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Taming tosyl azide: the development of a scalable continuous diazo transfer process

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1. Experimental Section:

1.1 General Procedures

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide, ethyl acetate was distilled from potassium carbonate, hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification unless otherwise stated.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet) and m (multiplet).

Infrared spectra were measured using a Perkin Elmer FTIR UATR2 spectrometer, or as potassium bromide discs (for solids) on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Inline infrared spectroscopy was conducted using a Mettler–Toledo FlowIR spectrometer fitted with a silicon optical window. Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV (254 nm) light absorption.

Elemental analysis was carried out by Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrosprayionization mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples prepared for either LRMS or HRMS by employing acetonitrile as solvent. Melting points were obtained using a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

1.2 Continuous-flow Setup

All continuous processes were performed using a Vapourtec R-Series flow reactor consisting of four pumps and up to four temperature controlled tubular reactors. To prepare the reactor for operation pumps were purged with acetonitrile or water (corresponding to the solvent to

be used in the reaction) prior to use. All reaction tubing, coils, inlets and connections were also purged thoroughly in a similar manner.

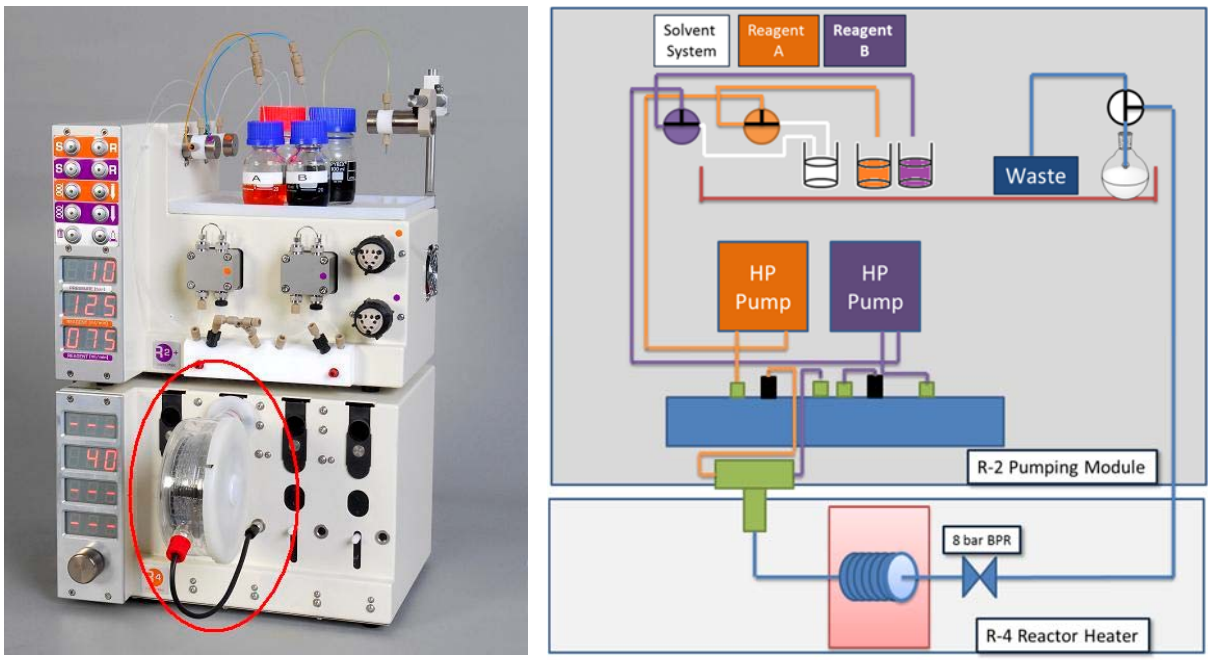
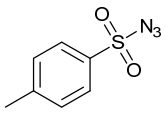


Figure S1.1: Vapourtec R-Series reactor and corresponding general schematic diagram

Table S1: General specifications for continuous-flow reactor

General Specifications	
Material of tubing	PFA
Diameter of tubing	1 mm
Working flow rates	0.05 mL/min – 9.99 mL/min
Tubular reactor working volume	10 mL
Temperature range	-70 ^{o}C to 250 ^{o}C

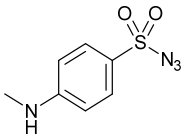
1.3 Procedure for Batch Preparation of *p*-Toluenesulfonyl Azide[1] (**1a**)



A solution of *p*-toluenesulfonyl chloride (**2a**) (12.23 g, 65.0 mmol, 1 eq.) in acetone (30 mL) was added dropwise over 15 min to a stirring solution of sodium azide (4.34 g, 66.0 mmol, 1 eq.) in water (15 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 2 hours after which time the acetone was removed under reduced pressure. The aqueous solution was extracted with dichloromethane (20 mL) and the organic layer was then washed with water (2 × 15 mL) and brine (10 mL). The organic layer was dried and concentrated under reduced pressure to give pure *p*-toluenesulfonyl azide (**1a**) as a colourless oil (98%) which crystallised to a white solid on refrigeration. ν_{max} (UATR)/cm^{-1}: 2128, 1595, 1371, 1167; δ_H ($CDCl_3$, 400 MHz): 2.49 (3H, s, CH_3), 7.41 (2H, d, *J* 8.3, ArH), 7.85 (2H, d, *J* 8.3, ArH).

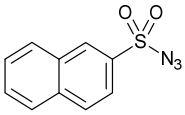
1.4 Preparation and Characterisation of Other Sulfonyl Azides

p-Acetamidobenzenesulfonyl azide[2] (1b)



The title compound was prepared by a known literature method and its spectroscopic properties were consistent with those found in the literature.[2]

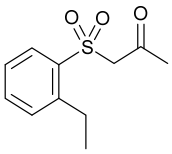
Naphthalenesulfonyl azide[3] (1c)



The title compound was prepared by a method similar to that used for preparation of *p*-toluenesulfonyl azide (**1a**), using 2-naphthalenesulfonyl chloride (110 mg, 0.48 mmol, 1 eq.) and sodium azide (32 mg 0.49 mmol, 1 eq.). The compound was recovered as a white solid with spectroscopic properties consistent with those found in the literature.[3]

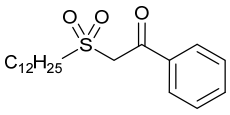
1.5 Preparation and Characterisation of β-Ketosulfone Substrates

1-((2-Ethylphenyl)sulfonyl)propan-2-one[4] (3k)



Potassium carbonate (8.81 g, 63.7 mmol) was added to 2-ethylbenzenethiol (8.00 g, 7.8 mL, 57.9 mmol) in acetone (175 mL) and stirred for 15 min before chloroacetone (5.36 g, 4.6 mL, 57.9 mmol) was added neat dropwise to the mixture. The resulting mixture was stirred under reflux for 20 h. The solution was cooled and filtered, to remove any insoluble salts, and concentrated under reduced pressure to give the crude sulfide, 1-[(2-ethylphenyl)thio]propan-2-one (7.61 g, 68%), isolated as a yellow oil, which was used without further purification (due to its malodorous nature). A solution of *m*CPBA (66% w/w, 13.1 g, 50.9 mmol) in dichloromethane (100 mL) was added dropwise to a solution of 1-[(2-ethylphenyl)thio]propan-2-one (4.5 g, 23.2 mmol) in dichloromethane (120 mL) over 30 min at 0°C. The mixture was stirred at 0 °C for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 21 h. The crude mixture was washed with saturated aqueous sodium metabisulfite solution (2 × 30 mL), saturated aqueous sodium bicarbonate (4 × 30 mL) and brine (30 mL) dried and concentrated under reduced pressure. After purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, 1-[(2-ethylphenyl)sulfonyl]propan-2-one (**3k**) (3.93 g, 75%) was isolated as a clear oil; ν_{max}/cm^{-1} (film): 2928, 1717, 1311, 1150, 746; δ_H ($CDCl_3$, 400 MHz): 1.34 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.41 (3H, s, $COCH_3$), 3.06 (2H, q, *J* 7.5, $ArCH_2CH_3$), 4.18 (2H, s, $SO_2CH_2CO_2CH_3$), 7.32–7.46 (2H, overlapping dd and ddd, appears as m, 2 × ArH), 7.60 (1H, ddd, *J* 1.3, 7.6, 7.6, ArH), 7.96 (1H, dd, *J* 1.2, 8.0, ArH); δ_c ($CDCl_3$, 100.6 MHz) 15.9 ($ArCH_2CH_3$), 26.1 ($ArCH_2CH_3$), 31.5 ($COCH_3$), 68.0 (SO_2CH_2CO), 126.6 (aromatic CH), 130.3 (aromatic CH), 131.2 (aromatic CH), 134.5 (aromatic CH), 136.5 (aromatic C), 144.5 (aromatic C), 195.7 (CO); HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_3S$ ($M+H^+$) 227.0742. Found 227.0723.

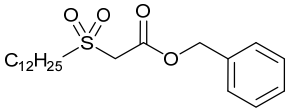
2-(Dodecylsulfonyl)-1-phenylethan-1-one[5] (3g)



The title compound was prepared using the procedure employed for 1-((2-ethylphenyl)sulfonyl)propan-2-one (**3k**), using 2-(dodecylsulfinyl)-1-phenylethanone 89 (2.01 g, 5.9 mmol) and *m*CPBA (77%, 1.33 g, 5.9 mmol) in dichloromethane (40 mL). The mixture was stirred at 0 °C for 1.5 h followed by 30 min at room temperature. Following the work up, 2-(dodecylsulfonyl)-1-phenylethanone (**3g**)(2.02 g, 97%) was isolated as a yellow solid, which was used without further purification, mp 61–63 °C; (Found C, 67.73; H, 9.22; S, 8.88, $C_{20}H_{32}O_3S$ requires C, 68.14; H, 9.15; S, 9.10%); ν_{max}/cm^{-1} (KBr): 1688, 1322, 1133; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 6.8, CH_3-12′), 1.20–1.38 (16H, m, CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′), 1.40–1.50 (2H, m, CH_2-3′), 1.84–1.94 (2H, m, CH_2-2′), 3.21–3.29 (2H, m, CH_2-1′), 4.55 (2H, s, SO_2CH_2CO), 7.50–7.56 (2H, m, 2 × ArH), 7.63–7.70 (1H, m, ArCH), 7.99–8.04 (2H, m, 2 × ArCH); δ_C ($CDCl_3$, 100.6 MHz) 14.1 (CH_3-12′), 21.9, 22.7, 28.4, 29.0, 29.2, 29.3, 29.5, 29.6 (2 overlapping signals), 31.9 (CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′,CH_2-5′, CH_2-4′, CH_2-3′, CH_2-2′), 53.8 (CH_2-1′), 59.6

(SO_2CH_2CO), 129.0 (2 × aromatic CH), 129.3 (2 × aromatic CH), 134.6 (aromatic CH) 135.8 (aromatic C), 189.3 (CO); m/z (ESI^+) 353.1 ($M+H^+$).

Benzyl 2-(Dodecylsulfonyl)acetate[6] (3h)



The title compound was prepared using the procedure employed for 1-((2-ethylphenyl)sulfonyl)propan-2-one (**3k**), using benzyl 2-(dodecylthio)acetate (18.0 g, 51.3 mmol) and *m*CPBA (77%, 35.4 g, 158 mmol) in dichloromethane (600 mL) stirred at 0 °C for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 23 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, benzyl 2-(dodecylsulfonyl)acetate (**3h**) (12.5 g, 86%) was isolated as a white solid, mp 62–64 °C; ν_{max}/cm^{-1} (film): 1730, 1326, 1159; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 6.8, CH_3-12′), 1.20–1.34 (18H, m, CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′,CH_2-6′, CH_2-5′, CH_2-4′), 1.34–1.45 (2H, m, CH_2-3′), 1.78–1.88 (2H, m, CH_2-2′), 3.15–3.23 (2H, m, CH_2-1′), 3.98 (2H, s, SCH_2CO), 5.24 (2H, s, CO_2CH_2Ph), 7.32–42 (5H, m, 5 × ArH); δ_C ($CDCl_3$, 100.6 MHz) 14.2 (CH_3-12′), 21.9, 22.7, 28.3, 29.0, 29.2, 29.3, 29.5, 29.6 (2 signals overlapping), 31.9 (CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′, CH_2-3′, CH_2-2′), 53.6, 57.4 (2 × CH_2, CH_2-1′, SO_2CH_2CO), 67.9 (OCH_2Ph), 128.6 (aromatic CH × 2), 128.8 (aromatic CH × 2), 128.9 (aromatic CH), 134.7 (aromatic C), 162.9 (CO).

1.6 Procedure for Destruction of Excess Inorganic Azide[7]

[Caution: This operation must be carried out in a well ventilated fumehood due to the resultant evolution of toxic nitric oxide gas. The addition of nitrite prior to sulfuric acid is also essential to avoid formation of hydrazoic acid (HN_3).] An aqueous solution containing no more than 5% (w/v) azide was transferred to a three-necked flask equipped with a stirrer and a dropping funnel. 20% (w/v) aqueous solution of sodium nitrite (40% excess per weight of azide) was added with stirring. A 20% (v/v) aqueous solution of sulfuric acid is then added gradually until the reaction mixture is acidic to litmus paper.[‡] When the evolution of nitrogen oxides ceases, the acidic solution is tested with starch iodide paper. If this paper turns blue, excess nitrite is present, and the decomposition is complete, allowing the solution to be disposed of as non-toxic aqueous waste.

1.7 Diazo Transfer to β-Keto Substrates

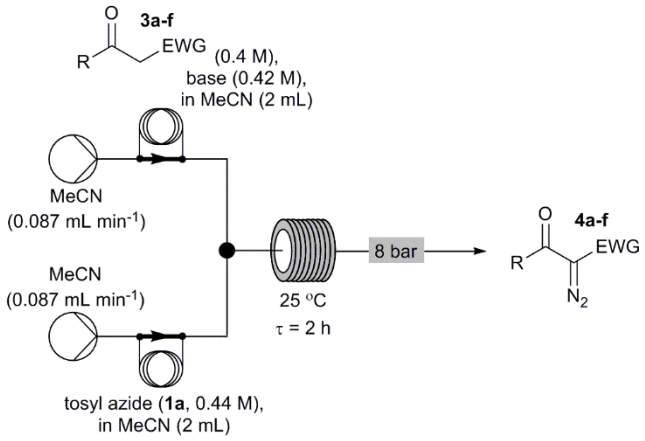
Diazo-transfer - batch mode

Triethylamine (0.210 g, 2.1 mmol, 1.05 eq.) was added to a stirring solution of substrate (2.0 mmol, 1 eq.) in MeCN (15 mL). After 2 min, *p*-toluenesulfonyl azide (0.430 g, 2.2 mmol, 1.05 eq.) in acetonitrile (2 mL) was added dropwise, at room temperature, over 15 minutes. The reaction mixture was stirred in MeCN for 2 hours. This was then concentrated under reduced

[‡] Acidification to pH 1 was typically employed during this work.

pressure. The crude product was extracted with diethyl ether (10 mL) and the organic layer was then washed with aqueous 9% KOH solution (2 × 12 mL) and water (10 mL). The organic layer was dried and concentrated under reduced pressure to give the diazo product.

Diazo-transfer – continuous mode (Table 2)

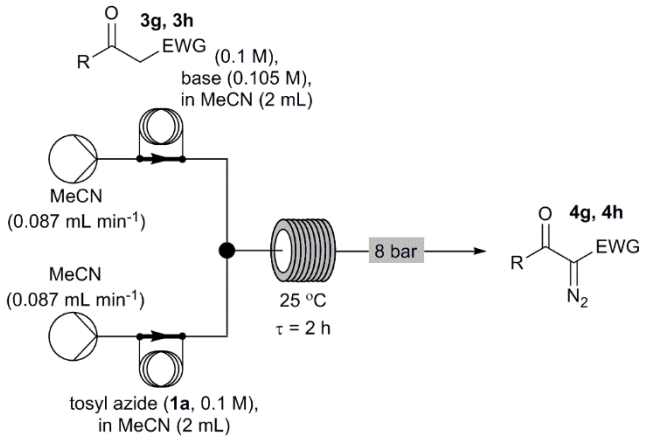


Scheme S1.1

*Substrates **3a-f***

A 5 mL solution of substrate (2.0 mmol, 1 eq.) and base (2.1 mmol, 1.05 eq.) in acetonitrile was prepared along with a 5 mL solution of *p*-toluenesulfonyl azide (**1a**) (0.430 g, 2.2 mmol, 1.1 eq.) in acetonitrile. The substrate/base solution was injected into a sample loop (2 mL) and then pumped (0.087 mL min^{-1}) to a T-piece where it combined with the TsN_3 solution which had been injected in a second stream (2 mL at 0.087 mL min^{-1}). The combined stream passed into a 20 mL reactor (25 °C, 120 min residence time) before passing through a back pressure regulator (8 bar). The product stream was collected in a round bottom flask and was then concentrated under reduced pressure. A ^{1}H NMR spectrum was obtained for the crude product collected. The crude product was extracted with diethyl ether (10 mL) and the organic layer was then washed with aqueous 9% KOH solution (2 × 12 mL) and water (10 mL). The organic layer was dried and concentrated under reduced pressure to give α-diazocarbonyl product as a yellow oil (>90% purity by ^{1}H NMR analysis).

Note: Tosyl azide quench was not employed when the reaction were conducted on small scale (<1 mmol).



