120.83 (3°), 128.97 (3°, double intensity), 155.93 (2°), 210.26 (4°); GC/MS (EI, 70 eV) m/e 256 (M^+), 135, 119, 107, 91; UV (MeOH) λ_{max} (ϵ) 270 (1071), 221 (8770), 202 (9246) nm. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.68; H, 7.79.

9b-(4-Pentenyl)-2,3,4a,9b-tetrahydro-4(1*H*)-dibenzofuran (19): IR (film) 3460, 3070, 2930, 2865, 1745, 1650, 1615, 1590, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25-1.42 (m, 4 H), 1.86-2.06 (m, 5 H), 2.41-2.51 (m, 3 H), 4.80 (s, 1 H), 4.84-4.92 (m, 2 H), 5.54-5.75 (m, 1 H), 6.90-7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.2 (2°), 22.99 (2°), 28.77 (2°), 29.98 (2°), 33.67 (2°), 38.99 (2°), 52.89 (4°), 93.86 (3°), 111.46 (3°), 114.86 (2°), 121.32 (3°), 123.16 (3°), 128.39 (3°), 134.94 (4°), 137.98 (3°), 158.35 (4°), 203.43 (4°); GC/MS (EI, 70 eV) m/e 256 (M^+), 187, 159; UV (MeOH) λ_{max} (ϵ) 273 (2580), 202 (11 157) nm; HRMS calcd for $C_{17}H_{20}O_2$ 256.1483, found 256.1464.

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Supplementary Material Available: Proton NMR spectra for **18a** and **18b**; carbon NMR spectra for compounds **8b**, **11**, **15a**, **17a**, and **19**; and full details on X-ray crystallographic analyses including tables of coordinates, anisotropic temperature factors, distances, and angles (41 pages). Ordering information is given on any current masthead page.

Preparation and 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allyl Enamines

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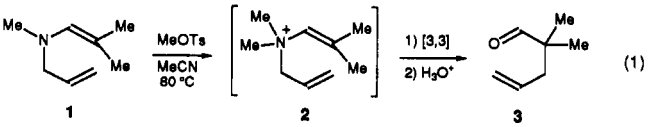
The [3,3] charge-accelerated rearrangement of *N*-allyl-*N*-isobutyl enamine substrates to γ,δ-unsaturated imine products and subsequent reduction to the corresponding *N*-alkyl δ,ϵ-unsaturated amines is reported. Several routes to the *N*-allyl-*N*-isobutyl enamines were established for the enamine prepared from isobutyraldehyde. With use of the most efficient route developed, enamines derived from butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were prepared in 58 to 92% overall yield in three steps from allylamine. In the case of butanal, the *E* isomer was formed exclusively, while the enamine from 2-phenylpropanal was prepared with an *E* to *Z* selectivity of 86:14. Heating these *N*-allyl-*N*-isobutyl enamines in refluxing dioxane with 0.5 equiv of HCl produced [3,3] rearrangement for substrates derived from isobutyraldehyde, 2-phenylpropanal, and cyclohexanone; the enamines of *n*-butanal and cyclopentanone were found to react through alternate pathways.

The study of the Claisen rearrangement, the [3,3] sigmatropic shift of allyl vinyl ethers, has provided many valuable contributions to the areas of mechanistic and synthetic chemistry.[1] Several features, including the convergent nature of the allyl enol ether preparation and subsequent C-C bond formation, have contributed to the extensive use of this reaction in organic synthesis. The products of this pericyclic process, γ,δ-unsaturated carbonyl compounds, are valuable synthons with different functionality at each terminus. Because of the different reactivity at each end, subsequent synthetic elaboration or incorporation of this fragment into a larger target molecule can be efficiently accomplished.

The nitrogen analogue of the Claisen rearrangement, the 3-aza-Cope rearrangement of **1**, has been reported to undergo thermally induced [3,3] sigmatropic rearrangement to the corresponding imine at 250 °C, and subsequent hydrolysis of the imine produced **3**.[2] Several approaches to rate enhancement of this transformation have been made through the electronic modification of the enamine functionality. Thermal rearrangement of the aniline-derived *N*-phenyl-*N*-allyl enamine was found to occur at a somewhat reduced temperature of 205 °C.[2] Rearrangement at lower reaction temperatures could be achieved by substrates with oxygen substituents at C-2. For example, ketene *N,O*-acetals underwent thermal sigmatropic transformation at 180 °C,[3] and allylamide enolates were found to rearrange at 130 °C.[4] The temperatures necessary for rearrangement to occur have been a major limiting feature of the 3-aza-Cope rearrangement. At the elevated temperatures for thermal rearrangement, technical difficulties commonly arise in setting up the reaction, monitoring its progress, and workup of the reaction mixture. Typically, in these cases the [3,3] transformation must be incorporated into multistep synthetic sequences early, so as not to disturb sensitive functionality.

Methods of promoting the aza-Cope rearrangement at even lower temperatures have involved the formation of cationic quaternary nitrogen centers. As shown in eq 1, one way to access an intermediate such as **2** has been accomplished by methylation of the *N*-alkyl-*N*-allyl enamine **1**. Under the 80 °C conditions for methylation of



1 2 3 (1)

allyl enamines, which has only been successfully performed on enamine substrates formed from 2-substituted aldehydes, rearrangement also occurred and hydrolytic workup of the reaction mixture produced **3**.[5] A modification of the methylation procedure, methylation of an *N*-allylimine

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(3) (a) Ireland, R. E.; Willard, A. K. *J. Org. Chem.* **1974**, *39*, 421. (b) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (c) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377.

