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

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Heat and shock sensitive tosyl azide was generated and used on demand in a telescoped diazo transfer process. Small quantities of tosyl azide were accessed in a 'one pot' batch procedure using shelf stable, readily available reagents. For large scale diazo transfer reactions tosyl azide was generated and used in a telescoped flow process, to mitigate the risks associated with handling potentially explosive reagents on scale. The *in situ* formed tosyl azide was used to rapidly perform diazo tranfer to a range of acceptors, including β-ketoesters, β-ketoamides, malonate esters and β-ketosulfones. An effective in-line quench of sulfonyl azides was also developed, whereby a sacrificial acceptor molecule ensured complete consumption of any residual hazardous diazo transfer reagent. The telescoped diazo transfer process with in-line quenching was used to safely prepare over 21 g of an α-diazocarbonyl in >98% purity without any column chromatography.

Introduction

Tosyl azide is a heat and shock sensitive reagent which is used in the Regitz diazo transfer to introduce diazo groups into organic compounds.[1–4] The α-diazocarbonyl compounds produced by diazo transfer are an important class of versatile synthetic intermediates due to their ability to generate reactive carbenes,[5–7] carbenoids,[7–20] ketenes and other heteroanalogous intermediates.[21–26]

Despite being routinely used in small scale α-diazocarbonyl synthesis, tosyl azide is not suitable for use at larger scales. Tosyl azide has an impact sensitivity of 50 kg·cm, and explosive thermal decomposition can initiate at 120 °C.[27] A range of sulfonyl azides has been developed as safer alternative diazo transfer reagents.[8,27,28] *p*-Acetamidobenzenesulfonyl azide (ABSA) and dodecylbenzenesulfonyl azide (DBSA) are less shock sensitive than tosyl azide but are still sensitive to heat. Imidazole-1-sulfonyl azide hydrochloride was also developed as a shelf stable diazo transfer reagent, but a number of safety issues were later reported.[29,30] Polystyrene supported benzenesulfonyl azide is another stable alternative to tosyl azide but the cost of this reagent is prohibitive.[31] There is no ideal alternative to tosyl azide and this reagent continues to be used by many, despite its dangers.[28,32–37] Consequently, progress in how tosyl azide is prepared and used is required.

Improving the safety profile of chemical processes is a major driving force behind the adoption of continuous processing within academia, and also the fine chemical and pharmaceutical industries. Enhanced heat and mass transfer, access to extreme reaction conditions, reproducibility and scale up, in-line workups and automated operation have all been reported as benefits of continuous processing.[38–45] The favourable safety profile of flow processing is perhaps the most compelling reason for its popularity. Sensitive reagents can be readily generated and used on demand inside a flow process, negating the need to stockpile hazardous intermediates or risk of operator exposure. The high surface-area-to-volume ratios of tubular reactors also ensures efficient removal of heat, thereby reducing the risk of reaction runaway.[45–47]

A number of hazardous intermediates including azides,[48–53] diazonium salts,[54–59] and diazo compounds,[60–72] to name but a few, have all been accessed using continuous processing techniques.[45–47] There have been few reports of the diazo transfer process in flow, and to date these have all employed sulfonyl azides directly as reagents.[68,69,73,74] Researchers at GlaxoSmithKline reported using 2,4,6-triisopropylbenzenesulfonyl azide to perform a diazo transfer to ethyl acetoacetate in a segmented flow system.[73] Rutjes and co-workers used imidazole-1-sulfonyl azide hydrochloride to prepare benzyl azide in a continuous diazo transfer to benzyl amine.[74] More recently Wirth and co-workers reported the use of ABSA in a telescoped flow process whereby diazophenyl acetate esters were prepared and used in metal catalysed X-H insertion and cyclopropanation reactions.[68,69] A disadvantage of all these continuous procedures is that they employ potentially hazardous sulfonyl azides directly as reagents. Such an approach limits the scale of the continuous diazo transfer as these reagents are hazardous to prepare at large scales.

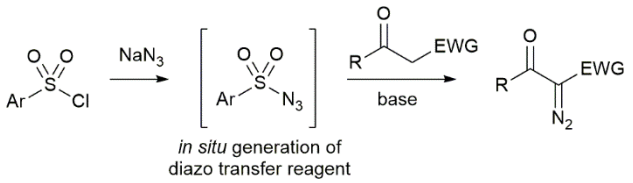
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Scheme 1. *In situ* generation and use of diazo transfer reagents.

