Regular Article

ORGANIC CHEMISTRY RESEARCH
Published by the
Iranian Chemical Society
www.orgchemres.org

Org. Chem. Res., *Vol. 5, No. 2, 159-166, September 2019.*

Four-component Cascade Reaction was Programmed and Catalyzed by $B(OH)_3.H_2O$ as an Efficient and Green Catalytic System

A.R. Moosavi-Zare[a,]*, H. Afshar-Hezarkhani[a], V. Khakyzadeh[b] and H. Goudarziafshar[a]

[a]*Sayyed Jamaleddin Asadabadi University, Asadabad, 6541861841, I. R. Iran*

[b]*Faculty of Science, Department of Chemistry, K. N. Toosi University of Technology, P. O. Box: 15875 - 4416, Tehran, Iran*

(Received 12 March 2018, Accepted 3 November 2018)

An aqueous solution of boric acid, as an efficient and green catalytic system, was efficiently utilized for four-component cascade reaction of aryl aldehydes, dimedone, β-ketoesters and ammonium acetate to give hexahydroquinolines. Reaction of boric acid with water led to the generation of H^+, and efficiently catalyzed the reaction under mild and green condition. Also, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)}.

Keywords: Boric acid, Hexahydroquinoline, Cascade reaction, Aqueous solution

INTRODUCTION

A cascade reaction, also known as a domino reaction or tandem reaction, is a chemical process through which at least two consecutive reactions are being carried out continuously without isolating any intermediates, changing reaction conditions and adding reagents. The cascade reaction is often fast because of its intramolecular nature. Clean reaction condition, high atomic economy and much complexity in effectively one step are among other main advantages of this reaction [1-7].

Quinolines with a 1,4-dihydropyridine structure are promising scaffolds due to their pharmacological activities. This part of quinoline derivatives has many applications in medicinal chemistry, and has been also applied as antiasthmatic, antibacterial antihypertensive, anti-inflammatory, antimalarial, and tyrosine kinase inhibiting compounds [8-13]. One of the significant classes of DHPs with a modified structural scaffold is hexahydroquinolines (HHQs) which could be synthesized by the Hantzsch reaction by the condensation of various aromatic aldehydes, dimedone, β-ketoesters and ammonium acetate *via* the one-pot multi-component condensation reaction using different catalysts including FeF_3 [14], $K_7[PW_{11}CoO_{40}]$ [15], PPA-SiO_2 [16], $HClO_4$-SiO_2 [17], silica-bonded imidazolium-sulfonic acid chloride [18], $[Dsim]HSO_4$ [19], magnetite nano-Fe_3O_4 [20], $[HMIM]C(NO_2)_3$ [21]. According to the relevant properties of HHQs, the employ of new catalysts with high novelty and effectiveness are still needed.

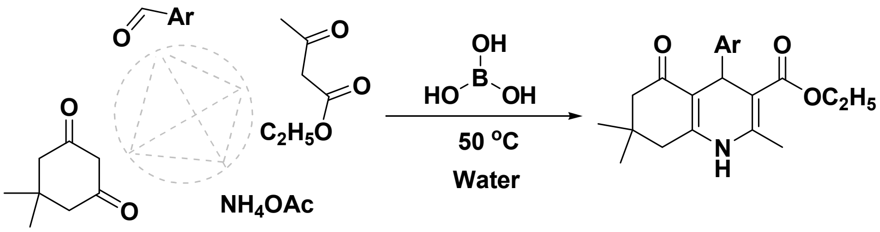
Herein, we have introduced the solvent-free synthesis of hexahydroquinolines using an aqueous solution of boric acid as an efficient and green catalytic system with high yields and short reaction times (Scheme 1). Optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)}.

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka chemical companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates.