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(5) (a) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1961**, *26*, 3576. (b) Gilbert, J. C.; Seneratne, K. P. A. *Tetrahedron Lett.* **1984**, *25*, 2303. (c) Welch, J. T.; De Corte, B.; De Kimpe, N. *J. Org. Chem.* **1990**, *55*, 4981.

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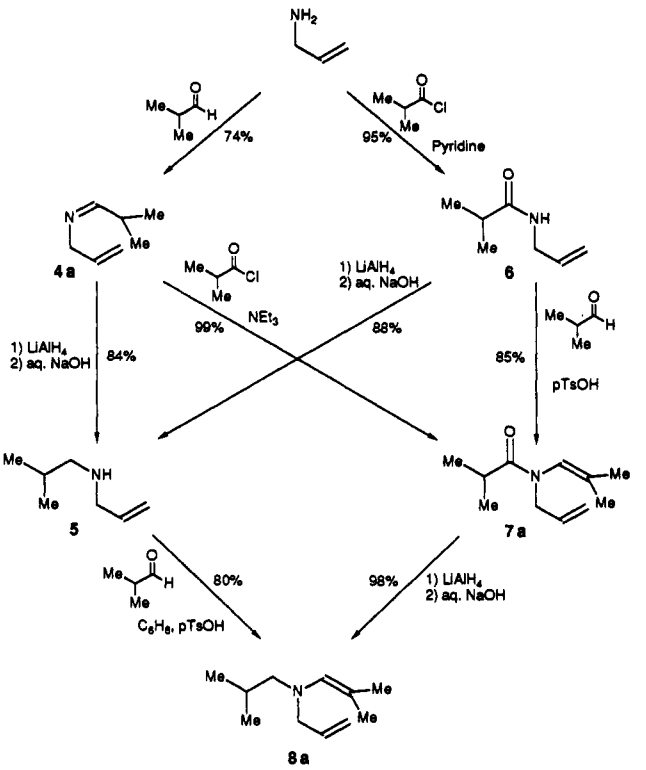
followed by the addition of a base, was found to produce rearrangement at 25 °C.[5c] More commonly, these quaternary ammonium intermediates have been obtained by allylation of N,N-dialkyl enamines at 80 °C, but problems involving N- versus C-allylation have limited the synthetic utility of this route to the use of symmetrical allyl groups.[6] Conjugate addition of a tertiary amine to ethyl propiolate has also been reported to produce [3,3] rearrangement through a charge-accelerated process.[7] Through these methods of rearrangement acceleration, reaction temperatures have been reduced by over 150 °C. In most cases, access to synthetically useful products was gained by hydrolytic removal of the amine functionality to form the corresponding carbonyl compound.

In a similar manner of reaction acceleration, Lewis acid catalysis of the aliphatic aza-Cope rearrangement has been reported.[8] In a landmark paper by Hill, N-phenyl-N-allyl enamines were found to rearrange at 80 °C when treated with 0.25 equiv of $TiCl_4$.[9] Coordination of the amine to the Lewis acid, generating an electron-deficient nitrogen center analogous to 2, has been suggested to produce this rate acceleration. Hill found that the in situ condensation of a carbonyl compound with a secondary amine, [3,3] rearrangement, and workup generally gave as high as 68% yield using aldehydes having only one α hydrogen. Unfortunately, only a 27% yield was obtained when straight chain aldehydes were used, and the reaction did not proceed with ketones as the carbonyl source. Bailey extended this chemistry to chiral substrates and was able to obtain asymmetric induction as high as 90% ee.[10] The use of $Pd(PPh_3)_4$ also has been reported to catalyze the rearrangement of either N-phenyl- or N-methyl-N-allyl enamines at 50 °C.[11] Although this reaction was found to work well for enamines derived from ketones or α-disubstituted aldehydes, π-allyl palladium intermediates were involved and the reaction did not proceed through a pericyclic reaction.

Two aspects of this chemistry have prevented the general application of the 3-aza-Cope rearrangement in organic synthesis. The first involves the limited methods available for preparation of the N-alkyl-N-allyl enamine substrates. Two methods have been reported for the synthesis of the required alkylallyl enamines. The most commonly used method is simply condensation of an acyclic secondary N-alkyl-N-allyl amine with aldehydes, accompanied by removal of water, to form the corresponding enamine.[4,5a,11] In practice, this works well for aldehydes that are branched at the α carbon but has been less effective at enamine formation from straight-chain aldehydes or ketones. In a second method, an N-alkyl-N-allyl amine has been used in condensation with ketones and diethyl (diazomethyl)-phosphonate to again produce the N-alkyl-N-allyl enamine of a 2-substituted aldehyde.[5b] The second limiting feature of the 3-aza-Cope reaction has been the difficulty in promoting the reaction at a reasonable temperature to obtain, upon reduction of the resulting imine, δ,ε-unsaturated amine products. A related system, the charge-accelerated 2-aza-Cope rearrangement developed by Overman, also has been promoted at mild temperatures. This methodology has led to many valuable contributions to synthetic organic chemistry including a number of elegant syntheses of biologically active alkaloids.[12]

Scheme I. Different Synthetic Routes to 8a



Our interests have focused on the use of the 3-aza-Cope rearrangement as an effective and convergent method of forming carbon–carbon bonds. This report describes the various routes used to efficiently prepare a variety of N-alkyl-N-allyl enamines, the proton-catalyzed [3,3] rearrangement of these compounds, and subsequent reduction of the intermediate imines to δ,ε-unsaturated amine products.

