Substituent Effects in the Aliphatic Claisen Rearrangement of Substituted (1-Methyl-3-oxahexa-1,5-dienyl)amines: Synthesis of Substituted 2-Aminopent-4-enals. Alternative [1,3]-Sigmatropic Shifts in Related Aromatic Systems

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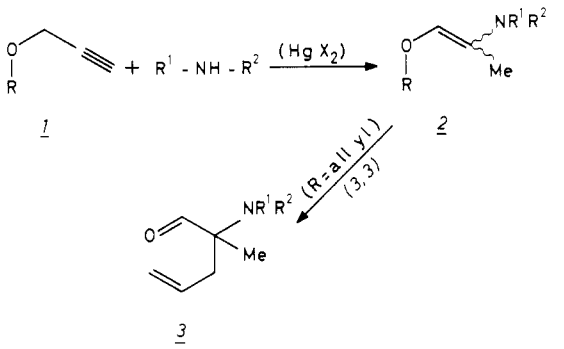
The series of substituted β-allyloxy enamines **4** was allowed to undergo Claisen rearrangement. The reaction proved to be faster for enamines derived from aliphatic than those from aromatic amines, the general substituent effects fitting Gajewski's oxaallyl–allyl radical model for these processes. The high stereoselectivity observed in these reactions leading to the 2-aminopent-4-enals **5** was assumed to occur via the more stable chairlike transition state. A different [1,3]-sigmatropic course, leading to the 2-amino-2-methylpropanals **20**, was observed when the allylic double bond is part of an aromatic system.

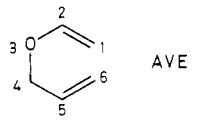
While investigating catalytic aminomercuriation of 3-oxy-substituted terminal alkynes **1**, a mild reaction which easily leads to β-oxy enamines **2**,[1] we observed that the allylic nature of the R substituent resulted in the low-temperature transformation of the first-formed enol ether enamine **2** into the 2-aminopent-4-enal **3** (Scheme I).[2] The ease of this aliphatic Claisen rearrangement **2** → **3** may be attributed to the accelerating effect of the substituents,[3] a topic surprisingly ignored in the past, but extensively studied recently by both synthetic[4] and theoretical[5] chemists. In this context, we wish to report our general findings about substituent effects on the rate of Claisen rearrangement and their rationalization in the light of the available theoretical models. In addition, several stereochemical features of the processes described here, as well as the different reaction course noticed when the allyl moiety is part of an aromatic system, are also reported.

Scheme I



Results and Discussion

Table I summarizes the Claisen rearrangement of the β-allyloxy enamines **4** into the 2-aminopent-4-enals **5**. All the enamines **4** may be viewed as substituted allyl vinyl ethers (AVEs), with two donor substituents on C_1 (NR^1R^2 and Me) and a third substituent at another position; as



exceptions, **4a** and **4i** lack this third substituent, and **4f** and **4m** show a double substitution at C_4. A general inspection of Table I reveals that all the β-allyloxy enamines **4** rearrange markedly faster than AVE does itself. This general trend can be attributed to an accelerating effect coming from the amino substituent, since such a rate acceleration is well documented when donor substituents are attached at C_1.[4] In general, compounds **4a–h** derived from aliphatic amines rearrange faster than compounds **4i–m** derived from aromatic ones. Within these two sets, the secondary effects of the remaining substituents should account for the observed differences in the reaction rates.

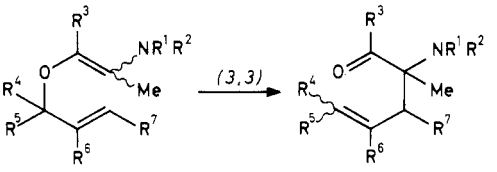
Three main models have been recently proposed in order to explain the substituent effects on the rate of Claisen rearrangement. In the Carpenter model,[5e] π-donor substituents are represented by a carbanion and π-acceptors by a carbenium ion. The difference in HMO π-electron energy between the transition-state (TS) and reactant models is calculated and then compared with that for the analogous unsubstituted reaction. Thus, if the former is greater than the latter, the substituent is predicted to decrease the reaction rate and vice versa. (See Table II for a summary of this model.)

