Exploiting the Continuous In Situ Generation of Mesyl Azide for Use in a Telescoped Process

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Abstract: The hazardous diazo transfer reagent mesyl azide has been safely generated and used in situ for continuous diazo transfer as part of an integrated synthetic process with an embedded safety quench. Diazo transfer to β-ketoesters and a β-ketosulfone was successful. In-line phase separation, by means of a continuous liquid–liquid separator, enabled direct telescoping with a thermal Wolff rearrangement.

Introduction

The Regitz diazo transfer methodology is widely regarded as the most convenient approach to preparation of α-diazo carbonyl compounds that bear two activating groups.[1] These synthetically valuable compounds represent precursors for carbenes[2] and carbenoids,[3] along with ketenes and their heteroanalogues[4] – reactive intermediates capable of diverse chemistries, often under mild conditions and with high selectively.

Continuous processing has been firmly established in facilitating safety improvement to chemical processes, spanning the pharmaceutical and fine chemical industries and academic research. The enhanced reaction control in flow that arises from use of high surface-area-to-volume ratio tubular reactors allows an efficiency of heat and mass transfer unattainable in batch. Consequently, access to extreme reaction conditions, ease of scale-up and increased reproducibility are key features of continuous systems.[5] Furthermore, the opportunities for automation, including control and feedback loops, the inherently rapid dissipation of heat and the facility for in situ generation and direct use of hazardous species[6] in minimal quantities all represent significant mitigations against reaction runaway or operator exposure. These improvements have made flow chemistry a key enabling technology for valuable synthetic methodologies that would previously have been avoided due to the risks posed at large scale.[7]

The use of azides, diazo compounds and even diazonium salts in flow is well documented.[8] Following several studies involving diazo transfer in flow that directly utilized sulfonyl azides, we recently reported a scalable continuous diazo transfer process where tosyl azide was generated and used in situ, overcoming the challenges of employing this hazardous reagent on large scales.[9] A similar approach has since been employed by Monbaliu as part of a strategy for continuous synthesis of Ritalin.[10] The development of a modified protocol for in situ generation of mesyl azide logically extends this methodology, with access to safe and efficient synthesis and use of diazo compounds as the ultimate goal.

Mesyl azide is a reagent which enables generation of α-diazo carbonyls by diazo transfer without the need for chromatographic purification.[11] Principally, it is employed where the relative ease of removal of mesyl amide byproduct in a simple aqueous wash is an important consideration for recovery of the desired diazo product. Tosyl azide,[1] the most commonly used diazo transfer reagent, produces tosyl amide, which requires use of a base wash to facilitate partitioning into an aqueous phase. While this advantage is not unique to mesyl azide, its low cost and the low molecular weight byproducts/reduced waste treatment burden, when compared to other suitable reagents, would make it a highly attractive option but for the substantial safety challenges associated with handling this material – specifically significant heat and shock sensitivity. Although mesyl azide possesses the same impact sensitivity as tosyl azide (50 kg cm), it has been shown to decompose at twice the rate.[12] This unfavourable safety profile has, to date, limited mesyl azide exclusively to use in small scale (typically <1 g in our lab) syntheses.

Despite the range of safer alternatives currently available, each of these diazo transfer reagents has limitations when compared to mesyl azide. While relatively safer,[12] tosyl azide has a poorer associated atom economy; tosyl sulfonamide is produced, which is both more challenging to remove than mesyl sulfonamide and represents an increased waste disposal requirement. The last decade has seen the emergence of imidazole-based diazo transfer reagents, such as the shelf stable imidazole-1-sulfonyl azide hydrochloride,[13] to enable easy separation of the sulfonamide byproducts. However, the expense of these compounds and ongoing safety concerns[14] have curtailed their use. Economic factors also continue to exclude polystyrene bound benzenesulfonyl azide[15] from use on large scale. Although proven to be considerably more stable than mesyl azide,[12] both *p*-acetamidobenzenesulfonyl azide (ABSA)[16] and *p*-dodecylbenzenesulfonyl azide (DBSA)[17] have similar atom economy issues to tosyl azide; they remain vulnerable to thermal decomposition and their sulfonamides usually require chromatographic separation. Hence, in the absence of an ideal diazo transfer reagent, the development of a process to adequately mitigate the dangers associated with mesyl azide while harnessing its advantages was of significant interest.