Results and Discussion

Substrate Synthesis. Four different routes for the synthesis of substrate **8a** starting from allylamine were explored. Starting from allylamine, two approaches were studied for the formation of **5**, which has been the standard intermediate for previous synthetic approaches to compounds similar to **8a** (Scheme I). The condensation of allylamine with isobutyraldehyde resulted in the formation of the desired imine **4a**, which could be isolated in 74%

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Table I. Isolated Yields for *N*-Alkyl-*N*-allyl Enamine Formation and Rearrangement

	yield, %			
	4	7	8	10
a	*a*	94	98	81
b	68	90[b]	95	0
d	*a*	79[c]	96[d]	77
f	*a*	82	98	99
g	*a*	68	90	10

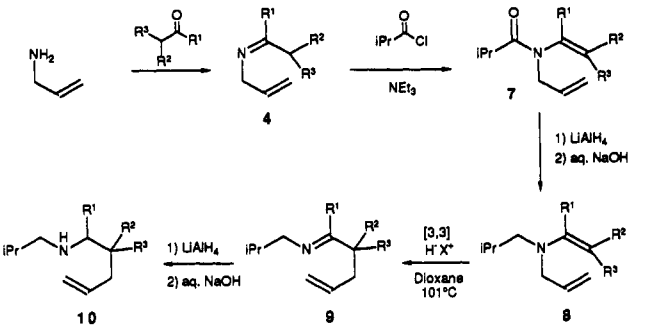
[a] Carried on to 7 without isolation. [b] Mixture of isomers b:c (63:37). [c] Mixture of isomers d:e (57:43). [d] Mixture of isomers d:e (86:14).

distilled yield. Reduction of this imine gave the corresponding amine **5** in 84% isolated yield. Alternatively, intermediate **5** could be prepared by acylation of allylamine with isobutyryl chloride to provide **6** in 95% yield, and subsequent $LiAlH_4$ reduction gave **5** in 88% isolated yield. Enamine formation by condensation of isobutyraldehyde with **5**, catalyzed by *p*-toluenesulfonic acid, produced **8a** in 80% distilled yield. Amide **6** could also be used for enamide formation with isobutyraldehyde, which gave an 85% yield of **7a**, but the reaction took 66 h to reach completion. A third route to **8a** was completed by the $LiAlH_4$ reduction of **7a** in 98% isolated yield. The final route was found to be the most efficient for the general preparation of *N*-alkyl-*N*-allyl enamine substrates. This route involved acylation of imine **4a** to form enamide **7a** in 99% isolated yield. The efficiency of this route could be optimized by initial formation of imine **4a** in benzene. Subsequent addition of NEt_3 and isobutyryl chloride, without isolation of the intermediate imine, resulted in a 94% isolated yield of enamide **7a** from allylamine. These enamide intermediates were more resistant to hydrolysis than the corresponding enamines and could be purified by silica gel chromatography. The previously described reduction with $LiAlH_4$ completed the synthesis of **8a** in 92% overall yield in the three-step process from allylamine.

With use of the optimum sequence for the synthesis of **8a**, the *N*-alkyl-*N*-allyl enamine derivatives of butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were also prepared (Scheme II, Table I). The *N*-alkyl-*N*-allyl enamine of butanal was prepared through the standard three-step process in order to investigate the selectivity of enamine formation. Reaction of *n*-butanal with allylamine gave predominantly the corresponding imine **4b**. Due to the volatility of the compound, isolation of **4b** was limited to 68% yield, but purification was necessary prior to acylation due to minor amounts of dimeric byproducts generated during imine formation. Acylation produced a 63:37 mixture of two enamine geometric isomers in 90% isolated yield. From ^1H NMR analysis using nuclear Overhauser enhancement, the major isomer was **7b**, the *E* enamine isomer, with the minor isomer **7c** having *Z* geometry. Acylation employing a different base, pyridine, produced a slightly higher 71:29 ratio of **7b**:**7c** in 86% yield. Reduction of the enamide mixture with $LiAlH_4$ gave a 95% yield of a single enamine isomer having *E* geometry (**8b**). The nature of the isomerization process of the minor product to the more thermodynamically stable enamine, whether during reduction conditions or workup of the reaction, has not yet been determined.

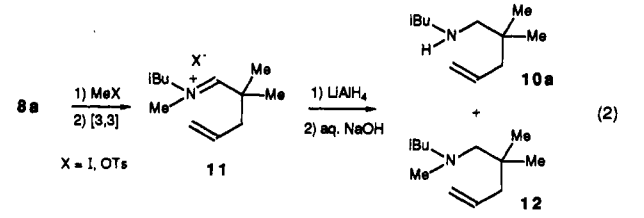
Similar results were observed for selective enamine formation using 2-phenylpropanal as the carbonyl source. Imine formation with allylamine in benzene, followed by reaction with isobutyryl chloride and NEt_3 without isolation of **4d**, gave **7d** in 79% overall yield for the two-step process. As was observed for the preparation of **7b**, the product was isolated as a 57:43 mixture of geometric enamine isomers. On the basis of nuclear Overhauser enhancement NMR experiments, the major enamine isomer was assigned as **7d** with *E* enamine geometry. Reduction of this mixture with $LiAlH_4$ also produced a change in the isomeric ratio. From reduction of the 57:43 mixture of isomers, an 86:14 mixture of isomers **8d**:**8e** was obtained.

