Registry No. acetaldehyde diethyl acetal, 105-57-7; ethyl vinyl ether, 109-92-2; ethoxyethyl cation, 87676-39-9; deuterium, 7782-39-0; acetaldehyde-2,2,2-d_3 diethyl acetal, 92144-49-5; acetaldehyde-1-d_1 diethyl acetal, 92184-46-8; ethyl vinyl-2,2-d_2 ether, 92144-50-8; ethyl vinyl-1-d_1 ether, 75213-98-8; methyl-d_3 iodide, 865-50-9; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7.

Supplementary Material Available: Tables of rate constants (4 pages). Ordering information is given on any current masthead page.

Robotic Orchestration of Organic Reactions: Yield Optimization via an Automated System with Operator-Specified Reaction Sequences[1]

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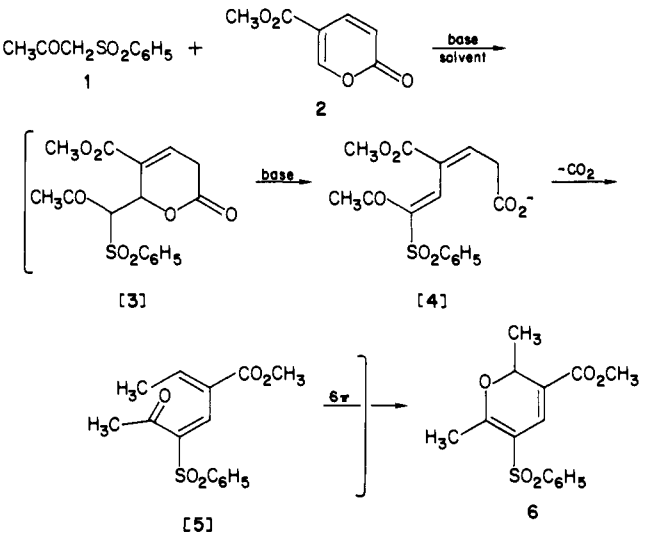
Abstract: A microcomputer-driven reaction protocol has been developed that allows a researcher to initiate a series of experiments which are performed automatically by a robot. The current system is capable of carrying out as many as nine simultaneous, operator-specified reactions complete with automated workup (aliquot quenching, extraction, and plug filtration) combined with automated HPLC yield analysis. Automated reactor cleaning allows multiple runs to be made without operator intervention. Application of this system to the yield optimization of a highly functionalized vinyl sulfone is described.

In our synthetic program we required access to substantial quantities of the trifunctional vinyl sulfone **6**.[2] Initial investigations revealed that this compound could be prepared in a one-pot sequence from the readily available keto-sulfone **1** and methyl coumalate **2**. The reaction apparently involves the base-catalyzed 1,6-addition[3] of the keto-sulfone anion to **2** thereby generating intermediate [**3**], which undergoes proton transfer, β-elimination (to produce [**4**]), decarboxylation (to yield [**5**]), and finally cyclization[4] to afford the desired adduct **6**. Unfortunately this reaction appears to be highly sensitive to the exact nature of the basic catalyst as well as the solvent employed. Initial product yields varied widely between 5 and 30%. It appeared that a detailed experimental study would be required to delineate optimal reaction conditions for this synthesis.

Production of a desired target molecule, whether a natural product, drug, or industrial chemical, requires a substantial experimental effort on the part of the practicing chemist. The problem presented by an inefficient chemical reaction is a familiar one in the organic laboratory; a choice must be made as to whether to "push ahead" with an inefficient synthesis (where additional time and effort is required in "going back to prepare more starting material") or to expend the resources necessary to optimize the offending reaction step. It seems clear that *given sufficient resources*, the most practical solution would be to immediately optimize each "bad" reaction as it is encountered along a synthetic sequence.