Our general observation that a C_1-amino substituent accelerates the rate of the rearrangement agrees with the Carpenter model; the rates of **4b** and **4c** (relative to the "methyl-unsubstitued" **4a**) and **4j** and **4k** (relative to **4i**) also are in agreement with such a model, provided that the Carpenter model can apply to polysubstituted AVEs, and insofar as the methyl group can be considered a π-donor.[6] However, this model predicts an opposite effect to that found for **4d** (with regard to **4a**), and **4l** (with regard to **4i**),[7] and is uncertain in the case of **4e**.

(1) Barluenga, J.; Aznar, F.; Liz, R. *Synthesis* **1984**, 304.
(2) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427.
(3) A catalytic action of mercury(II) species in these processes is not possible, since most enol ether enamines were distilled before rearrangement.
(4) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572 and ref 1 and 2 therein.
(5) (a) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 2747. (b) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (c) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11. (d) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733. (e) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984. (f) Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127.
(6) It has been suggested,[5d] however, that the Carpenter model does not apply to σ-inductive substituents.
(7) Other divergences with this model are also known when Me or MeO are attached at C_6. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002.

0022-3263/87/1952-5190$01.50/0

Table I. Claisen Rearrangements 4 → 5



4 5

rearrngmnt	R^1	R^2	R^3	R^4	R^5	R^6	R^7	temp,[a] °C	half-life, h
4a → 5a	$(CH_2)_2O(CH_2)_2$		H	H	H	H	H	40	29
4b → 5b			H	Me	H	H	H	40	3
4c → 5c			H	H	H	Me	H	40	(390)[b]
4d → 5d			H	H	H	H	Me	40	8
4e → 5e			H	H	H	H	Ph	20	*c*
4f → 5f			H	Me	Me	H	H	20	*c*
4g → 5g	$CH_2(CH_2)_2CH_2$		H	Me	H	H	H	20	*c*
(4h)[d] → 5h[e]	$(CH_2)_2O(CH_2)_2$		Me	H	H	H	H	80	*d*
4i → 5i	Ph	Me	H	H	H	H	H	110	1
4j → 5j			H	Me	H	H	H	110	0.3
								80	2
4k → 5k			H	H	H	Me	H	120	2
4l → 5l			H	H	H	H	Me	110	0.6
4m → 5m			H	Me	Me	H	H	20	*c*
AVE[f]								40	5.3×10^4[g]
								110	24.4[g]

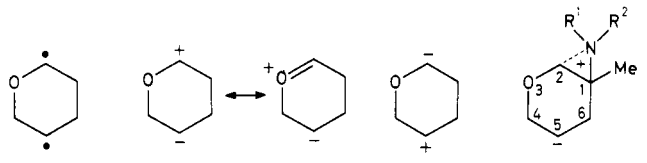
[a] Rearrangement temperature. [b] Calculated from the readily measured half-lives at 85 (1.5 h) and 130 °C (5 min) by using the Eyring equation. [c] The corresponding compound **5** is directly obtained in the room temperature attempted preparation of the corresponding **4**. [d] See text. [e] As an exception, this compound is not a 2-amino aldehyde but 3-methyl-3-morpholinohex-5-en-2-one. [f] Allyl vinyl ether; given for comparison. [g] Calculated from the activation parameters reported in ref 5e by using the Eyring equation.

Table II. Carpenter Predictions on Substituent Effects in Claisen Rearrangement

	substituent[a]	
positn	donor	acceptor
1	↑	↓
2	↑	↑
4	↑	↑
5	↓	(↑↓)[b]
6	↓	↓

[a] ↑ (↓): The substituent increases (decreases) the reaction rate relative to the unsubstituted case. [b] Depending on the chair or half-chair geometry adopted in the TS.

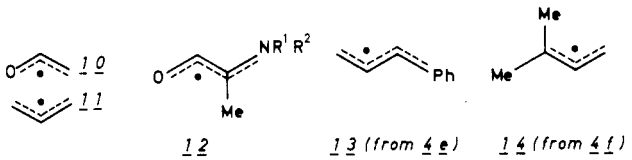
MNDO calculations on Claisen rearrangement led Dewar[5f] to propose the polarizable biradical 2-oxacyclohexane-1,4-diyl (**6**) as the TS model for the process. Two possible polarizations, **7** and **8**, can be envisaged, although the effect of the oxygen favors the former. In our case,



6 7 8 9

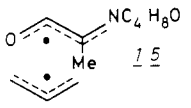
we assume that the additional effect of the amino group on C_1 should decisively favor the polarization **9**, analogous to **7**. Thus, the general rate-accelerating effect of a C_1-amino group, as well as the decelerating effect of a methyl group on C_5 (**4c** and **4k**), again squares with this model; however, the observed rate-accelerating effects of methyl groups on C_4 (**4b**, **4f**, **4j**, and **4m**) and C_6 (**4d** and **4l**)[7] clearly disagree.

