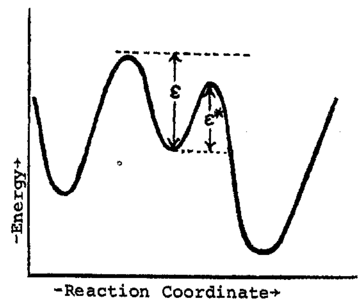

Figure 1—Energy *vs.* reaction coordinate diagram illustrating ϵ and ϵ^*.

inclusion of a "normal" A factor.[8] If a true intermediate, as opposed to a transition state, must have $\tau \geqslant 10^{-12}$ sec, then eq 4 obtains. Table I lists minimum

$$\epsilon^*/\epsilon = 1 - 10^{x/(6-2N)} \quad (x \geqslant 1.0) \qquad (4)$$

TABLE I

VALUES OF ϵ^*/ϵ *vs.* N FROM EQ 4 WITH $x = 1.0$

N	3	4	5	9	14	52
ϵ^*/ϵ	0.90	0.54	0.37	0.16	0.10	0.02

values of ϵ^*/ϵ which allow an intermediate to exist with $\tau = 10^{-12}$ sec *vs.* N calculated from eq 4; Figure 2 gives the corresponding plot of ϵ^*/ϵ *vs.* N.

An interesting result is revealed by the plot in Figure 2. As the number of atoms increases, the activation energy required to contain an intermediate for 10^{-12} sec falls off rapidly for any given internal energy. For example, a 27.0-kcal mol^{-1} activation energy is required to contain a 4-atom transient with 50 kcal mol^{-1} internal energy, while a mere 5.0-kcal mol^{-1} barrier will contain a 14-atom intermediate of the same internal energy for 10^{-12} sec.

Equation 4 and the plot in Figure 2 reflect the principle that the density of vibrational states increases directly with molecular size, and it is precisely this larger density of vibrational states which permits the complex molecule to form an intermediate while experiencing only a small barrier against spontaneous decomposition.

This conclusion forces a consideration of substituent effects on molecular rearrangements: Can the replacement of small groups with large groups make some nonconcerted reaction channel competitive with an otherwise dominant concerted path? Paquette and Epstein have suggested that replacement of two hydrogens with two phenyl groups perturbs the parent bicyclo[5.2.0]nona-2,5,8-triene system too severely to establish any mechanistic analogy.[15] This effect may contribute to the documented reactivity differences between ketene and diphenylketene,[16] 2,3,3,4-tetramethyl- and 2,4-diphenyl-3,3-dimethyltricyclo[3.2.0.^{2,4}0^{1,5}]hept-6-ene,[17] *meso*-3,4-dimethyl- and *meso*-3,4-diphenylhexa-1,5-diene,[18,19] and allene and phenyl-substituted allenes.[20]

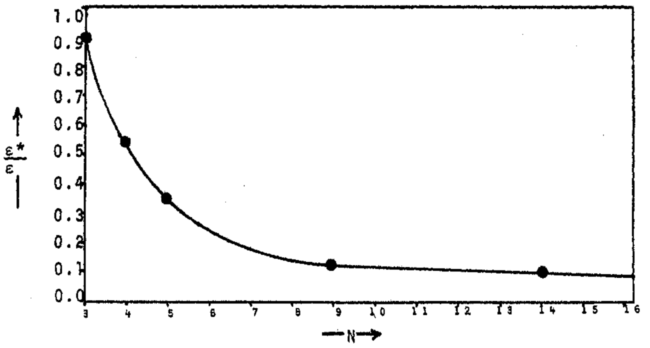

Figure 2—Plot of ϵ^*/ϵ *vs.* N from Table I.

Whether a given energized molecule may pass directly over a potential well separating it from isolable product while maintaining its internal energy above ϵ^* depends on the third parameter in eq 4, ϵ, and what opportunities for collisional deactivation may be present. Molecular beam experiments[8] on the energy dependence of bimolecular reactions have demonstrated the actual conversion of two-step, energetically nonconcerted reactions into one-step, fully concerted processes at higher internal energies.[21] Thus, even if a potential well of sufficient depth presents an opportunity for intermediate formation, it does not require that such an intermediate be formed![22,25]

In conclusion, concertedness depends not only on the nature of the potential energy surface itself, but also the motion of the system on this surface. Any empirical definition of concertedness which is adopted must focus on the dynamics of the reacting system and not simply intermediate potential well depth. Experiments aimed at distinguishing concerted from diradical or nonconcerted cycloreactions would be more meaningfully directed toward establishing maximum lifetimes of potential intermediates as a function of molecular size and reaction conditions.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLORADO 80302

A. HARRY ANDRIST

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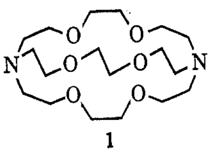
Flow Synthesis. A Substitute for the High-Dilution Steps in Cryptate Synthesis

Summary: Certain cyclization reactions, usually run under conditions of high dilution over long periods of time, give excellent yields in <1 min when the reagents are efficiently mixed in a suitable flow cell.

