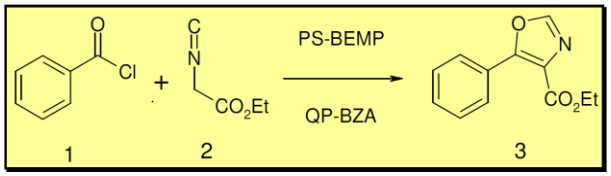
Application Note 10:

Heterocycle Formation in Flow: 4,5-Disubstituted Oxazoles

Produced by Vapourtec

Abstract

This Application Note illustrates how the R-2 pump/injector and R-4 flow reactor modules can be used to prepare oxazoles utilizing a combination of a tubing reactor and polymer-assisted continuous flow-through (PACT) reactors.[1] Reagents are introduced into the flow stream via sample loops attached to the injection valves.



In this example, benzoyl chloride 1 is mixed with ethyl isocyanoacetate 2 and incubated at 50 °C in a tubing reactor before elution through a PS-BEMP PACT reactor, also at 50 °C, to promote 4,5-oxazole formation. The outflow from the reactor passes through a Quadrapure BZA PACT scavenger column to effect in-line purification before the 4,5-disubstituted oxazole product 3 is collected with high purity using an automated fraction collector.

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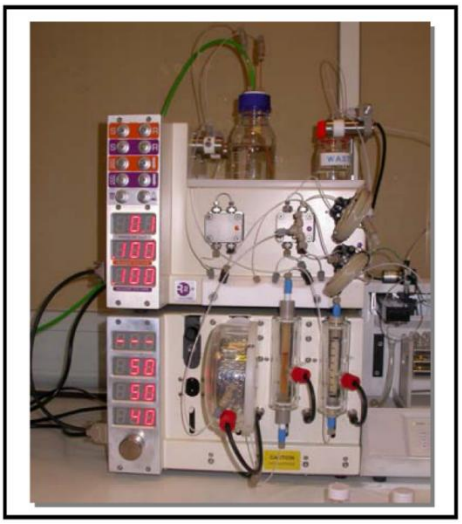
Setup



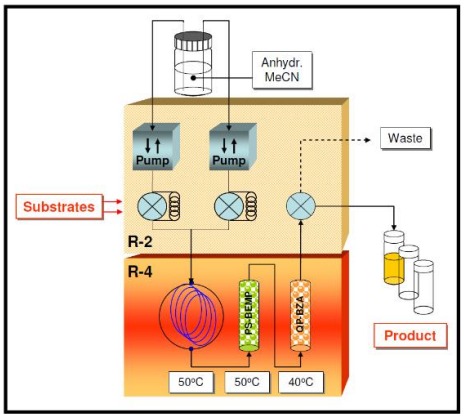


Figure 1. Actual and schematic flow reactor setup incorporating an in-line tubing reactor, a PACT reactor, and a PACT scavenger column.

The flow reactor was configured as shown in Figure 1. Each flow channel independently delivers anhydrous MeCN from a single solvent reservoir maintained under a positive nitrogen pressure (< 1 bar) to the two injection valves. Each injection valve is fitted with a 5 mL sample loop. The valves are connected by two identical lengths of PTFE tubing to a PEEK mixing T-piece, and then to a 1.0 mL tubing reactor (1.0 mm id PTFE). The tubing reactor is first connected to a PS-BEMP[2] PACT reactor (15 cm x 6.6 mm id), then to a QP-BZA[3] PACT scavenger (10 cm x 6.6 mm id), and finally to a fraction collector loaded with 4 mL collection vials.

Method

A PS-BEMP PACT reactor was slurry packed[2] with PS-BEMP (2.5 g x 2.2 mmol/g; 5.5 mmol) in MeCN, and a QP-BZA PACT scavenger was dry packed[3] with Quadrapure™ BZA (1.5 g x ~1.5 mmol/g; ~2.25 mmol) prior to elution with MeCN in *situ*. The flow reactor was assembled as described above and flushed at 1.0 mL/min with anhydrous MeCN for 10 min.

The flow rates of each channel were then adjusted to 0.10 mL/min, and the tubing reactor was equilibrated to 50 °C, the PS-BEMP PACT reactor to 50 °C, and the QP-BZA PACT scavenger to 40 °C. The sample loops were charged with a solution of benzoyl chloride 1 (4.0 mL x 0.75M; 3.0 mmol) and a solution of ethyl isocyanoacetate 2 (4.0 mL x 0.75M; 3.0 mmol) in MeCN respectively, and then simultaneously switched in-line. The fraction collector[4] was started and programmed to collect 6 x 4.0 mL fractions (experiment runtime = 2 h).

