Table I. Reaction of Alkyl Halides and Alkyl Methyl Ethers with $NO_2^+BF_4^-$ in CH_3CN Solvent

$$RX + NO_2BF_4 \xrightarrow{CH_3CN} RNHCOCH_3$$

structure (RX)	X	reaction time h	% acetamide isolated[a]
1-adamantyl	I	1.5	94
	Br	5	82 (85)[b]
	Cl	6	90
	F	15	85
	OCH_3	2	88
	OEt	2	88
	O-*n*-Pr	2	92
tert-butyl	I	2	61
	Br	2	81
	Cl	2	— (88)[c]
	OCH_3	6	77
exo-norbornyl	I	1.5	89
	Br	3.3	50 (80)[d]
	Cl	15	72
	OCH_3	3	62
cyclohexyl	I	1.67	71
	Br	21	51 (57)[e]
n-butyl	I	1.67	— (62)[f]
2-propyl	Br	4	44[g]
	I	1.5	— (57)

[a] Isolated yields obtained after a single recrystallization from pentane/methylene chloride. The yields given in parentheses were measured by gas chromatography. [b] Triphenylmethane was utilized as the internal standard. [c] Utilizing 1 equiv of NO_2BF_4 afforded a bicomponent mixture: 83% of *tert*-butylacetamide plus 5% of 1-nitro-2-methyl-2-acetamidopropane. [d] Utilized benzophenone as the internal standard. [e] Cyclodecane was used as the internal standard. [f] GC yield using pentadecane as the internal standard. A bicomponent mixture consisting of *N*-(1-butyl)-acetamide (25%) and *N*-(2-butyl)acetamide (37%) was observed. [g] Pentadecane was used as the internal standard.

Scheme I

$$R_3CX + NO_2^+BF_4^- \longrightarrow R_3C^+ + NO_2X$$

$$R_3C^+ \xrightarrow{CH_3CN} R_3CN{\equiv}CCH_3 \xrightarrow{H_2O} R_3CN(H)C(=O)CH_3$$

X = H, Br, Cl, F, OCH_3

RO^- paralleled the stability of the resulting carbenium ions (i.e., tertiary > secondary > primary). For practical purposes, primary and secondary alkyl fluorides and chlorides are unreactive under these conditions. The best results were obtained with the adamantyl compounds where even adamantyl fluoride afforded a high yield of acetamide product.

We have also demonstrated that the ether cleavage reaction is not restricted to methyl ethers. The ethyl and *n*-propyl ethers of adamantane afforded 1-acetamidoadamantane in high yield (Table I). However, ethers with secondary alkyl substituents can result in a mixture of products in compliance with the reaction given in eq 1.[10] We have also extended the reaction to include other nitriles. This synthetic procedure may be applied to the synthesis of hindered amides if more highly substituted (saturated) nitriles are employed as solvents or as co-solvents with methylene chloride. For example, adamantyl bromide afforded *N*-(1-adamantyl)isobutyramide (76%) and adamantyl methyl ether was converted to *N*-(1-adamantyl)trimethylacetamide (55%) when isobutyro- and trimethylacetonitrile were used as solvents.

We suggest a mechanism (Scheme I) that involves an initial Lewis acid–Lewis base reaction of NO_2^+ with the nonbonding electron pairs of the halogen or ether oxygen to form a nitronium intermediate that suffers heterolysis of the C–X bond. Supporting evidence for a nitro–bromonium complex comes from our observation[11] that similar reaction of (1*R*,2*R*,4*S*)-(−)-2-bromonorbornane afforded racemic *N*-(*exo*-2-norbornyl)acetamide. These data demand a symmetrical (cationic) intermediate along the reaction pathway. The formation of both *N*-(1-butyl)- and *N*-(2-butyl)acetamides in the reaction of *n*-butyl iodide (Table I) also requires a 1,2-hydride transfer to a positive center. Acetonitrile solvent performs the function of a highly efficient carbenium ion trap affording a "Ritter type"[12] intermediate which affords acetamide products upon hydrolytic work-up. The only prior example of this reaction utilized a mixture of concentrated H_2SO_4 and HNO_3 to generate the acetamide from 1-bromoadamantane in acetronitrile.[13] We attribute the overall success of the present study to the relatively mild reaction conditions utilized, which impeded further oxidative reaction of the nitrilium ion intermediate.

