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Mechanistic Study of In Situ Generation and of Use Methanesulfonyl Azide as a Diazo Transfer Reagent with Real-time Monitoring by FlowNMR

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Abstract: The mechanistic pathway by which the hazardous diazo transfer reagent methanesulfonyl azide can be formed in situ, from methanesulfonyl chloride and aqueous sodium azide, has been investigated using real-time reaction monitoring by FlowNMR. In the presence of triethylamine, rapid generation of methanylsufonyl azide is observed, via a mechanistic pathway consistent with involvement of a sulfene or methanesulfonyl triethylammonium intermediate. Accordingly, it is possible to generate and use methanesulfonyl azide in a single synthetic step for a diazo transfer process.

Introduction

α-Diazocarbonyl compounds are synthetically useful for the diverse and, frequently, highly selective nature of their reactions, often under mild conditions. The carbene and carbenoid species generated from α-diazocarbonyl precursors enable transformations not easily achievable by other means.[1] Ketene and certain ketene-type compounds, commonly of α-diazocarbonyl origin are also valuable synthetic intermediates. Despite their potential and versatility as reagents, the use of α-diazocarbonyl compounds is compromised both by their hazardous nature and that of their precursors in particular.

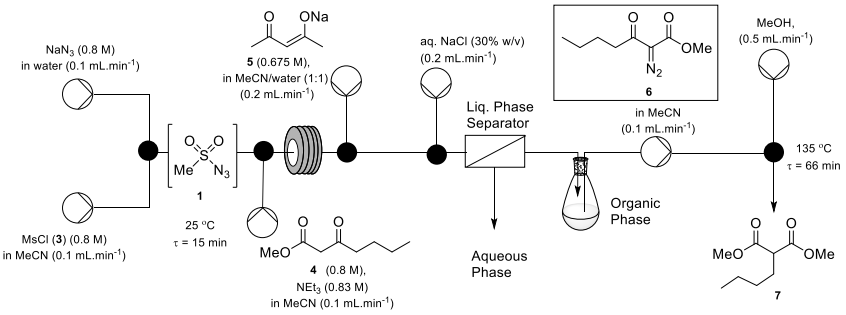
The Regitz diazo transfer reaction is generally acknowledged as the most convenient methodology for the generation of diazo compounds bearing two activating groups.[2] The process typically involves transfer of a diazo moiety from an azide-based reagent, commonly a sulfonyl azide. Although, sulfonyl azides exhibiting more favorable safety profiles have been reported more recently,[2] tosyl azide[3] and methanesulfonyl (mesyl) azide,[4] which are both impact-sensitive and explosive, continue to be widely used, as effective and low cost reagents. Furthermore, α-diazocarbonyl products of diazo transfer reactions present a hazard associated with the exothermic release of dinitrogen upon their decomposition.[5]

To address these safety challenges, the superior control enabled by continuous processing has afforded a well-documented strategy for generation and use of azides, diazo compounds and diazonium salts.[6] Among the key advantages of flow chemistry over more traditional batch methods, the high surface-area-to-volume ratio of tubular reactors, accommodating extremely efficient material throughput and transfer of heat, and the opportunity for automation, usually in the form of feedback loops and process controls, are especially noteworthy.[7] In order to maximize the benefits of process control, however, excellent mechanistic understanding is required. The ability to achieve such understanding is heavily contingent on spectroscopic methods, particularly those methods affording real-time experimental data.[8]

Many spectroscopic techniques are suitable for real-time reaction monitoring by in situ process analysis, including ultraviolet-visible (UV-vis), infrared (IR), Raman and nuclear magnetic resonance (NMR) spectroscopies.[9] These methods permit observation of a reaction system with minimal or negligible disturbance, which is particularly advantageous in determining an accurate kinetic profile. While online methods have been reported,[10] complementary techniques, such as mass spectrometry (MS) or chromatography (LC) generally require sampling for at-line/off-line analysis, and have associated delay times for delivery of results.

