Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information

Self-Amplified Depolymerization of Oligo(thiourethanes) for the Release of COS/H_2S

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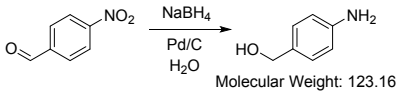
Materials and Methods

All reagents and solvents were obtained from commercial vendors and used as received unless otherwise stated. NMR spectra were measured on Agilent 400 MHz or Bruker 500 MHz spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to internal solvent resonances. Yields refer to compounds as isolated after requisite purification unless otherwise stated. Thin-layer chromatography (TLC) was performed on glass-backed silica plates and visualized by UV. UV-Vis experiments were conducted on a Varian Cary 100 Bio UV-Vis spectrophotometer with a scan rate of 600 nm/min (1 nm data intervals) with 0 and 100 % transmittance baseline corrections. H_2S release data acquired with a WPI ISO-H2S-100 electrochemical probe set to a constant 10 nA current.

Synthetic Procedures

Synthesis of 4-aminobenzyl alcohol (**4-AB**).



Molecular Weight: 123.16

$NaBH_4$ (1.50 g, 40 mmol) was dissolved in H_2O (40 mL) in a 2-necked round bottom flask under N_2 flow. To the flask was added 4-nitrobenzaldehyde (2.00 g 13.2 mmol) in one portion. Pd/C (0.070, 0.66 mmol) was then added slowly to the flask (***CAUTION: this step leads to vigorous H_2 gas evolution; a plastic spatula should be used to add Pd/C to reduce the risk of sparking***). The reaction mixture was stirred at rt until all of the solids dissolved (~ 1 h) to give a clear yellow solution. The reaction mixture was then filtered through packed Celite. The aqueous solution was extracted with EtOAc (3x, 30 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2. The pure product was obtained as an off-white solid (1.30 g, 80 % yield). ^{1}H NMR ($CDCl_3$): δ 7.14 (m, 2H), 6.66 (m, 2H), 4.53 (s, 2H) 3.60 (broad s, 2H). ^{13}C NMR ($CDCl_3$): δ 146.11, 131.16, 128.86, 115.24, 65.34.

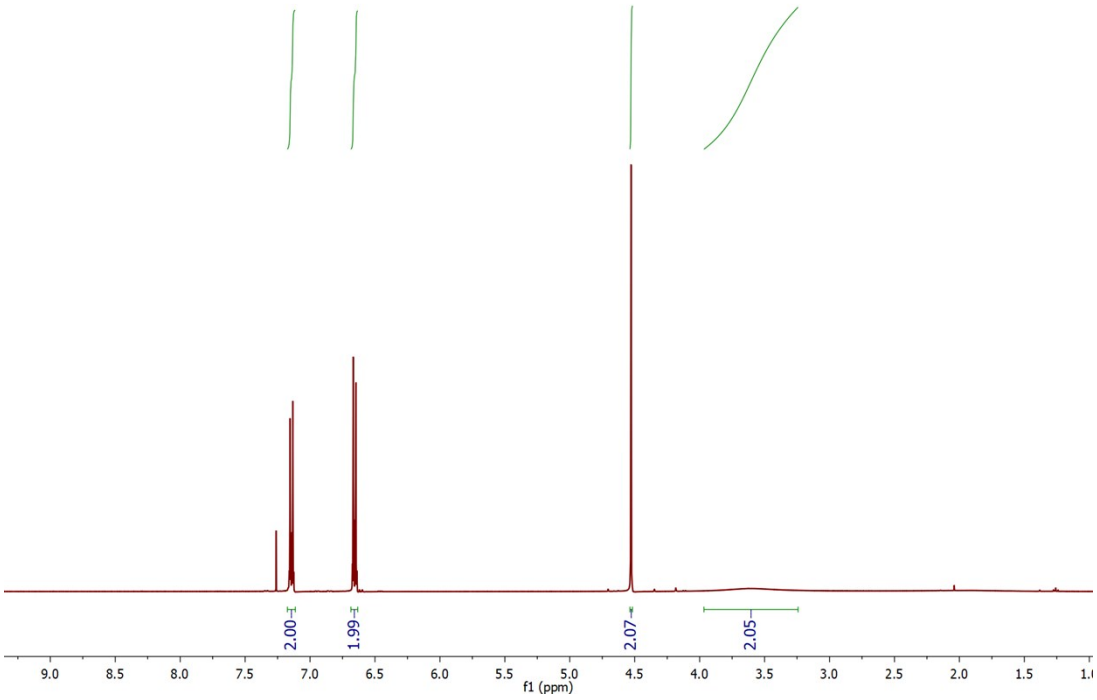


Figure S1. ^{1}H NMR spectrum of 4-aminobenzyl alcohol ($CDCl_3$).

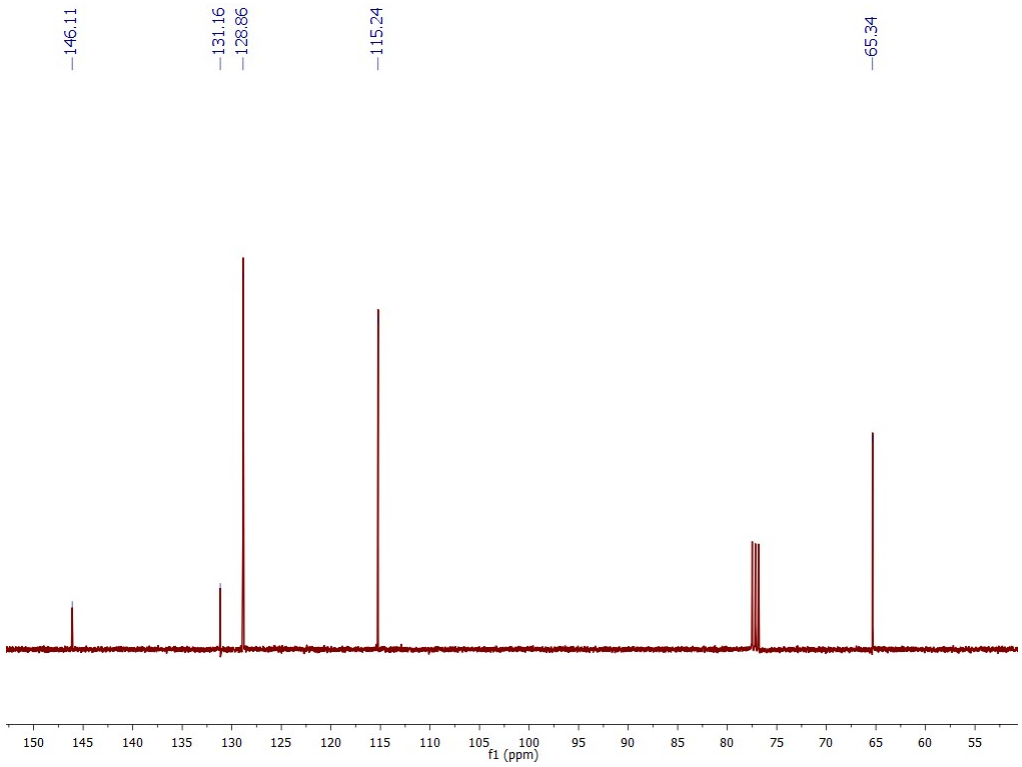
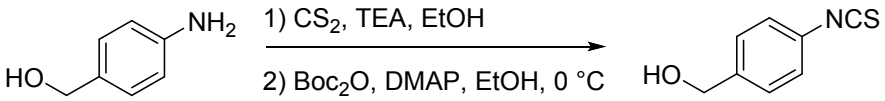


