

# A novel facile approach to obtain phenytoin and thiophenytoin using new deep eutectic solvent-like mixtures of urea, thiourea, and KOH

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## SUPPLEMENTARY INFORMATION

### 5-(3-chlorophenyl)-5-phenylimidazolidine-2,4-dione 1b.

Yield 95%. Mp 218-220 °C (lit. mp 227-228 °C [1])

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 11.24 (s, 1H), 9.40 (s, 1H), 8.00 – 6.95 (m, 10H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 174.76, 156.30, 142.51, 139.96, 133.69, 131.02, 129.20, 128.62, 126.84, 125.78, 70.18.

### 5-(4-chlorophenyl)-5-phenylimidazolidine-2,4-dione 1c.

Yield 71%. Mp 240-242 °C (lit. mp 243 °C [2]).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 11.10 (s, 1H), 9.28 (s, 1H), 7.37 – 7.17 (m, 9H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 175.00, 156.35, 140.08, 139.23, 133.36, 129.43, 129.13, 127.79, 127.47, 126.97, 70.20.

### 5-(3-bromophenyl)-5-phenylimidazolidine-2,4-dione 1d.

Yield 90%. Mp 200-202 °C (lit. mp 209-210 °C [1])

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 11.15 (s, 1H), 9.31 (s, 1H), 7.49 (dt, *J* = 7.1, 1.8 Hz, 1H), 7.43 (s, 1H), 7.33 – 7.22 (m, 7H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 174.75, 156.29, 142.72, 139.96, 131.29, 129.66, 129.21, 128.77, 126.91, 126.16, 70.13.

### 5-(4-bromophenyl)-5-phenylimidazolidine-2,4-dione 1e.

Yield 95%. Mp 232-234 °C (lit. mp 239 °C [1]).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 11.11 (s, 1H), 9.29 (s, 1H), 7.26 (d, *J* = 22.4 Hz, 9H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 174.95, 156.37, 140.02, 139.67, 131.95, 129.30, 129.13, 128.68, 126.98, 122.01, 70.28.

### 5-phenyl-5-(*p*-tolyl)imidazolidine-2,4-dione 1f.

Yield 87%. Mp 219-220 °C (lit. mp 223-225 °C [3]).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 10.98 (s, 1H), 9.18 (s, 1H), 7.37 – 7.07 (m, 9H), 2.19 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ, ppm: 175.41, 156.46, 140.51, 137.82, 137.51, 129.49, 128.92, 128.43, 127.04, 126.96, 70.50, 21.05.

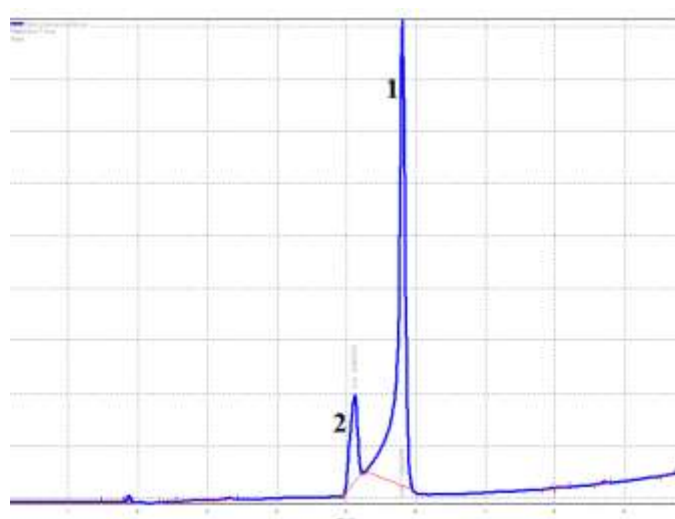


Figure S1. Chromatogram (HPLC) of the reaction mixture (urea:KOH:benzil = 3:1:0.5, 90°C) after 1 minute.

1 – phenytoin **1a** (retention time is 5.80 min.)

2 – glycoluril **3a** (retention time is 5.12 min.)

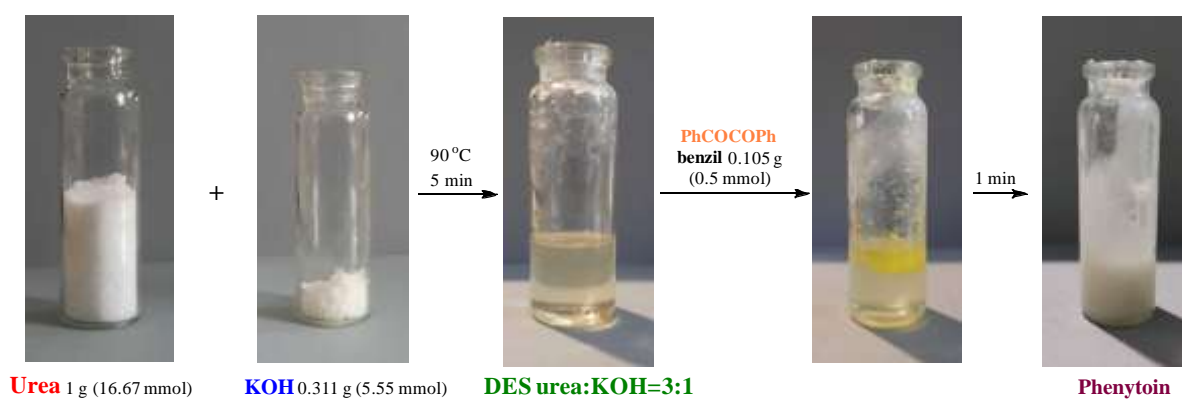


Figure S2. Obtaining phenytoin **1a** in DES urea:KOH =3:1

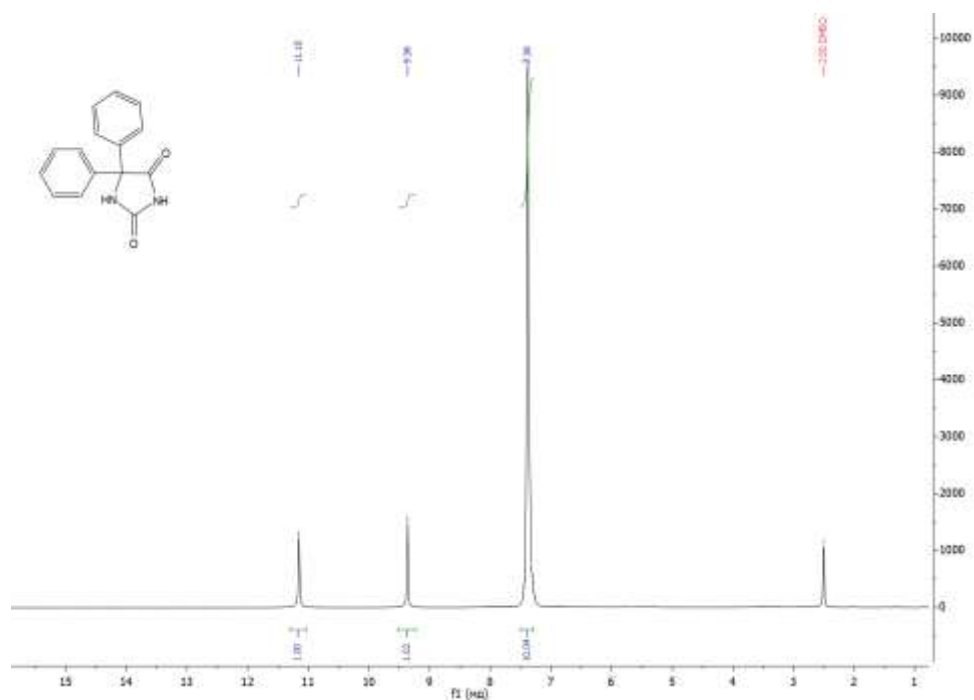


Figure S3. <sup>1</sup>H NMR spectrum of **1a**.