---

*Corresponding author. E-mail: author@institute.xxx



Scheme 1. The one-pot four-component preparation of hexahydroquinolines catalyzed by $B(OH)_3.H_2O$

The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance DPX-250 FT-NMR spectrometer (d in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Procedure for the Synthesis of Hexahydroquinolines

To a mixture of dimedone (1 mmol, 0.14 g), aryl aldehyde (1 mmol), ethyl acetoacetate (1 mmol, 0.13 g) and ammonium acetate (1.2 mmol, 0.092 g) in a 10 ml round-bottomed flask connected to a reflux condenser, was added boric acid (10 mol%, 0.0062 g) and a few drops of water, and the resulting mixture was stirred at 50 °C for an appropriate time. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The crude product was purified by recrystallization from ethanol (95%).

Spectral Data Analysis for Compounds Ethyl

2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1). White solid, isolated yield 81%; melting point: 204-205 °C (Ref. [20]: 203-205 °C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 0.85 (s, 3H), 1.00 (s, 3H), 1.13 (t, J = 7.0 Hz, 3H), 2.01-2.20 (m, 2H), 2.29 (s, 3H), 2.38-2.50 (m, 2H), 3.97 (q, J = 7.0 Hz, 2H), 4.82 (s, 1H), 7.05 (m, 1H), 7.18 (t, J = 6.7 Hz, 2H), 7.21 (t, J = 6.5 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 14.5, 18.8, 26.8, 29.5, 32.6, 36.5, 50.6, 59.6, 103.4, 109.9, 113.5, 126.9, 128.8, 130.5, 146.0, 150.3, 167.0, 194.7.

Ethyl 4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15). White solid, isolated yield 85%; melting point: 238-240 °C (Ref. [20]: 232-234 °C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 0.86 (s, 3H), 1.00 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H), 1.96 (d, J = 16.0 Hz, 1H), 2.15 (d, J = 16.1 Hz, 1H), 2.26 (s, 3H), 2.36-2.49 (m, 2H), 3.96 (q, J = 7.0 Hz, 2H), 4.74 (s, 1H), 6.56 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 8.1 Hz, 2H), 8.94 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 14.6, 18.7, 26.9, 29.6, 32.6, 35.3, 50.8, 59.4, 104.6, 110.8, 114.9, 128.8, 138.9, 144.8, 149.6, 155.7, 167.5, 194.7.

RESULTS AND DISCUSSION

At first, to find the best reaction condition for the synthesis of hexahydroquinoline derivatives, the reaction of dimedone (1 mmol), 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.2 mmol) was selected as a model reaction. To compare the efficiency of the reaction in solvent-free versus solvent conditions, the model reaction was tested in various solvents at 50 °C (Table 1).

From Table 1, as it is clear, higher yield and lowest reaction time were obtained in H_2O as solvent at 50 °C. The model reaction was also tested at 25 and 80 °C in H_2O; the best result was obtained at 50 °C. Therefore, water could be selected as a suitable solvent for the model reaction (entry 5). In sequence, to find the exact reaction condition for preparation of hexahydroquinolines, amounts of boric acid and temperature were selected as effective factors. The factors optimization was performed by central composite design (CCD). The yield of the reaction was chosen as a response. In this design, there are three points of cubic, coming from the factorial design, axial and center points.

Some preliminary experiments were initially done to determine the range of the variables (Table 2). According to the CCD methodology, eleven tests in different conditions were designed (Table 3). After performing the tests, our analysis showed that reaction could be modeled by a second order polynomial equation (Eq. (1)),

Table 1. Effect of a Few Drops of Different Solvents on the Reaction of Dimedone, 4-Nitrobenzaldehyde, Ethyl Acetoacetate and Ammonium Acetate, in the Presence of $B(OH)_3$ (0.006 g, 10 mol %)

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)[b]
1	$CHCl_3$	50	60	Trace
2	EtOAC	50	60	Trace
3	EtOH	50	60	Trace
4	CH_2Cl_2	Reflux	60	Trace
5	H_2O	50	5	92
6	Acetone	Reflux	60	Trace
7	THF	50	60	Trace
8	-	50	60	Trace

[a]All reactions were carried out at 50 °C except entries 4 and 6, which were proceeded at reflux temperature of solvent. [b]Isolated yield.

