*Iranian Journal of Catalysis 6(2), 2016, 147-152*

IRANIAN JOURNAL OF CATALYSIS

# Thiamine hydrochloride (Vit-$B_1$): An optimized green alternative for the synthesis of polyhydroquinoline derivatives

Somnath Gholap*, Navnath Gunjal

*Department of Chemistry, Padmashri Vikhe Patil College, Pravaranagar (Loni kd.), Tal- Rahata, Dist- Ahmednagar, Pin-413713(MS), India.*

Received 07 June 2014; received in revised form 23 November 2015; accepted 10 December 2015

ABSTRACT

Thiamine hydrochloride (Vitamin-$B_1$) has been utilized as an effective biodegradable catalyst for the one pot synthesis of polyhydroquinoline derivatives *via* four component reaction of dimedone, aldehyde, ethylacetoacetate and ammonium acetate in ethanol under mild conditions. The method presented here offers several advantages over reported procedures in terms of environmentally benign catalytic system and excellent product yields (75-98%) of polyhydroqninoline compounds. Aromatic and heteroaryl aldehyde with electron donating as well as electron withdrawing group undergo smooth reaction to afford the corresponding polyhydroquinoline derivatives. The synthesized polyhydroquinoline compounds were characterized by IR, NMR and Mass spectral data. The present article describes the new application of Vitamin-$B_1$.

***Keywords**: Thiamine hydrochloride (Vitamin-$B_1$), Dimedone, Aldehyde, Ethylacetoacetate, Ammonium acetate, Polyhydro-qninoline, Green protocol.*

## 1. Introduction

Multi-component reactions (MCRs) has been extensively used in the synthesis of various bioactive targets because they provide easy and rapid access to large libraries of organic compounds with diverse substitution pattern. As MCRs are one-pot reaction, they are easier to carry as compare to multistep synthesis. In 1882, Hantzsch reported first synthesis of symmetrical 1, 4-dihydropyridine derivatives by employing multicomponent process [1]. 4-substituted, 1,4-dihydropyridine (1,4-DHP) comprise a large family of biologically important molecules possessing pharmacological properties like antihypertensive, bronchodilator, antiterosclerotic, vasodilator, hepto-protective, antidibetic and antitumor agents [2]. They have commercial importance as calcium channel blockers [3] and exemplified by therapeutic agents such as nifedine (I), nitrendipine (II), nimodipine (III), felodipine (IV) and amiodipine (V) (Fig. 1) [4-6].

Derivatives of 1,4-dihydropyridine exhibits various medicinal function such as neuroprotectant, platelet antiaggregatory activity, cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizer in tumor therapy [7]. These examples clearly indicate the valuable potential of dihydropyridine (DHPs) derivatives as a source of valuable drug candidate. Moreover, the oxidation of these compounds to pyridine has also been extensively studied [8,9]. They have been meticulously used as a reducing agent for reductive amination of aldehyde and ketone [10]. Thus, the discovery of a milder and more practical route for the synthesis of DHP using green chemistry technology has great challenge in front of modern researchers.

The conventional process reported by Hantzsch, does not need the intervention of any additive or reagent and the reaction was originally conducted either in acetic acid or reflux in alcohol for long period with low to moderate yield of DHPs. Many classical methods such as conventional heating and other improved methods involving microwave irradiation (MW) and ultrasound [11,12] were well documented in literature. Various catalysts such as iodotrimethylsilane(TMSI) [13], ionic liquids [14-16], metal triflates [17,18], HY-Zeolite [19], $HClO_4$-$SiO_2$ [20], organocatalyst [21], montmorillonite K-10 [22], cerium(iv)ammonium nitrate [23], heteropolyacids [24], *p*-toluensulphonic

*Corresponding author email: ssgholap2002@gmail.com
Tel: +91 24 2227 3425; Fax: +91 24 2227 3426

