 1500; +91 40 6657 1581;
E-mail: manojitpal@rediffmail.com

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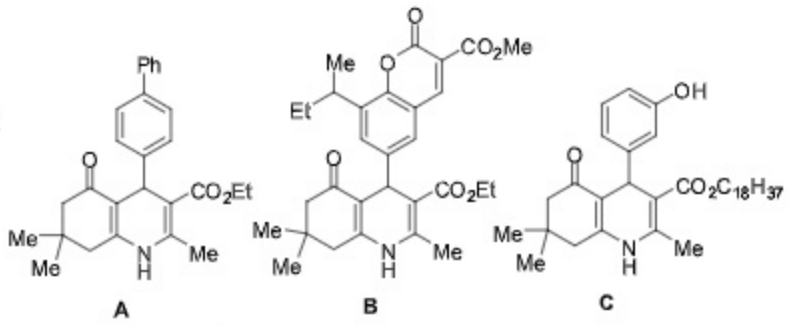


Fig. (1). Examples of bioactive polyhydroquinoline derivatives.

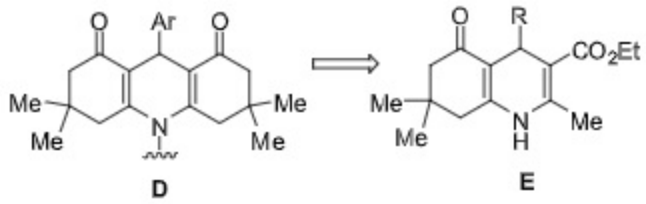
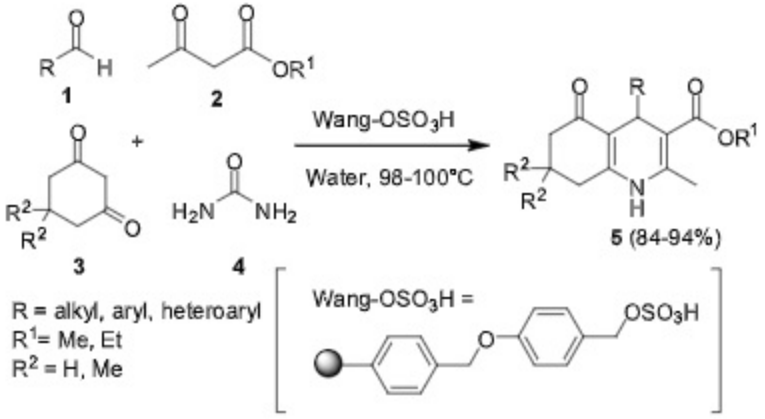


Fig. (2). Reported 1,8-dioxodecahydroacridines **D** and the targeted polyhydroquinolines **E**.



Scheme (1). Synthesis of polyhydroquinolines under green reaction conditions.

[20]. In further continuation of this study, we have explored the use of urea (mp 133-135°C) as an ammonia surrogate in the MCR (Scheme **1**), because as a key component in various fertilizers urea appeared to be relatively less hygroscopic in nature and possess less environmental concerns. Indeed, our aim was to maintain environmentally friendly reaction conditions so that a green synthesis of polyhydroquinolines could be achieved. We, therefore, continued to use the sulphonic acid-functionalized Wang resin (Wang-OSO_3H) as a polymeric and recoverable acidic catalyst in this reaction and pure water as a solvent [20]. We now report the details of this study and findings in the current full paper. To the best of our knowledge, the use of urea as an ammonia surrogate in the Hantzsch's synthesis of polyhydroquinolines is not common.

2. MATERIALS AND METHODS

2.1. General Methods

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualized with an ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using hexane and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in DMSO-d_6 and $CDCl_3$ solutions by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Melting points were determined using the melting point B-540 apparatus and are uncorrected. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus.

2.2. Synthesis of Polyhydroquinoline Derivatives (5)

To a stirred solution of aldehyde (**1**, 1.0 mmol), β-keto ester (**2**, 2.0 mmol), and 1,3-diketone (**3**, 1.0 mmol) urea (**4**, 3.0 mmol) in demineralized water (10 mL) was added resin bound Wang-SO_3H (10 %w/w) at room temperature. The mixture was stirred at room temperature for 10 min under

open air and then the temperature was slowly increased to 98-100°C. The stirring continued at this temperature for the time indicated in Table **3** (the progress of the reaction was monitored by TLC). After completion of the reaction the mixture was cooled, diluted with MeOH (100 mL) to dissolve the precipitated product and the catalyst was removed by filtration. The catalyst was washed with MeOH (3 x 50 mL). The filtrated and washings were collected, combined and concentrated under reduced pressure. The crude product obtained was re-crystallized from EtOH to give the pure product.

