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Safe and Reliable Synthesis of Diazoketones and Quinoxalines in a Continuous Flow Reactor

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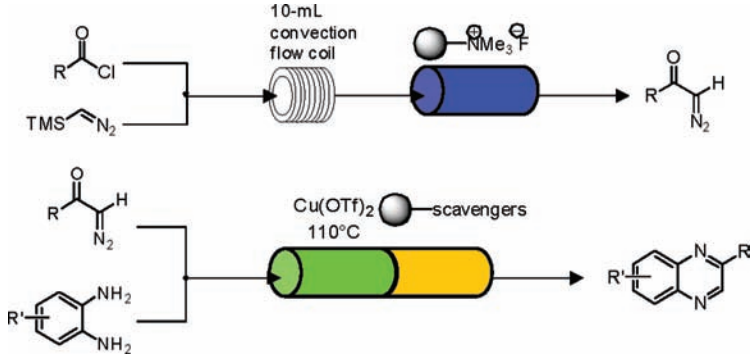
ABSTRACT



A flow method for the synthesis of aliphatic and aromatic diazoketones from acyl chloride precursors has been developed and used to prepare quinoxalines in a multistep sequence without isolation of the potentially explosive diazoketone. The protocol showcases an efficient in-line purification using supported scavengers with time-saving and safety benefits and in particular a reduction in the operator's exposure to carcinogenic phenylenediamines.

Diazo compounds and in particular diazocarbonyl compounds are extremely versatile intermediates for organic synthesis.[1] They can be used in cyclopropanation reactions; C−H, O−H, and N−H insersion reactions; Wolff rearrangements; and ylid formation.[2−4] However, diazo compounds often present a challenge with respect to their preparation and isolation due to thermal instability and lability toward acid (formation of diazonium salts). One efficient method to synthesize diazoketones is the reaction of an acyl chloride with diazomethane. Diazomethane (bp −23 °C) can be used in many organic reactions; however, it is highly toxic (skin irritant and carcinogen), as well as being thermally and photochemically labile. Consequently, its use in conventional batch synthesis requires the careful selection of glassware without ground-glass joints or sharp surfaces, and its application as a dilute Etheral solution precludes its use in easy scale-up. By comparison trimethylsilyldiazomethane ($TMSCHN_2$, bp 96 °C) is reported to be a less hazardous substitute for a wide range of applications.[5] Although it is thermally more

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(2) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.
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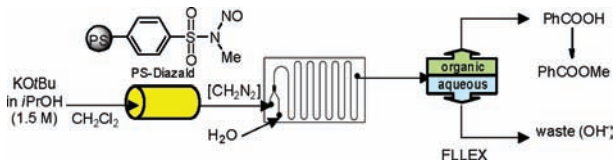
stable than diazomethane, it is still toxic[6] and therefore still requires careful handling.

Flow based synthesis can offer many advantages over batch sequencing including reduced processing times, precise parameter control, higher reproducibility, and enhanced selectivity.[7] In addition the application of microreactor technology gives highly efficient heat and mass transfer and allows for small reaction volumes which in turn increases the safety profile of handling exothermic reactions and reactions involving explosive and toxic materials.[8] In this paper we describe our most recent work toward designing a safe synthesis of diazoketones in a continuous flow mode.[9]

In order to evaluate the applicability of diazomethane precursors in flow, methylation of benzoic acid was used as a test reaction.[10] Various precursors were investigated using different flow setups. In particular early work was conducted using a polymer-supported Diazald (PS-Diazald).[11] Diazomethane was produced *in situ* by flowing a solution of KO*t*Bu in *i*PrOH through a glass cartridge packed with the PS-Diazald, using DCM as the system solvent. The output reaction stream was directed into a mixing chip and combined with a secondary stream of water. Extraction and separation of the resulting biphasic mixture was carried out using a FLLEX membrane device giving an organic flow which contained the diazomethane.[12] The organic stream was directed into a flask containing benzoic acid, generating the methyl ester (Scheme 1). Although this procedure showed promise it was ultimately abandoned due to consistently low conversion and relatively high pressures being generated by the solid-supported reagent.

