a weaker base in lower concentration promotes 4-hydroxylation, one can suppose that the former process is kinetically controlled. Orientation in substituted nitrobenzenes is much less sensitive to changes in the conditions and so far cannot be efficiently controlled.

The selected examples presented in Table I show the generality of this reaction. Since this simple process proceeds under mild conditions giving a variety of substituted nitrophenols in high yields, it can be of substantial value even in a large-scale synthesis. Moreover, some phenols which are not available by traditional methods, as, for example, 2-nitro-3-hyroxythiophene, can be readily prepared via direct VNS hydroxylation (entry 10).

The generality of the vicarious nucleophilic substitution of hydrogen with carbon, amino, and hydroxy substituents and the known nucleophilic replacements of hydrogen via oxidative pathways,[10,13] lead to the conclusion that there is a set of reactions by which hydrogen on electrophilic arenes can be replaced via nucleophilic attack. Due to their similarity in stoichiometry, these reactions can be considered to be a mirror reflection of electrophilic aromatic substitution.[14] There is also a similarity between these processes with respect to ipso substitution. Electrophilic replacement of substituents other than hydrogen on aromatic rings—ipso substitution—is possible, but the substitution of hydrogen is usually much faster.[15] Similarly, nucleophilic substitution of hydrogen on halonitroarenes via VNS, under properly selected conditions, proceeds much faster than conventional S_NAr of halogen (ipso substitution), making the latter a secondary process.[16]

Acknowledgment. This research was supported by the Polish Academy of Sciences Grant CPBP 01.13.1.

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Regioselective Aza-Cope Rearrangement of α-Halogenated and Nonhalogenated Imines

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Received April 4, 1990

Summary: The 3-aza-Cope rearrangement of α-halogenated and nonhalogenated ketimines by deprotonation of the corresponding iminium salts was found to be an especially facile and regioselective process. Deuterium labeling studies supported the proposed mechanism which required the rearrangement to be highly concerted.

The regioselective deprotonation of ketimines is an important reaction for the formation of new carbon–carbon double bonds via alkylation or via aldol-type addition to carbonyl groups.[1a] Dialkyl ketimines are generally deprotonated with high regioselectivity anti to the *N*-alkyl substituent. Highly diastereoselective alkylations of ketimine and aldimine anions have also been observed with optically active N-substituents capable of internally chelating the metal counterion of the 1-azaenolate.[1b,c]

Less work has been reported on the regioselective functionalization of halogenated imines or the stereoselectivity of the alkylation of haloazaenolates.[2] 2-Fluorocyclohexanone can be regiospecifically functionalized using the corresponding pyrrolidine enamine, without stereochemical control.[3] Recently we have shown that the fluoroacetone imine of valinol *O*-methyl ether and the 2-fluorocyclohexanone imine of phenylalaninol *O*-methyl ether can be regioselectively deprotonated and diastereoselectively alkylated to form optically enriched 3-fluoroalkanones and 2-fluoro-2-alkylcyclohexanones[3,4] in modest to good enantiomeric excess.[4]

Stereochemical control in the substitution of imines can also be achieved using the Cope or Claisen rearrangements.[5-11] The 3-aza-Cope rearrangement in particular has been used to form quaternary centers[12-14] or has been employed in natural products synthesis.[15,16] Unfortunately, the conditions for the rearrangement of these *N*-allylenamines are quite rigorous, often requiring high temperatures.[12,17-20] It has been reported that both

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Table I. Synthesis of β-Halogenated and Nonhalogenated *N*-Alkylideneallylamines 1 and γ,δ-Unsaturated Ketones 4

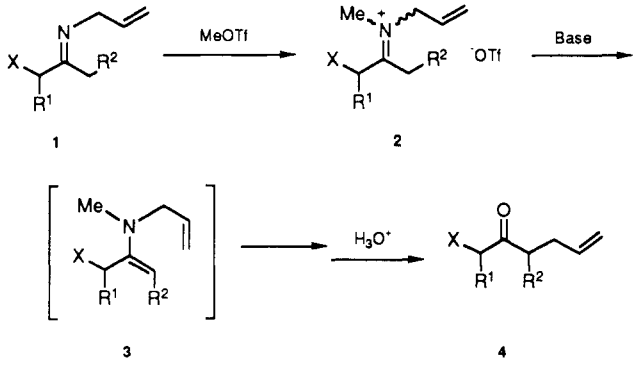
entry	R^1	R^2	X	method[a]	yield of imines 1,[b] %	yield of ketones 4, %
a	CH_3	H	H	A	67	45[c]
b	CH_3	H	CH_3	A	83	41[c]
c	CH_3	CH_3	H	A	74	36[c]
d	CH_3	H	Cl	A	63	55[c]
e	CH_3	H	F	B	94	54[c]
f	$(CH_2)_2$		H	A	81	13[d]
g	$(CH_2)_3$		H	A	85	36[d]
h	$(CH_2)_3$		CH_3	A	80	39[d]
i	$(CH_2)_4$		H	A	63	17[d]
j	$(CH_2)_3$		F	B	87	31[d]

