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An efficient, commercially viable process for preparation of Armodafinil, a Psychostimulant drug

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ABSTRACT

Synthesis of Armodafinil, a psychostimulant drug using diphenylmethanol as a starting material is described. In this route, the major by-product (S)-modafinic acid in the resolution step was recycled by converting it into diphenylmethyl chloride using a novel methodology which has increased the overall yield of the synthetic route and becoming highly suitable process for the large scale production of Armodafinil are the key features.

Keywords: *Armodafinil, (S)-Modafinic acid, (R)-Modafinic acid, Ppsychostimulant drug, Diphenylmethylchloride, Synthesis.*

INTRODUCTION

Narcolepsy is a chronic disorder, characterized by excessive daytime sleepiness, and is estimated to affect as many as three million people worldwide [1]. The excessive drowsiness associated with the disabling neurological disorder often interferes with normal daytime activities, and may cause a significant safety risk [2]. It has been found that Armodafinil (**1**) is one of effective drugs in the treatment of sleep disorders associated with narcolepsy [3, 4].

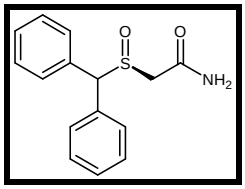

Fig. 1: Armodafinil (1)

The combination of potent biological activity and a relatively straight forward molecular structure of **1** have been fascinated many researchers to articulate its synthesis. In the previous approaches of synthesizing **1,** a diverse range of synthetic approaches, such as resolution [5], oxidation of prochiral sulfoxides [6-9], and catalytic systems [10], have been extensively explored. Among the methods that have been developed, they suffer with low yields, low enantioselectivities, oxidation products and use of the metal complexes. After comprehensive literature search, we came to a conclusion that recovery and recycling of the (*S*)-modafinic acid (**2**), a by-product in the resolution step which have been discarding as it cannot be subjected to racemization, could be the best strategy for the synthesis of **1**.

MATERIALS AND METHODS

All the raw materials were procured from merck laboratories and reagents and solvents were used without further purification.

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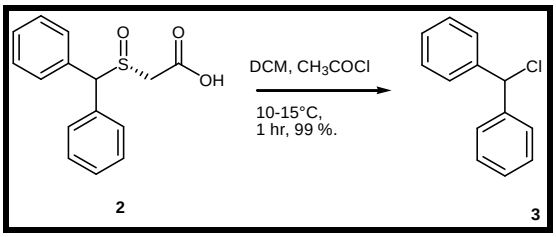
RESULTS AND DISCUSSION

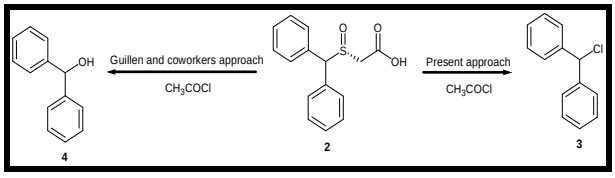
As a starting point in the present investigation, we have developed a new methodology for the recycling process of (*S*)-modafinic acid (**2**), in which **2** was converted into diphenylmethylchloride (**3**) by treating with halogenating agent as shown in Scheme 1.

Scheme 1. Preparation of diphenylmethyl chloride (3)



During the course of our investigation of the present methodology, we found that Guillen and coworkers [11] reported the formation of diphenylmethanol (**4**) from **2** using halogenating agents, due to the labile diphenylmethyl group and based on this point they have carried out their research investigation. But we have not observed the formation of **4** and confirmed the formation of **3** by ^{1}H NMR, IR, GC and GC-MS analysis. The new findings and previous results were schematically summarized in Scheme 2.

Scheme 2. Schematic representation of Guillen *et al.,* and the present approach



The conversion of **2** to **3** was studied by using a range of acid halides and some other halogenating agents (Table 1). In this screening process, we found that the reactions using acetyl chloride and acetyl bromide resulted good yields and purities.

Table 1. Optimization of halogenating agents for the conversion of 2 to 3.