Scheme S1.2

*Substrates **3g** and **3h***

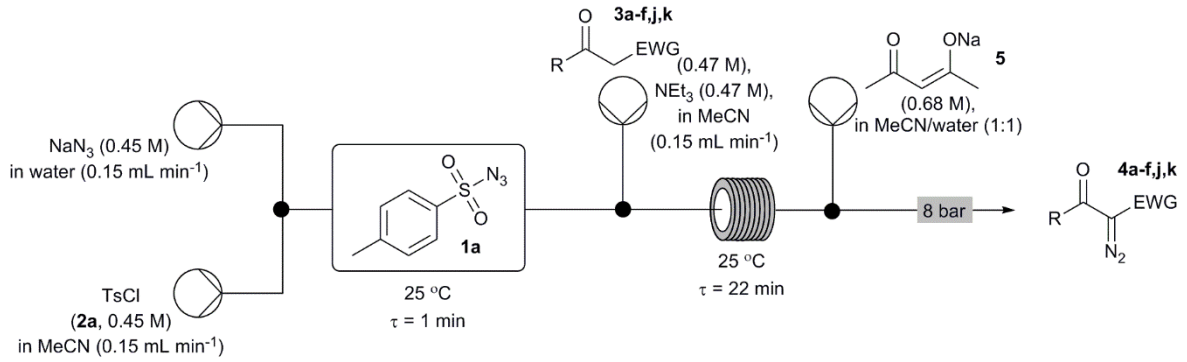
A 10 mL solution of substrate (1.0 mmol, 1 eq.) and base (1.05 mmol, 1.05 eq.) in acetonitrile was prepared along with a 5 mL solution of *p*-toluenesulfonyl azide (**1a**) (0.430 g, 1.1 mmol, 1.1 eq.) in acetonitrile. The substrate/base solution was injected into a sample loop (2 mL) and then pumped (0.087 mL min^{-1}) to a T-piece where it combined with the TsN_3 solution which had been injected in a second stream (2 mL at 0.087 mL min^{-1}). The combined stream passed into a 20 mL reactor (25 °C, 120 min residence time) before passing through a back pressure regulator (8 bar). The product stream was collected in a round bottom flask and was then concentrated under reduced pressure. A ^{1}H NMR spectrum was obtained for the crude product collected. The crude product was extracted with diethyl ether (10 mL) and the organic layer was then washed with aqueous 9% KOH solution (2 × 12 mL) and water (10 mL). The organic layer was dried and concentrated under reduced pressure to give α-diazocarbonyl product as a yellow oil (>90% purity by ^{1}H NMR analysis).

Note: Tosyl azide quench was not employed when the reactions were conducted on small scale (<1 mmol).

General *in situ* diazo-transfer – batch mode

Arylsulfonyl chloride (0.45 M, 1 eq.) in acetonitrile (10 mL) was added to a stirring aqueous solution of sodium azide (0.292 g in 10 mL, 0.45 M, 1 eq.) at room temperature. After stirring for 2 h, a solution of substrate (4.725 mmol, 1 eq.) and base (4.725 mmol, 1eq.) in acetonitrile (10 mL) (prepared as detailed below) was added to the reaction mixture. The reaction mixture was stirred for a further 2 h. The resulting mixture was then concentrated under reduced pressure to remove acetonitrile. The crude product was extracted with ethyl acetate (30 mL) and the organic layer was then washed with water (2 x 20 mL). The organic layer was dried and concentrated under reduced pressure to give the crude diazo product.

General *in situ* diazo-transfer – continuous mode (Table 5)



Scheme S1.3

A 10 mL solution of substrate (**3**, 4.725 mmol, 1.05 eq.) and base (4.725 mmol, 1.05 eq.) in acetonitrile was prepared as described below. A 10 mL solution of *p*-toluenesulfonyl chloride (**2a**) (0.858 g, 4.5 mmol, 1 eq.) in acetonitrile and a 10 mL aqueous solution of sodium azide (0.292 g, 4.5 mmol, 1 eq.) was prepared. A quench solution of sodium hydroxide (0.270 g, 6.75 mmol, 1.5 eq.) and acetyl acetone (0.676 g, 6.75 mmol, 1.5 eq.) in a 1:1 mixture of acetonitrile and water was also prepared.

The tosyl chloride solution was pumped (0.15 mL min^{-1}) into a T-piece where it met the aqueous sodium azide solution (0.15 mL min^{-1}). The combined stream passed through a 32 cm tube (1 min residence time) before it met the substrate/base solution at a T-piece (0.15 mL min^{-1}). This combined stream passed through a 10 mL reactor coil (25 °C, 22 min residence time) before meeting the quench solution (0.15 mL min^{-1}) at a T-piece. The quenched product stream passed through a 50 cm tube and a back pressure regulator (8 bar) before exiting the reactor. Reactor effluents were collected in a round bottom flask and then concentrated under reduced pressure to remove acetonitrile from the mixture. The remaining aqueous mixture was extracted with ethyl acetate (30 mL) and the organic layer was then washed with water (20 mL) and brine (20 mL), dried and concentrated under reduced pressure to give the crude product, of which a ^{1}H NMR spectrum was obtained. The crude product was extracted with ethyl acetate (30 mL) and the organic layer was then washed with aqueous 9% KOH solution (2 × 20 mL), water (20 mL) and brine (20 mL). The organic layer was dried and concentrated under reduced pressure to give isolated product.

Note: This procedure produces aqueous waste which can contain low levels of 1-diazopropan-2-one (**6**), which is potentially explosive when concentrated. All aqueous effluents were treated with sodium nitrite solution (20% v/v) and then dilute sulfuric acid (20% v/v) to decompose **6** and any possible trace inorganic azide (refer to Section 1.6 for procedure),[7] before being combined and disposed of as non-toxic waste.

Preparation of substrate solutions:

A 10 mL solution of ethyl acetoacetate (**3a**) (0.615 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of *te*rt-butyl acetoacetate (**3b**) (0.736 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of isoamyl acetoacetate (**3c**) (0.813 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of benzyl acetoacetate (**3d**) (0.908 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of ethyl benzoyl acetate (**3e**) (0.908 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of diethyl malonate (**3f**) (0.754 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

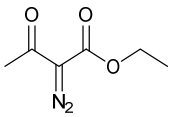
A 10 mL solution of *N,N*-diethyl-3-oxobutanamide (**3j**) (0.739 g, 4.725 mmol, 1.05 eq.) and triethylamine (0.470 g, 4.725 mmol, 1.05 eq.) in acetonitrile.

A 10 mL solution of 1-((2-ethylphenyl)sulfonyl)propan-2-one (**3k**) (0.26 g, 1.18 mmol, 1.05 eq.) and DBU (0.18 g, 1.18 mmol, 1.05 eq.) in acetonitrile.

1.8 Characterisation of α-Diazocarbonyl Compounds

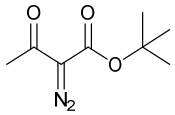
In all cases the spectral characteristics of previously known compounds were consistent with the literature data.

Ethyl 2-Diazo-3-oxobutanoate[8] (4a) (Table 5, entry 1)



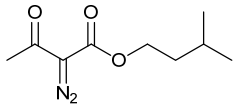
An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2140, 1720, 1661; δ_H ($CDCl_3$, 400 MHz): 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 2.49 (3H, s, $C(O)CH_3$), 4.32 (2H, q, *J* 7.1, OCH_2CH_3). δ_C ($CDCl_3$, 100.6 MHz): 14.3 (CH_3), 28.2 (CH_3), 61.4 (CH_2), 161.3 (C=O, ester), 190.1 (C=O, ketone), no signal observed for ($C=N_2$).

tert-Butyl 2-Diazo-3-oxobutanoate[9] (4b) (Table 5, entry 2)



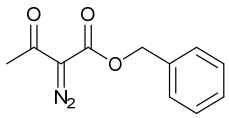
An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2134, 1715, 1660; δ_H ($CDCl_3$, 400 MHz): 1.54 (9H, s, 3 x CH_3 of *t*-butyl), 2.45 [3H, s, C(O)CH_3]. δ_C ($CDCl_3$, 100.6 MHz): 28.2 (CH_3), 28.3 (CH_3 x 3 of *t*-butyl), 83.1 (C), 160.6 (C=O ester), 190.6 (C=O, ketone), no signal observed for (C=N_2).

Isopentyl 2-Diazo-3-oxobutanoate[10] (4c) (Table 5, entry 3)



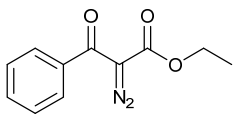
An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2141, 1721, 1662; δ_H ($CDCl_3$, 300 MHz): 0.95 (6H, d, *J* 6.5, 2 x CH_3), 1.54–1.62 (2H, m, OCH_2CH_2), 1.64–1.78 [1H, m, $CH(CH_3)_2$], 2.48 [3H, s, C(O)CH_3], 4.28 (2H, t, *J* 6.8, OCH_2CH_2); δ_C ($CDCl_3$, 75.5 MHz): 22.4 (CH_3 x 2), 25.1 (CH), 28.2 (CH_3), 37.3 (OCH_2CH_2), 64.1 (OCH_2), 161.5 (C=O, ester), 190.1 (C=O, ketone), no signal observed for (C=N_2).

Benzyl 2-Diazo-3-oxobutanoate[11] (4d) (Table 5, entry 4)



An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2144, 1719, 1656; δ_H ($CDCl_3$, 400 MHz): 2.49 (3H, s, CH_3), 5.27 (2H, s, CH_2), 7.26–7.41 (5H, m, 5 x ArH); δ_C ($CDCl_3$, 100.6 MHz): 28.3 (CH_3), 67.0 (OCH_2), 128.4, 128.7, 128.8 (aromatic CH), 135.2 (aromatic C) 161.3 (C=O, ester), 190.0 (C=O, ketone), no signal observed for (C=N_2).

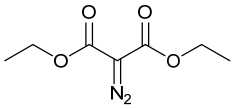
Ethyl 2-Diazo-3-oxo-3-phenylpropanoate[12] (4e) (Table 5, entry 5)



An analytically pure sample was obtained by wet flash chromatography on silica gel using 95:5 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2140, 1719,1293, 1262; δ_H ($CDCl_3$, 300 MHz): 1.26 (3H, t, *J* 7.1, CH_3), 4.25 (2*H*, q, *J* 7.1, CH_2),

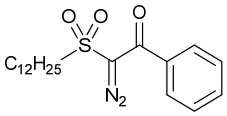
7.37–7.47 (2H, m, 2 x ArH), 7.49–7.57 (1H, m, ArH), 7.59–7.67 (2H, m, 2 x ArH). δ_C ($CDCl_3$, 75.5 MHz): 14.2 (CH_3), 61.6 (CH_2), 127.9, 128.3, 132.2 (aromatic CH), 137.16 (aromatic C), 161.0 (C=O, ester), 186.9 (C=O, ketone), no signal observed for (C=N_2).

Diethyl 2-Diazomalonate[13] (4f) (Table 5, entry 7)



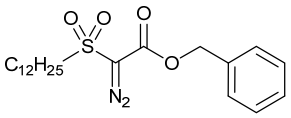
An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2133, 1732, 1688, 1313, 1072; δ_H ($CDCl_3$, 400 MHz): 1.32 (6H, t, 2 × CH_3, *J* 7.1), 4.31 (4H, q, CH_2, *J* 7.1); δ_C ($CDCl_3$, 100.6 MHz): 14.3 (CH_3), 61.6 (CH_2), 161.1 (C=O), no signal observed for (C=N_2).

2-Diazo-2-(dodecylsulfonyl)-1-phenylethan-1-one[5] (4g) (Table 2, entry 8)



An analytically pure sample was obtained by wet flash chromatography on silica gel using 90:10 hexane/ethyl acetate as eluent, followed by recrystallization from ethanol, which afforded the compound as a yellow solid, mp 79–81 °C; Found C, 63.63; H, 7.83, $C_{20}H_{30}N_2O_3S$ requires C, 63.46; H, 7.99%); v_{max}/cm^{-1} (film): 2123, 1668, 1322, 1121; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 6.6, CH_3-12′), 1.19–1.38 (16H, m, CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′), 1.39–1.50 (2H, m, CH_2-3′), 1.79–1.90 (2H, m, CH_2-2′), 3.50–3.58 (2H, m, CH_2-1′), 7.47–7.56 (2H, m, 2 × ArH), 7.58–7.65 (1H, m, ArH), 7.65–7.71 (2H, m, 2 × ArH); δ_C ($CDCl_3$, 100.6 MHz) 14.1 (CH_3-12′), 22.7 (2 overlapping peaks), 28.0, 29.0, 29.2, 29.3, 29.5, 29.6 (2 overlapping peaks), 31.9 (CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′, CH_2-3′, CH_2-2′), 56.8 (CH_2-1′), 127.4 (2 × aromatic CH), 129.1 (2 × aromatic CH × 2), 133.4 (aromatic CH) 135.7 (aromatic C), 183.4 (CO), no signal observed for (C=N_2); HRMS (ESI^+): Exact mass calculated for $C_{20}H_{31}N_2O_3S$ $(M+H)^+$ 379.2055. Found 379.2053.

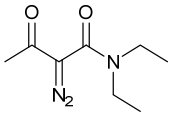
Benzyl 2-Diazo-2-(dodecylsulfonyl)acetate[6] (4h) (Table 2, entry 9)



An analytically pure sample was obtained by wet flash chromatography on silica gel using 90:10 hexane/ethyl acetate as eluent, followed by recrystallization from ethanol, which afforded the compound as a yellow solid, mp 48–50 °C; v_{max}/cm^{-1} (KBr): 2129, 1725, 1289, 1143; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 6.9, CH_2-12′), 1.22–1.44 (18H, m, CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′, CH_2-3′), 1.74–1.84 (2H, m, CH_2-2′), 3.32–3.39 (2H,

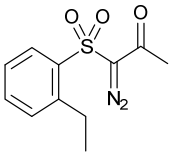
m, CH_2-1′), 5.30 (2H, s, OCH_2Ph), 7.34–7.45 (5H, m, 5 × Ar*H*); δ_C ($CDCl_3$, 100.6 MHz) 14.1 (CH_3-12′), 22.7 (2 signals overlapping), 28.0, 29.0, 29.2, 29.3, 29.5, 29.6 (2 signals overlapping), 31.9 (CH_2-11′, CH_2-10′, CH_2-9′, CH_2-8′, CH_2-7′, CH_2-6′, CH_2-5′, CH_2-4′, CH_2-3′, CH_2-2′), 56.7 (CH_2-1′), 67.9 (OCH_2Ph), 128.5 (2 × aromatic CH), 128.8 (2 × aromatic CH), 128.9 (aromatic CH), 134.6 (aromatic C), 160.1 (CO), no signal observed for ($C=N_2$).

_N,N_-Diethyl-2-diazo-3-oxobutanamide[14] (4j) (Table 5, entry 6)



An analytically pure sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (UATR)/cm^{-1}: 2097, 1622, 1422, 1258; δ_H ($CDCl_3$, 300 MHz): 1.21 (6H, t, *J* 7.1, CH_2CH_3,), 2.34 (3H, s, COCH_3), 3.38 (4H, q, *J* 7.1, NCH_2CH_3); δ_C ($CDCl_3$, 75.5 MHz): 13.2 (CH_3), 27.3 (CH_3), 41.9 (CH_2), 160.4 (C=O, ester), 190.1 (C=O, ketone), no signal observed for ($C=N_2$).

1-Diazo-1-((2-ethylphenyl)sulfonyl)propan-2-one[2] (4k) (Table 5, entry 8)

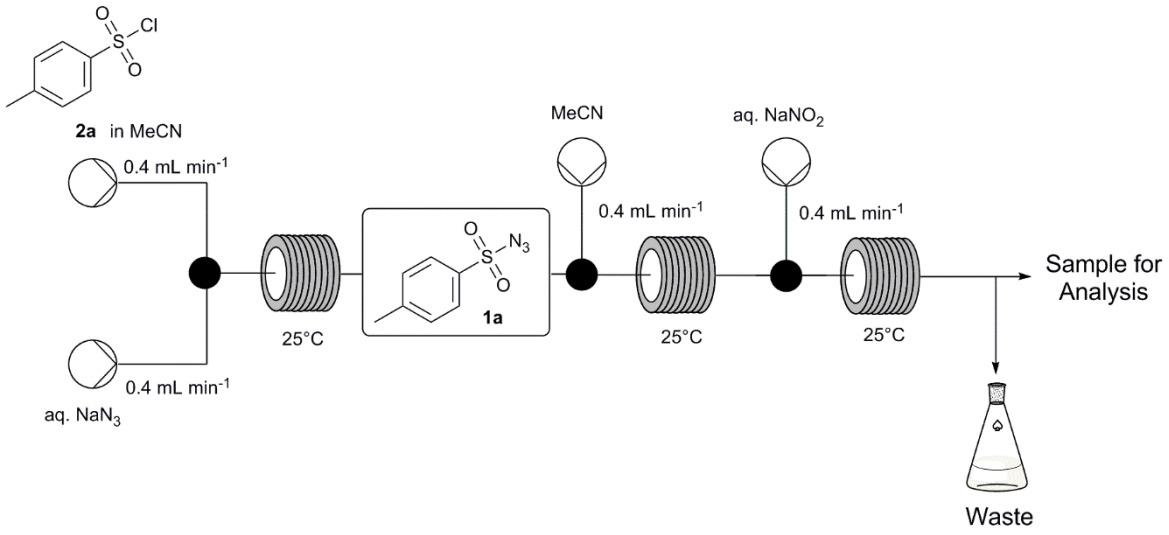


An analytically sample was obtained by wet flash chromatography on silica gel using 80:20 hexane/ethyl acetate as eluent, which afforded the compound as a yellow oil. (Found: C, 52.43; H 4.97; N, 10.70; $C_{11}H_{12}N_2O_3S$ requires; C, 52.37; H, 4.79; N, 11.0; %); ν_{max}/cm^{-1} (film): 2974, 2938, 2878, 2115, 1668, 1364, 1332, 1256, 1155, 764, 696; δ_H ($CDCl_3$, 300 MHz): 1.32 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.19 (3H, s, $COCH_3$), 2.98 (1H, q, *J* 7.5, $ArCH_2CH_3$), 7.36–7.49 (2H, overlapping dd and ddd, appears as m, 2 × ArH), 7.57 (1H, ddd, *J* 7.6, 7.5, 1.3, ArH), 8.10 (1H, dd, *J* 8.0, 1.2 ArH); δ_C ($CDCl_3$, 100.6 MHz): 15.0 (CH_3, $ArCH_2CH_3$), 25.7 ($ArCH_2CH_3$), 27.1 (CO*C*H_3), 126.5 (aromatic CH), 130.1 (aromatic CH), 131.2 (aromatic CH), 134.4 (aromatic CH), 139.2 (aromatic C), 143.6 (aromatic C), 186.2 (CO), no signal observed for ($C=N_2$). HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}N_2O_3S$ ($M+H^+$), 253.0647; Found 253.0643.

1.8 Quench Studies

A 10 mL solution of p-toluenesulfonyl chloride (**2a**, 0.858 g, 4.5 mmol , 1 eq.) in acetonitrile and a 10 mL aqueous solution of sodium azide (0.292 g, 4.5 mmol , 1 eq.) were prepared. A 10% (w/v) aq. solution of $NaNO_2$ solution and a 20% (v/v) H_2SO_4 solution were also prepared.