[a] Method A: 5 equiv of allylamine, diethyl ether as solvent, 0.6 equiv of $TiCl_4$. Method B: 2 equiv of allylamine, diethyl ether as solvent, activated molecular sieves. [b] Yield after bulb-to-bulb disillation. [c] Yield of reaction mixture (purity determined by NMR). [d] Yield determined by gas chromatography.

acid[16,21] and transition-metal[13,15] catalysts promote the rearrangement at much lower temperatures, enhancing the synthetic utility of the rearrangement. Also, N-allylated tertiary enamines, i.e. quaternary ammonium salts, tend to rearrange under milder conditions.[14,22,23] To the best of our knowledge, however, the rearrangement was never used as a tool for regioselective allylation of aliphatic compounds, except for the palladium(0)-catalyzed rearrangement of *N*-allyl-*N*-phenyl-2-methyl-1-cyclohexylamine, which gave 2-allyl-2-methylcyclohexanone on hydrolysis.[13]

Results and Discussion

We report here that a variety of halogenated and nonhalogenated *N*-allylenamines undergo a facile, highly regioselective rearrangement under surprisingly mild conditions. Two hours at room temperature is sufficient for compound **1** to form **4** following treatment with methyl trifluoromethanesulfonate and 1,8-bis(dimethylamino)-naphthalene in acetonitrile. The starting *N*-alkylideneallylamines **1d,f–i** were synthesized by condensation of an excess (5 equiv) of allylamine with the corresponding ketone in the presence of titanium(IV) chloride.[24,25]



The fluorinated ketimines **1e** and **1j** were synthesized by condensation of 2 equiv of allylamine with the corresponding α-fluoro ketone in the presence of activated molecular sieves (see Table I). The selective formation of the *E* isomer in the case of the dissymmetric nonhalogenated and halogenated ketimines was in agreement with previous observations.[4b,c,25,26]

Rearrangement Studies. In a typical procedure, 1.1 equiv of methyl trifluoromethanesulfonate was added to the *N*-alkylideneallylamine **1** at −80 °C. Upon warming to room temperature, the exothermic formation of the iminium salt **2** occurred at about −30 °C. ^1H, ^{13}C, and ^{19}F NMR data revealed that all the dissymmetric iminium salts **2** were present as a 1:1 mixture of the *E* and *Z* isomers. After standing for 15 min at room temperature, the iminium salt **2** was treated at −80 °C with 1.1 equiv of 1,8-bis(dimethylamino)naphthalene, dissolved in acetonitrile. The reaction mixture was allowed to warm up to room temperature. After 2 h of stirring at room temperature, the reaction mixture was quenched with 5 equiv of a 10% HCl solution and stirred for 2 h. The acetonitrile was evaporated in vacuo, and the residue was extracted 4 times with 10 mL of diethyl ether. The combined organic layers were filtered through silica gel and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the reaction mixtures were employed in spectroscopic analyses. While the yields are not by any means optimized, they are consistent with the reported yields for this type of process.[17] The yields of rearranged products were lowest with cyclic ketimines, an observation also consistent with published findings where related rearrangements occasionally did not proceed at all with cyclic

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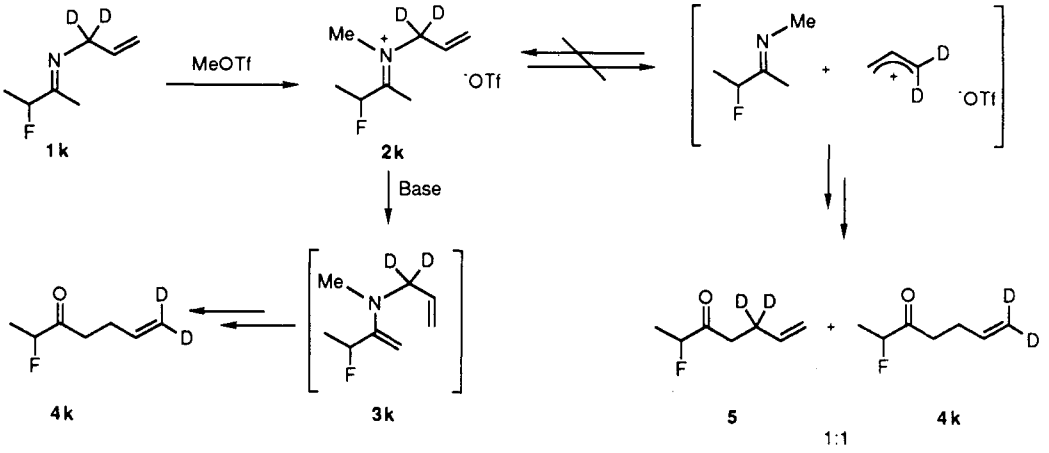
(24) A typical procedure for the preparation of imines such as *N*-2-butylidene-2-propenylamine (**1a**). To a solution of 0.05 mol (3.61 g) of 2-butanone in 50 mL of diethyl ether was added 0.25 mol (19 mL) of allylamine at room temperature under a N_2 atmosphere. The temperature of the solution was decreased to 0 °C. A solution of 0.03 mol (3.29 mL) of titanium(IV) chloride in 10 mL of dry pentane was added dropwise at 0 °C. The solution was stirred for 1 h at room temperature and quenched with 50 mL of 1 N sodium hydroxide. The water layer was washed with 3 × 20 mL of diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure. Bulb-to-bulb distillation at 50 °C at 0.50–0.75 mmHg yielded 5.55 g (66.7%) of *N*-2-butylidene-2-propenylamine.

