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Rapid Access to α-Alkoxy and α-Amino Acid Derivatives through Safe Continuous-Flow Generation of Diazoesters

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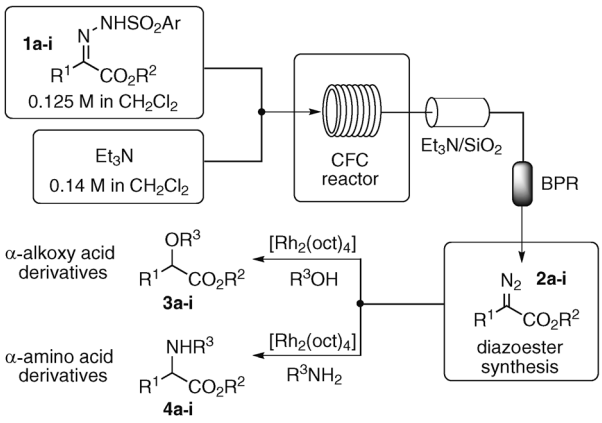
Despite the wide synthetic potential of diazo compounds (X−H insertion, ylide formation, cyclopropanation, cycloaddition etc.),[1] concerns over the hazards associated with their preparation, isolation, and use have hindered their full exploitation in both academic and industrial laboratories. A few diazo compounds are commercially available (e.g. ethyl and butyl diazoacetate, TMS-diazomethane and diazodimedone),[2] but safe and convenient access to a wider range of useful functionalized diazo species is still desirable.[3] Diazo transfer can be used to access α-diazocarbonyls, but this only partially addresses the safety concerns associated with the diazo species, as the use of equally hazardous azide-based diazo-transfer reagents is still required.[4] Ideally, it would be beneficial if the diazo species could be generated and consumed in situ so that handling of the hazardous diazo compound is avoided altogether.

Recent work by Ley,[5] Jamison,[6] Kappe,[7] and others[4,8–10] has shown that highly reactive diazo and azido compounds can be used in lab-scale continuous-flow reactors to achieve a number of very useful synthetic transformations, and indeed work from our own laboratory has shown that ethyl diazoacetate can be used in-flow to access β-keto esters.[11] We therefore wondered if it was possible to actually generate α-diazocarbonyl compounds under flow conditions and then use these materials directly in further synthetic manipulations, thus minimizing exposure to any potentially hazardous material. In effect, could we develop a continuous-flow diazo generator and then demonstrate its use to prepare a range of useful α-alkoxy (**3a–i**) and α-amino acid (**4a–i**) derivatives through O−H and N−H insertion (Scheme 1)?

At the outset we were aware that in order to provide an acceptable solution to the problem, we needed to identify a way to access the diazo compounds of interest (**2a–i**) from starting materials that showed an acceptable safety profile, that is, the precursor molecules and reagents should be safer to prepare and handle than the diazocarbonyl compounds being produced. Of the methods available for the generation of α-diazocarbonyl compounds, we were particularly attracted to the Bamford–Stevens reaction as it uses readily accessible arylsulfonylhydrazones (e.g., **1a–i**) as starting materials, with the corresponding diazocarbonyls being generated upon exposure to relatively weak base at moderate reaction temperatures.[12–14]



Scheme 1. Proposed flow process for diazoester synthesis. CFC = convection flow coil reactor, BPR = back-pressure regulator, oct = octanoate.

Thermal stability studies (DSC and TGA) were conducted on the tosylhydrazone **1b** and its corresponding methyl diazoester **2b**[15,16] in order to determine if a safe window of operation could be identified for the continuous-flow process (see the Supporting Information). The results clearly show that the rate of initial mass loss from diazoester **2b** peaks at 125 °C, which corresponds to a significant exotherm. In comparison tosylhydrazone **1b** has a rate of mass loss which peaks at 221 °C, indicating that it is substantially more thermally stable.[15] We therefore concluded that there would be significant safety benefits in adapting the Bamford–Stevens reaction for use in-flow to produce diazoesters, which in turn could be utilized immediately in subsequent transformations without needing to be isolated or purified. Reassured by these data, a wider range of arylsulfonylhydrazones **1a–i** was readily prepared from simple and inexpensive starting materials[17–19] (Scheme 2).