Table 4, entry 2: Quench of any excess azide (NaN_3 or TsN_3) – $NaNO_2$

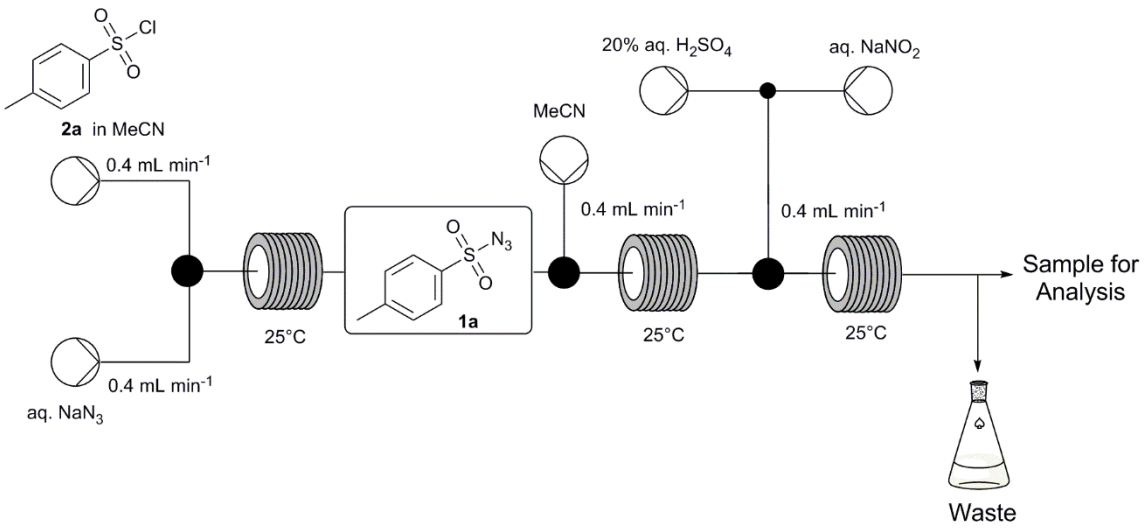


Scheme S1.4

Tosyl chloride (**2a**) solution was pumped (0.4 mL min^{-1}) into a T-piece where it met aqueous sodium azide solution (0.4 mL min^{-1}). The combined stream passed through a 32 cm tube (0.5 min residence time) and into a 10 mL reactor coil (25 °C, 8 min residence time) where tosyl azide (**1a**) formed. Aqueous $NaNO_2$ was pumped (0.4 mL min^{-1}) into a T-piece where it met the tosyl azide (**1a**) solution and passed through a coil (10 mL, 25°C, 8 min residence time) before passing through a back pressure regulator (8 bar). The reactor effluent was sent to a waste flask which contained a solution of $NaNO_2$. Approximately 2 mL of the reactor output was collected and extracted with ethyl acetate (5 mL). A sample of the organic layer was analysed by IR to check for the presence of sodium azide (2048 cm^{-1}) or tosyl azide (2135 cm^{-1}). Tosyl azide (**1a**) was clearly observed in the IR spectrum, indicating that it had not been quenched by $NaNO_2$.

In samples where the IR spectrum did not show the presence of sodium azide or tosyl azide organic phase was carefully concentrated to approximately 1 mL by rotary evaporation and then a sample was prepared in $CDCl_3$ and analysed by ^1H NMR spectroscopy to check for the presence of tosyl azide (7.41 ppm and 7.85 ppm). Tosyl azide (**1a**) was clearly observed in the ^1H NMR spectrum, indicating that it had not been quenched by $NaNO_2$. For a few samples where IR analysis indicated the presence of sodium azide or tosyl azide, samples were analysed directly without concentration and diluted in $CDCl_3$ for NMR analysis.

Table 4, entry 3: Quench of any excess azide (NaN_3 or TsN_3) – $NaNO_2$ and H_2SO_4



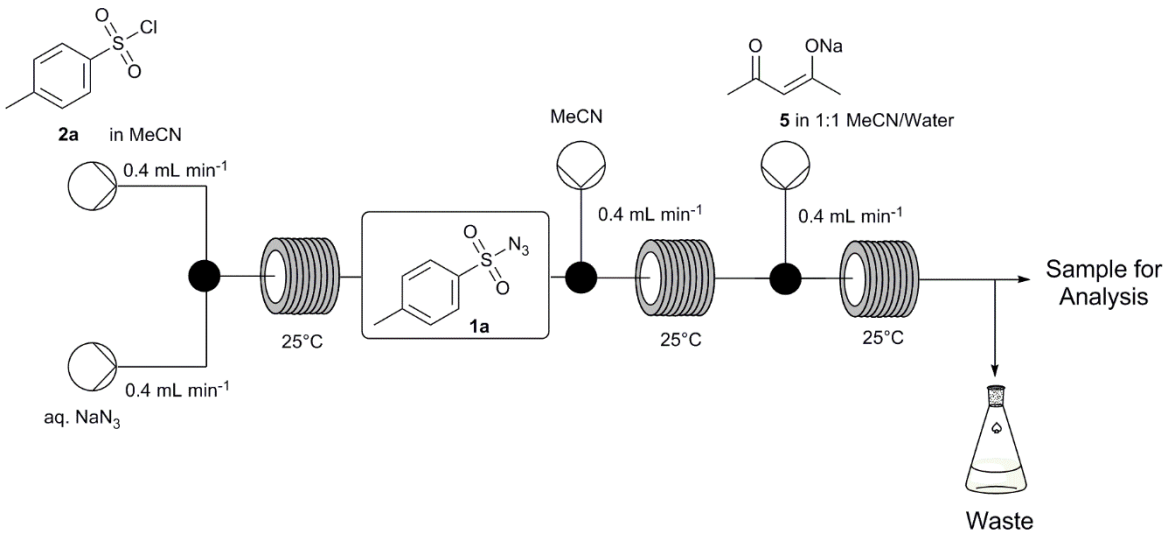
Scheme S1.5

Tosyl chloride (**2a**) solution was pumped (0.4 mL min^{-1}) into a T-piece where it met aqueous sodium azide solution (0.4 mL min^{-1}). The combined stream passed through a 32 cm tube (0.5 min residence time) and into a 10 mL reactor coil (25 °C, 8 min residence time) where tosyl azide (**1a**) formed. Aqueous $NaNO_2$ was pumped (0.4 mL min^{-1}) into a T-piece where it combined with the solution of aqueous H_2SO_4 (20% v/v) (0.4 mL min^{-1}). The combined aqueous $NaNO_2$ and H_2SO_4 stream was combined with the tosyl azide (**1a**) solution at a T-piece, passed through a coil (10 mL, 25°C, 8 min residence time) and then through a back pressure regulator (8 bar). The reactor effluent was sent to a waste flask which contained a solution of $NaNO_2$. Approximately 2 mL of the reactor output was collected and extracted with ethyl acetate (5 mL). A sample of the organic layer was analysed by IR to check for the presence of sodium azide (2048 cm^{-1}) or tosyl azide (2135 cm^{-1}). Tosyl azide (**1a**) was clearly observed in the IR spectrum, indicating that it had not been quenched by acidified $NaNO_2$.

In samples where the IR spectrum did not show the presence of sodium azide or tosyl azide organic phase was carefully concentrated to approximately 1 mL by rotary evaporation and then a sample was prepared in $CDCl_3$ and analysed by ^1H NMR spectroscopy to check for the presence of tosyl azide (7.41 ppm and 7.85 ppm). Tosyl azide (**1a**) was clearly observed in the ^1H NMR spectrum, indicating that it had not been quenched by $NaNO_2$. For a few samples where IR analysis indicated the presence of sodium azide or tosyl azide, samples were analysed directly without concentration and diluted in $CDCl_3$ for NMR analysis.

(CAUTION: The order of addition is essential. Poisonous, volatile hydrazoic acid (HN_3) will evolve if the acid is added to the azide before the nitrite. If the pump containing $NaNO_2$ fails the experiment must be stopped immediately. The waste outlet should be immersed in an aq. $NaNO_2$ solution to provide a backup quench system.)

Table 4, entry 4: Quench of excess azide (TsN_3) – acetylacetone and NaOH



Scheme S1.6

Tosyl chloride (**2a**) solution was pumped (0.4 mL min^{-1}) into a T-piece where it met aqueous sodium azide solution (0.4 mL min^{-1}). The combined stream passed through a 32 cm tube (0.5 min residence time) and into a 10 mL reactor coil (25 °C, 8 min residence time) where tosyl azide (**1a**) formed. A solution of acetylacetone (0.675 M) and NaOH (0.675 M) in acetonitrile/water (1:1) was pumped (0.4 mL min^{-1}) into a T-piece where it met the tosyl azide (**1a**) solution and passed through a coil (10 mL, 25°C, 8 min residence time) before passing through a back pressure regulator (8 bar). The reactor effluent was sent to a waste flask which contained a solution of $NaNO_2$. Approximately 2 mL of the reactor output was collected and extracted with ethyl acetate (5 mL). A sample of the organic layer was analysed by IR to check for the presence of tosyl azide (2135 cm^{-1}) but the large diazo band (2129 cm^{-1})of the α-diazocarbonyl quench product overlapped with this region of the spectrum.

The organic phase was carefully concentrated to approximately 1 mL by rotary evaporation and then a sample was prepared in $CDCl_3$ and analysed by ^1H NMR spectroscopy to check for the presence of tosyl azide (7.41 ppm and 7.85 ppm). Tosyl azide (**1a**) was not observed in the ^1H NMR spectrum, indicating that it had been successfully quenched by treatment with acetylacetone and NaOH.

Disposal of Aqueous Quench By-products

All aqueous waste generated during this work was treated for disposal using the procedure described in Section 1.6 for destruction of excess inorganic azide,[7] basing the required 40% excess of nitrite on the starting quantity of sodium azide employed in the process. This disposal procedure was also found to be adequate for the destruction of any diazo containing by-products of our acetylacetonate quench system, as indicated by IR spectroscopy. A stirring mixture of tosyl chloride (86 mg, 0.45 mmol , 1 eq.) in acetonitrile (1 mL) and sodium azide

(29 mg, 0.45 mmol , 1 eq.) in water (1 mL) was treated with sodium acetoacetonate solution (1 mL, 0.68 M in 1:1 acetonitrile/water, 1.5 eq.) and stirred for a further 30 min after which it was separated into two approximately equal portions. Brine (20 mL) was added to the first portion and after bilayer formation, diethylether (10 mL) was added and the layers were separated. A sample was taken from the organic layer and the solvent was allowed to evaporate before an IR spectrum was recorded, which indicated the presence of diazo species, with bands apparent near 2100 cm^{-1} (Figure S1.2). The second portion was evaporated under reduced pressure to remove acetonitrile and was then treated sequentially with aqueous 20% sodium nitrite (w/v) and 20% aqueous sulfuric acid (v/v) in the manner described for destruction of inorganic azide.[7] After all effervescence had ceased (a period of 4 h was allowed), the resulting aqueous mixture was diluted with brine (50 mL) and extracted with diethylether (50 mL). The organic phase was separated and concentrated under reduced pressure and an IR spectrum was recorded of the resulting residue, which demonstrated the absence of a characteristic diazo band (Figure S1.3).

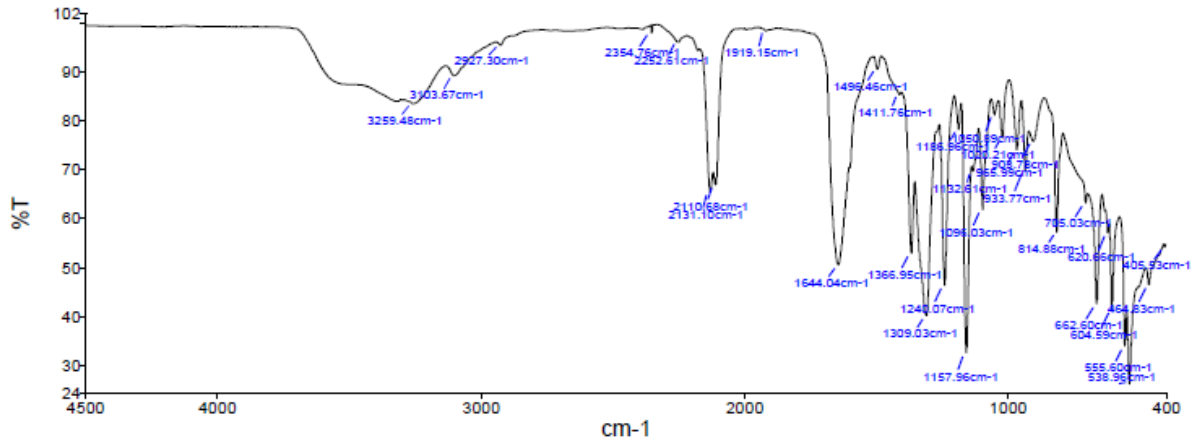


Figure S1.2: IR spectrum of extracted quench by-products before treatment with aqueous $NaNO_2/H_2SO_4$.

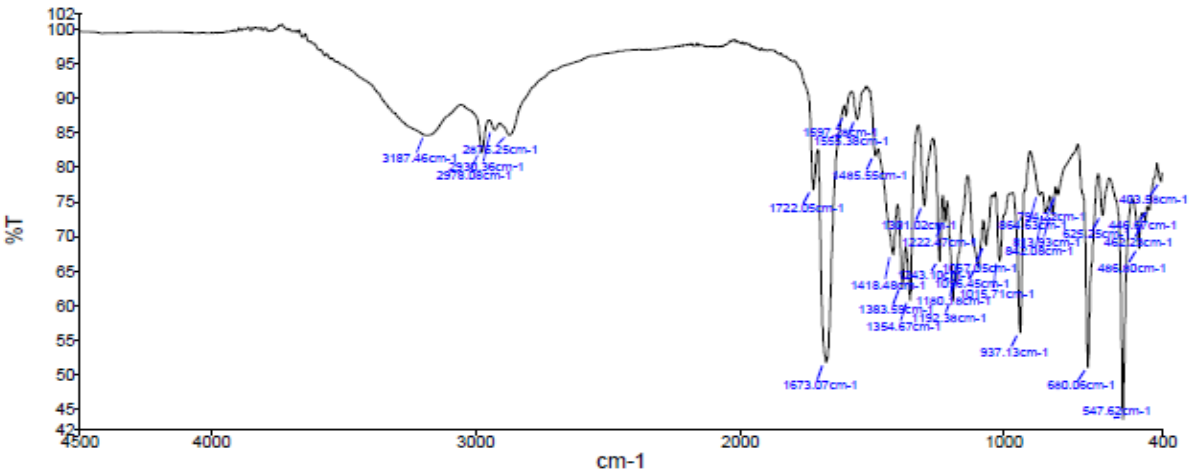


Figure S1.3: IR spectrum of extracted quench by-products after treatment with aqueous $NaNO_2/H_2SO_4$.

2. Copies of ^{1}H and ^{13}C NMR Spectra for Compounds 1a-c, 3g, 3h, 3j, 4a-h, 4j and 4k

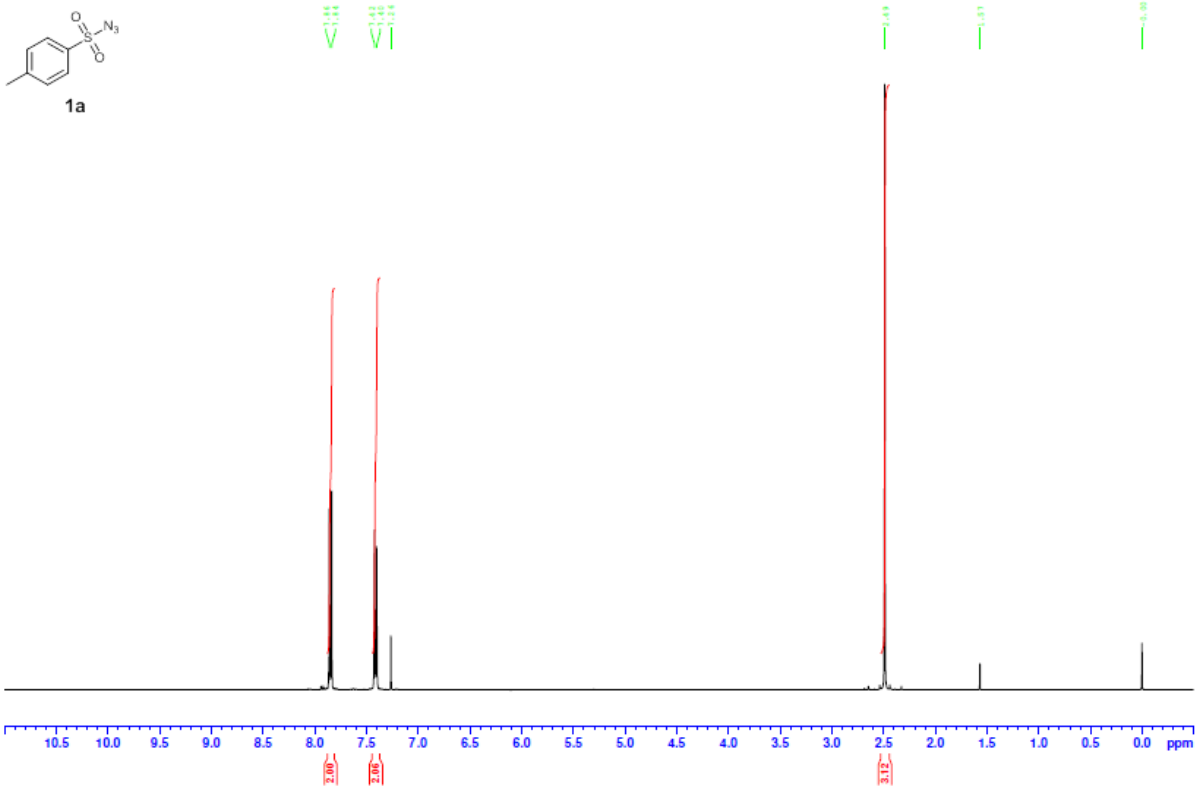


Figure S2.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *p*-toluenesulfonyl azide (**1a**).

