ORGANIC LETTERS

2006
Vol. 8, No. 23
5231−5234

Fully Automated Continuous Flow Synthesis of 4,5-Disubstituted Oxazoles

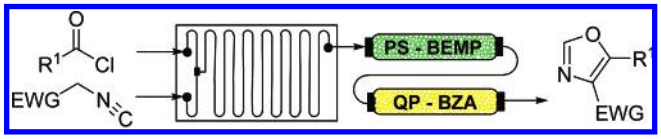
Marcus Baumann, Ian R. Baxendale, Steven V. Ley,* Christoper D. Smith, and Geoffrey K. Tranmer

Innovative Technology Center (ACS), Department of Chemistry, University of Cambridge, Cambridge, U.K., CB2 1EW

svl1000@cam.ac.uk

Received August 9, 2006

ABSTRACT



A multipurpose mesofluidic flow reactor capable of producing gram quantities of material has been developed as an automated synthesis platform for the rapid on-demand synthesis of key building blocks and small exploratory libraries. The reactor is configured to provide the maximum flexibility for screening of reaction parameters that incorporate on-chip mixing and columns of solid supported reagents to expedite the chemical syntheses.

The shift in practice away from the synthesis of large combinatorial libraries toward smaller and more focused subsets primarily devised as activity markers is significantly impacting medicinal synthesis practice.[1] These new interrogative compound arrays that expedite development cycle times through high-speed assaying and fast iterative design and synthesis loops have placed new emphasis on reliability and compound preparation times. In addition, synthetic chemists are being challenged by being expected to deliver improved properties in terms of yield, purity, and diversity of their compound collections. Consequently, new synthesis methods and flexible purification strategies are urgently required to assist in furthering these quality and productivity gains.[2]

We have been interested in the synergy provided by integrating the multistep synthetic expedience of solid-supported reagents, scavengers, and catalysts[3] with the processing capabilities of working in a fully automated flow system.[4,5] It is our belief that such an approach directly addresses many of the problems associated with existing synthesis strategies and enables the efficiency savings and turnaround times required by the chemical industry. This paper describes many of these concepts by exemplification of the synthesis of a selection of 4,5-disubstituted oxazoles using an automated flow reactor system.

Oxazoles are an important class of pharmaceutically interesting heterocycles, and consequently, many synthetic

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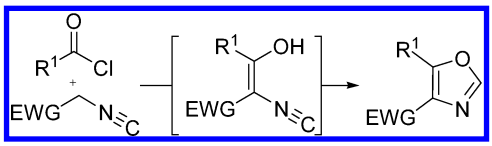
10.1021/ol061975c CCC: $33.50
Published on Web 10/11/2006

protocols have been devised to access their general structures.[6] However, far fewer methods are available for the regioselective preparation of compounds substituted at both the 4 and 5 positions.[7] As part of a medicinal chemistry project, we required an expedient method of preparing a library of such privileged substructures. We envisaged this could be achieved in flow via the addition of an alkyl isocyanoacetate to an acyl chloride with a base-catalyzed intramolecular cyclization (Scheme 1).[6,8] The chemistry

Scheme 1. 4,5-Disubstituted Oxazoles



described was successfully optimized, and a small compound collection was prepared using a bespoke small-footprint automated flow reactor (schematic presented in Supporting Information).

The Reactor: The current dual channel flow reactor is driven by two variable delivery pumps, each responsible for the independent supply of a solvent and reagent stream. The pumps are integrated with a multiposition liquid handler enabling the required starting materials and reagents to be selected and dispensed into two separate queuing ports which act as temporary reagent stores. Following aspiration into the reactor, the starting materials flow into a glass T-configured mixing chip where precise blending can be achieved. A modified hot plate heating block allows different reaction temperatures to be established and rapidly cycled to facilitate condition screening. Next, a highly flexible valve selection arrangement directs the reacting flow stream through a predetermined sequence of "reactor" cartridges containing solid-supported reagents, scavengers, or catalysts. An auxiliary heating or cooling system for these packed columns controls the reaction temperatures, easily allowing variable reaction parameters at each step of the process. The entire reaction progress is monitored in real time via a tuneable wavelength UV detection unit, permitting feedback of reaction information to earlier stages of the sequence. Aliquots of the reaction stream can also be sampled at any stage of the process and profiled through an LC-MS system. Furthermore, in-line preparative HPLC can be applied to purify intermediates or products if necessary in a fully automated fashion. Finally, the system is connected to a second liquid handler enabling sorting (fraction collection in the case of prep-HPLC) and easy collection of the various products. The entire process is completely computer controlled for repeatability, ease of use, and importantly assimilation and correlation of the information-rich experiments.