We were therefore interested in developing a continuous diazo transfer procedure which used relatively stable and readily available reagents to generate the diazo transfer reagent on demand (Scheme 1). Herein, we describe our work towards the *in situ* generation of tosyl azide, and its application in a rapid continuous diazo transfer process. A number of safety features were also developed to facilitate safe scale up of the process, including spectroscopic monitoring of tosyl azide and an in-line quench system to consume any residual tosyl azide. The safe generation and use of these reagents has the potential to make this chemistry accessible within the pharmaceutical and fine chemical industries.

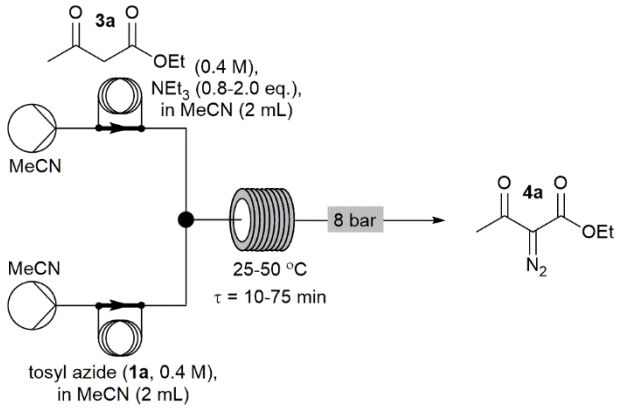
Results and Discussion

Continuous diazo transfer using batch prepared tosyl azide

The continuous diazo transfer process was initially investigated by employing tosyl azide which had been previously prepared in batch.[1,2] Under typical batch conditions, the diazo acceptor molecule is reacted with tosyl azide in the presence of a base, such as NEt_3, DBU or K_2CO_3, at ambient temperature over a period of up to 24 hours.[3,4,28,75–77] Reaction times longer than several hours can be difficult to achieve in tubular reactors, so we sought to optimize the continuous diazo transfer reaction over a short reaction time of 10 min (Table 1). It has previously been reported that the diazo transfer requires only catalytic quantities of base to proceed.[78,79] Under the short reaction time utilized in this study, the conversion of ethyl acetoacetate (**3a**) to the α-diazo-β-keto ester **4a** was less than 60% when one or less equivalents of base was employed (Table 1, entries 1 & 2). The conversion increased to 75–80% when a slight excess of base was employed (Table 1, entries 3 & 4), but larger excesses of base (1.5 and 2.0 equivalents) had no beneficial effect on the reaction progress over 10 min (Table 1, entries 5 & 6).

The influence of temperature on the continuous diazo transfer was also investigated. In contrast to the results reported by Wirth *et al.* where continuous diazo transfers using ABSA required elevated reaction temperatures of 60 °C for completion, we observed that the flow reaction with tosyl azide progressed well at only 25 °C (Table 1, entry 3).[68] Raising the reactor temperature to 40 °C had a negligible effect on the reaction progress (Table 1, entry 7), and as a further increase had no positive impact (Table 1, entry 8), higher temperatures were not further investigated. Given the heat sensitive nature of diazo transfer reagents it is a distinct advantage to have a process which only requires ambient conditions to achieve good reaction rates.

Table 1. Optimization of reaction conditions for continuous diazo transfer to ethyl acetoacetate (**3a**) using tosyl azide.



Entry	Equiv. of Base	Temperature (°C)	Time (min)	Conversion (%)[a]
1	0.8	25	10	53
2	1.0	25	10	60
3	1.05	25	10	75
4	1.10	25	10	80
5	1.5	25	10	77
6	2.0	25	10	74
7	1.05	40	10	78
8	1.05	50	10	58
9	1.05	25	25	82
10	1.05	25	50	93
11	1.05	25	75	100

a) Conversion determined by ^{1}H NMR spectroscopy.

The reaction time required to achieve complete consumption of the diazo transfer reagent was investigated (Table 1, entries 9–11). While the diazo transfer progressed quickly over the first 10 min, it was observed to subsequently slow down, with 82% and 93% conversions obtained at 25 and 50 min respectively. After a reaction time of 75 min the diazo transfer had run to completion (Table 1, entry 11).