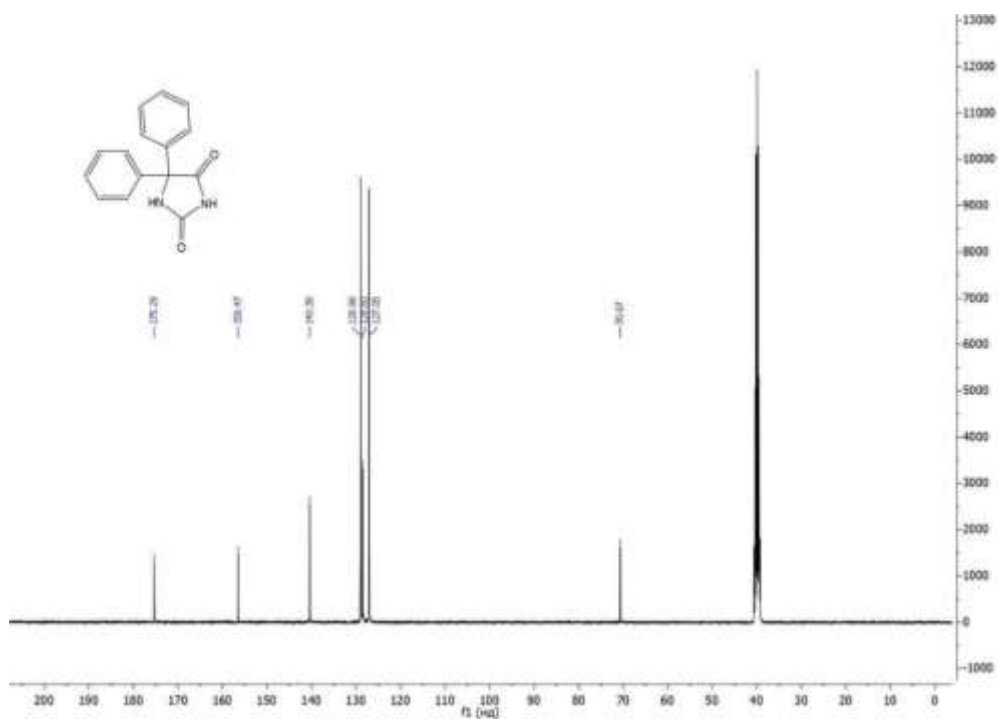


Figure S4. <sup>13</sup>C NMR spectrum of **1a**.

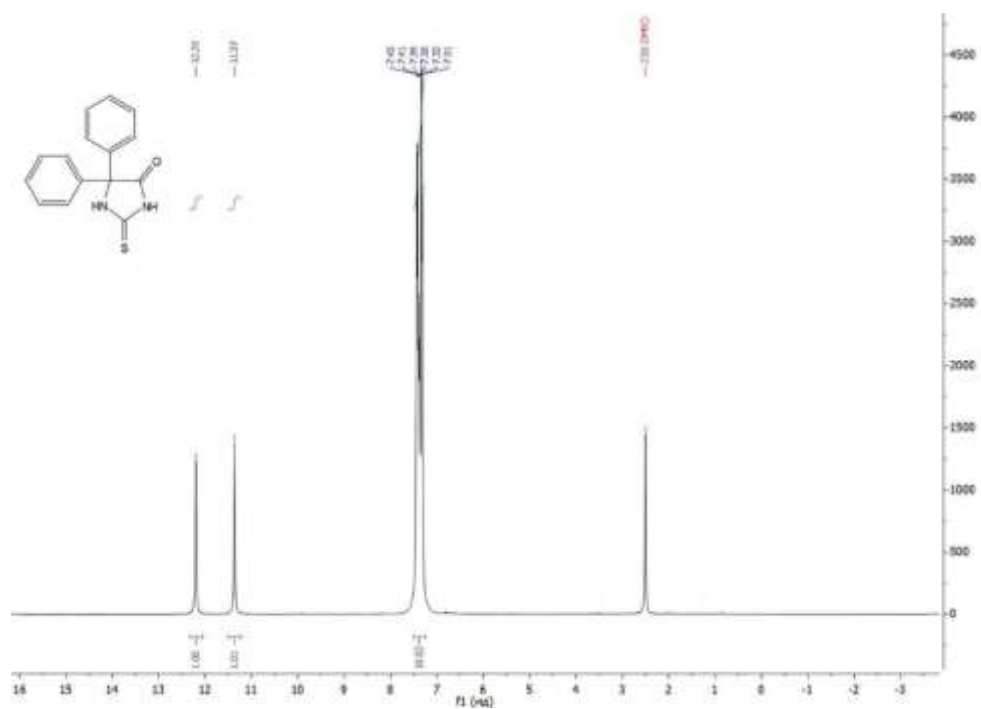


Figure S5.  $^1\text{H}$  NMR spectrum of **2a**.

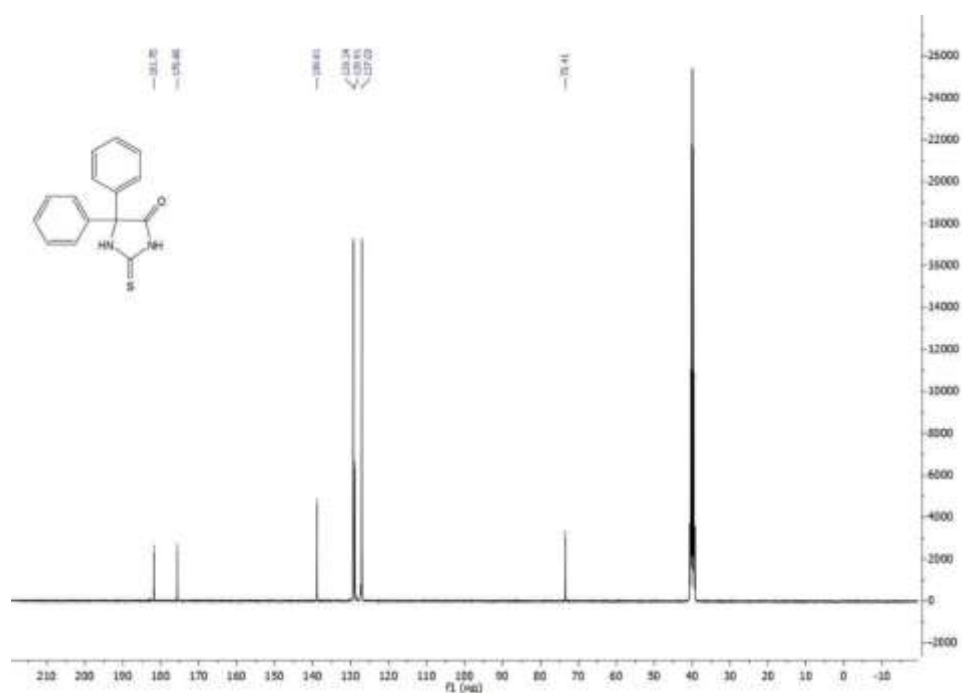


Figure S6.  $^{13}\text{C}$  NMR spectrum of **2a**.

