Hydrolysis, Nitrosyl Exchange, and Synthesis of Alkyl Nitrites

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Received January 24, 1983

Alkyl nitrites undergo relatively slow hydrolysis in phosphate-buffered aqueous media under neutral conditions with small but significant dependence of reactivity on structure. However, rapid nitrosyl exchange with alcohols is observed, and equilibrium constants for this transformation exhibit remarkable correlation with equilibrium constants for nitrosyl exchange of alcohols with nitrosyl chloride and with nitrous acid. *tert*-Butyl nitrite has the greatest driving force for nitrosyl transfer among the 12 alkyl nitrites examined, and this capability is used for the synthesis of alkyl nitrites derived from steroidal alcohols and of alkyl thionitrites.

In conjunction with investigations that we have undertaken into the nature of hemoprotein oxidation by alkyl nitrites,[1,2] we have had need to determine the rates for hydrolysis of a series of structurally variant alkyl nitrites under conditions that approximated those employed for hemoprotein oxidation. There has been considerable speculation that the oxidation of hemoproteins such as hemoglobin was due to nitrite ion formed by hydrolysis of alkyl nitrites.[3-5] Several reports have appeared recently of investigations of the hydrolysis of alkyl nitrites,[6,7] but none in aqueous phosphate-buffered media and none with the structural variance that we intended to employ. In the course of these investigations, we discovered that alkyl nitrites undergo rapid nitrosyl transfer to alcohols, amines, and thiols. Nitrosyl transfer to amines by alkyl nitrites has recently been reported,[8,9] but reversible nitrosyl exchange with alcohols has not been described or employed for synthetic advantage. We report our investigations of the hydrolysis of alkyl nitrites, their equilibrium nitrosyl exchange with alcohols, and the utilization of nitrosyl exchange for the synthesis of alkyl nitrites and thionitrites.

Results and Discussion

Hydrolysis of Alkyl Nitrites. Prior investigations have concentrated on acid or alkaline hydrolysis of alkyl nitrites. Compared to structurally equivalent carboxylate esters, alkaline hydrolysis of alkyl nitrites is much slower and acid hydrolysis is much faster.[9] The effects of substituents on the departing alkoxide group in alkaline hydrolyses of alkyl nitrites are characterized by a ρ^* value of +2.54 and a Taft δ value of 1.03,[9] signifying a larger polar and a smaller steric influence relative to comparable ester hydrolyses. Kinetic results from hydrolysis of structurally variant alkyl nitrites in phosphate-buffered media at pH 7.0 are presented in Table I. Because of their limited solubility in 9% aqueous acetonitrile, rates for hydrolysis of primary alkyl nitrites were obtained in 55% aqueous acetonitrile. Reported results were averaged from a minimum of three rate determinations, which followed pseudo-first-order kinetics through 2 half-lives; deviation from the kinetic relationship could be attributed to pH changes that characterize the hydrolysis transformation at that stage.

Table I. Rates for Hydrolysis of Alkyl Nitrites

alkyl nitrite	55% aqueous CH_3CN,[a,b] 10^6k_{obsd}, s^{-1}	9% aqueous CH_3CN,[a,c] 10^6k_{obsd}, s^{-1}	61% aqueous dioxane,[d] 10^6k, M^{-1} s^{-1}
EtONO	5.5	(87)[e]	
n-PrONO	9.2		76.2[f]
n-BuONO	8.5		56.2[g]
n-PentONO	12.8		
i-BuONO	10.0		
i-PentONO	16.2		
neo-PentONO	14.7		
i-PrONO		159	
sec-BuONO		123	13.8[g]
t-BuONO		117	1.37[f]

[a] First-order rate constants for reactions performed at 25.0 °C. [b] Concentration of phosphate buffer at pH 7.0 was 0.023 M. [c] Concentration of phosphate buffer at pH 7.0 was 0.050 M. [d] Second-order rate constants for reactions performed at 35.1 °C under alkaline conditions. [e] Rate constant for hydrolysis at 10.0 °C in 98% aqueous ethanol (ref 1). [f] Data taken from ref 7. [g] Data taken from ref 9.