From secondary deuterium kinetic isotope effects, Gajewski[5a-d] concludes that the chairlike TS for the Claisen rearrangement more resembles reactant than product and more resembles an oxaallyl radical–allyl radical pair, **10** and **11**, than it does the above biradical **6**. Thus, the stability of this pair of radicals must play a decisive role in the rate of the rearrangement. It is noteworthy that, apart from cases **4c** and **4k**, in which steric hindrance must play an important role in the energy balance, all the results shown in Table I can be rationalized in the light of this model.



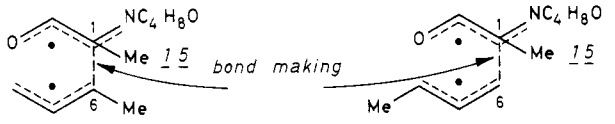
10 11 12 13 (from 4e) 14 (from 4f)

Thus, the stabilizing effect of the C_1-amino group in the 1-amino-1-methyl-3-oxaallyl radical **12** is expected to increase as the basicity of the amino substituent increases. This trend would explain the faster rearrangement observed for the aliphatic enamines, **4a–h**, relative to the aromatic ones, **4i–m**. In this context, the pyrrolidino enamine **4g** (pyrrolidine is ca. 10^3 times more basic than morpholine) rearranges at such a rate that it cannot be isolated; in fact, when its room temperature preparation is attempted, the δ,ε-unsaturated 2-amino aldehyde **5g** is directly obtained. Two similar instances in which the amino aldehydes are directly obtained are those of **4e** and **4f**; in these cases, inspection of the corresponding "allyl" radicals, **13** and **14**, reveals that they have in addition benzylic and tertiary nature, respectively. The series of rearrangement rates **4a < 4d < 4b** fits the following observation: All the three TS involve the same 1-methyl-1-morpholino-3-oxaallyl radical, **15**, but the corresponding "allyl" radical is the unsubstituted allyl itself, **16**, for **4a**, whereas the more stable 1-methylallyl radical, **17**, is involved for both **4d** and **4b**; furthermore, an additional steric hindrance in the C_1–C_6 bond formation is evident for the process **4d → 5d**, which, consequently, proceeds slower than the **4b → 5b** one. The case of **4c** is rather complex; although the involved methallyl radical **18** is more stable than the allyl radical, **4c** shows by far the slowest rearrangement rate among the aliphatic enamines **4a–h**.



15

16 (from 4a)

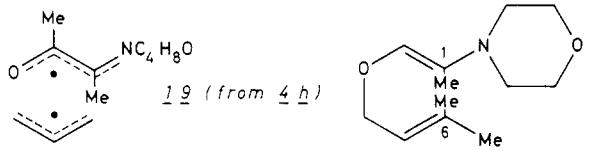


17 (from 4d) 17 (from 4b)

4c 18 (from 4c)

This fact can be understood if a pseudo-1,3-diaxial interaction between the two C_1- and C_5-methyl groups in the suitable conformation of **4c** occurs. This kind of steric hindrance was recently invoked to explain the observed regiochemistry in Claisen processes in which more than one allylic double bond can participate.[8]

The case of enamine **4h** is also striking. Its attempted conventional preparation (Scheme II) only affords the less substituted regioisomer, **4h'**, a behavior also known for several 1-methylprop-2-ynyl ethers and esters.[9] However, **4h'** was converted into the 3-methyl-3-morpholinohex-5-en-2-one (**5h**) by heating at 80 °C. Doubtless, **4h'** isomerizes to **4h**, which immediately rearranges[10] due to the high stability of the 1,2-dimethyl-1-morpholino-3-oxaallyl radical (**19**) involved.



