Tetrahedron Letters 51 (2010) 1187–1189

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and 1,4-dihydropyridines using ammonium carbonate in water

Fatemeh Tamaddon *, Zahra Razmi, Abbas Ali Jafari

Department of Chemistry, Faculty of Science, Yazd University, Yazd 89195-741, Iran

ARTICLE INFO

Article history:
Received 27 October 2009
Revised 8 December 2009
Accepted 16 December 2009
Available online 24 December 2009

Keywords:
Hantzsch reaction
Biginelli reaction
1,4-Dihydropyridines
3,4-Dihydropyrimidine-2(1*H*)-ones
$(NH_4)_2CO_3$

ABSTRACT

Various known and new 3,4-dihydropyrimidin-2(1*H*)-ones and 1,4-dihydropyridines are prepared efficiently via Biginelli and Hantzsch reactions using ammonium carbonate in water. Competition between Biginelli and Hantzsch reactions is observed with pyridine carbaldehydes. Using this methodology, Hantzsch esters are synthesized in higher yields and purities than with other procedures without the use of a catalyst or an organic solvent.

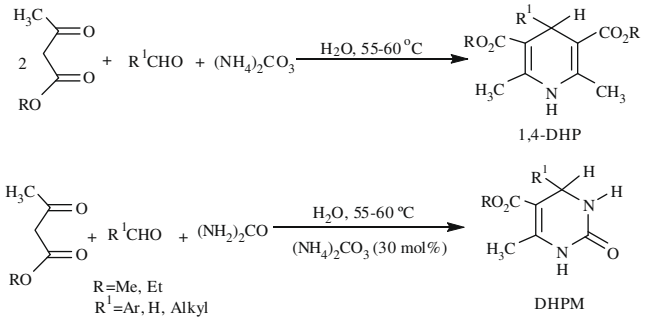
1. Introduction

Organic transformations in aqueous media without using hazardous reagents or solvents are of interest.[1] 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and 1,4-dihydropyridines (1,4-DHPs) are typically prepared via Biginelli[2] and Hantzsch[3] reactions. The structural similarity to hydrogenase coenzymes and the clinical use of 1,4-DHPs as calcium channel stimulating drugs have attracted the attention of organic chemists.[4–8] These reactions belong to the category of multi-component reactions involving the one-pot, acid-catalyzed condensation of aldehydes, β-keto esters and ammonia or urea as the source of nitrogen.[4a,9,10] Recently, a base-catalyzed version of these reactions was reported in EtOH at reflux.[11] Modified syntheses of 1,4-DHPs and DHPMs have been advanced also in aqueous media.[12] However, more efficient syntheses of these biologically active compounds in aqueous media is important.

We were interested in studying Biginelli and Hantzsch reactions in aqueous media using ammonium carbonate with the aim to develop an operationally simple method for the synthesis of a large range of 1,4-DHPs and DHPMs (Scheme 1).

We began our study with the base-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones via the Biginelli reaction. The model reaction of benzaldehyde, ethyl acetoacetate and urea in water was optimized by investigating various parameters such as base, solvent and conditions. The optimized conditions required heating with 30 mol % of ammonium carbonate in water for three hours at ~55–60 °C.

In order to study the scope and generality of the ammonium carbonate-catalyzed Biginelli reaction in water, a series of DHPMs was synthesized from the substituted heteroaromatic, aromatic and enolizable aliphatic aldehydes. In all cases, the desired products were isolated in excellent yields, except for pyridine carbaldehydes (Table 1). To our surprise, analysis of the products in these cases confirmed the formation of new Hantzsch esters in moderate yields (entries 10–12). Similar results were obtained when the model reaction of benzaldehyde and ethyl acetoacetate was attempted with thiourea or guanidine in water; diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridin-3,5-dicarboxylate was formed instead of a 3,4-dihydropyrimidinone.

