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COMMUNICATION

Efficient Atom and Step Economic (EASE) Synthesis of Smart Drug Modafinil

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Abstract : Modafinil, 2-[(Diphenylmethyl)sulfinyl]acetamide (MOD) is a key psychostimulant drug used for treatment of narcolepsy and other sleep disorders with very low addiction liability. Recently, MOD has been clinically investigated for the treatment of cocaine addiction and used by astronauts in long-term space missions. We have developed smart synthetic strategy for Smart Drug Modafinil. An efficient atom and step economic (EASE) synthesis has been done by direct reaction of benzhydrol and 2-mercaptoacetamide using recyclable heterogeneous catalyst Nafion-H along with post- sulphoxidation. This protocol exhibits improved green chemistry matrix. We have also developed a superior pre-sulfoxidation approach for Modafinil.

Smart drug,[1] Modafinil {1,2-[(diphenyl methyl) sulfinyl] acetamide} is utilized clinically as awake promoting agent for the treatment of narcolepsy and other sleeping disorders.[2,3,4] Modafinil has significant advantages over traditional anti-narcoleptic drugs such as amphetamine and methylphenidate as it rarely promotes abusive tendencies and exhibits reduced peripheral and central side-effects. As it is used for narcolepsy and enhances cognition independent of its known effects in sleep disordered populations therefore considered as the first well-validated pharmaceutical nootropic agent. Recently Modafinil entitled as the best example of "smart drug" or "dose of intelligence".[1]

The green chemistry started with an idea that chemists are highly creative profession but one of its profession to make the earth more pleasant using "Smart Chemistry".[5] At the silver jubilee of this science we have achieved some milestones and the concept is now honoured in both academia and industry. Although useful, the twelve principles of green chemistry are qualitative in nature but it does not define the clear matrices. Therefore various simple matrices[6,7] have been intercepted which have the basic parameters of these twelve principles like step economy, atom economy, mass intensity & E–factor etc. In this perspective we wish to report synthesis of smart drug Modafinil using smart chemistry-green chemistry with application of green chemistry matrix.

Various approaches have been proposed in the literature to synthesize Modafinil and its analogues such as in US Pat. No. 4177290, 2-(benzhydryl thio) acetic acid is prepared by first reacting benzhydrol with thiourea and 48% hydrobromic acid, then adding sodium hydroxide and chloroacetic acid. The reaction of 2-(benzhydryl thio)acetic acid with thionyl chloride in benzene affords 2-(benzhydryl thio)-acetyl chloride, which is treated with ammonia to give 2-(benzhydrylthio) acetamide[8]. In US Pat. No. 4098824, Bromo diphenyl methane is reacted with thiourea to give diphenyl methanthiol, which is then reacted with chloroacetic acid to give 2-(benzhydryl thio)acetic acid or with chloroacetonitrile to give 2-(benzhydyl thio)acetonitrile[9]. Both compounds can be transformed in to 2-(benzhydryl thio) acetamide by known methods. In EP528172, Benzhydrol is reacted with mercaptoacetic acid in trifluoroacetic acid to give 2-(benzhydrylthio)acetic acid, which is then converted to 2-(benzhydryl thio) acetamide[10]. In CA131 :299268, Chlorodiphenyl methane is reacted with 2-ethyl mercaptoacetate to give ethyl 2-(benzhydryl thio)acetate form which compound (II) is subsequently obtained[11]. In US 2004/0106829A1, 2-(benzhydryl thio) acetamide has been prepared from chlorodiphenyl methane and thiourea utilizing KI, NaOH and followed by chloroacetamide in DMSO[12]. In US 2007/0015836A1, 2-(benzhydryl thio) acetic acid is subjected firstly to oxidation then followed by the treatment of dimethyl sulphate in basic media.[13]

It is ascertained that above mentioned methods require the recovery of different intermediates and the use of costly and toxic reagents. Therefore there is the need to develop a method for the preparation of Modafinil devoid of previously

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Electronic Supplementary Information (ESI) available: [Experimental section, characterization of compounds, copies of ^{1}H and ^{13}C NMR spectra for compounds, See DOI: 10.1039/x0xx00000x

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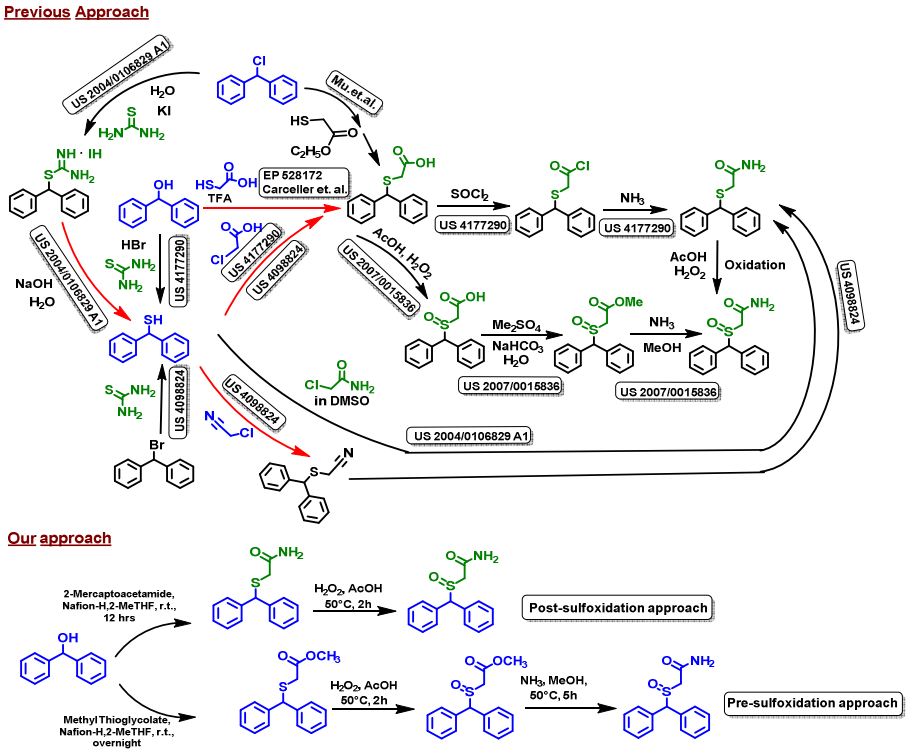


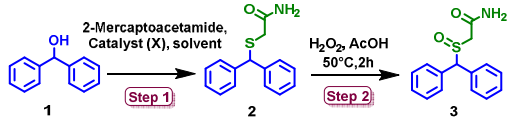
Scheme 1. Previous approach and our approach for synthesis of Modafinil

mentioned drawbacks. In order to increase the efficiency of reaction over previous traditional synthesis and in continuation to synthesize biologically as well as medicinally important compounds[14], we conduct stepwise approach of Modafinil explained in scheme 1.

Nafion-H, a perfluoroalkane sulfonic acid has been emerged as one of the promising and potential heterogeneous catalyst. It has been widely applied as a green, efficient and recyclable heterogeneous solid catalyst in diverse organic synthesis[15a] as a recyclable ionic heterogeneous catalyst. We have also demonstrated the presulfoxidation synthetic approach as an alternative route using same catalyst Nafion-H as used in post sulfoxidation approach.

At the outside of our study, previously we have examined our reaction in absence of any catalyst using benzhydrol and 2-mercaptoacetamide to synthesize 2-(benzhydrylthio)acetamide as precursor in variety of solvents, but the considerable result was not obtained. Starting from the catalytic amount of Brønsted acid using PTSA, MSA and TFA did not improve the yield of the desired product (2) (Table 1, entries 1-3). All the metal Lewis acids ($ZrCl_4$, zinc(II)triflate and copper(II)triflate), used in the reaction, also did not give promising results (Table 1, entries 4-6). Moving towards the heterogeneous catalyst, we further continued our screening using Nafion-H, Cell SA and Star SA eco-friendly and reusable catalysts, but results were not improved (Table 1, entries 7-9). However, when we carried out the reaction in 2-Methyl tetrahydrofuran taken as a solvent using solid superacid

Table 1 Optimization of reaction conditions of step 1.[a,d,e]



Entry	Catalyst (X)	Quantity (gm)	Solvent	Yield of 2(%)[c]
1	PTSA	0.1	MeCN	11
2	MSA	0.1	MeCN	10
3	TFA	0.1	MeCN	16
4	$Zn(OTf)_2$	0.1	MeCN	-
5	$ZrCl_4$	0.1	MeCN	-
6	$Cu(OTf)_2$	0.1	MeCN	-
7	Nafion-H	0.1	MeCN	38
8	CellSA	0.1	MeCN	12
9	StarSA	0.1	MeCN	14
10	Nafion-H	0.1	2Me-THF	64
11	Nafion-H	0.05	2Me-THF[b]	78
12	Nafion-H	0.02	2Me-THF[b]	88
13	Nafion-H	0.1	Toluene	24

[a]Reaction conditions: The reaction was conducted with diphenylmethanol (0.1 mol), 2-mercaptoacetamide (0.1 mol) in given solvent in heating condition for 24 hrs. [b]the reaction was carried out at r.t. for 12 hrs. [c]isolated yield. [d]The product 2-(benzhydrylthio)acetamide can be transformed in to 2-(benzhydryl thio) acetamide by oxidation using H_2O_2 in acidic conditions using acetic acid (see SI); [e]Abbreviations used in table: PTSA = p-Toluene sulfonic acid; MSA = Methane sulphonic acid; TFA = Trifluoroacetic acid; CellSA = Cellulose sulphuric acid; StarSA = Starch sulphuric acid; Nafion-H = Tetrafluoroethylene-perfluoro-3,6-dioxa-4-methyl-7-octenesulfonic acid.