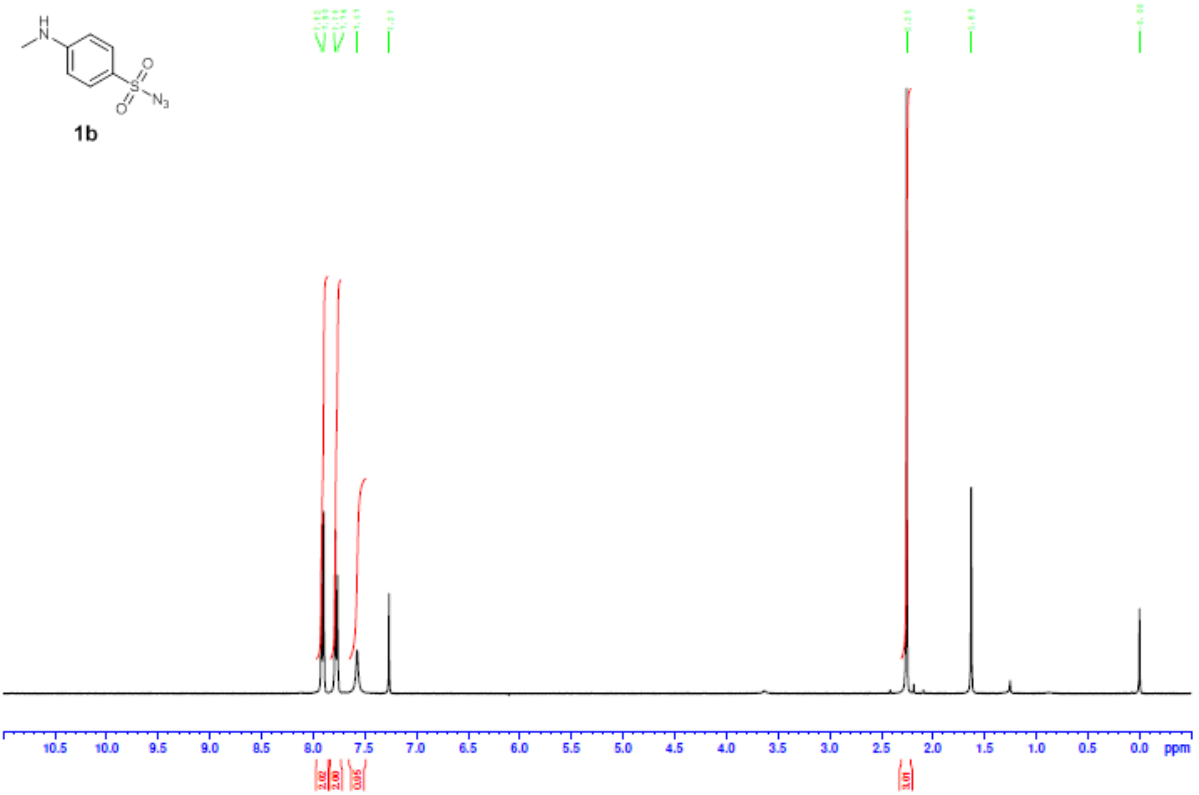


Figure S2.2: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *p*-acetamidobenzenesulfonyl azide (**1b**).

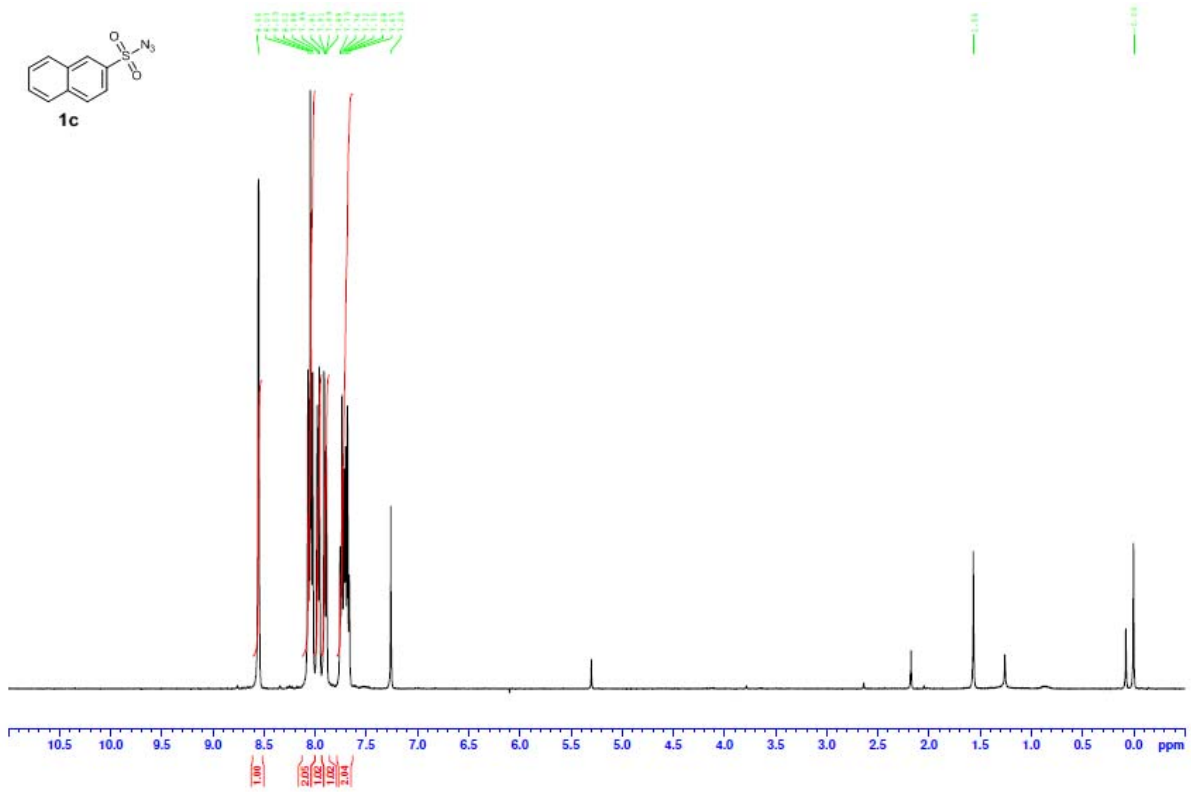


Figure S2.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-naphthalenesulfonyl azide (**1c**).

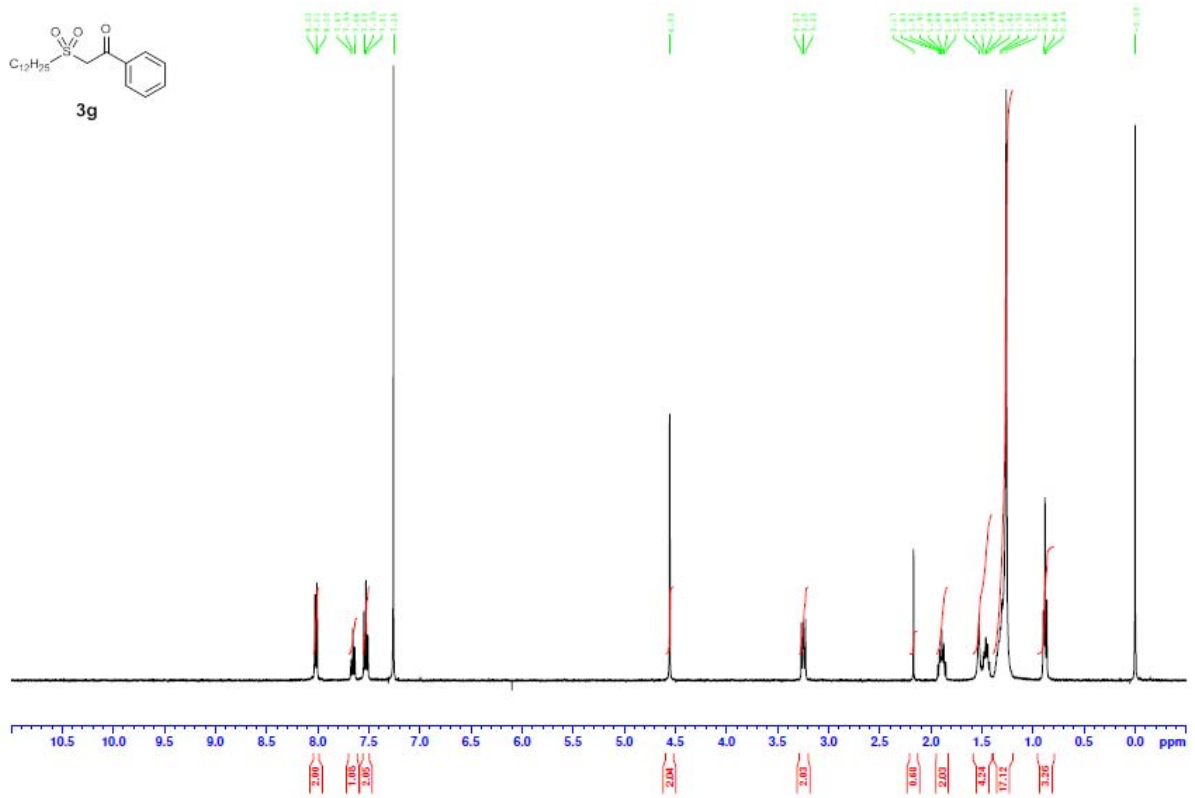


Figure S2.4: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-(dodecylsulfonyl)-1-phenylethan-1-one (**3g**).

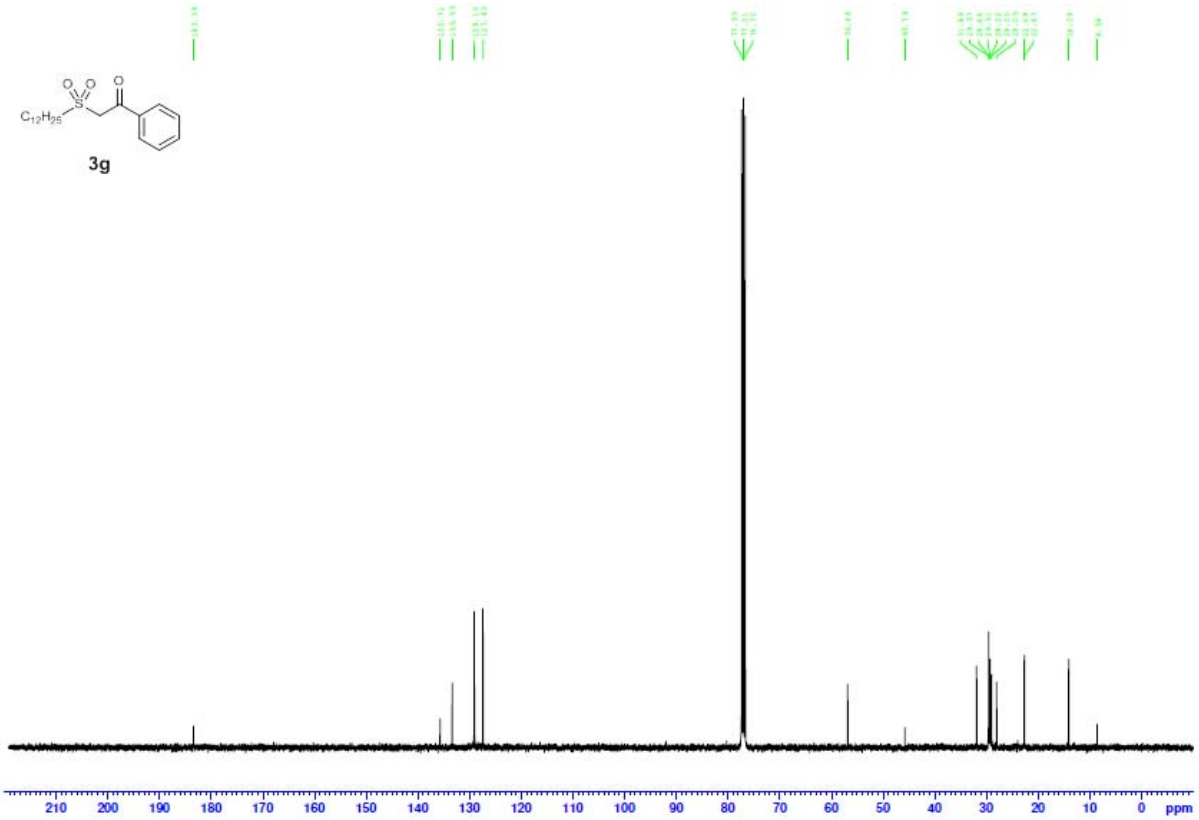


Figure S2.5: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of 2-(dodecylsulfonyl)-1-phenylethan-1-one (**3g**)**.**

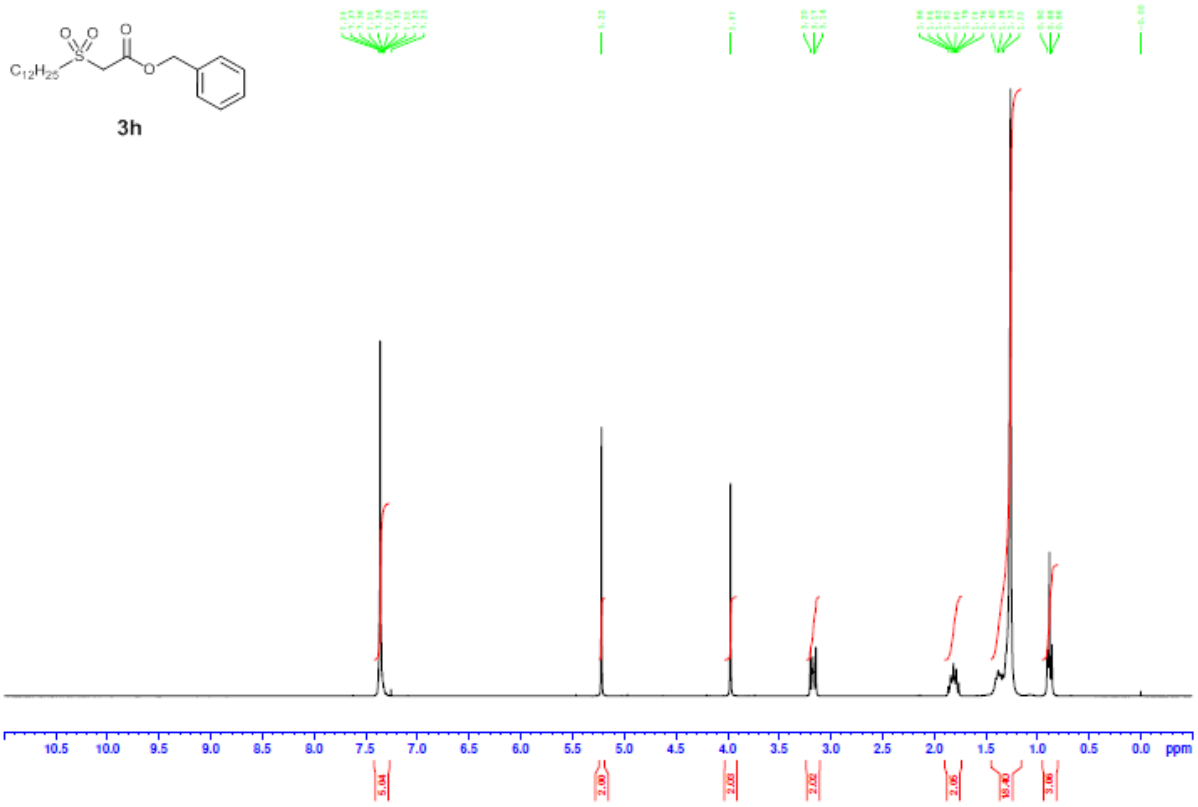


Figure S2.6: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of benzyl 2-(dodecylsulfonyl)acetate (**3h**).

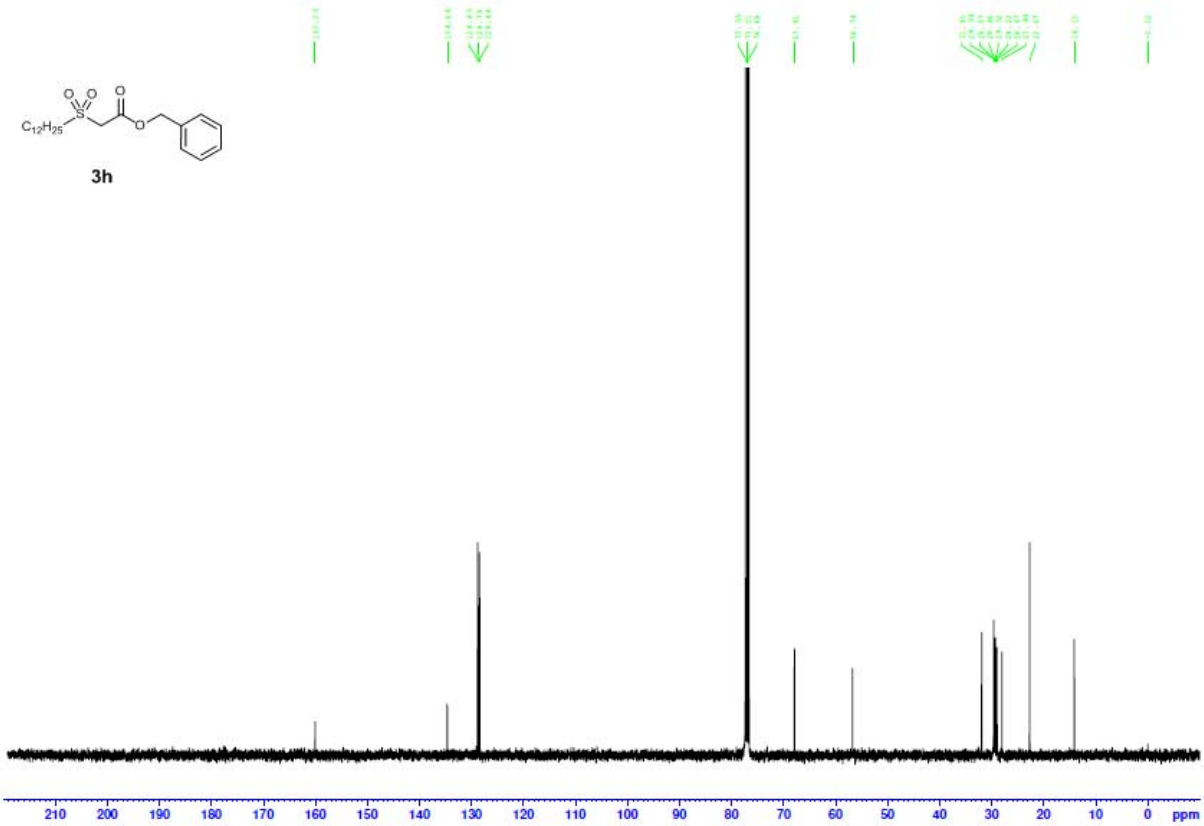


Figure S2.7: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of benzyl 2-(dodecylsulfonyl)acetate (**3h**).