Comparison of the data in Table I for the series of primary alkyl nitrites shows that the rate constants for hydrolysis are relatively insensitive to steric influences. Only a 3-fold change in rate is observed from ethyl to neopentyl nitrite. Surprisingly, increased alkyl substitution at the β-position of primary alkyl nitrites facilitates hydrolysis, but this effect is very small. Similarly, alkyl substitution at the α-position does not markedly affect the rate of hydrolysis in the phosphate-buffered media. Prior investigations have shown that under alkaline conditions the rate for hydrolysis of alkyl nitrites is significantly responsive to alkyl substitution at the α-position,[7,9] decreasing by a factor of 10 from *sec*-butyl to *tert*-butyl (Table I), whereas we observe only a 5% rate decrease in phosphate-buffered media at pH 7.0. The origin of this phenomenon is not established by this investigation but, analogous to bromide catalysis of alkyl nitrite hydrolysis under acidic conditions,[7] may be due to mono- and/or dibasic phosphate involvement in the hydrolysis transformation. To be certain, structural effects on the hydrolysis of alkyl nitrites under neutral conditions are more complex than previously envisioned.

Nitrosyl Exchange. In view of the slow rate for hydrolysis of alkyl nitrites, we were surprised to find that alkyl nitrites undergo rapid nitrosyl exchange with alcohols (eq 1). Addition of an alkyl nitrite to a large excess of a

$$\mathrm{RONO} + \mathrm{R'OH} \rightleftharpoons \mathrm{ROH} + \mathrm{R'ONO} \qquad (1)$$

pure alcohol results in complete nitrosyl exchange within 1 min at room temperature. To investigate this transformation in greater detail, we have measured the equi-

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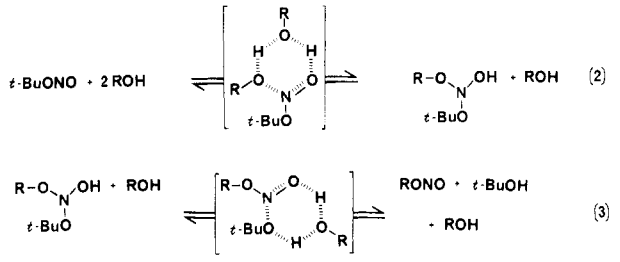
Table II. Equilibrium Constants for Nitrosyl Exchange

ROH, R =	t-BuONO, K_{eq},[a] 26 °C	NOCl, K_{eq},[b] 20 °C	HONO, K_{eq},[c] 0 °C
ethyl	10.6		
n-propyl	10.0		0.88
n-butyl	9.9	24	0.66
isobutyl	8.6	20	
neopentyl	10.2		
benzyl	3.3		
p-nitrobenzyl	1.2		
2-ethoxyethyl	5.8		
isopropyl	4.2	(10)[d]	0.25
2-adamantyl	3.8		
1-phenyl-2-propyl	2.2		
tert-butyl	1.0	2.4	<0.05

[a] Reactions performed between *tert*-butyl nitrite and alcohol in chloroform; initial reactant concentrations were 0.10 M. [b] Reactions performed in glacial acetic acid (ref 11). [c] Data taken from ref 12. [d] Value for cyclohexanol and extrapolated to isopropyl alcohol from *sec*-butyl alcohol and 2-pentanol.

Scheme I



librium constants for nitrosyl exchange in chloroform. Because of its availability and convenience in use,[10] *tert*-butyl nitrite was chosen as the nitrosyl source, although in several cases alternate alkyl nitrites were combined with *tert*-butyl alcohol in order to determine the authenticity of the equilibrium determination. Equilibrium constants obtained from this study are presented in Table II.

Primary alkyl nitrites are formed from *tert*-butyl nitrite with an equilibrium constant that is uniformly near 10. Alkyl substitution at the β-position does not, within experimental error, affect the equilibrium constant. Similarly, secondary alkyl nitrites are formed from *tert*-butyl nitrite with an equilibrium constant of approximately 4. The polar influences of alkyl substituents on the equilibrium constant are seen from results with 2-ethoxyethanol, benzyl alcohol, *p*-nitrobenzyl alcohol, and 1-phenyl-2-propanol.