Figure S2. ^{13}C NMR spectrum of 4-aminobenzyl alcohol ($CDCl_3$).

Synthesis of 4-isocyanatobenzyl alcohol **(SADM1)**



The procedure was adapted from a published procedure by Boas et al.[1] **4-AB** (2.0 g, 16 mmol) was dissolved in EtOH (40 mL) in a round bottom flask. To the flask was added CS_2 (10 mL, 170 mmol) followed by $N(Et)_3$ (2.3 mL, 17 mmol) resulting immediately in a clear yellow solution. The reaction mixture was allowed to stir at rt for 30 min. Reaction progress was monitored via TLC (2 % MeOH in CH_2Cl_2). Once complete consumption of **4-AB**, the reaction vessel was cooled to 0 °C in an ice bath. A solution of Boc_2O (3.2g, 15 mmol) in 10 mL of EtOH was added dropwise at 0 °C. DMAP (40 mg, 0.32 mmol) was subsequently added, and the reaction mixture was allowed to warm to rt while stirring for an additional 30 min. The reaction mixture was then diluted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, and concentrated by rotary evaporation to give a yellow-brown solid. The crude product was purified by a silica column, eluting with CH_2Cl_2 to yield a yellow/white solid. The solid was then recrystallized twice from hexanes to yield white, needle-like crystals (1.48 g, 56 % yield). ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 2H), 7.20 (m, 2H), 4.67 (s, 2H) 1.99 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 140.23, 135.37, 130.47, 128.05, 125.95, 64.56.

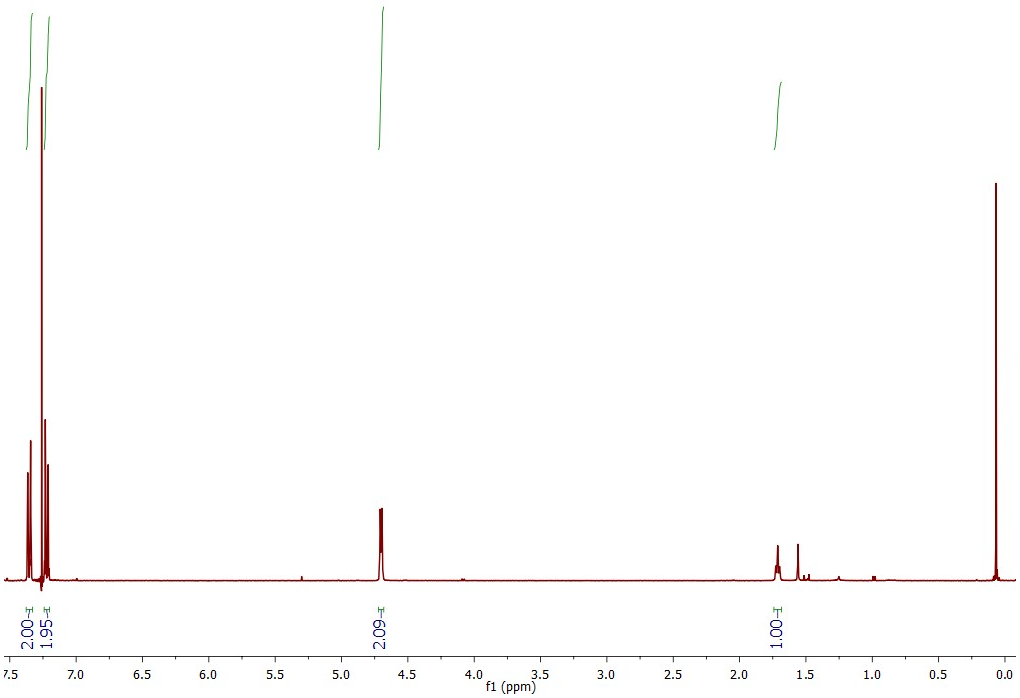


Figure S3. ^{1}H NMR spectrum of **SADM1** ($CDCl_3$).

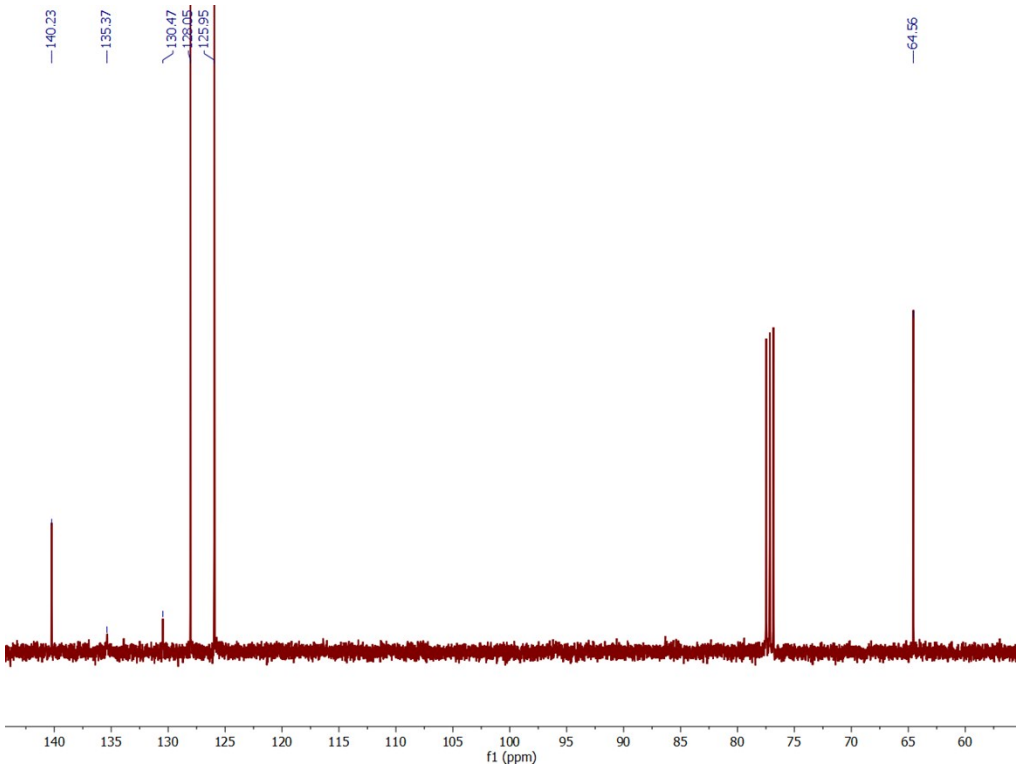
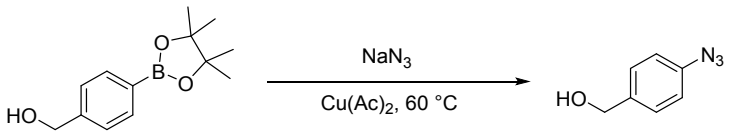