Among the in situ methods available, online process analysis by NMR spectroscopy is especially attractive for mechanistic investigation. NMR spectroscopic analysis provides sophisticated structural information, that is usually distinctive and characteristic, for all species possessing the nuclide under observation and is inherently quantitative in nature. The use of NMR cryoprobes has greatly enhanced the signal-to-noise ratio available, substantially alleviating the traditionally low sensitivity associated with NMR and increasing the probability of detecting minor or low level transient species. Over the past decade, among other NMR techniques,[11] the use of FlowNMR, where a reaction mixture is continuously transferred from a vessel external to the NMR magnet into the probe for analysis and returned via an insulated line, have been increasingly reported,[12] in tandem with the emergence of commercial reaction monitoring systems. Significant developments in solvent signal suppression methodology means that non-deuterated solvents can also be used, eliminating potential solvent isotope effects and reducing the cost burden associated with use of deuterated solvents. The experimental considerations intrinsic to use of FlowNMR have been documented,[13] along with its improved accuracy relative to static off-line NMR analysis of aliquots of reaction mixtures.[14]

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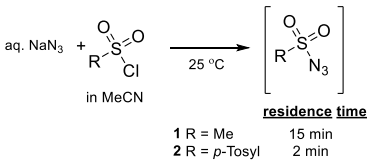


Scheme 1. Previously reported telescoped diazo transfer–thermal Wolff rearrangement.[15]

Recently, we reported a flow chemistry strategy for the preparation of mesyl azide, based on its in situ generation from mesyl chloride and sodium azide.[15] The continuous process enables the advantages of this reagent to be harnessed, while reducing and controlling the safety concerns arising from its use. The principal benefits include its low cost and, when compared to tosyl azide, its high atom economy, along with the facile extraction of the resulting sulfonamide byproduct by means of simple aqueous wash. The process was subsequently integrated into a telescoped system for synthesis and reaction of α-diazo-β-ketoesters (Scheme 1), avoiding isolation of either the diazo transfer reagent or the α-diazocarbonyl intermediate. A marked difference in the time required for in situ mesyl azide vs. tosyl azide generation (using an analogous method) prompted consideration that different reaction mechanisms might be operative in the production of the two compounds.

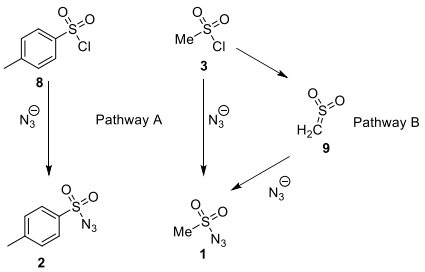
Results and Discussion

During development of our in situ protocol for generation of mesyl azide (**1**), a minimum time of 12 min was found to be necessary for complete consumption of sodium azide under the conditions employed for that work; analyzing the residue of an aliquot from the reaction mixture showed disappearance of the inorganic azide IR stretch at 2041 cm^{-1}, which was taken as diagnostic for reaction completion in these cases.[15] Interestingly, under similar conditions, tosyl azide (**2**) was found to take approximately only 1 min to form.[16] Hence, residence times of 15 min and 2 min had been used for the further continuous generation of mesyl azide (**1**) and tosyl azide (**2**), respectively (Scheme 2), although both processes were found to be concentration dependent. While tosyl azide can be formed effectively at a 0.23M concentration, mesyl azide required a 0.4M concentration for effective preparation, with lower concentrations impairing the reaction times required in both instances. Although initially a single phase, this process for generating mesyl azide results in a biphasic mixture, at a 0.4M concentration, prior to the diazo transfer process (which through dilution of the reaction mixture with acetonitrile, upon addition of the substrate solution, results in a single phase, at a 0.27M concentration). The biphasic nature of the mixture at 0.4M concentration was attributed to release of sodium chloride as a reaction by-product.[17]



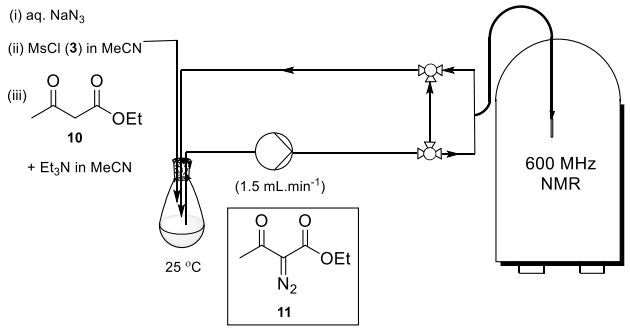
Scheme 2. In situ formation of sulfonyl azides **1**,**2** and residence times employed for previously reported continuous processes.[15,16]