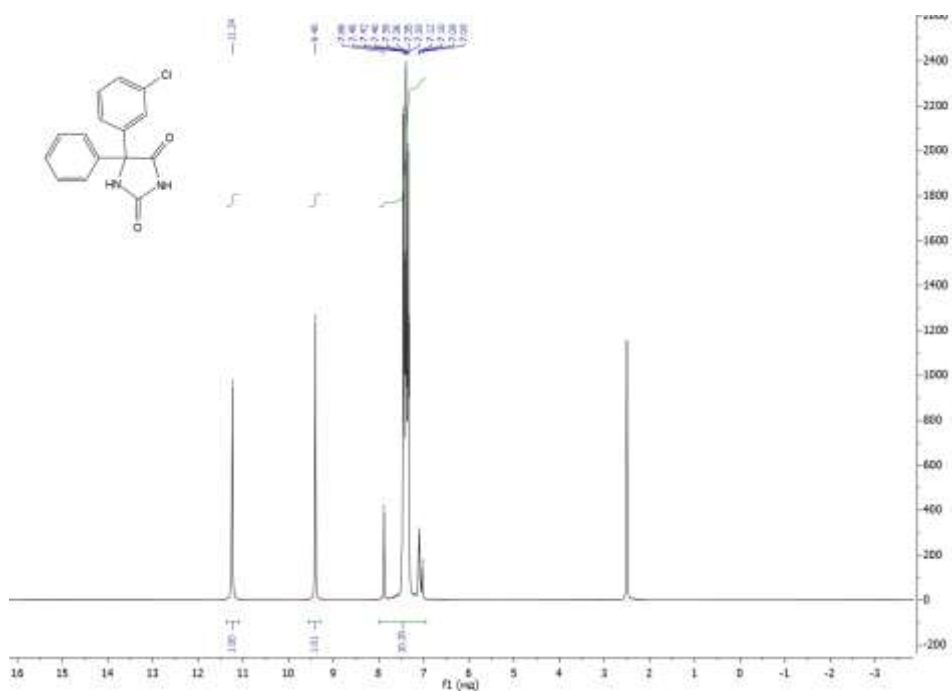


Figure S7. <sup>1</sup>H NMR spectrum of **1b**.

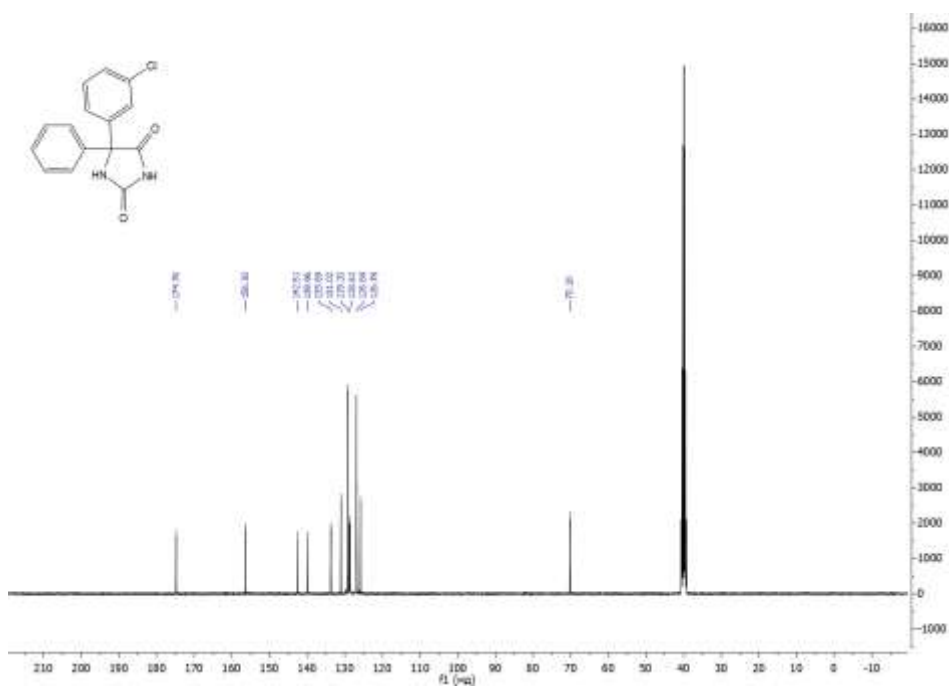


Figure S8. <sup>13</sup>C NMR spectrum of **1b**.

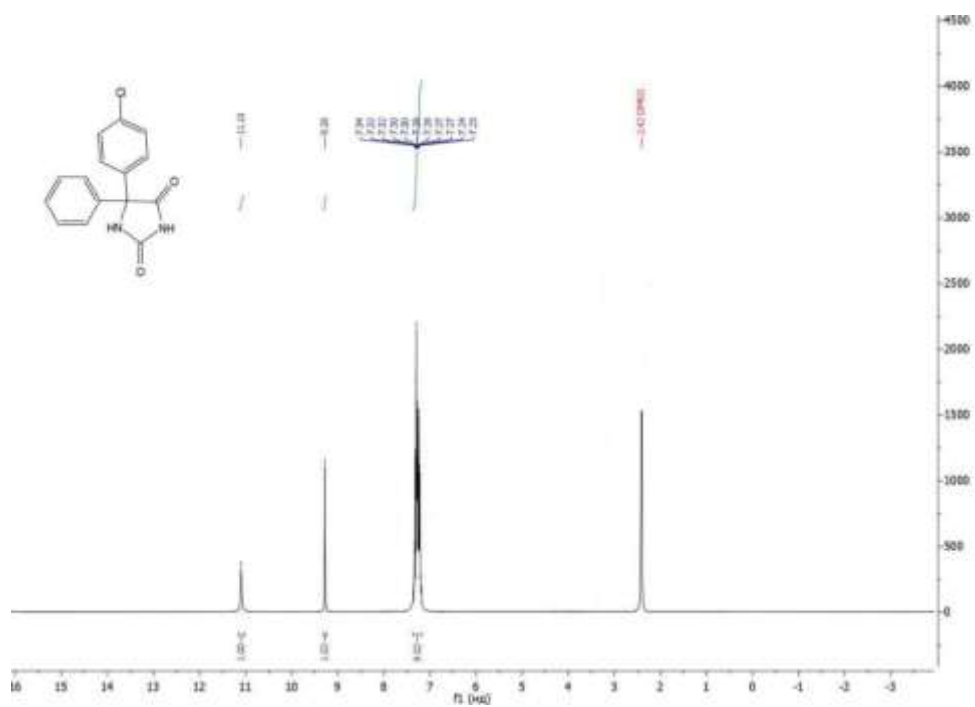


Figure S9.  $^1\text{H NMR}$  spectrum of **1c**.

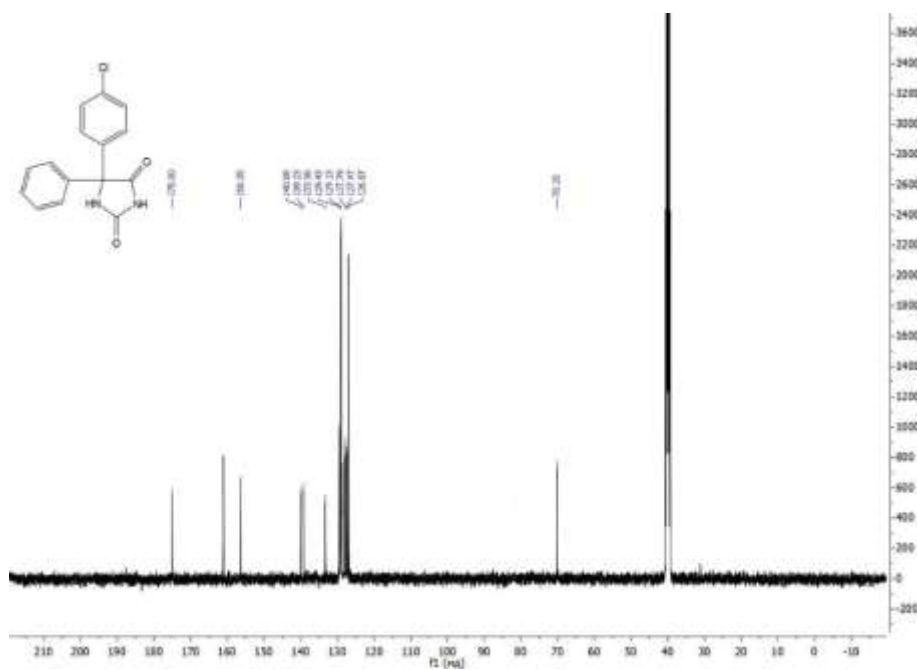


Figure S10.  $^{13}\text{C NMR}$  spectrum of **1c**.