Computer-driven technology already has had a profound impact upon organic synthesis on the macro (2000 gallon) scale.[5] A

Scheme I



number of pharmaceutical companies have recently implemented extensive computer-controlled modifications in their pilot plants. Synthesis automation on a more moderate scale (1–12 L) has been pioneered largely by French researchers.[6–9] Early efforts by these groups have dealt with automation of physical processes (material transfer, temperature, and pH control),[6,7] and more recently some of the control functions in their systems have been done with a microprocessor-based system.[8,9]

Single-reactor, closed-loop reaction systems have been developed on a scale (50–100 mL) which begins to approach that needed

(1) Laboratory Automation 1: Syntheses via Vinyl Sulfones. 14. For the previous paper in the latter series, see: P. R. Hamann, J. E. Toth, P. L. Fuchs, *J. Org. Chem.* in press.

(2) M. H. Nantz, unpublished results.

(3) While the 1,6-addition of "soft" nucleophiles to methyl coumalate is well-known,[3a–c] the synthesis of **6** apparently involves the first example of the formation of a carbon–carbon bond by this process. (a) L. Tsai, J. V. Silverton, and H. T. Linghi, *J. Org. Chem.* **43**, 4415 (1978). (b) N. P. Shusherina, V. L. Lapteva, and O. V. Khrusheheva, *Zh. Org. Khim., Engl. Transl.*, **13**, 1790 (1977). (c) K. Yamada, *Bull. Chem. Soc. Jpn.*, **35**, 1329 (1962).

(4) (a) R. G. Salomon, J. R. Burns, and W. J. Dominic, *J. Org. Chem.*, **41**, 2918 (1976). (b) A. deGroot, B. J. M. Jansen, *Tetrahedron Lett.*, 3407 (1975). (c) T. A. Goslink, *J. Org. Chem.*, **39**, 1942 (1974). (d) E. Marvell, G. Caple, T. A. Goslink, G. Zimmer, *J. Am. Chem. Soc.*, **88**, 619 (1966), and references cited therein.

(5) Pilot plant automation in the petroleum industry continues to be a rapidly evolving area. See preprints of "Division of Petroleum Chemistry, American Chemical Society" Vol. 24, abstracts of papers for the August 1983 Washington D.C. ACS meeting, No. 4.

(6) M. Legrand and A. Foucard, *J. Chem. Educ.*, **12**, 767 (1978).

(7) A. Delacroix, J. N. Veltz, and A. LeBerre, *Bull. Soc. Chem. Fr.*, **2**, 481 (1978).

(8) G. Lonchambon, A. Delacroix, J. Petit, and P. Lecomte, *Bull. Soc. Chem. Fr.*, *1*, 71 (1981).

(9) C. Porte, R. Borrin, S. Bouma, and A. Delacroix, *Bull. Soc. Chem. Fr.*, *1*, 90 (1982).

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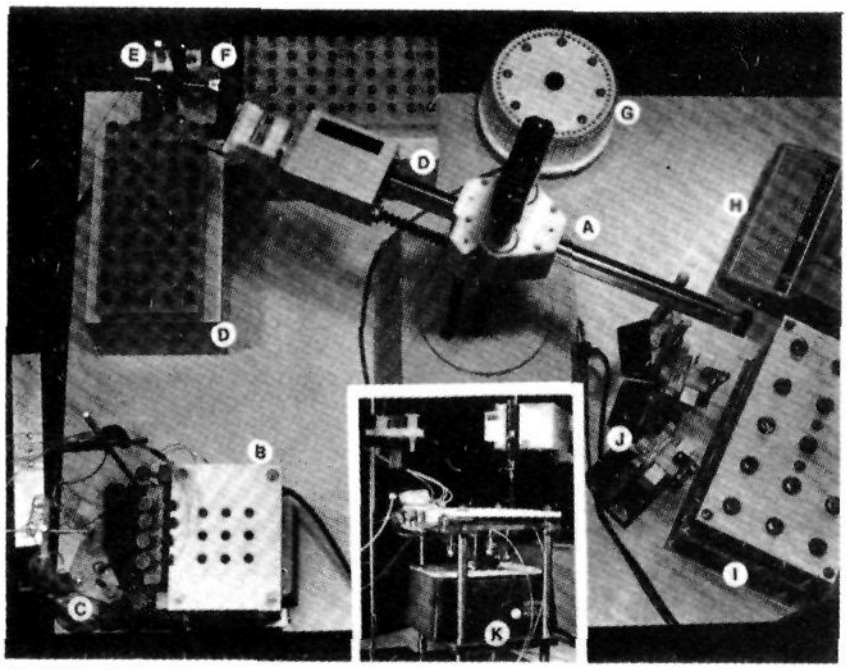