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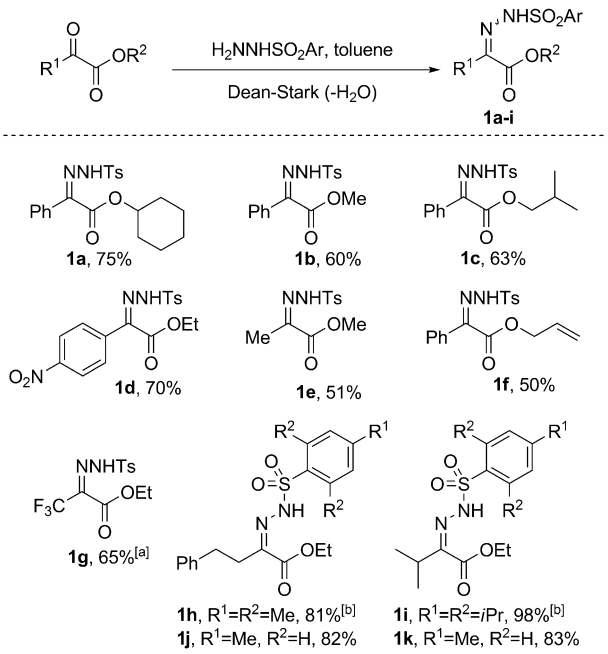
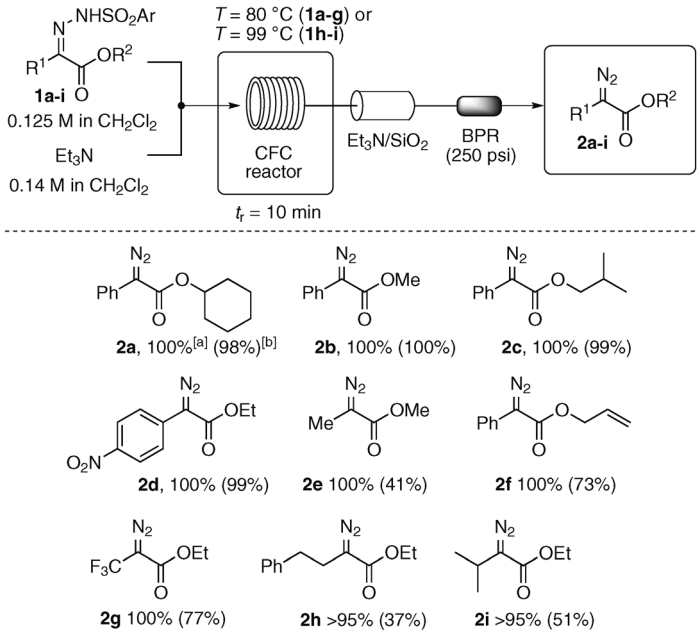


Scheme 2. Preparation of arylsulfonylhydrazone precursors **1a–i**. [a] $POCl_3$ was required to dehydrate the hemiaminal-type intermediate.[18] [b] EtOH used as solvent instead of toluene at room temp.

Our initial efforts to develop an in-flow diazoester synthesis focused upon studying the conversion of tosylhydrazone **1a** into the corresponding diazo compound **2a** under flow conditions (Scheme 3). To this end, a solution of the tosylhydrazone **1a** (0.125 M in dichloromethane) was injected into one of the sample loops of the R2+ unit of a Vapourtec



Scheme 3. In-flow preparation of diazoesters **2a–i**. [a] Conversion as judged by ^{1}H NMR spectroscopy. [b] Isolated yield.