2.3. Synthesis of Compound 6 (the Biginelli Product)

To a stirred solution of aldehyde (**1**, 1 mmol), ethyl acetoacetate (**2**, 1 mmol), and urea (**4**, 3.0 mmol) in demineralized water (10 mL) was added resin bound Wang-SO_3H (10 %w/w) at room temperature. The mixture was stirred at room temperature for 10 min under open air and then the temperature was slowly increased to 55-60°C. The stirring continued at this temperature for 1h. After completion of the reaction the mixture was cooled, diluted with MeOH (100 mL) to dissolve the precipitated product and the catalyst was removed by filtration. The catalyst was washed with MeOH (3 x 50 mL). The filtrated and washings were collected, combined and concentrated under reduced pressure. The crude product obtained was re-crystallized from EtOH to give the pure product.

2.4. Synthesis of Compound 7 (1,4-DHPs)

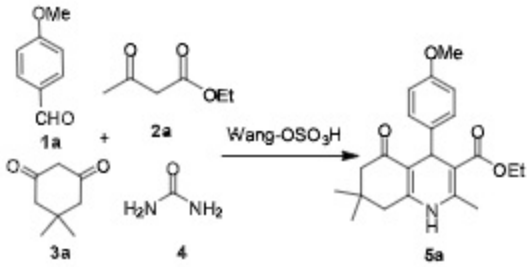
To a stirred solution of aldehyde (**1**, 1.0 mmol), ethyl acetoacetate (**2**, 1.0 mmol), and urea (**4**, 3.0 mmol) in demineralized water (10 mL) was added resin bound Wang-SO_3H (10 %w/w) at room temperature. The mixture was stirred at room temperature for 10 min under open air and then the temperature was slowly increased to 98-100°C. The stirring continued at this temperature for 1.1-1.3 h (the reaction was monitored by TLC). After completion of the reaction the mixture was cooled, diluted with MeOH (100 mL) to dissolve the precipitated product and the catalyst was removed by filtration. The catalyst was washed with MeOH (3 x 50 mL). The filtrated and washings were collected, combined and concentrated under reduced pressure. The crude product obtained was re-crystallized from EtOH to give the pure product.

Physical and spectroscopic characterization data of compounds (**5**, **6** and **7**) synthesized are given in supplementary material.

3. RESULTS AND DISCUSSION

To test the feasibility of the use of urea in place of ammonium salt and then establish the optimized reaction conditions the MCR of 4-methoxybenzaldehyde (**1a**), ethyl acetoacetate (**2a**), dimedone (**3a**) and urea (**4**) was performed in the presence of resin bound Wang-SO_3H (10 %w/w) under various conditions (Table **1**). Initially, the reaction was performed in DMF at 100°C for 2h (entry 1, Table **1**) when the desired product **3a** was obtained in 63% yield. Though we were delighted to isolate **3a** under this reaction conditions (especially when urea was used in place of ammonium salt) however the product yield was not to our satisfaction. Hence a range of other solvents including protic and non-protic solvents e.g. DMSO, EtOH, 1,4-dioxane, toluene, MeCN, MeOH and water was examined (entries 2-8, Table **1**). Except for DMSO, the reaction was carried out at a temperature corresponding to the boiling point of the solvent used. It is evident from Table **1** that among all these solvents tested the best yield of **5a** was obtained when the reaction was performed in demineralized water (entry 8, Table **1**). All these reactions were carried out using 10% w/w of catalyst. A decrease in catalyst loading to 5% w/w increased the reaction time from 1.5 h to 2h (entry 9, Table **1**) whereas product yield was dropped significantly when the catalyst was omitted (entry 10, Table **1**). While the increase of catalyst loading to 15 or 20% w/w decreased the reaction time from 1.5 h to 1.0 h however we preferred to use lower quantity (10% w/w) of catalyst. We also tested the use of ammonium salt e.g. NH_4Cl and NH_4HCO_3 under these new reaction conditions (entries 11 and 12, Table **1**). While the product **5a** was obtained in good yield in these cases the duration of the reaction was relatively longer. Overall, the condition of entry 8 of Table **1** was found to be optimum and therefore was used for further studies.