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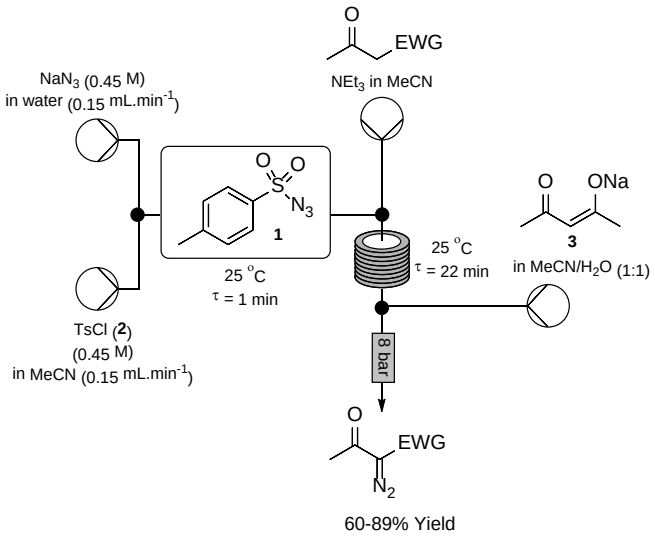
Results and Discussion

A continuous process for formation and use of tosyl azide **1** in situ has previously been developed within the group (Scheme 1).[9] This process involves combining a stream of aqueous sodium azide with a stream of tosyl chloride **2** in acetonitrile at ambient temperature leading to rapid generation of tosyl azide **1**. This combined stream is then mixed with a suitable diazo acceptor substrate and base in a reactor coil at 25 °C, resulting in diazo transfer. Finally, a quench solution of sodium acetoacetonate (**3**) is introduced to the product stream to safely destroy any residual unreacted tosyl azide, leaving a solution of the desired diazo carbonyl product along with tosyl amide and aqueous soluble byproducts.

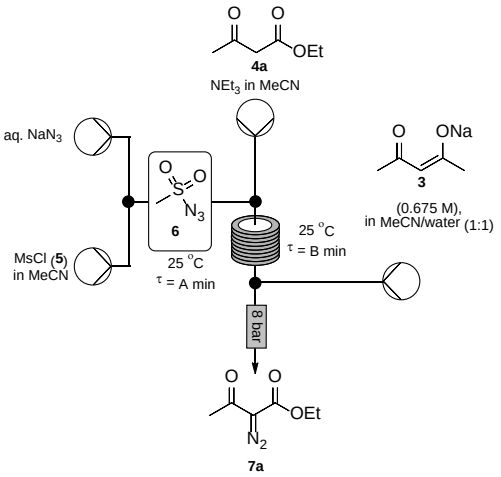


Scheme 1. Previously developed continuous process for in situ generation and use of tosyl azide.

Initial work was focused on adapting this approach to continuous in situ generation and use of tosyl azide to an analogous mesyl azide process. Among the key features of this methodology, retaining a room temperature (25 °C) diazo transfer and inclusion of the in-line sacrificial quench were regarded as most important for the ultimate safety profile of the system. With this in mind, a study was undertaken into diazo transfer to ethyl acetoacetate in flow, utilizing a mixture of mesyl chloride **5** and aqueous sodium azide to form mesyl azide **6** in situ (Table 1).

Interestingly, in contrast to the equivalent process employing tosyl chloride, where <2 min was required for complete formation of tosyl azide, approximately 15 min was required for complete mesyl azide formation. Corresponding reaction monitoring by IR of mesyl azide formation in batch indicated that approximately 12 min was required for complete disappearance of the sodium azide band (2041 cm^{-1}). This observation strongly suggests that the more lipophilic character of tosyl chloride is a significant factor in the rate at which the sulfonyl azide is generated in aqueous acetonitrile.

Table 1. Optimization of reaction conditions for continuous diazo transfer to ethyl acetoacetate (**3a**) using in situ generated mesyl azide (**6**).