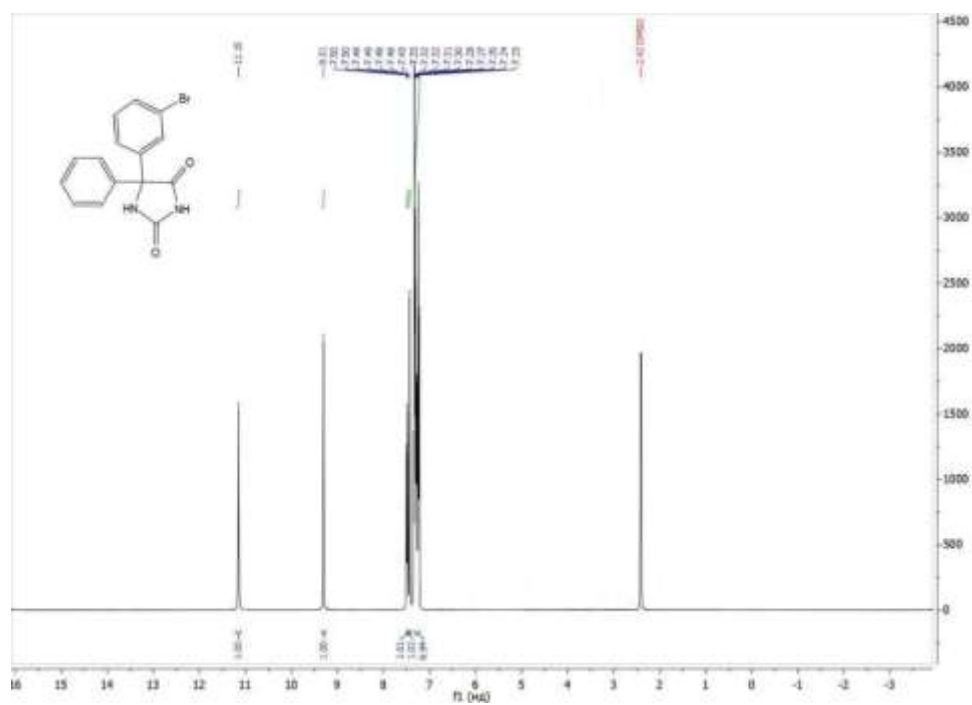


Figure S11.  $^1\text{H}$  NMR spectrum of **1d**.

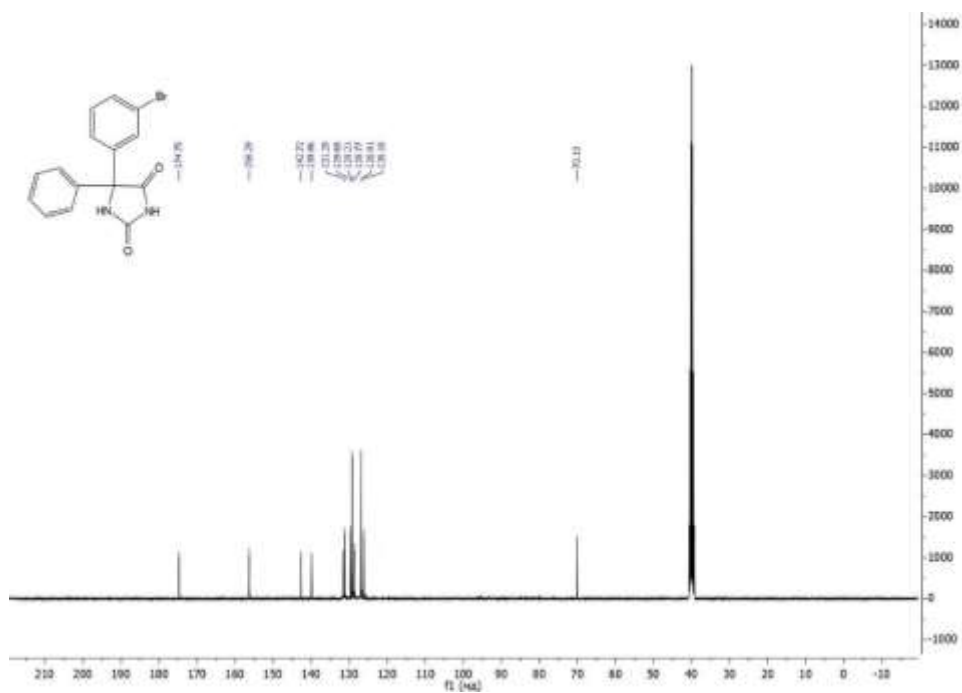


Figure S12.  $^{13}\text{C}$  NMR spectrum of **1d**.

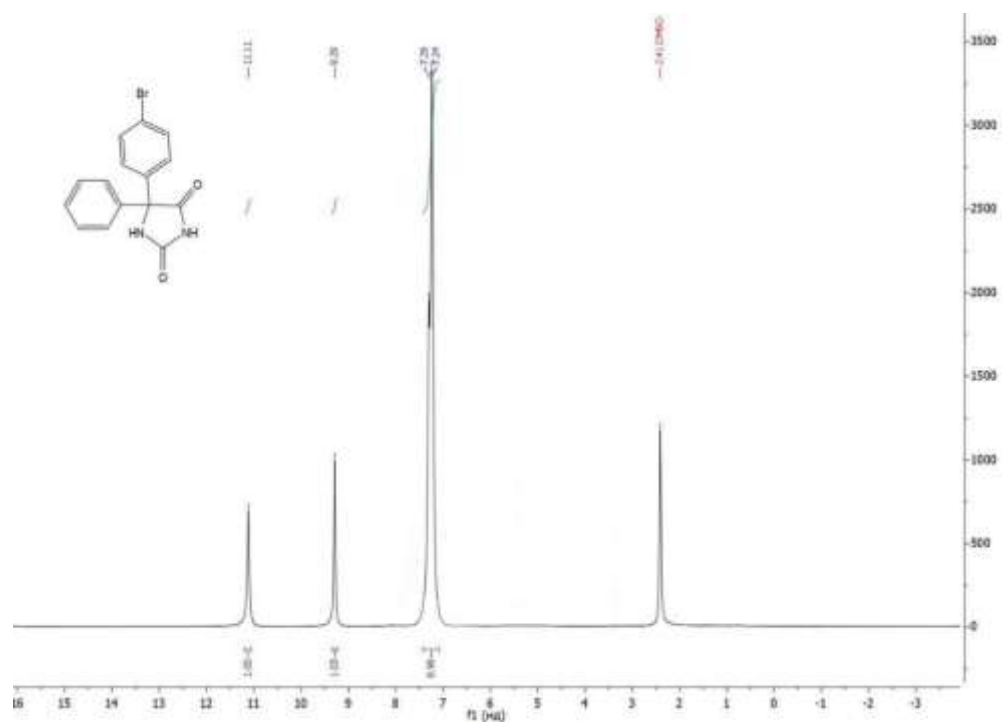


Figure S13.  $^1\text{H NMR}$  spectrum of **1e**.

