J. Mater. Environ. Sci. 5 (6) (2014) 1854-1859
ISSN : 2028-2508
CODEN: JMESCN

A Green protocol for chemo-and region-selective enamination of β-dicarbonyl compounds in the presence of Potassium Hydrogenophosphate as a heterogeneous and eco-friendly calatyst

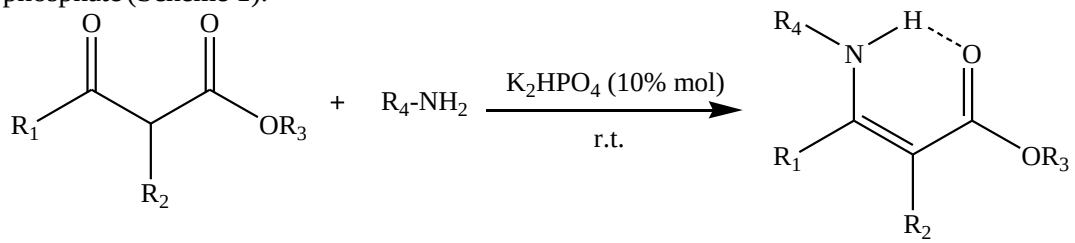
M.A. Harrad*[1], I. Houssini[1], B. Boualy[2]
[1]*Equipe de Chimie de Coordination et Catalyse, Faculté des Sciences Semlalia , Marrakech, Morocco.*
[2] *Equipe Chimie analytique et Modélisation Statistique, Faculté Polydisciplinaire de Khouribga Université Hassan 1er, Khouribga, Morocco*

Received 28 Jan 2014; Revised 10 Sept 2014; Accepted 10 Sept 2014
* *Corresponding author. E-mail: ma.harrad@yahoo.fr ; Tel: (+212 524 434649)*

Abstract:
The Potassium Hydrogenophosphate (K_2HPO_4) has been found to be an extremely efficient and eco-friendly catalyst for the synthesis of β-enaminoesters under solvent-free conditions. In addition, by employing this catalyst, a highly chemo and regio-selective enamination of carbonyl compounds has been developed. Using various aliphatic and aromatic amines, a variety of β-enaminoesters were achieved in good to excellent yields with high regioselectivities.

Keywords: β-Enaminoesters; K_2HPO_4; Catalytic enamination; β-ketoesters; Solvent-free.

1. Introduction
β-Enamino-esters have been extensively used as key intermediates in organic synthesis [1] and the chemistry of these compounds have been reviewed [2-4]. Due to their range of activity and importance, several methods have been developed [5-15]. The most well-know and exploited route toward these compounds involves the direct in aromatic [16]. Some improved procedures have been also reported wich such as p-TSA [17], HAc [18], trimethylsilyl trifluoromethanesulfonate (TMSTf) [19], montmorillonite K10 [20], $BF_3.OEt_2$[21], Silica gel [22], $CoCl_2.6H_2O$ [23], $Zn(ClO_4)_2.6H_2O$ [24], $CeCl_3.7H_2O$ [25], $NaAuCl_4$ [26], $Bi(OTf)_3$ [27], sulfated zirconia[28], and natural clays [29]. However, these approches suffer from some drawbacks such as long reaction times, the use of large amounts of costly catalysts, the low yields of the desired products, the requirement of high temperatures, additional ultrasound or microwave oven and suffer from poor regioselectivity [30-35].
As part of our ongoing program, to develop more efficient and environmentally benign methods for organic synthesis using economic and eco-friendly materials as catalysts [36-41]. Herein, we wish to describe a new, clean and efficient solvent-free method for the synthesis of β-enaminoesters from aromatic as well as aliphatic amines and β-ketoesters using a catalytic amount of cheap and readily accessible reagent Potassium Hydrogenophosphate (Scheme 1).



Scheme 1: Synthesis of β-enaminoesters catalyzed by K_2HPO_4.