Scheme II. Synthesis and Rearrangement of *N*-Allyl-*N*-isobutyl Enamine Substrates



	R^1	R^2	R^3
a	H	Me	Me
b	H	Et	H
c	H	H	Et
d	H	Ph	Me
e	H	Me	Ph
f	-(CH2)4-		H
g	-(CH2)3-		H

Rearrangement and Reduction of *N*-Alkyl-*N*-allyl Enamines. An initial approach to the δ,ϵ-unsaturated amine product **10a** utilized the known methylation of **8a** to produce acceleration of the [3,3] rearrangement and formation of **11** (eq 2). Methylation with MeI or MeOTs



in refluxing dioxane produced complete rearrangement to **11** within 17 h. Although treatment of each reaction mixture with $NaBH_4$ at ambient temperature gave multiple products, the use of $LiAlH_4$ under the same conditions gave more selective reduction of **11**. Reduction of the MeI-promoted rearrangement using $LiAlH_4$ produced an 89:11 mixture of **10a**:**12** in 59% isolated yield, and the corresponding reaction with MeOTs gave a lower 72:28 ratio of **10a**:**12** in 68% yield.[13]

An alternate method, the proton-catalyzed rearrangement of **8a** to **9a** followed by $LiAlH_4$ reduction to **10a** was much more effective. Initial evidence for this transfor-

(13) This tertiary amine was prepared independently by methylation of **10a** to give **12**.

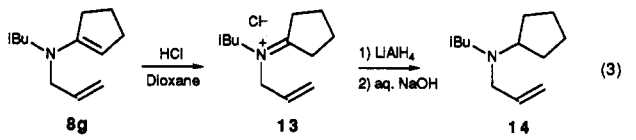
Table II. Various Conditions for HCl-Catalyzed Rearrangement of 8a to 9a

HCl, equiv	time, h	solvent/temp, °C	GLC yield, %
0.3	20	dioxane/101	74
0.3	6	toluene/111	70
0.5	6	dioxane/101	82
0.5	3	toluene/111	82
0.5	6	toluene/80	63
0.8	6	toluene/111	82

mation under protic conditions was observed when the reaction of **5** to **8a** was performed in toluene instead of benzene. Through azeotropic removal of water with refluxing benzene at 80 °C, **8a** was the only product of the acid-catalyzed enamine formation. However, at the higher temperature required for removal of water with refluxing toluene (111 °C), small amounts of acid-catalyzed rearrangement were observed after an extended period of time. In order to optimize reaction acceleration as well as facilitate reaction workup, anhydrous HCl was studied as a means of promoting these reactions.[14] Table II summarizes the results of the rearrangement of **8a** to **9a** using different equivalents of HCl, various reaction temperatures, and dioxane or toluene as solvent for the reaction. Optimum conditions were found to require 0.5 equiv of HCl at reflux in either toluene or dioxane. These conditions produced **9a** as the only volatile product in 82% yield by GLC analysis and, on a preparative scale, in situ reduction of **9a** allowed isolation of **10a** in 81% yield for the two-step process from **8a**. At lower temperatures (80 °C) or fewer equivalents of HCl (0.3 equiv), GLC reaction yields were slightly lower.

The rearrangement of **8** to **10** was highly dependent on the properties and substituent pattern of the enamine functionality. For the aldehyde substrates **8b** and **8d**, success was mixed. Substrate **8d**, which was similar in substitution pattern to **8a**, underwent complete rearrangement promoted by 0.5 equiv of HCl and, following $LiAlH_4$ reduction, **10d** was isolated in 77% yield. When a straight-chain aldehyde enamine such as **8b** was treated with HCl, a mixture of products resulted that did not contain **10b** after reduction. Although N-protonation of enamines has been reported to be kinetically favored by hard acids such as HCl, the thermodynamic product was the iminium ion resulting from C-protonation.[15] If the resulting iminium salts were unsubstituted α to the nitrogen and had minimal steric hindrance at the nucleophilic carbon of the corresponding enamine, rapid oligomerization was found to occur.[16] Similar N- versus C-alkylation pathways have led to reduced product selectivity during the previously mentioned allylation of related enamines[6] and have limited the methylation charge-acceleration studies of *N*-alkyl-*N*-allyl enamines to the derivatives of 2-substituted aldehydes.[5]

Similarly, proton-catalyzed rearrangement of the two ketone-derived substrates was found to be highly dependent on the properties of the carbonyl compound. Rearrangement of the cyclohexanone derivative **8f** proceeded quantitatively to **9f**. Subsequent reduction of this imine without prior isolation gave **10f**, which was obtained in 99% yield as a 90:10 mixture of diastereomers resulting from reduction with $LiAlH_4$. The use of more selective reducing agents was not pursued. In contrast, the results obtained for the cyclopentanone enamine **8g** were poor. As was found for the enamine of *n*-butanal, protonation at the nucleophilic carbon of the enamine to form **13** appeared to dominate over N-protonation. Because intermolecular oligomerization pathways were less favorable for the more sterically hindered iminium salt **13**, as compared to that of the aldehyde iminium salt produced by protonation of **8b**, alternate monomeric products were formed. Upon reduction of the reaction mixture containing **13** and **8g** with $LiAlH_4$, **14** (36%), **10g** (10%), and unreacted **8g** (9%) were obtained as a mixture of the only volatile products (eq 3).[17] Increasing the amount of catalyst to 1.0 equiv of HCl gave increased oligomerization of the substrate and, thus, resulted in reduced product recovery.