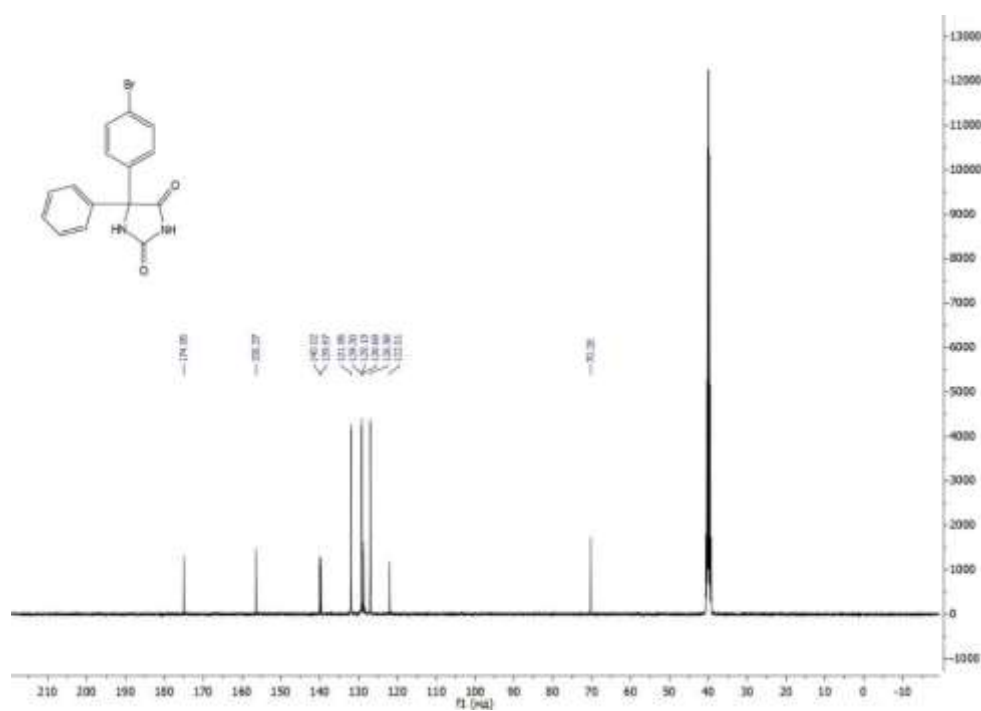


Figure S14.  $^{13}\text{C NMR}$  spectrum of **1e**.



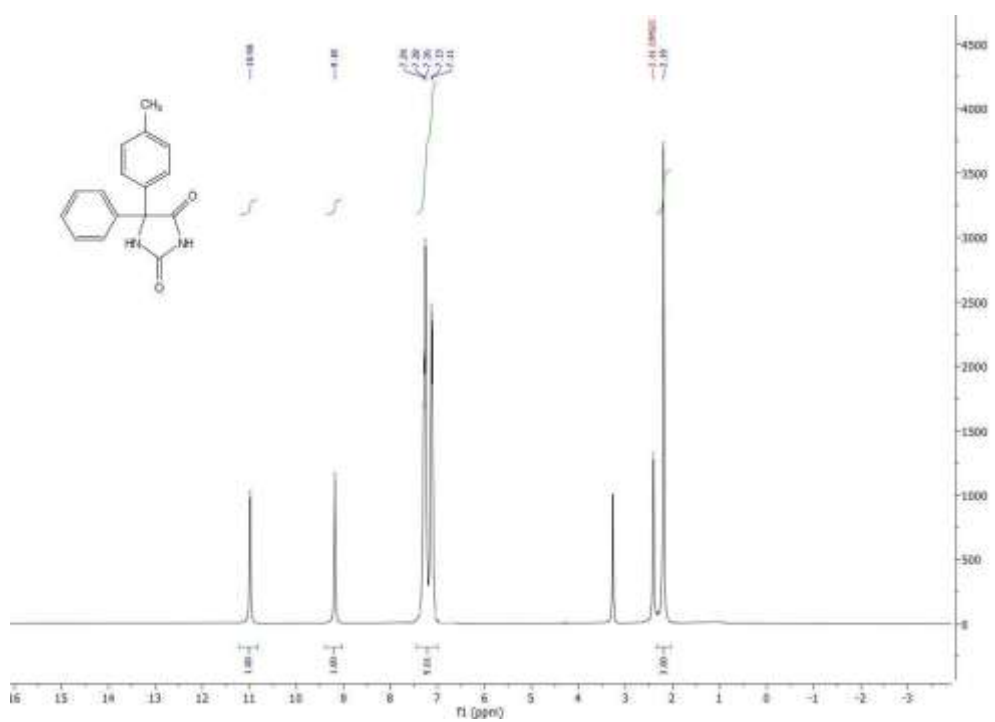


Figure S15.  $^1\text{H}$  NMR spectrum of **1f**.

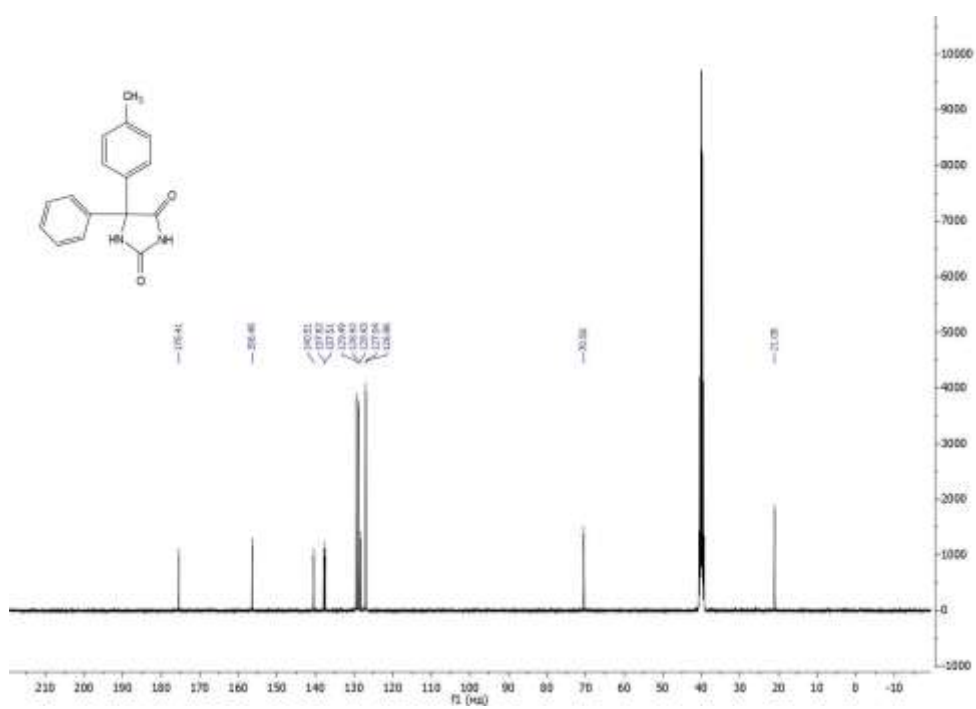


Figure S16.  $^{13}\text{C}$  NMR spectrum of **1f**.