2. Materials and methods
2.1. General Methods
All chemicals compounds were purchased from (Aldrich, Fluka, Acsos). The NMR studies were performed on a Bruker Avance 300 spectrometer in $CDCl_3$, chemicals shifts are given in ppm relative to external TMS and coupling constant (J) in Hz. Mass spectra were recorded on a GC–MS Thermofinnigan Polaris-Q mass spectrometer. All the spectroscopic data of the products were compared with those reported in the literature. Liquid chromatography was performed on silica gel (Merk 60, 220-440 mesh; eluent: hexane/ethylacetate).

ISSN : 2028-2508
CODEN: JMESCN

2.2. General experimental procedure

To a mixture of 1,3-diketoester compound (10 mmol) and amine (10 mmol) was added the Potassium Hydrogenophosphate (0.1 mmol). The resulting reaction mixture was stirred at room temperature for a specified period (see table 1). The completion of the reaction was confirmed by thin layer chromatography. Then the reaction mixture was diluted by adding ethyl acetate (20 mL) and washed with water, followed by brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude products were purified by column chromatography, using silica gel. All isolated pure products were fully characterized by 1H, 13C NMR and Mass spectra or otherwise compared with the known compounds.

2.3. Spectral data of products

(Z)-Methyl 3-(methylamino) but-2-enoate (1)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.66 (s, 3H), 2.69 (s, 3H), 3.32 (s, 3H), 4.15 (s, 1H), 8.20 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 19.02, 29.86, 49.7, 82.02, 162, 170.7. EIMS m/z 130.1 (M+1, 100). EIMS (*m*/*z*) 121.1 (M+1).

(Z)-Methyl 3-(cyclohexylamino) but-2-enoate (2)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 0.8 (m, 2H), 1.1 (s, 4H), 1.2 (m, 1H), 3.4 (s, 3H), 4.2 (s, 1H), 8.6 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 20.20, 22.41, 24.62, 35.82, 49.20, 51.63, 81.30, 160.11, 170.42. EIMS (*m*/*z*) 198.1 (M+1, 100).

(Z)-Methyl 3-(isopropylamino) but-2-enoate (3)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 0.88 (d, J= 7.0 Hz, 6H), 1.52 (s, 3H), 1.92 (s, 3H), 3.66 (m, 1H), 6.87 (s, 1H), 8.20 (brs, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 18.33, 23.59, 43.80, 48.93, 81.82, 159.92, 170.03 , EIMS (m/z) 157.1 (M+1, 100).

(Z)-Methyl 3-(benzylamino) but-2-enoate (4)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 11.75 (s, 3H), 3.47 (s, 3H), 4.27 (s, 2H), 4.36 (s, 1H), 7.09-22 (m, 7H), 8.86 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 19.25, 46.64, 49.76, 83.55, 126.5, 127.28, 128.78, 139.02, 160.99, 170.45. EIMS (*m*/*z*) 206.1 (M+1, 100).

(Z)-Methyl 3-(phenylamino) but-2-enoate (5)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.9 (s, 3H), 3.75 (s, 3H), 4.6 (s, 1H), 7.09-7.22 (m, 7H), 10.5 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 20.28, 50.11, 85.92, 124.40, 124.88, 129.02, 139.37, 158.54, 170.45. EIMS (*m*/*z*) 192.1 (M+1, 100).

(Z)-Ethyl 3-(o-tolylamino) but-2-enoate (6)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.21 (t, J= 6.9 Hz, 3H), 2.07 (s, 3H), 2.24 (s, 3H), 4.03 (q, J= 6.9 Hz, 2H), 4.70 (s, 1H), 6.98-7.17 (m, 4H), 10.28 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 12.31, 15.64, 17.65, 56.25, 83.12, 123.56, 133.74, 133.49, 133.73, 135.39, 157.26, 168.21. EIMS (*m*/*z*) 205 (M+, 44).