Table 2. The Levels and Range of the Independent Variables

Variables	Range and level				
	-α	-1	0	+1	+α
$B(OH)_3$ (mol%)	2.92	5	7.5	10	17.07
Temperature (°C)	15	25	50	75	85

$$X = -10.94 \times [A]^2 - 9.94 \times [B]^2 + 17.33 \times [A] + 10.67 \times [B] + 93.00 \quad (1)$$

where X is the yield of the reaction, and the terms are in the actual factor. The analysis of variance for the presented model is shown in Table 4.

The Model F-value of 47.7 and the p-value < 0.0001 prove the acceptability of the model. The prediction power of the model (Pred. R^2) was 0.88 which was in reasonable agreement with Adj. R^2 of 0.94 (the difference is less than 0.2).

By using of three-dimensional surface graphs, obtained from the model, the effect of the operating factors on the yield was investigated (Fig. 1). According to model and 3D graph and contour graph, optimal operational conditions are $B(OH)_3$ = 12 mmol and temperature = 55 °C which was in good agreement with experimental results.

To investigate the efficacy and the generality of the catalyst, dimedone was reacted with various aromatic aldehydes, ethyl acetoacetate and ammonium acetate under

Table 3. The Designed Experiments by CCD Methodology and Corresponding Responses

Test	The factors A = $B(OH)_3$ (mol%)	 B= Temperature (°C)	 Yield (%)[a]
1	5	25	40
2	10	50	93
3	10	50	93
4	5	75	64
5	2.92	50	50
6	17	50	95
7	15	25	85
8	10	85	93
9	15	75	94
10	10	15	56
11	10	50	93

[a] Isolated yield.

Table 4. Analysis of Variance for the Response Surface Quadratic Model

Source	Sum of squares	df	Mean square	F Value	p-value Prob > F
Model	4267.44	4	1066.86	47.70	0.0001
A-Boric acid	2402.62	1	2402.62	107.42	< 0.0001
B-Temperature	910.06	1	910.06	40.69	0.0007
A^2	675.55	1	675.55	30.20	0.0015
B^2	557.67	1	557.67	24.93	0.0025
Residual	134.19	6	22.37		Trace
Lack of fit	134.19	4	33.55		Trace
Pure error	0.000	2	0.000		Trace
Cor total	4401.64	10			