A: ROBOTIC ARM

B: REACTOR STATION: Nine reactor capacity; ambient temperature; inert atmosphere; variable speed stirrer.

C: MLS REMOTE DISPENSER: Solvent/gas/vacuum source for the Reactor Station.

D: ALIQUOT ARCHIVE STATION: Secured, septa-capped test tubes (100 total) for aliquot storage.

E: WORKUP STATION: Use in performing two-phase workup *procedures on reaction aliquots.*

F: SYRINGE AND NEEDLE WASH STATION

G: TURNTABLE: For plug filtering aliquots into the HPLC Injector collection tube prior to analysis.

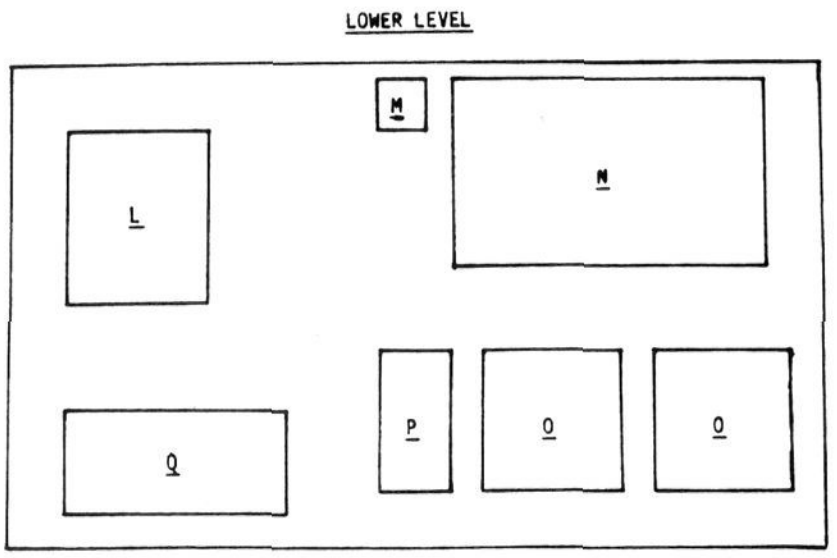
H: HP3390A REPORTING INTEGRATOR: Controlled by the Analytical Instrument Interface.

I: REAGENT STATION: The reagent source for the system. During operation, the pressure is equalized to ambient via a nitrogen bubbler system (not shown) to ensure accurate transfers.

J: HAND PARKING STATIONS

K: Front view of the reactor station and the syringe hand in use.

Figure 1.



L: VALVE ASSEMBLY: Solvent selection and channeling to various stations.

M: AUTO-INJECTOR VALVE: Controlled by the Analytical Instrument Interface.

N: WATERS HPLC: Model 440 UV DETECTOR; isocratic solvent system; Model 6000A pump; 5 μ, 15cm x 4.6mm Si column.

O: POWER AND EVENT CONTROLLER: Provides valve switching; controls automatic aspirators; provides switch closure inputs and A/D inputs.

P: ANALYTICAL INSTRUMENT INTERFACE: Allows crude "peak integration" for input to the robot; controls auto-injector and H.P. integrator.