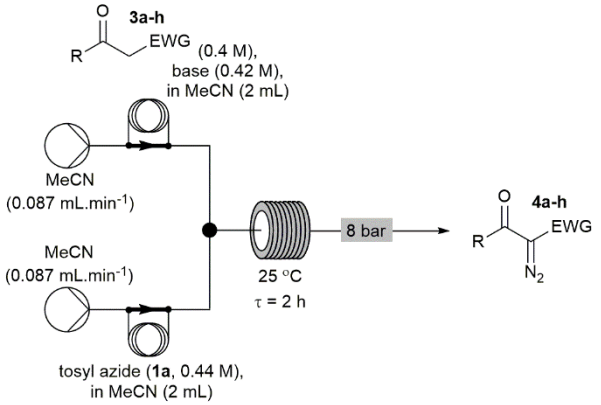
With optimized reaction conditions in hand we turned our attention to an investigation of the substrate scope. An initial substrate screen identified that several substrates required reaction times in excess of 75 min. Consequently, a diazo transfer residence time of 2 h was selected for the 1st generation continuous diazo transfer process (Table 2). Diazo transfer to ethyl acetoacetate (**3a**, Table 2, entry 1) and benzyl acetoacetate (**3d**, Table 2, entry 4) went to completion, as determined by ^{1}H NMR spectroscopy. The *tert*-butyl (**3b**, Table 2, entry 2) and isoamyl (**3c**, Table 2, entry 3) acetoacetate esters underwent diazo transfer more slowly and conversions of only

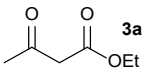
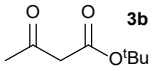
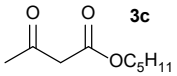
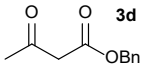
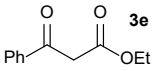
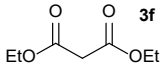
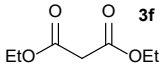
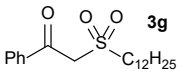
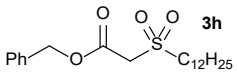
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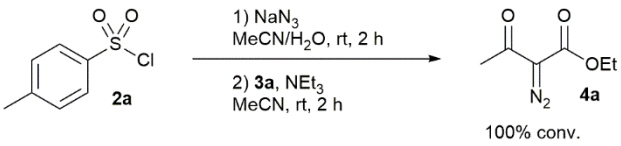
Table 2. Substrate scope of the 1st generation continuous diazo transfer process.



Entry	Substrate	Base	Conversion (%)[a]	Yield (%)[b]
1	 3a	NEt_3	100	54
2	 3b	NEt_3	80	46
3	 3c	NEt_3	95	84
4	 3d	NEt_3	100	61
5	 3e	NEt_3	100	61
6	 3f	NEt_3	20	–
7	 3f	DBU	100	53
8[c]	 3g	DBU	100	50
9[c]	 3h	DBU	100	65

a) Conversion determined by ^{1}H NMR spectroscopy after an aqueous wash workup. *b*) Yield of diazo product, >90% pure by ^{1}H NMR analysis after KOH wash workup. *c*) Reaction run at higher dilution due to substrate solubility: substrate (0.1 M), base (0.105 M) and tosyl azide (0.11 M).

80% and 95% respectively were obtained. Ethyl benzoyl acetate (**3e**) underwent complete diazo transfer in the time allowed (Table 2, entry 5). In contrast, diethyl malonate (**3f**) underwent



Scheme 2. Batch test of 'one pot' tosyl azide generation and diazo transfer.

a slow diazo transfer with only a 20% conversion being obtained after 2 h (Table 2, entry 6). It was hypothesized that this reduced conversion could be due to the lower acidity of the methylene protons in diethyl malonate (**3f**) (pK_a ~13) compared to the ketoester substrates (pK_a ~11).[80] To facilitate diazo transfer to less activated substrates we employed 1,8-diazabicycloundec-7-ene (DBU) as the base (Table 2, entry 7). With the stronger base DBU, diethyl malonate (**3f**) underwent complete diazo transfer in the 2 h residence time. Two β-ketosulfones (**3g, 3h**) were also successfully subjected to the continuous diazo transfer process (Table 2, entries 8 & 9), with DBU also chosen as the optimum base for the transfer.

The reduction in yields (Table 2) relative to the conversions, measured by ^{1}H NMR spectroscopy, is attributed to incomplete recovery of the product during the KOH wash employed in the workup. Whilst the conversions were assessed following an aqueous wash, isolation of the diazo products required a KOH wash to remove the toluenesulfonamide by-product of the diazo transfer.