There is striking similarity of this data with equilibrium constants obtained for nitrosyl exchange of alcohols with nitrosyl chloride[11] and with nitrous acid[12] (Table II). Correlation with equilibrium constants for nitrosyl exchange with *tert*-butyl nitrite under neutral conditions (Figure 1) and structural effects on rates for hydrolysis suggest a mechanism (Scheme I) analogous to that previously proposed by Dalcq and Bruylants[11,13] to explain nitrosyl transfer from NOCl to alcohols. As in their mechanism, acid catalysis is not a prerequisite for nitrosyl exchange, and, furthermore, Scheme I affords an explanation for the small structural response in rates for hydrolysis of alkyl nitrites under neutral conditions.[14]

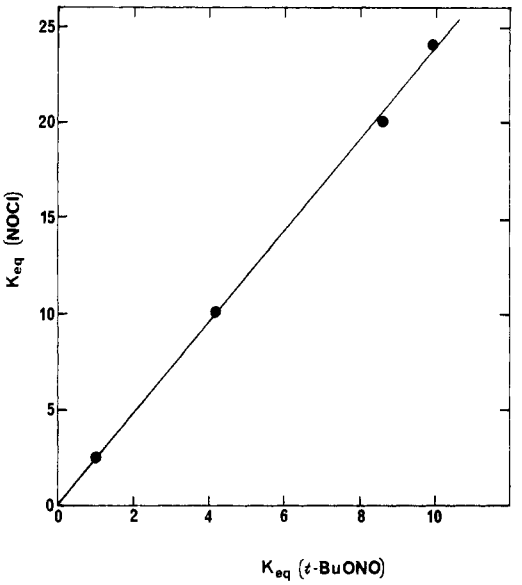


Figure 1. Correlation between nitrosyl exchange equilibrium constants for *tert*-butyl nitrite and nitrosyl chloride with alcohols.

Recently, 2-ethoxyethyl nitrite was advanced as having an exceptional capability for rapid nitrosation of amines in aqueous alkaline solution.[8] The uniqueness of alkyl nitrites bearing β-electron-withdrawing substituents was drawn from the rapid rates for hydrolysis and aminolysis of 2-ethoxyethyl nitrite in aqueous solution[8] relative to the much slower rates for hydrolysis and aminolysis of phenethyl nitrite in 61% dioxane–water.[9] The problem with this comparison is that an increasing percentage of a polar organic solvent such as acetonitrile (Table I) or dioxane[9] decreases the rate for nitrosyl transfer. In order to determine the existence of any unusual capability of 2-ethoxyethyl nitrite for nitrosyl transfer, we determined the equilibrium constants for nitrosyl exchange between 2-ethoxyethyl nitrite and neopentyl alcohol (1.76), benzyl alcohol (0.57), and *tert*-butyl alcohol (0.17). These results demonstrate that 2-ethoxyethyl nitrite is a less effective nitrosyl donor in exchange reactions than either benzyl nitrite or *tert*-butyl nitrite but is somewhat more effective than primary alkyl nitrites.

Synthesis of Alkyl Nitrites and Thionitrites. Several methods are available for the preparation of alkyl nitrites,[15] the most important of which are derived from reactions of alcohols with nitrous acid under acidic conditions[16] and with nitrosyl chloride in pyridine.[17,18] The former method has limited suitability and is principally employed for the synthesis of low-molecular-weight alkyl nitrites. The latter method has a more general applicability but requires the use of expensive gaseous nitrosyl chloride. Since *tert*-butyl nitrite undergoes rapid nitrosyl exchange under neutral conditions, we expected that this reagent could be conveniently utilized with advantages for

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(14) If the rate constant for hydrolysis is a composite of the equilibrium constant for addition of water across the nitrogen–oxygen double bond and the rate constant for dissociation of alcohol from this intermediate complex, the former favors alkyl nitrites in the order 3° > 2° > 1° whereas, from structural effects in alkaline hydrolysis, the latter favors alkyl nitrites in the order 1° > 2° > 3°.
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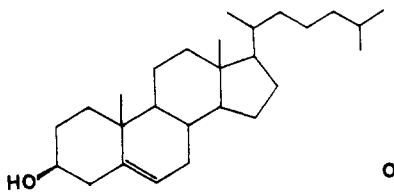
the synthesis of structurally more complex alkyl nitrites.

The *tert*-butyl nitrite method was applied to the synthesis of alkyl nitrites derived from steroidal alcohols 1 and 2. Treatment of the alcohol dissolved in chloroform with



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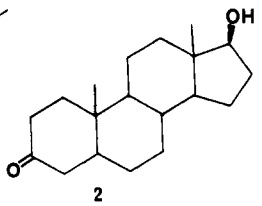

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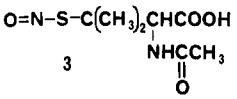
excess *tert*-butyl nitrite resulted in the production of the corresponding alkyl nitrite in quantitative yield. Nitrosyl transfer occurs readily even to the 17-hydroxyl of androstanolone (2); use of ethyl nitrite results in only partial nitrosylation even when a 10-fold molar excess of this reagent is employed.