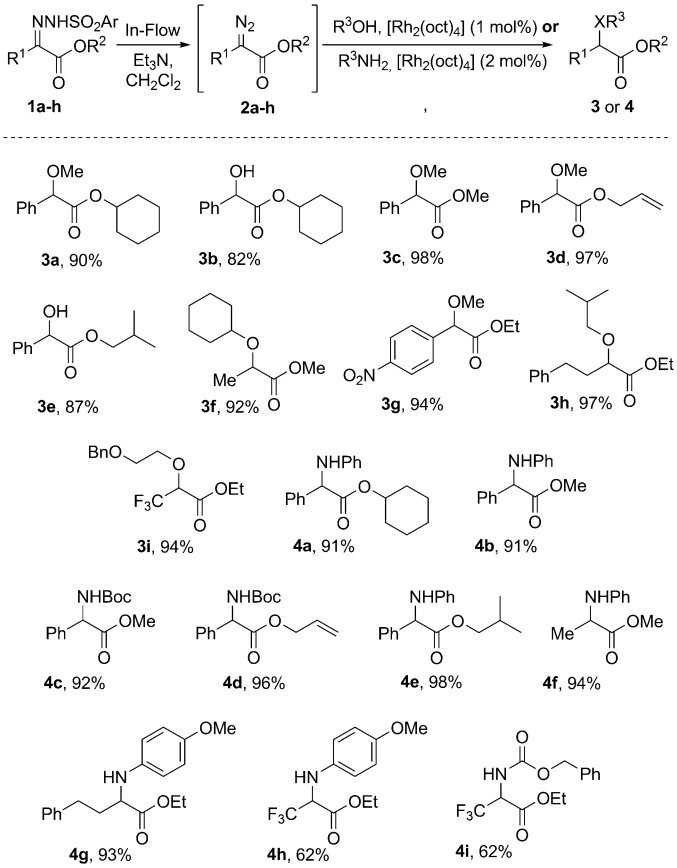
R2+/R4 reactor. The other sample loop was loaded with a solution of triethylamine (0.14 M in dichloromethane). The valves of the loop were set to load and the reagents were pumped through the system using CH_2Cl_2 as a system solvent at a flow rate of 0.100 mL min^{-1} (per pump, total flow rate of 0.200 mL min^{-1}). The reagents were combined in a T-piece before entering a 2 mL convection flow coil (CFC) reactor (inside diameter = 1 mm, length = 2.9 m; PFA[20]), which was maintained at 80 °C (residence time (t_r) = 10 min) by the R4 unit. The output from the CFC reactor was passed through a scavenger column packed with Et_3N pretreated silica gel (to remove the sulfinic acid byproduct). Finally a back pressure regulator (BPR, 250 psi) was added in line after the Et_3N/silica gel scavenger column and the output was concentrated before being analyzed for conversion into the desired diazo compound **2a**. ^{1}H NMR and IR spectroscopy[21] of the reaction mixture showed 100% conversion to the desired diazoester **2a**, and the product was stable enough to allow purification by column chromatography, which provided the desired diazoester **2a** in 98% isolated yield.

The optimized reaction conditions were next applied to the synthesis of a range of diazoesters **2a–i**, (Scheme 3). In most cases complete conversion of the tosylhydrazone into the desired diazoester was observed, but interestingly, the tosylhydrazones **1j** and **1k** did not undergo complete conversion to the corresponding diazoesters **2h** and **2i**, under the original (T = 80 °C), or slightly modified (T = 99 °C), flow conditions. However, the mesitylsulfonylhydrazone **1h** could be completely converted into the desired diazoester **2h** if the CFC reactor was heated to 99 °C. Further work showed that use of the 2,4,6-triisopropylsulfonylhydrazone derivative **1i** was required in order to obtain complete conversion into the desired diazoester **2i** (T = 99 °C).

These observations are in complete accord with the previous work of Reese et al.[19] who reported that the rate of base-mediated decomposition of arylsulfonylhydrazones into the corresponding diazo compounds increases with increasing steric bulk on the aryl portion (particularly of the *ortho* substituents) of the arylsulfonylhydrazone. In general, the flow conditions are tolerant of a useful range of α-substituents (e.g., aryl, alkyl, and trifluoromethyl), and a diverse array of ester groups is also compatible with the conditions. Gaining access to ethyl 3-trifluoro-2-diazopropionate (**2g**) is particularly satisfying, as this material is a versatile intermediate from which to prepare a wide range of trifluoromethyl containing products. In most cases, the diazoesters could be isolated and purified in high yield, but some of the diazo compounds (i.e., **2h** and **2i**), appeared to be more sensitive to purification and **2g** appeared to be somewhat volatile (b.p. 110 °C[18]). As conversion of the hydrazones to the corresponding diazoesters was universally good, we reasoned that the intermediate diazo species could be used directly in subsequent transformations without isolation or purification.