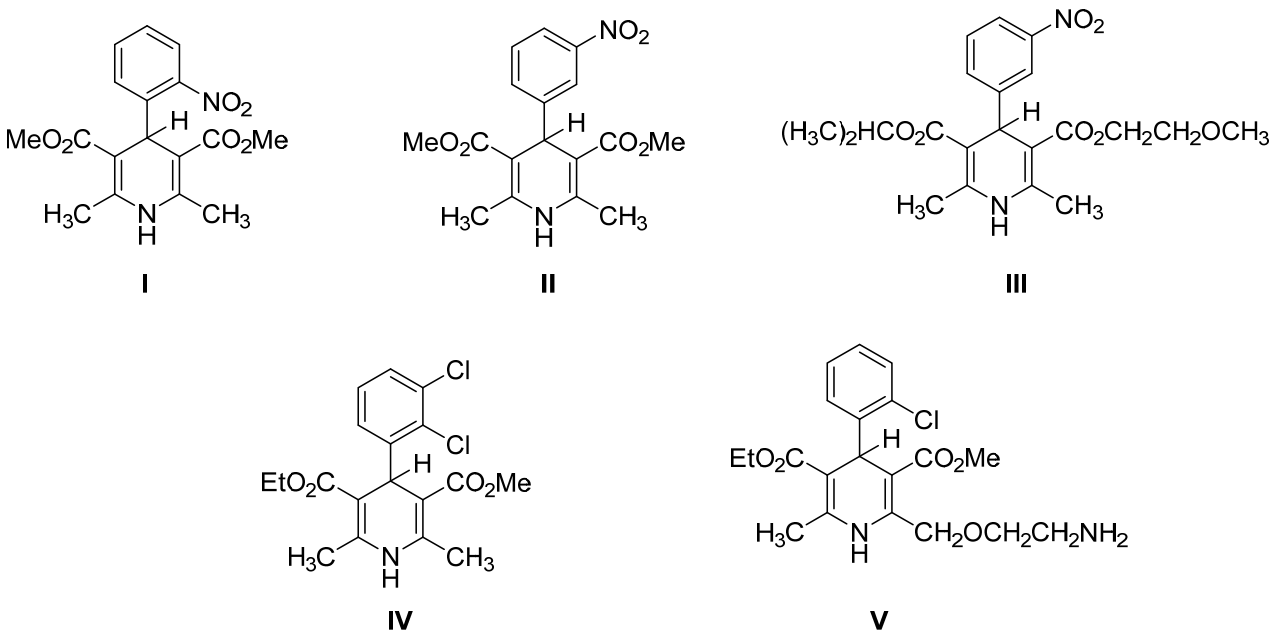



**Fig. 1.** Potentially active 1,4-DHPs.

acid (PTSA) [25], morpholine [26], $ZrCl_4$ [27], visible light [28], silica sulphuric acid [29], $Gd(OTf)_3$ [30], $Bi(NO_3)_3$ [31], cellulose sulfuric acid [32], ytterbium [33], phosphosulfonic acid [34] and protic pyridinium ionic liquid [35] were reported. However, the use of drastic reaction conditions, expensive metal catalysts, lack of biodegrability of catalyst and longer reaction time are some of the disadvantages of the reported methods. Therefore, search of a robust, efficient and cost effective chemical process is of prime importance.

Thiamine hydrochloride popularly known as vitamin-$B_1$ is a colorless organosulfur compound having molecular formula $C_{12}H_{17}N_4OS$ (MW = 265) synthesized by bacteria, fungi, and plants. Sunflower is one of the best source of vitamin-$B_1$. Molecular structure of $VB_1$ shows presence of aminopyrimidine and a thiazole ring linked by a methylene bridge (Fig. 2). It is soluble in polar solvents such as water, methanol, glycerol etc. and insoluble in less polar organic solvents. It is stable in acidic medium but unstable in alkaline medium [36,37]. The best-characterized form of thiamin is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids (Fig. 3). It has been found that catalytic activity of VB1 is due to possibility of formation of N-heterocyclic carbene as an intermediate under alkaline media, as observed in benzoin condensation. Due to structural features it has important role as biocatalyst and now a day it has been used as a powerful catalyst for varieties organic transformations [38-49]. In present work the application of thiamin hydrochloride for the multicomponent synthesis of polyhydroquinoline derivatives from aldehyde, ethylacetoacetate and ammonium acetate has been discussed.