Thionitrites have been previously prepared by several methods, including reactions of thiols with nitrous acid under acidic conditions[19,20] and with dinitrogen tetroxide in carbon tetrachloride or ether.[21] The nitrous acid method has limited applicability, and the use of N_2O_4 is complicated by the requirement for controlled stoichiometry and low reaction temperatures.[22] Use of *tert*-butyl nitrite was expected to be advantageous for the synthesis of a broad range of thionitrites without the restrictions normally encountered with the use of N_2O_4.

In chloroform, *tert*-butyl thionitrite and benzyl thionitrite were formed quantitatively from the corresponding thiols with use of a moderate excess of *tert*-butyl nitrite. With *N*-acetyl-D,L-penicillamine, which was insoluble in nonpolar media, the corresponding thionitrite 3 was



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formed in aqueous acetone and isolated in 76% yield. This same thionitrite had been produced in 63% yield by a more complex procedure that employed nitrous acid.[20]

tert-Butyl nitrite has the requisite chemical and physical properties of a useful synthetic reagent. The nitrite has a relatively low boiling point, and the corresponding alcohol can be easily removed from higher boiling or water-insoluble products. The use of this reagent for deamination reactions of primary amines has been previously described.[10] With secondary amines, quantitative formation of *N*-nitrosamines is observed.[9,23] As we now report, alkyl nitrites and thionitrites are conveniently formed by nitrosyl exchange reactions with *tert*-butyl nitrite.

Experimental Section

Materials and Methods. Proton magnetic resonance spectra were obtained with the Varian FT-80A spectrometer; chemical shifts are reported in δ units, with tetramethylsilane as the internal standard. Infrared spectra were obtained on the Pye Unicam 3-300 spectrophotometer, and UV/vis spectra were recorded with a Pye Unicam SP8-200 spectrophotometer. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol[16] or obtained from Aldrich Chemical Co. Other low-molecular-weight nitrites were prepared by the standard procedure[16] and distilled at atmospheric pressure prior to their use. Steroidal alcohols were commercially available.

Hydrolysis of Alkyl Nitrites. The rates for hydrolysis of alkyl nitrites were determined at 25.0 °C by monitoring the decrease in absorbance at 378 nm with time. Reactions were initiated with the injection of a freshly prepared anhydrous acetonitrile solution of the nitrite ester into an aqueous phosphate-buffered solution at pH 7.0. Initial concentrations of the nitrite esters in the reaction solution were less than 9.7×10^{-3} M. First-order kinetics were observed through 2 half-lives, and a minimum of three kinetic runs was employed for each alkyl nitrite. Reported hydrolytic rate constants are averaged values with deviations of ±5%. Linearity of absorbance with concentration ensured that the alkyl nitrites were soluble in the aqueous medium throughout the concentration range employed for kinetic determinations.

Equilibrium Constants for Nitrosyl Exchange. Equilibrium constants were determined by NMR spectroscopy. Stock solutions of *tert*-butyl nitrite (0.10 mL, 0.50 M) and the alcohol (0.10 mL, 0.50 M) dissolved in chloroform-*d* were added to 0.30 mL of chloroform-*d* contained in an NMR tube and thoroughly mixed. Spectra were taken and integrated at three different times, usually 0.5, 1.0, and 2.0 h, generally without observable change in the relative concentrations of the individual reaction components. Reported equilibrium constants were obtained from minimum duplicate determinations, and average values are given with deviations of ±5%. The chemical shift difference between protons on carbon adjacent to the nitrite functional group and those adjacent to the hydroxy group was δ 1.0–1.2 for primary substrates and δ 1.6–1.7 for secondary substrates. Equilibrium constants were also determined for the reverse reactions with *n*-butyl, isopentyl, isopropyl, and neopentyl nitrites by mixing the alkyl nitrite with *tert*-butyl alcohol to ensure that equilibrium had been attained in reactions originating with *tert*-butyl nitrite. In all cases, only nitrosyl transfer was observed.