Table 1. Optimization of reaction conditions[a].



Entry	Solvent	T (°C) / t (h)	Yield[b] (%)
1	DMF	100 / 2.0	63
2	DMSO	100 / 2.0	67
3	Ethanol	80 / 1.5	88
4	1,4-Dioxane	100/ 3.0	65
5	Toluene	110 / 3.5	65
6	Acetonitrile	80 / 3.5	85
7	Methanol	60 / 3.0	75
8	Water	100 / 1.5	95
9	Water	100/ 2.0	89[c]
10	Water	100 / 5.0	25[d]
11	Water	100 / 2.0	88[e]
12	Water	100 / 2.5	85[f]

[a]Reaction conditions: 4-Methoxybenzaldehyde (1a, 1.0 mmol), ethyl acetoacetate (2a, 2.0 mmol), dimedone (3a, 1.0 mmol) urea (4, 3.0 mmol) and resin bound Wang-SO_3H (10 %w/w) in a solvent (10 mL) under open air.

[b]Isolated yield after crystallization.

[c]The catalyst loading was 5% w/w.

[d]No catalyst used.

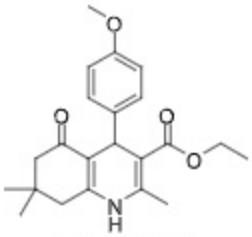
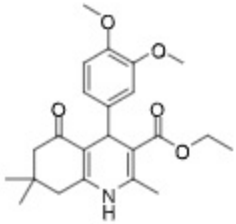
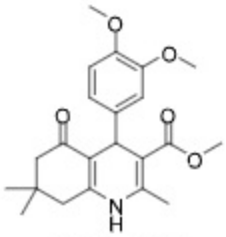
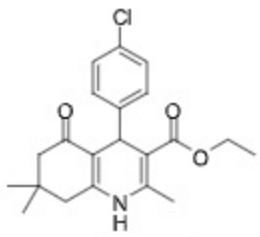
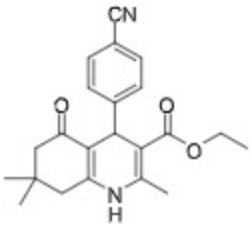
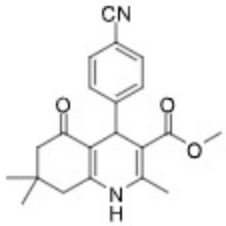
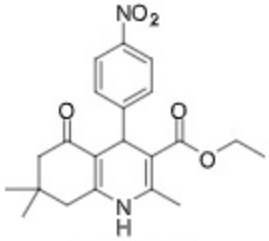
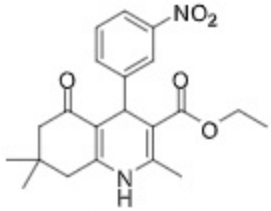
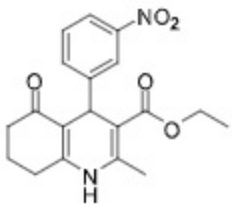
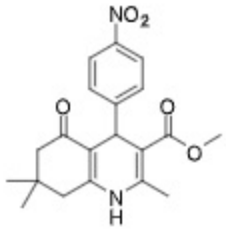
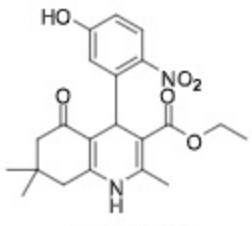
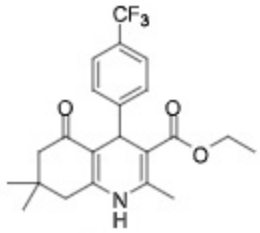
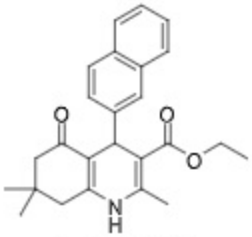
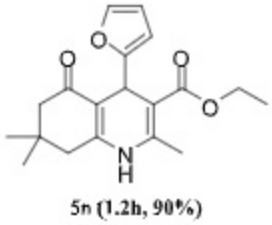
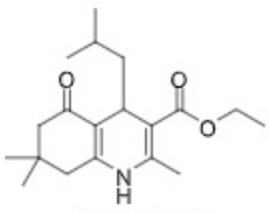
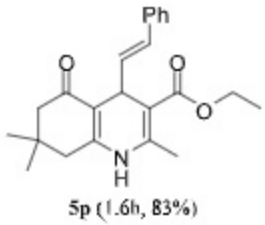
[e]NH_4Cl (3 mmol) was used in place of urea.