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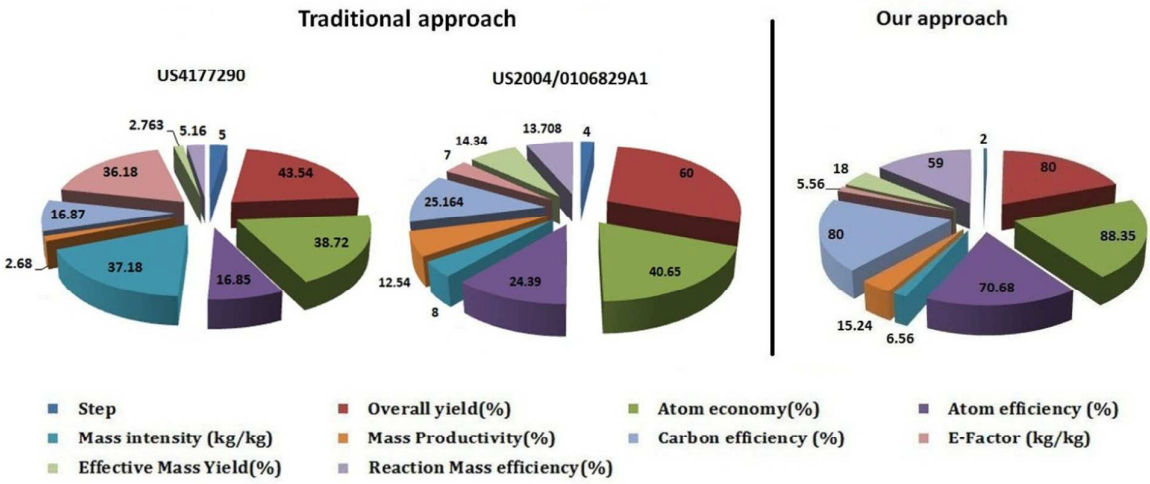


Fig. 1 Comparison of green matrices: Traditional vs our approach (Post-sulfoxidation approach)

Nafion-H at heating condition, surprisingly, we obtained the product (2) in higher amounts (64%) compared to any another catalyst used (Table 1, entry 10). On further optimization of catalyst we observed that 0.02 gm of catalyst has given best results for the formation of product (2). Further addition of catalyst did not improve the result, as probably fraction of acid groups, buried inside the shrunken polymer chain are unavailable for catalysis and do not attribute to effective acid concentration[15b-e](Table 1, entries 11-12). Moreover, we also employed the combination of Nafion-H with other solvent system like ACN and toluene, but satisfactory results were not obtained (Table 1, entries 7 & 13). Therefore, Nafion-H was proved to be the best catalyst for the reaction using 2-Methyl tetrahydrofuran as a solvent for the formation of 2-(benzhydrylthio)acetamide (Table 1, entry 12).

After that, the desired product 2-(benzhydrylthio)acetamide (2) can be easily converted to Modafinil via sulfoxidation using oxidising agent H_2O_2 in acidic condition. The step synthesis using Nafion-H can be considered as post-sulfoxidation synthesis because sulfoxidation was achieved in final step.

In order to access efficacy of our new EASE (efficient atom and step economic) synthesis of Modafinil over previous traditional post sulfoxidation approach ((US4177290 and US2004/0106820A1), we conduct stepwise synthesis of modafinil and compared the relevant important green matrices and parameters (step, atom economy, mass intensity, mass productivity, carbon sufficiency, E-factor and reaction mass efficiency etc.) and summarized in fig 1.

The recyclability of heterogeneous Nafion-H catalyst was also examined up to five times without any considerable loss of catalytic efficiency. (Fig 2).

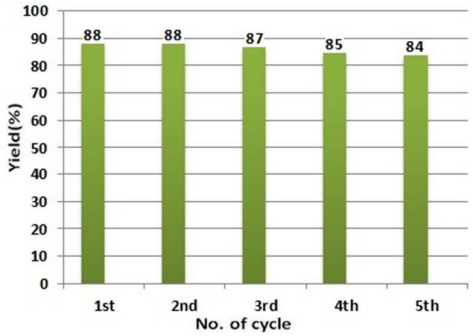
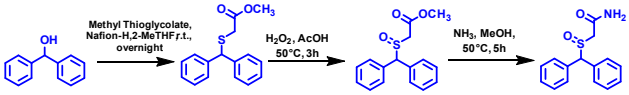


Fig. 2 Recycling studies of Nafion-H for entry 12 (Table 1)

We also examined the reaction utilizing the pre-sulfoxidation approach. In this case oxidation of methyl 2-(benzhydrylthio)acetate, which was previously synthesized by the reaction of benzhydrol and methyl thioglycolate using Nafion-H in 2-MeTHF taken as solvent, has been carried out using H_2O_2 in previous step followed by amidation in the presence of NH_3 in MeOH (3M methanolic ammonia) to afford the Modafinil in good yield (Scheme 2).



Scheme 2 Pre-sulfoxidation approach

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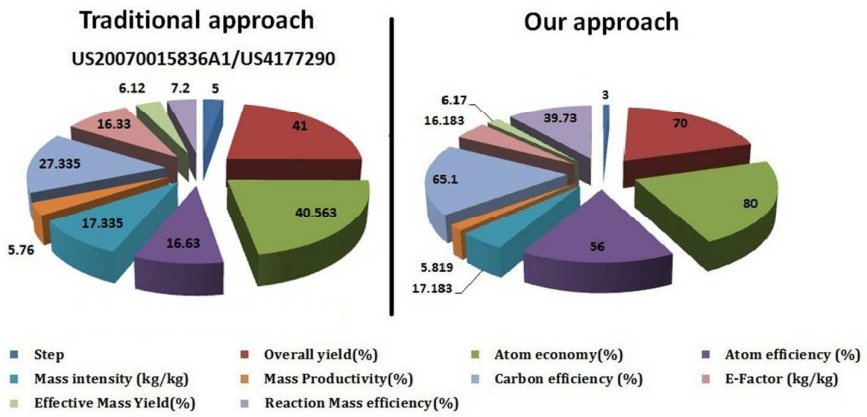

Fig. 3 Comparison of green matrices: Traditional vs our approach (Pre-sulfoxidation approach)

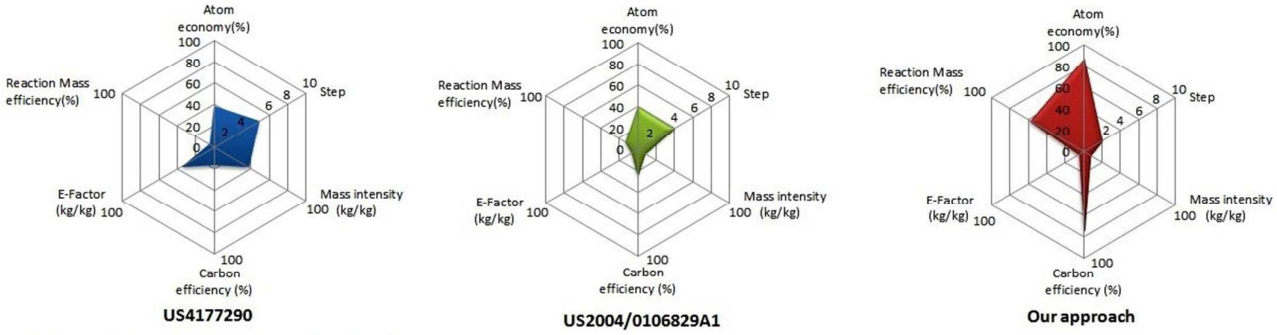

Fig. 4 A quick look on assessment of Modafinil synthetic improvement

We also investigate the green chemistry parameters in case of pre-sulfoxidaton approach and compared it with previously known traditional method (US20070015836A1/US4177290), shown in Fig. 3.