(Z)-Methyl 3-(p-tolylamino) but-2-enoate (7)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.96 (s, 3H), 2.33 (s, 3H), 3.5 (s, 3H), 4.6 (s, 1H), 6.98-7 (m, 4H), 10.28 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 20.01, 30.10, 49.80, 84.71, 123.56, 133.74, 133.49, 133.73, 135.39, 159.26, 170.73. . EIMS (*m*/*z*) 219.1 (M+1, 84).

(Z)-Methyl 3-(p-methoxyanilinlamino) but-2-enoate (8)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.76 (s, 3H), 3.51 (s, 3H), 4.55 (s, 1H), 6.83-6.93 (m, 4H), 10.12 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 19.94, 50.14, 85, 115, 116, 126.25, 126.62, 135, 158, 161, 170. EIMS m/z 222.1 (M+1, 100).

(Z)-Methyl 3-(p-nitroanilinlamino) but-2-enoate (9)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.32 (s, 3H), 1.73 (s, 3H), 5.10 (s, 1H), 7.46–7.94 (m, 5H, Ar), 8.02 (br s,1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 15.5, 24.5, 60.3, 97.7, 130.5, 131.9, 135.5, 149.4, 165.2, 167.1. EIMS m/z 236.2 (M+1, 100).

(Z)-Methyl 3-(p-fluoroanilinlamino) but-2-enoate (10)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.77 (s, 3H), 3.52 (s, 3H), 4.55 (s, 1H), 6.83-6.93 (m, 4H), 10.12 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 19.94, 50.14, 85.46, 115.66, 115.96, 120.25, 125.7, 135.2, 158.76, 162.01, 170.70. EIMS m/z 209.1 (M+1, 100).

(Z)-Methyl 3-(naphtylamino) but-2-enoate (11)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.77 (s, 3H), 3.62 (s, 3H), 4.67 (s, 1H), 7.13-7.96 (m, 7H), 10.48 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 20.03, 50.14, 85.17, 122.81, 123.46, 124.29, 124.71, 125.16, 125.8, 126.37, 128.19, 126.72, 126.52, 159.9, 170.7. EIMS m/z 241.1 (M+1, 100).

(Z)-Ethyl 3-(phenylamino)cyclohex-2-enoate (12)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.29 (t, J= 7.1 Hz, 3H), 1.58–1.65 (m, 4H), 2.31–2.37 (m, 4H), 4.17 (q, J= 7.1 Hz, 2H), 7–7. 02–7.28 (m, 5H), 10.79 (br s,1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 14.6, 21.97, 22.35, 27.11, 29.1, 60, 115.05, 118.42, 124.18, 124.4, 128.5, 140, 156.48, 172.76. EIMS m/z 246.1 (M+1, 100).

(Z)-Ethyl 3-(benzylamino)cyclohex-2-enoate (13)

^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.2 (t, J= 7.2 Hz, 3H), 1.62 (m, 4H), 1.8 (s, 2H), 2.7 (m,4H), 4.1 (q, J= 7.1 Hz, 2H), 6.90–6.99 (m, 3H), 7.10–7.15 (m, 2H), 11.05 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 14.6, 21.97, 22.35, 27.11, 29.1, 60, 115.05, 118.42, 124.18, 124.4, 128.5, 140, 156.48, 172.76. EIMS m/z 246.1 (M+1, 100).

(Z)-Ethyl 3-(isopropylamino)cyclohex-2-enoate (14)