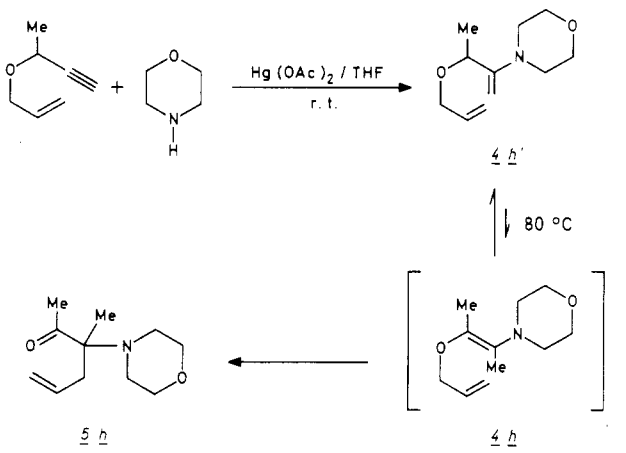
19 (from 4h)

16 4n

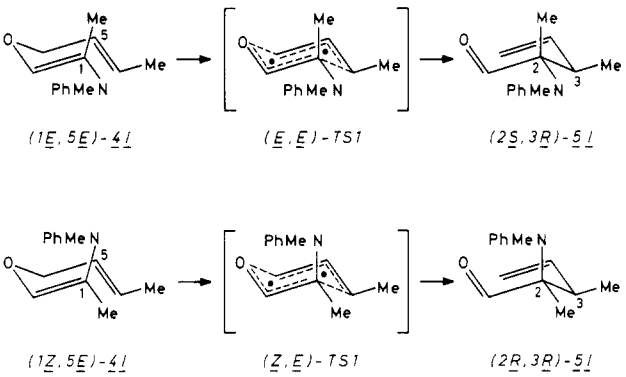
A further example showing the steric hindrance on the C_1–C_6 bond formation in the Claisen processes is provided by *N*-(1,6-dimethyl-3-oxahepta-1,5-dienyl)morpholine (**4n**). Although this enamine is easily obtained, its rearrangement is so slow that the corresponding amino aldehyde decomposes under the necessary prolonged heating at 80 °C.

As already noticed by us,[1] all the aliphatic enamines **4a–h** exist as a single C_1=C_2 double bond stereoisomer (probably *E*), but both *Z* and *E* isomers are present in the aromatic enamines **4i–m**. However, as it will be seen later, it seems clear that only the *E* form rearranges, thus forcing the $Z \rightleftharpoons E$ equilibrium to shift to the right-hand side. This fact fortunately does not preclude half-life measurements for compounds **4i–m**. Indeed, from the facts that **4m** rearranges at room temperature and that the *Z*/*E* molar ratio for each β-oxy enamine **4i–l** remains constant during the rearrangement (as deduced from NMR), one can infer

Scheme II



Scheme III



(1E,5E)-41 (E,E)-TS1 (2S,3R)-51

(1Z,5E)-41 (Z,E)-TS1 (2R,3R)-51

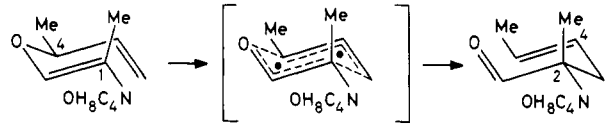
the *Z*/*E* equilibration to be faster than the rearrangement and, hence, not to interfere with kinetic calculations. Nevertheless, since half-lives were deduced from NMR experiments (see Experimental Section) and since the appropriate signals for the aromatic enamines **4i–l** were split, the tabularized values for these compounds are somewhat less accurate than they are for the aliphatic enamines. Even so, the substituent effects on the half-lives in the aromatic enamines **4i–m** show the same pattern as the aliphatic ones, though more vigorous reaction conditions are needed in the former case due to the lower basicity of the *N*-methylanilino group.

Some of the enamines **4** suffering the Claisen rearrangement considered here are not diastereoisomerically pure; thus, all the aromatic ones, **4i–m**, are ca. 2:1 mixtures of their *Z* and *E* forms on the enamine C_1=C_2 double bond. On the other hand, although the enamine moieties of **4b** and **4g** are *E* forms, these compounds have a chiral center at C_4 and are used as racemic mixtures; finally, **4j** combines the above two features. Despite these facts, the ^1H and ^{13}C NMR spectra of all the amino aldehydes **5** show the presence of a single diastereoisomer, i.e., the process is highly stereoselective.