A new green assessment web diagram has been shown in fig. 4, exhibits visible improvements in green chemistry parameters in the synthesis of Modafinil over previous traditional methods. Focusing on each green matrix concept reveals that our EASE synthesis has clear edge on traditional approaches: Step economy : Steps were reduced to 2 from 4-5 steps; Atom economy : Atom economy was increased to 88.35 while in previous approaches, it is 38.72 & 40.65; Reaction Mass Efficiency: A considerable increase has been seen in reaction mass efficiency to 59 % from 5.16 & 13.7%; Waste : The E –factor was reduced from 36.18 & 7 to 5.56; Carbon Efficiency: Carbon Efficiency was also increased to 80% from 16.87 & 25.16%; Mass intensity: It approaches to the lower value 6.56 from the previous 37.18 & 8. Besides these improvements in the synthesis of Modafinil, we have also chosen best solvent – catalytic system considering its efficiency, toxicity and recycling rate as 2-Me THF & Nafion H.

In summary we have developed an efficient atom and step economic (EASE) approach for the synthesis of Smart Drug Modafinil with full assessment on the basis of pi-chart and web chart diagram showing gate to gate analysis of green chemistry parameters. We think that this study will have immense future impact in planning green chemistry strategy for drugs.

Acknowledgements

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Efficient Atom and Step Economic (EASE) Synthesis of smart drug Modafinil

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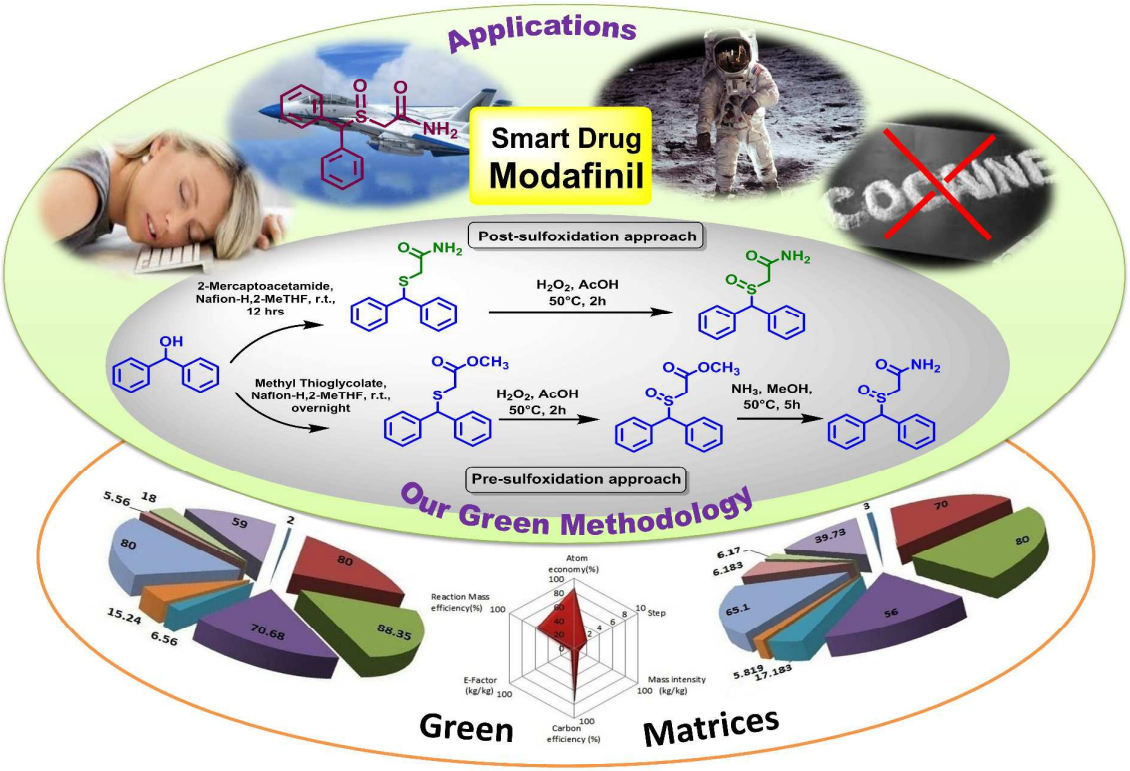
Abstract

We report an efficient atom and step economic (EASE) synthesis for Modafinil, a key psychostimulant drug, utilised for treatment of narcolepsy. The developed post-sulfoxidation protocol for the synthesis of Modafinil, exhibits improved green chemistry matrix, utilizing recyclable heterogeneous catalyst Nafion-H. Additionally a superior pre-sulfoxidation approach for Modafinil has been developed.



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SUPPORTING INFORMATION

Efficient Atom and Step Economic (EASE) Synthesis of smart drug Modafinil

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1. General information

All reagents and solvents were purchased from commercial sources and used as received. The progress of the reaction was monitored by analytical TLC on silica gel G/GF 254 plates. Reagent grade solvents were used for extraction and flash chromatography. The column chromatography was performed with silica gel 230-400 mesh. NMR (^{1}H and ^{13}C) spectra were recorded on a 300 & 400 MHz using TMS as an internal standard and chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Melting points are uncorrected were determined in capillary tubes on a hot stage melting point apparatus containing silicon oil. High-resolution mass spectra (ESI-HRMS) were recorded on Agilent 6520 ESI-QTOP mass spectrometer.. IR spectra were recorded using a FTIR spectrophotometer.

Background

Smart drug[1] Modafinil (2-(diphenylmethylsulfinyl)acetamide) is a wakefulness promoting agent approved by the Food and Drug Administration in the United States[2], used for treatment of disorders such as shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea[3]. It is a central nervous system stimulant reported to have little abuse potential. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil is under investigation as a possible method to treat cocaine dependence[4]. It is also used in militaries where soldiers face sleep deprivation as an alternative to amphetamine[5] as well as by astronauts on long-term missions aboard the International Space Station[6]. We report an efficient atom and step economic (EASE) synthesis for Modafinil, a key

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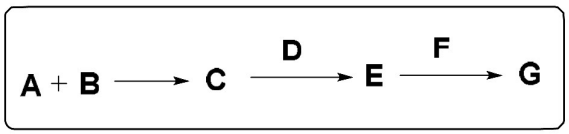
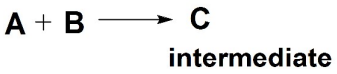
psychostimulant drug, utilised for treatment of narcolepsy[7,8]. The developed post-sulfoxidation protocol for the synthesis of Modafinil, exhibits improved green chemistry matrix, utilizing recyclable heterogeneous catalyst Nafion-H. Additionally a superior pre-sulfoxidation approach for Modafinil has been developed.

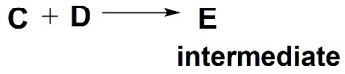
3. Green metrics calculations: Formulae used

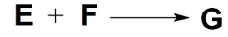
For a **linear synthetic process**[9,10]:



Steps involved in this process are:







The reactants and reagents efficiently participate in product formation excluding intermediates are:

1. No. of steps = No. of steps involved in the process

2. Atom economy =

[(M.W. of product G)/(M.W. of A+ M.W. of B+ M.W. of D+ M.W. ofF)]x100

3. % yield = (Observed yield/ Calculated yield) x100

4. Atom efficiency = % yield x Atom economy

5. Carbon efficiency =

[(no. of moles of product G x no. of carbons in product G)/{(no. of moles of A x no. of carbons in A)+ (no. of moles of B x no. of carbons in B)+ (no. of moles of D x no. of carbons in D)+ (no. of moles of F x no. of carbons in F)}]x100

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6. Mass intensity = (Total mass used in the process / Mass of the product)