Synthesis of Alkyl Nitrites by Nitrosyl Exchange. The synthesis of 17β-nitrito-5α-androstan-3-one from androstanolone (2) serves to exemplify the procedure employed. Androstanolone (581 mg, 2.00 mmol) dissolved in 10 mL of chloroform was stirred with 2.2 mL of *tert*-butyl nitrite for 30 min at room temperature. The solvent, excess nitrite, and *tert*-butyl alcohol were then rapidly evaporated to give 639 mg of a light yellow solid, mp 105–108 °C, whose spectral characteristics confirmed the absence of the hydroxyl group and the presence of the nitrite at the 17β-position (100% yield): IR (mineral oil) 1715 (C=O), 1655 and 1620 (N=O), 802 cm^{-1} (NO); NMR ($CDCl_3$) δ 5.26 (d of d, J = 9.0, 8.2 Hz, 17β-H), 2.6–2.0 (m, 4 H), 2.0–0.7 (m, 18 H), 1.02 (s, 3 H), 0.77 (s, 3 H); λ_{max} (ethyl ether) 391 nm (ϵ 47), 374 (ϵ 69), 320 (ϵ 488). Failure to remove volatile products rapidly results in the concentration of *tert*-butyl alcohol, which causes reverse nitrosyl transfer from the product nitrite. Cholesteryl nitrite was similarly prepared in quantitative yield; its physical and spectral properties were identical with those previously reported.[17]

Synthesis of Alkyl Thionitrites by Nitrosyl Exchange. Reactions with simple thiols were performed in chloroform as previously described for alkyl nitrite syntheses. Their structural identity and yields were obtained through reference to previously described spectral properties.[21] *N*-acetyl-D,L-penicillamine thionitrite (3) was synthesized through treatment of *N*-acetyl-D,L-penicillamine (382 mg, 2.00 mmol) in a solution composed of 15 mL of acetone and 1 mL of water with 2.0 mL of *tert*-butyl nitrite. After 30 min, the red solution was diluted with water, and the green thionitrite solid was filtered and then dried under vacuum (333 mg, 1.51 mmol, 76% yield).[24] The physical and spectral characteristics of this product were identical with those of 3 prepared by the nitrous acid method.[20]

Acknowledgment. We gratefully acknowledge the support of the National Institute of Environmental Health Sciences (ES 01673) for this work.

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(23) *N*-Methyl-*N*-nitrosoaniline and *N*-nitrosodiphenylamine were formed in quantitative yield following treatment of the corresponding amines with excess *tert*-butyl nitrite in chloroform or acetonitrile.
(24) This thionitrite was formed in 64% yield when only a 4-fold molar excess of *tert*-butyl nitrite was employed.

Registry No. 1, 57-88-5; 1 nitrite, 6709-70-2; 2, 521-18-6; 2 nitrite, 86727-47-1; 3, 67776-06-1; EtONO, 109-95-5; *n*-PrONO, 543-67-9; *n*-BuONO, 544-16-1; *n*-PentONO, 463-04-7; *i*-BuONO, 542-56-3; *i*-PentONO, 110-46-3; *neo*-PentONO, 77212-96-5; *i*-PrONO, 541-42-4; *sec*-BuONO, 924-43-6; *t*-BuONO, 540-80-7; EtOH, 64-17-5; *n*-PrOH, 71-23-8; *n*-BuOH, 71-36-3; *i*-BuOH, 78-83-1; *neo*-PentOH, 75-84-3; benzyl alcohol, 100-51-6; *p*-nitrobenzyl alcohol, 619-73-8; 2-ethoxyethyl alcohol, 110-80-5; *i*-PrOH, 67-63-0; 2-adamantyl alcohol, 700-57-2; 1-phenyl-2-propyl alcohol, 698-87-3; *t*-BuOH, 75-65-0; *N*-acetyl-D,L-penicillamine, 59-53-0; *tert*-butyl thionitrite, 15459-95-7; benzyl thionitrite, 4862-09-3; *tert*-butyl mercaptan, 75-66-1; benzyl mercaptan, 100-53-8.