Sir: In a recent synthesis of the polyoxa macrobicyclic diamine, **1**, which forms cage complexes (cryptates) with alkali and alkaline earth cations[1-3] and which can be used to dissolve alkali metals in amines and ethers,[4,5] we followed essentially the procedure of Dietrich, Lehn, and Sauvage.[1,6] Synthesis of both of the intermediates, **2** and **3**, from the appropriate diamine and diacid chloride used the high-dilution method recommended by Stetter and Marx.[7] Similar procedures were used by Simmons and Park[8,9] in the synthesis of diazabicycloalkanes and by Lehn and coworkers[10-13] in their continuing synthesis of a number of macrobicyclic and macrotricyclic ligands.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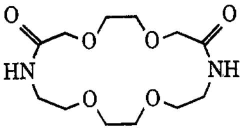
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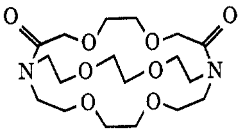
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The recommended procedure requires the slow addition with vigorous stirring (over a period of $\sim$8 hr) of dilute ($\sim$0.1 *M*) solutions of the two reagents in benzene into a reaction flask under a nitrogen atmosphere. We found that the yields were not greatly reduced by speeding up the addition process, provided that the stirring was sufficiently vigorous. This suggested that the most important factor in these reactions is efficient stoichiometric mixing. This supposition was tested by using a flow cell to carry out these steps.

The mixing chamber is of the type used in our laboratory for stopped-flow kinetics studies.[14,15] It has four tangential 1.0-mm inlets "drilled" into a 2.0-mm-i.d. Pyrex capillary. An Airbrasive unit (S. S. White Co.), which uses helium to drive Alundum through a nozzle at supersonic velocities, was used to make the inlet holes. (Presumably, conventional mixing chambers made of Teflon or metal could be used.) The reactant solutions were driven through the mixing chamber at flow velocities high enough to ensure turbulent mixing by applying about 3 atm of nitrogen pressure to the stock solutions. The heavy-walled vessels which contained the stock solutions were connected to the mixing chamber with 5-mm Solv-Seal joints (Fischer-Porter Co.) through Teflon needle-valve stopcocks (Kontes). The entire apparatus was surrounded by a metal safety shield.

Completion of the reaction between an amine and an acid chloride requires a base to remove the HCl formed. In the high-dilution method, either a 2:1 ratio of diamine to diacid chloride is used or else a tertiary amine such as triethylamine is used to scavenge HCl. However, in the formation of both **2** and **3**, we have found that triethylamine reduces the yield substantially. With the flow technique the required excess of amine may either be present in the amine stock solution or it may be in the receiver flask. The amine hydrochloride is removed by filtration and reconverted to the amine with very little net loss of material.

In a typical flow reaction, 200 ml of a 0.06 *M* solution of the diamine and 200 ml of a 0.03 *M* solution of diacid chloride in benzene were allowed to flow through the flow cell. The total flow time was $\sim$10 sec. Higher concentrations of reagents tended to cause blockage of the flow tube by the precipitated amine hydrochloride. The amine hydrochloride was removed by filtration and the dilactam, **2**, was recovered by removing the solvent in a rotary evaporator and purified by elution through an alumina column with benzene (mp 108–109°; pmr singlet at 3.90, multiplet at 3.50 ppm). The purified yield was 70% which is the same as the yield obtained for similar concentrations by the high-dilution method. Similar results were obtained in the synthesis of the bicyclic lactam, **3**. In all cases the yield was sensitive to the purity of the diacid chloride which is susceptible to decomposition upon vacuum distillation. Recrystallization from a mixture of ether and petroleum ether as recommended by Lehn[6] yields a pure product which can be stored for weeks at $-10°$ without decomposition.

Consideration of the kinetics to be expected in cyclization reactions suggests the requirements which must be met if the flow method is to be a useful replacement for high-dilution techniques. (1) Mixing must be rapid and complete so that the proper stoichiometry is maintained. (2) The initial step in the reaction must be fast enough to be substantially complete during the time of flow. (3) The cyclization step must be fast enough to compete with intermolecular reactions. It is likely that the type of reaction considered in this paper meets criteria 2 and 3 by the rapid formation of a cyclic acid–base complex or hydrochloride salt. The fact that the HCl scavenger may be placed in the receiver flask shows that it need not be present at the point of initial reaction. The precipitation of an amine hydrochloride in the flow tube shows that the reaction proceeds at least to this point in <10 msec.

Flow synthesis should be readily applicable to other than cyclization reactions. It would be a simple matter to add another mixer for sequential reactions or for the quenching of undesirable reactions. If the reaction of interest is fast and the products are sensitive to decomposition or secondary reactions under the conditions of the experiment, then we would expect flow methods to be applicable. The simplicity of the apparatus makes the method attractive for routine laboratory use.