Let us consider the case of **4l** as an example of the aromatic enamines **4i–m**. The sample was a ca. 2:1 mixture of (1*Z*,5*E*)- and (1*E*,5*E*)-*N*-methyl-*N*-(1-methyl-3-oxahept-1,5-dienyl)aniline, i.e., the allyl moiety has an *E* geometry. Although both stereoisomers can rearrange through two chairlike TS, only one of them is drawn for each stereoisomer in Scheme III. If the four TS were operative, a mixture of two diastereoisomers would be formed. Since only one diastereoisomer (enantiomeric pair) is obtained, we concluded that it must be the (2*R*,3*S*)- and (2*S*,3*R*)-2,3-dimethyl-2-(*N*-methylanilino)pent-4-enal, because the (2*R*,3*R*)- and (2*S*,3*S*)-**5l** enantiomeric pair

(8) Parker, K. A.; Farmar, J. G. *Tetrahedron Lett.* **1985**, *26*, 3655.
(9) Barluenga, J.; Aznar, F.; Liz, R.; Postigo, C. *J. Chem. Soc., Chem. Commun.* **1986**, 1465.
(10) Other examples of rate-accelerating effects in 1,2-bis-donor substituents systems are known. (a) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (b) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729.

Scheme IV



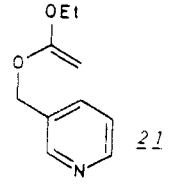
(1*E*,4*S*)-4**b** (*E*,*S*)-TS1 (2*S*,4*E*)-5**b**

would arise from two TS in which the bulky *N*-methylanilino group would be axially placed.[11] Thus, only the 1*E*,5*E* enamine rearranges at measurable rate, thus forcing the 1*Z*,5*E* ⇌ 1*E*,5*E* equilibrium to shift toward the 1*E*,5*E* stereoisomer.

Compound **4b** is a racemic mixture of (1*E*,4*R*)- and (1*E*,4*S*)-*N*-(1,4-dimethyl-3-oxahex-1,5-dienyl)morpholine. Since the enamine moiety has an *E* geometry, the bulkier morpholino group is always equatorially oriented in all the possible TS. Since a single diastereoisomer (a pair of enantiomers) is again observed in the resulting amino aldehyde **5b**, we assume this to be the (2*R*,4*E*)- and (2*S*,4*E*)-2-methyl-2-morpholinohept-4-enal, coming from the 1*E*,4*R* enamine through one of the two possible chairlike TS and from the 1*E*,4*S* enamine through the other chairlike TS. As shown in Scheme IV, the depicted (*E*,*S*)-TS1, as well as the other mentioned TS, has only one methyl group axially placed. The (2*S*,4*Z*)- and (2*R*,4*Z*)-**5b** enantiomeric pair was never detected since it would be produced through the two remaining TS, in which two methyl groups would be axially oriented. The stereochemistry of the **4g** → **5g** rearrangement can be explained in the same way.

The **4j** → **5j** rearrangement represents the most complex example, since both possible *Z*/*E* and *R*/*S* isomerisms can exist for the starting **4j**. However, a detailed study is not necessary, since it would result in a combination of the above two cases. In conclusion, although eight TS can be envisaged, only four of them bear a single group axially placed, and two of these can be ruled out since the axially oriented substituent would be the bulky *N*-methylanilino. Thus, only two TS, leading to the (2*R*,4*E*)- and (2*S*-4*E*)-2-methyl-2-(*N*-methylanilino)hept-4-enal enantiomeric pair should operate.

Finally, we wish also to report that a completely different reaction path is observed when the allylic double bond is contained in an aromatic carbo- or heterocycle. In these cases, the tendency of the system to preserve its aromaticity seems to account for the [1,3]-sigmatropic shift which exclusively takes place, leading to the 2-amino-2-methylpropanals **20** (see Table III). Only a few analogous examples are known in which an alkyl group migrates from a heteroatom;[12] it is also somewhat surprising that a system such as **21**, closely related to **2e**, has been reported to undergo only [3,3]-rearrangement.[13]

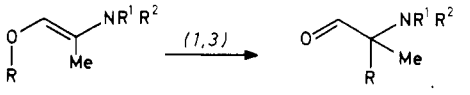


21

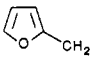
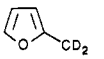
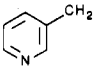
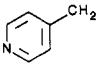
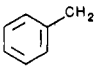
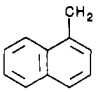
(11) (a) Similar, although weaker 1,3-diaxial-like interactions were recently invoked to explain the ca. 5:1 diastereoselectivities observed in a series of ortho ester Claisen rearrangements. Daub, G. W.; Shanklin, P. L.; Tata, C. *J. Org. Chem.* **1986**, *51*, 3402. (b) In the closely related rearrangement of several, nonisolated 2-amino-AVEs, the authors deduce the stereochemistry of the reagent from that of the product, assuming a chair-like transition state. Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679.