In principle, the diazoesters generated using this methodology could be utilized as versatile synthetic intermediates

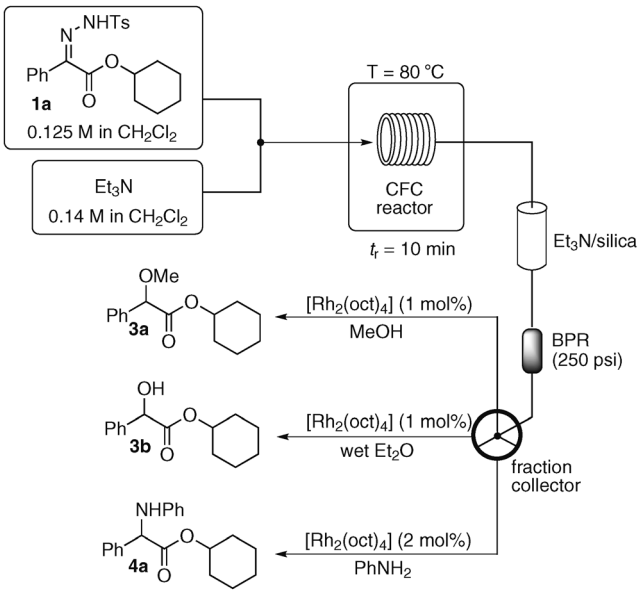
for the preparation of novel compound arrays. To assess the application of our flow process to the synthesis of α-alkoxy (**3a–i**) and α-amino acid (**4a–i**) acids, the diazoesters (**2a–i**) formed in-flow from the arylsulfonylhydrazones (**1a–i**) were used directly in a range of O–H or N–H insertion reactions (Scheme 4). The O–H insertion reactions were performed



Scheme 4. In-flow diazoester formation and subsequent O–H and N–H insertion reactions.

by flowing the intermediate diazoester into a reaction vessel charged with $[Rh_2(oct)_4]$ (oct = octanoate) in the presence of the appropriate alcohol, or "wet" Et_2O, to give the desired O–H insertion products **3a–i** in excellent overall yield over the two steps.[17,22] In addition, N–H insertions also proceeded in excellent yield using aniline, *p*-anisidine, *tert*-butyl carbamate, or benzyl carbamate to give α-amino acid derivatives **4a–i**.[23] The high overall yields obtained for these continuous-flow diazoester formation-X-H insertion reactions confirms that the intermediate diazoesters are formed efficiently in-flow, and that purification of the diazoester is not required. A very good illustration of this is provided in the 94% overall yield obtained for the formation of **3i** from **1g**, whereas the maximum yield obtained for the formation of the purified diazoester intermediate **2g** is 77%.

Having developed an efficient continuous-flow process for diazoester formation and demonstrated their direct use in X–H insertion reactions, we next explored the potential for this procedure to be fully automated. To this end, a fraction collector was connected to the output of the flow apparatus and the Vapourtec flow commander software was employed to control the reaction. The tosylhydrazone **1a** was selected as an example, and the diazoester formation reaction was performed using our optimized conditions. The steady-state flow output was automatically divided into three separate vials, each containing the reagents required for a subsequent transformation (Scheme 5). Analysis of these reactions



Scheme 5. Automated O–H and N–H insertion reactions.

showed complete consumption of the starting material tosylhydrazone **1a**. In addition, comparison of the ^{1}H NMR spectra of each reaction mixture with a pure sample of the appropriate product (**3a**, **3b** and **4a**) indicated efficient (>95%) and selective conversion of the intermediate diazoester **2a** into the desired products.[24] This automation study shows the potential for this process to be employed in the synthesis of arrays of carbene-derived products from stable tosylhydrazone precursors (via the diazoester intermediates) without the need to handle any hazardous diazo compounds. If large quantities of any single α-alkoxy (**3a–i**) or α-amino acid (**4a–i**) acid are required, although technically more challenging, it could be potentially andvantageous to perform an in-flow OH or NH insertion quenching step. However, our studies in this area are not yet complete and the results of that work will be reported in due course when the full account of this study is published.