Entry	Concentration [mol L^{-1}]	MsN_3 Formation time A [min]	Diazo transfer time B [min]	Conversion [%][a]
1	0.45	1	22	50
2	0.45	33	22	66
3	0.45	50	33	73
4	0.45	15	66	80
5	0.90	15	66	100
6	0.80	16	11	49
7	0.80	16	22	60
8	0.80	16	33	71
9	0.80	15	66	100

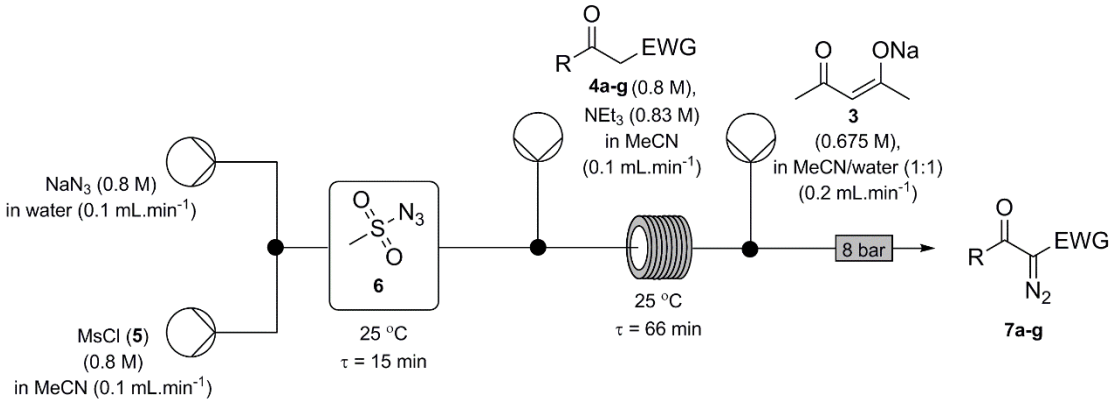
[a] Conversion determined by ^{1}H NMR analysis of the crude product obtained after removal of MeCN under reduced pressure, extraction into Et_2O followed by aqueous wash and removal of solvent in vacuo.

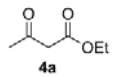
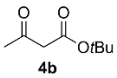
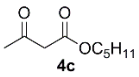
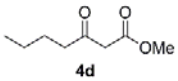
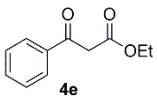
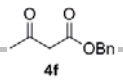
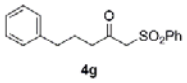
Somewhat surprisingly, the rate of diazo transfer was also found to be longer for the mesyl azide process compared to use of tosyl azide. While a residence time of 22 min was found to be sufficient for complete diazo transfer across a range of acceptor substrates using in situ generated tosyl azide, in general using mesyl azide the transformation was found to be complete within 66 min, with a 33 min residence time giving ~70 % conversion. This result supports a positive hydrophobic effect[18] on the rate of diazo

transfer from tosyl azide in an aqueous medium. Indeed, the residence time required for diazo transfer from mesyl azide is more consistent with that observed for continuous diazo transfer from pre-formed tosyl azide entirely in acetonitrile, where reaction times of 1–2 h were needed to achieve reaction completion. The reaction profile of the quenching process for unreacted mesyl azide, treatment with the strong diazo acceptor, sodium acetoacetonate was found to closely mirror that observed for tosyl azide. Again, the diazo transfer reagent was found to be fully consumed after less than 2 min exposure to the quench solution, as indicated by IR analysis – specifically, disappearance of the mesyl azide stretch at 2143 cm^{-1}.

Futhermore, concentration was found to be an important factor for the residence time required for successful diazo transfer, with an increased rate of diazo transfer observed as concentration was increased. A concentration of 0.8 M was ultimately chosen to enable complete diazo transfer while minimizing the potential for precipitation of inorganic salts from the aqueous acetonitrile system. Using the optimised conditions for diazo transfer to ethyl acetoacetate (**4a**), a substrate scope investigation with in situ generated mesyl azide was undertaken (Table 2). A range of α-diazo-β-ketoesters **7a-f** were prepared in moderate to good yields, along with α-diazo-β-ketosulfone **7g**. The higher yield observed for **7g** (Table 2, entry 7) suggested that higher

Table 2. Substrate scope of optimized diazo transfer using in situ generated mesyl azide (**6**).