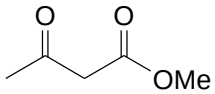
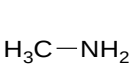
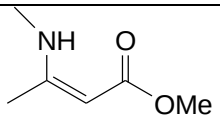
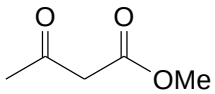
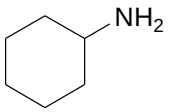
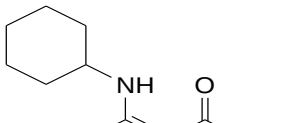
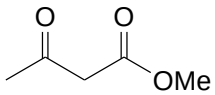
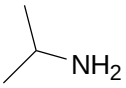
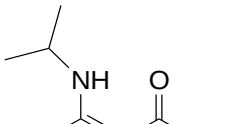
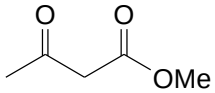
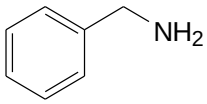
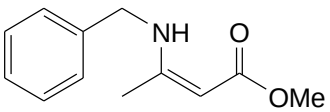
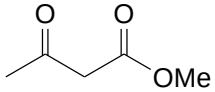
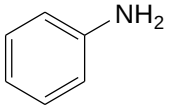
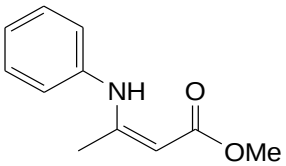
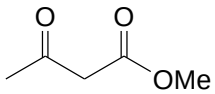
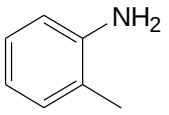
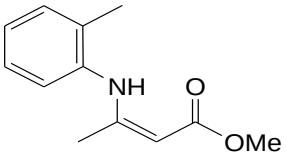
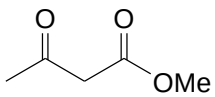
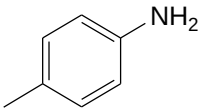
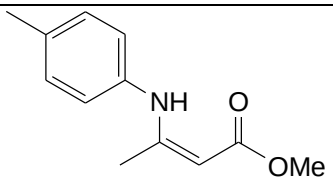
^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.1 (t, J=6.9 Hz, 3H), 1.5 (m, 2H), 1.6 (m, 2H), 2.1 (t, 2H), 2.2 (t, 2H), 3.7 (m, 1H), 4.1 (q, J=6.9 Hz, 2H), 8.9 (br s, 1H, NH); ^{13}C RMN (75 MHz, $CDCl_3$) : δ 13.69, 21.41, 21.95, 22.92, 23.13, 23.38, 26.9, 40.42, 59.77, 88, 157.29, 171. EIMS m/z 212.1 (M+1, 100).