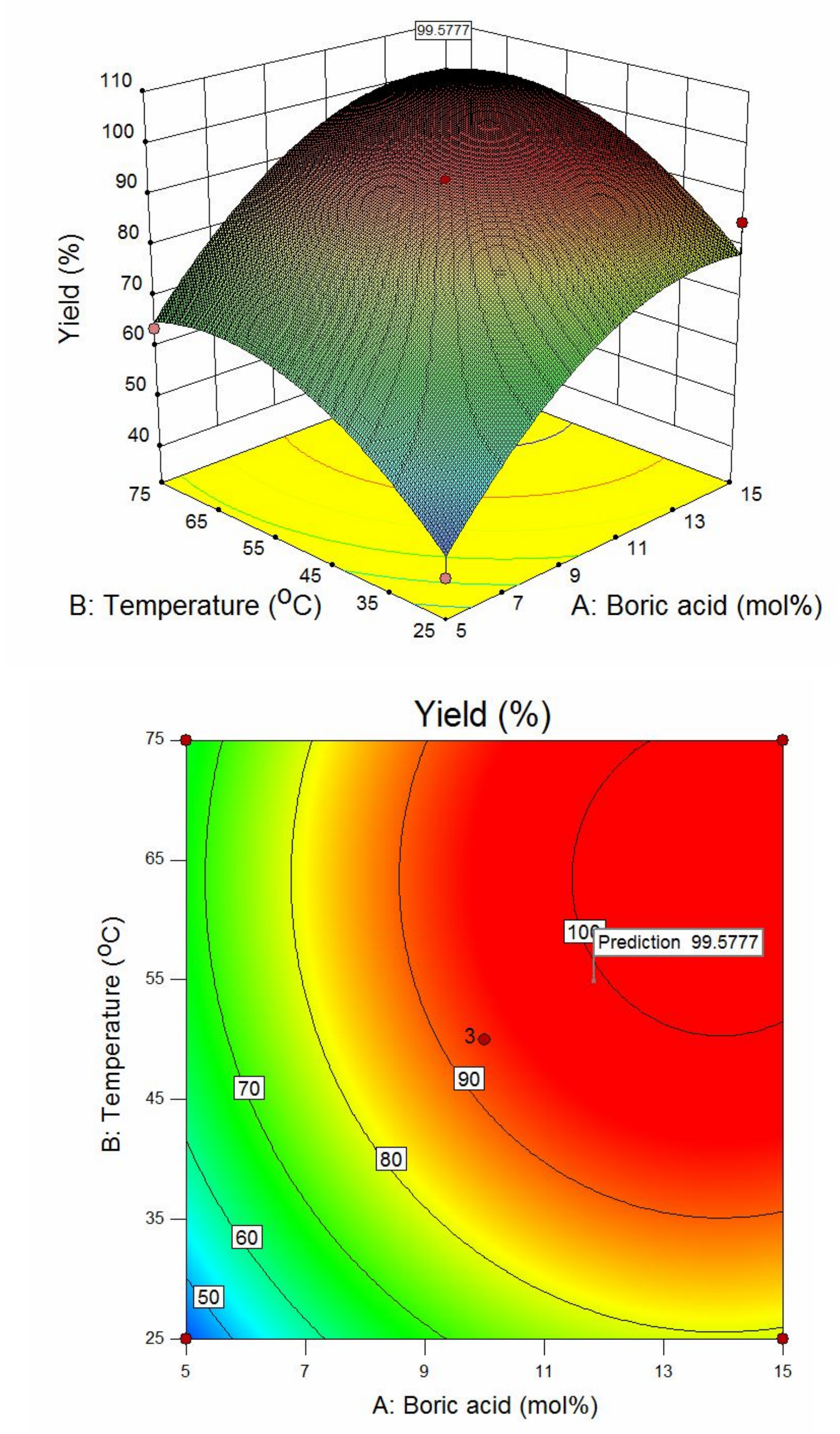
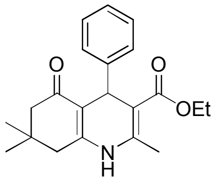
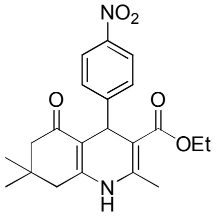


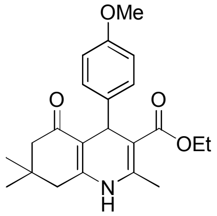
Fig. 1. Three-dimensional response surfaces for the effect of factors on the yield of the reaction time. Left (3D graph), right (contour graph).



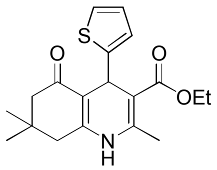
Entry 1
Time: 7 min
Yield: 81%
MP: 204-205 °C
(Lit.203-205 °C [20])



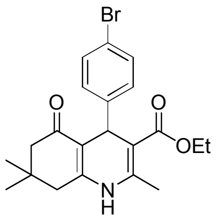
Entry 2
Time: 5 min
Yield: 92%
MP: 245-258 °C
(Lit.242-244 °C [20])



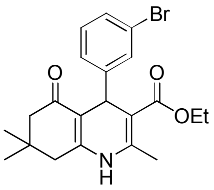
Entry 3
Time: 5 min
Yield: 90%
MP: 255-259 °C
(Lit.257-259 °C [20])



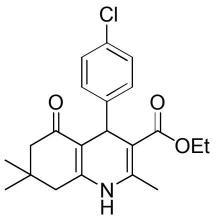
Entry 4
Time: 10 min
Yield: 87%
MP: 235-238 °C
(Lit.- [24])



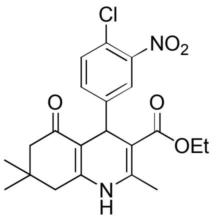
Entry 5
Time: 5 min
Yield: 92%
MP: 249-253 °C
(Lit.255-257 °C [20])



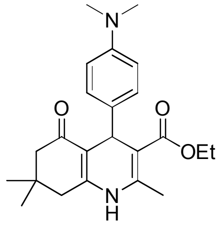
Entry 6
Time: 6 min
Yield: 75%
MP: 227-230 °C
(Lit.235-237 °C [20])