Entry	Substrate	Yield in flow (%)[a]			Yield in batch (%)[a]		
		Conversion (%)[b]	with aq. KOH workup	with SALLE separation	Conversion (%)[b]	with aq. KOH workup	with SALLE separation
1	 **4a**	100	50	51	100	55	52
2	 **4b**	100	59	49	100	51	54
3	 **4c**	100	64	58	100	61	66
4	 **4d**	100	44	56	100	50	62
5	 **4e**	100	68	57	100	68	72
6	 **4f**	100	63	62	100	55	57
7	 **4g**	100	71	70	100	81	84

[a] Yield of diazo product, >95% pure by ^{1}H NMR analysis after workup and without chromatography. [b] Conversion determined by ^{1}H NMR analysis of the crude product obtained after removal of MeCN under reduced pressure, extraction into Et_2O followed by aqueous wash and removal of solvent in vacuo.

molecular weight acceptor substrates/product are likely to be easier to recover during partitioning from the aqueous layer.

As relatively easy separation of the mesyl amide byproduct is the key benefit of diazo transfer from mesyl azide, in order to exploit this advantage, a suitable strategy was required to enable the desired diazo product to be successfully separated from the aqueous byproducts present in the aqueous acetonitrile product stream. Ideally, this strategy would allow a fully integrated system, cleanly affording the α-diazo carbonyl compound in an organic phase that would provide a substrate solution for an immediate telescoped transformation involving further reaction of the diazo species. Salting out liquid–liquid extraction (SALLE) is a technique used to separate water from miscible liquids such as acetone, methanol or acetonitrile.[19] Although reported since the late 1980s, the technique has not been widely investigated or used. SALLE involves the addition of concentrated aqueous sodium chloride solution to induce a phase separation. Altering the concentration and volume of sodium chloride solution used allows the degree of separation to be controlled. Addition of 20–30 % w/v aqueous sodium chloride was found to afford separation of acetonitrile from the aqueous phase with product recovery comparable to that obtained using the standard 9 % aqueous KOH wash, in terms of both yield and purity.

As summarized in Table 2, diazo transfer to the range of substrates **4a-g** was investigated both in batch and in flow using both the traditional partitioning between aqueous KOH and diethyl ether and SALLE separation. The results from the batch experiments show that the SALLE approach is comparable in terms of efficiency and overall yield to the base extraction, but with the clear safety and operational advantage of obviating concentration of acetonitrile solution of the diazo products. Interestingly, while the yields recovered in flow were slightly reduced relative to batch, the clear safety benefit, ease of scale up and potential to telescope with subsequent reactions render this flow approach advantageous overall. Notably, the NMR spectra of the α-diazo-β-ketoesters **7a-f** and α-diazo-β-ketosulfone **7g** recovered from each of the reactions in Table 2 showed material sufficiently pure to use in further reactions without chromatographic purification (see SI).

For comparison purposes, the SALLE approach was applied to a diazo transfer to **4b** using tosyl azide, and tosyl amide was clearly evident in the crude reaction product. Therefore, as removal of mesyl amide in the phase separation is much more efficient than that of tosyl amide, use of in situ generated mesyl azide for diazo transfer offers a distinct advantage over the comparable tosyl azide transfer process. This is particularly significant with regard to the potential to telescope diazo transfer with subsequent reactions that could not be conducted in the presence of an equimolar quantity of sulfonamide. Furthermore, the sodium acetylacetonate quench and byproducts partition completely into the aqueous layer, once more enabling telescoping.

Following the addition of the salt solution, the two immiscible phases must be efficiently separated from each other for this to be practical. Typical separation methodologies at the end of a flow process would require both phases to be collected prior to using a separating funnel to remove the waste aqueous phase. However, this methodology not only disrupts the continuous nature of the reaction process, but also introduces a step requiring accumulation and direct handling of a hazardous (potentially explosive) product. Accordingly, a continuous liquid–liquid separator (Figure 1) was designed, manufactured and its use investigated to overcome these challenges.