The fractions were individually analyzed by UV-HPLC, taking a 30 µL aliquot from each and diluting these with MeCN (0.70 mL) containing toluene (15 µL) as an internal reference standard (Rt = 2.98 min). The results are represented in Figure 2. Although it is evident that some dispersion has occurred as the reaction plug passes through the flow reactors, complete conversion to the desired oxazole product 3 was observed across all the fractions.

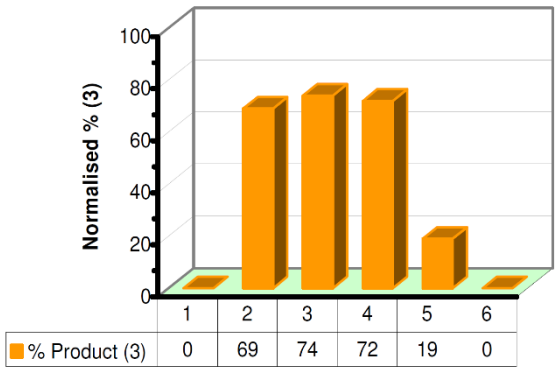


Figure 2. Graphical representation of plug dispersion for an 8 mL reaction plug in a homogeneous flowthrough system after passing through three different types of flow-through reactor. Each fraction is 4 mL. Normalization is AUC relative to a constant concentration of toluene in the LC aliquot diluent.

Fractions 2 through 5 were combined and the solvent removed in vacuo to afford the desired 4,5-oxazole 3 as a pale brown oil (639 mg; 98%).

LC-MS (ESI +ve): (*m/z* 218.0 (MH+)); R_t = 2.76 min, 95%.

^{1}H NMR (400 MHz, $CDCL_3$): δ_H 8.10 (m, 2H), 8.92 (s, 1H), 7.48 (m, 3H), 4.42 (q, J = 7, 2H), 1.45 (t, J = 7, 3H).

^{13}C NMR (100 MHz, CDCL3): δ_C 162.3 (C), 155.8 (C), 130.8 (CH), 128.8 (CH), 128.8 (CH), 127.1 (C), 127.0 (C), 61.7 (CH_2), 14.6 (CH_3).

IR (ATR): 2982 (w), 1717 (s), 1585 (w), 1567 (w), 1523 (w), 1493 (m), 1373 (m), 1303 (m), 1224 (s), 1181 (s), 1083 (s), 835 (m), 763 (s), 691 (s) cm^{-1}.

The flow experiment was repeated using the same set-up, and the same pre-prepared stock solutions; this time doubling the flow to a combined rate of 0.40 mL/min. Again the output was collected over 6 x 4 mL fractions (experiment time = 1 h). Fractions 2 through 5 were combined and the solvent was removed in vacuo to afford the 4,5-oxazole 3 as a brown oil (645 mg, 99%). However, the purity at this higher flowrate was shown to be slightly lower (approximately 85% by ^{1}H NMR) than that obtained previously, with the major contaminant being derived from the isonitrile 2.

Conclusions

- Oxazoles are a chemotype that is well represented in drug-like molecules. The integrated synthesis described herein demonstrates how a combination of a tubing reactor ('mixer'), PACT reactor and PACT scavenger can be readily accommodated by the R-2/R-4 flow reactor platform to deliver oxazoles in high intrinsic purities by a multi-step process utilizing a single flow-through platform.
- The R-2/R-4 may be used in combination with a simple timed fraction collector to perform plug flow synthesis such that the product is collected in a minimal volume of system solvent. In this example, a total sample volume of 8 mL is isolated as a 16 mL plug after passing through three different flow reactors connected in series.

Notes

1. **Fully Automated Continuous Flow Synthesis of 4,5-Disubstituted Oxazoles**. Baumann, M., Baxendale, I. R., Smith, C. D., Tranmer, G. K., Org. Lett., 2006, 8(23), 5231-5234.
2. The PS-BEMP (Fluka: 20026 ~2.2 mmol/g) beaded polystyrene used in this example swells very little upon exposure to MeCN. However, the resin is somewhat 'sticky' and therefore it is difficult to load the 6.6 mm id OmniFit® column unless the resin is first suspended in MeCN and manipulated as a suspension.
3. QuadraPure™ BZA (Aldrich: 668591, ~1.5 mmol/g) is a highly cross-linked microporous resin, that swells very little upon exposure to MeCN. As such it is straightforward to pour the resin beads into the OmniFit® column and to then pump MeCN through the column from the bottom to both wash and solvate the resin. This latter operation may be performed with both fixed end-fittings in place.
4. A Gilson 203B fraction collector was used fitted with a code 23 rack filled with 4 mL OmniChrom™ sample vials. The instrument was programmed to run automatically and independently of the flow reactor in timed collection mode.