Entry	Halogenating agents	Product (%)
1	CH_3COCl	99.3
2[a]	CH_3COBr	99
3	CH_3CH_2COCl	70.9
4	$CH_3CH_2CH_2COCl$	75.9
5	$CH_3CH_2CH_2CH_2COCl$	70
6	CH_3SO_2Cl	-
7	C_2H_5OH. HCl	48.6
8	CH_3COOH	-
9	$SOCl_2$	99.2

[a] here product is diphenylmethyl bromide

Through the solvent optimization process, as shown in Table 2, dichloromethane was proved to be relatively efficient for the conversion of **2** to **3**.

Table 2. Optimization of solvents for the conversion of 2 to 3.

Entry	Solvent	Product (%)
1	Acetic acid	82
2	N,N-Dimethylformamide	64.2
3	Dichloromethane	99.3

The effects of mole ratio of acetyl chloride and temperature on the reaction were also studied (Table 3). At the higher temperatures, formation of diphenyl methyl thiol and its dimer were observed. The best conversion of the reaction was happened at 10-15 °C using three mole equivalent of acetyl chloride.

Table 3. Optimization of mole ratio of acid chloride and temperature

Entry	Mole ratio of AcCl	Temperature (°C)	Time (h)	Product (%)
1	1.0	10-15	3	82
2	1.5	10-15	2	80
3	1.75	25-30	1.5	86
4	2.2	25-30	1.5	91.3
5	3	10-15	1	99.3
6	2	25-30	2	81
7	2	10-15	3	82
8	2.2	10-15	2.5	92.7

Having obtained the optimal reaction conditions, we explored the scope and generality of the reaction on a variety number of substrates as shown in Table 4.

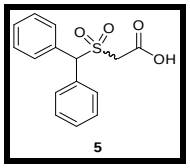


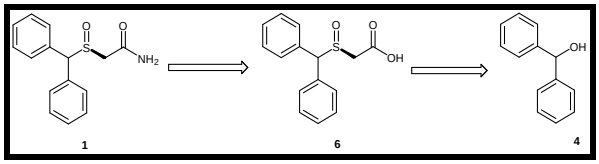
Fig. 2: 2-[(Diphenylmethyl)sulfonyl]acetic acid (5)

Table 4. Effect of methodology on different sulfinyl derivatives.

Entry	Compound	Product (%)
1	1	92.5
2	2	99.3
3	5	80
4	8	-
5	11	35.3

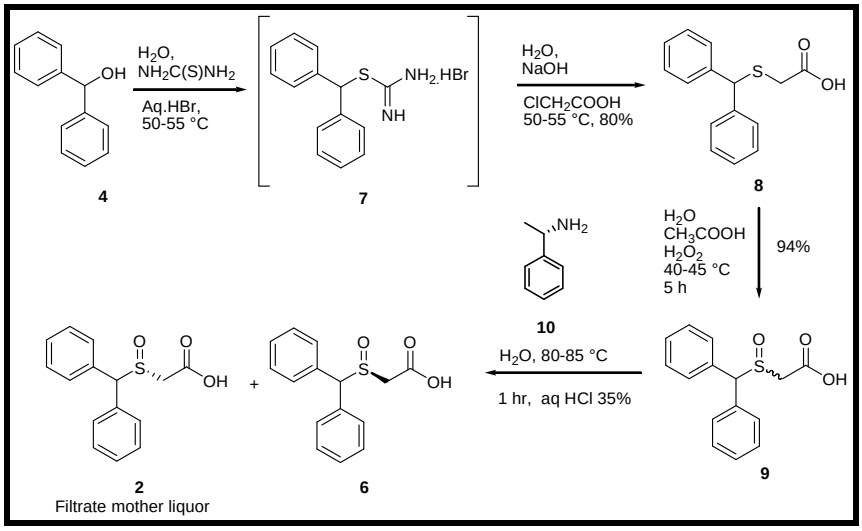
Coming to the synthetic part of **1**, our retrosynthetic approach was shown in Scheme 3, we envisaged that the target molecule **1** can be achieved from armodafinic acid (**8**) and **8** inturn could be achieved from Diphenylmethanol (**4**).