(12) Arnold, R. T.; Kulenović, S. T. *J. Org. Chem.* **1980**, *45*, 891.

Table III. [1,3]-Sigmatropic Shifts 2 → 20



2 **20**

rearrngmnt	R^1,R^2	R	temp, °C	half-life, h
2a → **20a**	$CH_2(CH_2)_2CH_2$		20	*b*
2b → **20b**	$CH_2(CH_2)_3CH_2$		80	0.36
2c → **20c**	$(CH_2)_2O(CH_2)_2$		80	0.72
2d → **20d**			80	1.32
2e → **20e**			130	0.43
2f → **20f**			130	0.47
2g → **20g**			130	0.85
2h → **20h**			140	*c*

[a] Rearrangement temperature. [b] Compound **20a** is directly obtained in the room temperature attempted preparation of **2a**. [c] Compounds **2h** rearranges into **20h** during the distillation step.

In order to ascertain if these [1,3]-rearrangements are stepwise or concerted processes, *N*-[4,4-dideuterio-4-(2-furyl)-1-methyl-3-oxabut-1-enyl]morpholine (**2d**) was prepared and allowed to rearrange to the corresponding 2-amino aldehyde **20d**. Relative to the analogous nondeuteriated enamine **2c**, **2d** shows a secondary deuterium kinetic isotope effects as large as 1.83, which strongly suggests that there is complete C–O bond breaking in the rate-determining step of the reaction.[14]

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded on a Pye Unicam SP-1025 spectrometer. The ^1H NMR spectra were determined on a Varian FT-80A spectrometer with internal tetramethylsilane as the reference. The ^{13}C NMR spectra were determined on a Varian FT-80A set for performing "off-resonance". Mass spectra were taken on a Hewlett-Packard 5930A spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240 instrument.

Materials. Substituted allyl prop-2-ynyl ethers used as starting materials (except allyl 1-methylprop-2-ynyl ether) were prepared in a conventional manner from the corresponding sodium prop-2-enyl oxide and prop-2-ynyl bromide (THF, reflux, 4 h). Dideuterio(2-furyl)methanol used in the preparation of dideuterio(2-furyl)methyl prop-2-ynyl ether was obtained by $LiAlD_4$ reduction (THF, reflux, 6 h) of 2-furoic acid. Allyl 1-methylprop-2-ynyl ether was prepared by treating but-3-yn-2-ol with 2 equiv of butyllithium (THF, −70 °C); the temperature was then allowed to rise to 20 °C overnight. Finally, allyl bromide was added and the system refluxed for 4 h.

Mercury(II) salts and amines were of the best commercial grade available. Amines were previously dried (refluxing over potassium hydroxide) and distilled under argon.

General Preparative Procedure for Aliphatic β-Oxy Enamines 4a-h and 2a-h. Dry mercury(II) acetate (4.78 g, 15 mmol) was added under argon to a stirred solution of the appropriate allyl prop-2-ynyl ether **1** (20 mmol) and dry aliphatic amine (60 mmol) in anhydrous THF (60 mL). The mixture was stirred

(13) Costin, C. R.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1976**, *41*, 535.

(14) Gajewski, J. J., private communication.

during 6 h at room temperature and then filtered under argon and the liquid phase evaporated under reduced pressure (0.05 Torr). The resulting residue was stirred with anydrous *n*-hexane (60 mL) during 1 h and filtered under argon, and the liquid phase concentrated in vacuo (0.05 Torr). The crude reaction product was an essentially pure, yellow liquid which was trap-to-trap condensed in vacuo (0.001 Torr; preheated oil bath temperature, 80–90 °C).

