Asian Journal of Chemistry; Vol. 30, No. 10 (2018), 2322-2324

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21480

Organocatalyzed Biomimetic Selective Reduction of C=C Double Bonds of Chalcones

VISHWA DEEPAK TRIPATHI[1,*] and ANAND MOHAN JHA[2]

[1]Department of Chemistry, M.K. College, Darbhanga-846 003, India
[2]Department of Chemistry, K.S.R. College, Sarairanjan, Samastipur-848 127, India

*Corresponding author: E-mail: vishwadeepak66@gmail.com

Received: 26 May 2018; *Accepted*: 13 June 2018; *Published online*: 31 August 2018; AJC-19066

In this article, we reported a biomimetic approach for chemoselective reduction of C=C double bonds in chalcones under metal and acid free conditions, that relies on olefin activation by hydrogen bond formation. The process requires only catalytic amount of ephedrine as hydrogen bond donor and utilizes Hantzsch esters for transfer hydrogenation.

Keywords: Biomimetic, Reduction, Hydrogenation, Hantzsch ester, Chalcones.

INTRODUCTION

Reduction of carbon-carbon double bonds in compounds such as carbonyls, imines, and olefins are of great importance in chemistry, biology and as well as from the industrial perspective. Reduction of double bond-containing such compounds and various other α,β-unsaturated systems *via* hydrogenation often involves the use of metal catalysts [1,2] or stoichiometric amount of metal hydrides [3,4]. Several metal free catalytic hydrogenations of olefins have also been reported in area of green catalysis [5-9]. The resulting products are important frameworks in medicinal chemistry and have direct applications to drug discovery process.

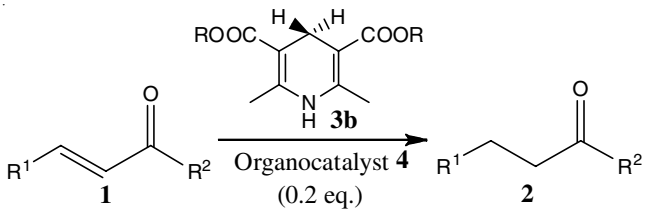
The reduction of carbon-carbon double bonds of α,β-unsaturated systems is very important synthetic transformation but this particular step is a tricky one because (a) both 1,2- and 1,4-reductions readily occur simultaneously (b) low selectivity for either of the two pathways and (c) functional groups which are sensitive to metal hydrogenation conditions such as ester, nitro and nitrile groups are usually not tolerated. Thus, it is of great importance to develop a mild, catalytic, one-pot, chemoselective and green methodology for this reaction.

Chalcones are well reported for their wide range of biological activities, including antimalarial [10], anticancer [11,12], antituberculosis [13], cardiovascular [14], antileishmanial [15], antimitotic [16], antihyperglycemic [17], nitric oxide inhibition [18,19], anti-inflammatory [20], tyrosinase inhibition [21] activities. They are one of the key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine [22], pyrazolines [23], 1,4-diketones [24] and flavones [25]. Selective hydrogenation of C=C bonds of α,β-unsaturated carbonyl compounds (chalcones) is an important organic transformation in the synthesis of many drugs molecules such as pioglitazone, rosiglitazone, troglitazone, *etc*.

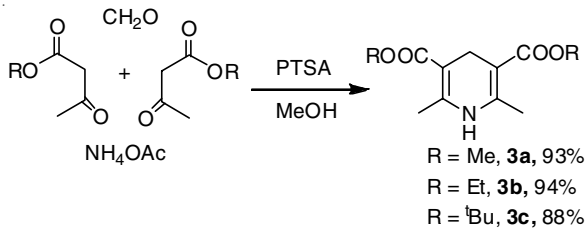
The natural product enzyme cofactors NAD(P) and NAD(P)H have been a stimulus for the investigation of use of Hantzsch ester as attractive biomimetic reducing agents [26-30]. Recently, an increasing interest has been focused over the application of Hantzsch esters as reducing agents [31-35]. The role of small organic molecules as catalyst in organic synthesis is one of the most attractive research area for chemists during last several years. The observation encouraged us to investigate an organocatalytic reduction of chalcones by catalytic amount of ephedrine as hydrogen bond donor. We reasoned that activation of chalcone **1** by H-bonding would enable hydrogen transfer from dihydropyrimidine (**3**) to generate a reduced chalcone **2** in a similar fashion reported by Menche *et al*. [36,37] in reductive amination (**Scheme-I**).