While tosyl azide (**2**) arises through a nucleophilic substitution pathway at sulfur, two mechanistic possibilities can be envisaged in the case of mesyl azide (**1**) (Scheme 3); one involving substitution at sulfur (Pathway A) and the other involving a sulfene intermediate **9** that is subsequently trapped by azide ion (Pathway B), analogous to the accepted mechanism for mesylation of alcohols.[18] Evidence supporting a direct substitution mechanism for mesyl azide production, if such were available, would provide a basis for a comparison with tosyl azide using reagent concentration(s) and flow rates as the key criteria. Assessment could then be made based on the intrinsic electronic properties of the compounds, and in the context of a potential accelerating hydrophobic effect[19] for tosyl azide, induced by the aqueous solvent system and apparent during the subsequent diazo transfer.



Scheme 3. Mechanistic pathways for generation of sulfonyl azides **1**,**2**.

Therefore, in order to evaluate the operative mechanism for mesyl azide formation, a spectroscopic study of the process, including a subsequent diazo transfer to ethyl acetoacetate, was undertaken using FlowNMR and ReactIR for real-time reaction monitoring (Scheme 4). A batch experiment was setup with a 600 MHz NMR spectrometer online, whereby a metering pump was employed to transfer the reaction solution between the spectrometer cryoprobe and the reaction vessel via a jacketed transfer line while maintaining a constant temperature throughout.



Scheme 4. Schematic representation of reaction monitoring setup for in situ pre-generation of mesyl azide (**1**) and subsequent conversion into ethyl 2-diazoacetoacetate (**11**).

'Pre-generation' of mesyl azide (**1**) under these conditions was achieved by rapid addition of methanesulfonyl (mesyl) chloride to an aqueous acetonitrile solution of sodium azide, with close to complete formation of **1** observed after 40 min by ^{1}H NMR analysis (Figure 1). A more dilute (0.08M) concentration was used to ensure a single-phase system throughout the experiment. At the higher concentration employed for the continuous process (0.4M),[15] a biphasic mixture is observed upon complete mesyl azide formation, prior to diazo transfer, which occurs in a single phase (at a 0.27M concentration). The conversion of mesyl chloride (**3**) into mesyl azide (**1**) could be clearly followed using the singlet resonances for mesyl chloride (3.79 ppm) and mesyl azide (3.35 ppm), and produced no evidence for a sulfene intermediate in the process. Reaction monitoring by IR spectroscopy was also attempted but proved unsuitable for this process. Mesyl azide and mesyl chloride share a number of characteristic IR absorptions which were found to overlap in solution; the sulfonyl stretches of both compounds, for example, overlap at 1376 cm^{-1}. Unfortunately, the frequency of the inorganic azide stretching absorption could not be distinguished from that of the corresponding absorption of mesyl azide in solution under the conditions employed for this study.

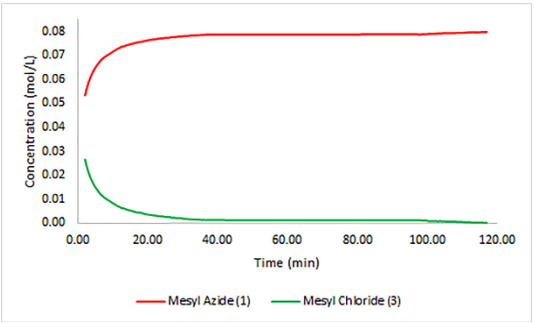


Figure 1. Plot of component concentration vs. time for 'pre-generation' of mesyl azide (**1**) from mesyl chloride (**3**) and sodium azide.[20]

Subsequent addition of ethyl acetoacetate (**10**) and triethylamine to the reaction mixture resulted in a diazo transfer process which was again followed spectroscopically. Characteristic resonances for ethyl acetoacetate and ethyl 2-diazoacetoacetate (**11**) (triplets at 1.18 and 1.23 ppm respectively) and signals for mesyl azide (**1**) and methanesulfonamide (**12**) (singlets at 3.35 ppm and 2.99 ppm respectively) were used to track reaction progress through the ^{1}H NMR spectra acquired during monitoring (Figure 2). Notably, a change in the chemical shift of the water signal was observed upon increasing the ratio of acetonitrile in the solvent composition,[21] following addition of the substrate. Again, here, IR spectroscopy was unsuccessful in monitoring the reaction progress; the diazo stretch of the product coinciding with the azide stretch of mesyl azide in solution. Where these stretches are distinct (as reported for methyl diazophenylacetate[22] and *N,N*-diethyl 2-diazoacetoacetamide[16]), IR has served as a highly valuable tool for reaction monitoring.