## 2. Experimental

### *2.1. General*

All of the products are known compounds and were identified by comparison of their physical and spectral data with those of reported. Melting points were recorded in open capillary using paraffin bath and are uncorrected. Progress of the reaction was using thin layer chromatography(TLC) in petroleum ether: ethy cuetale (4.5: 0.5) solvent system. IR spectra were recorded using KBr disc. $^1$HNMR spectras were recorded 300 MHz instrument using $CDCl_3$ solvent and TMS as a internal standard.

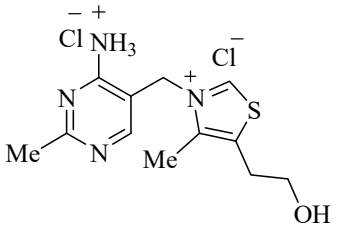



**Fig. 2.** Thiamine hydrochloride (VB1).

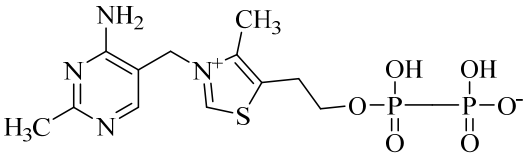



**Fig. 3.** Thiamine pyrophosphate.

*2.2. General procedure for the synthesis of polyhydroquinoline **5 (a-l)***

A mixture of dimedone (5mmol), aromatic aldehyde (5mmol), ethyl acetoacetate (5mmol), ammonium acetate (5.5 mmol ) and vitamin-$B_1$ (0.2 equiv.) was refluxed in ethanol (5ml) for specified time (Scheme 1). After completion of the reaction (as indicated by TLC, solvent system: petroleum ether:ethyl acetate= 4.5:0.5), reaction mixture was poured in ice (10 g). Solid product was separated and further purified by recrystalization in ethanol to afforded the pure crystalline polyhydro quinoline products.

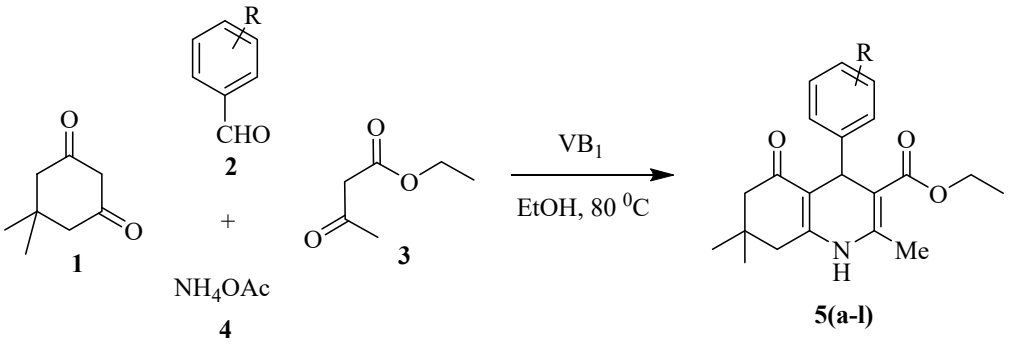
*Spectral data of representative polyhydroqniline derivative **(5l):***

m.p. = 191-193°C. IR (KBr): $\bar{\nu}$= 3415, 3410, 3350, 3316, 2810, 1717, 1650, 1410, 1308, 860,757 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ= 8.88 (s, 1H), 7.12-7.59 (m, 5H), 4.91 (s,1H), 4.15 (q, 2H, *J* = 7.2), 1.20 (s, 3H), 1.18 (s, 3H) 2.21 (s, 6H), 2.12 (s, 2H), 1.9 (s, 2H), 1.72 (t, 3H) ppm. Mass: m/z=455.2, $C_{22}H_{28}N_3O_3Cl$, M.W.= 453.5.

## 3. Results and Discussion

In continuation to our research on development of novel methodologies for synthesis of biologically active compounds [50-55], we explored the catalytic efficiency of vitamin-$B_1$ for the multicomponent synthesis of 1,4-DHP derivatives by the reaction of active methylene group containing compound, aromatic aldehyde and ammonium acetate.