Synthesis, Regiochemistry, and Reactions of Dichlorocyclobutenones[1]

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Received February 16, 1983

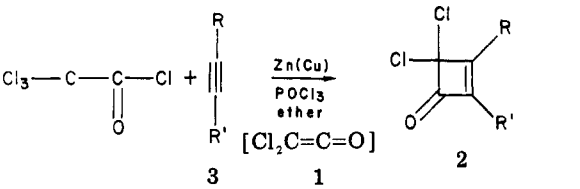
Dichlorocyclobutenones previously obtained only with difficulty were prepared by the cycloaddition of dichloroketene with alkynes in the presence of phosphorus oxychloride in fair to good yields. The regiochemistry of addition can be rationalized on the basis of electronic factors except in the case of (trimethylsilyl)acetylenes which exhibit unusual regioselectivity. Thermolysis of the cyclobutenones in the presence of alcohol led to electrocyclic ring cleavage, giving vinylketene intermediates which were trapped by the alcohol; on the other hand, reaction with alkoxide took place at room temperature and led either to ring opening or allylic substitution.

Our interest in cyclobutanone chemistry[2] led us to a study of cyclobutenones since the latter provide a route to vinylketenes by thermal electrocyclic ring opening.[3] While the cycloaddition of dichloroketene to alkenes has received considerable attention,[2,4] relatively few studies have appeared regarding analogous reactions with alkynes.[5-7] Historically, investigators have been unable to effect the cycloaddition of dichloroketene to unactivated alkynes with good efficacy, and only strained or electron-rich alkynes were found to give good yields of adducts.[5,6a] For example, dehydrohalogenation of dichloroacetyl chloride in the presence of 2-butyne produced 4,4-dichloro-2,3-dimethyl-2-cyclobuten-1-one in only 12% yield.[6b] These results prompted us to investigate whether dichloroketene is intrinsically unreactive toward unactivated alkynes or whether suitable reaction conditions or methodology had remained undiscovered. Recently we reported an improved synthesis of a variety of dichlorocyclobutenones[7] using a method previously developed in our laboratory for related cycloadditions.[8] In this paper we describe the detailed results regarding the synthesis of these compounds as well as the regiochemistry of addition and some reactions of the resulting adducts.

Results and Discussion

(A) Synthesis of Cyclobutenones 2 and Structure Assignment. Reaction of 2-butyne with dichloroketene 1, generated in situ by zinc dehalogenation of trichloroacetyl chloride in the presence of phosphorus oxychloride,[7,8] produces 4,4-dichloro-2,3-dimethyl-2-cyclobuten-1-one (**2a**) in 85% yield. A variety of additional alkynes were shown to react by this procedure (Table I).

Table I. Formation of Cyclobutenones 2 from Reaction of Dichloroketene with Alkynes 3

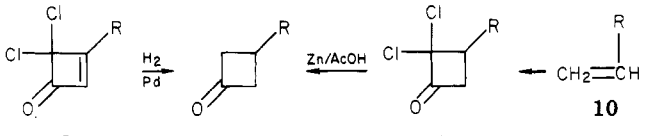


3 1 2

2	R	R'	% yield[a]
a	Me	Me	85
b	Et	Et	57
c	Ph	Ph	45
d	$CH_3(CH_2)_3$	H	77
e	$CH_3(CH_2)_4$	H	70
f	Ph	H	75
g	Me_3Si	H	60
h	Me_3Si	Me	30[b]
i	Me	Me_3Si	30[b]
j	isopropenyl	H	45

[a] Isolated. [b] Yield determined by NMR of mixture (ratio of 2h to 2i was 7:5).

Scheme I[a]



2 4 5 10

[a] f, R = Ph; g, R = $SiMe_3$.

The advantage of added $POCl_3$ lies in a cleaner reaction and the higher yield of adducts **2**. The reaction of 3-hexyne with **1** in the presence of $POCl_3$ gave **2b** in 57% yield, while without $POCl_3$ a tarry reaction product was obtained which was difficult to purify.

The reaction works well with mono- as well as disubstituted alkynes and is regioselective[9] (see **2d-g**). Addition

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(8) Hassner, A.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 2897.
(9) The term *regioselective*, proposed by A. Hassner (*J. Org. Chem.* **1968**, *33*, 2684) refers to *selectivity* in bond formation (or breaking) at one of two different locations *involving the same functional group*, whereas the term *chemoselective* (see: Trost, B. M. *Science (Washington, D.C.)* **1983**, *219*, 245) is used when *differentiation between two functional groups occurs*. Although **2j** was isolated only in 45% yield, no other product was detected.

0022-3263/83/1948-3382$01.50/0