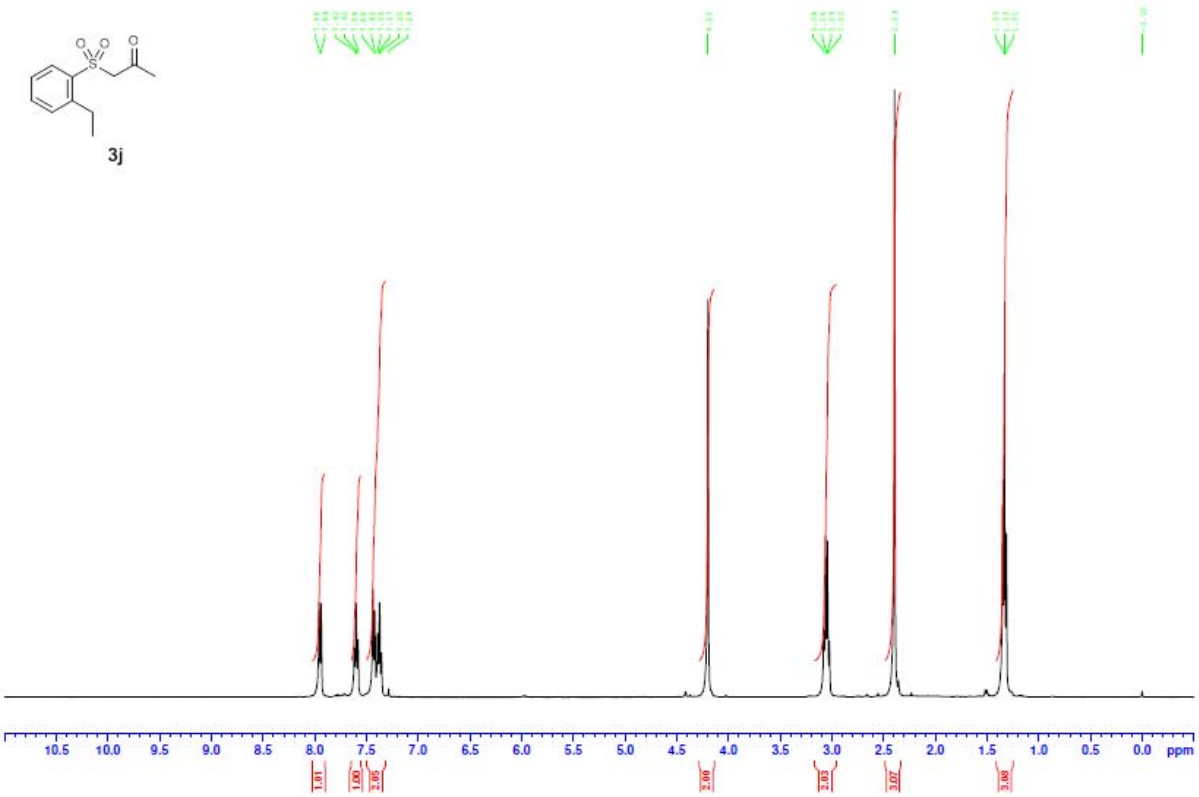


Figure S2.8: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of [(2-ethylphenyl)sulfonyl]propan-2-one (**3j**).

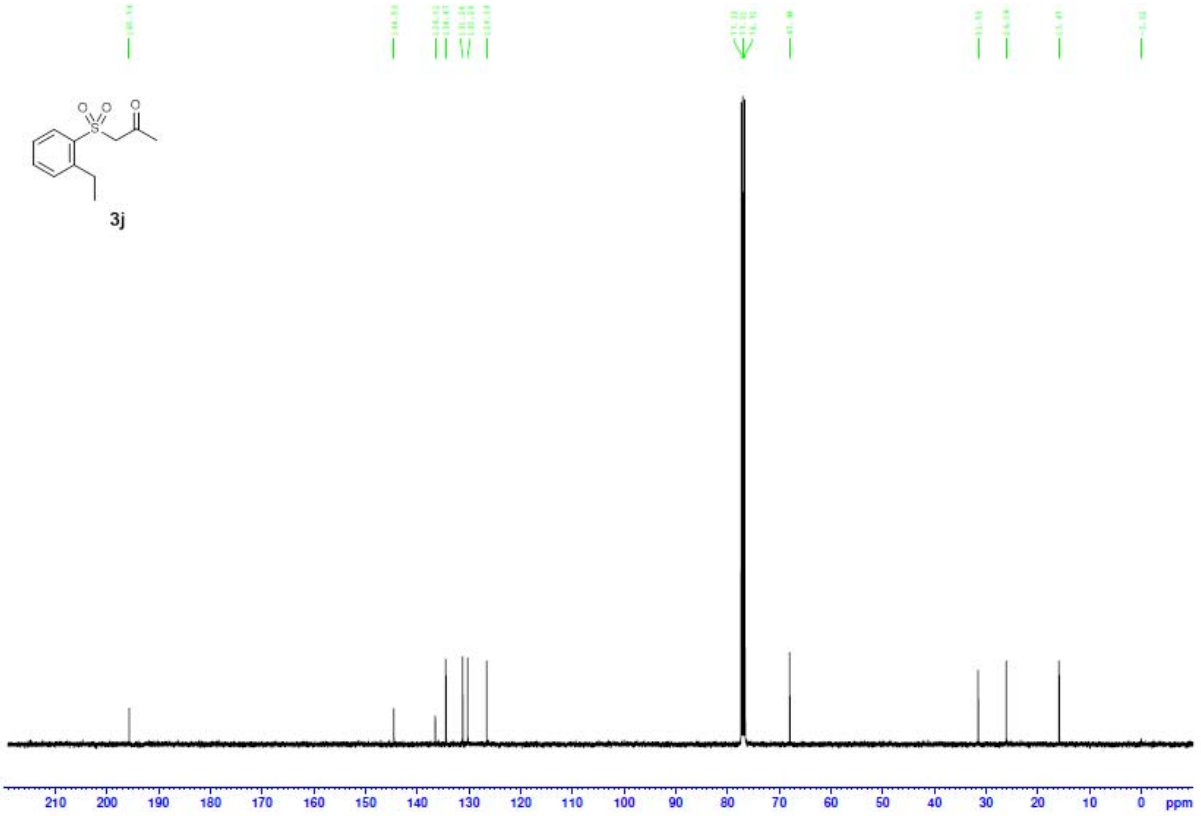


Figure S2.9: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of [(2-ethylphenyl)sulfonyl]propan-2-one (**3j**).

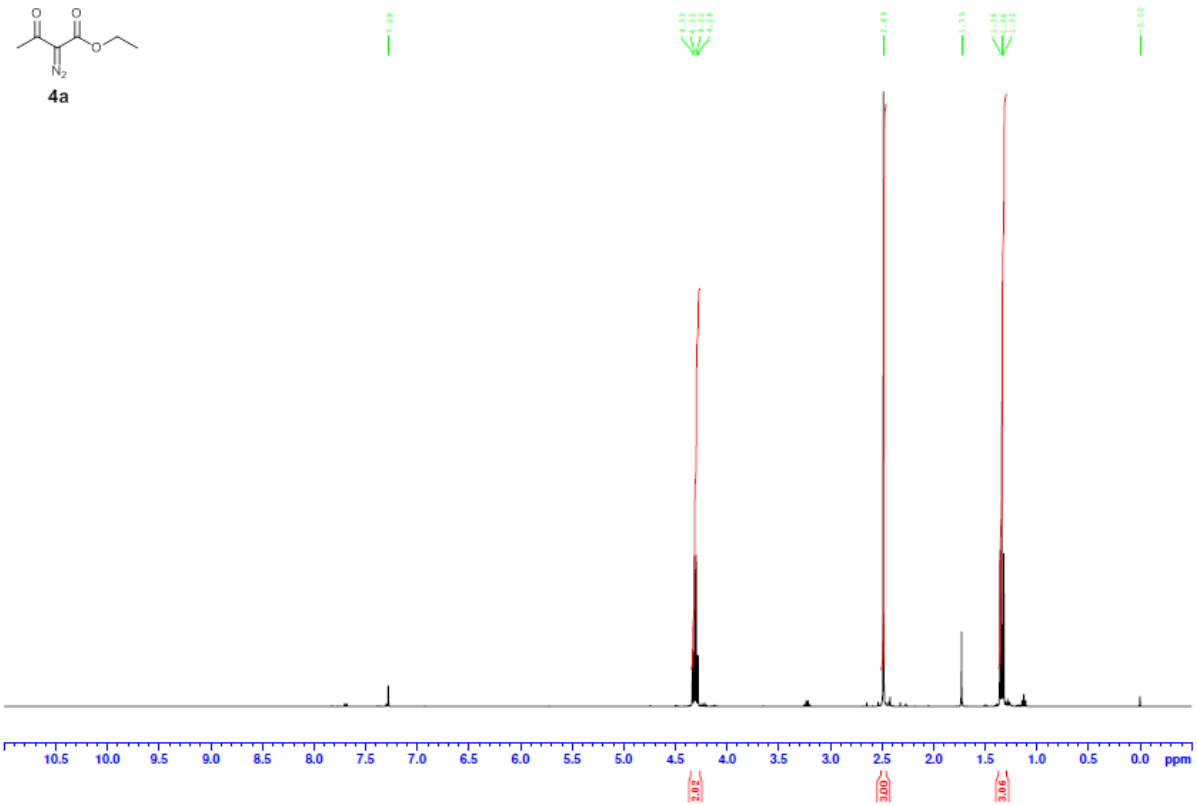


Figure S2.10: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-3-oxobutanoate (**4a**).

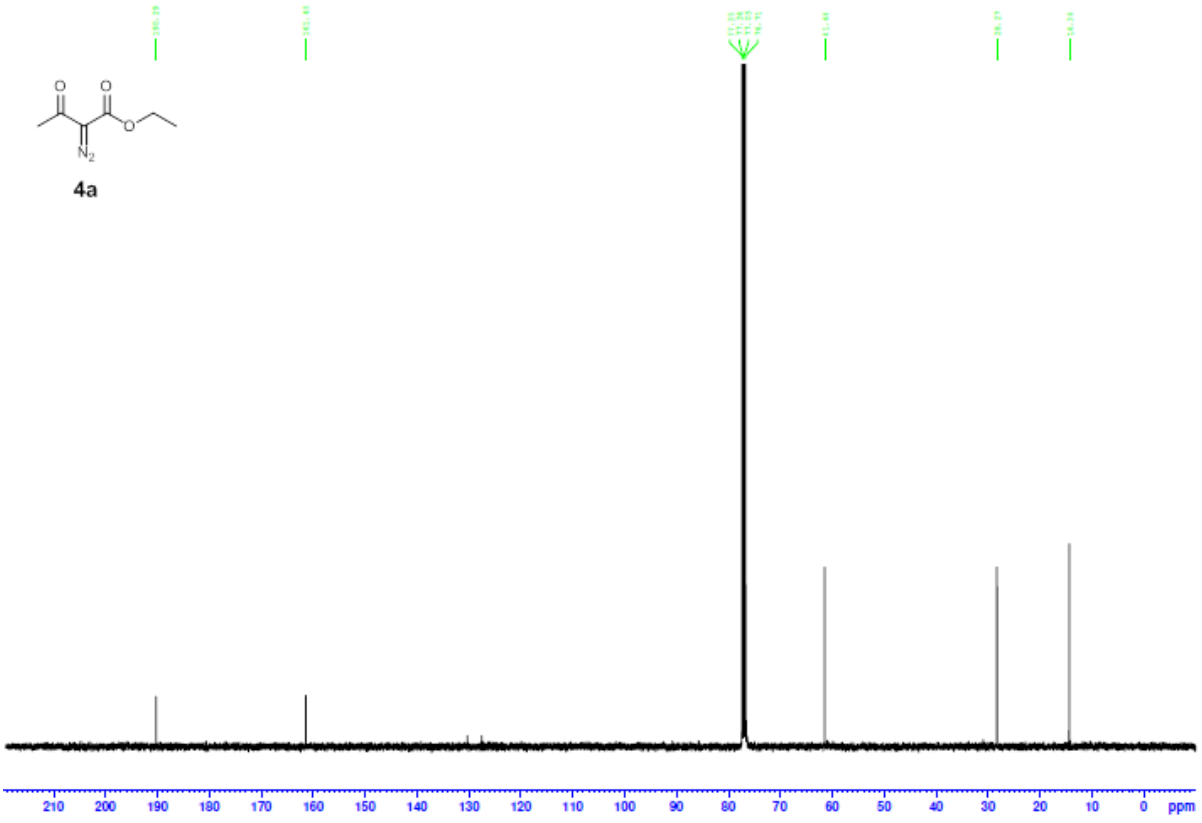


Figure S2.11: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-3-oxobutanoate (**4a**).

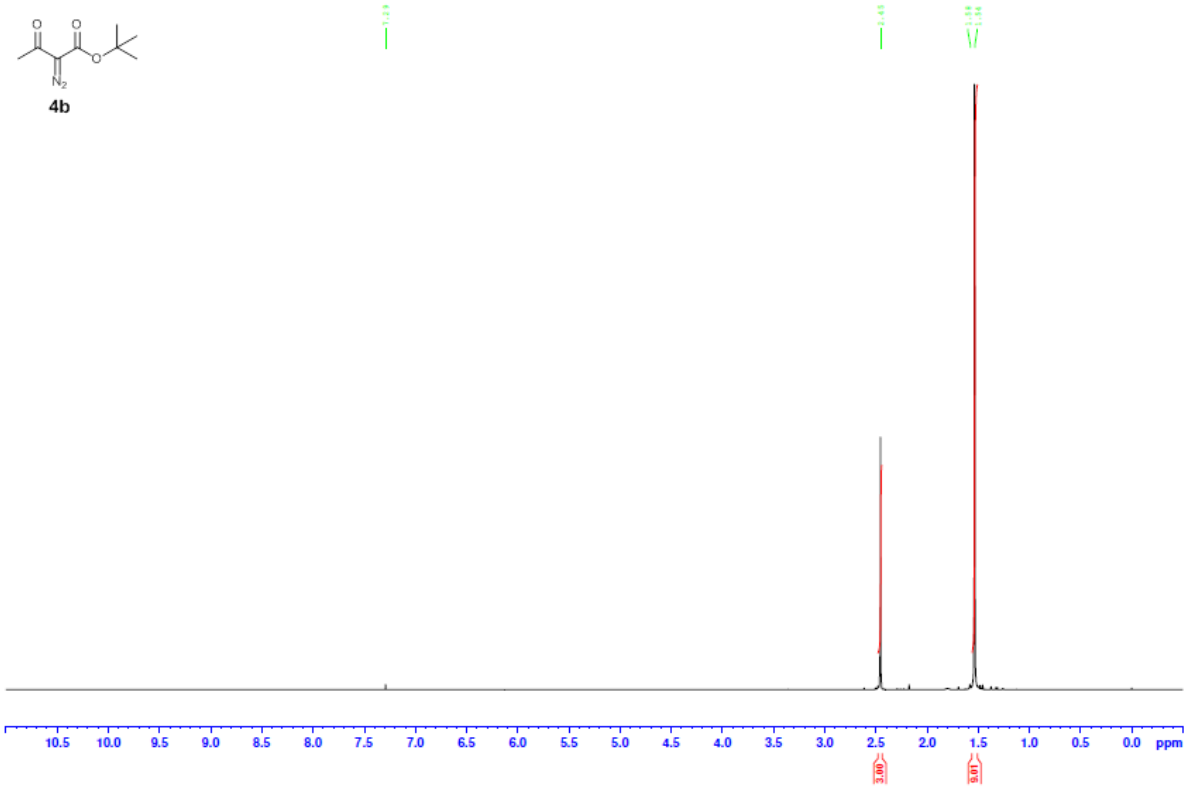


Figure S2.12: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *tert*-butyl 2-diazo-3-oxobutanoate (**4b**).

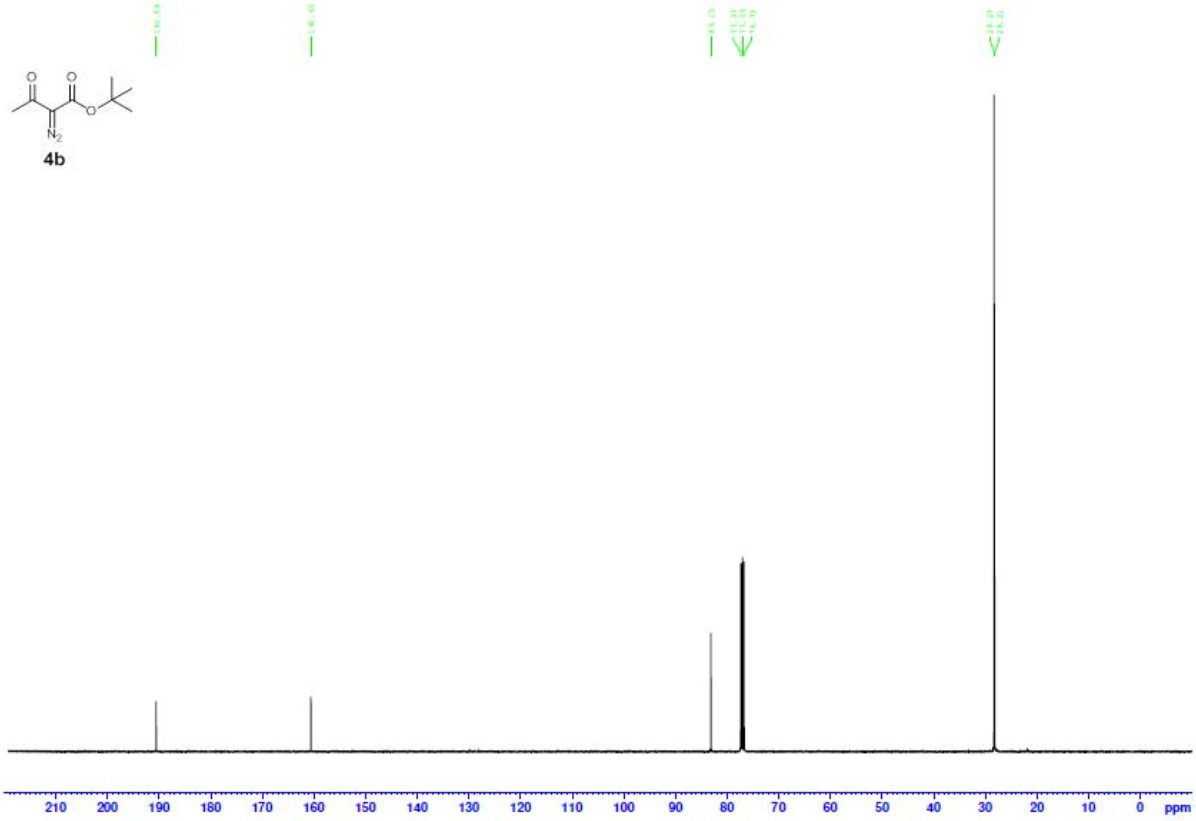


Figure S2.13: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of *tert*-butyl 2-diazo-3-oxobutanoate (**4b**).