Figure S4. ^{13}C NMR spectrum of **SADM1** ($CDCl_3$).

Synthesis of (4-azidophenyl)methanol (**EC1**)



The procedure was adapted from published procedures by Aldrich et al.[2] A roundbottom flask was charged with 4-(hydroxymethyl)phenyl boronic acid pinacol ester (0.500 g, 2.16 mmol) and a stirbar. The pinacol boronic ester starting material was dissolved in methanol (10 mL). Sodium azide (0.211 g, 3.25 mmol) was added followed by copper(II) acetate monohydrate (0.43 g, 0.22 mmol). The resulting suspension was warmed to 60 °C in an oil bath and stirred vigorously. The reaction was monitored by TLC (20 % MeOH in EtOAc). Once complete, the reaction was cooled to rt, silica gel was added to the reaction mixture, and the slurry was concentrated to dryness by rotary evaporation. The dry-loaded crude product was purified on a silica gel column (eluting with Et_2O) to obtain the pure product as a yellow oil (0.220 g, 70 % yield). ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 2H), 7.02 (m, 2H), 4.67 (s, 2H) 1.68 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 139.53, 137.71, 128.69, 119.27, 64.90.

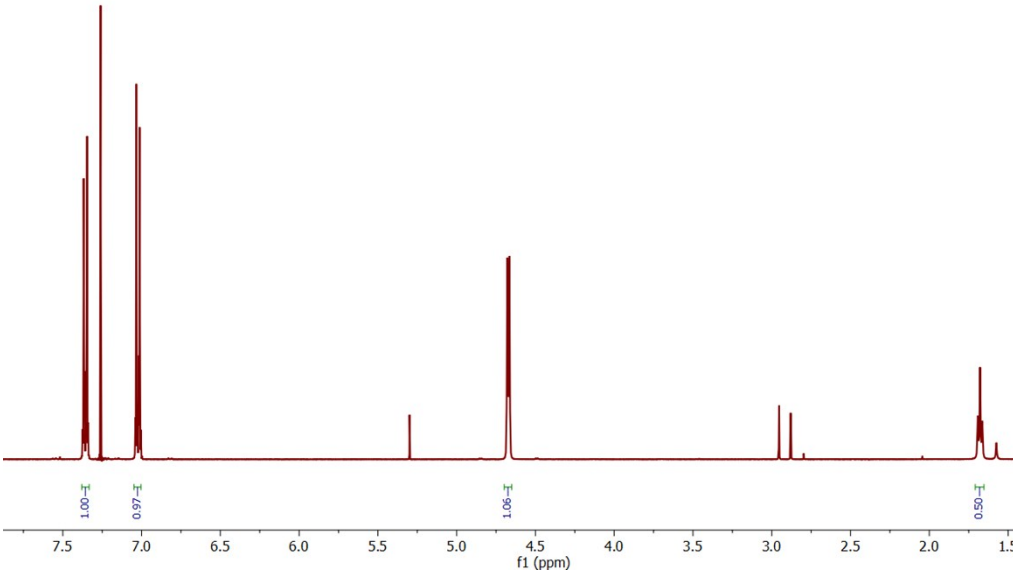


Figure S5. ^{1}H NMR spectrum of **EC1** ($CDCl_3$).

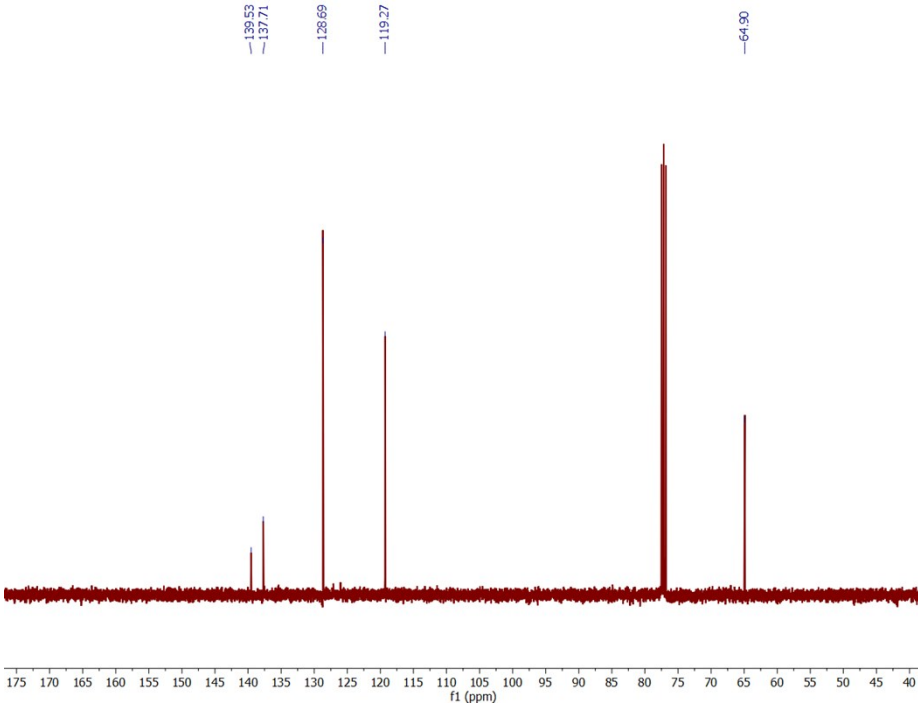
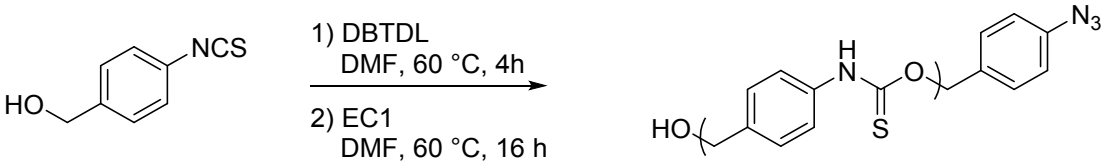


Figure S6. ^{13}C NMR of **EC1** ($CDCl_3$).