EXPERIMENTAL

Unless otherwise specified all the reagents were purchased from Sigma-Aldrich and were used without further any purification. The common organic solvents were used was of LR grade and purchased from Ranchem. Organic solutions were



Scheme-I: Ephedrine catalyzed transfer hydrogenation of α,β-unsaturated carbonyl compounds



Scheme-II: Synthesis of reducing agent

concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on 60-100 mesh silica gel. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or $KMnO_4$ staining. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX -300 Spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. Mass spectra (ESI MS) were obtained by Micromass Quattro II instrument.

Synthetic procedure for synthesis of Hantzsch esters: All the three derivatives were synthesized *via* well known multicomponent Hantzsch reaction. Alkyl acetoacetate, formaldehyde and ammonium acetate were mixed in ethanol in eqimolar ratio and stirred at room temperature in 50 mL ethanol for 4 h. White precipitate formed was filtered off and recrystallized in ethanol to get the pure product.

Synthetic procedure for reduction of C=C in chalcones: Chalcone derivative (1 mol eq.) and Hantzsch ester (1.1 mol eq.) was dissolved in 20 mL toluene and stirred at room temperature followed by slow addition of organocatalyst ephedrin (20 mol %). Resulting mixture was stirred at room temperature upto disappearance of chalcone spot on TLC. After completion solvent was removed in rotavapor and residue was purified using silica coloumn chromatography and ethyl acetate: hexane as mobile phase. Reduced chalcone isolated were further characterized by ^1H and ^{13}C NMR spectroscopy.

1,3-Diphenylpropan-1-one (1): Light yellow oil; ESI MS (*m/z*) = 211.26 [M+1]. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.94 (d, *J* = 8Hz, 2H), 7.62-7.55 (m, 3H), 7.40-7.27 (m, 5H), 2.88 (t, *J* = 8Hz, 2H), 2.71 (t, *J* = 8 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 200.1, 141.3, 140.2, 133.5, 128.8, 128.2, 127.9, 127.7, 126.4, 125.9, 43.9, 30.6.

RESULTS AND DISCUSSION

We synthesized Hantzsch esters **3** (reducing agent) *via* one-pot coupling of formaldehyde, acetoacetate ester and ammonium acetate in the presence of catalytic amount of *p*-toluene sulphonic acid (**Scheme-II**). Methyl, ethyl and *t*-butyl Hantzsch esters were prepared. Among the three Hantzsch esters synthesized, ethyl Hantzsch ester (**3b**) was found to be the best for transfer hydrogenation. Hence, further experiments were carried out using 3b as reducing agent.

Initial experiments focused on the examination of various organocatalysts for this transformation (Table-1). We used several organocatalyst (5-20 mol %) to catalyze the reduction of chalcone **1a**. In each instance, the reaction was carried out with 1.1 equivalents of Hantzsch esters **3b** in toluene for several hours. In the absence of organocatalyst, little hydrogen transfer was observed. Ephedrine was proved to be the best organocatalyst for this reaction showing the fastest reaction rate and best yields of saturated ketone (entry 6, Table-1). However, thiourea was also showing promising catalytic activity.