***N*-(1,4-Dimethyl-3-oxahexa-1,5-dienyl)morpholine (4b):** ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.75 (s, 3 H), 2.6–3.0 (m, 4 H), 3.6–3.8 (m, 4 H), 4.0–4.2 (m, 1 H), 5.1–5.4 (m, 2 H), 5.6 (s, 1 H), 5.65–6.2 (m, 1 H); ^{13}C NMR (neat) δ 13.6 (q), 22.2 (q), 51.8 (t), 68.2 (t), 79.4 (d), 116.4 (t), 130.7 (d), 132.7 (s), 141.8 (d).

General Preparative Procedure for Aromatic β-Oxy Enamines 4i–m. The method is the same as for compounds **4a–h** and **2a–h**, except that dry mercury(II) chloride (0.54 g, 2 mmol), the appropriate allyl prop-2-ynyl ether 1 (20 mmol), dry *N*-methylaniline (10.8 mL, 100 mmol), anhydrous THF (15 mL), and potassium carbonate (0.55 g, 4 mmol) were used. The crude reaction product was an essentially pure, yellow liquid which was trap-to-trap condensed in vacuo (0.001 Torr; preheated oil bath temperature, 100–110 °C).

***N*-Methyl-*N*-(1-methyl-3-oxahexa-1,5-dienyl)aniline (4i):** ^{1}H NMR ($CDCl_3$) δ 1.65 and 1.75 (2 s, 3 H), 3.05 and 3.0 (2 s, 3 H), 4.25 (d, 2 H), 5.05–5.5 (m, 3 H), 5.9 and 6.25 (2 s, 1 H), 6.6–7.35 (m, 5 H); ^{13}C NMR (neat) δ 15.3 and 11.5 (2 q, $CH_3C(N)$=CH), 37.6 and 39.9 (2 q, CH_3N), 73.1 and 73.5 (2 t,CH_2O), 121.4 and 124.8 (2 s, NC=CH), 141.5 and 147.2 (2 d, NC=CH). (First values in duplicate signals refer to the *E* isomer.)

Determination of Rearrangement Half-Lives. The half-lives shown in Tables I and III were measured by using ^{13}C NMR spectroscopy. For compounds **4a–d** and **2a–g** a peak at ca. δ 52 (assigned to C-2 and C-6 of the morpholino moiety of the β-oxy enamines) gradually disappeared and a new peak at ca. δ 49 (assigned to the analogous nuclei of the aminoaldehydes, which are expected to have similar relaxation times) appeared at the same rate. For compounds **4i–l** the change in the methyl signal of the *N*-methylanilino moiety from ca. δ 37 and 40 for the (*E*)- and (*Z*)-enamine, respectively, to ca. δ 38 for the amino aldehyde was observed. The approximate half-lives were deduced from the reasonably time-independent first-order rate constant obtained for each transformation.

Prolonged heating of β-oxy enamines **2** and **4** under argon atmosphere at the appropriate temperature, over a period of ca. $10t_{1/2}$, followed by fractional condensation at 0.001 Torr, results in almost quantitative transformation into the corresponding amino aldehyde **20** or **5**.

2,3-Dimethyl-2-morpholinopent-4-enal (5d): IR (Nujol 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9–1.3 (m, 6 H), 2.3–3.0 (m, 5 H), 3.6–3.85 (m, 4 H), 4.9–5.3 (m, 3 H), 5.7–6.4 (m, 1 H), 9.5 (s, 1 H); ^{13}C NMR (neat) δ 12.1 (q), 15.2 (q), 41.5 (d), 48.5 (t), 68.9 (t), 70.6 (s), 116.6 (t), 140.4 (d), 193.4 (d).

2-Methyl-2-morpholino-3-(3-pyridyl)propenal (20e): IR (Nujol) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 3 H), 2.5–2.8 (m, 4 H), 2.9 (dd, 2 H), 3.4–3.85 (m, 4 H), 7.0–7.8 (m, 2 H), 8.3–8.65 (m, 2 H), 9.45 (s, 1 H); ^{13}C NMR (neat) δ 15.7 (q), 36.0 (t), 48.4 (t), 68.7 (t), 69.1 (s), 124.4 (d), 134.0 (s), 139.5 (d), 149.0 (d), 152.8 (d), 195.1 (d).