For reaction optimization, the reaction of diemidone (5 mmol), ethyl acetoacetate (5 mmol), benzaldehyde (5 mmol) and ammonium acetate (5.5mmol) in the absence of catalyst was investigated. No product was observed even after 18 h under solvent-free conditions. Then the same reaction was performed using vitamin-$B_1$ (10 mol%) as a catalyst, only 18% of product has been isolated after 10 hours. So, we have studied the effect of solvents for formation of **5a.** Various solvents such as ethyl alcohol, N,N-dimethyl formamide, acetonitrile, water and 1,4-dioxane were tested with varying amount of $VB_1$ (Table 1). Results obtained were clearly indicated that when the reaction was conducted in ethanol using 20mol% vitamin-$B_1$, excellent yield of **5a** (98%, Table 3. entry 1) was obtained after 40 min under reflux conditions.




**Scheme 1.**

**Table 1**. Effect of solvent and catalyst conentration for the formation of '5a'

| Entry | Solvent | Amount of $VB_1$ (mol%) | Time (h) | Yield of **5a** (%)[a] |
|---|---|---|---|---|
| 1 | Solvent-free | None | 18 | - |
| | | 10 | 10 | 18 |
| 2 | Water | 10 | 7.5 | 30 |
| 3 | Ethanol | 10 | 40 min | 72 |
| | | 15 | 40 min | 81 |
| | | 20 | 40 min | 98 |
| 4 | DMF | 20 | 2.5 | 65 |
| 5 | Acetonitrile | 20 | 6 | 58 |
| 6 | 1,4-dioxane | 20 | 10 | 46 |

[a]Isolated yield.

After optimization of the reaction, we have conducted the reactions using various aromatic aldehydes with diverse functionalities (Table 3). It has been observed that aromatic aldehyde carrying electron withdrawing substituent underwent smooth reaction and excellent yields of the products were obtained in shorter reaction time as compare to electron donating substituents bearing aromatic aldehydes (Table 3, entry 5).

In addition, heteroarylaldehyde such as 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde undergo cyclocondensation under present reaction conditions to afford the corresponding dihydropyrimidine derivative in 79 % yield (Table 3, entry 12).

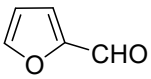
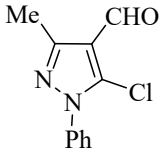
The tentative mechanism to rationalize the formation of DHPs is represented in Fig. 4. Vit-$B_1$ supposed to facilitate the Knoevenogel condensation for the formation of 'A' or 'C' and the Michael addition 'B' to 'A' or 'D' to 'C' followed by cyclocondensation to afford polyhydroquinoline derivatives.

**Table 2.** Comparison of the results for the formation of '5a' with the reported procedures.

| Entry | Catalytic system | Time | Yield (%)[a] | Ref. |
|---|---|---|---|---|
| 1. | *p*-TSA/EtOH/rt | 2 hr | 93 | [25] |
| 2. | $ZrCl_4$/EtOH/rt | 2 hr | 94 | [27] |
| 3. | L-proline/EtOH/reflux | 6 hr | 92 | [21] |
| 4. | Morpholine/solventfree/rt | 60 min | 95 | [26] |
| 5. | HY-Zeolite | 2.0 hr | 93 | [19] |
| 6. | $VB_1$/EtOH/80 $^0$C | 40 min | 97 | --- |

[a]Isolated yield of the product after recrystalization.

**Table 3**. Synthesis of polyhydroquinoline *via* multicomponent reaction of diemidone, aldehyde, ethyl acetoacetate and ammonium acetate catalyzed by $VB_1$.

| Entry | Aldehyde | DHP | Time (min) | Yield (%)[a,b] | m.p. (°C) | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | Found | Reported | |
| 1 | $C_6H_5CHO$ | **5a** | 40 | 98 | 202-204 | 202-205 | [21] |
| 2 | 2-$ClC_6H_4CHO$ | **5b** | 30 | 83 | 204-205 | 206-208 | [27] |
| 3 | 3-$NO_2C_6H_4CHO$ | **5c** | 25 | 95 | 177-179 | 176-179 | [21] |
| 4 | 4-$ClC_6H_4CHO$ | **5d** | 60 | 90 | 233-235 | 230-232 | [21] |
| 5 | 4-$MeOC_6H_4CHO$ | **5e** | 65 | 92 | 253-255 | 252-254 | [21] |
| 6 | 4-$MeC_6H_4CHO$ | **5f** | 120 | 89 | 259-261 | 258-260 | [21] |
| 7 | $C_6H_5$ CH=CH CHO | **5g** | 50 | 81 | 204-206 | 204-206 | [27] |
| 8 | 3-MeO,4-$HOC_6H_3CHO$ | **5h** | 85 | 90 | 208-209 | 208-210 | [21] |
| 9 |  | **5i** | 40 | 86 | 245-246 | 245-247 | [27] |
| 10 | 4-$HOC_6H_4CHO$ | **5j** | 120 | 93 | 232-234 | 234-237 | [21] |
| 11 | 4-$NO_2C_6H_4CHO$ | **5k** | 30 | 98 | 242-244 | 241-243 | [21] |
| 12 |  | **5l** | 45 | 79 | 191-193 | - | - |