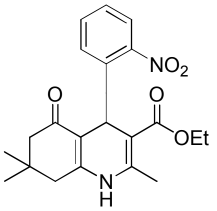
Entry 7
Time: 8 min
Yield: 80%
MP: 250-251 °C
(Lit.245-256 °C [20])



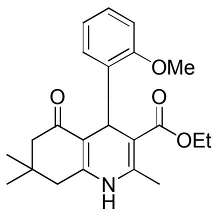
Entry 8
Time: 7 min
Yield: 73%
MP: 214-216 °C
(Lit.220 °C [20])



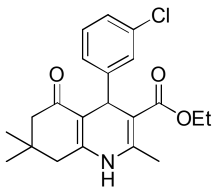
Entry 9
Time: 10 min
Yield: 85%
MP: 239-240 °C
(Lit.246 °C [20])



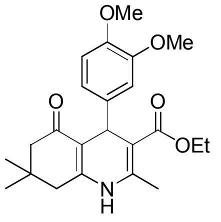
Entry 10
Time: 7 min
Yield: 95%
MP: 205-207 °C
(Lit.205-207 °C [20])



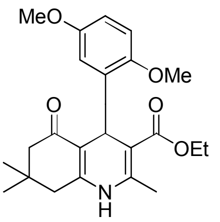
Entry 11
Time: 5 min
Yield: 92%
MP: 255-256 °C
(Lit.257-258 °C [20])



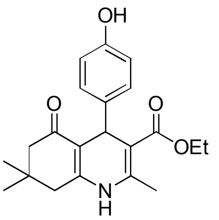
Entry 12
Time: 6 min
Yield: 90%
MP: 231-233 °C
(Lit.235-237 °C [20])



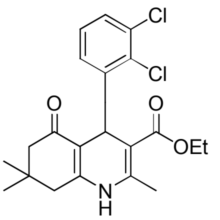
Entry 13
Time: 5 min
Yield: 95%
MP: 247-251 °C
(Lit.245-256 °C [25])



Entry 14
Time: 6 min
Yield: 75%
MP: 227-230 °C
(Lit.235-237 °C [21])

