

Supporting Information

Synthesis of Organosulfur and Related Heterocycles under Mechanochemical Conditions

Tanmay Chatterjee^{*,a} and Brindaban C. Ranu^{*,b}

^a*Department of Chemistry, Birla Institute of Technology and Science, Pilani (BITS Pilani), Hyderabad Campus, Jawahar Nagar, Hyderabad 500078, Telangana, India*

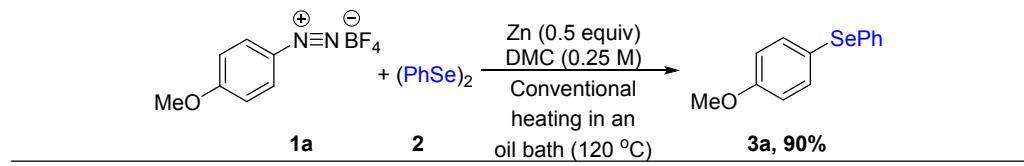
Email: tanmay@hyderabad.bits-pilani.ac.in

^b*School of Chemical Sciences, Indian Association for the Cultivation of Science, Jadavpur, Kolkata – 700032, India. Email: ocbcr@iacs.res.in*

Contents

1. Calculation of E-factor and EcoScale Score for the synthesis of (4-methoxyphenyl) (phenyl)selane from 4-Methoxybenzenediazonium tetrafluoroborate and diphenyl diselenide under	
Table S1. conventional heating conditions	S-2
Table S2. microwave heating conditions	S-3
Table S3. mechanochemical conditions	S-4
2. Calculation of E-factor and EcoScale Score for the synthesis of diphenyl disulfide from thiophenol under	
Table S4. photochemical conditions	S-5
Table S5. mechanochemical conditions	S-6
3. Calculation of E-factor and EcoScale score for the C-H α -sulenylation of 2-naphthol using diphenyl disulfide to synthesize 1-(phenylthio)naphthalen-2-ol under	
Table S6. conventional heating conditions	S-7
Table S7. mechanochemical conditions	S-8
4. Reference	S-9

Table S1. Calculation of E-factor and EcoScale score for the synthesis of (4-methoxyphenyl)(phenyl)selane from 4-methoxybenzenediazonium tetrafluoroborate and diphenyl diselenide under the conventional heating conditions



E-factor calculation for the synthesis of 3a under conventional heating conditions:

Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate	0.222 g	1 mmol	FW 221.95
Reactant 2 (2): Diphenyl diselenide:	0.156 g	0.5 mmol	FW 312.13
Reagent: Zn dust:	0.325 g	0.5 mmol	FW 65.38
Solvent: DMC (4 mL, 3.738 g):	3.738 g	41.499 mmol	FW 90.08
Auxiliary: -----	-----	-----	-----
Product: (4-Methoxyphenyl)(phenyl)selane:	0.236 g	0.9 mmol	FW 263.19

Product yield = 90%

$$\text{E-factor} = \frac{0.222 + 0.156 + 0.325 + 3.738 - 0.236}{0.236} = \mathbf{17.82 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 3a under conventional heating conditions:

EcoScale score = 100 - Sum of individual penalties

Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

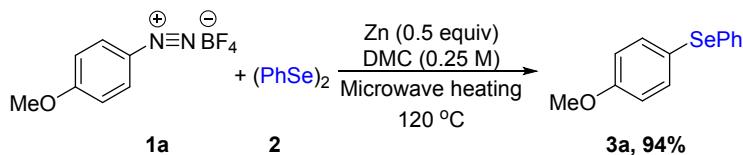
A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 90)/2 = 5$	5
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 4-Methoxybenzenediazonium tetrafluoroborate = 11.11 mmol = 2.466 g = USD 1.87 [Synthesis cost: Required chemicals: ¹ i) p-anisidine = 1.41 g = USD 0.34 ii) NaNO ₂ = 0.81 g = USD 0.41 iii) HBF ₄ (50% in water) = 3.46 mL = USD 1.12 Hence total cost of synthesis = USD (0.34 + 0.41 + 1.12) = USD 1.87]	
b. Diphenyl diselenide = 5.55 mmol = 1.734 g = USD 7.49	
c. Zn dust = 5.55 mmol = 0.363 g = USD 0.18	
d. DMC = 44.44 mL = USD 2.44 (All the given prices are as per Sigma Aldrich)	
Hence total price (USD) = (1.87 + 7.49 + 0.18 + 2.44) = USD 11.98	3
(Thus expensive since total price > USD 10)	
3. Safety	
a. Reactant 2 (2): Diphenyl diselenide Toxic (T)	5
b. Solvent: Dimethyl carbonate (DMC) Highly flammable (F)	5
c. Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate Explosive (E)	10
4. Technical Setup	
Common Setup	0
5. Temperature/Time	
Heating, >1h	3
6. Workup and purification	
Classical chromatography	10
Total penalty points	41