TABLE-1
ORGANOCATALYZED REDUCTION OF C=C BOND OF CHALCONE **1a**

Entry[a]	Organocatalyst (**4**)	**4** (mol %)	Time (h)	Yield (%)[b]
1	None	20	72	< 5
2	Pyrolidine (**4a**)	20	48	45
3	Morpholine (**4b**)	20	48	53
4	Cinconidine (**4c**)	20	48	58
5	Thiourea (**4d**)	20	36	84
6	Ephedrine (**4e**)	20	36	95
7	Ephedrine (**4e**)	10	36	87
8	Ephedrine (**4e**)	5	36	79

[a]Reaction conditions: All reactions were performed using chalcone **1a** (1 mmol), Hantzsch ester **3b** (1.1 mmol) in toluene at 60 °C using organocatalyst **4** under N_2 atomosphere.
[b]Isolated yield after column chromatography.

Further exploration of ephedrine and thiourea catalyzed transfer hydrogenation concentrated on the solvent employed (Table-2). Best results were obtained in non-polar solvents such as toluene, benzene at elevated temperature with ephedrine as organocatalyst. Performing the reaction at lower temperature (30 ºC instead of 60 ºC) resulted in lower yield and longer reaction time. Surprisingly in more polar media, the reaction was sluggish and yields were considerably diminished (entry 6 and 7, Table-3).

The general applicability of this procedure was also studied. Various sterically, electronically, and functionally diverse chalcones were reduced smoothly in excellent yields. Ethyl Hantzsch ester was taken as reducing agent and ephedrine as catalyst. Other reducible functional groups present in chalcones

TABLE-2
SOLVENT EFFECT ON ORGANOCATALYSED HYDROGENATION[a]

Entry	Solvent	Thiourea (**4d**)		Ephedrine (**4e**)	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	Toluene	36	85	36	95
2	Benzene	36	84	36	94
3	CH_2Cl_2	48	72	48	81
4	$CHCl_3$	48	71	48	82
5	MeCN	48	78	48	78
6	MeOH	48	65	48	65
7	EtOH	48	68	48	66

[a]Reaction conditions: All reactions were performed using chalcone **1a** (1 mmol), Hantzsch ester **3b** (1.1 mmol) using organocatalyst **4** under N_2 atomosphere.
[b]Isolated yield after column chromatography.

TABLE-3
BIOMIMETIC REDUCTION OF C=C DOUBLE BONDS OF CHALCONES[a]

Entry	R^1	R^2	Product	Time (h)	Yield (%)[b]
1	C_6H_5	C_6H_5	**2a**	48	95
2	C_6H_5	4-HO-C_6H_4	**2b**	48	94
3	C_6H_5	4-CH_3O-C_6H_4	**2c**	48	95
4	4-HO-C_6H_4	C_6H_5	**2d**	48	93
5	4-F-C_6H_4	4-NO_2-C_6H_4	**2e**	36	98
6	3-CH_3O-C_6H_4	C_6H_5	**2f**	48	96
7	4-Cl-C_6H_4	C_6H_5	**2g**	48	95
8	4-CH_3O-C_6H_4	3-CH_3O-C_6H_4	**2i**	48	94
9	2-NO_2-C_6H_4	C_6H_5	**2j**	36	94
10	3-NO_2-C_6H_4	C_6H_5	**2k**	48	96
11	4-NO_2-C_6H_4	C_6H_5	**2l**	36	95
12	1-Naphthyl	C_6H_5	**2m**	48	95
13	2-Thenyl	C_6H_5	**2n**	48	93
14	2-Furyl	C_6H_5	**2o**	48	95

[a]Reaction conditions: Chalcone (1 mmol), ethyl Hantzsch ester **3b** (1.1 mmol), ephedrine (0.2 mmol), toluene, 60 °C, N_2 atmosphere.
[b]Isolated yield after column chromatography.

(*e.g.* NO_2, CO, *etc.*) were not affected under reaction conditions. Thus this biomimetic reduction offers selective reduction of C=C of chalcones.