[f]NH_4HCO_3 (3 mmol) was used in place of urea.

Table 2. Recyclability of the catalyst in the MCR of 1a, 2a, 3a and 4 to afford 5a under the reaction condition of entry 8 of Table 1.

Cycle	Time (h)	Yield (%)	pH of the Reaction Mass
1[st]	1.5	95	2.4
2[nd]	1.8	95	2.4
3[rd]	1.8	92	2.5
4[th]	2.0	90	2.6

Table 3. Green synthesis of polyhydroquinoline derivatives 5 (Scheme 1)[a,b].

 5a (1.5h, 95%)	 5b (1.3h, 94%)	 5c (1.3h, 94%)[c]	 5d (1.5h, 94%)
 5e (1.3h, 93%)	 5f (1.3h, 90%)[c]	 5g (1.6h, 95%)	 5h (1.2h, 92%)
 5i (1.4h, 93%)	 5j (1.1h, 90%)[c]	 5k (1.2h, 89%)	 5l (1.3h, 90%)
 5m (1.3h, 94%)	 5n (1.2h, 90%)	 5o (1.3h, 85%)	 5p (1.6h, 83%)

[a]Reaction conditions: aldehyde (1, 1.0 mmol), β-keto ester (2, 2.0 mmol), 1,3-diketone (3, 1.0 mmol) urea (4, 3.0 mmol) and resin bound Wang-SO_3H (10 %w/w) in demineralized water (10 mL) at 98-100 °C under open air.

[b]Figures in the bracket indicate reaction time and %yield, reppectively.

[c]The methyl acetoacetate (2b) was used as the β-keto ester component in this case.

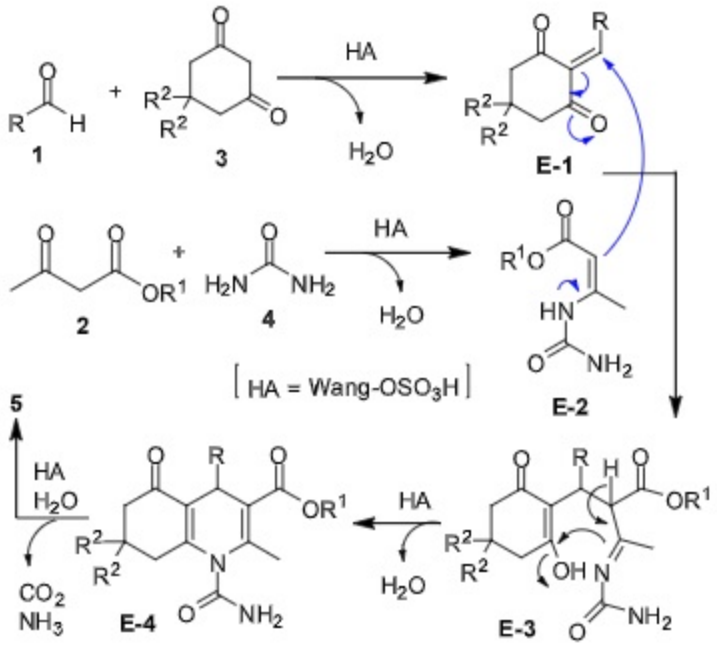
We then examined the recovery and reuse of the catalyst used i.e. Wang-OSO_3H in the synthesis of polyhydroquinoline **5a** using urea as a new reactant. Accordingly, after completion of the reaction (the first cycle, Table **2**) the reaction mixture was diluted with MeOH (100 mL) and the catalyst was recovered by simple filtration. The recovered catalyst was washed with MeOH (3 x 50 mL), water (10 mL) and acetone (10 mL) and dried under vacuum. The catalyst was

then reused several times (2nd, 3rd and 4th cycle, Table **2**) without significant loss of activity as evident from the product yield. The retention of catalytic activities of the recovered catalyst was further indicated by the pH of reaction mass that was found to be almost the same for all four runs (Table **2**).