B) EcoScale calculation:

EcoScale Score: $(100 - 41) = \mathbf{59}$ (an acceptable synthesis)

Table S2. Calculation of E-factor and EcoScale Score for the synthesis of (4-methoxyphenyl) (phenyl)selane from 4-Methoxybenzenediazonium tetrafluoroborate and diphenyl diselenide under the microwave heating conditions



E-factor calculation for the synthesis of 3a under microwave heating conditions:

Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate	: 0.222 g	1 mmol	FW 221.95
Reactant 2 (2): Diphenyl diselenide:	0.156 g	0.5 mmol	FW 312.13
Reagent: Zn dust:	0.325 g	0.5 mmol	FW 65.38
Solvent: DMC (4 mL, 3.738 g):	3.738 g	41.499 mmol	FW 90.08
Auxiliary: -----	-----	-----	-----
Product (3a): (4-Methoxyphenyl)(phenyl)selane:	0.247 g	0.94 mmol	FW 263.19

Product yield = 94%

$$\text{E-factor} = \frac{0.222 + 0.156 + 0.325 + 3.738 - 0.247}{0.247} = \mathbf{16.98 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 3a under microwave heating conditions:

EcoScale score = 100 - Sum of individual penalties

Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

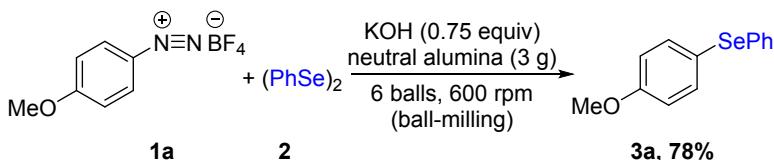
A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 94)/2 = 3$	3
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 4-Methoxybenzenediazonium tetrafluoroborate = 10.63 mmol = 2.361 g = USD 1.8 [Synthesis cost: Required chemicals: ¹ i) <i>p</i> -anisidine = 1.36 g = USD 0.33 ii) NaNO ₂ = 0.77 g = USD 0.39 iii) HBF ₄ (50% in water) = 3.31 mL = USD 1.08 Hence total cost of synthesis = USD (0.33 + 0.39 + 1.08) = USD 1.8] b. Diphenyl diselenide = 5.55 mmol = 1.734 g = USD 7.49 c. Zn dust = 5.55 mmol = 0.363 g = USD 0.18 d. DMC = 44.44 mL = USD 2.44 (All the given prices are as per Sigma Aldrich) Hence total price (USD) = (1.8 + 7.49 + 0.18 + 2.44) = USD 11.91 (Thus expensive since total price > USD 10)	3
3. Safety	
a. Reactant 2 (2): Diphenyl diselenide Toxic (T)	5
b. Solvent: Dimethyl carbonate (DMC) Highly flammable (F)	5
c. Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate Explosive (E)	10
4. Technical Setup Unconventional activation technique (Microwave activation)	2
5. Temperature/Time Heating, >1h	3
6. Workup and purification Classical chromatography	10
Total penalty points	41

B) EcoScale calculation:

EcoScale Score: $(100 - 41) = \mathbf{59}$ (an acceptable synthesis)

Table S3. Calculation of E-factor and EcoScale score for the synthesis of (4-methoxyphenyl) (phenyl)selane from 4-Methoxybenzenediazonium tetrafluoroborate and diphenyl diselenide under the mechanochemical conditions



E-factor calculation for the synthesis of 3a under mechanochemical conditions:

Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate	: 0.222 g	1 mmol	FW 221.95
Reactant 2 (2): Diphenyl diselenide:	0.156 g	0.5 mmol	FW 312.13
Reagent: KOH:	0.042 g	0.75 mmol	FW 56.11
Solvent: -----	-----	-----	-----
Auxiliary (grinding): neutral alumina	3g	29.4 mmol	FW 101.96
Product (3a): (4-Methoxyphenyl)(phenyl)selane:	0.205 g	0.78 mmol	FW 263.19

