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Enantioselective Synthesis of Modafinil Drug using Chiral Complex of Titanium and Diethyltartarate

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Abstract

Modafinil (Diphenyl methyl Sulfinyl acetamid) is used clinically in the treatment of narcolepsy and sleeping disorders. The synthesis of R-modafinil, have started with the reaction of benzhydrol and thioglycolic acid in trifluoroacetic acid to afford benzhydryl sulfanyl acetic acid. The reaction of acid with thionyl chloride in benzene followed by treatment with ammonium hydroxide gave acetamide. The process occurs at room temperature in toluene as a solvent and in the presence of a bidendate diethyltartarate–titanium isopropoxide complex as chiral catalyst. The reaction using this catalyst exhibits very good yield and appropriate enantioselectivity. The obtained products were characterized with FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectral. The ee of the obtained sulphoxide has been determined by high performance liquid chromatography (HPLC).

Keywords**:** *Diphenyl methyl sulfinyl acetamid, Modafinil drug, Diethyltartarate ligands.*

Introduction

Enantiopure sulfoxides are important auxiliaries in asymmetric synthesis and chiral ligands in enantioselective catalysis [1–4]. Several methods can be find in literature for preparation of the enantiopure sulfoxides. The preparation of enantiopure sulfoxides achieved, mainly via asymmetric oxidation of the corresponding thioether. The most popular method to date was discovered independently by Kagan [5,6] and Modena [7] using a modified Sharpless catalytic system. Andersen was the first to describe a general method using a chiral sulfinate intermediate.[8,9] After this success, many catalytic and enantioselective methods were also described in which were competible with the Sharpless/Kagan system [2]. Among these systems, a catalytic organometallic complex of a vanadium-chiral Schiff base using hydrogen peroxide as a terminal oxidant

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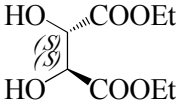
was developed by Bolm [10,11]. This method was later improved by Anson using the Schiff base to give higher enantioselectivities [12]. Bolm also developed a method involving iron and the Schiff base [13,14]. Salen–manganese complexes, can also be used for the enantioselective oxidation of thioethers [15]. In 2005, Cephalon patented the preparation of (R)-modafinil from the corresponding thioether using a Kagan system, with a good yield and excellent enantioselectivity [16]. However, this method gave disappointing results on the related compounds, modafinic acid and diphenyl methyl thioacetamide.

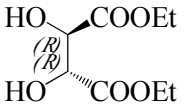
In this paper, we reported a enantioselective oxidation reaction of sulfide,2-(benzhydrylthio) acetamide, with various peroxide using bidendate diethyltartarate-Ti(IV)isopropoxide complex as chiral catalyst, that can be readily assembled from commercially available a simple and efficient method has been reported. We applied titaniume complex of the bidendate diethyltartarate (Fig 1) as catalyst for enantioselective synthesis of R-modafinil.

At the first, a new derivative of chiral ligands **1, 2** (containing hydroxyl group) in one step from a cheap and readily available substrate (L/D-Tartaric acid) were synthesized in good yield (Fig 2) [17-25]. Then, this chiral ligand immobilized on titanium isopropoxide through its hydroxyl group, in optimized reaction condition [26-29]. The obtained new complex was used in oxidation of 2-(benzhydrylthio) acetamide. These reactions exhibits very good yield and enantioselectivity. The synthesis of R-modafinil, started with the reaction of benzhydrol and thioglycolic acid in trifluoroacetic acid to afford benzhydryl sulfanyl acetic acid. The reaction of acid with thionyl chloride in benzene followed by treatment with ammonium hydroxide gave acetamide. Then, bidendate diethyltartarate was examined using 10 mol% Lewis acid as catalyst in a typical reaction of oxidation 2-(benzhydrylthio) acetamide with oxidants in various solvent (Scheme 1). Results are summarized in Table 1.