Summary

An efficient and general synthesis of *N*-allyl-*N*-isobutyl enamines **8** from allylamine has been established. Initial condensation of the appropriate carbonyl compounds with allylamine formed the intermediate imines **4**, which were treated with isobutyryl chloride to produce the corresponding enamide substrates **7**. Reduction of the enamide intermediates with $LiAlH_4$ gave **8** in good yield. For substrates that could produce isomeric (*E*)- and (*Z*)-**8**, dominant formation of the enamine with *E* geometry was observed. The *E* isomeric selectivity for the 2-phenylpropanal enamine was 86:14 while that of *n*-butanal was observed to produce exclusively the *E* enamine isomer. Proton-catalyzed [3,3] rearrangement and subsequent imine reduction to form the corresponding δ,ϵ-unsaturated amines was efficiently accomplished for the substrates prepared from isobutyraldehyde (81%), 2-phenylpropanal (77%), and cyclohexanone (99%). However, the enamines derived from butanal and cyclopentanone did not undergo high-yielding charge-accelerated [3,3] rearrangement but instead gave mixtures of products resulting predominantly from protonation at carbon.

Experimental Section

General Methods. All reactions were carried out by using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Dichloromethane, acetonitrile, pyridine, and triethylamine were heated at reflux over calcium hydride for a minimum of 12 h and then distilled immediately prior to use. 1,4-Dioxane was dried over $LiAlH_4$ and distilled. Solutions of HCl (1 M in Et_2O) and $LiAlH_4$ (1 M in THF) were obtained from Aldrich Chemical Co. Unless specified, concentration of mixtures was performed on a Büchi rotary evaporator.

Gas chromatographic (GLC) analyses were carried out on a Perkin-Elmer 8500 instrument using a 50-m RSL-200 capillary column (5% methyl phenyl silicone) and an FID detector using a 220 °C injector temperature and 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. NMR spectra were obtained on Varian Gemini 300 or VXR-300 spectrometers using $CDCl_3$ as solvent. Data are reported as follows: chemical shift relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet), integration, and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

(14) HCl is available as a 1 M solution in Et_2O from Aldrich Chemical Co.

(15) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. Protonation of enamines is discussed on pages 1998–2000.

(16) Hinman, R. L. *Tetrahedron* **1968**, *24*, 185, and references therein.

(17) This tertiary amine was prepared independently by $LiAlH_4$ reduction of the imine formed from allylamine and cyclopentanone, followed by reaction with isobutyryl chloride and reduction to give **14**.

***N*-Allyl-*N*-isobutylideneamine (4a).** A mixture of allylamine (3.54 g, 62 mmol), isobutyraldehyde (4.47 g, 62 mmol), and 4-Å molecular sieves in 100 mL of Et_2O was stirred for 2 h at ambient temperature. The solution was then removed from the insoluble material via cannula and distilled at atmospheric pressure to give **4a** (5.11 g, 50.0 mmol) in 74% yield (bp 112–114 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, 6 H, J = 6.9 Hz), 2.42 (dsept, 1 H, J = 4.9, 6.9 Hz), 3.95 (d, 2 H, J = 5.6 Hz), 5.05 (dd, 1 H, J = 1.8, 10.3 Hz), 5.10 (dd, 1 H, J = 1.8, 17.2 Hz), 5.93 (ddt, 1 H, J = 10.3, 17.2, 5.6 Hz), 7.51 (d, 1 H, J = 4.9 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 34.1, 63.2, 115.5, 136.1, 170.9; IR (neat) 3083, 3013, 2967, 2932, 2874, 2824, 2674, 1466, 1456, 1437, 1366, 1103, 1019, 995, 916 cm^{-1}.

***N*-Allylisobutyramide (6).** To a mixture of allylamine (9.02 g, 158 mmol) and pyridine (12.48 g, 158 mmol) in 600 mL of dry THF at 0 °C was added isobutyryl chloride (16.84 g, 158 mmol) at a dropwise rate. After addition was complete, the mixture was heated at reflux for 5 h, cooled to ambient temperature, and then washed with 50 mL of 15% aqueous NaOH. The aqueous layer was then extracted with 4 × 20 mL of Et_2O, and the organic fractions were combined and dried over $MgSO_4$. After removal of solvents by rotary evaporation, the resulting oil was distilled to give **6** (18.99 g, 149 mmol) in 95% yield (bp 78 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.13 (d, 6 H, J = 6.9 Hz), 2.37 (sept, 1 H, J = 6.9 Hz), 3.84 (ddd, 2 H, J = 1.6, 1.6, 6.6 Hz), 5.09 (ddt, 1 H, J = 1.4, 10.2, 1.6 Hz), 5.14 (ddt, 1 H, J = 1.4, 17.1, 1.6 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.1, 6.6 Hz), 5.85 (br s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 35.3, 41.5, 116.2, 134.6, 177.3; IR (neat) 3293, 3085, 3015, 2971, 2934, 2876, 1645, 1545, 1470, 1422, 1387, 1242, 1098, 988, 918 cm^{-1}. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.04; H, 9.91; N, 11.85.