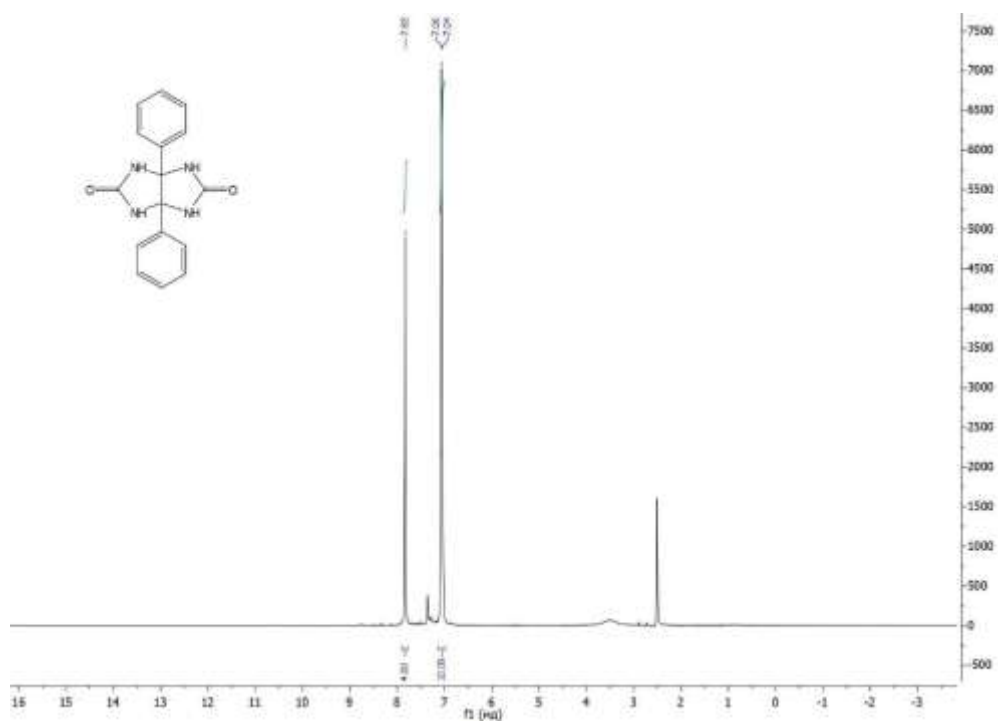


Figure S17. <sup>1</sup>H NMR spectrum of **3a**.

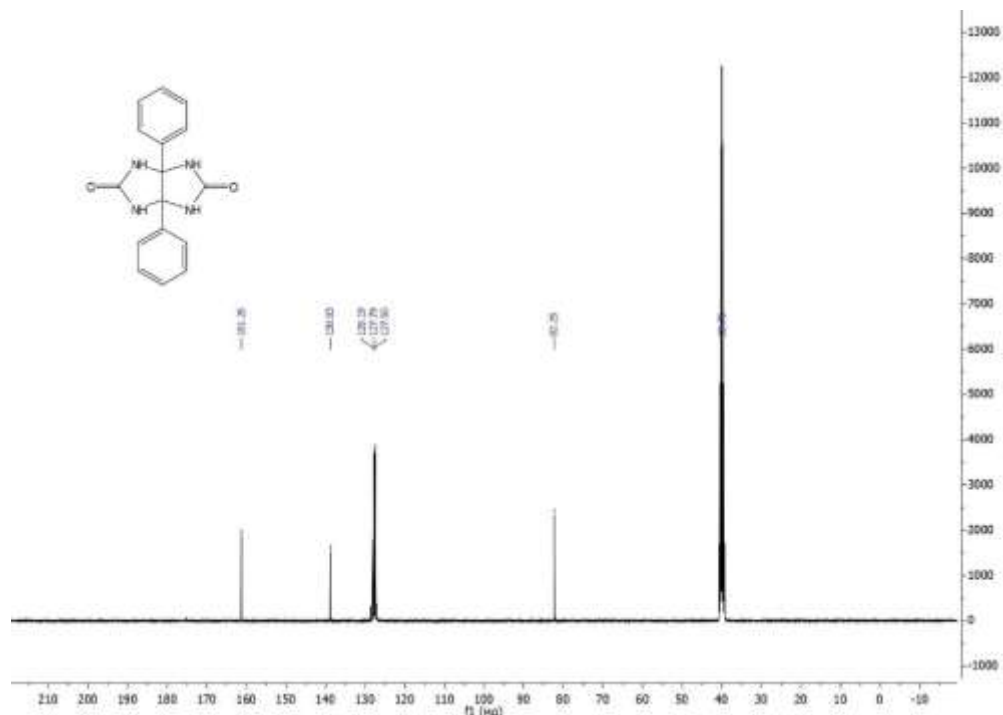


Figure S18. <sup>13</sup>C NMR spectrum of **3a**.