(25) Because of their instability toward chromatography and fractional distillation, the thus obtained *N*-allylimines were purified by bulb-to-bulb distillation (50 °C at 0.50–0.75 mmHg).

(26) A typical procedure for the preparation of imines such as *N*-(3-fluoro-2-butylidene)-2-propenylamine, **1e**. To a mixture of 0.05 mol (2.86 g) of allylamine and 28 g of activated molecular sieves in 50 mL of diethyl ether was added 0.025 mol (2.25 g) of 3-fluorobutanone at 0 °C under a N_2 atmosphere. The mixture was stirred slowly for 2 h at room temperature, filtered over anhydrous sodium sulfate, and evaporated at reduced pressure. Bulb-to-bulb distillation yielded 3.04 g (94.2%) of *N*-(3-fluorobutylidene)-2-propenylamine.

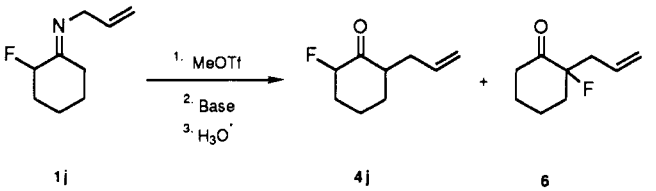
Scheme I



substrates.[23] While **3** must be formed regioselectively in the course of the reaction, it is not likely that it is the enamine which undergoes the rearrangement. A protonated enamine species, recognized to undergo facile sigmatropic rearrangements,[17] may be formed either by proton transfer from the conjugate acid of the base employed or during the acidic hydrolysis. An investigation of these possibilities is underway.

An alternative mechanism of C-allylation must be considered in addition to sigmatropic rearrangement.[27] This reaction pathway would result from a heterolytic dissociation of the iminium salt **2** into the methyl imine and an allylic cation. A labeling experiment, employing 1,1-dideuterated allyl imine, would give a 1:1 mixture of 7,7-dideuterio-2-fluoro-6-hepten-3-one, **4k**, and 5,5-dideuterio-2-fluoro-6-hepten-3-one (**5**) in the latter case. However, methylation with methyl triflate of *N*-(3-fluoro-2-butylidene)-1,1-dideuterio-2-propenylamine, **1k**, followed by treatment with 1,8-bis(dimethylamino)-naphthalene and hydrolysis, yielded only the 7,7-dideuterio-2-fluoro-6-hepten-3-one, **4k**, suggesting that the product is not formed via a dissociative pathway (see Scheme I).

Surprisingly, the regioselectivity of the aza-Cope rearrangement was very high, in all cases except in the rearrangement of **1j**, only the formation of **4** was observed. This was attributed to the selective formation of enamine **3**, most likely resulting from steric interaction on approach of the bulky base required for deprotonation. In order to investigate the electronic effects of halogen substitution, *N*-(2-fluoro-1-cyclohexylidene)allylamine, **1j**, was treated under the same rearrangement conditions. As fluorine



is a non sterically demanding substituent,[28] a 1:1 mixture of 6-allyl-2-fluorocyclohexanone (**4j**) to 2-allyl-2-fluorocyclohexanone (**6**) would be expected in the absence of electronic effects. However, ^{19}F NMR data indicated formation of **4j** and **6** as a 12:1 mixture.

Although the yields of the rearrangements may be less than that desired optimally, presumably as a result of the instability of the intermediate methyl imine, the reaction conditions are surprisingly mild. Both steric and electronic effects can moderate the regioselectivity of this transformation. Moreover, the regioselectivity of the rearrangement illustrates the potential of this approach for the synthesis of α-halogenated γ,δ-unsaturated carbonyl compounds. Further work on the stereoselectivity of the rearrangement is now in progress.

Acknowledgment. Financial support of this work by the National Science Foundation Grant number CHE-8520875, NATO Grant number 0735-87, and DARPA Contract DAAL 0398KO198 is gratefully acknowledged.

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