Reduction of 4a to *N*-Allyl-*N*-isobutylamine (5). To a suspension of $LiAlH_4$ (1.37 g, 36 mmol) in 150 mL of Et_2O at 0 °C was slowly added 3.34 g (30 mmol) of *N*-allyl-*N*-isobutylideneamine (**4a**). After being stirred for 2 h, the solution was cooled to 0 °C and quenched by addition of 1.4 mL of H_2O, followed by 1.4 mL of 15% aqueous NaOH, and finally 4.1 mL of H_2O. The mixture was stirred for 1 h and then filtered through Na_2SO_4. Solvent was removed and the allylic amine was distilled at atmospheric pressure to give **5** (2.84 g, 25.1 mmol) in 84% yield (bp 122–124 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, 6 H, J = 6.7 Hz), 1.00 (br s, 1 H), 1.70 (tsept, 1 H, J = 6.8, 6.7 Hz), 2.38 (d, 2 H, J = 6.8), 3.20 (ddd, 2 H, J = 1.4, 1.4, 6.0 Hz), 5.04 (ddt, 1 H, J = 1.7, 10.2, 1.4 Hz), 5.13 (ddt, 1 H, J = 1.7, 17.2, 1.4 Hz), 5.88 (ddt, 1 H, J = 10.2, 17.2, 6.0 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.7, 28.3, 52.6, 57.5, 115.5, 137.2; IR (neat) 3407, 3081, 2959, 2934, 2874, 2811, 1646, 1466, 1385, 1368, 1129, 918 cm^{-1}. Anal. Calcd for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.43; H, 13.69; N, 12.21.

Reduction of 6 to *N*-Allyl-*N*-isobutylamine (5). To a suspension of $LiAlH_4$ (1.85 g, 48.6 mmol) in 200 mL of Et_2O at 0 °C was slowly added 5.62 g (44.2 mmol) of *N*-allylisobutyramide (**6**). The mixture was heated at reflux for 3 h, after which the solution was cooled to 0 °C and quenched by addition of 2 mL of water, followed by 2 mL of 15% aqueous NaOH, and again with 6 mL of water. After being stirred for 2 h, the solution was filtered through Na_2SO_4 and the solvent was removed by rotary evaporation at 0 °C. The residue was distilled at atmospheric pressure to give **5** (4.38 g, 38.7 mmol) in 88% yield (bp 125 °C). Spectroscopic data were identical with that reported for the product obtained by reduction of **4a**.

Synthesis of 7a by Acylation of 4a. To 100 mL of dry THF were added 2.00 g (18 mmol) of *N*-allyl-*N*-isobutylideneamine (**4a**) and 1.82 g (18 mmol) of NEt_3. The mixture was cooled to 0 °C and 1.92 g (0.018 mmol) of isobutyryl chloride was added dropwise. After being heated at reflux for 2 h, the solution was cooled to ambient temperature and washed with 30 mL of 15% aqueous NaOH. The aqueous layer was extracted with 2 × 75 mL of Et_2O and then dried over Na_2SO_4. The solvents were removed under reduced pressure, and the resulting enamide was distilled via Kugelrohr distillation under vacuum to give **7a** (3.24 g, 17.9 mmol) in 99% yield (bp 55–65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.02 (d, 6 H, J = 6.8 Hz), 1.57 (s, 3 H), 1.70 (s, 3 H), 2.65 (sept, 1 H, J = 6.8 Hz), 3.89 (d, 2 H, J = 6.2 Hz), 5.04 (dd, 1 H, J = 1.6, 11.3 Hz), 5.06 (dd, 1 H, J = 1.6, 16.0 Hz), 5.74 (ddt, 1 H, J = 11.3, 16.0, 6.2 Hz), 5.85 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.3, 18.8, 21.5, 30.9, 50.0, 116.9, 123.5, 133.4, 135.9, 177.7; IR (neat) 3083, 2975, 2936, 2876, 1653, 1472, 1404, 1242, 1208, 1092, 993, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.84; H, 10.78; N, 7.72.

Preparation of 8a by Condensation of Isobutyraldehyde with 5. A flask containing **5** (1.70 g, 15 mmol), isobutyraldehyde (1.08 g, 15 mmol), and *p*-toluenesulfonic acid (0.007 g, 0.04 mmol) in 75 mL of benzene was fitted with a Dean–Stark trap containing 4-Å molecular sieves. The solution was heated at reflux for 28 h and the cooled to ambient temperature. After removing the benzene under reduced pressure, the resulting oil was distilled via Kugelrohr distillation under vacuum to give **8a** (2.00 g, 12.0 mmol) in 80% yield (bp 45–50 °C, 8 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, J = 6.6 Hz), 1.58 (d, 3 H, J = 1.3 Hz), 1.58 (tsept, 1 H, J = 7.3, 6.6 Hz), 1.65 (d, 3 H, J = 1.3 Hz), 2.25 (d, 2 H, J = 7.3 Hz), 3.15 (ddd, 2 H, J = 1.6, 1.6, 6.2 Hz), 5.02 (ddt, 1 H, J = 2.0, 10.2, 1.6 Hz), 5.08 (ddt, 1 H, J = 2.0, 17.2, 1.6 Hz), 5.22 (qq, 1 H, J = 1.3, 1.3 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.2, 6.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.4, 20.4, 22.0, 27.4, 59.6, 63.1, 115.9, 122.8, 135.8, 136.9; IR (neat) 3081, 3009, 2955, 2926, 2870, 2803, 1676, 1644, 1468, 1449, 1377, 1337, 1194, 1117, 1101, 995, 916 cm^{-1}. Anal. Calcd for $C_{11}H_{21}N$: C, 78.98; H, 12.65; N, 8.37. Found: C, 79.18; H, 12.83; N, 8.48.