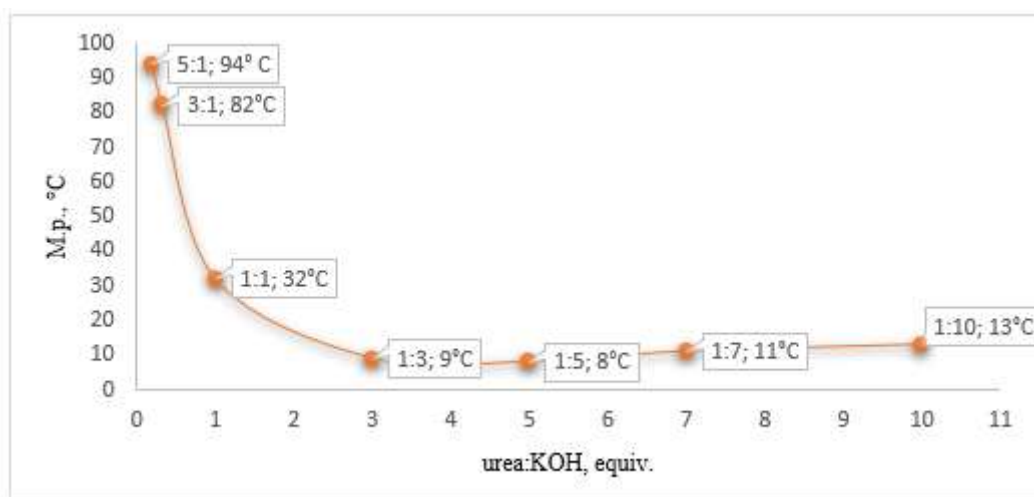


Figure S19. Melting points of urea:KOH mixtures

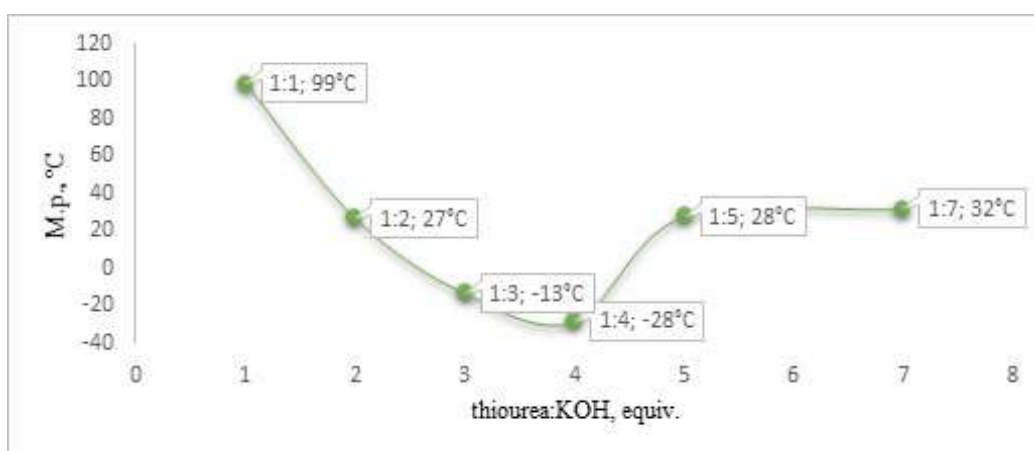


Figure S20. Melting points of thiourea:KOH mixtures

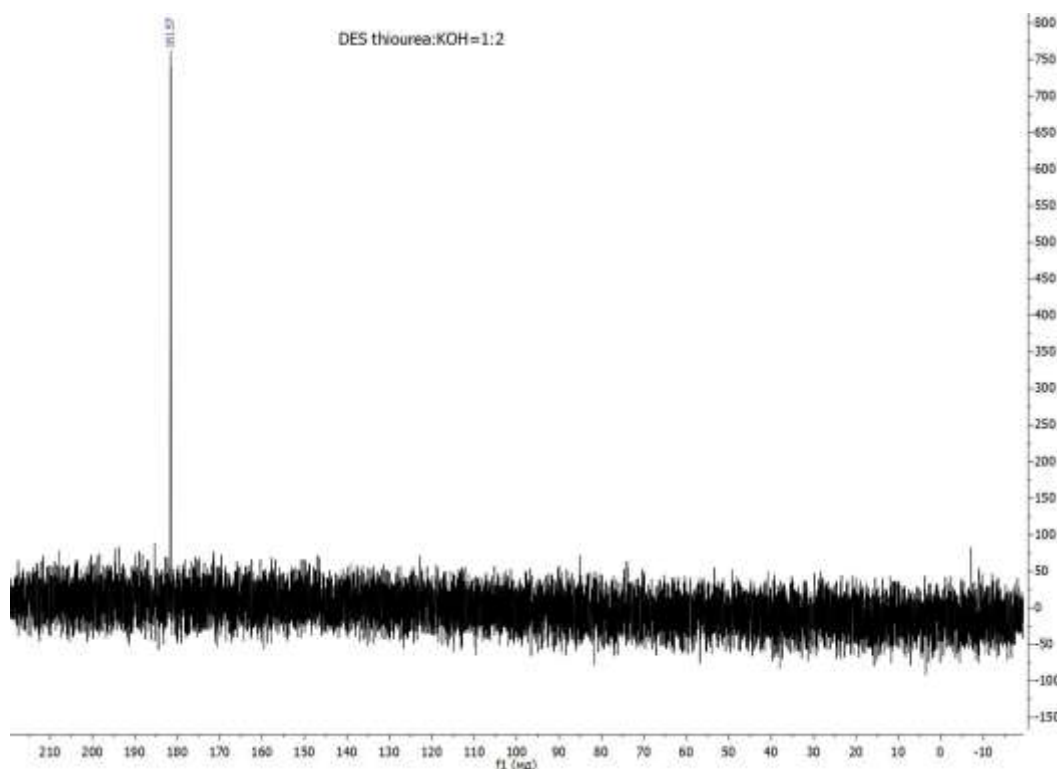


Figure S21.  $^{13}\text{C}$  NMR spectrum of DES thiourea:KOH=1:2 (solvent  $\text{D}_2\text{O}$ ).

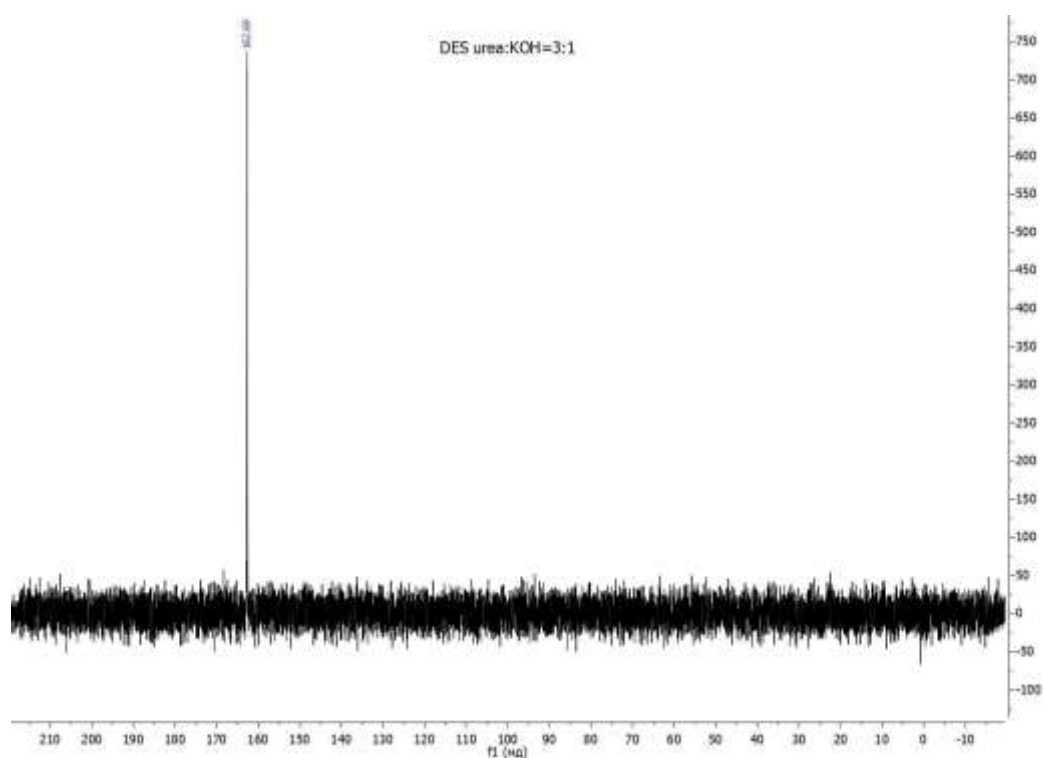


Figure S22.  $^{13}\text{C}$  NMR spectrum of DES urea:KOH=3:1 (solvent  $\text{D}_2\text{O}$ ).

Table S1. Melting points of prepared DES-like mixtures urea:KOH

urea:KOH, Equiv.	M.p., °C
1:10	13
1:7	11
1:5	8
1:3	9
1:1	32
3:1	82
5:1	94

Table S2. Melting points of prepared DES-like mixtures thiourea:KOH

thiourea:KOH, Equiv.	M.p., °C
1:7	32
1:5	28
1:4	-28
1:3	-13
1:2	27
1:1	99

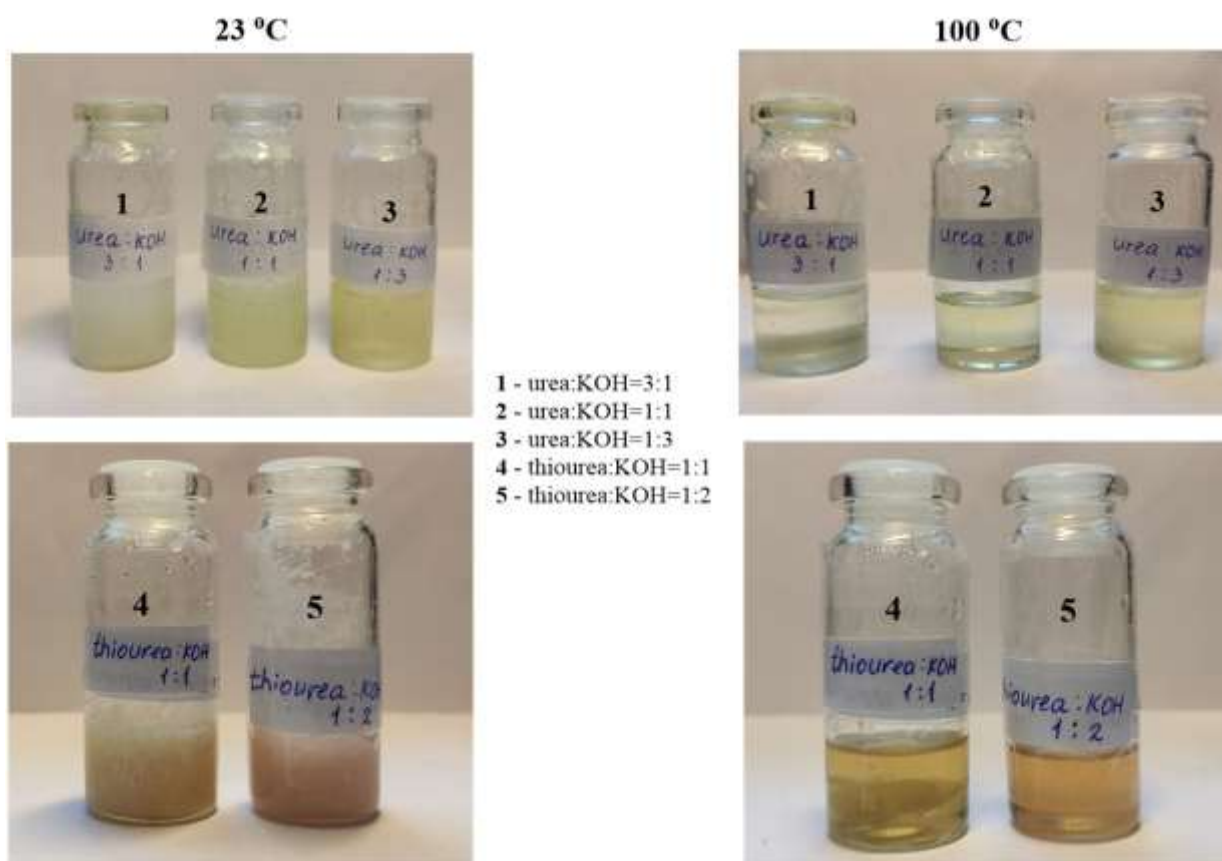


Figure S23. DES urea/KOH and thiourea/KOH in various ratios.