1

(2*S*,3*S*)-diethyl 2,3-dihydroxysuccinate



2

(2*R*,3*R*)-diethyl 2,3-dihydroxysuccinate

Figure 1.chiral diethyltartarate ligands **1** and **2.**

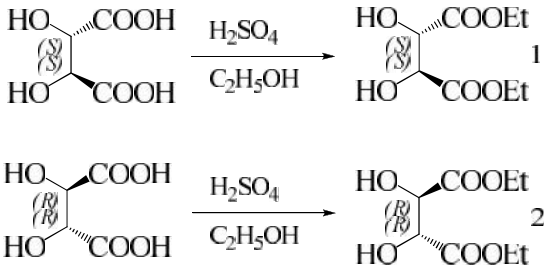
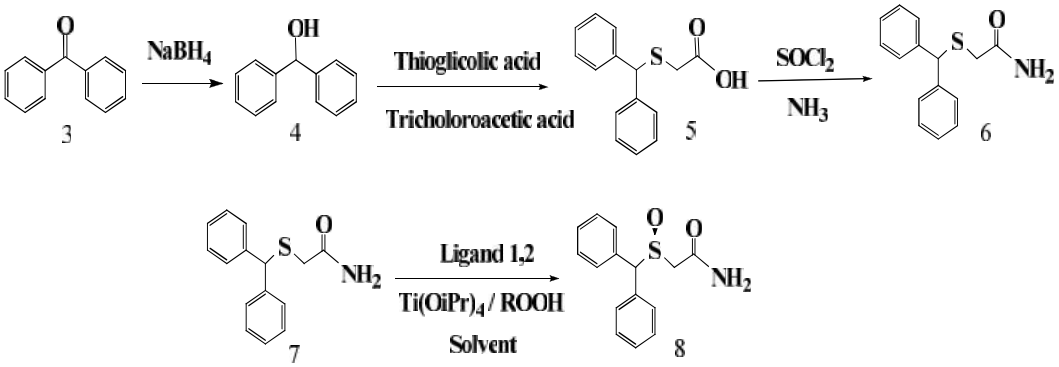


Figure 2.synthesis of chiral diethyltartarate ligands **1** and **2.**



Scheme 1. Asymmetric synthesis of modafinil.

Result and discussion

The highest enantioselectivity (80%) and high yield was achieved by employing toluene as solvent (Table 1, by comparison of entries 1-10). Considering the toluene as the best solvent, we tested the effect of temperature. The yields and enantiomeric excess of the products showed the temperature dependence in this process. A decrease in the reaction temperature from 25 ^{o}C to 0 ^{o}C and -25^{o}C decreased the reaction yield and enantioselectivity (entries 7-10) and increase in the reaction temperature from 25 ^{o}C to 55 ^{o}C decreased the time of reaction and increased yield and enantioselectivity (entries 9 and 10).

Table 1. Asymmetric synthesis of modafinil with various solvent.

Entry	Solvent	T (°C)	Time(h)	**8**[a]	
				Yield (%)[b]	ee(%)[c]
1	CH_2Cl_2	0	24	55	23
2	CH_2Cl_2	25	24	62	25
3	CH_2Cl_2	55	24	65	33
4	$CHCl_3$	25	24	61	17
5	EtOAc	25	48	38	race
6	EtOAc	55	48	45	race
7	$PhCH_3$	-25	48	45	race
8	$PhCH_3$	0	48	53	37
9	$PhCH_3$	25	48	60	68
10	$PhCH_3$	55	24	72	80

[a]reaction was carried out in 10ml of solvent in the presence of 10% catalyst $Ti(OiPr)_4$ unless otherwise noted
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.