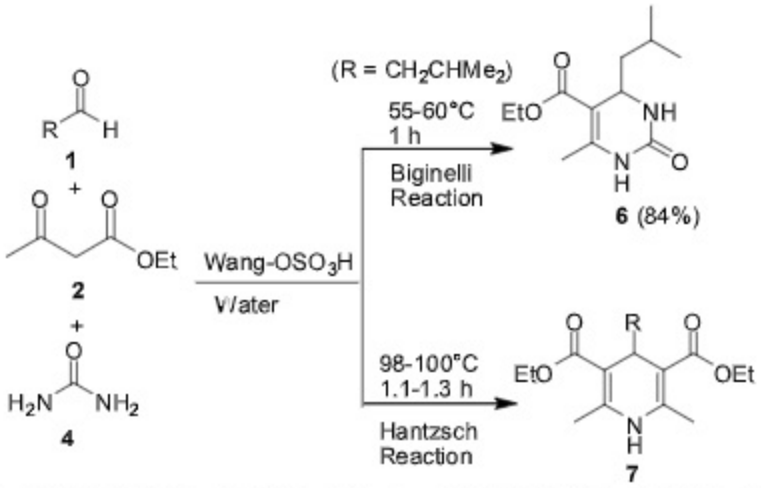
We demonstrated that urea could be an effective alternative for the ammonium salt used in the synthesis of polyhydroquinoline under green reaction conditions. To expand the generality and substrate scope of this methodology we employed a range of aldehydes in this MCR and the results are summarized in Table **3**. The aromatic aldehydes may contain various substituent e.g. strong and mild electron-donating group such as OMe (**5a-c**), OH (**5k**), Cl (**5d**), etc and strong electron-withdrawing group such as CN (**5e-f**), NO_2 (**5g-j**), CF_3 (**5l**), etc. The use of naphthaldehyde (**5m**), heteroaryl aldehyde (**5n**), aliphatic aldehyde (**5o**) and cinnamaldehyde (**5p**) was also explored. Both ethyl (**2a**) and methyl acetoacetate (2b) were used as the -keto ester component in this MCR. The reaction proceeded well in all these cases affording the corresponding products in good yield (> 90% in most cases). Further to assess the scale-up potential of this methodology the preparation of **5a** was undertaken in gram scale. Thus aldehyde **1a** (1.36 g, 10 mmol), β-keto ester **2a** (2.60 g, 20 mmol), and 1,3-diketone **3a** (1.40 g, 10 mmol) and urea **4** (1.8 g, 30 mmol) were reacted in the presence of resin bound Wang-SO_3H (0.136 g, 10% w/w) in demineralized water (100 mL) under the conditions of entry 8 of Table **1** when the product **5a** was obtained almost in quantitative yield (3.68 g).

Mechanistically (Scheme **2**), the reaction seems to proceed *via* generation of two key intermediates *in situ* e.g. (i) **E-1** formed as a result of Knoevenagel condensation of aldehyde (**1**) with one equivalent of dimedone (**3**) and (ii) the β-uraminocrotonic ester **E-2** formed *via* acid catalyzed condensation of β-ketoester (**2**) with urea (**4**) [21]. Subsequent cyclo-condensation of E-1 and E-2 afforded E-4 via E-3 in the presence of an acid catalyst. Finally, the acid catalyzed hydrolysis [22] of the *N*-carboxamide moiety of **E-4** afforded the desired polyhydroquinoline (**5**). While our attempt to isolate the intermediate **E-2** or **E-4** by changing the reaction conditions was not successful however we have observed that the reaction followed different paths when the use of 1,3-diketone (**3**) was omitted. Indeed, a Biginelli reaction [23] took place when the reaction was carried out at lower temperatures (55-60°C) with the change in the role of urea affording the corresponding product **6** in good yield (Scheme **3**). On the other hand, the reaction afforded 1,4-dihydropyridines **7** (1,4-DHPs) when performed at a higher temperature (98-100°C) following the Hantzsch pathway (Scheme 3) [24, 25]. Once again urea played the role of an effective ammonia surrogate in this case. Overall, polyhydroquinolines or Biginelli product or 1,4-DHPs can be synthesized under green conditions depending on the nature of reaction conditions employed. Notably, the use of ethyl 4,4,4-trifluoroacetoacetate (**2c**) in place of the β-keto ester **2b** in the synthesis of corresponding nitro derivative **5j** under the conditions of entry 8 of Table **1** afforded a complex mixture of unidentified products rather than the desired product. However, under the condition of Hantzsch reaction i.e. in the absence of 1,3-diketone (**3**) (*cf* Scheme **3**) the reaction perhaps proceeded *via* a 1,5-diketone intermediate leading to the formation of undehydrated product **8** as the last dehydration step did not occur in this case (Scheme **4**) [26].