7. Mass productivity = (1/ Mass intensity) x100

8. E- factor = (Mass intensity – 1)

9. Effective Mass Yield = (1/ E- factor) x100

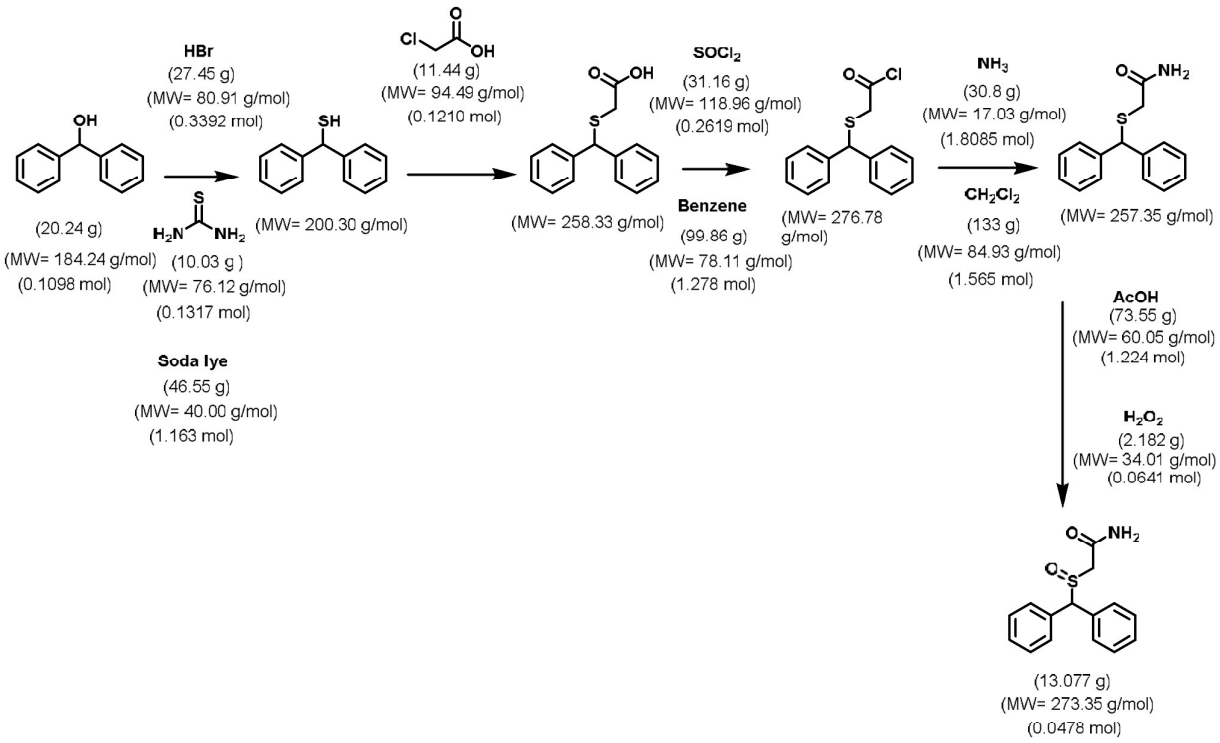
10. Reaction Mass Efficiency =

[(Mass of product G) / (Mass of A + Mass of B + Mass of D + Mass of F)] x 100

3. Green metrics calculations:

Post-Sulfoxidation approach:

US4177290



Scheme 1.1

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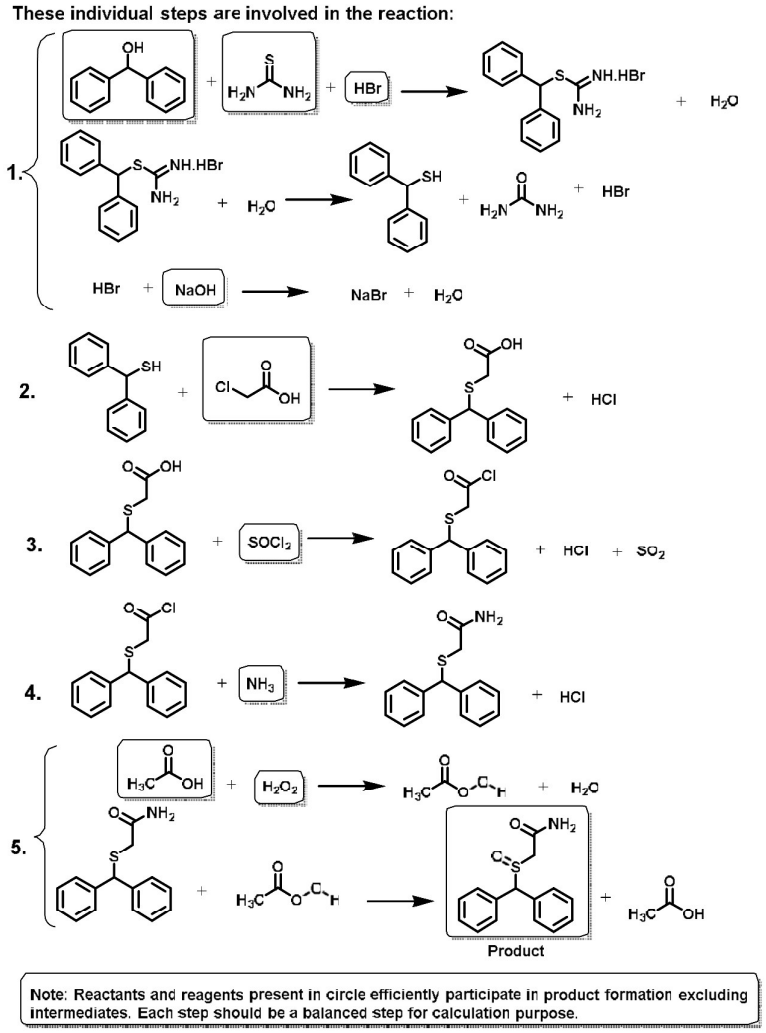
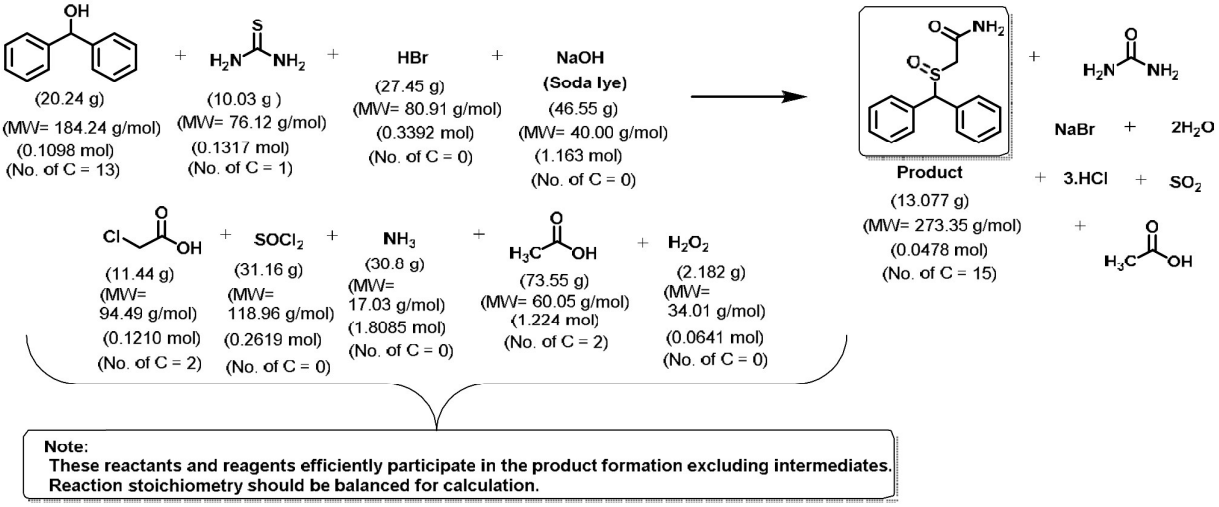


Scheme 1.2



Scheme 1.3

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1. No of steps = 5

2. Atom economy =
{(273.35)/(184.24+76.12+80.91+40.00+94.49+118.96+17.03+60.05+34.01)}x100 = 38.72%

3. % yield = (13.077/30.029)x100 = 43.54%

4. Atom efficiency = (43.54/100) x 38.72 = 16.85

5. Carbon efficiency =

[(0.0478x15)/{(0.1098x13)+(0.1317x1)+(0.3392x0)+(1.163x0)+(0.1210x2)+(0.2619x0)+(1.8085x0)+(1.224x2)+(0.0641x0)}]x100

= 16.87%

6. Mass intensity =
(20.24+10.03+27.45+46.55+11.44+31.16+99.86+30.8+133+73.55+2.182)/(13.077) = 37.184 kg/kg

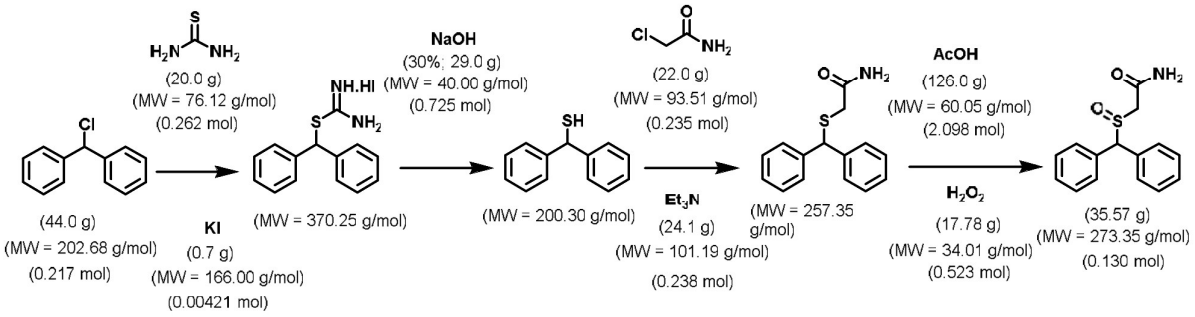
7. Mass productivity = (1 / 37.184) x100 = 2.689 %