[a]Isolated yield of the product.

[b]Products were characterized by IR, $^1$HNMR, Mass and by comparing physical constants with those of reported in literature.

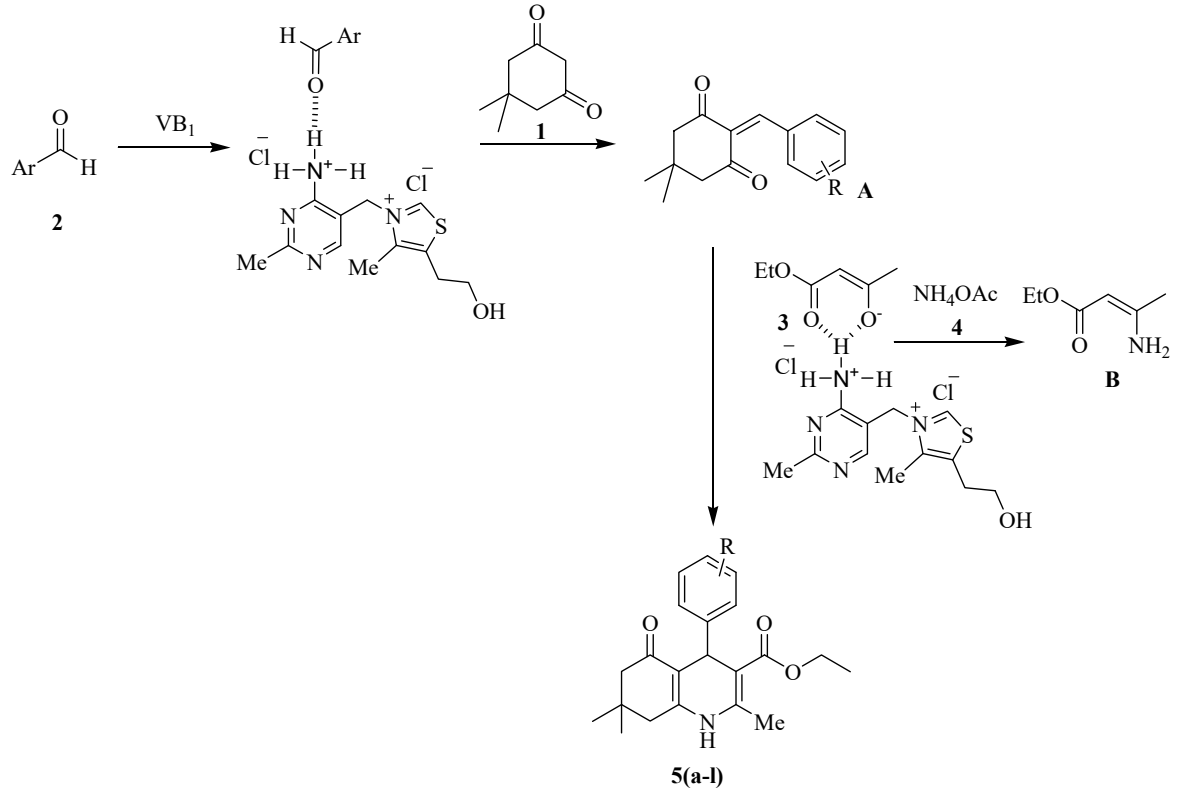



**Fig. 4.** Plausible mechanism of synthesis of polyhydroquinoline derivatives.

## 4. Conclusions

In conclusion, we have developed a new application of vitamin-$B_1$ for Hantzch multicomponent synthesis of polyhydroquinoline with diverse functional groups.The present method offers several advantages such as excellent yield of products, operational simpicity and biodegradable catalytic system over the reported procedures.