Representative polymerization of **SADM1**



The procedure was adapted from published procedures by Shabat et al.[3] A two-neck roundbottom flask equipped with a glass stopper and vacuum adapter was charged with a magnetic stirbar and flame-dried under vacuum. The flask was then put under positive N_2 pressure and charged with **SADM1** (60 mg, 0.36 mmol). **SADM1** was then dissolved in dry DMF (0.4 mL) to give a clear, colorless solution. The solution was then heated to 60 °C in an oil bath, and DBTDL (11 µL, 0.018 mmol) was added at temperature. The reaction mixture was allowed to stir at 60 °C under N_2 atmosphere for 7.5 h, resulting in a clear, yellow solution. In a separate flask, **EC1** (54 mg, 0.36 mmol) was dissolved in dry DMF (0.4 mL) and subsequently added to the reaction mixture. The reaction mixture was stirred for 14 h at 60 °C. The polymerization was then cooled to rt and precipitated twice into Et_2O to afford **SADP1** as a yellow/brown solid (32 mg).

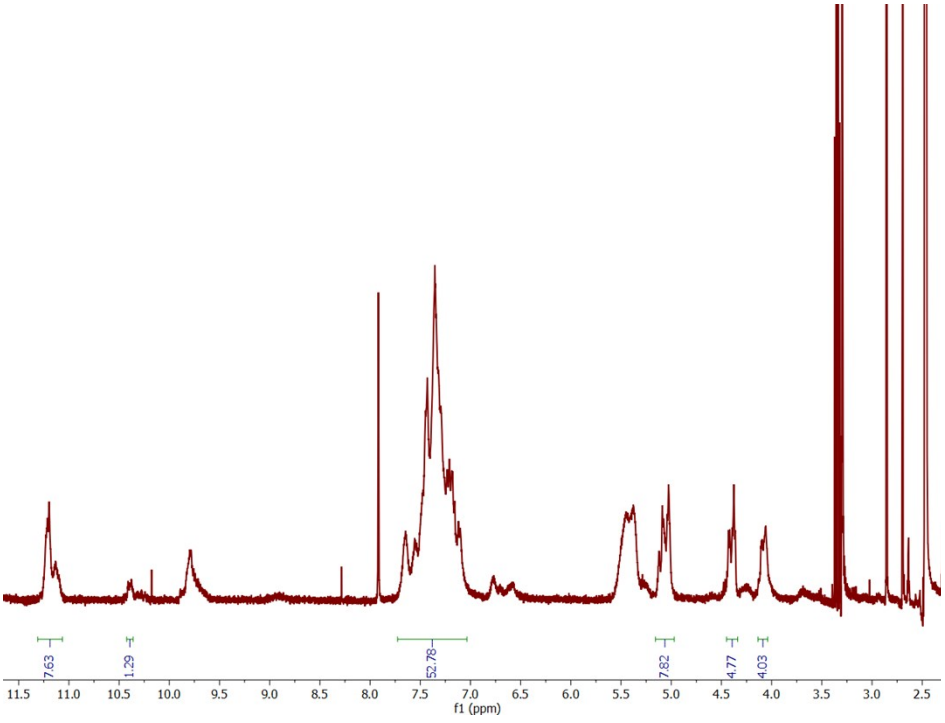


Figure S7. ^{1}H NMR spectrum of **SADP1** (DMSO-d_6).

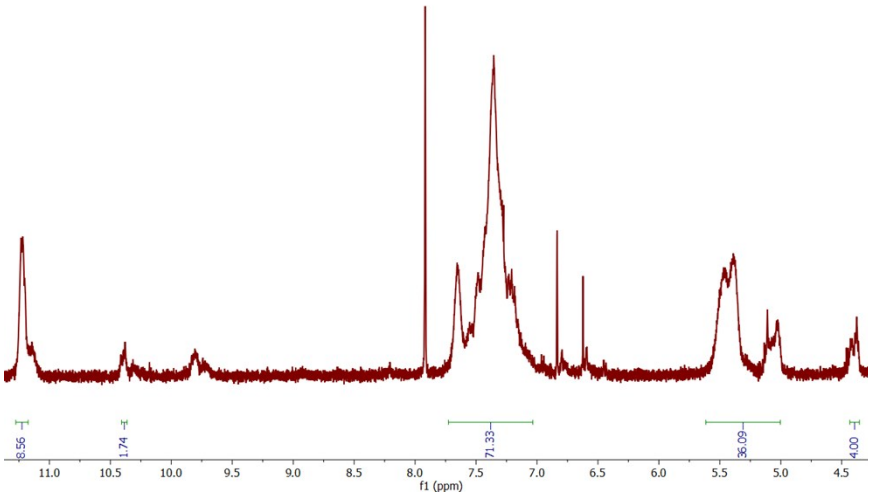


Figure S8. ^{1}H NMR spectrum of **Ctrl-SADP** in (DMSO-d_6).

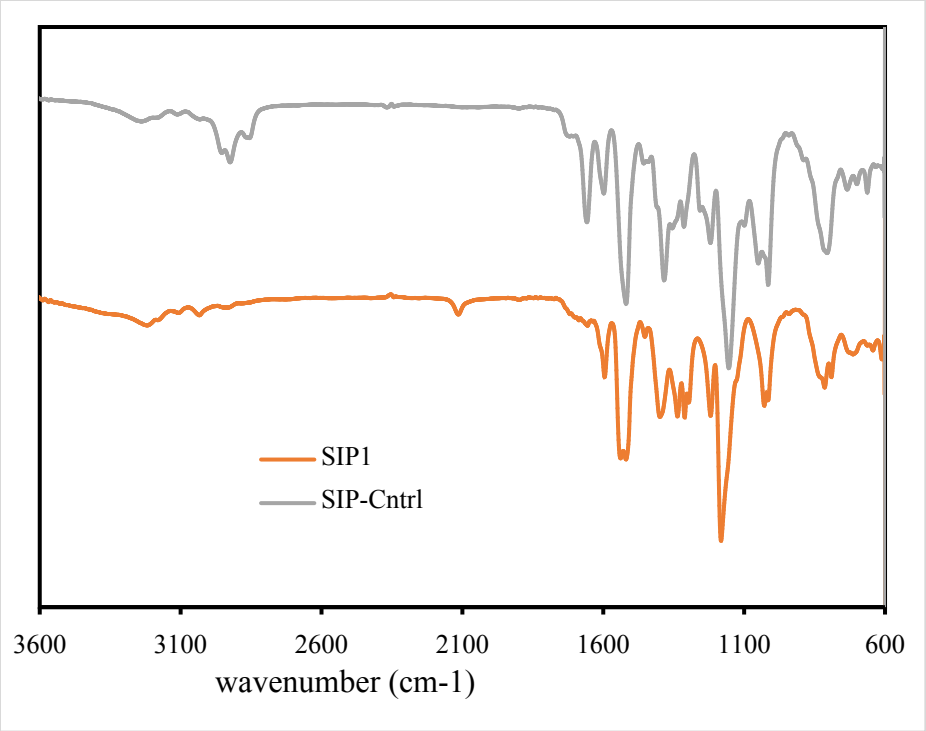


Figure S9. Offset FTIR spectra of **SADP1** and **SADP-Ctrl**. The absorbance band at ~2100 cm^{-1} confirms the presence of the aryl azide end group of **SADP1**.