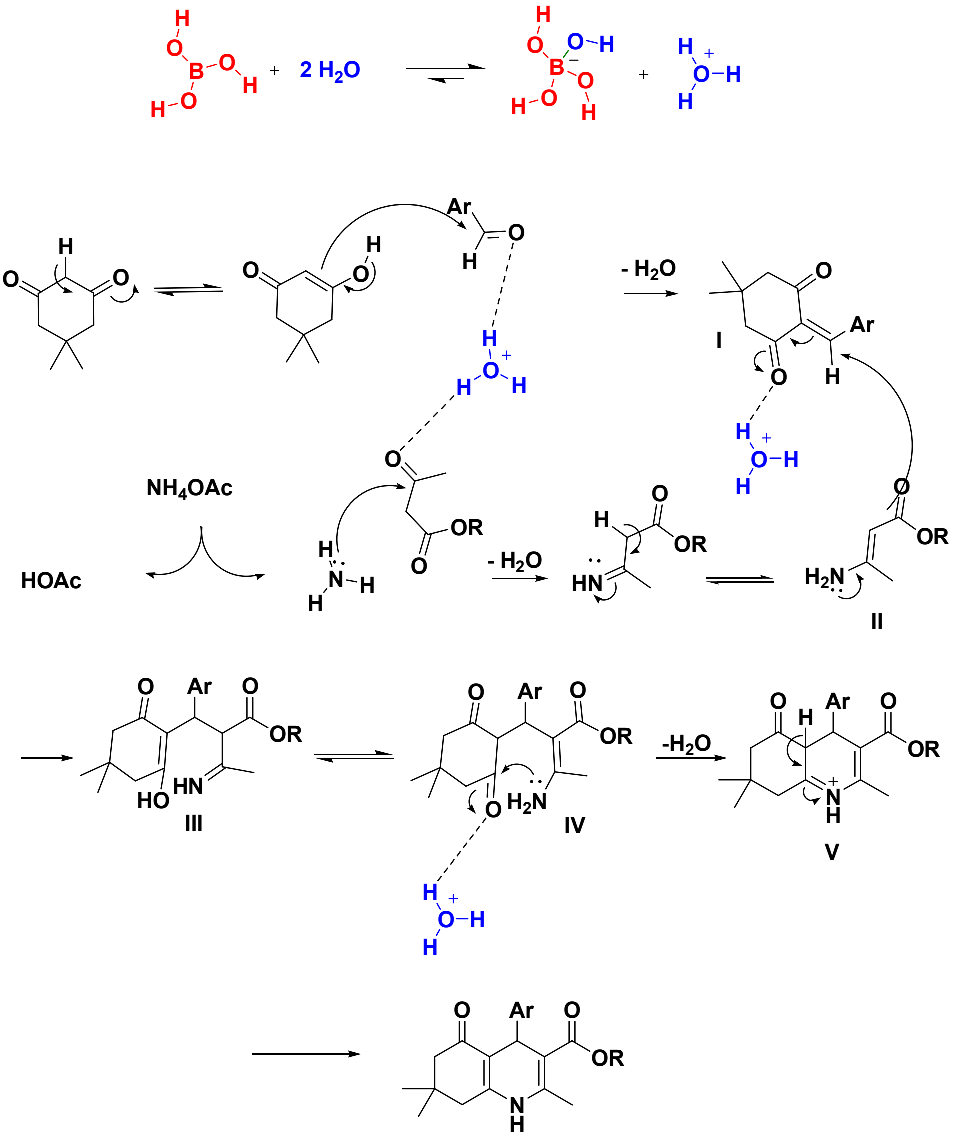


Entry 15
Time: 7 min
Yield: 85%
MP: 238-240 °C
(Lit.232-234 °C [20])



Entry 16
Time: 5 min
Yield: 89%
MP: 229-234 °C
(Lit.229-234 °C [20])

Fig. 2. The synthesis of HHQs from dimedone, aryl aldehydes, *β*-ketoesters and ammonium acetate catalyzed by $B(OH)_3.H_2O$ at 50 °C.



Scheme 2. Proposed mechanism for the preparation of hexahydroquinolines using $B(OH)_3.H_2O$

the optimized reaction conditions. All reactions proceeded efficiently to give the desired hexahydroquinoline derivatives in high yields and in short reaction times. Therefore, aqueous solution of boric acid was a highly efficient and general catalytic system for the preparation of HHQs (Fig. 2).

$B(OH)_4^-$ and H^+ are generated in the aqueous solution through interaction of $B(OH)_3$ with water and attraction of OH^- with boric acid [22,23]. In the mechanism supported by the literature [18-25], at first, dimedone is converted to its enol form and then reacts with activated aldehyde (by H^+) to give intermediate I. Also, the activated ethyl acetoacetate (by H^+) reacts with ammonia (resulted from ammonium acetate) to afford enamine II. Then, the intermediate I and enamine II react with each other to produce intermediate III. III is converted to IV by tautomerization, and intermediate IV gives V by an intramolecular nucleophilic attack of the NH_2 group to the activated carbonyl group and by the elimination of one molecule H_2O. Finally, hexahydroquinonine is formed by tautomerization of V (Scheme 2).

CONCLUSIONS

In this work, we have reported four-component cascade reaction of aryl aldehydes, dimedone, β-ketoesters and ammonium acetate to give hexahydroquinolines using an aqueous solution of a boric acid at 50 °C under mild and green conditions.

ACKNOWLEDGEMENTS

We are thankful to the Sayyed Jamaleddin Assadabadi University for the support to this work.

REFERENCES

[1] A.R. Moosavi-Zare, M.A. Zolfigol, O. Khaledian, V. Khakyzadeh, M.D. Farahani, M.H. Beyzavi, H.G. Kruger, Chem. Engin. J. 248 (2014) 122.

[2] A.R. Moosavi-Zare, M.A. Zolfigol, O. Khaledian, V. Khakyzadeh, M.D. Farahani, H.G. Kruger, New J. Chem. 38 (2014) 2342.