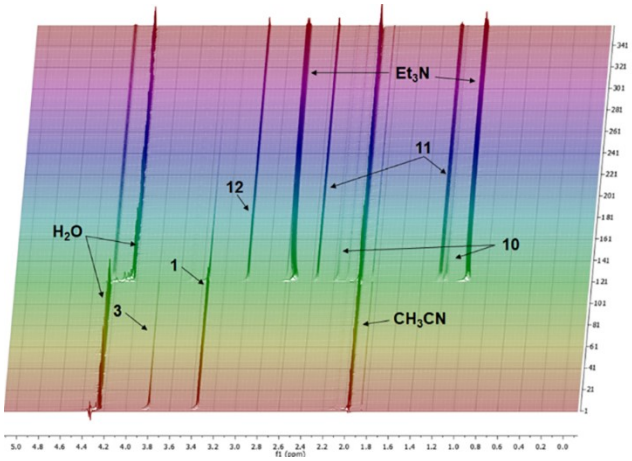


Figure 2. ^{1}H NMR reaction profile for mesyl azide generation at 25 °C followed by subsequent diazo transfer, showing characteristic signals for mesyl chloride (**3**), mesyl azide (**1**), methanesulfonamide (**12**), ethyl 2-diazoacetoacetate (**11**), ethyl acetoacetate (**10**), triethylamine, acetonitrile and water.

Interestingly, high levels of conversion to the diazo product **11** were evident after 126 min (Figure 3), corresponding to the typical residence time (66 min) employed for the continuous diazo transfer process (Scheme 1),[15] despite the reduced concentration (0.05M) vs. (0.27M) for the typical continuous process. The comparable results may possibly be attributed to the single phase nature of the process at the lower concentration. The presence of a minor reaction pathway resulting in unproductive conversion of mesyl azide (**1**) to methanesufonamide (**12**) was also evident.

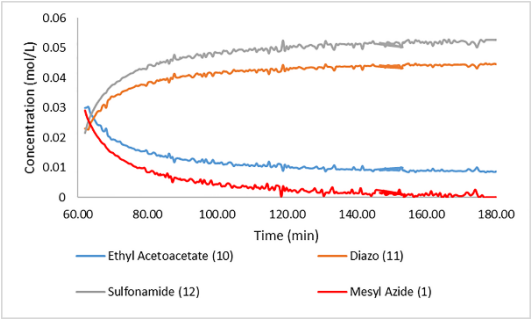
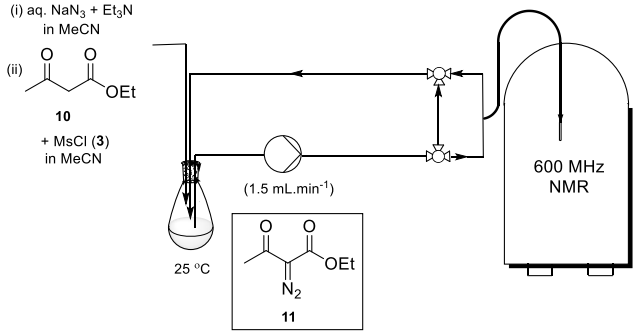


Figure 3. Plot of component concentration vs. time for diazo transfer to ethyl acetoacetate (**10**) at a 0.05M concentration, following pre-generation of mesyl azide (**1**).[20]

In the context of these results, a direct substitution mechanism appeared to be likely for reaction conditions where mesyl azide (**1**) is 'pre-generated'. Conditions where a sulfene pathway might be more likely were therefore examined, with a view to testing this conclusion.