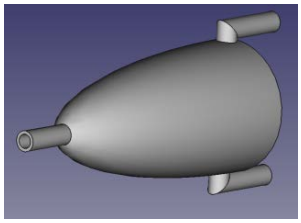


Figure 1. Computer Aided Design (CAD) rendering of the designed liquid–liquid separator utilised in this work. The mixed organic and aqueous streams enter the unit from the inlet on the left hand side while the separated organic stream continuously leaves from the exit port on the top and the waste aqueous stream exits from the bottom port.

The mixed aqueous and organic phases enter the separator from the left (Figures 1 & 2) through the single ¼" inlet (reduced to 1 mm internal diameter via needle inlet valve). The unit is designed to minimize the vertical velocity component of the fluid flow which facilitates the continuous separation of the immiscible fluids by gravitational means with the result that the lighter organic stream exits the separator.

Computational fluid dynamics (CFD) were utilized to model the fluid velocity profile in the unit and the degree of separation of the phases (Figure 2). Subsequently, the optimized separator design was 3D printed (from 316L stainless steel) which has a length of 50 mm, an inner diameter (at the wide end) of 30 mm, a radius of curvature of 15 mm and a wall thickness of 1 mm.

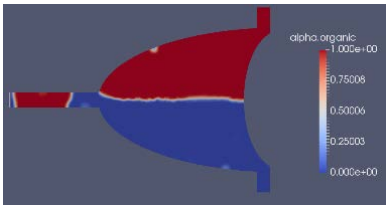
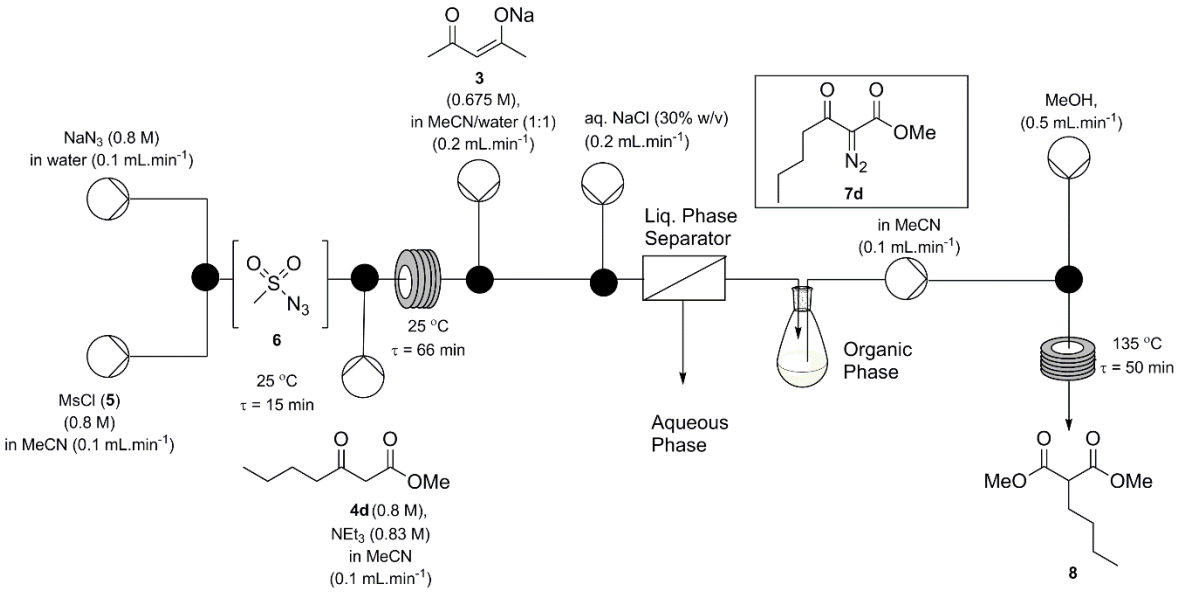


Figure 2. Computational Fluid Dynamics (CFD) illustration of the separation which is continuously occurring in the liquid–liquid separator during operation. The red region represents the organic phase and the blue region represents the aqueous phase.