Scheme 1. Generation of Diazomethane in Flow



Significantly better results were obtained using commercially available $TMSCHN_2$ (2 M solution in Et_2O) as the precursor. Using this reagent in a Vapourtec R2+/R4 combination reactor[13] quantitative methylation of benzoic acid was possible; however, a large excess of reagent was needed to achieve complete conversion. The reactor configuration required two independent injection loops (5 mL internal volume, PFA, 1 mm id), one loaded with a solution of benzoic acid (0.35 M in MeOH) and the other loaded with a solution of $TMSCHN_2$ (0.8 M in Et_2O, 3 equiv). The reagents were mixed at a T-piece and then flowed at a combined flow rate of 400 μL/min into a 10 mL convection flow coil (CFC; 10 mL internal volume, 1 mm id, residence time 25 min) mounted on the Vapourtec R4 unit. Following careful evaporation of the solvent and the excess $TMSCHN_2$, clean methyl ester was obtained quantitatively, with no requirement for further purification.

Expanding upon this encouraging result, we decided to investigate the formation of diazoketone in flow using $TMSCHN_2$ as the preferred diazotizing source. Based upon on the work of Shiori,[14] we designed a flow setup using a twin injection loop configuration (2 mL internal volume, PFA, 1 mm id). The first sample loop was loaded with a solution of an acyl chloride (1 M in MeCN/THF 1:1), and the second with a solution of $TMSCHN_2$ (1.5 M in Et_2O/MeCN/THF 5.7:1:1). The two reagent streams were combined at a T-piece and passed at a combined flow rate of 200 μL/min through a cartridge containing an immobilized base (PS-NMe_2 A-21, PS-NEt_2 or PS-N*i*Pr_2, 1−3 equiv). A back-pressure regulator (BPR) was used to maintain the system pressure at 8 bar. The exiting solution was collected and concentrated under reduced pressure prior to analysis. Using 1-naphthoylchloride as the starting material 62% conversion to the diazoketone was achieved using polymer-supported diethylamine (3 equiv) at rt. The only side products observed were the TMS-protected diazoketone (22%) and 1-chloroacetylnaphthalene (3%) with the remaining material being unreacted acylchloride (13%).[15] Treatment of the crude reaction mixture with a PS-tetraalkylammonium fluoride salt[16] smoothly transformed all of the TMS-protected diazoketone to the corresponding diazoketone. Indeed, it was found that, in our flow setup, the amine base could be simply replaced by the PS-fluoride. The final flow setup was comprised of two flow streams (each at a flow rate of 200 μL/min) of the acyl chloride and $TMSCHN_2$ which met at a T-piece and were then directed into a 10 mL CFC. The incubated reaction mixture was finally passed through a glass cartridge containing the PS-fluoride (1.5 equiv, 15 mm id) at rt. The exiting flow stream was collected, and the solvent evaporated to afford the desired product within 2 h at rt (vs

(6) http://www.canadaeast.com/front/article/666039.

(7) Anderson, N. *Org Process Res. Dev.* **2001**, *5*, 613–621. Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D. M. *Chem.—Eur. J.* **2008**, *14*, 7470–7477. Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655–1681. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *J. Chem. Soc., Chem. Commun.* **2006**, *24*, 2566–2568. Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, *3*, 427–430.

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(9) Industrial scale continuous diazomethane production is carried out by Phoenix Chemicals: US6962983. This is achieved by feeding a base and diazomethane precursor into a reactor vessel that generates diazomethane which can be removed using a diluent gas.

(10) Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* **2008**, *10*, 41–43. Struempel, M.; Ondruschka, B.; Stark, A. *Org. Process Res. Dev.* **2009**, *13*, 1014–1021.

(11) PS-Diazald was prepared from a commercially available polymer-supported tosyl chloride in two steps: see Supporting Information.

(12) Flow Liquid Liquid Extraction machine, available from Syrris, http://www.syrris.com.

(13) http://www.vapourtec.co.uk.