Formation of 7a from Condensation of Isobutyraldehyde with 6. To 300 mL of benzene were added *N*-allylisobutyramide (3.51 g, 27.6 mmol), isobutyraldehyde (2.38 g, 33.1 mmol), and *p*-toluenesulfonic acid (0.48 g, 2.8 mmol). The reaction flask was fitted with a Dean–Stark trap containing 4-Å molecular sieves, and the solution was heated at reflux for 66 h. After cooling the mixture, the volatiles were removed under reduced pressure, and the enamide was distilled under vacuum to give *N*-allyl-*N*-isobutylideneisobutyramide (**7a**, 4.24 g, 23.4 mmol) in 85% yield (bp 60–70 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of **4a**.

General Method for Two-Step Synthesis of 7 from Allylamine. Allylamine (50 to 250 mmol, 1.0 equiv) and the necessary aldehyde (1.0 equiv) were taken up in benzene (0.35–0.375 M solution). A Dean–Stark trap was fitted on the apparatus and the solution was heated to reflux to azeotropically remove the resulting water. After heating for 19–22 h, the water was removed, 4-Å molecular sieves were added to the Dean–Stark trap, and reflux was continued for 2 h. The solution was cooled to ambient temperature and NEt_3 (1.0 equiv) and isobutyryl chloride (1.0 equiv) were added, sequentially, and then heated at reflux for 3 h. The mixture was filtered to remove solids, and after benzene was removed under reduced pressure, the crude oil was purified by flash column chromatography (silica, 230–400 mesh; eluent 70:30 Et_2O:petroleum ether). The solvents were evaporated and the enamide was distilled under vacuum to give **7**.

7a: 42.68 g, (23.5 mmol, 94% yield) (bp 50–54 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of **4a**.

General Method for Reduction of 7 to *N*-Allyl-*N*-isobutyl Enamines 8. To a suspension of $LiAlH_4$ (1.1 mmol/1.0 mmol **7**) in Et_2O (0.2 M solution) at 0 °C was added **7** (1.0 equiv, 9 to 66 mmol reaction scale) slowly via syringe. After addition was complete, the reaction was warmed to ambient temperature and stirred for 2–3 h. The reaction was then cooled to 0 °C and quenched by addition of water (1 mL/g $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$), and then again water (3 mL/g $LiAlH_4$). The mixture was stirred for 2 h and then filtered through Na_2SO_4. Solvent was removed under reduced pressure and enamine **8** was distilled via short-path or Kugelrohr distillation.

8a: 9.84 g (58.8 mmol, 98% yield) (bp 54–55 °C, 8 mmHg). Spectroscopic data were consistent with that reported for the preparation of **8a** by condensation of **5** with isobutyraldehyde.

General Procedure for HCl Rearrangement of 8 Followed by Reduction to 10. Enamine **8** (1.0 equiv) was dissolved in 1,4-dioxane (0.2 M solution) and 0.5 equiv of HCl (1 M solution of HCl in Et_2O) and then heated to reflux. After 9–10 h, the solution was cooled to ambient temperature and $LiAlH_4$ (1.1 equiv, 1 M in THF) was added. After being stirred for 2 h, the solution was then cooled to 0 °C and quenched by addition of water (1 mL/g $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$), and then again water (3 mL/g $LiAlH_4$). The mixture was allowed to stir for 1 h and then filtered to remove aluminum salts.[18] Solvent

was removed under reduced pressure and the oil was Kugelrohr distilled under vacuum to give **10**.

10a: 1.37 g (8.1 mmol, 81% yield) (bp 50–60 °C, 8 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.85 (s, 6 H), 0.86 (d, 6 H, J = 6.6 Hz), 0.87 (bs, 1 H), 1.71 (tsept, 1 H, J = 6.9, 6.6 Hz), 1.98 (d, 2 H, J = 7.5 Hz), 2.29 (s, 2 H), 2.35 (d, 2 H, J = 6.9 Hz), 4.99 (m, 2 H), 5.79 (ddt, 1 H, J = 9.2, 17.9, 7.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60.3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{23}N$: C, 78.04; H, 13.69; N, 8.27. Found: C, 77.64; H, 13.87; N, 7.68.

***N*-Methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (12).** To 25 mL of dry acetonitrile were added 0.847 g (5 mmol) of **10a** and 0.710 g (5 mmol) of MeI. The solution was heated to reflux for 12.5 h and then cooled to ambient temperature. Solvent was removed under reduced pressure and the residue was washed with 10 mL of 15% aqueous NaOH and extracted with 3 × 50 mL portions of Et_2O. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Kugelrohr distillation under vacuum gave 0.739 g (4.0 mmol, 81% yield) of **12** (bp 60–70 °C, 10 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.82 (s, 6 H), 0.87 (d, 6 H, J = 6.6 Hz), 1.65 (tsept, 1 H, J = 7.4, 6.6 Hz), 1.97 (d, 2 H, J = 7.4 Hz), 2.07 (s, 2 H), 2.10 (d, 2 H, J = 7.4 Hz), 2.18 (s, 3 H), 4.97 (m, 2 H), 5.81 (ddt, 1 H, J = 11.0, 18.8, 7.4 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.4, 26.8, 36.0, 44.9, 45.0, 69.5, 70.2, 116.6, 136.4; IR (neat) 3077, 2978, 2843, 2786, 1640, 1470, 1385, 1366, 1250, 1105, 1040, 993, 909, 850 cm^{-1}. Anal. Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.74; N, 7.64. Found: C, 78.55; H, 13.48; N, 7.70.