The Synthesis: Initially, we focused on using ethyl isocyanoacetate as the starting isocyanide and aimed to introduce diversity by varying the acyl chloride component. Hence, when equimolar mixtures of ethyl isocyanoacetate and 3-nitrobenzoyl chloride (10 mM in acetonitrile) were combined (variable residence time mixing chip from 274 μL to 1 mL) in a stream of acetonitrile at a flow rate of 0.2 mL/min, automated analysis of the reaction stream indicated the formation of an intermediate addition adduct. Progressing this combined reaction stream through a packed cartridge of base (PS-BEMP[9]) facilitated a rapid base-catalyzed intramolecular cyclization yielding the 4,5-disubstituted oxazole as the sole product after 20−30 min. In these initial experiments, direct automated collection and evaporation of the solvent stream yielded the oxazole products in >80% isolated yield and in 90% purity as determined by HPLC and ^{1}H NMR.

Interestingly, the overall isolated yield and kinetics of the transformation were found to be dependent on the specific period of mixing prior to contact with the immobilized base. The reason for this is not entirely evident from the implied mechanism, and repeated attempts to isolate the precyclization intermediate have proven unsuccessful. However, in situ NMR analysis of a reaction performed in the reactor using d_3-MeCN prior to base contact indicated formation of an adduct where acylation had occurred exclusively at the methylene site. Such an intermediate would then undergo a very facile base-catalyzed formal 5-enol-*endo*-dig cyclization. This is in contrast to the work carried out by Huang *et al.*[8a] who reported the chemoselective addition of the same isocyanide functional group directly to the acid chloride furnishing the intermediate α-ketoimidoyl chlorides (albeit under basic conditions) which spontaneously cyclized to the alternative 2,5-disubstituted oxazoles. We were unable to prepare such intermediates or the correspondingly derived products despite extensive screening of the reaction conditions even in the presence of added base (K_2CO_3, DBU, BEMP, Et_3N); in all our reactions, only the 4,5-disubstituted oxazole was detected.

For additional comparative purposes, we also ran the same reactions as a standard batch process at ambient temperature as well as at 40 and 70 °C in both MeCN and DCM (sealed tubes). We found such conditions gave comparatively poor conversions (50−70%) and much lower purities (<70%) for both solvents and all temperatures, even after a 10 h reaction. At present, we are unable to conclusively identify any reason for the enhanced conversions or kinetics attained in the flow

(6) For a review of classical methods of preparing oxazoles, see: (a) Turchi, I. J. *Oxazoles in Heterocyclic Compounds*;Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45. (b) Hartner, F. W. *Oxazoles in Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 6, pp 262 and references cited therein.