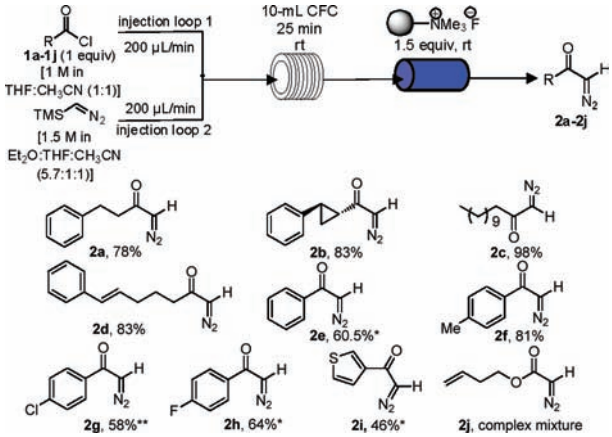
(14) Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1981**, *29*, 3249–3255.

(15) Similar results were obtained starting from 3-phenyl propionyl chloride **1a**; we observed formation of the expected diazoketone **2a** (62%) and the TMS-protected diazoketone (31%).

(16) A23: 2−3 mmol, commercially available from Sigma-Aldrich.

24−90 h at 0 °C in batch) in purities above 95%[17] as determined by LC-MS and ^{1}H NMR (Scheme 2).

Scheme 2. Flow Synthesis of Diazoketones[a]



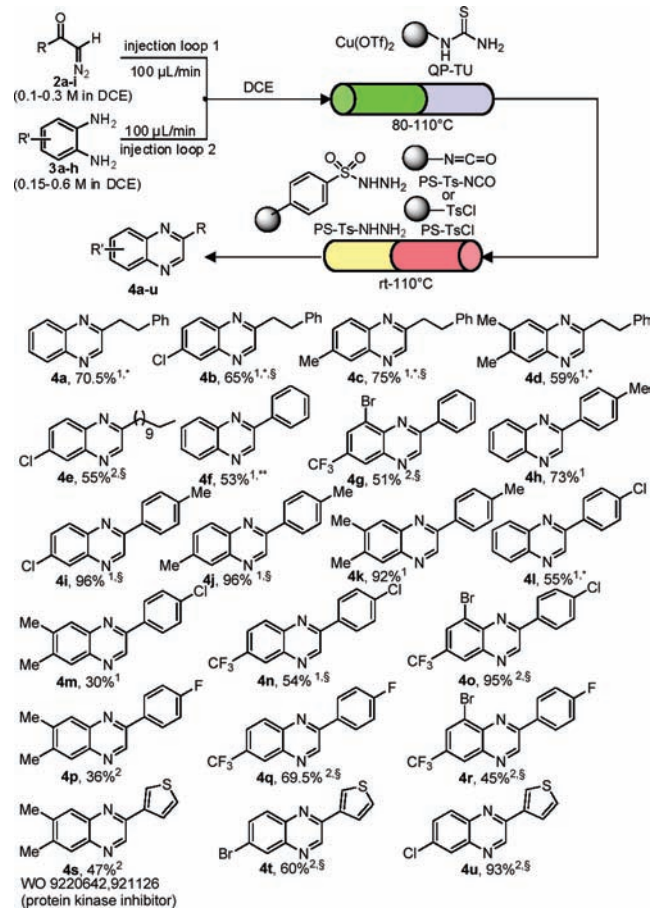
[a] (*) Yield after purification by flash chromatography. (**) Yield after purification by trituration in hexane.

As can be seen from the illustrated examples, both aliphatic and aromatic/heteroaromatic diazoketones could be obtained in good yield with additional functionalities such as an alkene, cyclopropane, and halogens being tolerated. However, some limitations were encountered with 3-butenylchloroformate giving a complex mixture containing only traces of expected diazoketone **2j**.