Polymerization kinetics

Polymerizations were performed as described in *Representative polymerization of SADPs* with 1,3,5-trimethoxybenzene added to the reaction mixture as an internal standard. The polymerization was monitored by removing aliquots from the reaction mixture at predetermined timepoints via an N_2-purged syringe. Aliquots were cooled rapidly in an ice bath and then dissolved in DMSO-d_6 (0.6 mL) for ^{1}H NMR spectroscopic analysis. ^{1}H NMR analysis was done on a Bruker 500 MHz spectrometer (64 scans; T_1 relaxation = 5 s).

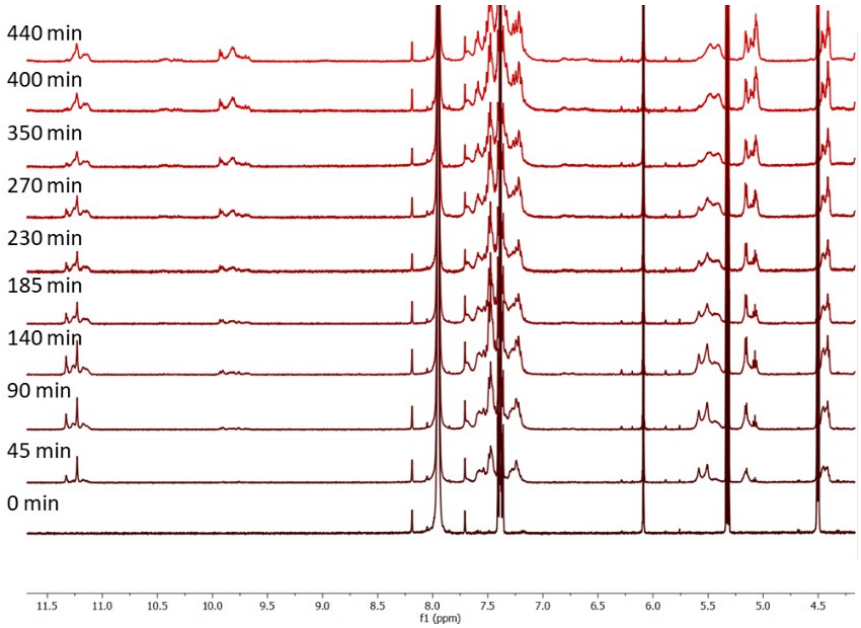


Figure S10. Stacked ^{1}H NMR spectra for the polymerization kinetic analysis of **SADM1 (SADM1** monomer on bottom; time increasing going upward). 1,3,5-trimethoxybenzene (δ = 6.09, 7.38 ppm) was added as an internal standard. Monomer concentration was determined by integrating the methoxy proton signal for 1,3,5-trimethoxybenzene relative to the methylene of **SADM1** (δ = 4.50).

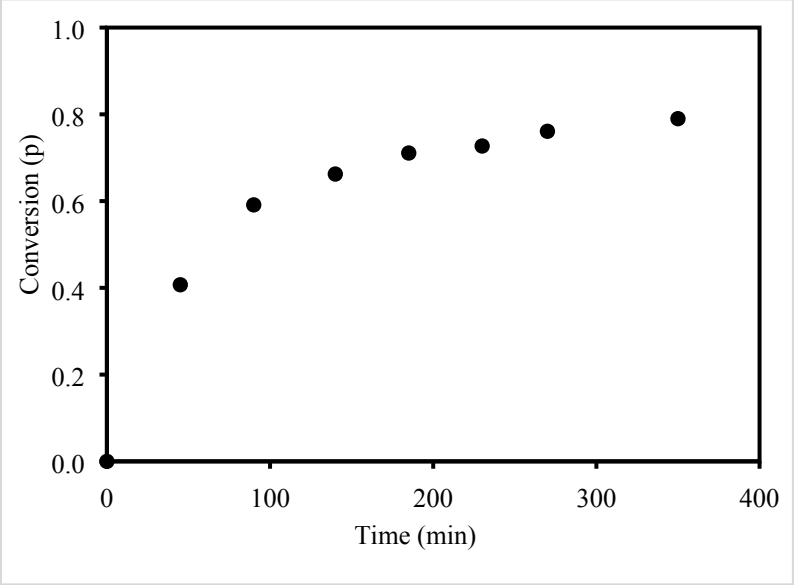


Figure S11. Plot of monomer conversion (p) over time for the polymerization of **SADM1**. Monomer conversion was determined by the measuring concentration of monomer remaining in the reaction mixture at a given timepoint relative to the internal standard using ^{1}H NMR spectroscopy.

Depolymerization analysis – ^1H NMR spectroscopy

In a 1-dram vial, a stock solution of TCEP (6.5 mg) and $N(Et)_3$ (7.25 µL), in DMSO-d_6 (500 µL) was prepared. In a separate vial, a solution of **SADP1** (2.4 mg) was prepared by dissolving it in DMSO-d_6 (958 µL). A t_0 timepoint was then recorded on a Bruker Avance II 500 MHz spectrometer (32 scans, 5 s T_1 relaxation time). The stock solution of TCEP/$N(Et)_3$ (53.5 µL) was then added to the NMR tube containing **SADP1**, and the tube was capped. This solution was mixed, and the NMR tube cap was wrapped with Parafilm. ^1H NMR spectra were collected using the aforementioned protocol every day for eight days.