Scheme 3. Retrosynthetic approach: Present work



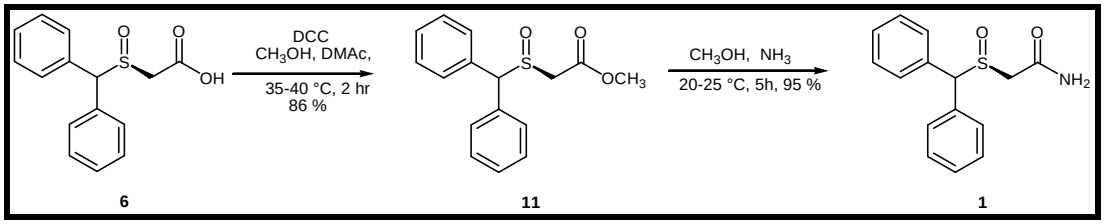
The synthesis was commenced by taking Diphenylmethanol (**4**) as the starting material. **4** on reaction with Aq. HBr, thiourea resulted (diphenylmethyl) thiouronium hydrobromide salt (**7**) and subsequently, **7** on treating with NaOH, chloroacetic acid obtained 2-[(diphenylmethyl) thio] acetic acid (**8**), which on oxidation gives racemic 2-[(diphenylmethyl) sulfinyl] acetic acid (**9**). This in-turn on resolution with (*S*)-(+)-methyl benzylamine (**10**) gives the 2-(*R*)-(-)-[(diphenylmethyl) sulfinyl] acetic acid (**6**) as precipitated solid and **2** (Scheme 4) remains in the filtrate mother liquor, which was used further for the recovery and recycle process to achieve **1**.

Scheme 4. Preparation of 2-(*R*)-(-)-[(diphenylmethyl) sulfinyl] acetic acid (6)



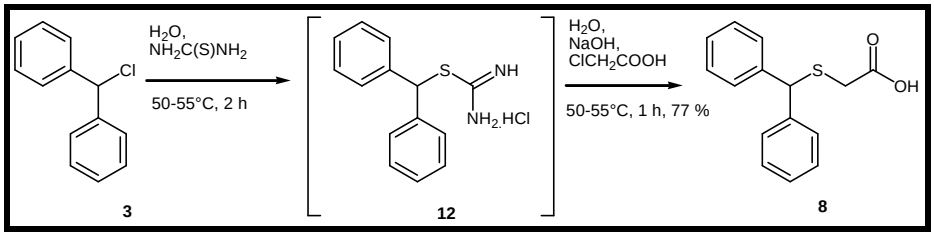
Esterification of **6** with methanol using coupling agent DCC (Dicyclohexylcarbodiimide) produced methyl (*R*)-(-)-diphenylmethyl sulfinyl acetate (**11**). This on ammonolysis with methanolic ammonia yields **1** with overall yield of 40% (Scheme 5).

Scheme 5. Preparation of Armodafinil (1)



After completing the total synthesis of **1**, coming to the recovery part of **2**, the developed methodology was employed successfully and achieved **3** as shown in Scheme 1. Thiourea was added to **3** gives diphenylmethyl thiouronium hydrochloride salt (**12**). At this stage we observed one important note *i.e.* the formation of **12** is not happening from **4** by using aq. HCl and thiourea.

Scheme 6. Preparation of 2-[(diphenylmethyl) thio] acetic acid (8) from diphenylmethyl chloride (3)



12 on reaction with NaOH, chloroacetic acid in water gives the key intermediate 2-[(diphenylmethyl) thio] acetic acid (**8**). Again **8** was on oxidation, resolution, esterification and ammonolysis produced **1**, meeting all the regulatory requirements, with excellent quality, as shown in Scheme 4 and Scheme 5.

In summary, we have developed an efficient, commercially viable process has been developed for synthesis of Armodafinil with an overall yield of 60% and ~99.6% purity. This route also including a novel methodology for conversion of diphenylmethyl sulfinyl derivatives into diphenylmethyl chloride and use of this method in large scale synthesis of Armodafinil by recycling the major by-product (*S*)-modafinic acid in the resolution step by converting it into diphenylmethyl chloride.