Diazoketones are versatile intermediates which can be converted to a variety of downstream products.[18] We were particularly interested in flow approaches to quinoxaline which would involve potentially explosive diazoketone and toxic phenylenediamine. Quinoxaline derivatives exhibit a diverse range of therapeutic properties including kinase inhibition, together with antitumor, cytotoxic, antiviral, antibacterial, and anti-inflammatory activity.[19] Consequently their synthesis has attracted significant attention.[20] However, many of the methods developed employ expensive metal catalysts and harsh conditions such as strong oxidizing reagents and require tedious reaction workup. We therefore sought a continuous flow mode preparation which would additionally take advantage of the use of PS-scavengers to purify the reaction stream thereby minimizing worker exposure to the toxic intermediates. Our end goal was to carry out the multistep reaction in a single telescoped flow sequence involving the formation of the diazoketone followed by quinoxaline synthesis, without intermediate isolation.

To evaluate the feasibility of forming quinoxalines in flow we first investigated the coupling of diazoketones with various 1,2-diaminobenzenes (Scheme 3).

Scheme 3. Copper-Catalyzed Quinoxaline Synthesis[a]



[a] (1) PS-TsNCO; (2) PS-TsCl; (*) Yield after purification by catch and release (with QP-SA); (**) Yield after purification by flash chromatography; (§) Mixture of regioisomers (∼1:1).

Again, a simple setup using a twin sample loop injection system was utilized (2 mL, PFA, 1 mm id). One loop was loaded with a solution of diazoketone (1 equiv), and the second with a solution of the diamine (1.5−2 equiv). The two streams (flow rate 100 μL/min) were mixed at a T-piece and then directed into a glass cartridge (6.6 mm id) containing a pad of solid metal catalyst (0.2−0.8 equiv) followed by a plug of PS-thiourea (QP-TU, 1.5 equiv) to capture any dissolved metal salts. The reaction stream progressed through a second cartridge (10 mm id, heated at 110 °C) containing either PS-isocyanate (PS-TsNCO, 3 equiv) or PS-tosylchloride (PS-TsCl, 3 equiv) which

(17) Except for **2e**, **2g**, **2h**, and **2i**: crude reaction mixtures gave purities >85%; a batch purification was carried out for these compounds (see footnote Scheme 2).

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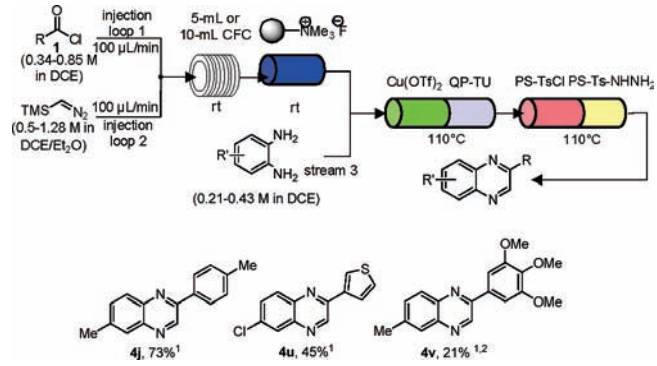
was used to remove any unreacted diamine and reduced quinoxaline derivatives. An additional column of PS-tosylhydrazine (PS-$TsNHNH_2$, 6 equiv) was placed in-line to sequester residual diazoketone. Finally, a BPR was inserted at the end of the reactor to maintain a consistent internal pressure of 8 bar. The exiting flow stream was collected and concentrated in vacuum. The initial quinoxaline formation was optimized using diazoketone **2a**. It was discovered that copper(II) triflate was the most effective catalyst for this transformation[21] especially when used in combination with DCE as the solvent. The effect of reaction temperature was also investigated, which indicated that the best conversions were obtained at an elevated temperature of 110 °C. Significantly lower conversion was obtained at reduced temperatures, and decomposition of the catalyst was observed at 120 °C. In order to have a sufficiently sized copper plug (1−0.5 mm length) between 0.5 and 0.8 equiv of the copper triflate salt was used (0.3 mmol scale); however, this cartridge could be reused multiple times without loss of activity. Finally, it was found that PS-TsCl at 110 °C gave better results than PS-TsNCO with respect to removal of unreacted ortho-substituted 1,2-diamines and the purity of the final products (**4g**, **4o**, **4r**, Scheme 3). Aliphatic, aromatic, and heteroaromatic diazoketones underwent reaction with phenylenediamines to give the quinoxalines in good purity (>95% by LC/MS and ^{1}HNMR) after only evaporation of the solvent.[22] Quinoxalines were obtained as single regioisomer or an ∼1:1 ratio of the two regioisomers when using an unsymmetrical diamine.[23] Good conversions were also obtained starting from ortho-substituted phenylene diamines; for example, quinoxaline **4o** was obtained as a crystalline material in 95% yield and excellent purity (crystal data: see Supporting Information). The continuous reaction/purification sequence took 2 h and required a total volume of 24 mL of solvent (vs batch reaction then extraction then flash chromatography: total time ∼5 h, solvent consumption: ∼100 mL). Unfortunately, not all starting substrates were compatible with this procedure; starting from the cyclopropane containing diazoketone **2b** only decomposition was observed after purification by catch and release, and starting from 3,4-diaminophenylboronic acid pinacol ester **3h** a mixture of boronic ester and boronic acid substituted quinoxalines was observed. However, in general this route provides a convenient, rapid, and improved synthesis of a variety of quinoxalines with minimal manual involvement.