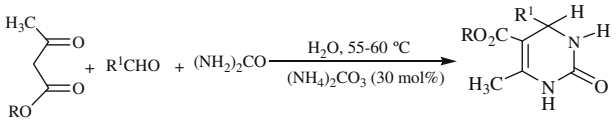


Scheme 1. Ammonium carbonate-mediated synthesis of 1,4-DHPs and DHPMs in water

* Corresponding author. Tel.: +98 3518122666; fax: +98 3518210644.
E-mail address: ftamaddon@yazduni.ac.ir (F. Tamaddon).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.098

Table 1
Ammonium carbonate-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using urea in water



Entry	R	Time (h)	Mp (°C) found (reported)	Yield[a] (%)
1	C_6H_5	4	200–203 (200–202)[11c]	92
2	4-MeC_6H_4	4.5	215–216 (216–217)[11c]	90
3	4-ClC_6H_4	4.5	210–212 (209–211)[9c]	95
4	3-ClC_6H_4	4	190–192 (192–193)[13]	95
5	4-$MeOC_6H_4$	3.5	200–202 (199–201)[14]	89
6	3-$MeOC_6H_4$	3.5	207–208 (207–208)[15]	93
7	4-HOC_6H_4	3.5	220–223 (225–226)[11c]	92
8	4-$O_2NC_6H_4$	3	208–211 (207–210)[14]	94
9	2-Furyl	3	206–208 (206–208)[16]	91
10	2-Pyridyl[b]	4	—[b]	—[b]
11	3-Pyridyl[b]	3.5	—[b]	—[b]
12	4-Pyridyl[b]	3	—[b]	—[b]

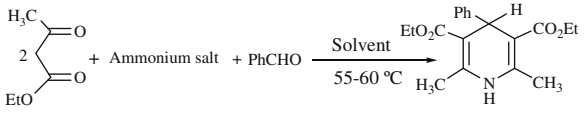
[a] Isolated yield
[b] 1,4-DHP product was isolated.

The competition between the Hantzsch and Biginelli reactions in the presence of ammonium carbonate encouraged us to investigate the ammonium carbonate-mediated Hantzsch reaction in water by controlling the mole ratio of ethyl acetoacetate.

Although the preparation of DHPs via Hantzsch reaction has been studied,[4–6] there is no report on the effect of the ammonia source on this reaction. Thus, we studied a model four-component condensation of ethyl acetoacetate, benzaldehyde and an ammonium salt (mole ratio = 2:1:1) in water under different conditions (Table 2). We were pleased to find that among the conditions screened, the corresponding 1,4-DHP was obtained quantitatively with $(NH_4)_2CO_3$ at ~55–60 °C in water (entry 6) in the absence of any catalyst. This process is less laborious than previously reported procedures.

Ammonium carbonate is a less toxic (LD_{50} = 1497 mg/kg), low melting (58 °C) solid source of ammonia which is used as baking powder. It decomposes in aqueous media to produce two moles of ammonia.

Table 2
Catalyst-free Hantzsch reaction with various ammonium salts in water



Entry	Ammonium salt	Solvent	Time (h)	Yield[a] (%)
1	NH_4Cl	EtOH	5	0
2	NH_4Cl	H_2O	5	0
3	NH_4OAc	EtOH	5	45
4	NH_4OAc	H_2O	5	50
5	$(NH_4)_2CO_3$	EtOH	3.5	90
6	$(NH_4)_2CO_3$	H_2O	3.5	99
7	$(NH_4)_2CO_3$	H_2O/EtOH (50:50)	3.5	97
8	$(NH_4)_2CO_3$	None	5	62
9	$(NH_4)_2SO_4$	H_2O	5	0
10	NH_4NO_3	H_2O/EtOH (50:50)	5	60[b]
11	$(NH_4)_6Mo_7O_{24}$	H_2O/EtOH (50:50)	5	0
12	NH_4VO_3	H_2O/EtOH (50:50)	5	0
13	$(NH_4)_2[Ce(NO_3)_6]$	H_2O/EtOH (50:50)	5	15
14	NH_4HCO_3	H_2O	4	80
15	$H_4N^+HCOO^-$	H_2O	4	68
16	$NH_4CO_2NH_2$	H_2O	4	83

[a] Isolated yield
[b] A mixture of the 1,4-DHP and pyridine products was isolated.