Considering the toluene as the best solvent and the 55oC as the best temprature, we tested the effect of oxidants and ligands (Table 2). In all cases, the ligand **1** proved to be the best ligand source with ee to 80% (entry 1) whiles other entries led to a decrease in the ee from 17 to 68% and increase in yield by 68–85%. Changing oxidant using of cumenehydroperoxide and tert-butyl hydroperoxide instead of hydrogen peroxide gave the better enantioselectivity. The effects of catalyst loading were also investigated and the best results were obtained when 10 mol % catalyst loading was used in the reaction. The ligand-to-metal ratio of 1:1 using 20 mol % of ligand was investigated under the similar conditions and the isolated yields and enantioselectivity led to decrease in the results (entry 7 and 8). Lowering the catalyst loading to less than 10 mol % led to a sharp decrease in the results. It should be noted, the addition of additives such as MS 4A, 3A did not give any observable changes in the results of the reaction and even lead to decreasing yields.

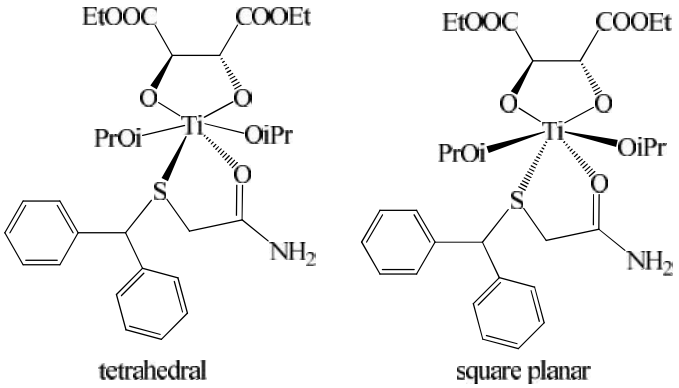
Table 2. Asymmetric synthesis of of R-modafinil **8.**

Entry	Ligand	Oxidant	%Yield	Ee%[a]
1	1	Cumenehydroperoxide	72	80
2	1	tert-Butyl hydroperoxide	75	68
3	1	Hydrogen peroxide	85	37
4	2	Cumenehydroperoxide	68	46
5	2	tert-Butyl hydroperoxide	73	30
6	2	Hydrogen peroxide	78	31
7	1	Cumenehydroperoxide	56	17[b]
8	2	Cumenehydroperoxide	66	19[b]