As summarized in Scheme 2, in situ generated mesyl azide **6** was employed to effect diazo transfer to methyl 3-oxoheptanoate (**4d**). Addition of brine solution (30% w/v NaCl) followed by passage through the in-line liquid–liquid separator provided the α-diazo-β-ketoester **7d** in acetonitrile. To demonstrate the ease of telescoping this diazo transfer with subsequent reactions, **7d** was subjected to thermal Wolff rearrangement[20] via superheating the solution, with methanol as a ketene trap to form the malonate derivative **8,** without ever isolating or handling either mesyl azide or the diazo ester **7d**, or indeed having significant amounts of either compound generated at any given time in the process. This telescoped process, transforming **4d** to the Wolff rearrangement product **8** exemplifies the synthetic potential of diazo transfer employing in situ generated mesyl azide. The principal component evident in the crude product stream of the telescoped process was the Wolff rearrangement product **8**. The overall yield from the telescoped process is 31% following chromatography.

Direct comparison of the process efficiency with a conventional batch process is not possible under thermal, metal-free conditions as **8** does not form under reflux in this solvent system. While Wolff rearrangements can be effected through microwave heating,[20c,d] this process is not comparable as it would not be amenable to scale-up or to telescoping with the diazo transfer step. The efficiency of the in-line liquid–liquid separator is evidenced by effective removal of water, with no competing reaction with water observed in the ketene trapping. As O–H insertion into water is a known side reaction in transformations of diazo carbonyl compounds, efficient removal of water using this approach (the SALLE technique with in-line liquid–liquid separator) is a very significant factor in the broader synthetic potential of this telescoping of synthesis and reactions of α-diazo carbonyl compounds.



Scheme 2. Telescoped diazo transfer and thermal Wolff rearrangement.

Conclusions

A practical continuous method for in situ generation of mesyl azide was developed and employed for preparation of a series of α-diazo-β-ketoesters and an α-diazo-β-ketosulfone, with an embedded safety quench. Using the SALLE separation technique in conjunction with a designed in-line liquid–liquid separator, an organic product stream (containing the desired diazo compound in acetonitrile) could be partitioned from the aqueous soluble byproducts, including mesyl amide, and readily and safely telescoped with subsequent reaction of the diazo product.

Experimental Section

General Methods: 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-Phenylsulfonyl-5-phenylpentan-2-one (**4g**) was prepared according to literature methods.[21] ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Splitting patterns in ^{1}H spectra are designated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Infrared spectra were measured using a Perkin Elmer FTIR UATR2 spectrometer. Wet flash 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. Reactions in continuous flow were carried out in 1 mm internal diameter PFA tubing using either HPLC (working flow rate: 0.05–9.99 mL min^{-1}) or peristaltic pumps (working flow rate: 0.02–10.00 mL min^{-1}). In-line liquid–liquid separations were achieved using a 3D printed separator (316L stainless steel) with a length of 50 mm, an inner diameter (at the wide end) of 30 mm, a radius of curvature of 15 mm and a wall thickness of 1 mm. All aqueous waste streams were treated with sodium nitrite and dilute sulfuric acid prior to disposal, taking all relevant safety precautions.[22]

General flow procedure for preparation of diazo compounds 7a–g (Table 2): A solution of substrate (10 mL, 0.8 M, 8.0 mmol, 1.0 eq.) and triethylamine (1.15 mL, 8.2 mmol, 1.05 eq.) in acetonitrile was prepared along with a solution of methanesulfonyl chloride (10 mL, 0.92 g, 8.0 mmol, 1.0 eq.) in acetonitrile and an aqueous solution of sodium azide (10 mL, 0.52 g, 8.0 mmol, 1.0 eq.). A 10 mL quench solution of sodium acetoacetonate (0.675 M in 1:1 acetonitrile/water) was prepared with sodium hydroxide (0.270 g, 6.75 mmol, 1.5 eq.) and acetylacetone (0.676 g, 6.75 mmol, 1.5 eq.). The flow reactor, including all HPLC pumps, was purged with the appropriate solvents (4 mL min^{-1} for 4 min). The methanesulfonyl chloride solution was pumped (0.10 mL min^{-1}) into a T-piece where it met the aq. sodium azide solution (0.10 mL min^{-1}). The combined stream passed through a tube (412 cm, 16 min residence time) where it met the substrate solution at a T-piece (0.10 mL min^{-1}). This combined stream passed into a reactor coil (2 x 10 mL, 25 °C, 66 min residence time) before meeting the quench solution and then passed through a tube (50 cm) followed by a back pressure regulator (8 bar). All reactor effluents were collected in a round bottom flask and the desired diazo product was isolated using either Method A (aqueous KOH wash) or Method B (SALLE separation). Method A consisted of concentrating the reactor effluents under reduced pressure to remove acetonitrile, before the crude product was extracted with diethyl ether (50 mL) and the organic layer was washed with 9 % KOH (2 × 20 mL) and water (10 mL). The organic layer was dried and concentrated under reduced pressure to give the diazo product (see Table 2 for yield). Method B consisted of addition of aq. NaCl solution (30 mL, 30 % w/v) to the reactor effluents to enable separation of an organic (acetonitrile) layer that was dried and concentrated under reduced pressure to give the diazo product (see Table 2 for yield). Compounds synthesised using Method A or B demonstrated comparable spectroscopic properties.