EXPERIMENTAL SECTION

^{1}**H** NMR, ^{13}C NMR and DEPT spectral data were performed in dimethyl sulfoxide (DMSO-d_6) at 300 MHz spectrometer. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethyl silane (TMS, δ = 0.0) as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet) as well as brs (broad). Coupling constants (*J*) are given in hertz. IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer spectrum one Fourier trans form (FT)-IR spectrophotometer. Mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector. HPLC Chromatographic purity was determined by using area normalization (AN) method. The solvents and reagents were used without purification.

2-[(diphenylmethyl) thio] acetic acid (**8**):

Added acetyl chloride (86 kg, 1.10 kmol) to the cooled suspension of (S)-2-[(diphenylmethyl)sulfinyl] acetic acid (**2**) (100 kg, 0.36 kmol) in dichloromethane (500 L) at 10-15 ˚C over a period of 30 min and stirred about 3 h. To the resulting solution, added aqueous solution of thiourea (30.5 kg, 0.40 kmol in 70 L of water) at 0-15 ˚C raised the temperature till the reaction mass temperature reached to 58-62 ˚C and continued the stirring for 2 h. The resulting diphenylmethyl isothiouranium hydrochloride salt (**13**) was filtered and washed with water. The wet material (~116.7 kg; M.C.18.25%) was suspended in water (800 L) and heated to 58-62 ˚C. A solution of sodium hydroxide (58.3 kg, 0.68 kmol in 150 L of water) was added followed by an aqueous solution of chloroacetic acid (36.2 kg, 0.38 kmol in 100 L of water) at 58-62 ˚C. The reaction mixture was stirred for 1 h and was cooled to 40-45 ˚C, adjusted the pH to 1.5-2.0 with aqueous hydrochloric acid. The resulting precipitate was filtered, purified in toluene (200 L) to afford 2-[(diphenylmethyl) thio] acetic acid (**8**). Yield: 73.1 kg. (77%). HPLC purity: 99.90% (AN). ^{1}H NMR (DMSO, 300MHz, δ ppm): 12.85 (bs, 1H), 7.45-7.23 (m, 10H), 5.41 (s, 1H), 3.09 (s, 2H); ^{13}C NMR (DMSO, 300MHz, δ ppm): 170.9, 140.8, 128.6, 128, 127.3, 53, 33.7.

2-[(diphenylmethyl) sulfinyl] acetic acid (**9**):

50% aqueous hydrogen peroxide (22 L) was added to the solution of **8** (70 kg, 0.27 kmol) in a mixture of acetic acid and water. Contents were heated to 40-45 ˚C and stirred for 5 h. The resulting solution was cooled to 30-35 ˚C and quenched with 3% w/w aqueous solution of sodium metabisulfite (10.3 kg, 0.1 kmol in 100 L of water) at 30-35 ˚C. Cyclohexane (140 L) and water (600 L) were added to the resulting slurry and the suspension was stirred for 30 min to afford the racemic 2-[(diphenylmethyl) sulfinyl] acetic acid (**9**). Yield: 70.2 kg. (92%). HPLC purity: 99.8% (AN).

^{1}H NMR (DMSO, 300MHz, δ ppm): 13.20 (bs, 1H), 7.34 – 7.52 (m, 10H), 5.40 (s, 1H), 3.56 (d, *J* = 14 Hz , 1H), 3.32 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (DMSO, 300MHz, δ ppm): 167.3, 136.6, 134.8, 129.6, 129, 128.6, 128.5, 128.1, 128, 69.3, 55.4.