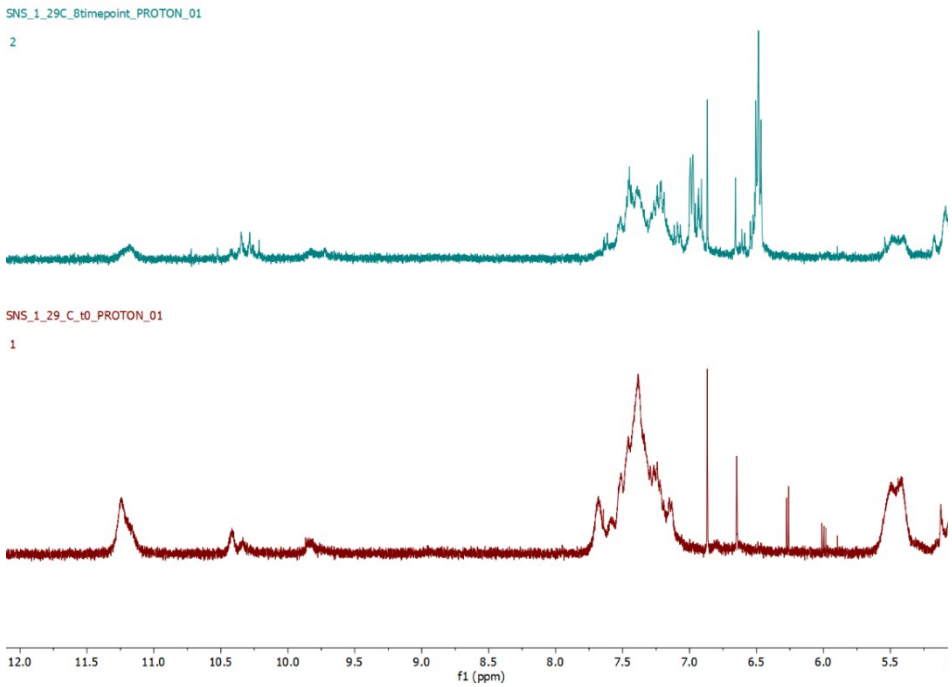


Figure S12. ^1H NMR spectra of **SADP1** in the presence of TCEP (1.5 equiv) and $N(Et)_3$ at time 0 (red) and after 8 days (blue). A decrease in the peak attributed to the thiocarbamate repeat unit (Ar–N**H**C(S)O) (δ = 11.25 ppm) as well as peaks attributed to 4-AB growing in (d, δ = 6.5, 7.0) was observed, indicating depolymerization.

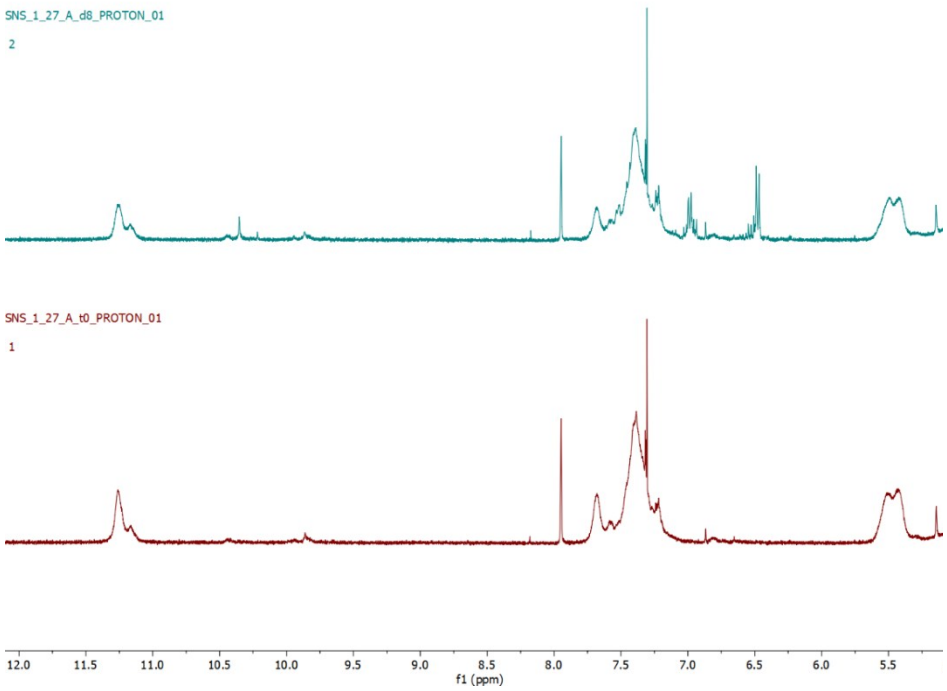


Figure S13. ^{1}H NMR spectra of **Cntrl-SADP** in DMSO-d_6 in the presence of TCEP (1.5 eq) and $N(Et)_3$ (1.5 eq) at t_0 (red) and after 8 days (blue). A small amount of hydrolysis under these conditions is evidenced by the appearance of peaks attributed to 4-AB (d, δ = 6.5, 7.0).

Depolymerization analysis – UV-Vis

A vial was charged with 1X PBS (1.48 mL, pH 7.4), CTAB (1 mL, 3 mM in PBS), DTPA (0.5 mL, 60 µM in PBS), and CA (20 µL, 75 µM in PBS). **SADP1** (81 µL, 370 µM) was added to the vial, and the contents were transferred to a quartz cuvette with a threaded lid. The cuvette was capped, and an absorption spectrum was recorded as the zero timepoint (t_0). To the vial the desired reducing agent was added (10 µL), and then the vial was shaken to mix and placed back into the spectrometer. Absorbance spectra were recorded every 10 min after the addition of reducing agent for 2 h total. Kinetic analysis was performed by normalizing the absorbance (λ = 284 nm) of each timepoint to the t_0 timepoint.

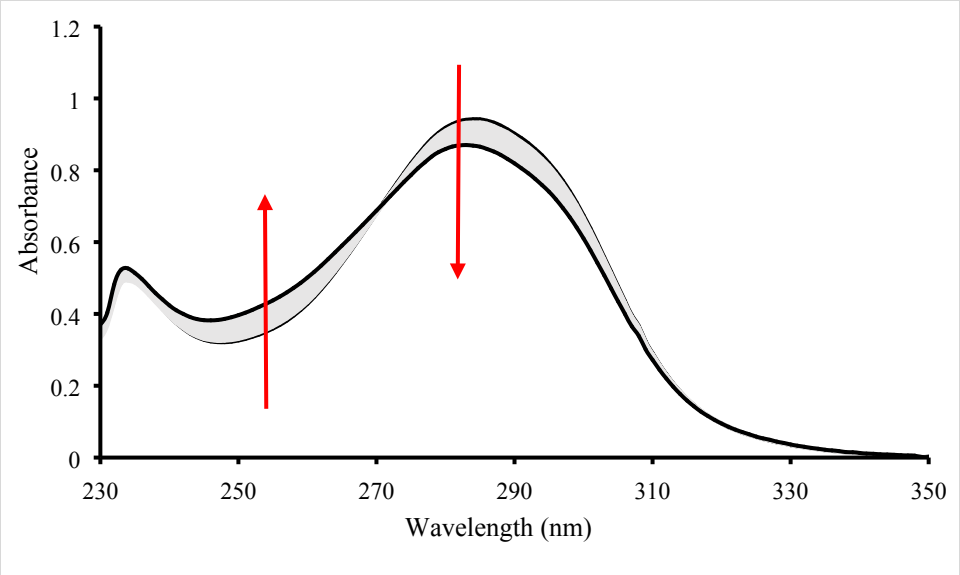


Figure S14. Representative absorbance spectra of **Ctrl-SADP** in the presence of Na_2S (0.1 equiv) during the course of a depolymerization kinetic analysis by UV-Vis (2 h). Similar to **SADP1**, a broad absorbance band (λ_{max} = 284 nm) can be observed prior to addition of Na_2S, followed by a gradual red shift after the addition of Na_2S.