In summary, a new acid and metal free efficient organocatalytic, biomimetic and selective hydrogenation of C=C bonds of chalcones using Hantzsch esters as reducing agent is developed. The C=C bond is selectively reduced in excellent yields without affecting the other reducible functional groups present in chalcones. The operational simplicity, practicability and mild reaction conditions render it an attractive approach to saturated chalcones.

ACKNOWLEDGEMENTS

One of the authors, Vishwa Deepak Tripathi is thankful to CSIR-New Delhi for financial support in the form of a Junior Research Fellowship.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M.A. Esteruelas and L.A. Oro, *Chem. Rev.*, **98**, 577 (1998); https://doi.org/10.1021/cr970322u.
2. G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.*, **92**, 1051 (1992); https://doi.org/10.1021/cr00013a015.
3. B.C. Ranu and S. Samanta, *Tetrahedron*, **59**, 7901 (2003); https://doi.org/10.1016/j.tet.2003.08.022.
4. T. Suwa, E. Sugiyama, I. Shibata and A. Baba, *Synlett*, 556 (2000); https://doi.org/10.1055/s-2000-6585.
5. D.B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, **47**, 651 (2006); https://doi.org/10.1016/j.tetlet.2005.11.128.
6. H. Adolfsson, *Angew. Chem. Int. Ed.*, **44**, 3340 (2005); https://doi.org/10.1002/anie.200500827.
7. J.W. Yang, M.T. Hechavarria Fonseca, N. Vignola and B. List, *Angew. Chem. Int. Ed.*, **44**, 108 (2005); https://doi.org/10.1002/anie.200462432.
8. S.G. Ouellet, J.B. Tuttle and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **127**, 32 (2005); https://doi.org/10.1021/ja043834g.
9. S.J. Garden, C.R.W. Guimarães, M.B. Corréa, C.A.F. Oliveira, A.C. Pinto and R. Bicca de Alencastro, *J. Org. Chem.*, **68**, 8815 (2003); https://doi.org/10.1021/jo034921e.
10. M. Liu, P. Wilairat and M.-L. Go, *J. Med. Chem.*, **44**, 4443 (2001); https://doi.org/10.1021/jm0101747.
11. M.L. Edwards, D.M. Stemerick and P.S. Sunkara, *J. Med. Chem.*, **33**, 1948 (1990); https://doi.org/10.1021/jm00169a021.
12. F. Bois, C. Beney, A. Boumendjel, A.M. Mariotte, G. Conseil and A. Di Pietro, *J. Med. Chem.*, **41**, 4161 (1998); https://doi.org/10.1021/jm9810194.
13. Y.-M. Lin, Y. Zhou, M.T. Flavin, L.-M. Zhou, W. Nie and F.-C. Chen, *Bioorg. Med. Chem.*, **10**, 2795 (2002); https://doi.org/10.1016/S0968-0896(02)00094-9.
14. C. Furman, J. Lebeau, J.-C. Fruchart, J.-L. Bernier, P. Duriez, N. Cotelle and E. Teissier, *Biochem. Mol. Toxicol.*, **15**, 270 (2001); https://doi.org/10.1002/jbt.10003.
15. S.F. Nielsen, S.B. Christensen, G. Cruciani, A. Kharazmi and T. Liljefors, *J. Med. Chem.*, **41**, 4819 (1998); https://doi.org/10.1021/jm980410m.
16. S. Ducki, R. Forrest, J.A. Hadfield, A. Kendall, N.J. Lawrence, A.T. McGown and D. Rennison, *Bioorg. Med. Chem. Lett.*, **8**, 1051 (1998); https://doi.org/10.1016/S0960-894X(98)00162-0.