Product yield = 78%

$$\text{E-factor} = \frac{0.222 + 0.156 + 0.042 + 3 - (0.205)}{0.205} = \mathbf{15.68 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 3a under mechanochemical conditions:

EcoScale score = 100 - Sum of individual penalties

Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

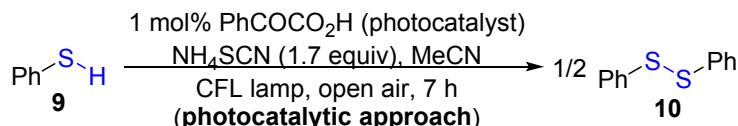
A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: (100 - % of yield)/2 = (100 - 78)/2 = 11	11
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 4-Methoxybenzenediazonium tetrafluoroborate = 12.82 mmol = 2.845 g = USD 2.17 [Synthesis cost: Required chemicals: ¹ i) p-anisidine = 1.64 g = USD 0.4 ii) NaNO ₂ = 0.93 g = USD 0.47 iii) HBF ₄ (50% in water) = 3.99 mL = USD 1.3 Hence total cost of synthesis = USD (0.4 + 0.47 + 1.3) = USD 2.17]	
b. Diphenyl diselenide = 6.41 mmol = 2 g = USD 8.64	
c. KOH = 9.62 mmol = 0.54 g = USD 0.03	
d. Neutral alumina (grinding auxiliary) = 337.2 mmol = 38.46 g = USD 2.86 (All the given prices are as per Sigma Aldrich) Hence total price (USD) = (2.17 + 8.64 + 0.03 + 2.86) = USD 13.7 (Thus expensive since total price > USD 10)	3
3. Safety	
a. Reactant 2 (2): Diphenyl diselenide Toxic (T)	5
b. Reactant 1 (1a): 4-Methoxybenzenediazonium tetrafluoroborate Explosive (E)	10
4. Technical Setup Unconventional activation technique (Mechanochemical activation)	2
5. Temperature/Time Room temperature, <1h	0
6. Workup and purification Classical chromatography	10
Total penalty points	41

B) EcoScale calculation:

EcoScale Score: (100 - 41) = **59** (an acceptable synthesis)

Table S4. Calculation of E-factor and EcoScale Score for the synthesis of diphenyl disulfide from thiophenol under photochemical conditions



E-factor calculation for the synthesis of 10 under photochemical conditions:

Reactant (9): Thiophenol :	0.055 g	0.5 mmol	FW 110.18
Catalyst: Phenylglyoxylic acid:	0.0008 g	0.005 mmol	FW 150.13
Reagent: NH ₄ SCN:	0.065 g	0.85 mmol	FW 76.12
Solvent: MeCN:(2 mL, 1.572 g)	1.572 g	38.29 mmol	FW 41.05
Auxiliary: -----	-----	-----	-----
Product: 1,2-diphenyldisulfane:	0.052 g	0.24 mmol	FW 218.33

Product yield = 96%

$$\text{E-factor} = \frac{0.055 + 0.0008 + 0.065 + 1.572 - 0.052}{0.052} = \mathbf{31.55 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 10 under the photochemical conditions:

EcoScale score = 100 - Sum of individual penalties
Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

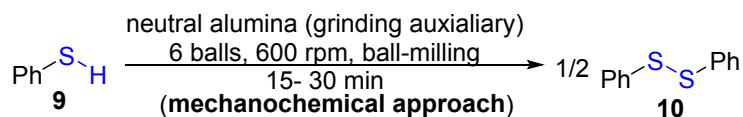
A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 96)/2 = 2$	2
2. Price of reaction components (To obtain 10 mmol of end product)	
a. Thiophenol = 20.83 mmol = 2.295 g = USD 0.461	
b. Phenylglyoxylic acid = 0.208 mmol = 0.032 g = USD 0.104	
c. NH ₄ SCN = 35.42 mmol = 2.696 g = USD 0.444	
d. MeCN = 83.33 mL = USD 7.45 (All the given prices are as per Sigma Aldrich)	
Hence total price (USD) = $(0.461 + 0.104 + 0.444 + 7.45) = \mathbf{USD 8.46}$	0
(Thus inexpensive since total price < USD 10)	
3. Safety	
a. Reactant (9): Thiophenol Toxic (T)	5
b. Solvent: Acetonitrile (MeCN) Toxic (T) Highly flammable (F)	5
4. Technical Setup	2
Unconventional activation technique (Photochemical activation)	
5. Temperature/Time	1
room temperature, <24 h	
6. Workup and purification	
Liquid-liquid extraction	3
Classical chromatography	10
Total penalty points	33

