Increasing ω_1 to 2513 s^{-1} from 200 s^{-1} causes a large percentage reduction in the ammonium contribution to the exchange broadening, while that from the imidazole protons is affected only slightly (see Figure 1). A maximum diminution occurs at pH 4.2. Such a maximum effect can only occur if the broadenings are additive as in eq 2. The separated broadenings are then used to calculate τ_{IMH^+} and $\tau_{NH_3^+}$ by using eq 2. The rate law for 0.0596 M histamine is described by eq 3 where $[BH^+]$ is the molar

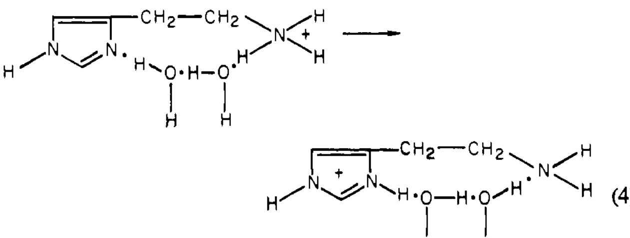
$$1/\tau_{NH_3^+} = 0.151/[H^+] \qquad (3a)$$

$$1/\tau_{IMH^+} = 2940 + 2050/(1 + 550[H^+]) + 1.95 \times 10^7[BH^+] \qquad (3b)$$

concentration of singly protonated histamine.

Additional evidence in favor of the additive broadening scheme is obtained from the maximum value of Δ/C^{14} (Figure 2). If the two NH sites were exchange averaged by a rapid, direct N-H-N process, the observed chemical shift would be the weighted mean of δ_{IMH^+} and $\delta_{NH_3^+}$. The Δ/C maximum calculated for this case would be 73 for $\omega_1 = 200$ s^{-1} rather than the observed value of 48.

The final fit of a large body of experimental data showed excellent agreement with the separate rate expressions for $\tau_{NH_3^+}$ and τ_{IMH^+}. Although the rate laws found are too complex to fully justify here, we will outline an important conclusion and present the detailed kinetic analysis elsewhere. A very rapid intramolecular proton transfer was detected in singly protonated histamine. Specifically, a proton initially bonded to an amino nitrogen is transferred to an imidazole nitrogen via one or two water molecules with a rate constant of $(1.9 \pm 0.1) \times 10^5$ s^{-1} (eq 4). The reaction



(4)

is illustrated with two water molecules. This is the upper limit as determined at high pH with ^{17}O-labeled water.[15,16] Since it has been reported that imidazole itself catalyzes ^{17}O-H exchange in a reaction which is kinetically indistinguishable from reaction 4[17] in the accessible pH range for such measurements, we can only infer the range of 1-2 water molecules.

Since the distance between the ammonium and imidazolium nitrogens in this reaction is comparable to that between acid-base centers in enzymes, it is probable that such intramolecular proton transfers are important at the active sites of enzymes. That hydrogen-bonded water molecules can fit molecular contours suggests that such intramolecular processes provide a route for proton transfers between "sterically inaccessible" functional groups.

It is noteworthy that the intramolecular reaction can compete favorably with bimolecular reactions at physiological pH. For example, the bimolecular reaction of an enzyme (E), $E + H^+ \rightarrow EH^+$, has a rate constant typically between 10^9 and 10^{10} L mol^{-1} s^{-1}. At pH 7.4, the lifetime of the enzyme will be ca. 10^{-2} s from the bimolecular reaction. For the intramolecular proton transfer from an ammonium ion to imidazole, the lifetime of the imidazole is only 5×10^{-6} s, suggesting that such a process could be dominant near neutrality.

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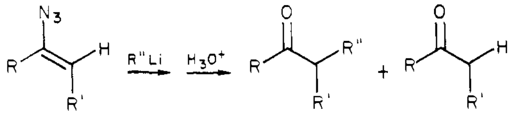
Umpolung of Alkyl Anions by Reactions with Vinyl Azides. In Situ Generation of Primary Enamines[1]

Sir:

The concept of umpolung[2] (dipole reversal in organic reagents) has been shown to be of considerable utility in organic synthesis. Among the better known examples are the use of a dithiane[3] or an oxazoline[4] anion as a masked electrophile (carbonyl). We report an example in which simple alkyl anions, in reactions with vinyl azides, are transformed into alkyl cation reagents.

Vinyl azides have been shown to be versatile compounds in organic synthesis,[5] and though they are attacked by electrophiles,[6] their reaction with carbanions has not been documented. We have found that vinyl azides (**1**) react with readily available alkyllithium

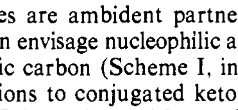


1 **2** **3**

reagents to yield, after acidic treatment, mainly ketones or aldehydes (**2**) that result from regiospecific alkylation at the β-vinylic carbon in **1** (see Table I). Ketones (**3**) are minor byproducts of these transformations.

Since vinyl azides are ambident partners in reactions with electrophiles, one can envisage nucleophilic attack by alkyllithium either at the olefinic carbon (Scheme I, in analogy with organocopper 1,4-additions to conjugated ketones) or at the azide function (Scheme II, in analogy with reactions of simple azides with nucleophiles, including Grignard reagents).[7]

We were able to show that triazenes are intermediates in these reactions by omitting the acidic workup. For instance, triazene **7** is obtained in 91% yield from reaction of **1c** with CH_3Li followed



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by workup with water.[8] This provides evidence for carbanionic attack at the terminal nitrogen of the vinyl azides. The possibility

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(8) The NMR spectrum (CCl_4) of **7** showed two doublets (1 H each) at δ 5.8 and δ 6.8 (J = 14 Hz), a broad singlet (NH) at δ 7.8, a methyl singlet at δ 3.1, and a *tert*-butyl singlet at δ 1.14. Similar triazene intermediates can be isolated in other cases.