All the polyhydroquinolines (**5**) synthesized were characterized by spectral data (see the supplementary material). Briefly, a singlet near 4.7-5.0 δ and a pair of singlets near 0.8-1.1 δ in the ^1H NMR spectra of **5** were due to the C-4 proton (except **5o**) and protons of double methyl groups at the C-7 position (except **5i**), respectively. The C-4 proton appeared near 3.8 δ in the case of **5o** whereas C-7 methyl groups were absent in the case of **5i**. A broad singlet appeared near or

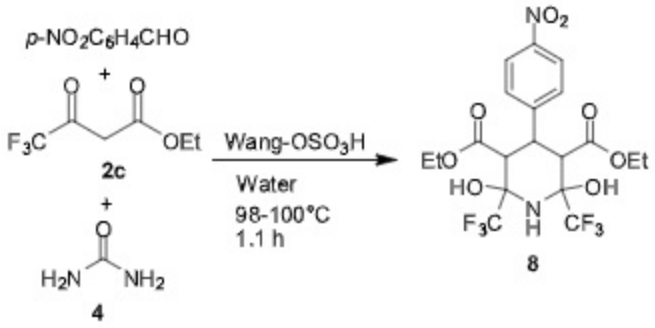


Scheme (2). The proposed reaction mechanism for the formation of polyhydroquinoline.



[R = Ph (7a, 96%); 2-thienyl (7b, 94%), 3-MeOC$_6$H$_4$ (7c, 85%), 2-naphthyl (7d, 90%), 3-ClC$_6$H$_4$ (7e, 90%), 2-FC$_6$H$_4$ (7f, 90%), 2-HOC$_6$H$_4$ (7g, 89%)]

Scheme (3). MCR performed in the absence of 1,3-diketone (3).



Scheme (4). The use of ethyl 4,4,4-trifluoroacetoacetate (2c) under Hantzsch reaction conditions.

above 9 δ was due to the -NH- moiety of the central ring of **5**. The ^{13}C signals near 194 and 166 ppm in the corresponding ^{13}C NMR spectra were due to two C=O groups e.g. keto and ester moieties respectively. Notably, C-4 proton appeared near 4.3 or 4.8-5.7 in the case of compound **6** and **7**, respectively in their corresponding ^{1}H NMR spectra. However, unlike compound **5** the ^{13}C signal due to the keto carbonyl (C=O) was absent in these cases due to the obvious reason.

CONCLUSION

In conclusion, we demonstrated that urea can be used as an effective ammonia surrogate in Hantzsch's synthesis of polyhydroquinolines/1,4-dihydropyridines under green reaction conditions. This allowed avoiding the use of hygroscopic and moderately toxic ammonium salt as one of the key reactants in the MCR. Initially, polyhydroquinolines were synthesized *via* the MCR of aldehyde, β-ketoester, 1,3-diketone and urea using pure water as a solvent. The MCR was catalyzed by the sulphonic acid functionalized Wang resin (Wang-OSO$_3$H) as a polymeric and recoverable acidic catalyst. The methodology afforded a range of polyhydroquinolines in good yields (> 90% in most cases) and did not require the use of column chromatographic purification of products obtained (products were purified by simple recrystallization from EtOH). Depending on the nature of reaction conditions employed the MCR afforded Biginelli product or 1,4-DHPs when the use of 1,3-diketone was omitted. Overall, the green methodology reported here may find wide applications in synthesizing the library of small molecules based on three *N*-heterocycles.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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