***In situ* generation and use of tosyl azide**

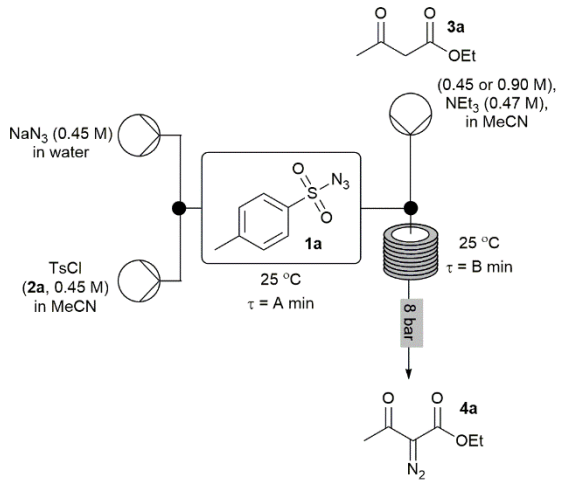
A significant disadvantage of the 1st generation continuous diazo transfer process was the requirement for tosyl azide to be prepared in batch mode. The preparation of sulfonyl azide diazo transfer reagents are hazardous procedures which require extreme care.[3,4,8,27,28,75] In a typical preparation of tosyl azide a solution of tosyl chloride in MeCN is added slowly to an aqueous solution of sodium azide. As the substitution reaction is exothermic, the reaction must be kept at 0 °C to prevent explosive decomposition of the heat sensitive tosyl azide. In the subsequent workup, care must also be taken to avoid applying shock to the touch sensitive product. The touch sensitive nature of tosyl azide also makes its use in diazo transfer reactions a particular challenge as it exists as a solid when stored in a freezer. In our lab it is gently melted before transferring as an oil with extreme care taken to ensure there are no scratches on the glassware. To facilitate continuous diazo transfer chemistry it would be advantageous to have a procedure whereby the diazo transfer reagent was generated *in situ* and used without requiring handling by the operator. To this end, we investigated options for the *in situ* formation and use of tosyl azide.

Our first attempt to form tosyl azide *in situ* involved the use of tetra-*N*-butylammonium azide as an azide salt, which is soluble in the MeCN solvent system used for the diazo transfer reaction. This azide salt has previously been employed in flow reactions as a substitute for sodium azide.[52] Unfortunately, in this case we found no evidence of diazo transfer after the acceptor molecule was added to a pre-stirred mixture of tetra-*N*-butylammonium azide and tosyl chloride in MeCN. Due to the potentially unstable nature of the reaction species, we did not examine this reaction any further and instead returned our

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Table 3. Optimisation of reaction times for the telescoped tosyl azide generation and diazo transfer in flow.



Entry	Generation Time A (min)	Diazo Transfer Time B (min)	Eq. of Acceptor (**3a**)	Conversion (%)[a]
1	50	66	1.0	100
2	2	66	1.0	100
3	2	66	2.0	50[b]
4	1	16	2.0	50[b]
5	0.5	8	2.0	50[b]
6	0.5	8	1.0	95

a) Conversion determined by ^{1}H NMR spectroscopy. *b*) When 2 equivalents of acceptor were employed a conversion of 50% indicates that tosyl azide formation was complete.

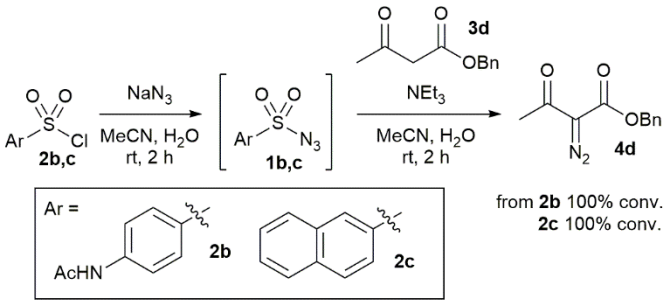
attention to the use of sodium azide for the *in situ* reagent generation.

It has been reported that the diazo transfer can be performed under aqueous conditions.[78] With this in mind, we explored the *in situ* formation of tosyl azide and subsequent diazo transfer reactions in batch mode using a MeCN/water solvent system (Scheme 2). ^{1}H NMR spectroscopy of an ethyl acetate extract of the reaction mixture revealed that ethyl acetoacetate (**3a**) had been completely converted to the diazo product **4a** after just 2 h.