The reaction proceeded in a considerably lower yield under solvent-free conditions due to sublimation of ammonium carbonate (entry 8). No significant change was observed on the results using 0.5 equiv of ammonium carbonate. This trend suggests that hydrogen bonding, the mild buffered pH of the reaction media and the assistance of water to break down $(NH_4)_2CO_3$ may all be responsible for acceleration of the reaction rate.

The optimized reaction conditions were extended to the condensation of other aldehydes with β-keto esters and ammonium carbonate at 55–60 °C. Aromatic aldehydes bearing both electron-deficient and electron-rich substituents as well as aliphatic aldehydes afforded the desired 1,4-DHPs in excellent yields (Table 3). Problematic substrates such as enolizable aliphatic aldehydes (entries 16–19) and heteroaryl aldehydes including 2-furyl and 2-, 3- and 4-pyridine carbaldehydes reacted efficiently with ethyl acetoacetate and $(NH_4)_2CO_3$ to afford the desired 1,4-DHPs in excellent yields (entries 12–15).

The structures of the products were determined by IR, ^1H NMR and ^{13}C NMR spectroscopy, mass, CHN analysis and also by comparison with authentic samples.

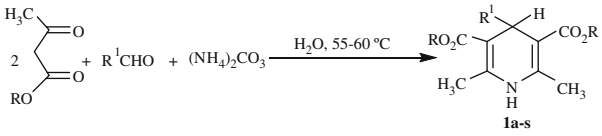
To evaluate the utility of this procedure in large scale reactions, a 10-fold scale Hantzsch reaction was carried out successfully on the model reaction to give the corresponding product **1a** in 95% yield.

In conclusion, we have prepared a variety of known and new 3,4-dihydropyrimidin-2(1*H*)-ones and 1,4-dihydropyridines in water via Biginelli and Hantzsch reactions using ammonium carbonate as a solid ammonia source. The products were obtained in high yields and purities compared with previous methods without the use of a catalyst or an organic solvent.

2. General experimental procedure for the synthesis of 3,4-dihydropyrimidinones in water

Aldehyde (2 mmol), alkyl acetoacetate (2 mmol) and either urea/thiourea or guanidine (2.5 mmol) were stirred together fol-

Table 3
Catalyst-free synthesis of 1,4-dihydropyridines using ammonium carbonate in water



Entry	R	R^1	Time (h)	Product	Yield[a] (%)
1	OEt	C_6H_5	3.5	**1a**	99
2	OMe	C_6H_5	2	**1b**	95
3	OEt	4-ClC_6H_4	3	**1c**	98
4	OMe	4-ClC_6H_4	2	**1d**	95
5	OMe	4-$MeOC_6H_4$	3	**1e**	98
6	OEt	4-$MeOC_6H_4$	3.5	**1f**	95
7	OEt	4-HOC_6H_4	2.5	**1g**	95
8	OEt	3-HOC_6H_4	3	**1h**	95
9	OEt	4-$O_2NC_6H_4$	2	**1i**	98
10	OMe	4-$O_2NC_6H_4$	2	**1j**	95
11	OEt	2-$O_2NC_6H_4$	4	**1k**	90
12	OEt	2-Pyridyl	2.5	**1l**	90
13	OEt	3-Pyridyl	2	**1m**	98
14	OEt	4-Pyridyl	2	**1n**	95
15	OEt	2-Furyl	1.5	**1o**	98
16	OEt	Cinnamyl	2.5	**1p**	93
17	OMe	Cinnamyl	3	**1q**	91
18	OEt	*n*-Propyl	3.5	**1r**	82
19	OEt	*iso*-Propyl	4	**1s**	88

[a] Isolated yield.

lowed by the addition of a catalytic amount of $(NH_4)_2CO_3$ (30 mol %) in H_2O (1 mL) and the reaction was heated at 55–60 °C for the appropriate time (Table 1). After completion of the reaction (TLC monitoring), ice-cold water was added to the reaction mixture and the precipitate was filtered. In some cases the products were recrystallized from EtOH/H_2O.