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DEPARTMENT OF CHEMISTRY
MICHIGAN STATE UNIVERSITY
EAST LANSING, MICHIGAN 48823

JAMES L. DYE*
MEI TAK LOK
FREDERICK J. TEHAN
JOSEPH M. CERASO
KENT J. VOORHEES

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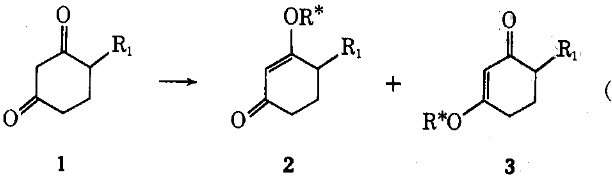
The Regiospecific Alkylation of Cyclic β Diketone Enol Ethers. A General Synthesis of 4-Alkylcyclohexenones

Summary: The alkylation of the kinetic enolate derived from 3-alkoxycyclohexenones is shown to take place in high yield at C$_6$, thus leading to a general synthesis of 4-alkyl-2-cyclohexenones free of double-bond isomers.

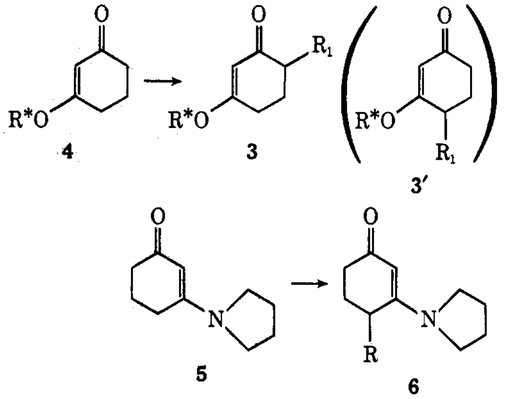
Sir: Enol ethers of cyclic β diketones are very valuable synthetic intermediates, *e.g.*, in the construction of cyclohexenones.[1] Unfortunately, there is no general method for the regiospecific formation of a given enol ether when the starting diketone is unsymmetrical. In such a situation, enol ether formation leads to mixtures of the two possible products (*cf.* **1** → **2** and **3**, eq 1).



(1)

We now wish to present a solution to this problem which should greatly extend the utility of cyclic β diketones as synthetic intermediates: We have found that monoalkylation of the enol ether of symmetrical cyclic β diketones, *e.g.*, **4**, can be effected regiospecifically to give **3**, a result especially noteworthy as the alkylation of the related enamine has recently been reported to follow a different course (*e.g.*, **5** → **6**,[2] eq 2).

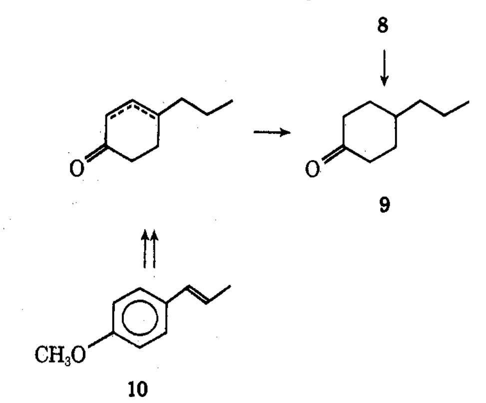
The alkylations are especially clean with reactive (allylic) halides. For instance, the lithium enolate (made at −78° in tetrahydrofuran with lithium diisopropylamide) of **4** (R* = isobutyl[3]) was treated with 1.1 equiv of allyl bromide, finally at room temperature, to yield, in almost quantitative yield, the monoallylated product (**7**) of **3** (R* = isobutyl; R$_1$ = allyl), needles of mp 37–38°. The gross structure was only compatible with either **3** or **3′** because of the mass spectrum (*m/e* 208) and the obvious presence of one allyl residue in the nmr, which retained the vinyl hydrogen of the enone system as a singlet at δ 5.3.



(2)

The correctness of structure **3** was demonstrated by a sequence which also serves to illustrate one of the important uses of substances of this type, the *synthesis of pure 4-alkyl-Δ^2-cyclohexenones*, essentially free from the (usually) more stable Δ^3 isomer. Lithium aluminum hydride reduction (refluxing ether) and hydrolysis (2 *N* hydrochloric acid, 30-min stirring, room temperature), gave, in $\sim$80% overall yield from **4**, 4-allyl-2-cyclohexenone (**8**, eq 3), bp 87–88° (7 mm), *m/e* 136.0863, free of β,γ isomer as shown by the nmr (1 H split doublet at δ 7.0 due to the β hydrogen of the α,β system) and the ir absorption at 5.93 μ.

Catalytic hydrogenation of **8** (10% Pd/C in ethanol) gave 4-propylcyclohexanone **9**, identical (by glc on 5% SE-30, 100°, and ir) with an authentic sample made from anethole (**10**) by the sequence Birch reduction (lithium–ammonia–methanol), hydrolysis (3 *N* hydrochloric acid–aqueous methanol), and hydrogenation of the α,β–β,γ mixture of 4-propylcyclohexenones (eq 3).



(3)

It is especially remarkable and synthetically useful that proton transfer reactions between the initial lithium enolates of 1,3 diketone enol ethers (*e.g.*, of **4**) and the monoalkylated product (*e.g.*, **3**) are extremely

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