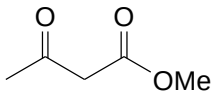
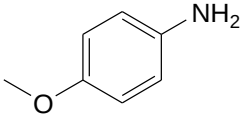
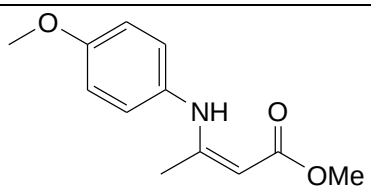
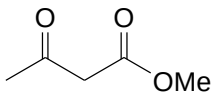
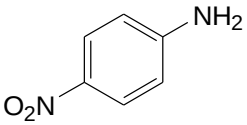
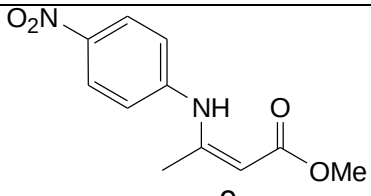
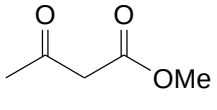
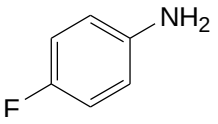
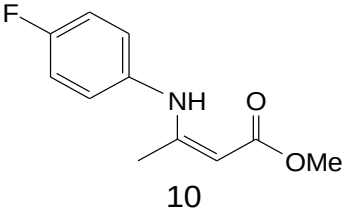
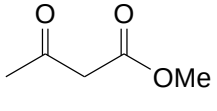
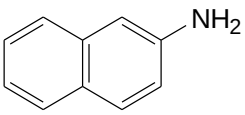
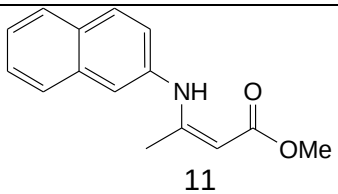
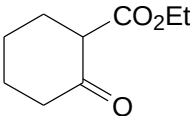
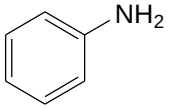
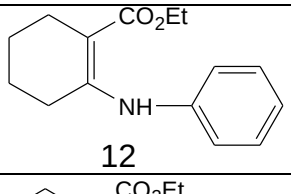
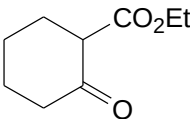
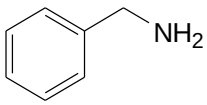
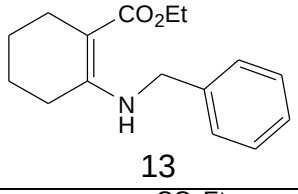
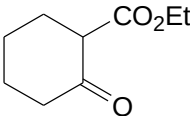
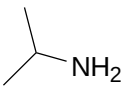
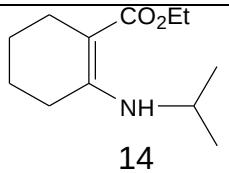
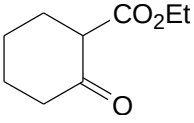
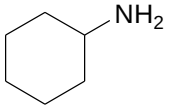
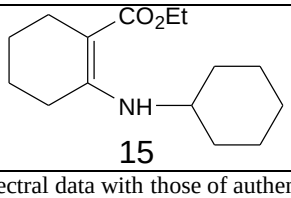
(Z)-Ethyl 3-(cyclohexylamino)cyclohex-2-enoate (15)
^{1}H RMN (300 MHz, $CDCl_3$) : δ 1.05–1.25 (m, 9H), 1.44–1.57 (m, 4H), 2.16–2.25 (m, 4H), 3.55–3.61 (m, 1H), 4.01 (q, J= 6.9 Hz, 2H), 8.84 (br s, 1H, NH); RMN^{13}C ($CDCl_3$, 75 MHz) δ: 13.69, 21.41, 21.95, 22.92, 23.13, 23.38, 26.9, 40.42, 59.77, 88, 157.29, 171. EIMS m/z 212.1 (M+1, 100).

3. Results and Discussion

The experimental procedure for this reaction is remarkably simple and does not require the use of organic solvents or inert atmospheres. A catalytic quantity of Potassium Hydrogenophosphate (10%, 0.1 mmol) and the required amine were added to a stirred solution of the 1,3-dicarbonyl compound, and the mixture was stirred at room temperature. The generality of this process was illustrated by the wide range of amines and 1,3-dicarbonyl compounds examined to explore the scope of the reaction. Thus, a variety of aliphatic and aromatic amines reacted effectively with linear and cyclic β-ketoesters to afford the corresponding β-enaminoesters compounds (Table 1).

Table 1: Enamination of β-ketoesters catalyzed by K_2HPO_4 under solvent-free conditions.

Entry	β-ketoester	Amine	Product[a]	Time min)	Yield[b] (%)
1			 1	10	99
2			 2	20	98
3			 3	12	98
4			 4	20	97
5			 5	30	90
6			 6	120	91
7			 7	60	98

8			 8	60	98
9			 9	240	30
10			 10	30	90
11			 11	240	80
12			 12	60	72
13			 13	30	93
14			 14	30	98
15			 15	30	94

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.[36-42]
[b] Yield based on GC analysis.