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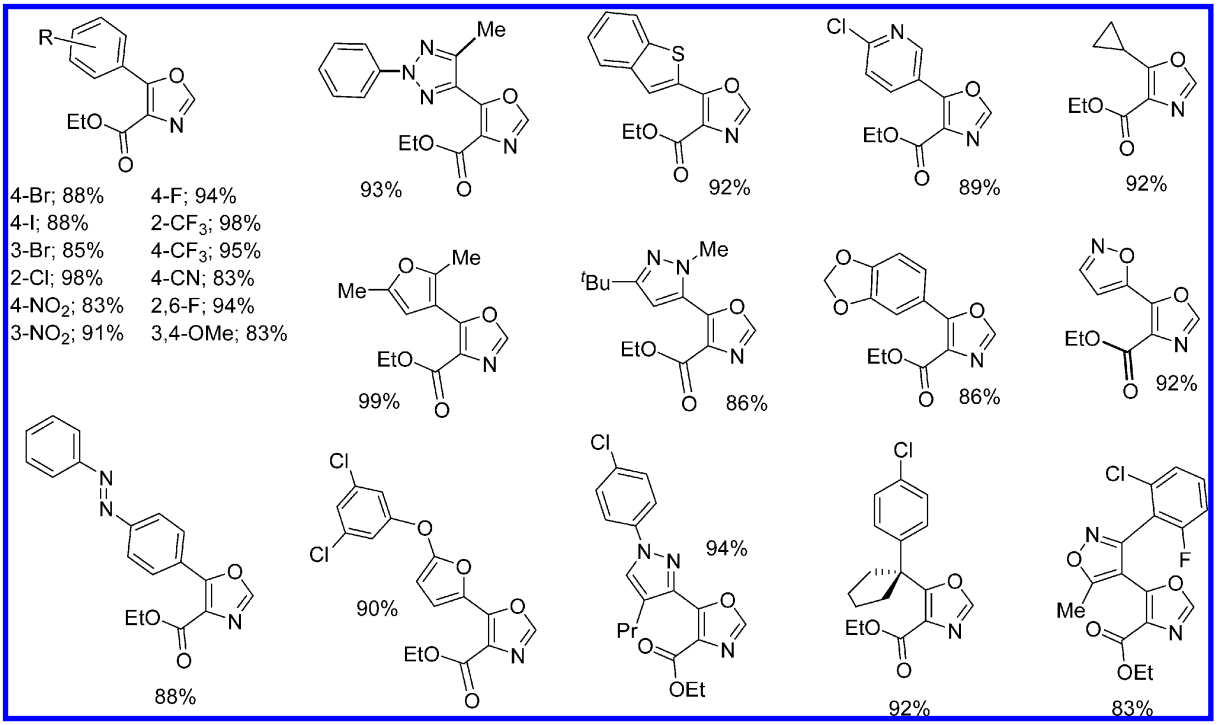
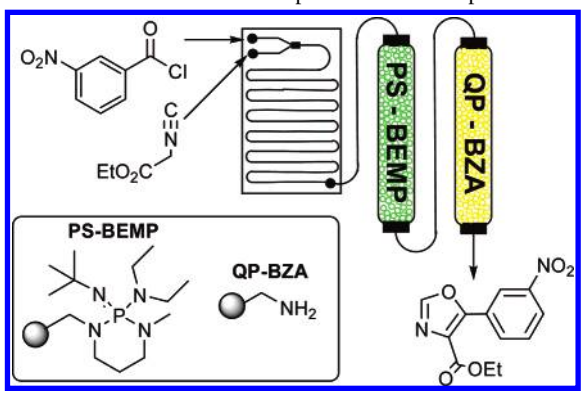


Figure 1. Oxazoles prepared with isolated yields.

reactor, and aspects of the mixing and possible catalysis by the reactor material are under investigation.[10] A comprehensive automated screening cycle of the reaction conditions was programmed to profile the reaction in terms of optimum solvent, concentration, stoichiometry, residence time, and reaction temperatures. This led to the rapid identification of a modified set of reaction parameters incorporating an additional nucleophilic scavenger step to enhance the final product purity (Scheme 2). The high-loading Quadrapure

Scheme 2. Example Reaction Setup



resin, QP-BZA, was found to be the most effective reagent for this clean-up sequence.[11]

Using the general conditions as shown in Scheme 2, we were able to prepare rapidly, as required, a diverse set of 25 different oxazoles in yields between 83 and 99%, enabling quantities of up to 10 g of material to be prepared (Figure 1). In the case of the larger-scale preparations (5−10 g), larger-dimensioned columns (17.5 × 45 mm id; ∼15 g) of the PS-BEMP could be easily integrated into the configuration. Alternatively for smaller-scale reactions (≤100 mg), the same PS-BEMP column (6 × 30 mm id; ∼0.3 g) could be effectively used for 3 successive oxazole preparations without cross contamination of the different products.

It was also shown that it was feasible to recycle the PS-BEMP-containing columns between runs. This was achieved very simply by eluting the column with a stream of solution-phase BEMP (1.15 equiv in relation to the PS-BEMP) in hexane (for solubility) followed by washing with MeCN. Such a process was easily automated as part of the reaction sequence, and the material regenerated could be successfully used in the subsequent run, as exemplified by up to 20 reaction/recycle steps. It was also shown that dilute solutions of NaOMe or ^{t}BuOK in MeOH could also be used; however, overall, this was shown to be a less-effective cleaning process because of the extended timeframes involved.

In an attempt to extend the versatility of the synthesis, we next investigated the replacement of the electron-withdrawing ester group with both a tosyl and a phosphonate

(9) PS-BEMP refers to 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene 2% DVB.