Generation and use of tosyl azide in flow

The batch procedure for *in situ* generation of tosyl azide was transformed into a continuous process whereby an aqueous solution of sodium azide was combined with a MeCN solution of tosyl chloride, and reacted inside a tubular reactor at 25 °C. A third stream, containing ethyl acetoacetate (**3a**) and triethylamine, was then introduced so that the diazo transfer could proceed within a second tubular reactor which was also held at 25 °C. A series of experiments were conducted to determine the residence times required for both the tosyl azide formation and diazo transfer steps (Table 3). With initial residence times of 50 min for tosyl azide formation, and 66 min for diazo transfer, the reaction was observed to go to completion (Table 3, entry 1). Drastically reducing the time for the tosyl azide formation to only 2 min had no detrimental effect on the reaction progress (Table 3, entry 2). Due to the unstable, hazardous nature of tosyl azide we wished to avoid optimising the tosyl azide formation in isolation. To gain some insight into the progress of the tosyl azide generation, we employed an excess (2 equivalents) of the diazo acceptor molecule **3a**. Under these conditions the diazo transfer will not progress beyond 50% consumption of the acceptor molecule, and will only reach this maximum if the tosyl azide formation went to completion. With this strategy, the residence time of the tosyl azide formation was reduced from 2 min down to 0.5 min (Table 3, entries 3–5). It should be noted that the residence time of the diazo transfer reaction was concurrently reduced due to the increased flow rates being employed. The diazo transfer reaction still went to its theoretical maximum conversion (50%) with residence times as low as 0.5 min and 8 min for tosyl azide formation and diazo transfer respectively (Table 3, entry 5). Reducing the equivalents of acceptor molecule **3a** back to one resulted in a slight reduction of the conversion to 95% (Entry 6), which can be attributed to the reduced rate of the diazo transfer when only one equivalent of acceptor is used.

Scheme 3. Generation and use of alternative diazo transfer reagents.



The batch procedure for *in situ* generation of the sulfonyl azide reagent was also applied to acetamidobenzenesulfonyl chloride (**2b**) and 2-napthalenesulfonyl chloride (**2c**) (Scheme 3). In both cases, the diazo transfer reagent **1b, 1c** was formed within 2 h at ambient temperature. Subsequent reaction of the *in situ* generated sulfonyl azides with benzyl acetoacetate (**3d**) was observed to go to completion within 2 h. Unfortunately, the sulfonyl azides (**1b, 1c**) were found to be insoluble in the 1:1 water/MeCN reaction medium and precipitation was observed prior to the addition of the diazo acceptor **3d**, as a solution in MeCN. While there are strategies for handling precipitation in flow reactions,[81–83] there is an ever present danger that hazardous solid material will accumulate inside the reactor. Whereas use of tosyl azide avoids the problems asscociated with solid azide precipitation, the potentially explosive nature of the solid sulfonyl azides **1b**, **1c** generated in these reactions meant they could not be safely used in the flow process we report here.

Reaction monitoring by in-line infrared spectroscopy

In-line infrared (IR) spectroscopy has been reported as a valuable tool for the monitoring of hazardous components in flow reactions.[48,58,68,84–86] Tosyl azide exhibits a strong N=N=N stretching mode which can be used to assess the purity of the

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Table 4. Evaluation of methods for the quenching of tosyl azide.

Entry	Quench Method	Time (min)	Result[a]
1	None	120	no tosyl azide quenched
2	$NaNO_2$	120	no tosyl azide quenched
3	H_2SO_4 / $NaNO_2$	120	no tosyl azide quenched
4	Acetylacetone / NaOH	120	100% tosyl azide quenched
5	Acetylacetone / NaOH	2	100% tosyl azide quenched

a) Tosyl azide quenching followed by IR spectroscopy at 2135 cm^{-1} and ^1H NMR spectroscopy at 7.41 ppm and 7.85 ppm.

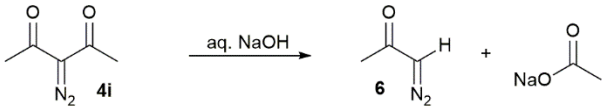
batch prepared reagent.[3] To verify the complete formation of tosyl azide from sodium azide and tosyl chloride, the reagents were mixed and then flowed through an in-line IR spectrometer after residence times of between 10 to 120 s. The formation of tosyl azide was followed by the strong azide band at 2135 cm^{-1} while the consumption of sodium azide was concurrently observed by monitoring 2048 cm^{-1}. After only 10 s we observed approximately 60% conversion of sodium azide to tosyl azide. After 1 min of residence time there was less than 10% of the sodium azide remaining and after 2 min the formation of tosyl azide was observed to be complete.