As shown in Table 1, all reactions proceeded efficiently at room temperature and the desired products were obtained in high to excellent yields with high regio-and chemo-selectivity. Both the yields and reactions times listed in table 1 suggest that the isopropyl-amine and methylamine appears to be the most reactive (entry 1,3).
At first, we examine the treatment of methyl acetoacetate, as a linear ketoester, with aliphatic amines in the presence of Potassium Hydrogenophosphate. The reaction gave the corresponding β-enaminoesters in excellent yields and in shorter reaction times (entries 1-4). To confirm the role of catalyst, a blank reaction was carried out

at similar reaction conditions with benzyl amine and methylacetoacetate in absence of catalyst. But no progress was found even after stirring for a long reaction time (10h). It clearly shows the role of catalyst Potassium Hydrogenophosphate for activation of the carbonyl group. Moreover, a series of aromatic amines bearing electron-donating or electron-withdrawing groups on aromatic ring were investigated (entries 5-11). In general, aryl amines having no substituent or electron-donating substituent on the aromatic ring were more reactive and afforded the corresponding β-enaminoesters in good yields (entries 7 and 8). The substituent groups on the aromatic ring associated with amines show obvious effects in terms of yields and reaction times. It should be pointed out that the aniline with a strongly electron-withdrawing group such as nitro functional group gives the lowest yield under the similar reaction conditions (entry 9) [36-40].
In contrast, with halogen group both in the para and ortho positions, the corresponding products were obtained in 90% (entries 10). On the other hand, under the similar condition reactions we have investigated the efficiency of this reaction using a cyclic β-ketoesters (entries 12-15). The reaction was also successfully carried out and the corresponding products were obtained in high to excellent yields.
This methodology proved to be efficient in term of chemo-selectivity. The amines react selectively with the ketone of the β-ketoesters and in all of the cases no reaction with ester was observed to give the corresponding amide. The (Z)-selectivity in the products derived from β-ketoesters was secured by intramolecular hydrogen bonding and confirmed by spectroscopic data of the isolated products [36-41].

Conclusion

In summary, we have developed a new efficient method for the synthesis of β-enaminoesters from amines and β-dicarbonyl compounds using Potassium Hydrogenophosphate under solvent-free conditions. The advantages the presented methodology are efficiency, simplicity, high yield, low cost, cleaner reaction profile, easy product isolation, agreement with the green chemistry protocols and finally an attractive strategy for the preparation of β-enaminoesters compounds.