8. E-factor = (37.184 -1) = 36.184 kg/kg

9. Effective Mass Yield = (1/36.184) x100 = 2.763%

10. Reaction Mass Efficiency =
[(13.077)/(20.24+10.03+27.45+46.55+11.44+31.16+30.8+73.55+2.182)] x100 = 5.16%

US2004/0106829 A1



Scheme 2.1

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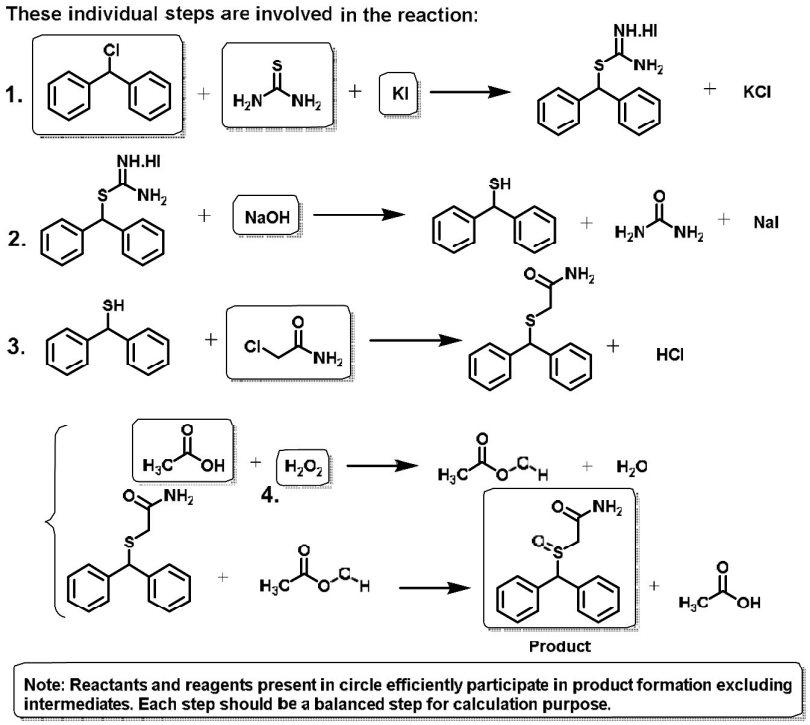
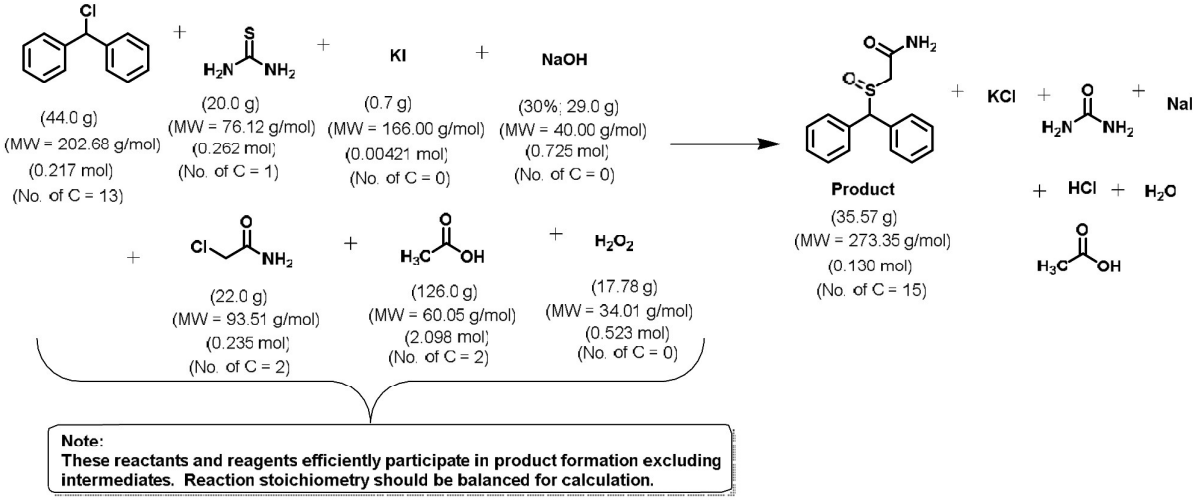


Scheme 2.2



Scheme 2.3

1. No of steps = 4

2. Atom economy = {(273.35)/(202.68+76.12+166.00+40.00+93.51+60.05+34.01)}x100 = 40.65%

3. % yield = (35.57/59.34)x100 = 60%

4. Atom efficiency = (60/100) x 40.65% = 24.39

5. Carbon efficiency =

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[(0.130x15)/{(0.217x13)+(0.262x1)+(0.00421x0)+(0.725x0)+(0.235x2)+(2.098x2)+(0.523x0)}]x100

= 25.164%

6. Mass intensity = (44.0+20.0+0.7+29.0+22.0+24.1+17.78+126.0)/(35.57) = 7.972kg/kg ≈8kg/kg

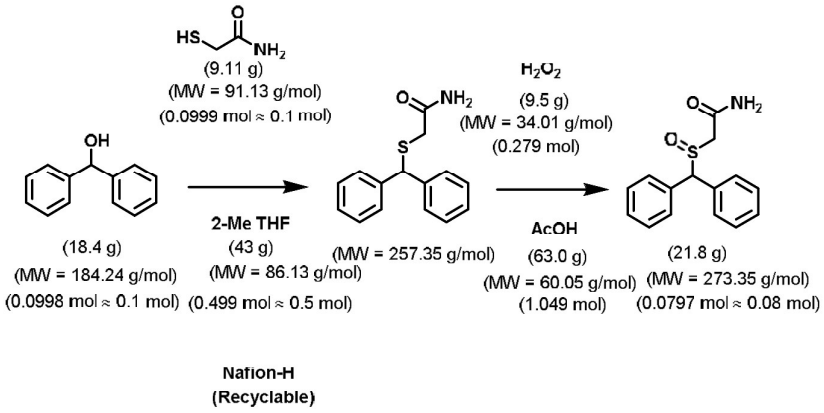
7. Mass productivity = (1 / 7.972) x100 = 12.54 %

8. E-factor = (7.972 -1) = 6.972kg/kg ≈ 7kg/kg

9. Effective Mass Yield = (1/6.972) x100 = 14.343%

10. Reaction Mass Efficiency = [(35.57)/(44.0+20.0+0.7+29.0+22.0+126.0+17.78)] x100 = 13.708%

Our work



Scheme 3.

1. No of steps = 2

2. Atom economy = {(273.35)/(184.24+91.13+34.01)}x100 = 88.35%

3. % yield = (21.8/27.29)x100 = 80%

4. Atom efficiency = (80/100) x 88.35 = 70.68

5. Carbon efficiency = [(0.08x15)/{(0.1x13)+(0.1x2)+(0.279x0)}]x100 = 80.0%

6. Mass intensity = (18.4+9.11+43.0+63.0+9.5)/(21.8) = 6.56 kg/kg

7. Mass productivity = (1 / 6.56) x100 = 15.24 %

8. E-factor = (6.56 -1) = 5.56 kg/kg

9. Effective Mass Yield = (1/5.56) x100 = 17.98% ≈ 18 %

10. Reaction Mass Efficiency = [(21.8)/(18.4+9.11+9.5)] x100 = 59.0%

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Pre-Sulfoxidation approach:

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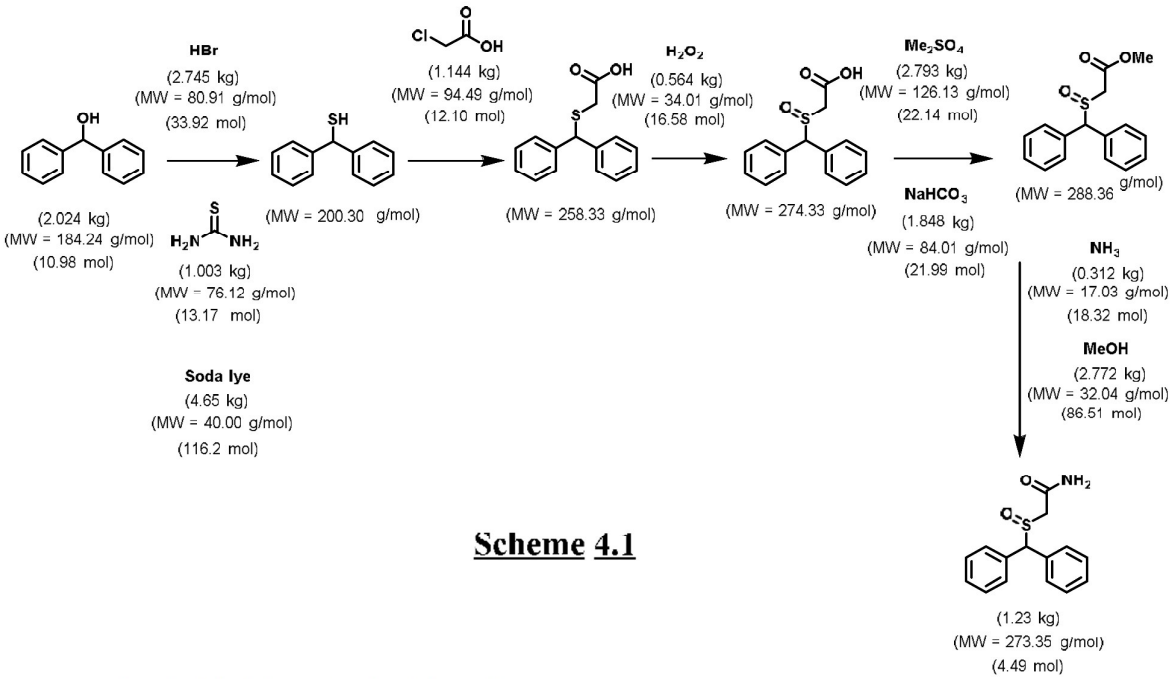
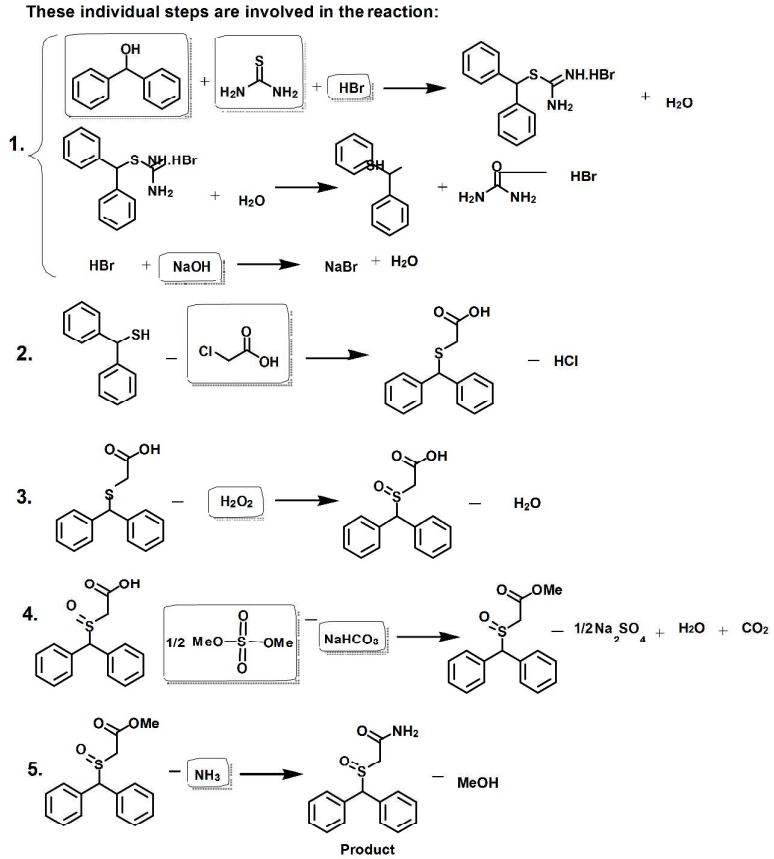


Scheme 4.1

These individual steps are involved in the reaction:



Note: Reactants and reagents present in circle efficiently participate in product formation excluding intermediates. Each step should be a balanced step for calculation purpose.

Scheme 4.2

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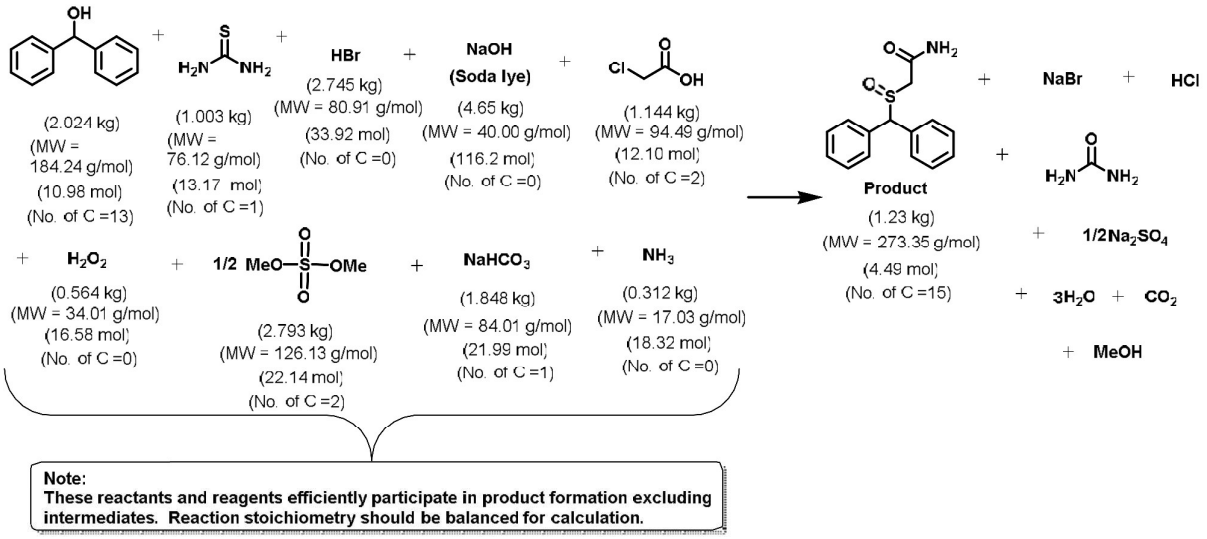

Scheme 4.3

.

1. No of steps = 5

2. Atom economy =

{(273.35)/(184.24+76.12+80.91+40.00+94.49+34.01+(0.5x126.13)+84.01+17.03)}x100 = 40.563%

3. % yield = (1.23/3.00)x100 = 41%

4. Atom efficiency = (41/100) x 40.563 = 16.63

5. Carbon efficiency =

[(4.49x15)/{(10.98x13)+(13.17x1)+(33.92x0)+(116.2x0)+(12.10x2)+(16.58x0)+(22.14x2)+(21.99x1)+(18.32x0)}]x100

– 27.335%

6. Mass intensity =

(2.024+1.003+2.745+4.655+1.144+0.564+2.793+1.848+1.463+0.312+2.772)/(1.23) = 17.335 kg/kg

7. Mass productivity = (1 / 17.335) x100 = 5.768 %

8. E-factor = (17.335 -1) = 16.335 kg/kg

9. Effective Mass Yield = (1/16.335) x100 = 6.121 %

10. Reaction Mass Efficiency =

[(1.23)/(2.024+1.003+2.745+4.65+1.144+0.564+2.793+1.848+0.312)] x100 = 7.20 %

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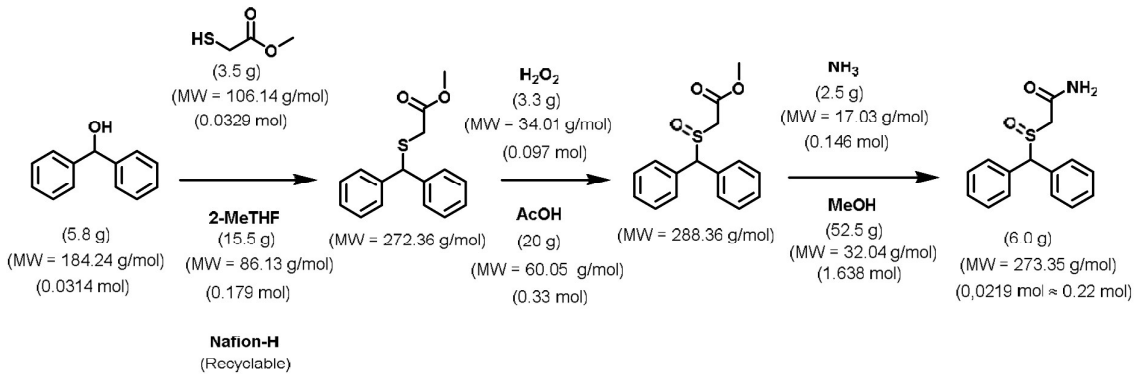
Our work



Scheme 5.

1. No of steps = 3

2. Atom economy = {(273.35)/(184.24+106.14+34.01+17.03)}x100 = 80.0%

3. % yield = (6.0/8.6)x100 = 70%

4. Atom efficiency = (70/100) x 80.0 = 56

5. Carbon efficiency = [(0.0219x15)/{(0.0314x13)+(0.0329x3)}]x100 = 65.1%

6. Mass intensity = (5.8+3.5+15.5+20.0+3.3+2.5+52.5)/(6.0) = 17.183 kg/kg

7. Mass productivity = (1 / 17.183) x100 = 5.819 %

8. E-factor = (17.183 -1) = 16.183 kg/kg

9. Effective Mass Yield = (1/ 16.183) x100 = 6.17 %

10. Reaction Mass Efficiency = [(6.0)/(5.8+3.5+3.3+2.5)] x100 = 39.73%

4. Experimental procedure : Post-Sulfoxidation approach:

Synthesis of 2-(benzhydrylthio)acetamide: Mixture of 2-mercaptoacetamide (0.1 mol), diphenylmethanol (0.1 mol) and Nafion-H (0.02 gm) in 2-Me THF (50 ml) was stirred at r.t. overnight. The solvent was removed, the mixture was diluted with H_2O (20 mL), extracted and dried with Na_2SO_4. The solvent was removed and obtained white pure product (Yield 88%).