(10) The observation of differences in kinetics could be a consequence of local concentration effects or polarity changes in the environment of the polymeric species.

(11) Quadrapure BZA is a primary amine-functionalized resin with an effective loading of ∼5.5 mmol/g. Available from Reaxa Ltd. (Blackley, Manchester, U.K.).

moiety. As expected, the tosyl unit proved a very reliable substituent giving the modified sulfonates (nine examples, Figure 2) in excellent yields (81−94%). The same was true

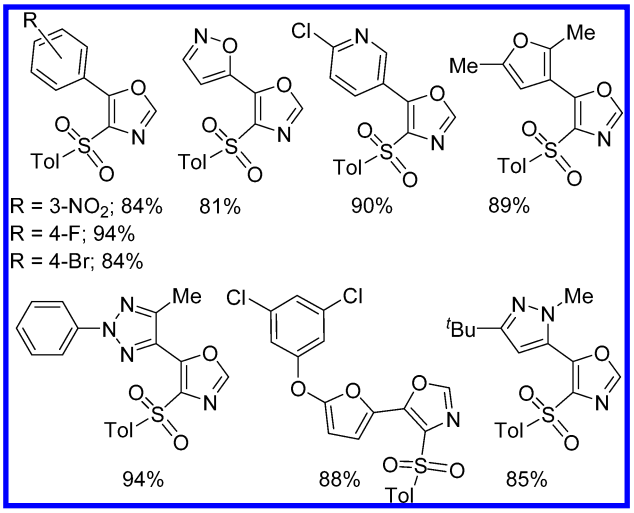


Figure 2. Oxazoles prepared with isolated yields.

for the corresponding phosphonates (Figure 2); however, a slight modification of the previous protocol was required (method A). To attain high yields (>89%) and purities (>98%), it was found to be necessary to reduce the flow rates and to heat the solution as it passed through the PS-BEMP-containing column. To achieve this, an R-4 reactor heater[12] was used which allowed a constant temperature of 85 °C to be maintained, the optimum for these reactions. This lower reactivity of the phosphonate is probably an effect of the additional steric hindrance associated with the larger phosphonate termini resulting in the slower reaction kinetics.

Alternatively, a different reaction configuration (method B) could be applied involving the simultaneous addition of an equivalent of solution-phase BEMP to the phosphonate starting material feed (prepared in THF). Configuring the immobilized reagent columns to include a preliminary PS−sulfonic acid cartridge for removal of the solution-phase BEMP prior to flowing into the original PS−BEMP and Quadrapure BZA reagent stacks provided the desired products in excellent yields and purities (Figure 3).

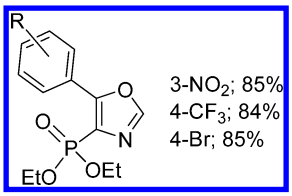


Figure 3. Oxazoles prepared with isolated yields.

The use and sequencing of the PS−SO_3H was critical, although an excess of the BEMP (5 equiv) could be used to force the reaction toward the cyclized oxazole product (~80% conversion); separation of this product from the BEMP residues was not possible. However, separation after the initial alkylation step was achieved quantitatively using the column version of the reaction.

In conclusion, this work describes the successful continuous flow synthesis of a selection of 4,5-disubstituted oxazoles in good yields and high purities. The flow reactor configuration and its ready modular capability provide an excellent platform for synthesis intensification and for the future practice of compound assembly.

Acknowledgment. We gratefully acknowledge financial support from the RS Wolfson Fellowship (to I.R.B. and S.V.L.), Syngenta for financial support (C.D.S.), the Natural Sciences and Engineering Research Council of Canada for a Postdoctoral Fellowship (to G.K.T.), Erasmus Council for support (to M.B.) and the BP endowment, and the Novartis Research Fellowship (to S.V.L.). We also wish to thank J. E. Davis for determining the crystal structures of all compounds presented in the Supporting Information and the EPSRC for a financial contribution toward the purchase of the diffractometer. All persons involved in the preparation of this paper are affiliated with the Department of Chemistry, University of Cambridge, Cambridge, U.K., CB2 1EW.

Supporting Information Available: General experimental procedures and characterization data for all new compounds including associated X-ray crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A Vapourtec R-4 flow reactor heater is available from Vapourtec Ltd., Place farm, Ingham, Suffolk, IP31 1NQ, U.K. (www.vapourtec.com).