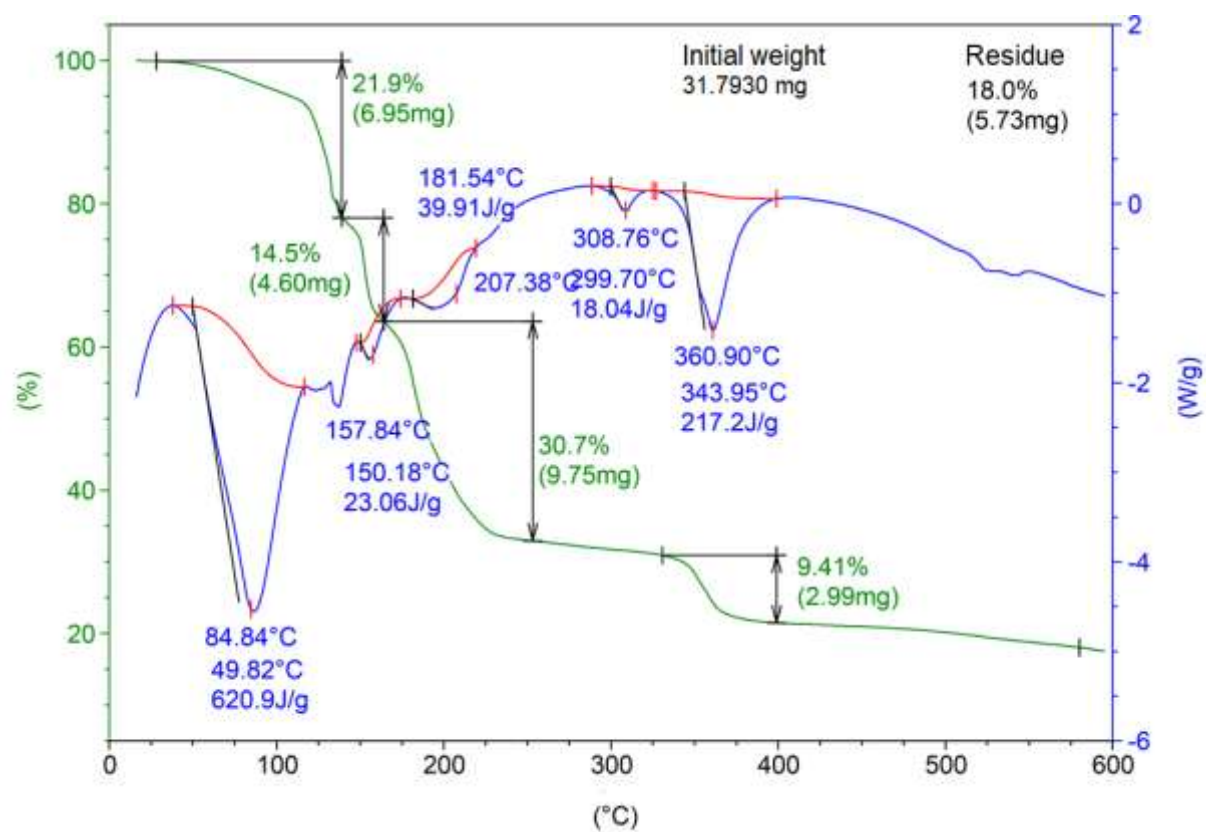


Figure S24. DSC-TGA of urea:KOH mixture 3:1

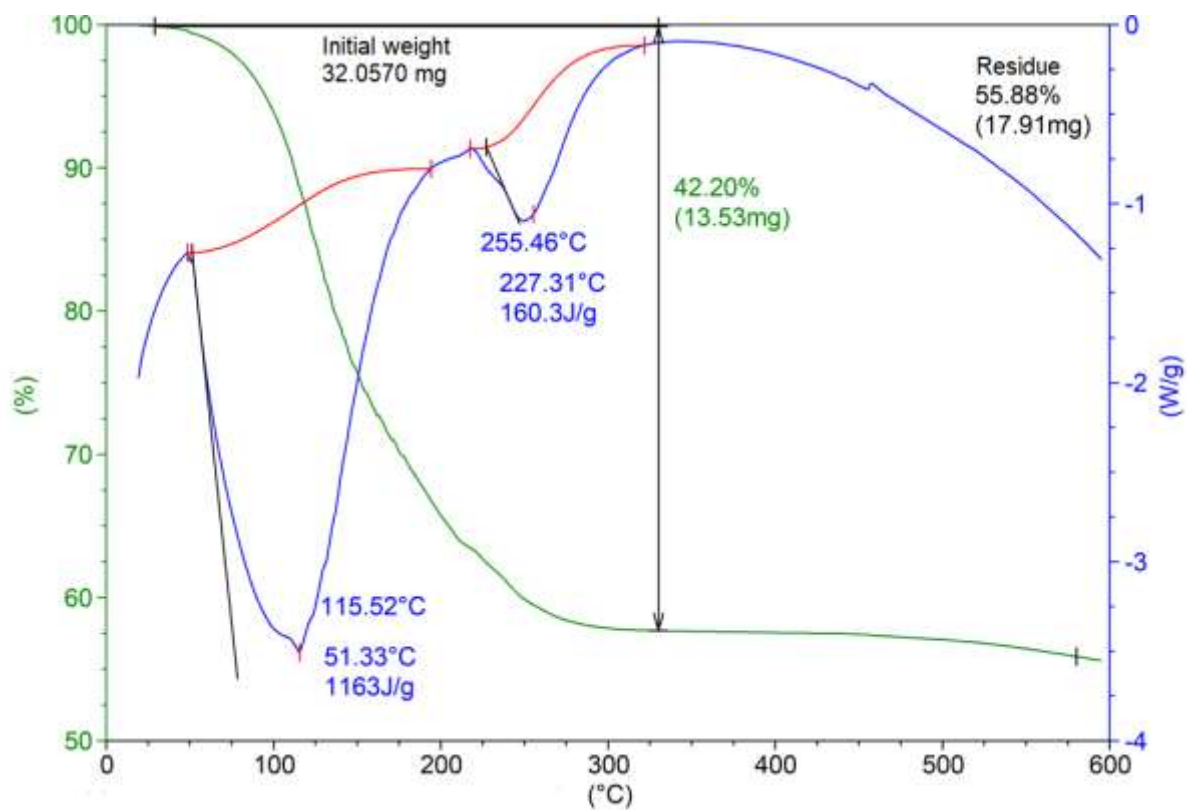


Figure S25. DSC-TGA of urea:KOH mixture 1:3

## References

1. Melton, J. W.; Henze, H. R. *J. Am. Chem. Soc.*, **1947**, *69*, 2018-2020.
2. Henze, H. R.; *Patent US2409754*, **1946**.
3. Safari, J.; Arani, N. M.; Isfahani, A. R. *Chinese J. Chem.* **2010**, *28*, 255–258.