3. General experimental procedure for the catalyst-free one-pot synthesis of 1,4-dihydropyridines in water

A mixture of aldehyde (2 mmol), alkyl acetoacetate (4 mmol) and anhydrous ammonium carbonate (2 mmol) was stirred in H_2O (2 mL) at 55–60 °C. After completion of the reaction (TLC monitoring), the mixture was diluted with cold H_2O (20 mL) and filtered to remove the precipitated product which was further purified by recrystallization in some cases.

4. Spectral data for new compounds

4.1. Diethyl 2,6-dimethyl-4-(3-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1h)

Pale yellow solid, mp = 180–182 °C, FT-IR: ν_{max} (KBr): 3349 (*OH* and *NH* stretching), 1648 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 6H, 2×*CH*$_3$–CH_2), 2.33 (s, 6H, 2 × *CH*$_3$), 4.09–4.18 (m, 4H, O–*CH*$_2$$CH_3$), 5.00 (s, 1H, *CH*), 5.13 (br s, 1H, *OH*), 5.70 (br s, 1H, *NH*), 6.63 (dd, J = 7.95, 2.39 Hz, $1H_{arom}$), 6.80 (s, $1H_{arom}$), 6.89 (d, J = 7.69 Hz, $1H_{arom}$), 7.09 (t, J = 7.8 Hz, $1H_{arom}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.62, 19.22, 39.44, 59.64, 103.22, 113.36, 115.39, 119.43, 149.97, 157.07, 168.15 ppm. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.04; H, 6.67; N, 4.00.

4.2. Diethyl 2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (1l)

Pale yellow solid, mp = 192–194 °C, FT-IR: ν_{max} (KBr): 3174 (*NH* stretching), 1688 (C = O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.11 Hz, 6H, 2 × *CH*$_3$–CH_2), 2.28 (s, 6H, 2 × *CH*$_3$), 4.06–4.12 (m, 4H, O–*CH*$_2$$CH_3$), 5.22 (s, 1H, *CH*), 7.16 (td, J = 4.88, 0.63 Hz, 1H), 7.43 (d, J = 7.77, 1H), 7.61 (td, J = 7.66, 1.69 Hz, 1H), 8.53 (d, J = 3.98 Hz, 1H), 8.62 (br s, 1H, *NH*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.71, 19.31, 43.24, 59.96, 102.15, 122.19, 124.71, 136.11, 146.73, 148.65, 165.63, 168.14 ppm. MS (EI): *m/z*: 330 (M^+, 8.5), 307 (8), 285 (7), 252 (100), 239 (7), 224 (10), 196 (18), 170 (7), 106 (5), 78 (7), 51 (5).

4.3. Diethyl 2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (1m)

Pale yellow solid, mp = 190–192 °C, FT-IR: ν_{max} (KBr): 3174 (*NH* stretching), 1688 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.13 Hz, 6H, 2 × *CH*$_3$–CH_2), 2.36 (s, 6H, 2 × *CH*$_3$), 4.07–4.14 (m, 4H, O–*CH*$_2$$CH_3$), 5.01 (s, 1H, *CH*), 6.61 (s, 1H, *NH*), 7.19 (dd, J = 7.83, 4.98 Hz, 1H), 7.64–7.66 (m, 1H), 8.39 (dd, J = 4.79, 1.57 Hz, 1H), 8.55 (d, J = 1.94 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.68, 19.75, 38.23, 60.27, 103.57, 123.55, 136.27, 144.00, 145.39, 147.40, 149.80, 167.64 ppm. MS (EI): *m/z*: 330 (M^+, 40), 301 (55), 285 (54), 252 (100), 224 (85), 196 (85), 150 (28), 106 (22), 51 (18).