For a case where triethylamine was present with mesyl chloride (**3**) and sodium azide, we postulated that a sulfene-type mechanism would likely be operative (Figure 1, Pathway B). Hence, a 'one-pot' approach was investigated, whereby a solution of mesyl chloride and ethyl acetoacetate (**10**) was added to an aqueous acetonitrile solution of sodium azide and triethylamine and the reaction progress was once again followed by FlowNMR (Scheme 5).



Scheme 5. Schematic representation of the reaction monitoring setup for generation of mesyl azide (**1**) and direct diazo transfer to form ethyl 2-diazoacetoacetate (**11**) in a single step at 0.05M concentration.

In contrast to the process pre-generating mesyl azide (**1**) (Figure 1), generation of mesyl azide in the presence of triethylamine essentially appeared instantaneous upon addition of mesyl chloride (**3**) to the reaction mixture (Figure 4). The ^{1}H NMR spectra showed the absence of the characteristic mesyl chloride signal at 3.79 ppm, while signals for both mesyl azide and methanesulfonamide (**12**) were observed and formation of ethyl 2-diazoacetoacetate (**11**) was evident from the outset. After 66 min, substantial diazo transfer was again observed (Figure 4) – broadly in line with that seen where mesyl azide was pre-generated, but with no induction time required for the pre-generation step. Critically, the formation of mesyl azide from mesyl chloride and sodium azide was monitored with additions of triethylamine in separate FlowNMR experiments at 2 min and at 19 min; in both cases, immediate complete transformation of mesyl chloride to mesyl azide was observed upon addition of triethylamine (see SI).

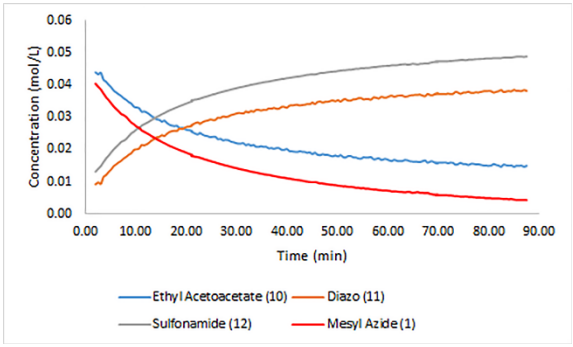
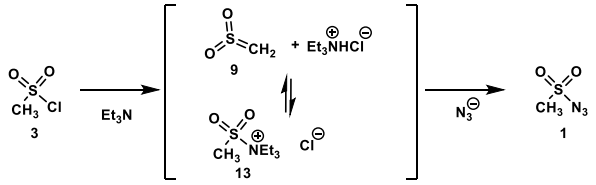


Figure 4. Plot of component concentration vs. time for generation of mesyl azide (**1**) and direct diazo transfer to form ethyl 2-diazoacetoacetate (**11**) in a single step at a 0.05M concentration.[20]

With identical concentrations in use, the significant increase in the rate of formation of mesyl azide (**1**) suggested that an alternative mechanism of formation to Pathway A is operative here, one similar to Pathway B (Scheme 3), with formation of an intermediate sulfene **9** or methanesulfonyl triethylammonium ion **13** preceding mesyl azide generation (Scheme 6).



Scheme 6. Possible mechanism for generation of mesyl azide (**1**) from mesyl chloride (**3**) in the presence of triethylamine.

Conclusions

The in situ generation of mesyl azide can be readily monitored using real-time FlowNMR enabled spectroscopic analysis, though

the process posed challenges for resolution of signals required for reaction monitoring by ReactIR. Under neutral conditions, formation of mesyl azide appears to proceed without a sulfene-type intermediate, while more rapid generation of the compound is seen in the presence of triethylamine, consistent with the intermediacy of a sulfene species or nucleophilic catalysis by the amine. Importantly, our study further suggests that generation and use of mesyl azide is possible in a single step, or stream, employing a homogeneous aqueous–organic solvent system, with significant safety advantages.

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Keywords: Diazo transfer • Flow Chemistry • Telescoped Process • FlowNMR

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[20] Following an addition to the reaction vessel, NMR spectroscopic data obtained for the subsequent 2 min was not analysed as it was deemed unrepresentative of the total reaction mixture; the total volume of the FlowNMR system is 3.7 mL and the reaction mixture was carried at a flow rate of 1.5 mL/min.

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