Q: MASTER LABORATORY STATION (MLS): Automated triple syringe drive. Used for solvent dispensing, aspiration of samples into auto-injector sample loop and repriming the HPLC pump if necessary.

Figure 2.

for practical optimization work;[10] moreover, the value of the robot in the chemical laboratory has recently been demonstrated for repetitive analytical procedures.[11]

We wish to report our preliminary experiments pursuant to the next logical step in the evolution of laboratory automation: *the development of a microcomputer-driven reaction protocol that allows a researcher to initiate a series of experiments which are performed automatically by a robot.*

Our modular system presently features six major bench-top components[12-14] (see Figures 1 and 2). The central location is occupied by a microprocessor-controlled Zymark[15] robot with three remote hands. Around the periphery of the robot are a reagent station, a reactor station, an aliquot archive area, a workup station, and an analysis station. The reagent station holds up to fifteen 30–100 mL septum-capped bottles containing standardized reagent solutions and serves as the "stockroom" for the system. The reaction station holds up to nine magnetically stirred reactors. The reactors are thick-walled 5-mL Wheaton vials[16] with conical interiors, fitted with triangular stir bars; these vials bear a threaded septum holder and have been modified by attaching an exit port to a hole drilled from the side into the bottom of the conical depression. The reactor area is also equipped with outlets from the master laboratory station[12,15] for the introduction of solvents, vacuum, and gasses with the aid of the general purpose robot hand. The archive storage area is a pair of storage racks which accommodate a total of 100 septum-capped test tubes. The workup station consists of a vortex mixer[15] equipped with inlet tubes for aqueous and organic solvents as well as an eductor tube for vacuum removal of the aliquot residues. Stationed nearby is a syringe and needle cleaner. The analysis station includes a motorized base[15] which bears a custom machined turntable capable of holding up to 140 disposable pipets; this apparatus permits "plug filtration chromatography" of each of the reaction aliquots prior to HPLC analysis. Below the outlet of the plug filtration apparatus is a self-cleaning receptacle which serves as the inlet for the automatic HPLC injector.[12]

Application of the robotic system for the optimization of the synthesis of vinyl sulfone **6** was accomplished as follows: Initially, the synthesis of **6** was screened with eight different bases using acetonitrile as a solvent (see Table I). From these initial results, two of the bases were selected for further evaluation in four different solvents (see Figure 3).[17]

The experimental procedure involved preparing and storing standard ethereal solutions of both β-keto-sulfone **1** and methyl coumalate **2** (containing a known amount of diphenyl sulfone as

(10) (a) H. Winicov, J. Schainbaum, J. Buckley, G. Longino, J. Hill, and C. E. Berkoff, *Anal. Chim. Acta*, **103**, 469 (1978). (b) D. F. Chodosh, F. E. Wdzieckowski, J. Schainbaum, and C. E. Berkoff, *J. Autom. Chem.*, **5**, 99 (1983); (c) *ibid.*, **5**, 103 (1983).

(11) (a) R. Dessy, *Anal. Chem.*, **55**, 1100A, (1983); (b) *ibid.*, **55**, 1232A (1983).

(12) Ancillary equipment (shown in Figure 2) essential to the operation of the optimization system is located under the laboratory bench and includes the following: two power and event controllers,[15] a master laboratory station[15] (a three-syringe liquid delivery system), an HPLC instrument interface,[15] an analytical HPLC, as well as the necessary electrical/gas/solvent/vacuum lines.[14]