## Acknowledgements

Authors are thankful to BCUD, University of Pune for finantial assistance, Dr.S.R.walunj, Principal, Padmashri Vikhe Patil College, Pravaranagar for providing necessary laboratory facilities Dr. G. R. Pandhare for constant encouragement.

## References

[1] A. Hantzsch, Justus Liebigs Ann. Chem. 215 (1882) 1-82.
[2] A.C. Guadio, A. Korkkovas, Y.J. Takahata, Pharm Sci. 83 (1994) 1110-1115.
[3] N. Pedemonte, D. Boido, O. Moran, M. Giampieri, M. Mazzei, R. Ravazzolo, L.J.V. Galietta, Mol. Pharmacol. 72 (2007) 197-207.
[4] F. Rossert, W. Vater, US Patent (1969) 3485847.
[5] V.H. Meyer, F. Rossert, W. Vater, K. Stoepel, US Patent, (1974) 3799934.
[6] J. Jacques, V. Eynde, A. Mayence, Molecules 8 (2003) 381-391.
[7] R. Boer, V. Gekeler, Drugs Future 20 (1995) 499-509.
[8] D. Zhang, L.Z. Wu, L. Zhou, X. Han, Q.Z. Yang, L.P. Zhang, C.H. Tung, J. Am. Chem Soc. 126 (2004) 3440-3441.
[9] M.M. Heravi, F.K. Behabahani, H.A. Oskooie, R.H. Shoar, Tetrahedron Lett. 46 (2005) 2775-2777.
[10] T. Itoh, K. Nagata, A. Kurihara, M. Miyazaki, A. Ohsawa, Tetrahedron Lett. 43 (2002) 3105-3108.
[11] M. Li, Z. Zuo, L. Wen, S. Wang, J. Comb Chem. 10 (2008) 436-340.
[12] S.J. Tu, J.F. Zhou, X. Deng, P.J. Cai, H. Wang, J.C. Feng, Chinese J. Org. Chem. 21 (2001) 313-316.
[13] G. Sabitha, G.S.K. Reddy, C.S. Reddy, J.S. Yadav, Tetrahedron Lett. 44 (2003) 4129-4131.
[14] S.J. Ji, Z.Q. Jiang, J. Lu, T.P. Loa, Synlett (2004) 831-835.
[15] M.Z. Ghodsi, B.A. Reza, K. Yegane, H. Mahbobeh, Iran. J. Chem. Chem. Eng. 29 (2010) 1-10.
[16] M.M. Heran, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshitiha, A. Davoodnia, Synth. Commun. 40 (2010) 523-529.
[17] L.M. Wang, J. Sheng, J.W. Zhang, J.W. Han, Y. Fan, H. Tian, C. T. Qian, Tetrahedron 61 (2005) 1539-1543.
[18] J.L. Donelson, A. Gibbs, S.K. De, J. Mol. Catal. A: Chem. 256 (2006) 309-311.
[19] B. Das, B. Ravikanth, R. Ramu, R.B. Vittal, Chem. Pharm. Bull. 54 (2006) 1044-1045.