17. M. Satyanarayana, P. Tiwari, B.K. Tripathi, A.K. Srivastava and R. Pratap, *Bioorg. Med. Chem.*, **12**, 883 (2004); https://doi.org/10.1016/j.bmc.2003.12.026.
18. F. Herencia, M.L. Ferrandiz, A. Ubeda, I. Guillen, J.N. Dominguez, J.E. Charris, G.M. Lobo and M.J. Alcaraz, *Free Radic. Biol. Med.*, **30**, 43 (2001); https://doi.org/10.1016/S0891-5849(00)00443-3.
19. J. Rojas, M. Paya, J.N. Dominguez and M. Luisa Ferrandiz, *Bioorg. Med. Chem. Lett.*, **12**, 1951 (2002); https://doi.org/10.1016/S0960-894X(02)00317-7.
20. F. Herencia, M.L. Ferrándiz, A. Ubeda, J.N. Domínguez, J.E. Charris, G.M. Lobo and M.J. Alcaraz, *Bioorg. Med. Chem. Lett.*, **8**, 1169 (1998); https://doi.org/10.1016/S0960-894X(98)00179-6.
21. E.B. Yang, Y.J. Guo, K. Zhang, Y.Z. Chen and P. Mack, *Biochim. Biophys. Acta*, **1550**, 144 (2001); https://doi.org/10.1016/S0167-4838(01)00276-X.
22. O. Prakash, A. Kumar, A. Sadana, R. Prakash, S.P. Singh, R.M. Claramunt, D. Sanz, I. Alkorta and J. Elguero, *Tetrahedron*, **61**, 6642 (2005); https://doi.org/10.1016/j.tet.2005.03.035.
23. Y. Rajendra Prasad, A. Lakshmana Rao, L. Prasoona, K. Murali and P. Ravi Kumar, *Bioorg. Med. Chem. Lett.*, **15**, 5030 (2005); https://doi.org/10.1016/j.bmcl.2005.08.040.
24. S. Raghavan and K. Anuradha, *Tetrahedron Lett.*, **43**, 5181 (2002); https://doi.org/10.1016/S0040-4039(02)00972-3.
25. B.A. Bohm, Introduction to Flavonoids, Harwood Academic: Amsterdam (1998).
26. S. Ranganathan and J.E. Gready, *J. Phys. Chem. B*, **101**, 5614 (1997); https://doi.org/10.1021/jp971051u.
27. D. Ross, D. Siegel, H. Beall, A.S. Prakash, R.T. Mulcahy and N.W. Gibson, *Cancer Metastasis Rev.*, **12**, 83 (1993); https://doi.org/10.1007/BF00689803.
28. T. Wymore, H.B. Nicholas and J. Hempel, *J. Chem. Biol. Interact.*, **130-132**, 201 (2001); https://doi.org/10.1016/S0009-2797(00)00278-7.
29. M.A. Cunningham, L.L. Ho, D.T. Nguyen, R.E. Gillilan and P.A. Bash, *Biochemistry*, **36**, 4800 (1997); https://doi.org/10.1021/bi962734n.
30. Y. Murakami, J.-I. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, **96**, 721 (1996); https://doi.org/10.1021/cr9403704.
31. N.J.A. Martin and B.J. List, *J. Am. Chem. Soc.*, **128**, 13368 (2006); https://doi.org/10.1021/ja065708d.
32. J.W. Yang and B. List, *Org. Lett.*, **8**, 5653 (2006); https://doi.org/10.1021/ol0624373.
33. S.-L. You, *Chem. Asian J.*, **2**, 820 (2007); https://doi.org/10.1002/asia.200700081.
34. J.W. Yang, M.T. Hechavarria Fonseca and B. List, *Angew. Chem. Int. Ed.*, **43**, 6660 (2004); https://doi.org/10.1002/anie.200461816.
35. J.B. Tuttle, S.G. Ouellet and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **128**, 12662 (2006); https://doi.org/10.1021/ja0653066.
36. D. Menche and F. Arikan, *Synlett*, **2006**, 841 (2006); https://doi.org/10.1055/s-2006-939052.
37. D. Menche, J. Hassfeld, J. Li, G. Menche, A. Ritter and S. Rudolph, *Org. Lett.*, **8**, 741 (2006); https://doi.org/10.1021/ol053001a.