Ethyl 2-Diazo-3-oxobutanoate (7a):[23] Prepared from **4a** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2140, 1720, 1661; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 1.33 (3H, t, *J*=7.2, OCH_2CH_3), 2.51 (3H, s, $C(O)CH_3$), 4.32 (2H, q, *J*=7.2, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 14.3 (CH_3), 28.2 (CH_3), 62.4 (CH_2), 161.4 (C=O, ester), 190.3 (C=O, ketone), no signal observed for ($C=N_2$).

***tert*-Butyl 2-Diazo-3-oxobutanoate** (**7b):**[24] Prepared from **4b** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2134, 1715, 1660; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 1.55 (9H, s, 3 x CH_3 of *t*-butyl), 2.49 (3H, s, $C(O)CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 27.9 (CH_3), 28.2 (CH_3 x 3 of *t*-butyl), 83.1 (C), 160.2 (C=O, ester), 190.6 (C=O) ketone, no signal observed for ($C=N_2$).

Isopentyl 2-Diazo-3-oxobutanoate (7c):[25] Prepared from **4c** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2141, 1721, 1662; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 0.94 (6H, d, *J*=6.6, 2 x CH_3), 1.55–1.62 (2H, m, OCH_2CH_2), 1.64–1.75 (1H, m, $CH(CH_3)_2$), 2.48 (3H, s, $C(O)CH_3$), 4.27 (2H, t, *J*=6.6, OCH_2CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 22.4 (CH_3 x 2), 25.1 (CH), 28.3 (CH_3), 37.3 (OCH_2CH_2), 64.1 (OCH_2), 161.5 (C=O, ester), 190.3 (C=O, ketone), no signal observed for ($C=N_2$).

Methyl 2-diazo-3-oxoheptanoate (7d):[20c] Prepared from **4d** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2141, 1721, 1642; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 0.93 (t, *J*=7.4, 3H, CH_2CH_3), 1.33–1.43 (2H, m, CH_2), 1.58–1.65 (2H, m, CH_2) 2.85 (t, *J*=7.5, 2H, $C(O)CH_2CH_2$), 3.84 (3H, s, $C(O)CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 13.7(CH_3), 22.2(CH_2), 26.3 (CH_2), 39.8 ($C(O)CH_2$), 52.1 (OCH_3), 161.7 (C=O, ester), 192.7 (C=O, ketone), no signal observed for ($C=N_2$).

Ethyl 2-Diazo-3-oxo-3-phenylpropanoate (7e):[26] Prepared from **4e** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2140, 1719, 1293, 1262; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 1.29 (t, 3H, *J*=7.0, CH_3), 4.23 (q, *J*=7.0, 2H, CH_2), 7.42-7.62 (5H, m, 5 x ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 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 ($C=N_2$).

Benzyl 2-Diazo-3-oxobutanoate (7f):[27] Prepared from **4f** according to the general method and was obtained as a yellow oil that could be used without any need for further purification. (UATR)/cm^{-1}: 2144, 1719, 1656; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 2.48 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 7.26-7.41 (m, 5H, 5 x ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 28.3 (CH_3), 66.9 (OCH_2), 75.5 ($C=N_2$), 128.4, 128.7, 128.8 (aromatic CH), 135.2 (aromatic C) 161.7 (C=O, ester), 189.9 (C=O, ketone).