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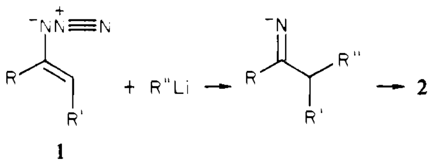
Table I. Formation of Alkylated Ketones or Aldehydes (2) by Reaction of Vinyl Azides (1) with Alkyllithium[a]

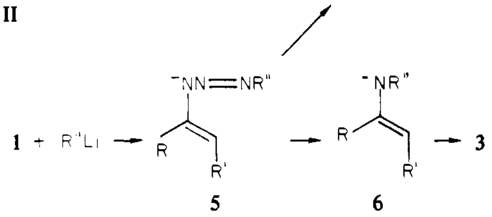
vinyl azide (1)	R''Li	2[b]	yield,[c] %
1a; R = Ph, R' = H	CH_3Li	2a, $PhC(O)CH_2CH_3$	69
1a	BuLi	2b, $PhC(O)CH_2Bu$	20
		2c, $PhC(O)CH_2$-*sec*-Bu	59
1a	*t*-BuLi	2d, $PhC(O)CH_2$-*t*-Bu	82
1a	EtLi	2e, $PhC(O)CH_2CH_2CH_3$	52
1b; R = Ph, R' = CH_3	CH_3Li	2f, $PhC(O)CH(CH_3)_2$	32
1c; R = H, R' = *t*-Bu	CH_3Li	2g, *t*-$BuCH(CH_3)CHO$	71
1d; R = Bu, R' = H	CH_3Li	2h, $BuC(O)CH_2CH_3$	82

[a] Followed by workup with dilute HCl. [b] Identified by IR and NMR comparison with authentic compounds. In addition to 2, 5–10% of nonalkylated ketone or aldehyde was present in the crude product. [c] As determined by GC after distillation of the carbonyl products.

Scheme I

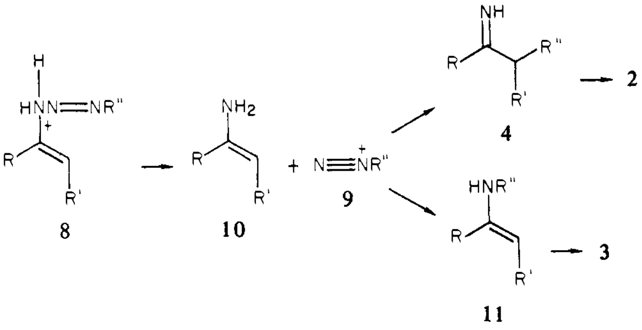


Scheme II



that anion **5** may lead to the alkylated ketones (**2**) can be discounted since treatment of **7** with CH_3Li or other bases led to isolation of starting material.

On the other hand, acid treatment of triazene **7** gave the alkylated aldehyde **2g** in high yield together with small amounts of aldehyde **3g**. This suggests a pathway involving cleavage of the protonated triazene **8** to vinylamine **10** and alkanediazonium ion **9**. An analogy for the reaction **8** → **9** + **10** is provided by the acid-catalyzed decomposition of arylvinyltriazenes,[9,10] which leads to a mixture of products, among them aniline. Diazonium ions (e.g., **9**) can decompose to alkyl cations, and either of these species may alkylate the vinylamine at the N or the β carbon, leading to **3** via **11** or to alkylated product **2** via **4**. An indication of an alkyl cation with enough lifetime to undergo rearrangement is provided by the isolation of β-methylvalerophenone (**2c**) in 59% yield from the reaction of *n*-BuLi with styryl azide **1a**.



Although tertiary enamines are well-known and can be alkylated with alkyl halides, acid chlorides, or unsaturated carbonyl compounds,[11] there seems to be no precedent for the alkylation of nonaromatic primary enamines (e.g., **10**) with diazonium salts. The predominance of alkylated vs. nonalkylated ketone products may indicate the preference of primary enamines to alkylate on carbon rather than on nitrogen.

Since vinyl azides are readily accessible from olefins,[12] their alkylation provides a synthetically useful conversion of alkenes to alkylated ketones, as shown below. It is interesting that even

$$RCH{=}CH_2 \longrightarrow RC(N_3){=}CH_2 \longrightarrow RC(O)CH_2R''$$

the usually nonnucleophilic *tert*-butyllithium reacts readily with vinyl azides to lead to *tert*-butyl transfer in 82% yield.

The reaction can be carried out as a "one-pot" process. The vinyl azide (10 mmol) in 50 mL of anhydrous ether is treated with 1.1 equiv[13] of alkyllithium solution[14] at −78 °C. The reaction mixture is allowed to warm to room temperature and stirred for 5–12 h. After slow addition of 2 mL of water, the mixture is poured into 5% hydrochloric acid and stirred for several hours. The organic products are purified by distillation.

The formation of α-alkylated ketones or aldehydes by this process has several attractive features. First, it leads to ketones regiospecifically alkylated at the olefinic β carbon of the starting vinyl azides. Second, the reaction gives only monoalkylated and no polyalkylated products. Finally, it is experimentally simple and can be performed without isolation of intermediates. While there is no direct analogy for the conversion of olefins into alkylated ketones, such transformations can be achieved by a hydration–oxidation (to ketone)–alkylation sequence. The yields of alkylated ketone in our "one-pot" process compare favorably with those found in enolate or enamine alkylations.[15]

Further studies on the detailed mechanism and the synthetic scope of the reaction are in progress.

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