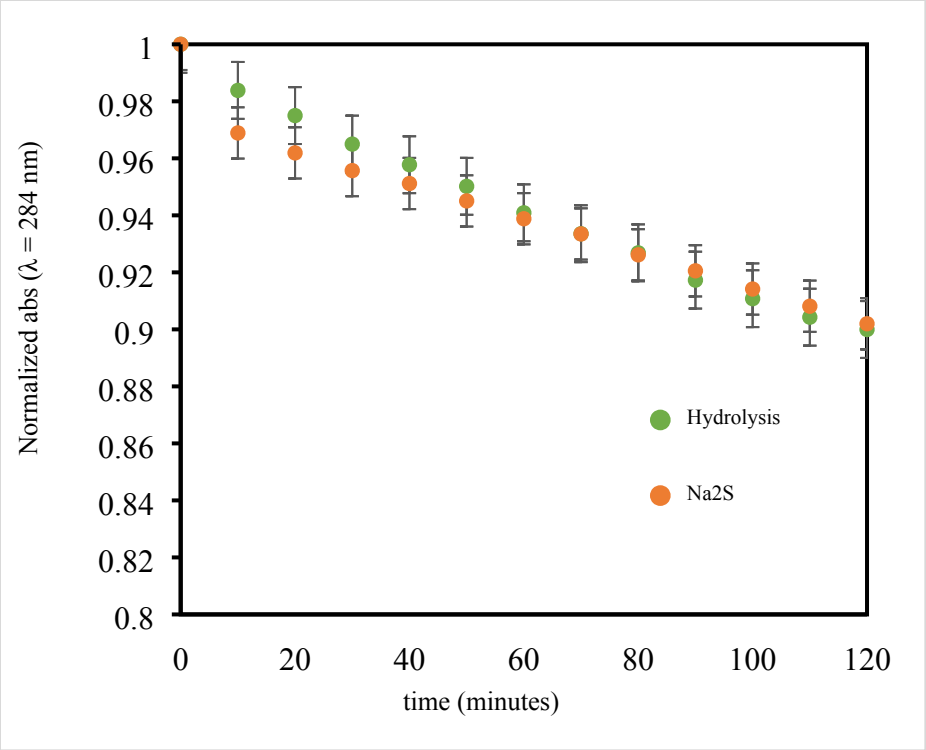


Figure S15. UV-Vis depolymerization data for **Ctrl-SADP** in the presence and absence of Na_2S (0.1 equiv). No significant difference between the two set of conditions was observed, indicating that sulfide does not degrade the benzyl thiocarbamate moiety.

H_2S release data

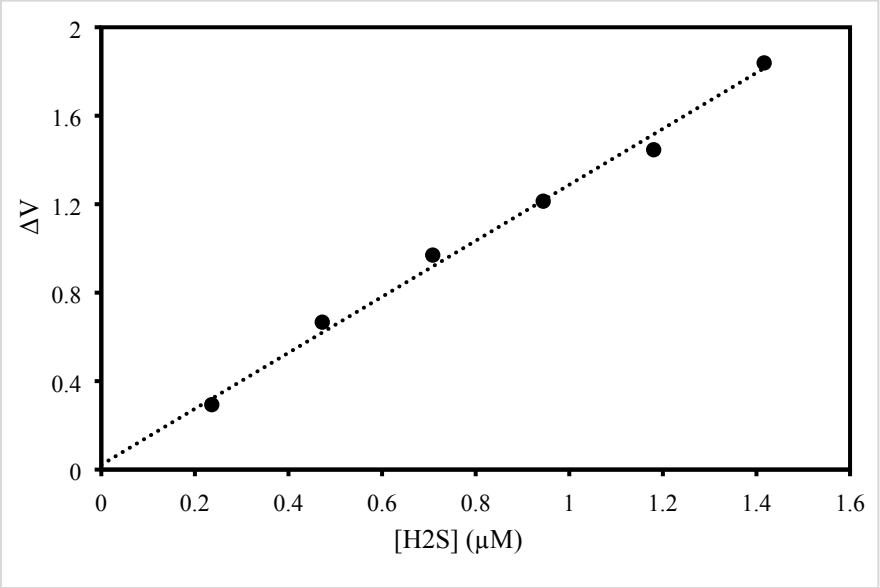
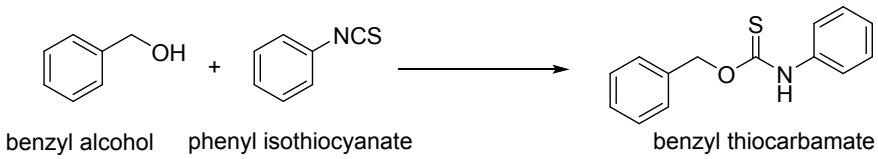


Figure S16. Calibration curve constructed for the H_2S-selective electrochemical probe. Values on the x-axis indicate the concentration of Na_2S in solution (PBS buffer, pH 7.4). Values on the y-axis indicate the change in output voltage after each successive addition of Na_2S. Concentration of H_2S calculated via the equation $[H_2S] = [Na_2S]/\{1 + \frac{K_a{}^1}{[H^+]} + \frac{K_a{}^1 K_a{}^2}{[H^+]}\}$ where $pK_a^1 = 6.89$ and $pK_a^2 = 19$ for the chemical equation [total sulfide] = $[H_2S] + [HS^-] + [S^{2-}]$.[4]

A scintillation vial was charged with 8.31 mL of 1X PBS buffer (pH 7.4), 0.25 mL of DMSO, 400 μL of **SADP1** solution (2.5 mM in DMSO), 1.0 mL CTAB solution (10 mM in 1X PBS), and a small magnetic stir bar. Final concentrations in the reaction vial were 100 μM **SADP1** and 1 mM CTAB. Once all of the reagents had been added, the probe was immediately inserted into the solution, and the output voltage was recorded. After allowing the probe to equilibrate for about 10 min, 20 μL of CA solution (150 μM in 1X PBS) was added to the reaction vial amounting to a final concentration of 300 nM. Following this, 20 μL Na_2S solution (5 mM in PBS) was added into the reaction vial with final concentration of 10 μM. Peaking times of H_2S in solution were measured at the point where the current readout reached a global maximum for the dataset. Δ

Theoretical calculations of ΔG

The density functional theory calculations were performed using the Gaussian 09[5] suite of software. Geometries and harmonic frequencies for phenyl isothiocyanate, benzyl alcohol, and benzyl thiocarbamate were optimized using the M06-2X functional, the aug-cc-pVDZ basis set, and an ultrafine integration grid, and considered implicit DMF solvation (PCM model). The Gibbs energies listed in **Table S1** below were calculated at 60 °C.