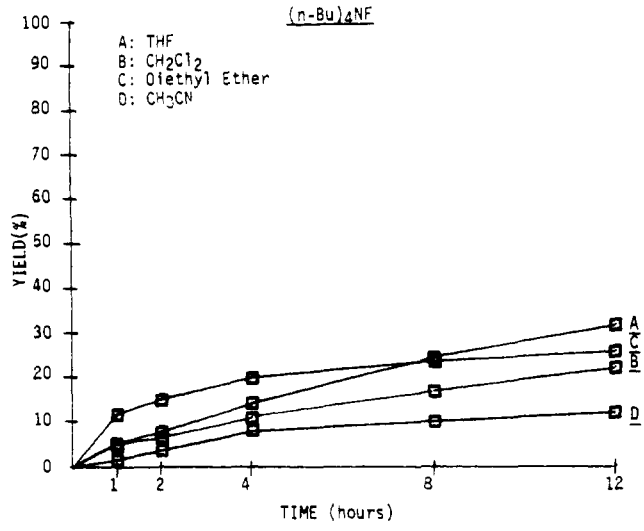
(13) Remote services[14] not shown in Figures 1 and 2 include the Zymate system controller;[15] solvent lines running to standing stills, HPLC solvent reservoir, computer-actuated water aspirators; nitrogen lines emanating from a computer-controlled pneumatic mainfold; and a line printer.[15]

(14) A detailed mechanical/electrical description of the various pieces of equipment constructed for this project as well as a schematic of the plumbing diagram will be described in a subsequent paper.

(15) Zymark Corporation, Hopkinton, MA 01748.

(16) These vials are available from Wheaton Scientific, Millville NJ 08332.

(17) This procedure should be more accurately categorized as an initial Plackett-Burman [*Brometrika*, **33**, 305 (1946)] prescreen followed by a non-factorial partial optimization. In the near future a SIMPLEX algorithm [Review: S. N. Deming, S. L. Morgan, *Anal. Chem.*, **45**, 278A (1973)] will be added to the system so that the optimization process may be "computer-directed".



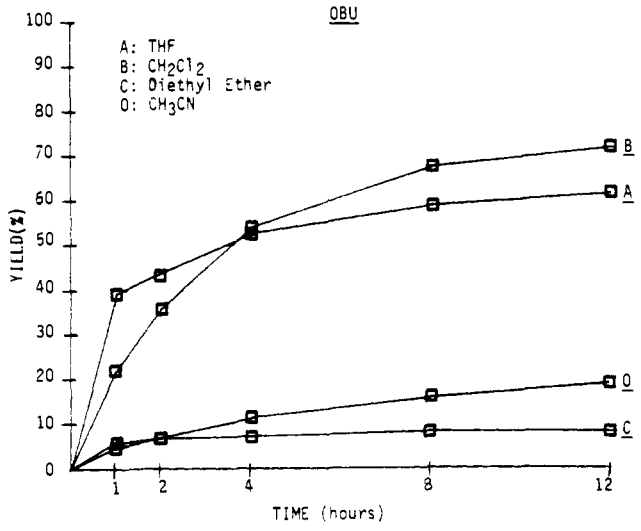


Figure 3.

Table I. Initial Base Screen[a]

base	% yield	base	% yield
(n-Bu)$_4$NF	12	TMEDA	9
DBU	23	proton sponge[b]	6
dimethylaniline	<1	diisopropylethylamine	8
triethylamine	11	DMAP	4

[a] (1) All reactions were carried out in acetonitrile. (2) Aliquots were taken at 1, 2, 4, 8, and 12 h. Yields given are after 12 h. (3) Some starting material is remaining after 12 h. [b] 1,8-Bis(dimethylamino)-naphthalene.