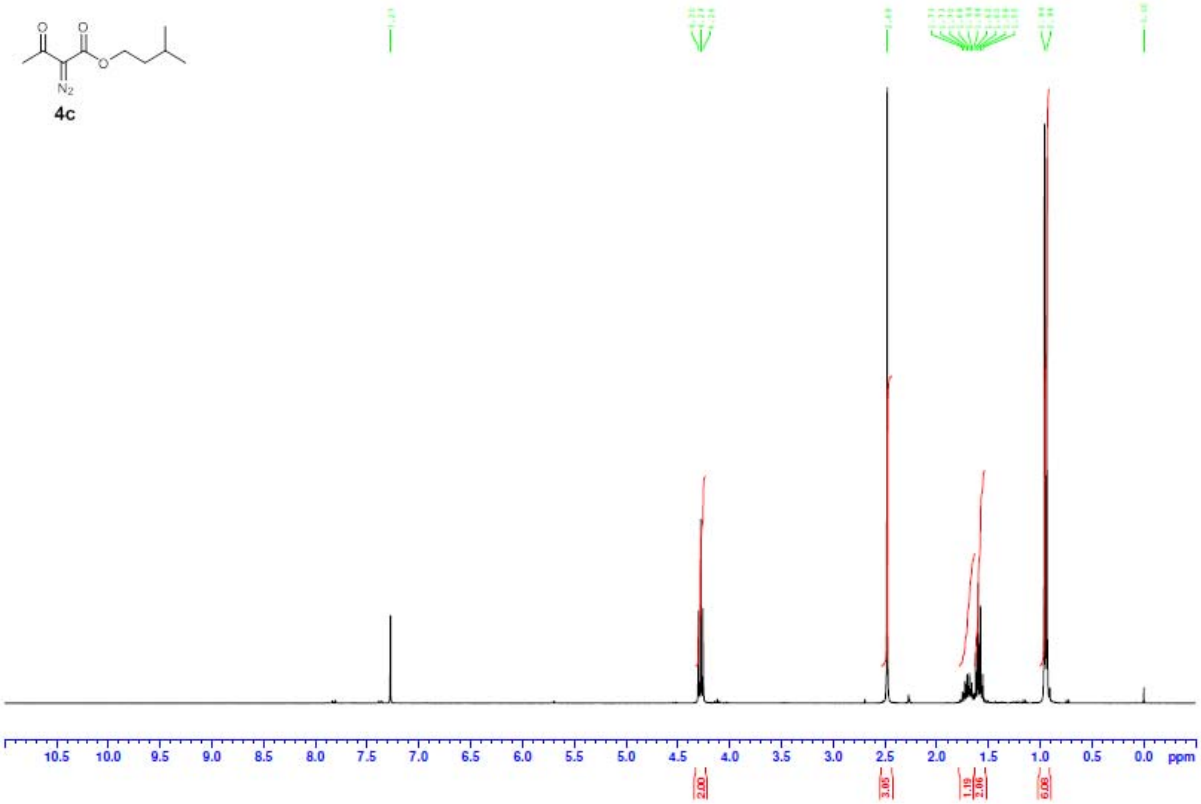


Figure S2.14: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of isopentyl 2-diazo-3-oxobutanoate (**4c**).

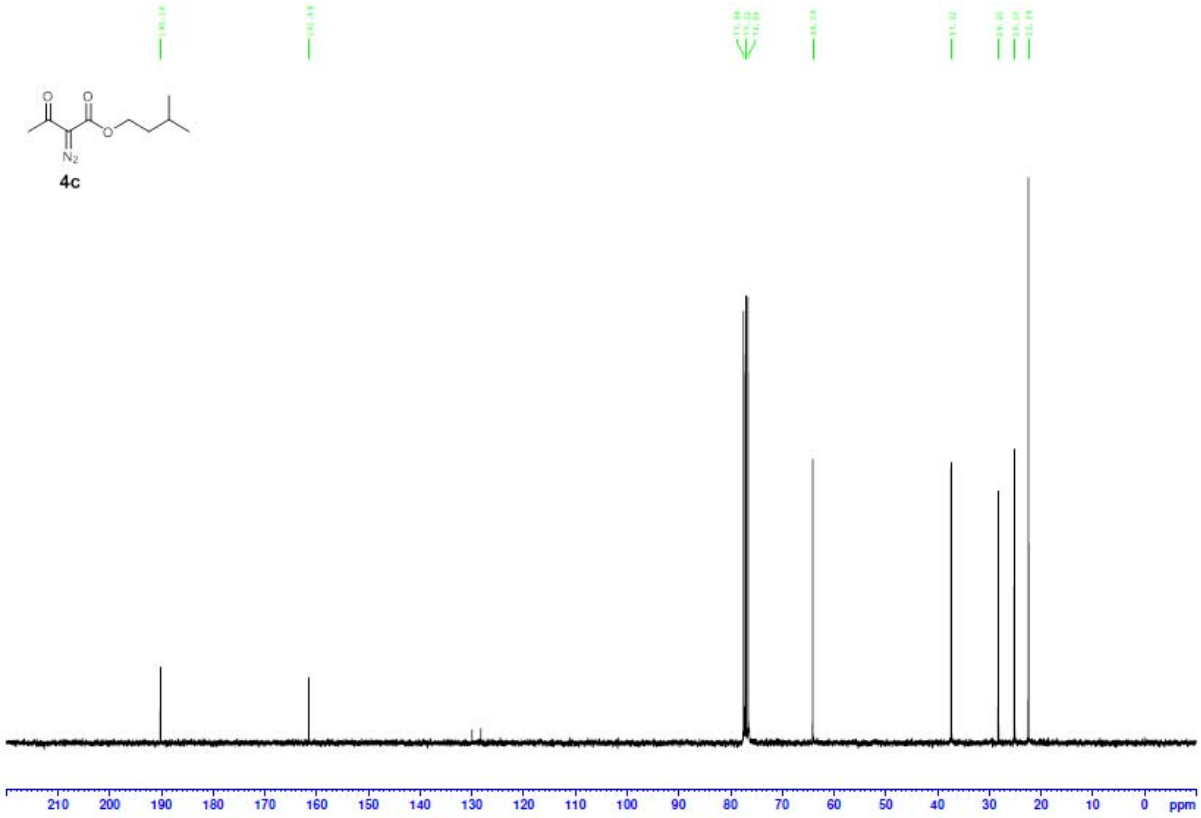


Figure S2.15: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of isopentyl 2-diazo-3-oxobutanoate (**4c**).

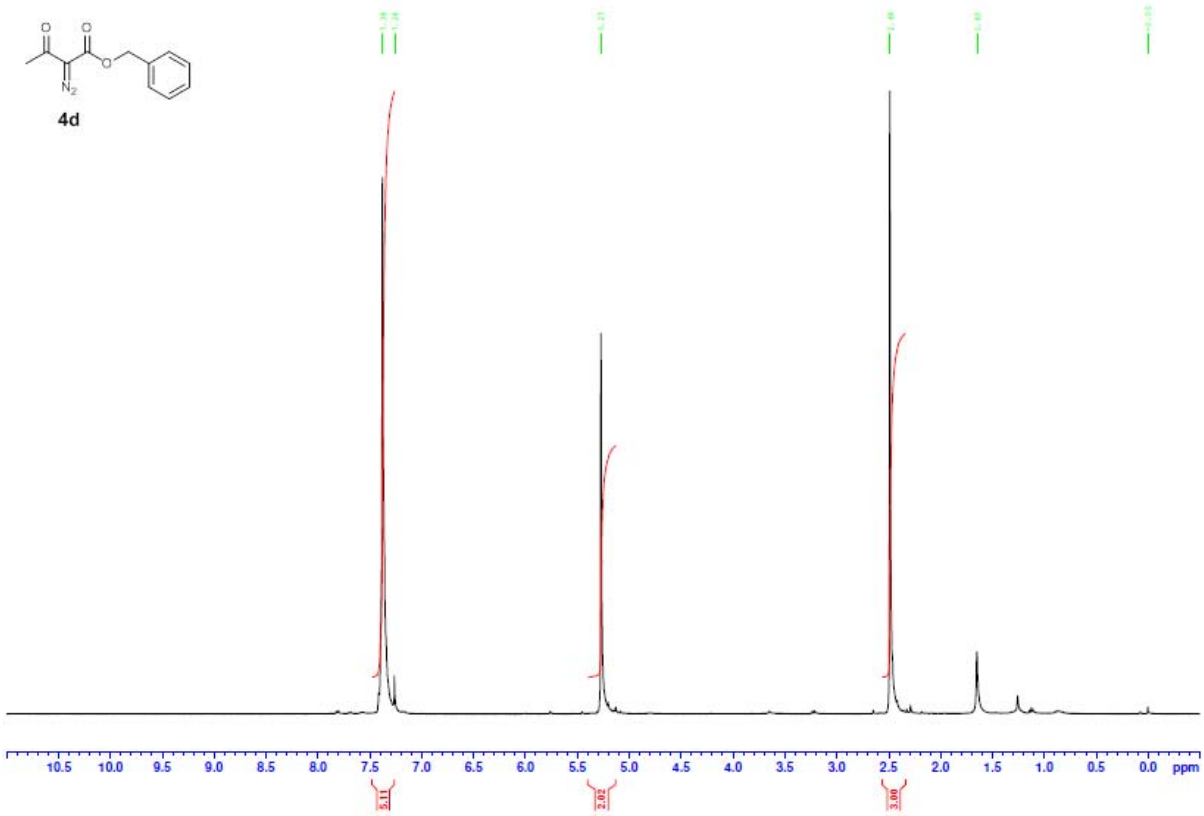


Figure S2.16: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-diazo-3-oxobutanoate (**4d**).

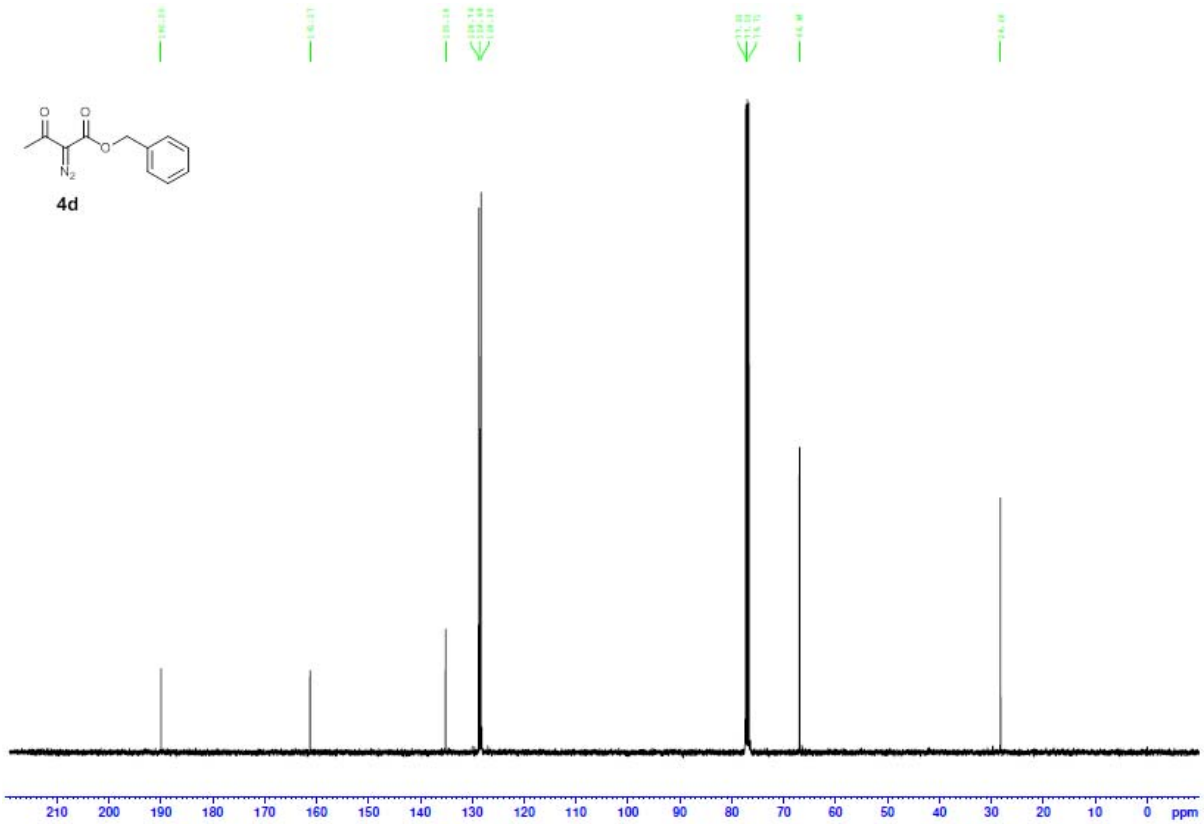


Figure S2.17: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of 2-diazo-3-oxobutanoate (**4d**).

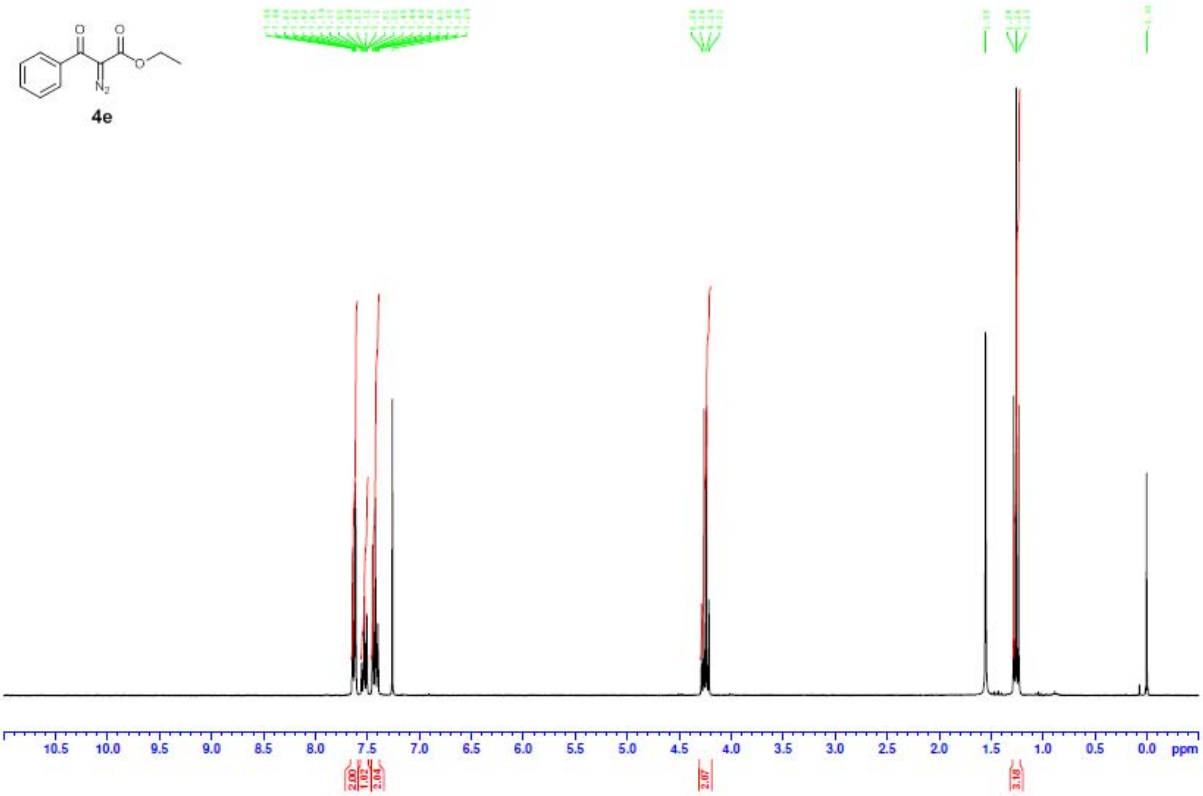


Figure S2.18: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-3-oxo-3-phenylpropanoate (**4e**).

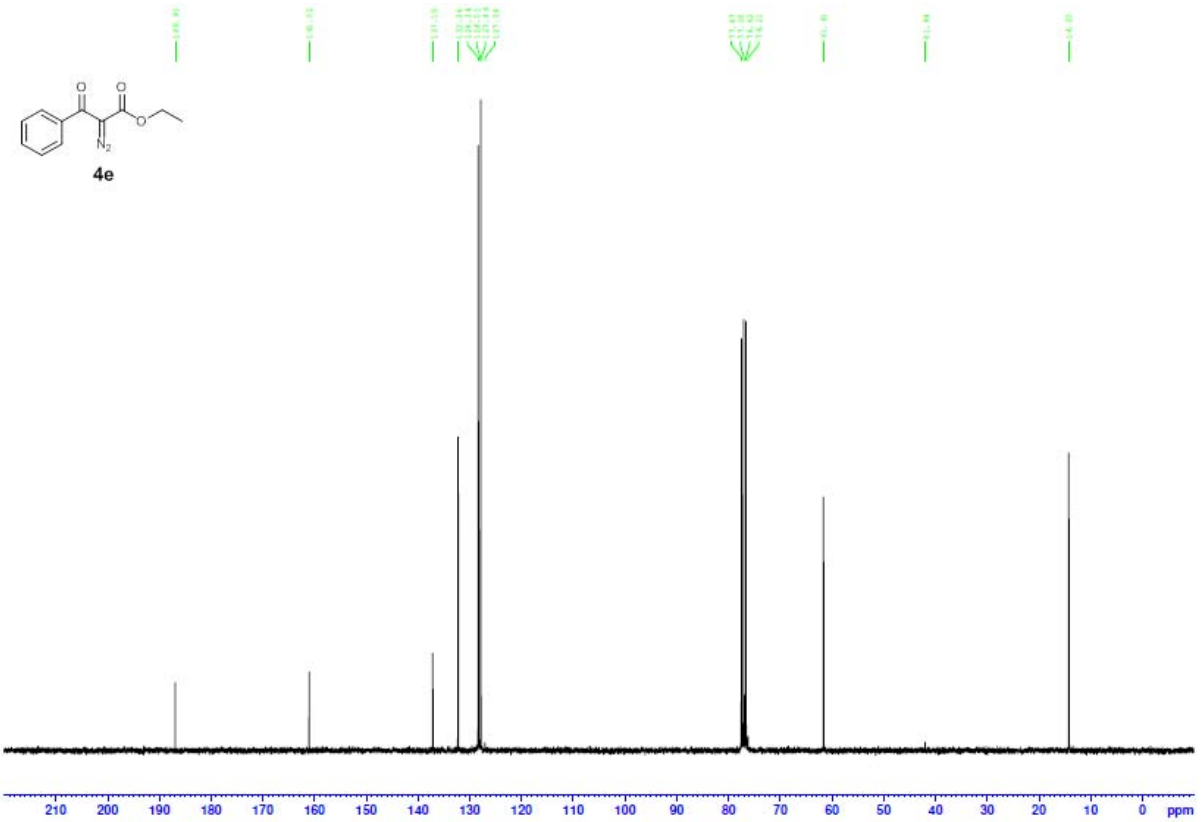


Figure S2.19: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-3-oxo-3-phenylpropanoate (**4e**).