In conclusion, we have developed a highly efficient and safe process for the synthesis of diazoesters under continuous-flow conditions from stable precursors. In addition we have shown that a two-step procedure can be employed in which the in-flow generated diazoesters can be directly converted into a range of different α-alkoxy (**3a–i**) and α-amino acid (**4a–i**) derivatives in good to excellent yield without ex-

posure to the potentially hazardous diazo species. Furthermore, we have also shown the potential for automating this procedure, which would further reduce the potential hazards associated with the use of diazo compounds in both academic and industrial environments.

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Keywords: amino acids · carbenoids · continuous-flow chemistry · diazo compounds

[1] a) T. Ye, A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269; c) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–935; d) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903; e) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[2] Ethyl and butyl diazoacetate, TMS-diazomethane and diazodimedone are all available from Sigma Aldrich.

[3] G. Maas, *Angew. Chem.* **2009**, *121*, 8332–8341; *Angew. Chem. Int. Ed.* **2009**, *48*, 8186–8195.

[4] R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald, B. H. Warrington, *Org. Process Res. Dev.* **2007**, *11*, 704–710.

[5] a) L. J. Martin, A. L. Marzinzik, S. V. Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320–323; b) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077–4081; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021.

[6] P. B. Palde, T. F. Jamison, *Angew. Chem.* **2011**, *123*, 3587–3590; *Angew. Chem. Int. Ed.* **2011**, *50*, 3525–3528.

[7] B. Gutmann, J-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem.* **2010**, *122*, 7255–7259; *Angew. Chem. Int. Ed.* **2010**, *49*, 7101–7105.

[8] L. D. Proctor, A. J. Warr, *Org. Process Res. Dev.* **2002**, *6*, 884–892.

[9] J. D. Clark, J. D. Heise, A. S. Shah, J. C. Peterson, S. K. Chou, J. Levine, A. M. Karakas, Y. Ma, K-Y. Ng, L. Patelis, J. R. Springer, D. R. Stano, R. H. Wettach, G. A. Dutra, *Org. Process Res. Dev.* **2004**, *8*, 176–185.

[10] P. Pollet, E. D. Cope, M. K. Kassner, R. Charney, S. H. Terett, K. W. Richman, W. Dubay, J. Stringer, C. A. Eckert, C. L. Liotta, *Ind. Eng. Chem. Res.* **2009**, *48*, 7032–7036.

[11] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *J. Org. Chem.* **2010**, *75*, 8674–8676.

[12] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735–4740.

[13] M. Regitz, G. Maas, *Diazocompounds: Properties and Synthesis*, Academic Press, New York, **1986**.

[14] J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, 1479–1492.

[15] See the Supporting Information for copies of DSC (differential scanning calorimetry) and TGA (thermogravimetric analysis) data for **1b** and **2b**.

[16] For previous thermal stability studies on ethyl diazoacetate see: J. D. Clark, A. S. Shah, J. C. Peterson, L. Patelis, R. J. A. Kersten, A. H. Heemskerk, M. Grogan, S. Camden, *Thermochimica Acta* **2002**, *386*, 65–72.

[17] D. J. Miller, C. J. Moody, C. N. Morfitt, *Aust. J. Chem.* **1999**, *52*, 97–107.

[18] G. Shi, Y. Xu, *J. Chem. Soc. Chem. Commun.* **1989**, 607–608.

[19] C. C. Dudman, C. B. Reese, *Synthesis* **1982**, 419–421.

[20] PFA = perfluoroalkoxy polymer.

[21] The course of the reaction can be monitored by infrared spectroscopy by observing the loss of the N–H stretch ($\approx$3200 cm^{-1}) for the arylsulfonylhydrazone, and observing the gain of a prominent C=N$_2$ stretch ($\approx$2100 cm^{-1}) for the diazoester.

[22] D. J. Miller, C. J. Moody, *Tetrahedron* **1995**, *51*, 10811–10843.

[23] E. Aller, R. T. Buck, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson, J. B. Sanghera, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2879–2884.

[24] See the Supporting Information for a comparison of the ^{1}H NMR spectra of the initial reaction mixtures and the purified products.

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