1-Diazo-1-phenylsulfonyl-5-phenylpentan-2-one (7g):[28] Prepared from **4g** according to the general method and was obtained as a yellow solid without any need for further purification. mp 80–82 °C; (lit., 78–81 °C); UATR)/cm^{-1} 2122, 1677, 1154. ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 1.90 (q, J 7.4, 2H, $C(4)H_2$), 2.53, 2.55 (4H, 2 × overlapping t, J 7.5 × 2, $C(5)H_2$ and $C(3)H_2$), 7.09–7.11 (2H, m, aromatic H of phenyl group), 7.18–7.29 (3H, m, aromatic H of phenyl group), 7.49–7.53 (2H, m, aromatic H of phenylsulfonyl group), 7.64-7.68 (1H, m, aromatic H of phenylsulfonyl group), 7.89–7.91 (2H, m, aromatic H of phenylsulfonyl group). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 25.0 ($C(4)H_2$), 34.7 ($C(5)H_2$), 38.3 ($C(3)H_2$), 126.1 (CH, aromatic *C*H), 127.3 (CH, aromatic *C*H), 128.5 (CH, aromatic *C*H), 129.5 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 141.1 (C, aromatic *C*), 142.0 (C, aromatic), 188.2 (*C*=O, ketone), no signal observed for ($C=N_2$).

Procedure for Telescoped Thermal Wolff Rearrangement: The flow reactor, including all HPLC pumps, was purged with the appropriate solvents (4 mL min^{-1} for 4 min). Methanesulfonyl chloride solution was pumped (8.0 mL, 0.8 M, 0.10 ml min^{-1}) into a T-piece where it met aq. sodium azide solution (8.0 mL, 0.8 M, 0.10 ml min^{-1}). The combined stream passed through a tube (412 cm, 16 min residence time) where it met substrate solution (7.8 mL, [**4d**] 0.80 M, [triethylamine] 0.83 M, 0.10 mL min^{-1}) at a T-piece. This combined stream passed into a reactor coil (2 x 10 mL, 25 °C, 66 min residence time) before meeting the quench solution (13.31 mL, 0.675 M, 0.2 ml min^{-1}) which then passed through a tube (50 cm). The reaction stream then met aq. NaCl solution (30% w/v) at a T-piece which passed through a 75 cm tube and then passed through a back pressure regulator (8 bar). The biphasic reactor effluents were then separated by an in-line liquid–liquid separator. The collected acetonitrile layer (9 mL), containing diazo product **7d**, was directly fed to another pump. The pump delivered the separated diazo product solution (8 mL, 0.10 mL min^{-1}) to a T-piece where it met MeOH (0.50 mL min^{-1}) which then passed through a reactor coil (3 x 10 mL, 135 °C, 50 min residence time), and then passed through a back pressure regulator (8 bar). The reactor effluents were all collected in a round bottom flask and were then concentrated under reduced pressure. The crude product was purified by wet flash chromatography using 9:1 hexane/EtOAc as eluent to afford dimethyl 2-butylmalonate (**8**)[29] (0.327 g, 31 % yield) as a clear oil. (UATR)/cm^{-1}: 2957, 1733, 1152. ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ = 0.90 (t, *J*=7.0 Hz, 3H, CH_2CH_3), 1.23–1.41 (m, 4H, 2 × CH_2), 1.90 (br q, *J*=7.6 Hz, 2H, $CHCH_2$), 3.36 (t, *J*=7.6 Hz, 1H, CH), 3.74 (s, 6H, 2 × OCH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 300 K) δ = 13.8 (CH_2CH_3), 22.3, 28.5, 29.5 (all CH_2), 51.7 (CH), 52.4 (OCH_3), 170.0 (C=O).

Note: Yield is based on recovery of pure **8** (following chromatography) from initial substrate **4d**, *incorporating the diazo transfer, in-line separation, Wolff rearrangement and methanol trapping*, assuming all of the product is partitioned into the acetonitrile layer during separation.

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Keywords: Diazo transfer • Flow Chemistry • Telescoped Process

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