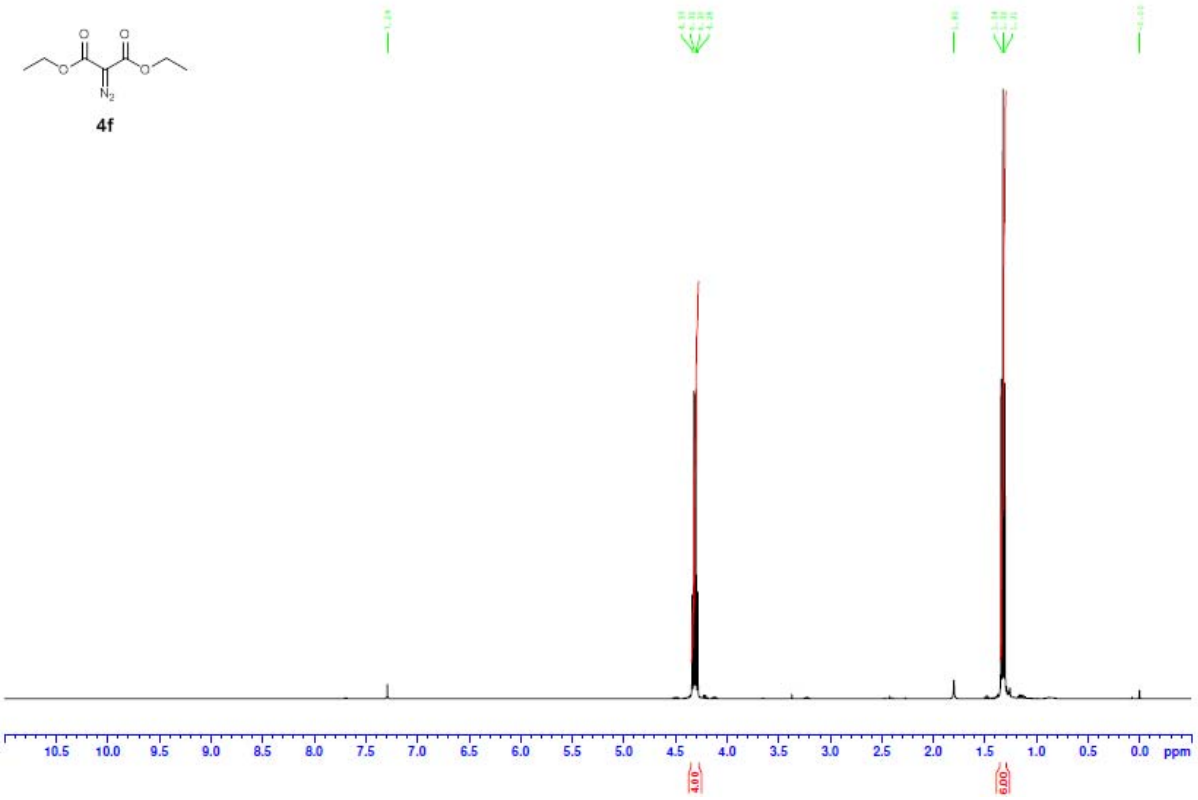


Figure S2.20: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of diethyl 2-diazomalonate (**4f**).

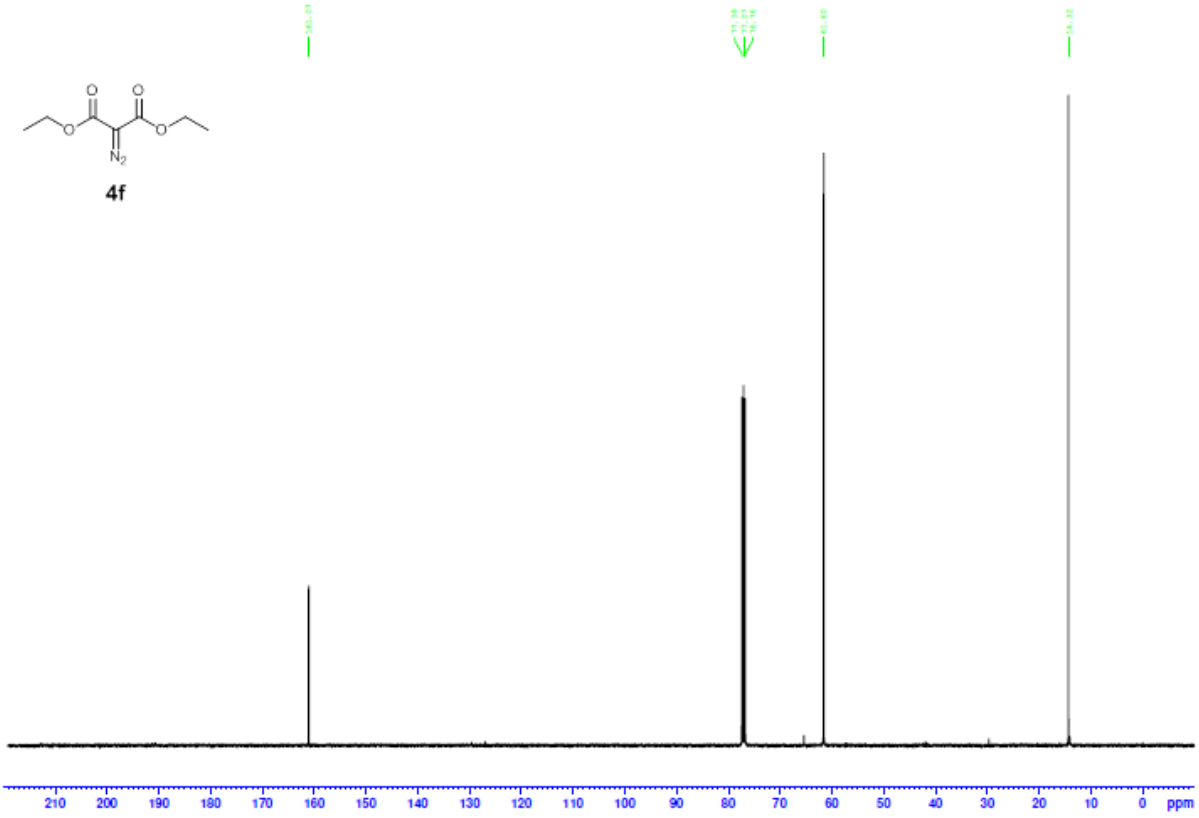


Figure S2.21: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of diethyl 2-diazomalonate (**4f**).

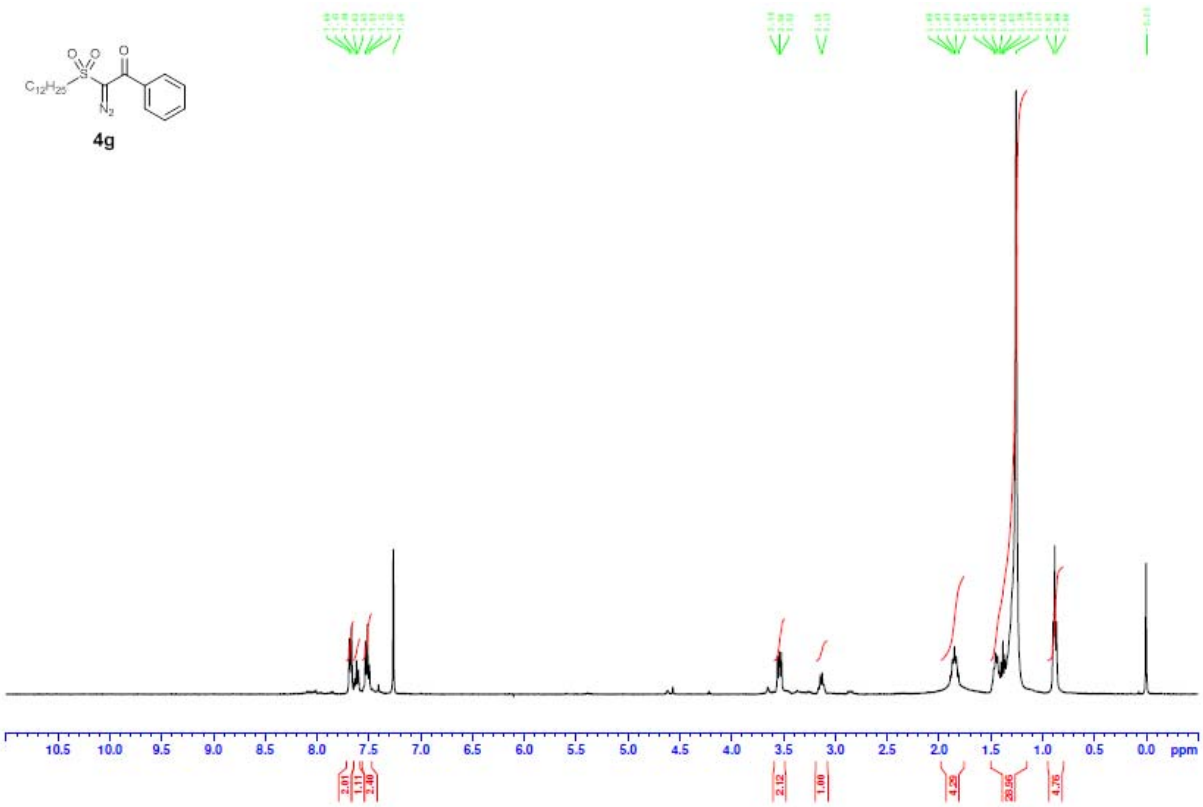


Figure S2.22: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-diazo-2-(dodecylsulfonyl)-1-phenylethan-1-one (**4g**).

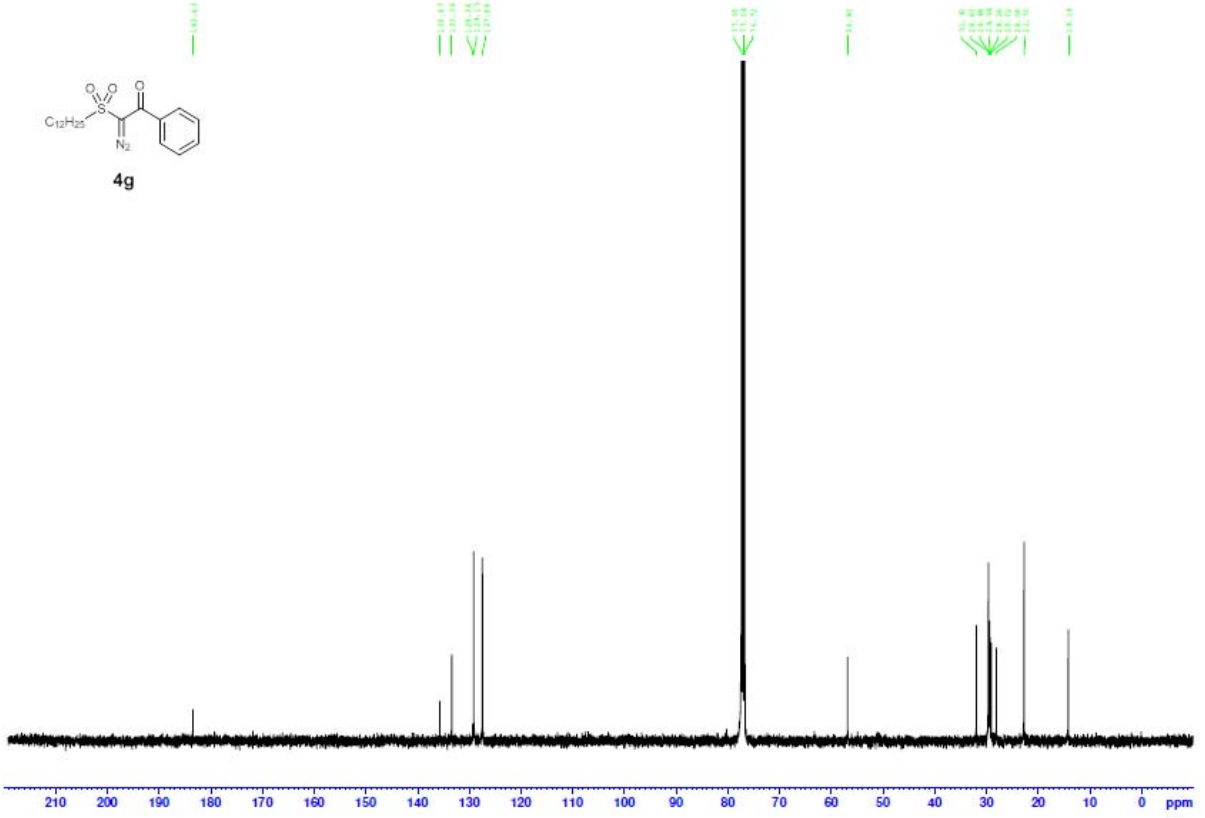


Figure S2.21: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of 2-diazo-2-(dodecylsulfonyl)-1-phenylethan-1-one (**4g**).

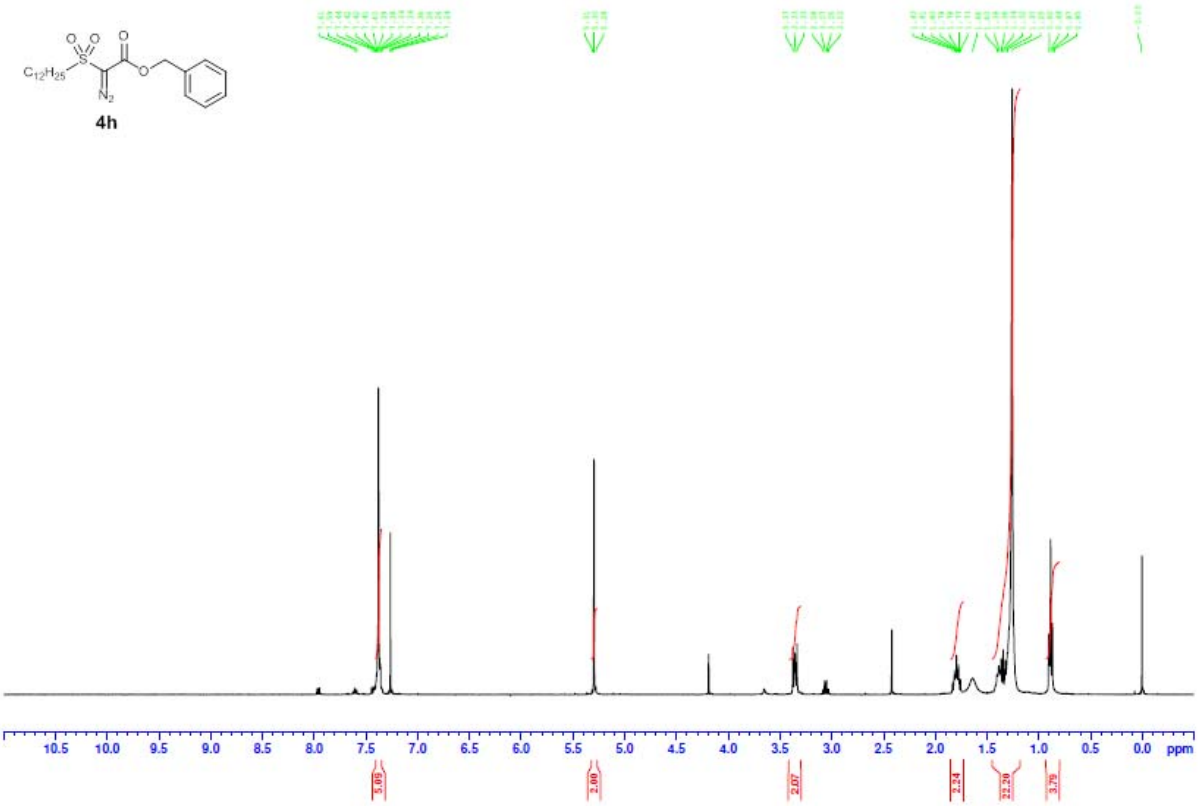


Figure S2.22: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of benzyl 2-diazo-2-(dodecylsulfonyl)acetate (**4h**).