References

1. Kuckländer V., in: Rappoport Z (Eds.): The Chemistry of Enamines, *John Wiley & Sons, New York*, Part 1 (1994) 525.
2. Vohra R. K., Renaud J. L., Bruneau C., *Collect. Czech. Chem. Commun*. 70 (2005) 1943.
3. Stevens C.V., Kesteleyn B., Alonso E. R., De Kimpe N., *Tetrahedron.* 57 (2001) 7685.
4. Chen J-X., Zhang C-F., Gao W-X., Jin H-L., Ding J-C., Wu H-Y., *J. Braz. Chem. Soc*. (2010) 1.
5. Mohammadizadeh M. R., Hasaninejad A., Bahramzadeh M., Khanjarloo Z., *Synth. Commun*. 39 (2009) 1152.
6. Valduga C. J., Squizani A., Braibante H. S., Braibante M. E. F., *Synthesis*. 7 (1998) 1019.
7. Gholap A. R., Chakor N. S., Daniel T., Lahoti R. J., Srinivasan K. V., *J. Mol. Catal A: Chem.* 245 (2006) 37.
8. Nagaiah K., *J. Mol. Catal. A: Chem*. 256 (2006) 234.
9. Lue P., Greenhill J. V., *Adv. Heterocycl. Chem*. 67 (1997) 207.
10. Katritzky A. R., Hayden A. E., Kirichenko K., Pelphrey P., Ji Y., *J. Org. Chem*. 69 (2004) 5108.
11. Bartoli G., Cimarelli C., Dalpozzo R., Palmieri G., Tetrahedron. 51 (1995) 8613.
12. Reddy D. S., Rajale T.V., Shivakumar R. K., Iqbal J., Tetrahedron Lett. 46 (2005) 979.
13. Elaridi J., Thaqi A., Prosser A., Jackson W.R., Robinson A.J., *Tetrahedron: Asymmetry*. 16 (2005) 1309.
14. Khodaei M. M., Khosropour R., Kookhazadeh M., *Can. J. Chem*. 83 (2005) 209.
15. Zhang Z. H., Yin L., Wang Y.M., *Adv. Synth. Catal*. 348 (2006) 184.
16. Martin D. F., Janusonis G. A., Martin B. B., *J. Am. Chem. Soc.* 83 (1961) 73.
17. Baraldi P.G., Simoni D., Manfredini S., *Synthesis.* 11 (1983) 902.
18. Adams D., Dominguez J., Russo V. L., De Rekowski N. M., *Gazz. Chim. Ital*. 119 (1989) 281.
19. Marin C. P. C., Henderson D. G., Soeder R. W., *Synth. Commun*. 27 (1997) 4275.
20. M. E. F. Braibante, H. S. Braibante, L. Missio, A. Andricopulo, *Synthesis*. 9 (1994) 898.
21. B. Stefane, S. Polanc, Synlett. 4 (2004) 698.
22. Gao Y. H., Zhang Q. H., Xu J. X., *Synth. Commun*. 34 (2004) 909.
23. Zhang Z. H., Hu J. Y., *J. Braz. Chem. Soc*. 17 (2006) 1447.
24. Bartoli G., Bosco M., Locatelli M., Marcantoni E., Melchiorre P., Sambri L., *Synlett*. 2 (2004) 239.
25. Khodaei M. M., Khosropour A. R., Kookhazadeh M., *Synlett*. 11 (2004) 1980.
26. Arcadi A., Bianchi G., Giuseppe S.D., Marinelli F., *Green. Chem*. 5 (2003) 64.
27. Khosropour A. R., Khodaei M. M., Kookhazadeh M., *Tetrahedron. Lett*. 45 (2004) 1725.
28. Zhang Z. H., Song L.M., *J. Chem. Res*. 12 (2005) 817.
29. Silva F. C., De Souza M.C.B.V., Ferreira V.F., Sabino S.J., Antunes O.A.C., *Catal. Commun*. 5 (2004) 151.
30. Vohra R. K., Renaud J. L., Bruneau C., *Collect. Czech Chem. Commun*. 70 (2005) 1943.
31. Biswanath D., Venkateswarlu K., Majhi A., Reddy M.R., Reddy K.N., Rao Y.K., Ravikumar K., Sridhar B., *J .Mol. Catal A: Chem*. 246 (2006) 276.
32. Gogoi S., Bhuyan R., Barua N.C., *Synth. Commun*. 35 (2005) 2811.

33. Zhao Y., Zhao J., Zhou Y., Lei Z., Li L., Zhang H., *New. J. Chem*. 29 (2005) 769.
34. Lenin R., Raju R.M., *Arkivoc*. 8 (2007) 204.
35. Mo L. P., Liu F. S., Li W.Z., *J. Chin. Chem. Soc*. 54 (2007) 879.
36. Harrad M. A., Outtouch R., Ait Ali M., El Firdoussi L., Karim A., Roucoux A., *Catal. Commun*. 11 (2010) 442.
37. M. A. Harrad, B. Boualy, M. Ait Ali, L. El Firdoussi, R. Corrado, *Acta. Cryst*. E67 (2011) o1269.
38. M. A. Harrad, B. Boualy, A. Oudehmane, D. Avignant, *Acta. Cryst*. E67 (2011) o1818.
39. M. A. Harrad, B. Boualy, M. Ait Ali, L. El Firdoussi, H. Stoeckli-Evans. *Acta Cryst*. E68 (2012) o2855.
40. M. A. Harrad, B. Boualy, *J. Mater. Environ. Sci*. 4 (2013) 566.
41. M. A. Harrad, B. Boualy, M. Ait Ali, L. El Firdoussi., *American Journal of chem.* 2 (2012) 276.
42. M. A. Harrad, B. Boualy, I. Houssini, M. Ait Ali, M. Loughzail, *Chemistry and Materials Research* 6 (2014) 31.

(2014) ; http://www.jmaterenvironsci.com