[a]Determined by chiral HPLC analysis
[b]20% catalyst is used

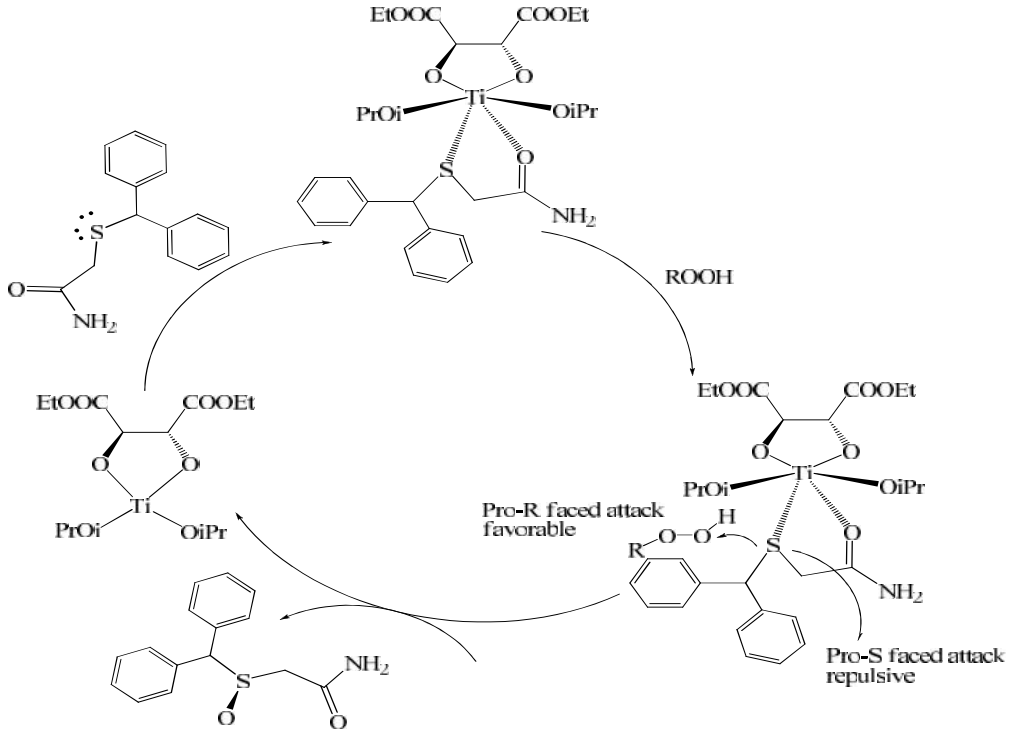
The structures of adducts were characterized on the basis of spectroscopic data. Thus, the IR spectrum of *R*-modafinil 8 showed two absorption at 1676 cm-1 and 1373 cm-1 indicating the presence of carbonyl group and sulfoxide group respectively. The ^{1}HNMR spectrum of modafinil exhibits two doublet of double signal at δ = 3.2 ppm and a doublet at δ = 3.3 ppm with $^{3}J_{HH}$ of about 13Hz which are related to H band Ha protons diastreotopics and confirmed unambiguously the formation of a chiral sulfoxide group. The off resonance decoupled ^{13}C NMR spectra of 8 exhibited characteristic peaks for the carbonyl group and methylene group attached to the sulfoxide at 166.6 and 56.2 ppm respectively. The formation of the product was confirmed by mass spectral. In the mass spectrum modafinil be seen the message ion molecule in m/z 273 and the message base peak on the m/z 167 for ion diphenyl methylene and m/z 152 for ion molecular.

The sense of asymmetric induction for the reported reactions is stereo-regular over the range of substrates examined in this study. By inspection, it is evident that the stereo chemical course of the reaction is dictated by the geometry of the catalyst-2-(benzhydrylthio)acetamide complex at the metal center where the square planar and tetrahedral complexes shield opposite faces of the 2-(benzhydrylthio)acetamide (Scheme 2). The sense of asymmetric induction in these reactions can be rationalized by assuming that the reaction proceeds via the intermediacy of the non-reasonable square-planar rather than tetrahedral catalyst-2-(benzhydrylthio) acetamide complex (Scheme 2).



Scheme 2. Transition state square planar and transition state tetrahedral.

The following reaction mechanism and transition state for the reactions are proposed (Scheme 3). The reactions of proxides with 2-(benzhydrylthio)acetamide are controlled, in order to obtain an increased reaction rate, **1,2**-Ti(Oipr)$_4$ coordinates to the 2-(benzhydrylthio)acetamide to form square planar geometry. Despite the fact that two different enantiomers could be obtained theoretically, further enantiomer of *R*-modafinil was formed in high yield in all the cases that studied here. On the basis of the absolute structure of the one chiral centers in the *R*-modafinil, it is determined that the peroxide attack to the Pro-R face of the 2-(benzhydrylthio)acetamide when coordinated to the bidendate complex. Based on the stereochemistry of the oxidation, the transition state and the reaction pathway were proposed as below:



Scheme 3.A suggested reaction pathway for the enantioselective synthesis of modafinil.

Conclusion

In conclusion, we applied complex of titanium isopropoxide with bidendate diethyltartarate as chiral catalyst for asymmetric synthesis of R-modafinil. We reported a enantioselective oxidation reaction of sulfide, 2-(benzhydrylthio)acetic acid, with peroxides using bidendate diethyltartarate-titanium isopropoxide complex for asymmetric synthesis of R-modafinil. This catalyst can be readily prepared from commercially available, simple and efficient starting material (diethyltartarate). The structures of the products were elucidated using IR, ^{1}H NMR, ^{13}CNMR, and mass spectral data.