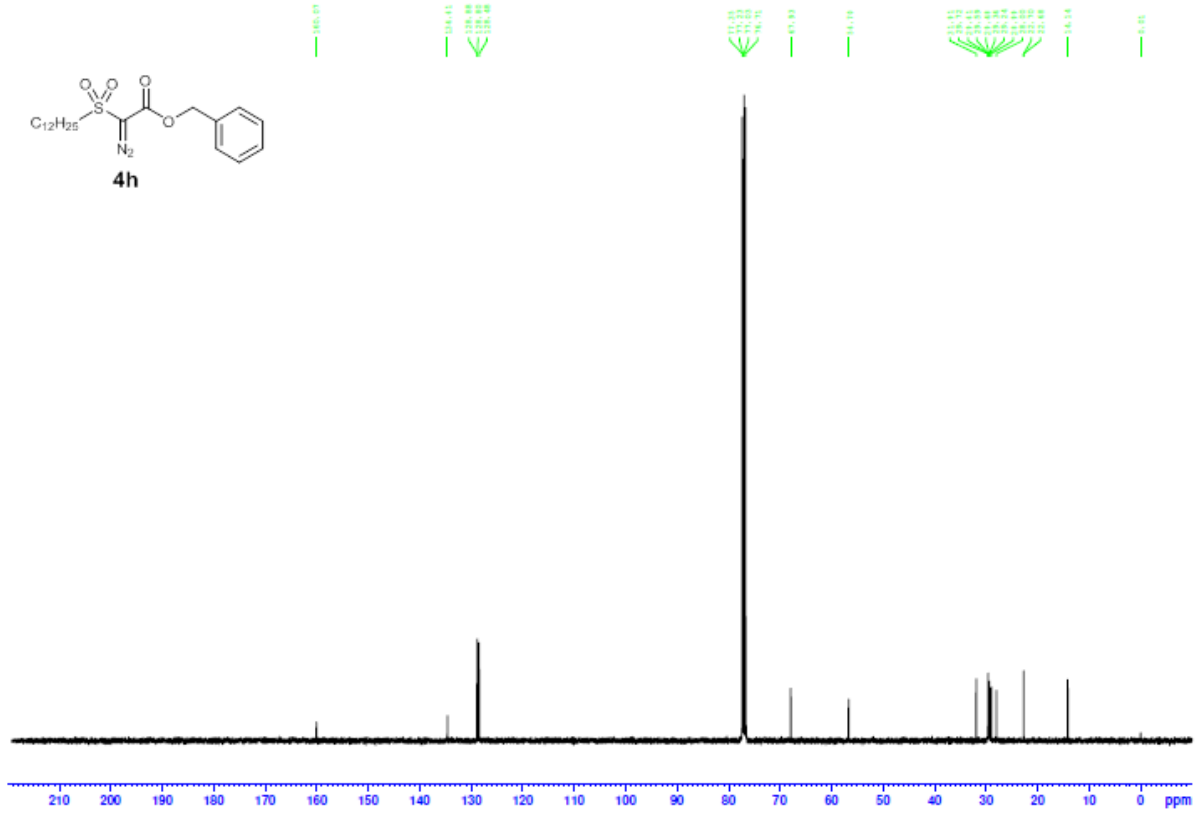


Figure S2.23: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of benzyl 2-diazo-2-(dodecylsulfonyl)acetate (**4h**).

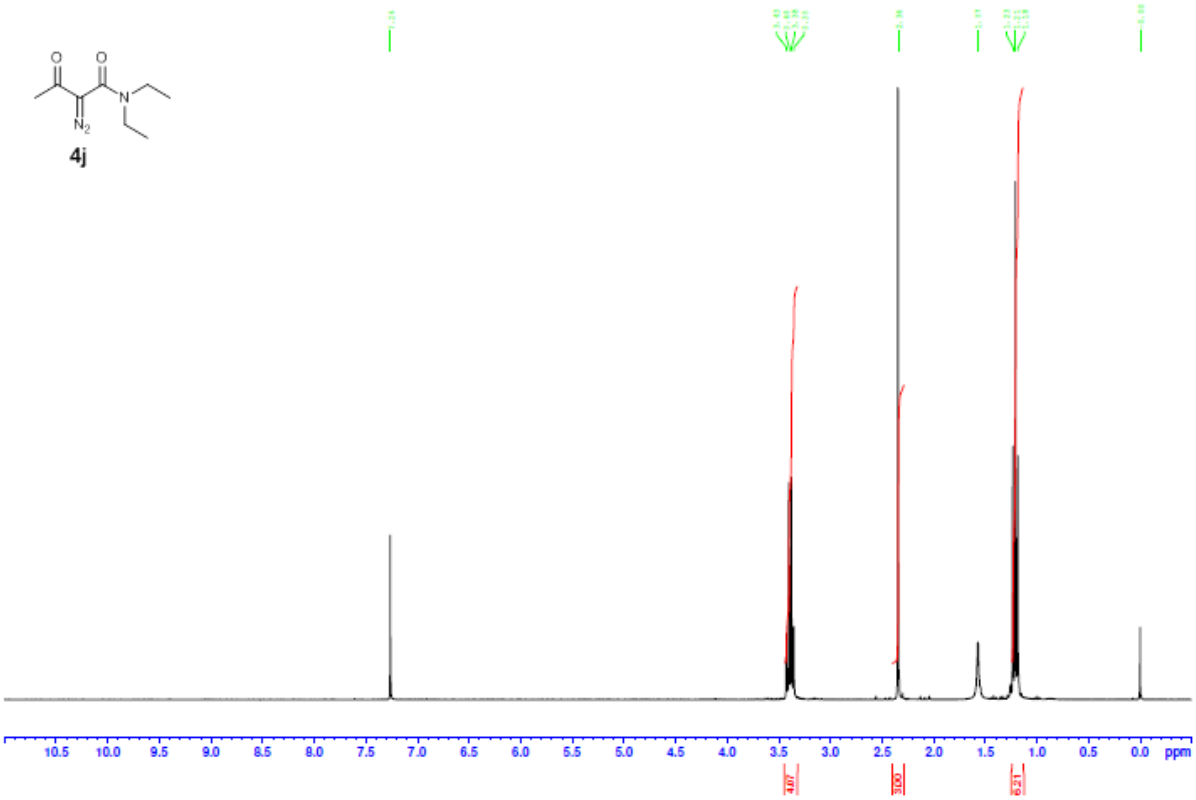


Figure S2.24: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of *N,N*-diethyl-2-diazo-3-oxobutanamide (**4j**).

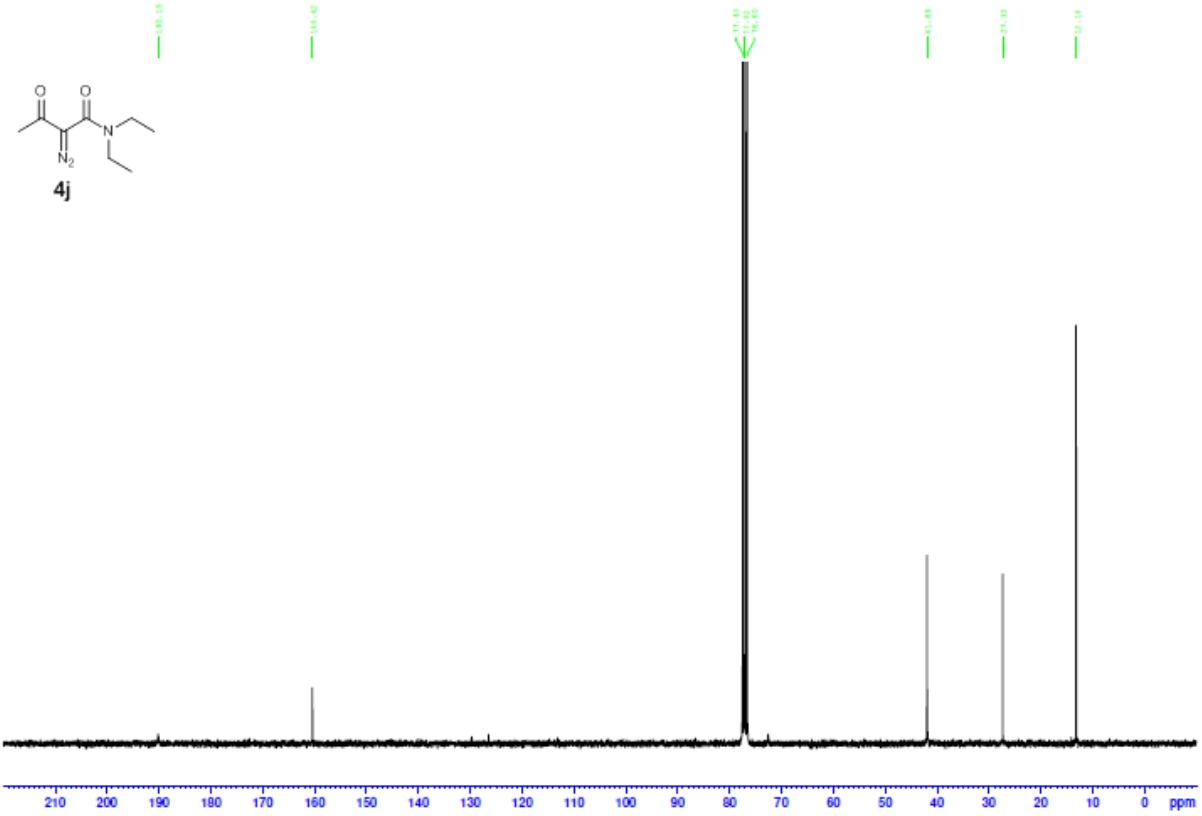


Figure S2.25: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of *N,N*-diethyl-2-diazo-3-oxobutanamide (**4j**).

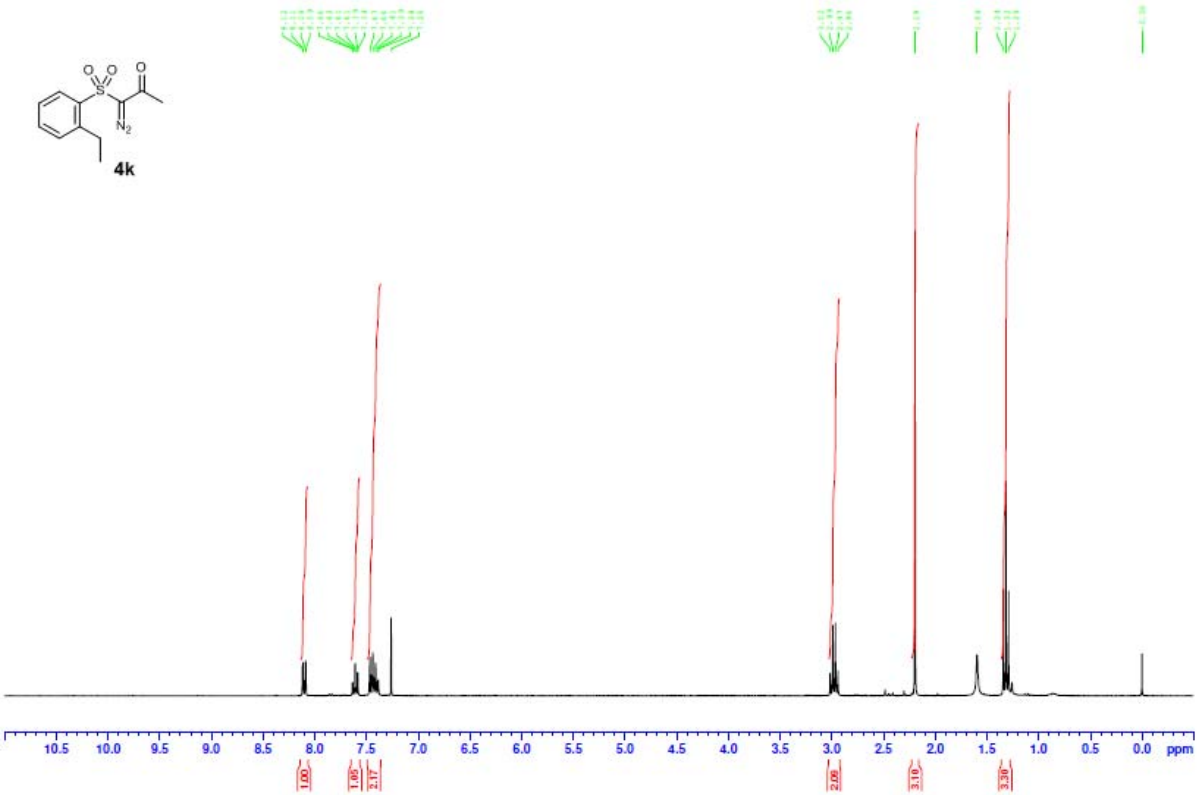


Figure S2.26: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 1-diazo-1-((2-ethylphenyl)sulfonyl)propan-2-one (**4k**).

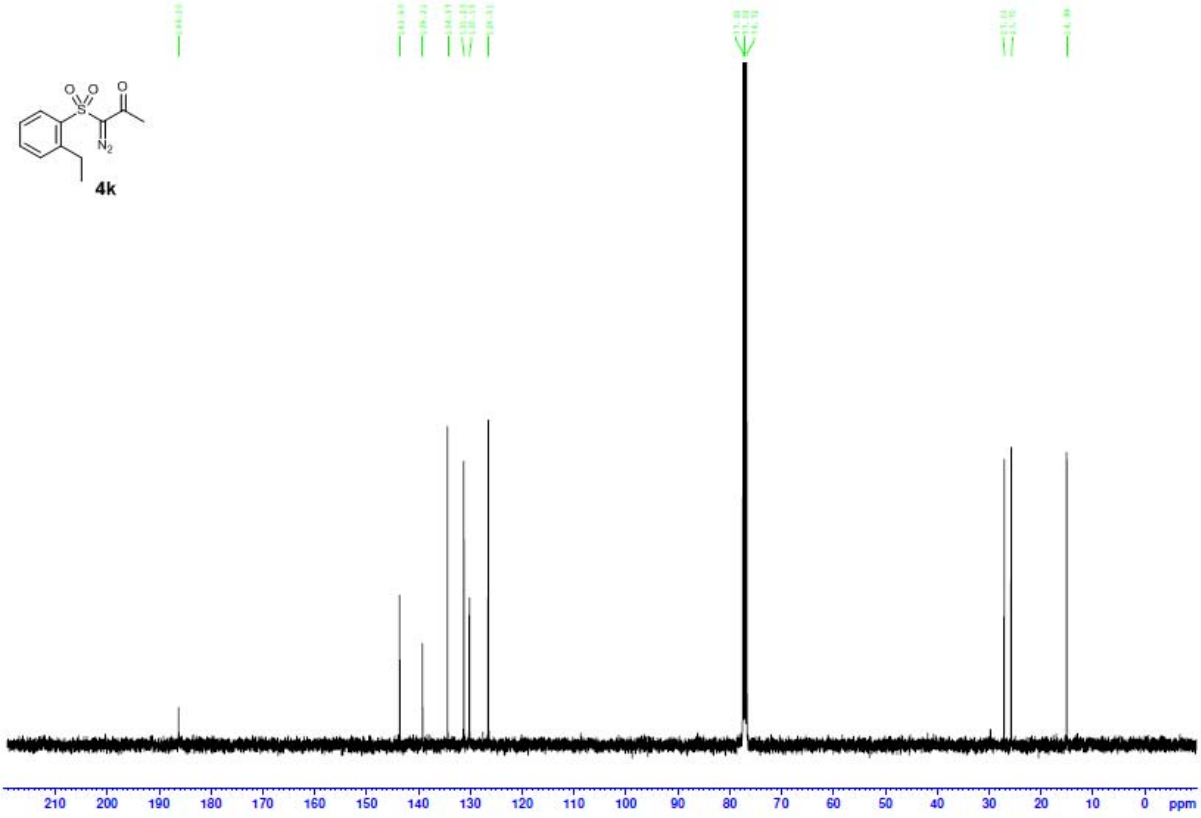


Figure S2.27: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of 1-diazo-1-((2-ethylphenyl)sulfonyl)propan-2-one (**4j**).

3. Graphic from In-line IR Monitoring of Diazo Transfer to β-Ketoamide 3j

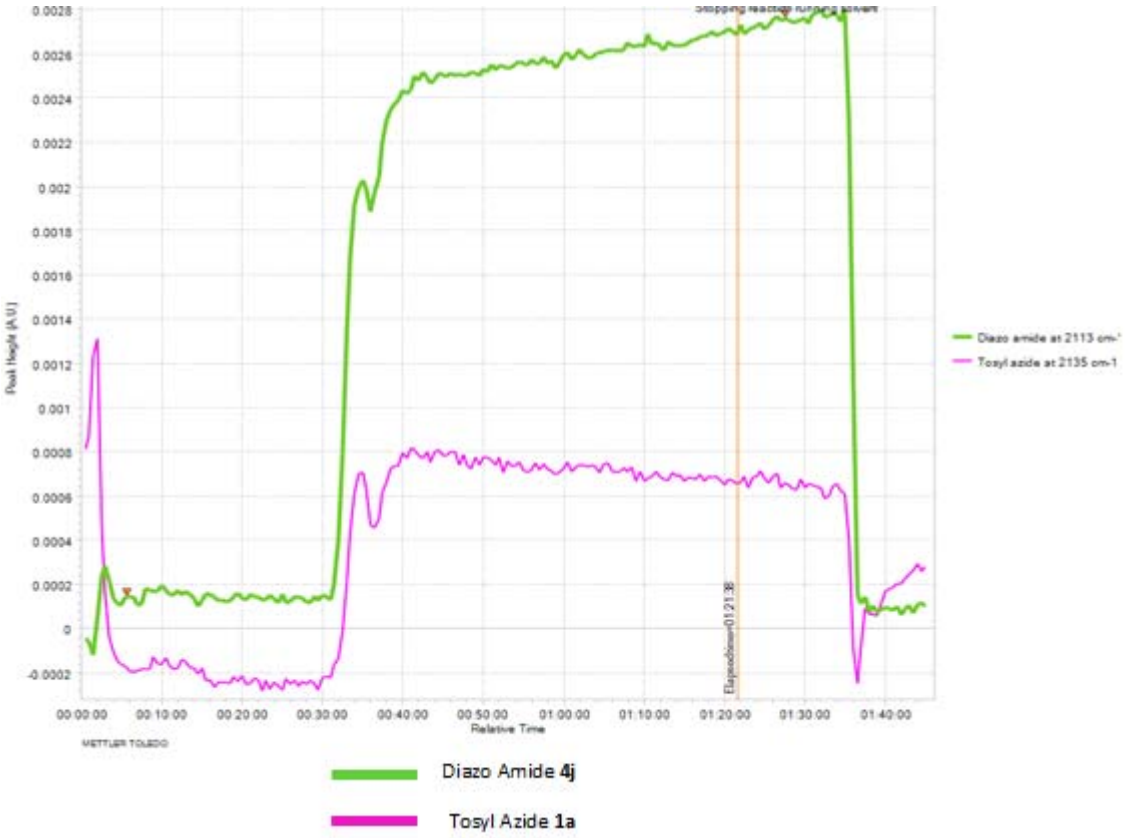


Figure S3.1: In-line IR monitoring of diazo transfer to β-ketoamide **3j** using tosyl azide (**1a**).

4. References

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