The diazo group exhibits a characteristic band in the IR spectrum between 1950 and 2300 cm^{-1}. Wirth and co-workers have demonstrated that in-line IR spectroscopy can be used to follow the formation of diazomethyl phenylacetate and the consumption of the diazo acceptor molecule.[68,69] When we attempted a continuous diazo transfer to diethyl acetoacetamide (**3j**) the reaction progress was followed by the appearance of a diazo IR absorption peak at 2113 cm^{-1}. A reduction in the tosyl azide absorption at 2135 cm^{-1} is also observed if diazo transfer occurs. By in-line IR it was observed that the diazo transfer to diethyl acetoacetamide (**3j**) went to approximately 33% conversion when the flow reactor was operated with a residence time of 8 min for the diazo transfer.

In-line quenching of tosyl azide

While continuous processing is ideal for handling reactive intermediates and reagents safely, it is essential that the chemist fully considers the consequences of a reactor malfunction. Even something as simple as a reaction not going to completion can result in an unexpected build-up of the hazardous reactive species within the collection reservoir at the reactor outlet. One of the most effective ways to minimise this risk is to introduce a quench stream before the reactor outlet. The ideal quench stream should react rapidly with the unstable intermediates to produce stable by-products. A further requirement is that the quench should not consume the product of the reaction.

Free inorganic azides can be quenched by treatment with sodium nitrite and sulfuric acid which, when combined produce the active nitrous acid quench agent.[87] To examine the effect of



Scheme 4. Hydrolysis of the diazo quench by-product.

sodium nitrite based quench systems on tosyl azide we conducted a series of tests using FT-IR and ^1H NMR spectroscopy to check for quenching of the azide (Table 4). A generous reaction time of 2 h was initially allowed for even though an effective quench would be required to act much more rapidly. Reacting tosyl azide with sodium nitrite did not result in any detectable reduction of the tosyl azide peaks by either FT-IR or ^1H NMR spectroscopy (Table 4, entry 2). Employing sodium nitrite and sulfuric acid was similarly ineffective in quenching tosyl azide (Table 4, entry 3). We concluded that the free inorganic azide quench method is not effective for quenching tosyl azide.

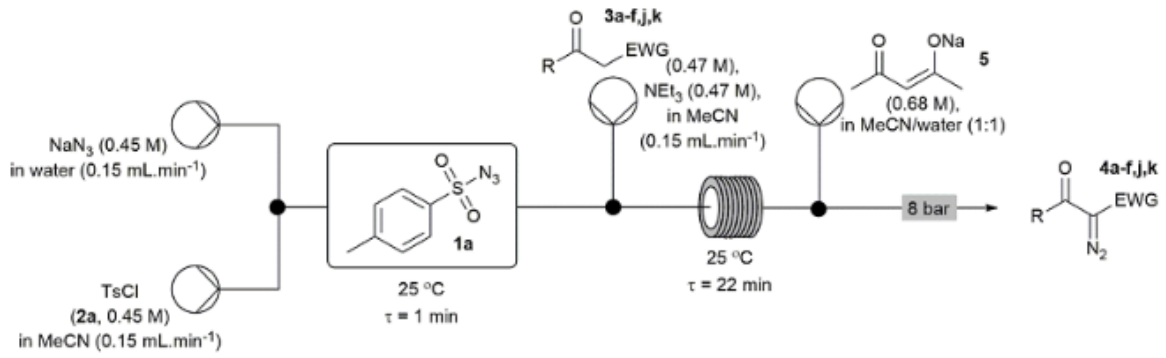
As there was a significant need for an effective quench method for sulfonyl azides, we considered the concept of using a sacrificial diazo acceptor molecule. Acetylacetone was dissolved in a sodium hydroxide solution to form sodium acetylacetonate (**5**), a reactive acceptor molecule for diazo transfer. As expected, reacting tosyl azide with an excess of the acetylacetonate resulted in complete consumption of the tosyl azide (Table 4, entry 4). Further analysis revealed that the acetylacetonate quench of tosyl azide was complete in under 2 min (Table 4, entry 5). Implementation of this quench system in our research did not require any changes to our existing diazo transfer workup procedures. The excess acetylacetonate (**5**) quench reagent is readily soluble in the aqueous partition during liquid-liquid extraction workup. A further advantage of this method is that the diazocarbonyl by-product of the quench reaction can be hydrolysed to 1-diazopropan-2-one (**6**) and acetate (Scheme 4).[88] During the reaction work-up both of these components are readily extracted by washing with aqueous 9% KOH solution. We have found that treatment of the aqueous washings with sodium nitrite and dilute sulfuric acid safely decomposes 1-diazopropan-2-one (**6**).[89]