Synthesis of 2-(benzhydrylsulfinyl)acetamide (Modafinil): H_2O_2 (35% w/w aqueous solution; 0.28 mol) was slowly added in 2-(benzhydrylthio)acetamide (0.087 mol) in AcOH (60 ml; d = 1.05 g/cm^3). The reaction was stirred and heated in water bath at 50°C for 2 hrs and reaction progress was monitored by TLC. The mixture was cooled by adding ice

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followed by vacuum filtration to obtain the crude solid which upon recrystallization in aqueous methanol yield white solid (Yield 91%).

Pre-Sulfoxidation approach:

Synthesis of Methyl 2-(benzhydrylthio)acetate: A mixture of Diphenylmethanol (0.034 mol) and methylthioglycolate (0.033 mol) and Nafion-H (0.05 mol) in 2-MeTHF (18 mL; d=0.86 g/ml) was stirred at r.t. overnight. The solvent was removed, the mixture was diluted with H_2O (20 mL), extracted and dried with Na_2SO_4. The solvent was removed and obtained light red (oily) pure product (Yield 92%).

Synthesis of Methyl 2-(benzhydrylsulfinyl)acetate : H_2O_2 (35% w/w aqueous solution; 0.097 mol) was slowly added in Methyl 2-(benzhydrylthio)acetate (0.029 mol) in AcOH (19 ml; d=1.05 g/cm^3). The reaction was stirred and heated in water bath at 50°C for 2 hrs and reaction progress was monitored by TLC. The mixture was cooled by adding ice followed by vacuum filtration to obtain pale yellow gummy liquid (Yield 96%).

Synthesis of 2-(benzhydrylsulfinyl)acetamide (Modafinil): A mixture of Methyl 2-(benzhydrylsulfinyl)acetate (0.0277 mol), NH_3 (2.5 g) solution in MeOH (50 ml) (ie. 50 ml, methanolic ammonia 3M) was stirred at 50 °C for 4-5 hr. Reaction mixture was filtered, filtrate was collected and dried to get white solid pure product (Yield 79%).

Regeneration of catalyst: The catalyst was washed with acetone and deionized water then dried overnight at 100°**C** to reuse.

Table. Recyclability studies of Nafion-H in the synthesis of 2-(benzhydrylthio)acetamide (2)

Run	1st	2nd	3rd	4th	5th
Yield	88	88	87	85	84

5. Spectral charts

Modafinil Physical State – White solid; M.p. 158-159ºC, IR (KBr): 3383, 3314, 3256, 1690, 1616, 1494, 1376, 1027, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm): 3.14(d, *J*=14.3 Hz, 1H); 3.48(d, *J*=14.3 Hz, 1H); 5.24(s, 1H); 5.88(br s, 1H); 7.09(br s, 1H); 7.29-7.43(m, 7H); 7.43-7.51(m, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 52.00, 71.61, 128.80, 128.98, 129.10, 129.58, 129.62, 134.30, 134.74, 166.46; Molecular formula $C_{15}H_{15}NO_2S$; ESI-MS (m/z): 274.1 $(M+H)^+$.

2-(Benzhydrylthio)acetamide Physical State – White solid; M.p. 108-110ºC, IR (KBr): 3383, 3026, 1643, 1490, 1449, 1409, 696cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm): 3.12(s, 2H); 5.20(s, 1H), 5.55(br s, 1H); 6.54(br s, 1H); 7.26-7.30(m, 2H); 7.30-7.37(m, 4H); 7.37-7.45(m, 4H). ^{13}C NMR ($CDCl_3$) δ(ppm): 35.60, 54.75, 127.65, 128.29, 128.78, 140.24, 171.48. Molecular formula $C_{15}H_{15}NOS$; ESI-MS (m/z): 258.3 $(M+H)^+$.

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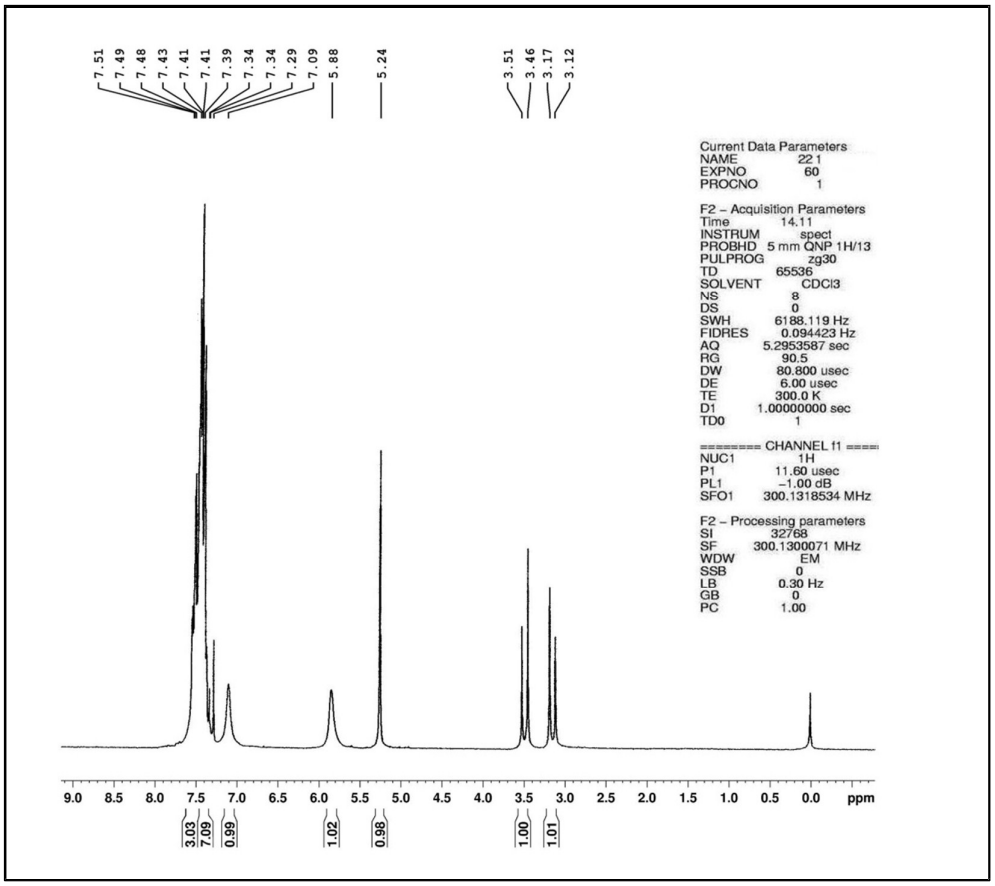
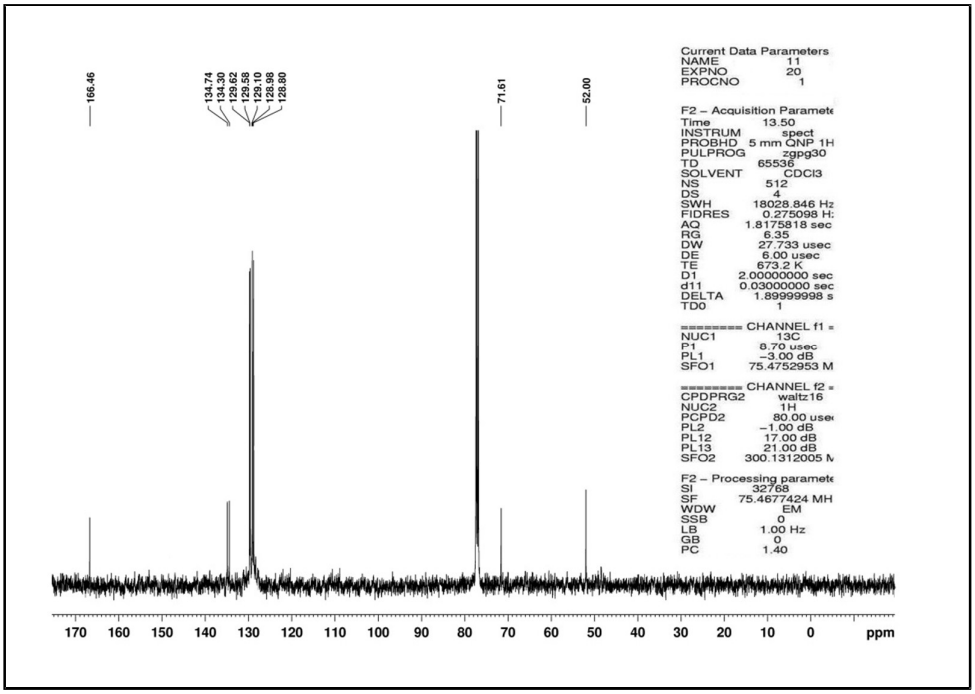