Scheme S1. Small molecule analog reaction modeled by Gaussian for theoretical value of ΔG.

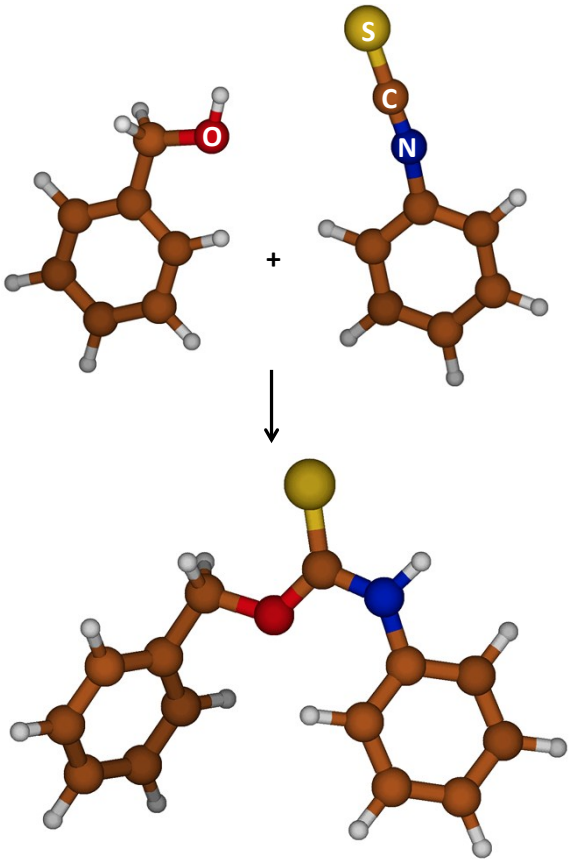


Figure S17. Optimum geometries for the reaction in Scheme S1.

	Benzyl alcohol (a.u.)	Phenyl isothiocyanate (a.u.)	Benzyl thiocarbamate product (a.u.)	ΔG (kcal/mol)
Free energy (60°C)	-346.587719	-722.529357	-1069.120716	-2.28

Table S1. Theoretical 60 °C Gibbs energies for the reaction between benzyl alcohol and phenyl isothiocyanate.

XYZ coordinates (Angstrom)

Benzyl Alcohol

C,0,0.0068573336,0.0017655845,0.
C,0,0.4779658105,1.4351491076,0.
C,0,-0.4137581393,2.508740476,0.
C,0,0.0646894539,3.8226236502,0.
C,0,1.4355500262,4.0737265573,0.
C,0,2.3319845399,3.0010175157,0.
C,0,1.8546426322,1.6927567862,0.
H,0,2.5582171277,0.8587650676,0.
H,0,3.4055268554,3.1862257331,0.
H,0,1.8066954609,5.0976822054,0.
H,0,-0.640738733,4.6529750578,0.
H,0,-1.484161035,2.3156707696,0.
O,0,-1.4111691256,-0.0425087137,0.
H,0,-1.6816942586,-0.9663575888,0.
H,0,0.4094375256,-0.5083416042,-0.8885787758
H,0,0.4094375256,-0.5083416042,0.8885787758

Phenyl isothiocyanate

C,0,-0.0563844529,0.0753527376,0.
C,0,0.5876926816,1.3143868743,0.
C,0,1.9824779203,1.3768742552,0.
C,0,2.7399436923,0.2085493131,0.
C,0,2.081345314,-1.0253825481,0.
C,0,0.6841138717,-1.1035030958,0.
H,0,0.19948116,-2.077482543,0.
N,0,2.8252109528,-2.1924498321,0.
C,0,3.3827094772,-3.2277759013,0.
S,0,4.1617414047,-4.634675564,0.
H,0,3.8274146891,0.2375282866,0.
H,0,2.4871094791,2.3413232458,0.
H,0,0.0019856606,2.2319131091,0.

H,0,-1.1436818508,0.0238056625,0.

Benzyl thiocarbamate

C,0,0.0390143447,0.0051711038,0.1984358323
O,0,1.3882131716,-0.5054451515,0.1895148316
C,0,2.4055055147,0.3351094303,0.2688022158
N,0,3.6029197401,-0.2816299712,0.2136227216
C,0,3.944261816,-1.6457131406,0.0326280333
C,0,5.2471388284,-1.8912002327,-0.4235588244
C,0,5.6950079335,-3.1952813879,-0.6051217118
C,0,4.8488554872,-4.2725994086,-0.3369090323
C,0,3.5571186827,-4.0246903104,0.1242052207
C,0,3.0951098549,-2.7222264728,0.3181569099
H,0,2.0909863158,-2.5596579827,0.6911047174
H,0,2.8898909233,-4.8560202492,0.3469776775
H,0,5.1955878328,-5.2940610334,-0.4819299366
H,0,6.7093433639,-3.3675736562,-0.9612638688
H,0,5.9082989999,-1.0518057317,-0.6379665849
H,0,4.3817613888,0.3651788988,0.2220613883
S,0,2.2754433388,2.005748908,0.4187770677
C,0,-0.8760710256,-1.1851251824,0.1064144645
C,0,-1.8844684972,-1.3733233876,1.052282322
C,0,-2.749439988,-2.4660056021,0.9531107466
C,0,-2.5997035196,-3.381308533,-0.0874030516
C,0,-1.5857510115,-3.2009044639,-1.0327430828
C,0,-0.7316136988,-2.1047405874,-0.9391745084
H,0,0.0579211807,-1.9627592092,-1.6771020396
H,0,-1.4656585206,-3.9148047058,-1.846296431
H,0,-3.2698055485,-4.2364536868,-0.163295851
H,0,-3.5355523973,-2.6038140125,1.6939817309
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H,0,-0.1226679469,0.5694954111,1.1220638084
H,0,-0.073666532,0.6807962082,-0.6573772157

References.

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