4.4. Diethyl 2,6-dimethyl-4-(4-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (1n)

Pale yellow solid, mp = 178–180 °C, FT-IR: ν_{max} (KBr): 3200 (*NH* stretching), 1704 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.11 Hz, 6H, 2 × *CH*$_3$–CH_2), 2.37 (s, 6H, 2 × CH_3), 4.07–4.15 (m, 4H, O–CH_2CH_3), 5.03 (s, 1H, *CH*), 6.63 (br s, 1H, *NH*), 7.25 (dd, J = 4.61, 1.48 Hz, 2H), 8.45 (dd, J = 4.60, 1.49 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.67, 19.78, 39.89, 60.34, 102.93, 123.79, 145.67, 149.55, 156.76, 167.62 ppm. MS (EI): *m/z*: 330 (M^+, 1), 307 (100), 278 (30), 262 (38), 233 (24), 178 (5), 105 (11), 77 (11), 51 (10).

Acknowledgement

We acknowledge the research council of Yazd University.

References and notes

1. (a) Li, C. J.; Chang, T. H. In *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998; (c) Lindstrom, U. M. *Organic Reactions in Water*; Blackwell, 2007; (d) Ziyaei-Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2008**, *40*, 1244; (e) Jafari, A. A.; Moradgholi, F.; Tamaddon, F. *Eur. J. Org. Chem.* **2009**, 1249.
2. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
3. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637; (b) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *1*, 215.
4. (a)*Name Reactions in Heterocyclic Chemistry*; Li, J.-J., Corey, E. J., Eds.; Wiley Interscience, 2005; p 301. Chapter 8; (b)*Lehninger Principles of Biochemistry*; Cox, M. M., Nelson, D. L., Eds.; Oxford, 2005; p 190; (c) Khoshneviszadeh, M.; Edraki, N.; Javidnia, K.; Alborzi, A.; Pourabbas, B.; Mardaneh, J.; Miri, R. *Bioorg. Med. Chem.* **2009**, *17*, 1579.
5. Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **1995**, *38*, 2851.
6. (a) Safak, C.; Simsek, R. *Mini Rev. Med. Chem.* **2006**, *6*, 747; (b) Velazquez, C.; Knaus, E. E. *Bioorg. Med. Chem.* **2004**, *12*, 3831; (c) Regen, S. L.; Koteed, C. J. *J. Am. Chem. Soc.* **1977**, *99*, 3837.
7. Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S. *Tetrahedron Lett.* **2009**, *50*, 5248.
8. Quan, A.; Chavanu, K.; Merkel, J. *Am. J. Cardiovasc. Drugs* **2006**, *6*, 103.
9. (a) Svetlik, J.; Veizerova, L.; Kittmann, V. *Tetrahedron Lett.* **2008**, *49*, 3520; (b) Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861; (c) Shaabani, A.; Bazgir, A.; Teimouri, F. *Tetrahedron Lett.* **2003**, *44*, 857.
10. (a) Kumar, B. R. P.; Masih, P.; Lukose, C. R.; Abraham, N.; Priya, D.; Xavier, R. M.; Saji, K.; Adhikary, L. *J. Heterocycl. Chem.* **2009**, *46*, 336; (b) Kormos, C. M.; Hull, R. M.; Leadbeater, N. E. *Aust. J. Chem.* **2009**, *62*, 51; (c) Karimi, B.; Zamani, A.; Abedi, S.; Clark, J. H. *Green Chem.* **2009**, *11*, 109.
11. (a) Suzuki, I.; Iwata, Y.; Takeda, K. *Tetrahedron Lett.* **2008**, *49*, 3238; (b) Chitra, S.; Pandiarajan, K. *Tetrahedron Lett.* **2009**, *50*, 2222; (c) Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2008**, *49*, 6119; (d) Hida, T.; Nogusa, H. *Tetrahedron* **2009**, *65*, 270.
12. (a) Kumar, A.; Maurya, R. A. *Synlett* **2008**, 883; (b) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 7343.
13. Lu, J.; Ma, H. *Synlett* **2000**, 63.
14. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
15. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
16. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1241.