(18) In the case of the more volatile compounds **10a** and **10b**, an excess of aqueous HCl was added, and the solution was concentrated under reduced pressure. The residue was treated with 15% aqueous NaOH to a pH of 14, the amine was extracted with 3 × 50 mL portions of Et_2O, and the organic layers were dried ($MgSO_4$) prior to distillation.

MeI-Promoted Rearrangement of 8a Followed by $LiAlH_4$ Reduction. To 15 mL of 1,4-dioxane were added 1.34 g (8 mmol) of enamine **8a** and 1.14 g (8 mmol) of MeI. The solution was heated to reflux for 17 h and then cooled to 0 °C. The reaction was reduced by addition of $LiAlH_4$ (16.0 mL, 1 M in THF, 16 mmol), warming to ambient temperature, and then stirring for 2 h. The solution was then cooled to 0 °C and quenched by addition of 0.6 mL of water, 0.6 mL of 15% aqueous NaOH, and 1.8 mL of water. After being stirred for 1 h, the mixture was filtered and then treated with an excess of aqueous HCl. The solution was concentrated under reduced pressure and the residue was treated with 15% aqueous NaOH to a pH of 14. The amine products were extracted with 3 × 50 mL portions of Et_2O and the organic layer was dried ($MgSO_4$). Volatiles were removed by rotary evaporation and the oil was Kugelrohr distilled under vacuum to give 0.81 g (59% yield) of an 89:11 mixture of *N*-isobutyl-2,2-dimethylpent-4-enamine (**10a**) and *N*-methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (**12**) (bp 60–65 °C, 10 mmHg).

MeOTs-Promoted Rearrangement of 8a Followed by $LiAlH_4$ Reduction. The reaction was performed under conditions identical with those described above, using 1.49 g (8 mmol) of MeOTs. Distillation after workup gave 0.95 g (68% yield) of a 72:28 mixture of *N*-isobutyl-2,2-dimethylpent-4-enamine (**10a**) and *N*-methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (**12**) (bp 60–65 °C, 10 mmHg).

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Supplementary Material Available: Experimental procedures and physical data for the series of compounds **b–g** (5 pages). Ordering information is given on any current masthead page.

Metal-Ion Catalysis in Nucleophilic Displacement Reactions at Carbon, Phosphorus, and Sulfur Centers.† 5. Alkali-Metal Ion Catalysis and Inhibition in the Reaction of *p*-(Trifluoromethyl)phenyl Methanesulfonate with Ethoxide Ion

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The reactions of alkali-metal ethoxides with *p*-(trifluoromethyl)phenyl methanesulfonate (1) in anhydrous ethanol at 25 °C, yielding *p*-(trifluoromethyl)phenolate ion and ethyl methanesulfonate, have been investigated in order to reveal the effects of alkali-metal ions on reaction rates. Kinetic spectrophotometric studies of the nucleophilic displacement reaction of 1 with alkali-metal ethoxides in the absence and presence of complexing agents showed that the observed rate constants increase in the order LiOEt < EtO^- < NaOEt < CsOEt < KOEt. Thus, Li^+ inhibits the reaction of ethoxide ion, while the other alkali-metal ions all act as catalysts. The kinetic data are analyzed in terms of parallel reactions of free ethoxide ion and alkali-metal ethoxide ion pairs, and rate constants for the reactions of these species are calculated. Association constants governing the interaction of the various metal ions with the transition state for the reaction of ethoxide ion with 1 are derived from the kinetic data and compared to association constants for interaction of metal ions with ethoxide ion in the ground state. The trend in the sizes of the association constants for the methanesulfonate transition state, Li^+ < Na^+ < K^+ < Cs^+, is believed to arise from ion pairing of the transition state with solvated metal ions. A similar ordering is observed for the transition state in the reaction of *p*-nitrophenyl benzenesulfonate (2) with alkali metal ethoxides, while an inverted ordering is seen for the transition state for the reaction of ethoxides with *p*-nitrophenyl diphenylphosphinate (3). These results are interpreted in terms of the extent of charge delocalization in the transition states and its effect on interactions with bare or solvated metal ions.

Introduction

As part of a series of systematic studies of the mechanisms of reaction of carbon-, phosphorus-, and sulfur-based esters, and the effects of alkali-metal ions on these reactions, we report here on alkali-metal ion catalysis and inhibition in the reaction of ethoxide ion with *p*-(trifluoromethyl)phenyl methanesulfonate (1) in anhydrous ethanol at 25 °C. The purpose of these studies has been to explain the interesting and unusual finding that some alkali-metal ions catalyze the reactions of ethoxide ion with 1 and with *p*-nitrophenyl benzenesulfonate (2), while

†This paper is an extension of our series on Bond Scission in Sulfur Compounds. For previous papers in this series, see ref 1.

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