^{1}H Spectra of Modafinil



^{13}C Spectra of Modafinil

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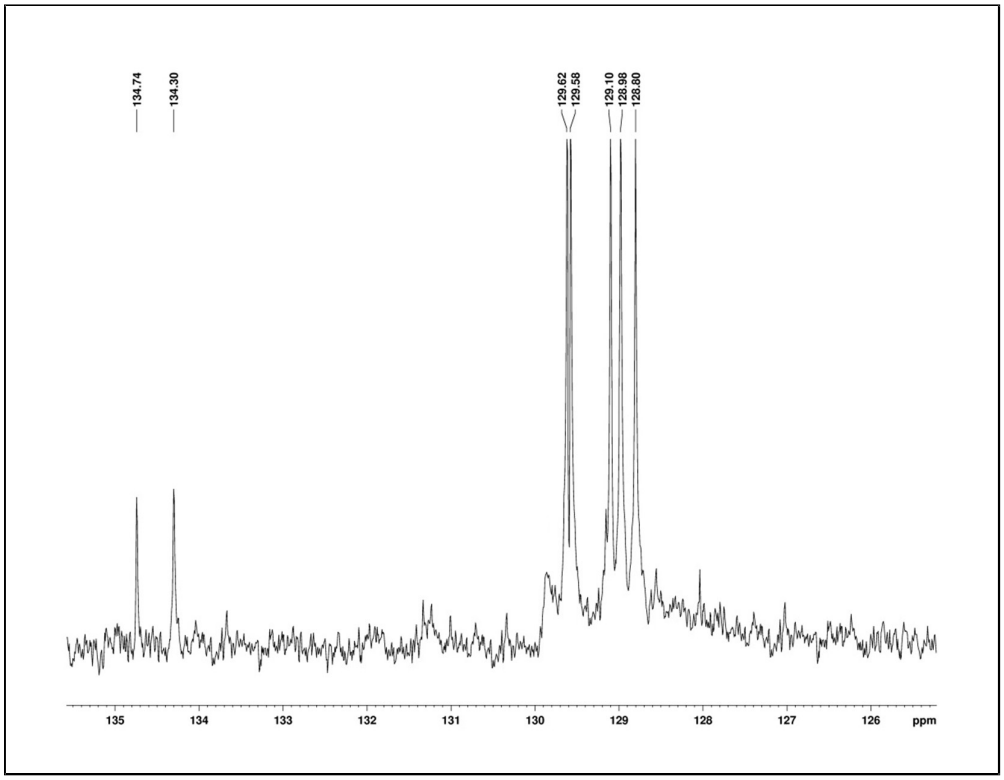
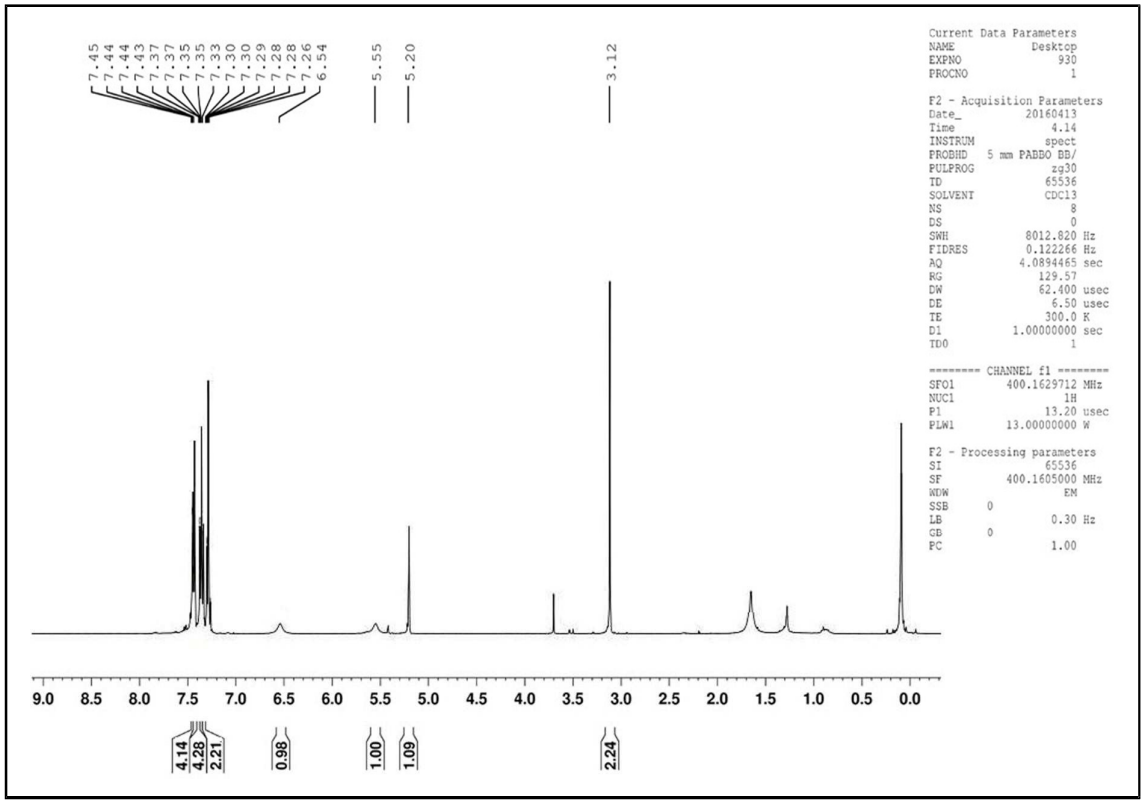


13C NMR spectrum of modafinil expanded in the aromatic region



[1]H Spectra of 2-(Benzhydrylthio)acetamide

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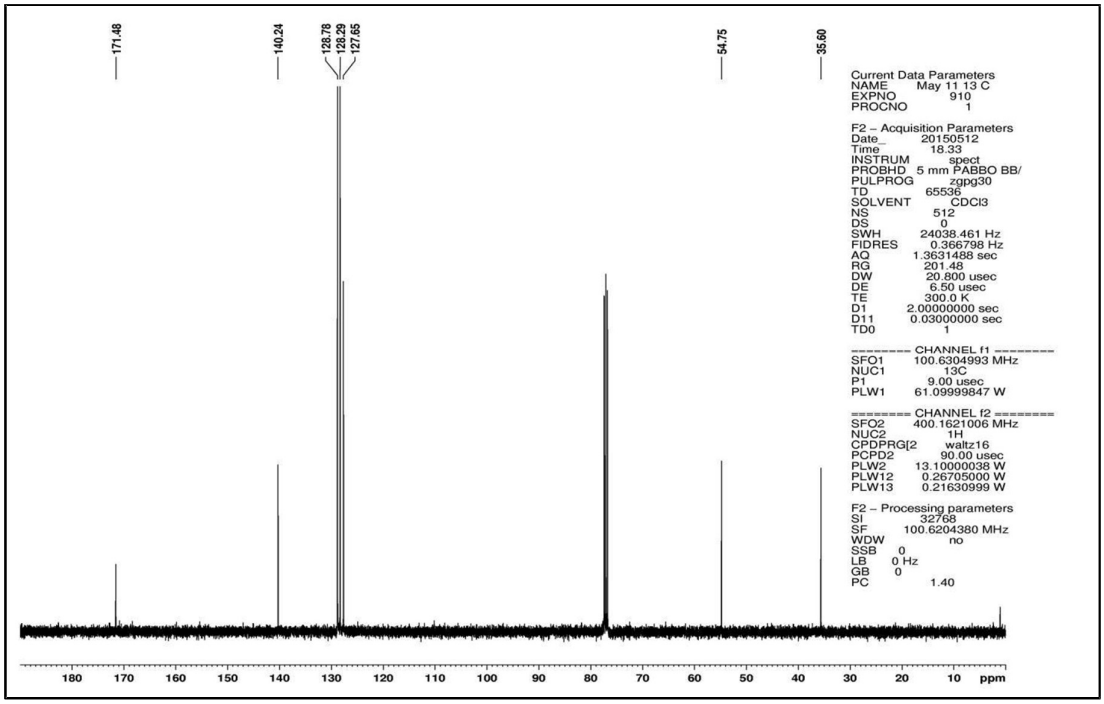

^{13}C Spectra of 2-(Benzhydrylthio)acetamide

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