an internal standard) in the reagent station. The system, using the syringe hand, delivered 0.10-mmol aliquots of each of the two reactants to each of four vials in the reactor station. The stirrer was automatically started, and vacuum was applied successively to each of the four reactors to remove the ether (ca. 10 min required). The system then added 3.0 mL of a different solvent (THF, ether, CH_3CN, and CH_2Cl_2) to each of the reactors via the MLS-remote dispenser[15] and the general purpose hand. A catalytic amount (10 mol %) of base was added to a reactor via the syringe hand to initiate the reaction. The starting times for subsequent reactions were offset by 6-min intervals to facilitate periodic sampling. System timers were set so that aliquots were taken from each reactor after 1.0, 2.0, 4.0, 8.0, and 12.0 hr. At the specified times the syringe hand removed a 0.3-mL aliquot and added it to the vortex mixer which had been automatically prefilled with a 1.0-mL portion of ether and a 2.5-mL portion of dilute aqueous HCl (to quench the reaction). The vortex mixer was run for 20 s, and the phases were allowed to separate while the syringe and needle were automatically being washed. The syringe hand then removed 0.7 mL of the ether phase and deposited it through a septum into a 9-mm test tube in the archive storage area.[18] The syringe and needle were again cleaned by insertion into the "syringe-washer" which allowed a series of water and THF washes. Aliquots from the other three reactors were processed identically. When HPLC analysis time was available, the syringe hand transferred a portion of each aliquot to the turntable (which houses disposable pipets charged with ca. 1-cm plugs of silica gel) in order to remove polar reaction impurities and dry the sample. The reaction aliquot eluted from the silica plug directly into the collector tube for the automatic HPLC injector. The sample was retained in this area until an HPLC analysis had been performed in triplicate and the analytical results printed out by the digital integrator. On completing analysis of the first aliquot, the inlet/injector area was automatically cleaned. Subsequent aliquots were analyzed similarly.

When the final (12 h) sample from the last of the four reactions was removed, extracted, plug filtered, and analyzed, the system was ready to cycle into the second reaction set. The reactors were cleaned by introducing nitrogen through the top septum of each reactor thereby ejecting the remaining reaction solutions through the bottom port into a reservoir from which it is removed by aspirator vacuum to waste. Several water and THF washes of each reactor, followed by nitrogen drying, returned the system to its original configuration. At that point, the reactors were charged as before, a new base was added, and the process was automatically repeated. In this way a series of 16 reactions [(8 bases × one solvent) + (2 bases × 4 solvents)] each having five analytical aliquots (80 averaged data points from 240 HPLC analyses) were automatically executed by the system over the course of 50 h.[19]

The results of these experiments are shown in Table I and Figure 3. As can be seen from Table I, the initial results with a series of eight bases demonstrated that tetrabutylammonium fluoride and DBU were superior to the other six bases examined. The reactions were then repeated with use of these two bases in four different solvents (Figure 3). These results demonstrated the marked dependence of this reaction on both the solvent and the nature of the base. To verify these findings, the reaction was conducted under the methylene chloride/DBU conditions on a 50-mmol scale; in this case the isolated yield of purified vinyl sulfone **6** was 67%.

These experiments demonstrate the potential of an automated reaction optimization system. It seems clear that subsequent generations of this type of system will have a substantial impact upon the current practice of laboratory science.

Acknowledgment. We thank W. E. Baitinger, director of the Chemistry Department Instrument Group, both for providing the stimulation to initiate this project and for his invaluable council as it continues to evolve. We are grateful to Tom Ridley of the machine shop and John Pirolo of the glass shop for their assistance in the design and construction of the special equipment described in this paper. We wish to thank the Zymark Corporation for their instant responses to our technical questions. Special thanks are due to Drs. Gabriel Saucy and John Scott and Hoffmann-La Roche Inc. for having the insight to provide us the robotics equipment. Partial salary support was provided by NSF CHE-7903953.

Registry No. 1, 5000-44-2; **2**, 6018-41-3; **6**, 92345-45-4.

(18) The archive storage area serves two functions: (1) it permits efficient processing of aliquots with respect to the timing of extraction and HPLC analysis, and (2) it provides reaction aliquots in the event of failure in the automatic HPLC analysis (the computer verifies several HPLC parameters prior to proceeding with the injection command).

(19) It should be noted that the number of samples processed during this time period was less than 25% of the capacity of the *four-reactor* system because of the "dead" time between the 4.0-, 8.0-, and 12.0-h aliquots. Future modifications of this system will employ at least *nine* reactors and will use real-time monitoring of the system to permit the computer to decide when a reaction is complete, so that its reactor may be cleaned and recharged.