B) EcoScale calculation:

EcoScale Score: $(100 - 33) = \mathbf{67}$ (an acceptable synthesis)

Table S5. Calculation of E-factor and EcoScale Score for the synthesis of diphenyl disulfide from thiophenol under mechanochemical conditions



E-factor calculation for the synthesis of 10 under mechanochemical conditions:

Reactant (9): Thiophenol :	0.110 g	1 mmol	FW 110.18
Catalyst:	-----	-----	-----
Reagent:	-----	-----	-----
Solvent:	-----	-----	-----
Auxiliary (grinding): neutral Al ₂ O ₃	3 g	29.4	FW 101.96
Recycled auxiliary: neutral Al ₂ O ₃	3 g	29.4	FW 101.96
Product: 1,2-diphenyldisulfane:	0.108 g	0.495 mmol	FW 218.33

Product yield = 99%

$$\text{E-factor} = \frac{0.11 + 3 - (3 + 0.108)}{0.108} = \mathbf{0.019 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 10 under the mechanochemical conditions:

EcoScale score = 100 - Sum of individual penalties

Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

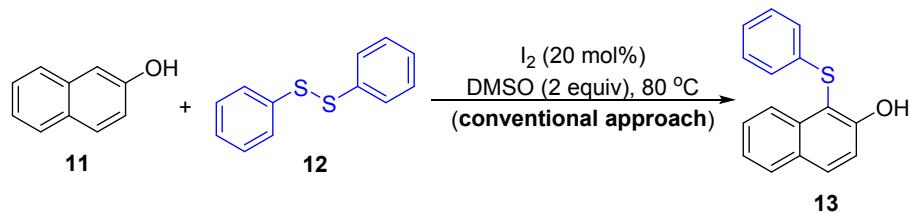
A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 99)/2 = 2$	0.5
2. Price of reaction components (To obtain 10 mmol of end product)	
a. Thiophenol = 20.2 mmol = 2.226 g = USD 0.446	
b. neutral alumina (grinding auxiliary) = 594.4 mmol = 60.6 g = USD 4.5	
Hence total price (USD) = (0.446 + 4.5) = USD 4.946	
(Thus inexpensive since total price < USD 10)	
3. Safety	0
a. Reactant (9): Thiophenol	
Toxic (T)	5
4. Technical Setup	2
Unconventional activation technique (mechanochemical activation)	
5. Temperature/Time	0
room temperature, <1 h	
6. Workup and purification	0
Adding solvent (ethanol) for washing the solid mass	0
Removal of solvent (ethanol) with bp<150 °C	0

Removal of solvent (c)

Total penalty points

Table S6. Calculation of E-factor and EcoScale score for the C-H α -sulfenylation of 2-naphthol using diphenyl disulfide to synthesize 1-(phenylthio)naphthalen-2-ol under the conventional heating conditions



E-factor calculation for the synthesis of 13 under conventional conditions:

Reactant 1 (11): 2-Naphthol:	0.072 g	0.5 mmol	FW 144.17;
Reactant 2 (12): Diphenyl disulfide:	0.055 g	0.25 mmol	FW 218.34;
Catalyst: Iodine:	0.0254 g	0.1 mmol	FW 253.81
Reagent: DMSO (0.073 mL):	0.078 g	1 mmol	FW 78.12
Solvent: -----	-----	-----	-----
Auxiliary: -----	-----	-----	-----
(Product: 1-(phenylthio)naphthalen-2-ol: 0.097 g	0.385 mmol	FW 252.33)	

Product yield = 77%

$$\text{E-factor} = \frac{0.072 + 0.055 + 0.0254 + 0.078 - 0.097}{0.097} = 1.38 \text{ Kg waste/1 Kg product}$$

EcoScale score calculation for the synthesis of 13 under the conventional conditions:

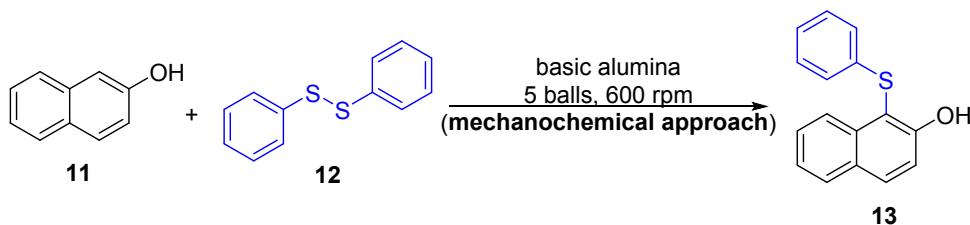
EcoScale score = 100 - Sum of individual penalties
Score on Ecocale: >75, Excellent; >50, acceptable; <50, inadequate

A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 77)/2 = 2$	12.5
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 2-Naphthol = 12.99 mmol = 1.87 g = USD 0.404	
b. Diphenyl disulfide = 6.49 mmol = 1.42 g = USD 0.91	
c. Iodine = 2.6 mmol = 0.66 g = USD 0.2	
d. DMSO = 1.9 mL = USD 0.13 (All the given prices are as per Sigma Aldrich)	
Hence total price (USD) = $(0.404 + 0.91 + 0.2 + 0.13) = \text{USD } 1.644$ (Thus inexpensive since total price < USD 10)	0
3. Safety	
a. 2-Naphthol Toxic (T)	5
b. Diphenyl disulfide Toxic (T)	5
c. Iodine: Toxic (T)	5
4. Technical Setup Common setup	0
5. Temperature/Time heating, >1 h	3
6. Workup and purification Liquid-liquid extraction Classical chromatography	3 10
Total penalty points	43.5

B) EcoScale calculation:
EcoScale Score: $(100 - 43.5) = 56.5$ (an acceptable synthesis)

Table S7. Calculation of E-factor and EcoScale score for the C-H α -sulfonylation of 2-naphthol using diphenyl disulfide to synthesize 1-(phenylthio)naphthalen-2-ol under the mechanochemical conditions



E-factor calculation for the synthesis of 13 under mechanochemical conditions:

Reactant 1 (11): 2-Naphthol:	0.029 g	0.2 mmol	FW 144.17
Reactant 2 (12): Diphenyl disulfide:	0.044 g	0.2 mmol	FW 218.34
Solvent:	-----	-----	-----
Auxiliary: basic alumina:	10 g	98 mmol	FW 101.96
Reused auxiliary: basic alumina:	10 g	98 mmol	FW 101.96
Product: 1-(phenylthio)naphthalen-2-ol:	0.044 g	0.176 mmol	FW 252.33

Product yield = 88%

$$\text{E-factor} = \frac{0.029 + 0.044 + 10 - (10 + 0.044)}{0.044} = \mathbf{0.66 \text{ Kg waste/1 Kg product}}$$

EcoScale score calculation for the synthesis of 13 under the mechanochemical conditions:

EcoScale score = 100 - Sum of individual penalties

Score on Ecoscale: >75, Excellent; >50, acceptable; <50, inadequate

A) Calculation of penalty points:

Parameters	Penalty points
1. Yield: $(100 - \% \text{ of yield})/2 = (100 - 88)/2 = 2$	6
2. Price of reaction components (To obtain 10 mmol of end product)	
a. 2-Naphthol = 11.36 mmol = 1.64 g = USD 0.354 b. Diphenyl disulfide = 11.36 mmol = 2.48 g = USD 1.59 c. basic alumina = 5.57 mol = 568 g = USD 16.76 (All the given prices are as per Sigma Aldrich)	
Hence total price (USD) = $(0.354 + 1.59 + 16.76) = \mathbf{\text{USD } 18.7}$ (Thus expensive since total price > USD 10)	3
3. Safety	
a. 2-Naphthol Toxic (T)	5
b. Diphenyl disulfide Toxic (T)	5
4. Technical Setup Unconventional activation technique (mechanochemical activation)	2
5. Temperature/Time room temperature, 1 h	0
6. Workup and purification	
Classical chromatography	10
Total penalty points	31

B) EcoScale calculation:

$$\text{EcoScale Score: } (100 - 31) = \mathbf{69 \text{ (an acceptable synthesis)}}$$

Reference:

1. Liu, X.; Luo, X.-S.; Deng, H.-L.; Fan, W.; Wang, S.; Yang, C.; Sun, X.-Y.; Chen, S.-L.; Huang, M.-H. Functional Porous Organic Polymers Comprising a Triaminotriphenylazobenzene Subunit as a Platform for CopperCatalyzed Aerobic C–H Oxidation. *Chem. Mater.* **2019**, *31*, 5421–5430.