[3] A. Khazaei, F. Abbasi, A.R. Moosavi-Zare, New J. Chem. 38 (2014) 5287.

[4] M.A. Zolfigol, A. Khazaei, A.R. Moosavi-Zare, J. Afsar, V. Khakyzadeh, O. Khaledian, J. Chin. Chem. Soc. 62 (2015) 398.

[5] A.R. Moosavi-Zare, M.A. Zolfigol, M. Zarei, A. Zare, V. Khakyzadeh, A. Hasaninejad, Appl. Catal. A: Gen. 467 (2013) 61.

[6] A. Khazaei, A.R. Moosavi-Zare, Z. Mohammadi, V. Khakyzadeh, J. Afsar, J. Chin. Chem. Soc. 63 (2016) 165.

[7] M.A. Zolfigol, S. Baghery, A.R. Moosavi-Zare, S.M. Vahdat, J. Mol. Catal. A: Chem. 409 (2015) 216.

[8] R. Simsek, U.B. Ismailoglu, C. Safak, I. Sahin-Erdemli, Farmaco. 55 (2000) 665.

[9] R.D. Larsen, E.G. Corley, A.O. King, J.D. Carrol, P. Davis, T.R. Verhoeven, P.J. Reider, M. Labelle, J.Y. Gauthier, Y.B. Xiang, R. Zamboni, J. Org. Chem. 61 (1996) 3398.

[10] Y.L. Chen, K.C. Fang, J.Y. Sheu, S.L. Hsu, C.C. Tzeng, J. Med. Chem. 44 (2001) 2374.

[11] G. Roma, M.D. Braccio, G. Grossi, M. Chia, Eur. J. Med. Chem. 35 (2000) 1021.

[12] D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J.P. Falgueyeret, R.W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari, R.N. Yong, Bioorg. Med. Chem. Lett. 8 (1998) 1255.

[13] M.P. Maguire, K.R. Sheets, K. Mcvety, A.P. Spada, A. Ziberstein, J. Med. Chem. 37 (1994) 2129.

[14] R. Surasani, D. Kalita, A.V.D. Rao, K. Yarbagi, K.B. Chandrasekhar, J. Fluorine Chem. 135 (2012) 91.

[15] M.M. Heravi, K. Bakhtiari, N.M. Javadi, F.F. Bamoharram, M. Saeedi, H.A. Oskooie, J. Mol. Catal. A: Chem. 264 (2007) 50.

[16] A. Khojastehnezhad, F. Moeinpour, A. Davoodnia, Chin. Chem. Lett. 22 (2011) 807.

[17] M. Maheswara, V. Siddaiah, G..L.V. Damu, C.V. Rao, ARKIVOC. 2 (2006) 201.

[18] A.R. Moosavi-Zare, M.A. Zolfigol, M. Zarei, A. Zare, J. Afsar, Appl. Catal. A: Gen. 505 (2015) 224.

[19] A. Zare, F. Abi, A.R. Moosavi-Zare, M.H. Beyzavi, M.A. Zolfigol, J. Mol. Liq. 178 (2013) 113.

[20] A. Khazaei, A.R. Moosavi-Zare, H. Afshar-Hezarkhani, V. Khakyzadeh, RSC Adv. 4 (2014) 32142.

[21] M.A. Zolfigol, S. Baghery, A.R. Moosavi-Zare, S.M. Vahdat, H. Alinezhad, M. Norouzi, RSC Adv. 4 (2014) 57662.

[22] W.L. Jolly, Mc Graw-Hill. (1984) 198.

[23] A. Khazaei, H.A. Alavi Nik, A.R. Moosavi-Zare, J. Chin. Chem. Soc. 62 (2015) 675.

[24] A. Tadjarodi, A. Azad, M.G. Dekamin, S. Afshar, R. Hejazi, A. Mollahosseini, JNS. 5 (2015) 327.

[25] G. Mohammadi Ziarani, A. Badiei, Y. Khaniania, M. Haddadpour, J. Chem. Chem. Eng. 29 (2010).