Acknowledgment

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References

[1] H. Pellissier, *Tetrahedron*, 62, 5559 (2006).

[2] C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu and Z. Han, *Aldrichim. Acta*, 38, 93(2005).

[3] M. C. Carren O, *Chem. Rev*., 95, 1717 (1995).

[4] I. Fernandez and N. Khiar, *Chem. Rev*., 103, 3651(2003).

[5] P. Pitchen and H. B. Kagan, *Tetrahedron Lett.*, 25, 1049 (1984).

[6] P. Pitchen, E. Dunach, M. N. Deshmukh and H. B Kagan, *J. Am. Chem. Soc.*, 106, 8188 (1984).

[7] F. D. Furia, G. Modena and R. Seraglia, *Synthesis*, 325 (1984).

[8] K. K. Andersen, *Tetrahedron Lett*., 18, 93 (1962).

[9] K. K. Andersen, W. Gaffield, N. I. Papanikolaou, J. W. Foley, R. I. Perkins, *J. Am. Chem. Soc.*, 86, 5637 (1964).

[10] C. Bolmand F. Bienewald, *Angew. Chem., Int. Ed. Engl*., 34, 2640 (1995).

[11] C. Bolm, G. Schlingloffand F. Bienewald, *J. Mol. Catal. A: Chem.,* 117, 347 (1997).

[12] B. Pe´lotier, M. S. Anson, I. B. Campbell, S. J. F. MacDonald, G. Priem and R. F. W. Jackson, *Synlett*, 1055 (2002).

[13] J. Legros, C. Bolm, *Angew. Chem., Int. Ed*., 42, 5487 (2003).

[14] J. Legros, C. Bolm, *Chem. Eur. J.,* 11, 1086 (2005).

[15] M. Palucki, P. Hanson and E. N. Jacobsen, *Tetrahedron Lett*., 33, 7111 (1992).

[16] I. Cephalon, *EU. Patent*, 516, 869 (2005).

[17] M. H. Fonseca, B. König, *Adv. Synth. Catal.,* 345, 1173 (2003).

[18] E. Uhlemann, M. Z. Plath, *Chem*., 9, 234 (1969).

[19] H. Mimoun, J. Y. d. S. Laumer, L. Giannini, R.Scopelliti, C.Floriani, *J. Am.Chem. Soc,,* 727, 6158 (1999).

[20] X.Wang, K. Ding, *Chem. Eur. J.,* 12, 4568 (2006).

[21] G. Malaise, L.Barloy, J. A.Osborn, *Tetrahedron Lett*., 42, 7417 (2001).

[22] G. Malaise,J.B.Sortais, L. Barloy, M. Pfeffer,N.Kyritsakas, *Polyhedron*, 25, 3349 (2006).

[23] A. S. Abu-Surrah,M. Kettunen, K. Lappalainen,U. Piironen, M. Klinga,M. Leskela, *Polyhedron*, 27, 27 (2002).

[24] H. Brunner,G. Riepl, Angew. *Chem. Int. Ed. Engl*., 21, 377 (1982).

[25] V. Rodeschini,N. S. Simpkins,F. Zhang, *Org. Synth*., 84, 306 (2007).

[26] Q. Huo, D. I. Margolese, U. Ciesla, P. Feng, T. E. Gier, P. Sieger, R. Leon, P. M. Petroff, F. Schüth, G. D. Stucky, *Nature*, 368, 317 (1994).

[27] P. T. Tanev and T. Pinnavaia, *J. Science,* 267, 865 (1995).

[28] Z. Yang, Y. Lu and Z. Yang, *Chem. Commun*., 2270 (2009).

[29] R. I. Kureshy, I. Ahmad, N. H. Khan, S. H. R. Abdi, K. Pathak and R. V. Jasra, *J. Catal.,* 238, 134 (2006).