[20] M. Mageswara, V. Siddaiah, G.L. Damu, R.C. Venkata, ARKIVOC (2006) 201-206.
[21] N.N. Karade, V.H. Budhewar, S.V. Shinde, W.N. Jadhav, Lett. Org. Chem. 4 (2007) 16-19.
[22] G. Song, B. Wang, X. Wu, Y. Kang, L. Yang, Synth. Commun. 35 (2005) 2875-2880.
[23] C.S. Readdy, M. Raghu, Chin. Chem. Lett. 19 (2008) 775-779.
[24] M.M. Heravi, K. Bakhtiri, N.M. Javadi, F.F. Bamoharram, M. Saeedi, H.A. Oskooi, J. Mol. Catal A: Chem. 264 (2007) 50-52.
[25] S.R. Cherkupally, R. Mekala, Chem. Pharm. Bull. 56 (2008) 1002-1004.
[26] M.M. Heran, M. Zaker, S. Pooremamy, H.A. Oskooie, Synth. Commun. 41 (2011) 113-120.
[27] C.S. Raddy, M. Raghu, Indian J. Chem. 47B (2008) 1578-1582.
[28] S. Ghosh, F. Saikh, J. Das, A.K. Pramanik, Tetrahedron Lett. 54 (2013) 58-62.
[29] E. Kolvari, M.A. Zulfigol, N. Koukabi, B. Shirmardi-Shaghasemi, Chem. Pap. 65 (2011) 898-902.
[30] S.S. Mansoor, K. Aswin, K. Logaiya, S.P.N. Sudhan, Arabian J. Chem. (2012) http://dx.doi.org/10.1016/j.arabjc.2012.10.017
[31] D. Bandyopadhyay, S. Maldonado, B.K. Banik, Molecules 17 (2012) 2643-2662.
[32] J. Safari, S.H. Banitaba, S.D. Khalili, J. Mol. Catal. A: Chem. 335 (2011) 46.
[33] S. Sueki, R. Takei, J. Abe, I. Shimizu, Tetrahedron Lett. 52 (2011) 4473.
[34] A.R. Kiasata, H. Almasia, S.J. Saghanezhadb, Org. Chem. Res. 1 (2015) 72-77.
[35] M.Tajbakhsh, H. Alinezhad, M. Norouzi, S. Baghery, M. Akbari, J. Mol. Liq. 177 (2013) 44-48.
[36] L.K. Mahan, S. Escott, In Stump, Krause's Food, Nutrition & Diet Therapy, 10th Ed. Philadelphia: W.B. Saunders Company (2000).
[37] V. Tanphaichitr, M.E. Shils, J.A. Olsen, M. Shike, In Modern Nutrition in Health and Disease. 9th Ed. Baltimore: Lippincott Williams & Wilkins (1999).
[38] A. Yasuhara, N. Suzuki, T. Sakamoto, Chem. Pharm. Bull. 50 (2002) 143-145.
[39] D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, J. Org. Chem. 69 (2004) 2896-2898.
[40] T. Hiyama, Y. Hatanaka, Pure App. Chem. 66 (1994) 1471-1478.
[41] R.K. Sharma, J.L. Fry, J. Org. Chem. 48 (1983) 2112-2114.
[42] H. Sun, S.G.J. Di Magno, J. Am. Chem. Soc., 127 (2005) 2050-2051.
[43] R. Siddiqui, P. Rai, Rahila, A. Srivastava, A. Srivastava, A. Srivastava, New J. Chem. 37 (2013) 3798-3804.
[44] V.B. Purohit, S.C. Karad, K.H. Patel, D.K. Raval, Catal. Sci. Technol. 5 (2015) 3113-3118.
[45] T. Lu, X. Li, L. Gu, Y. Zhang, Environ. Chem. Lett. 10 (2012) 369-375.
[46] P.G. Mandhane, R.S. Joshi, D.R. Nagargoje, C.H. Gill, Chin. Chem. Lett. 22 (2011) 563.
[47] Y. Chen, W. Shan, M. Lei, L. Hua, Tetrahedron Lett. 53 (2012) 5923-5925.
[48] F. Chen, M. Lei, L. Hu Tetrahedron 69 (2013) 2954-2960.
[49] J. Liu, M. Lei, L. Hu, Green Chem. 2012, 14, 840.
[50] S.S. Gholap, C.H. Gill, G.R. Pandhare, Indian J. Heterocycl. Chem. 18 (2009) 279-282.
[51] S.S. Gholap, Heterocycl. Lett. 2 (2012) 461-466.
[52] S.S. Gholap, N. Gunjal, Arabian J. Chem. (2013) http://dx.doi.org/10.1016/j.arabjc.2013.10.021
[53] S.S. Gholap, M.S. Tambe, N.V. Gunjal, Iran. J. Catal. 3 (2013) 171-176.
[54] S.S. Gholap, V.D. Dhakane, S.S. Gholap, Jordan J. Chem. 7 (2012) 279-285.
[55] S.S. Gholap, B.P. Bandgar, H.V. Chavan, V.D. Dhakane, U.P. Deshmukh, C. R. Chim. 17 (2014) 431-436.