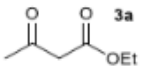
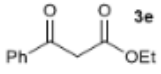
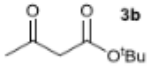
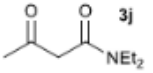
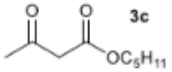
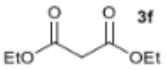
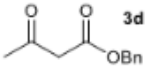
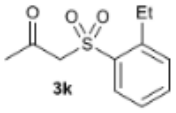
The quench method for tosyl azide allowed us to safely proceed with an investigation of the substrate scope of the 2nd generation continuous diazo transfer process (Table 5). To further improve the safety of the process, a slight excess (1.05 equivalents) of the diazo acceptor molecules (**3a–f, 3i and 3j**) were employed. In this mode of operation tosyl azide was the limiting reagent and would thus be completely consumed if the reaction went to completion. In situations where the reaction did not go to completion the acetoacetonate quench (**5**) would act to remove the remaining tosyl azide.

The ethyl (**3a**, Table 5, entry 1), *tert*-butyl (**3b**, Table 5, entry 2), isoamyl (**3c**, Entry 3) and benzyl (**3d**, Table 5, entry 4) acetoacetate esters all underwent diazo transfer to a maximum conversion of 95% (based on use of 1.05 equivalents of substrate) with good yields of 68 to 77% obtained. Ethyl benzoyl

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Table 5. Substrate scope of the 2nd generation continuous diazo transfer process.



Entry	Substrate	Base	Conversion (%)[a]	Yield (%)[b]	Entry	Substrate	Base	Conversion (%)[a]	Yield (%)[b]
1	 **3a**	NEt_3	95	75	5	 **3e**	NEt_3	95	89
2	 **3b**	NEt_3	95	68	6[d]	 **3j**	NEt_3	77	–[g]
3	 **3c**	NEt_3	95	74	7[e]	 **3f**	DBU	65	–[g]
4	 **3d**	NEt_3	95	77 (88[c])	8[f]	 **3k**	DBU	95	60

a) Conversion determined by ^{1}H NMR spectroscopy and based on use of 1.05 eq. of substrate. *b*) Yield of diazo product, >90% pure by ^{1}H NMR analysis after workup and without chromatography. *c*) Yield for large scale diazo transfer, employing a flow rate of 0.45 ml.min^{-1}. *d*) Residence time was 44 min. *e*) Residence time was 66 min. *f*) Reaction run at higher dilution due to substrate solubility: substrate (0.12 M), base (0.12 M). *g*) Product was not isolated as the reaction did not go to completion.

acetate (**3e**, Table 5, entry 5) also underwent efficient diazo transfer to provide an excellent yield (89%) of the diazo product. Diazo transfer to diethyl acetoacetamide (**3j**, Table 5, entry 6) was attempted in flow but the reaction proceeded slowly with 77% conversion being observed after an extended residence time of 44 min. Less activated diazo acceptors were also studied, but with DBU used as the base instead of triethylamine. While diazo transfer to aryl ketosulfone (**3k**)[90] went to completion (Table 5, entry 8), diethyl malonate (**3f**) was found to react slowly under these conditions, with a conversion of only 65% being observed even after an extended residence time of 66 min (Table 5, entry 7).

Enabling the large scale synthesis of α-diazocarbonyls

A significant advantage of this continuous diazo transfer process is that readily available shelf stable reagents are used to generate the hazardous tosyl azide on demand. This makes the process particularly attractive for the scale up of the diazo transfer reaction. The diazo transfer to benzyl 3-oxobutyrate (**3d**, Table 5, entry 4) was operated continuously for ten hours to produce over 21 g of benzyl 2–diazo-3-oxobutyrate (**4d**) in 88% yield. This continuous process is particularly notable for providing the α-diazocarbonyl product in >98% purity without the need for any column chromatography.