2-[(R)-(diphenylmethyl) sulfinyl] acetic acid (**6**):

The mixture of 2-[(diphenylmethyl) sulfinyl] acetic acid (**9**) (70 kg, 0.25 kmol) and (S)-(-)-methyl benzyl amine (**10**)(34 kg, 0.28 kmol) in water (840 L) was heated to 80-85 ˚C and stirred for 30 min. Temperature of reaction mass was brought to 35-40 ˚C and stirred for 1 hr. The precipitated solid was filtered and purified in water (500 L). Again precipitated solid was filtered and suspended in water, adjusted the pH to 1.5- 2.0 with aqueous hydrochloric acid to afford 2-[(R)-(diphenylmethyl) sulfinyl] acetic acid (**6**). Yield 24.5 kg (70% based on optical purity) HPLC purity: 99.85% (AN); Chiral HPLC purity: 99.9% (AN), (S)- isomer : 0.1 (AN). ^{1}H NMR (DMSO, 300MHz, δ ppm): 7.54 – 7.32 (m, 10H), 5.42 (s, 1H), 3.59 (d, *J* = 14.5 Hz, 1H), 3.35 (d, *J* = 14 Hz, 1H); ^{13}C NMR (DMSO, 300MHz, δ ppm):167.3, 136.6, 134.8, 129.6, 129.1, 128.5, 128.1, 128, 69.3, 55.4; Optical rotation $\alpha_D^{20^\circ C}$ (C=1, CH_3OH) = -35 ˚

Methyl 2-[(R)-(diphenylmethyl) sulfinyl] acetate (**11**):

Added a solution of dicyclohexylcarbodiimide (DCC), (11.85 kg, 0.057 kmol in 15 L of methanol) to cooled suspension of 2-[(R)-(diphenylmethyl) sulfinyl] acetic acid (**6**) (15 kg, 0.054 kmol) in methanol (75 L) at 10-40 ˚C and stirred at 35-40 ˚C for 2 h. The reaction mass was diluted with N, N-dimethyl acetamide (15 L) and cooled to 10-15 ˚C. Remove the byproduct, DCU (N, N'-Dicyclohexyl urea) by filtration and concentrated the filtrate. The concentrated mass was diluted with methylene chloride and washed with aqueous sodium bicarbonate solution. The organic layer was concentrated and crystallized with cyclohexane (75 L) to afford methyl 2-[(R)-(diphenylmethyl) sulfinyl] acetate (**11**) as white crystalline powder. Yield: 13.50 kg (86%); HPLC purity: 99.48% (AN); Chiral purity: 99.9% (AN), (S) - isomer: 0.1% (AN). ^{1}H NMR (DMSO, 300MHz, δ ppm): 7.53 – 7.35 (m, 10H), 5.44 (s, 1H), 3.68 (d, *J* = 14 Hz, 1H), 3.62 (s, 3H), 3.48 (d, *J* = 15 Hz, 1H); ^{13}C NMR (DMSO,

300MHz, δ ppm): 166.2, 136.2, 134.8, 129.5, 129.1, 128.6, 128.5, 128.1, 69.7, 54.9,52.4; Optical rotation $\alpha_D^{20^0C}$(C=4, CH_3OH)= -22.5°

2-[(R)-(diphenylmethyl) sulfinyl] acetamide (**1**):

Methyl 2-[(R)-(diphenylmethyl)sulfinyl]acetate (**11**) (10 kg, 0.0347 kmol) was suspended in a precooled mixture of methanol (20 L) and methanolic ammonia (38 L, 18-20% w/w) at 0-5°C. Heated the contents to 20-25 °C and stirred for 5 h. Added water (100 L) and cyclohexane (30 L) to afford Armodafinil (**1)** as white crystalline powder. Yield: 9 kg (95%); HPLC purity: 99.6% (AN); Chiral purity: 99.99% (AN) ; (S)- isomer: 0.01% (AN); Dicyclo hexyl urea content=0.004% (by HPLC). ^{1}H NMR (DMSO, 300MHz, δ ppm): 7.66 (bs, 1H), 7.52 – 7.34 (m, 10H), 7.29(bs, 1H), 5.34 (s, 1H), 3.38-3.33 (ABq, *J* = 12 Hz 1H), 3.23-3.21 (d, *J* = 8.1, 1 H); ^{13}C NMR (DMSO, 300MHz, δ ppm):166.5, 137.1, 134.9, 129, 128.5, 128; 68.9, 56.2.

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