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Registry No. 1-I, 51580-41-7; 1-II, 109930-19-0; 1-III, 109930-20-3; 1-IV, 79705-05-8; 1-V, 109930-21-4; 1-VI, 109930-22-5; 1-VII, 93740-57-9; 1-VIII, 32904-79-3; 1-IX, 109330-23-6; 1-X, 72421-08-0; 1-XI, 95547-66-3; 1-XII, 4039-82-1; 1-XIII, 109930-24-7; (*E*)-**2a**, 109930-39-4; (*E*)-**2b**, 109930-40-7; (*E*)-**2c**, 109930-41-8; (*E*)-**2d**, 109930-42-9; (*E*)-**2e**, 109930-43-0; (*E*)-**2f**, 109930-44-1; (*E*)-**2g**, 109930-45-2; (*E*)-**2h**, 109930-46-3; (*E*)-**4a**, 109930-26-9; (*E*)-(±)-**4b**, 109930-27-0; (*E*)-**4c**, 109930-28-1; (*E,E*)-**4d**, 109930-29-2; (*E,E*)-**4e**, 109930-30-5; (*E*)-**4f**, 109930-31-6; (*E*)-(±)-**4g**, 109930-32-7; (*E*)-**4h**, 109930-33-8; (*E*)-**4i**, 109930-34-9; (*Z*)-**4i**, 109930-63-4; (*E*)-**4j**, 109930-35-0; (*Z*)-**4j**, 109930-64-5; (*E*)-**4k**, 109930-36-1; (*Z*)-**4k**, 109930-65-6; (*E,E*)-**4l**, 109930-37-2; (*Z,E*)-**4l**, 109930-66-7; (*E*)-**4m**, 109930-38-3; (*Z*)-**4m**, 109930-67-8; (±)-5a, 109930-47-4; (*E*)-(±)-**5b**, 109930-48-5; (±)-**5c**, 109930-49-6; **5d**, 95064-81-6; **5e**, 109930-50-9; (±)-**5f**, 109930-51-0; (±)-**5g**, 109930-52-1; (±)-**5h**, 109930-53-2; (±)-**5i**, 109930-54-3; **5j**, 109930-55-4; (±)-**5k**, 109930-56-5; (*R*,S**)-(±)-**5l**, 109995-88-2; (±)-**5m**, 109930-57-6; **20a**, 95064-87-2; **20b**, 95064-88-3; **20c**, 95064-86-1; **20d**, 109930-58-7; **20e**, 109930-59-8; **20f**, 109930-60-1; **20g**, 109930-61-2; **20h**, 109930-62-3; CH≡CCH(OH)Me, 2028-63-9; CH_2=$CHCH_2Br$, 106-95-6; 2-furoic acid, 88-14-2; dideuterio(2-furyl)methanol, 109930-25-8.

Supplementary Material Available: Spectral and analytical data for compounds **1**, **2**, **4**, **5**, and **20** (7 pages). Ordering information is given on any current masthead page.

Hydrolyses of 2- and 4-Fluoro N-Heterocycles. 2.[1] Nucleophilic Catalysis by Buffer Bases in the Hydrolysis of 2-Fluoro-1-methylpyridinium Iodide

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Pseudo-first-order rate constants are reported for hydrolysis of 2-fluoro-1-methylpyridinium iodide (1) in carboxylate buffers. The reaction is catalyzed by the carboxylase bases, with a Brønsted slope of 0.66. Hydrolyses in 99% ^{18}O-labeled water with 0.04 M unlabeled acetate and complementary hydrolyses in unlabeled water with 90% ^{18}O-labeled acetate indicate that 85–95% of the oxygen in product **2** is derived from the acetate rather than from water. The results are consistent with nucleophilic catalysis by acetate (and presumably by the other carboxylate bases) rather than general base catalysis.

Among mechanisms for nucleophilic substitution, those most frequently observed in reactions of acyl compounds and activated aromatic compounds share in common their addition–elimination pathways, as well as other features. In particular, their reactions with protic nucleophiles are often base catalyzed, and (in addition to specific base catalysis by hydroxide) that catalysis may be by either general base or nucleophilic catalysis routes. General base catalysis results from a rate-limiting proton transfer to the catalytic base or transfer during a rate-limiting step. For the nucleophilic catalysis route to predominate, of necessity an intermediate substitution product must be formed by

(1) For the previous paper, see: Clark, H. R.; Beth, L. D.; Burton, R. M.; Garrett, D. L.; Miller, A. L.; Muscio, Jr., O. J. *J. Org. Chem.* **1981**, *46*, 4363–4369.

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