Our next step was to develop a modular flow platform that would allow the integrated synthesis of quinoxalines without the isolation of the unstable diazoketones. DCE was found to be the best solvent for conducting the two reactions as a telescoped process. The flow setup consisted of three pumps and two injection loops (2 mL, PFA, 1 mm id). Sample loop 1 was loaded with a solution of acyl chloride (0.34−0.85 M in DCE) and loop 2 with a solution of $TMSCHN_2$ (0.5−1.28 M in Et_2O/DCE 1:0.6). The two channels were mixed at a T-piece and then passed through a 5 to 10 mL CFC (100 μL/min per channel, residence times 25 to 50 min) at rt. The intermediate diazoketone product stream progressed through a cartridge containing PS-fluoride before mixing at a second T-piece with a flow stream delivering a stock solution of the diamine (0.21−0.43 M) from the third pump. The combined flow path was then passed through a cartridge containing a sequential plug of $Cu(OTf)_2$ then QP-TU heated at 110 °C. A further heated cartridge (110 °C) was used for scavenger clean up and contained PS-TsCl and PS-$TsNHNH_2$. The out flow was collected, and the solvent evaporated to yield clean quinoxaline (Scheme 4). Using this setup, three quinoxalines were synthesized from the corresponding acyl chlorides. In particular crystalline quinoxaline **4u** was isolated in 45% overall yield and high purity (>97%) (vs 43% overall yield in two separate flow steps).

Scheme 4. Multistep Diazoketone/Quinoxaline Flow Synthesis[a]



[a] (1) Mixture of regioisomers (∼1:1); (2) Yield after purification by flash chromatography (crude purity >80%).

In summary, we have developed an efficient, rapid, and safe process for the synthesis of diazoketones and their further transformation into interesting heterocycles such as quinoxaline. This method allows the isolation of pure products in good yield by using in-line purification thus saving time (little off-line purification), reducing environmental impact (less solvent), and eliminating operator exposure to toxic/explosive compounds (no isolation of diazoketone and minimal handling of the phenylenediamine). Further transformations are currently being investigated, in particular thiazole and aminothiazole synthesis.

Acknowledgment. We thank Novartis Pharma AG for funding this research as well as the Royal Society (I.R.B.) and the BP 1702 Fellowship (S.V.L.).

Supporting Information Available: Experimental procedures and characterization for compounds **1d**, **1i**, **2a**−**i**, and **4a**−**v**; X-ray data of compound **4o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) With cupric acetylacetonate or rhodium octanoate dimer: only recovered diazoketone was obsereved. With rhodium acetate dimer, numerous side products were identified starting from **2a**.

(22) Crude mixture **4a**−**4d** presented an unidentified impurity which could not be removed using scavengers. Purification was carried out by a catch and release technique: see Supporting Information.

(23) Attempts to preferentially form one of the regioisomers by forming one imine as a first step by dehydration of the flow stream failed.