Experimental

Typical Diazo Transfer in Continuous Mode Using Tosyl Azide

A 5 mL solution of ethyl-3-oxobutanoate (**3a**) (0.260 g, 2.0 mmol, 1 eq.) and NEt_3 (0.210 g, 2.1 mmol, 1.05 eq.) in MeCN was prepared along with a 5 mL solution of tosyl azide (0.430 g, 2.2 mmol, 1.1 eq.) in MeCN. The ethyl-3-oxobutanoate (**3a**)/NEt_3 solution was injected into a sample loop and then pumped to a T-piece where it combined with the tosyl azide solution which had been injected in a second stream (2 mL at 0.087 mL.min^{-1}). The combined stream passed through a 20 mL reactor (25 °C, 120 min residence time) before passing through a back pressure regulator (8 bar). The product stream was collected and then concentrated under reduced pressure to

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provide a mixture of the α-diazocarbonyl product (**4a**) and toluenesulfonamide by-product. Reaction conversion of 100% was determined by ^{1}H NMR spectroscopy and the α-diazocarbonyl product (**4a**) was identified by comparison with the literature data. Tosyl azide quench was not employed when the reactions were conducted on small scale (<1 mmol).

Large Scale Diazo Transfer in Continuous Mode with *In Situ* Generation of Tosyl Azide

A 270 mL solution of benzyl 3-oxobutyrate (**3d**), (24.52 g, 0.4725 M, 1.05 eq.) and NEt_3 (0.4725 M, 1.05 eq.) in MeCN was prepared. A 270 mL solution of tosyl chloride (**2a**) (23.17 g, 0.45 M, 1 eq.) in MeCN and a 270 mL aqueous solution of sodium azide (7.89 g, 0.45 M, 1 eq.) were prepared. A quench solution of sodium hydroxide (7.29 g, 0.675 M, 1.5 eq.) and acetyl acetone (18.25 g, 0.675 M, 1.5 eq.) in a 50:50 mixture of MeCN and water was also prepared. The tosyl chloride (**2a**) solution was pumped (0.45 ml.min^{-1}) into a T-piece where it met the aqueous sodium azide solution (0.45 ml mL.min^{-1}). The combined stream passed through a 96 cm tube (1 min residence time) before it met the benzyl 3-oxobutyrate (**3d**)/NEt_3 solution (0.45 ml.min-1) at a T-piece. This combined stream passed through a series of three 10 mL reactor coils (25 °C, 22 min residence time). The reaction stream was then combined with the sodium acetylacetonate (**5**) solution (0.45 ml.min-1) at a T-piece to quench any remaining tosyl azide (**1a**). The combined stream passed through a 150 cm tube and a back pressure regulator (8 bar) before exiting the reactor. The reactor effluents were collected over a period of 10 h and then concentrated under reduced pressure. The crude product was collected in 3 batches. These were concentrated under reduced pressure to remove acetonitrile. These were then dissolved in EtOAc (100 mL) and washed with 9% aqueous KOH (2 × 50 mL), brine (50 mL) and water (50 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure to give the α-diazocarbonyl product (**4d**) (21.8 g, >98% purity, 88% yield) as a yellow oil. (UATR)/cm^{-1}: 2144, 1719, 1656; δ_H ($CDCl_3$, 400 MHz): 2.52 (3H, s, CH_3), 5.31 (2H, s, CH_2), 7.26-7.41 (5H, m, 5 x aromatic CH); δ_C ($CDCl_3$, 75.5 MHz): 28.3 (CH_3), 66.9 (OCH_2), 128.4, 128.7, 128.8 (aromatic CH), 135.2 (aromatic C) 161.7 (C=O, ester), 189.9 (C=O, ketone), no signal observed for ($C=N_2$). The aqueous waste was treated with dilute solutions of sodium nitrite (20% v/v) and then sulfuric acid (20% v/v) to safely decompose any sodium azide and 1-diazopropan-2-one (**6**) in the aqueous layer.

Conclusions

We have presented herein a procedure for the *in situ* generation and use of tosyl azide from safer, readily available reagents. This procedure can be conducted in batch mode, however the true power of the *in situ* tosyl azide generation is best realised by using continuous processing to enable diazo transfer on a large scale. Methods for quenching free inorganic azides were tested for their effect on tosyl azide and found to be ineffective. A new quench system, consisting of a sacrificial diazo acceptor molecule, was therefore developed and then successfully applied in the continuous process to remove unreacted tosyl azide from the reaction. In-line infrared (IR) spectroscopy could also be used to monitor the formation and consumption of key reaction components. The telescoped continuous process was used to transfer a diazo group to a range of acceptor types. Continuous operation of the process allowed over 21 g of an α-diazocarbonyl to be produced safely. The continuous generation and use of tosyl azide has the potential to make diazo transfer chemistry more accessible to the pharmaceutical and fine chemical industries.

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