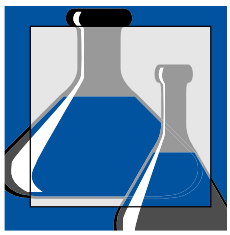
APPLICATION NOTE

ARGONAUT TECHNOLOGIES

Solution-Phase Synthesis of Oxime Ethers and Product Isolation by Liquid-Liquid Extraction using the Quest™ 210



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The Quest™ 210 was successfully used to alkylate the sodium salt of acetophenone oxime with a series of alkylating agents (Figure 1). Although highly volatile alkylating agents were used, there was no sign of cross-contamination from vessel-to-vessel. In addition, parallel *in situ* liquid-liquid extraction was performed on the Quest to remove excess reagents and salts, followed by addition of solid drying agent to the reaction vessels and on-line filtration of reaction mixtures.

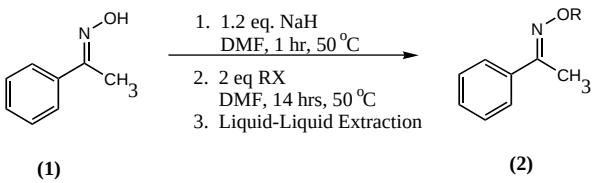
INTRODUCTION

Solution-Phase parallel synthesis has become an increasingly important complement to solid-phase methods in organic compound discovery.[1] The objective of this study was to demonstrate the capability of the Quest 210 to:

- Facilitate removal of mineral oil from sodium hydride *via* washing of the reagent with hexane.
- Provide an inert environment to facilitate the use of moisture sensitive reagents.
- Perform syntheses using a highly volatile reagent, without vessel-to-vessel cross-contamination.
- Perform on-line liquid-liquid extraction and solution drying/filtration.

Reactions were set up in parallel using three different alkylating agents (MeI, EtI, AllylBr). To check for cross-contamination and reproducibility, the three alkylating agents and control reactions without alkylating agent were alternated over the bank of ten reaction vessels.

Figure 1. Solution Phase Synthesis of Oxime Ethers



(1) (2)

EXPERIMENTAL

In a typical experiment, sodium hydride (65% in mineral oil, 0.48 mmol) was added manually as a solid to ten 5 mL Teflon reaction vessels on the Quest 210. Using the Solvent Wash Delivery system, hexane (3 mL) was added to each vessel. The mixture was agitated for 5 minutes to solubilize the mineral oil. Once the agitation was stopped, the hexane/mineral oil mixture was drained into the glass waste rack. A total of three hexane washes were performed allowing the recovery of pure sodium hydride in the reaction vessels. Acetophenone oxime Figure 1, (1) (2 mL, 0.2 M in DMF, 0.4 mmol) was added manually *via* syringe to the reaction vessels. The reaction mixture was agitated for 1 hour at 50 ˚C to form the oxime sodium salt. The reaction mixture was cooled to room temperature, the upper manifold was closed (the Teflon membrane sealing the reaction vessels off from one another was pressurized)[2] and the appropriate alkylating agent (0.80 mmol) was added manually *via* syringe. With the manifold closed the reaction mixture was agitated on the Quest 210 for 14 hours at 50 ˚C. The reaction was allowed to cool to room temperature and excess reagents and salts were removed by liquid-liquid extraction.

Saturated aqueous NH_4Cl (1 mL) and diethyl ether (2.5 mL) were added to each reaction vessel and the biphasic solution was agitated for 5 minutes. Following agitation, the two layers were allowed to separate and the lower layer was drained into the glass waste rack. Four more extractions, another saturated NH_4Cl, two H_2O, and one brine extraction, were performed as described above. Solid magnesium sulfate was added to each reaction vessel *via* the addition ports located on the upper manifold and the mixture agitated for 1 hour. After filtration into 20 mL scintillation vials, the oxime ether products were analyzed by GC to assess the product purities, and check for possible cross-contamination between reaction vessels (Table 1) .

Table 1. Analysis of Oxime Ether Products

Alkylating Agent (B.P./˚C)	% Product by GC	% Starting Material by GC	% Cross-Contamination
MeI (41-43)	98.1	0.0	0
EtI (69-70)	99.1	0.0	0
AllylBr (71-73)	95.8	4.2	0
MeI (41-43)	99.2	0.0	0
EtI (69-70)	98.9	1.1	0
AllylBr (71-73)	97.6	2.4	0
MeI (41-43)	91.0	6.4	0
None	N/A	99.7	0
MeI (41-43)	98.7	0.0	0
None	N/A	100.0	0

Results

GC analysis indicated excellent conversion of the acetophenone oxime to the oxime ethers and in very high purity (Table 1).[3] To check for cross-contamination and reproducibility, the three alkylating agents were alternated in the first six reaction vessels and methyl iodide (MeI, b.p.= 42 ˚C), the most volatile alkylating agent, and control reactions were alternated in the last four reaction vessels. By using methyl iodide above its boiling point (reaction temperature = 50 ˚C) we were able to use the GC data to evaluate for cross-contamination between reaction vessels. GC analyses indicated that no cross-contamination from vessel-to-vessel occurred during the synthesis and verifies the closed nature of the Quest's manifold system.

Summary

- The Quest 210 was used to efficiently synthesize various oxime ethers by reacting acetophenone oxime sodium salt with different alkylating agents.
- The Quest 210 provided an inert environment which facilitated the use of moisture sensitive sodium hydride.
- The Quest was used in place of a series of separatory funnels since liquid-liquid extraction was performed directly in the reaction vessels.
- Oxime ether products were isolated in very high purity (>91%).
- A highly volatile reagent (MeI) was used and heated above its boiling point without contaminating other reaction vessels.
- Lack of cross-contamination from vessel-to-vessel verifies that the Quest's sealed manifold prevents reagents in one reaction vessel from crossing over and entering into another reaction vessel on the same manifold.

References and Notes

1. For examples of parallel solution-phase chemistry see: (a) Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* 1997, *38*, 513. (b) Kaldor, S.W.; Siegel, M.G.; Fritz,J.E.; Dressman, B.A.; Hahn, P.J. *Tetrahedron Lett.* 1996, *37*, 7193.
2. During a previous experiment, the alkylating agents were added with the manifold open, thus under a nitrogen sweep to maintain an inert environment. Upon addition of the reagents, the manifold was closed and remained closed until the work-up. GC data showed that in this case, a small amount (<0.8%) of cross-contamination occured in vicinal reaction vessels using methyl iodide as alkylating agent.
3. GC Method: 125 ºC (3 min), 20 ºC/min to 200 ºC, hold 4 min.

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