In conclusion, we have provided a novel method for the cleavage of alkyl ethers and halides to their corresponding amides. Direct reduction of the amides with lithium aluminum hydride is readily achieved providing a synthesis of substituted amines.

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(9) Unpublished results with Badger, R. C.
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Synthesis of Imidazo[1,5-*a*]-1,3,5-triazinones by Cyclization–Rearrangement

Summary: A novel rearrangement has been utilized for the synthesis of imidazo[1,5-*a*]-1,3-5-triazinones which are analogues of 9-substituted hypoxanthines and guanines.

Sir: A strong case has been made for the desirability of synthesis and biological evaluation of nucleosides and nucleotides of guanine analogues.[1] We have discovered an originally un-

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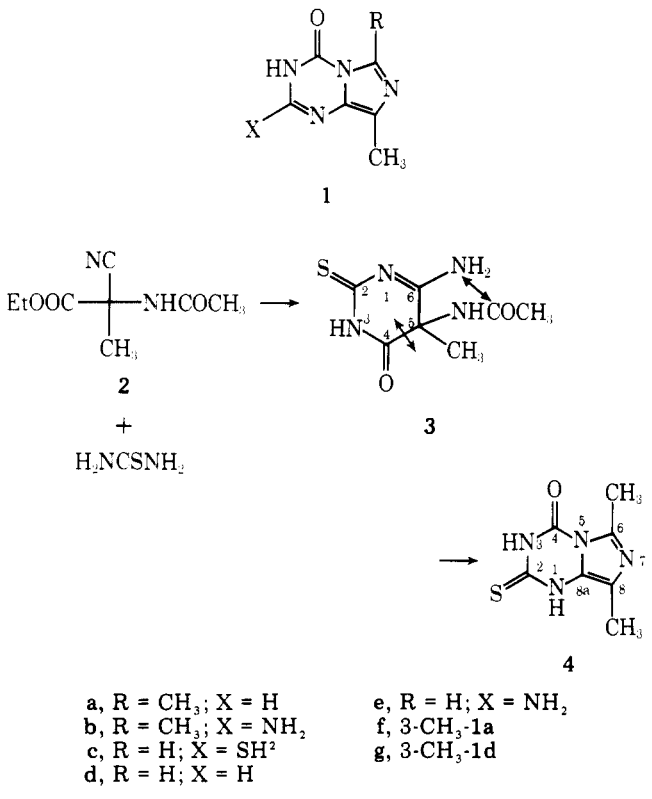

a, R = CH_3; X = H
b, R = CH_3; X = NH_2
c, R = H; X = SH^2
d, R = H; X = H
e, R = H; X = NH_2
f, 3-CH_3-**1a**
g, 3-CH_3-**1d**

intended rearrangement that leads effectively to imidazo[1,5-*a*]-1,3,5-triazinones (**1**) which are analogues of 9-substituted guanines, xanthines, and hypoxanthines. Structures were established in this series (**1**) on the basis of precursors and routes of synthesis, ^1H and ^{13}C NMR spectra, and X-ray crystallographic analysis of one member (**1a**) among the interrelated compounds in the series. Prior description of the imidazo[1,5-*a*]-1,3,5-triazine ring system is limited to a synthesis by Biltz[3] of 1,7-dimethyl-2,4,6,8-tetraoxoperhydroimidazo[1,5-*a*]-1,3,5-triazine.

Condensation of ethyl 2-acetamido-2-cyanopropionate (**2**)[4] with thiourea in hot ethanol containing excess sodium ethoxide, followed by cooling and addition of 10% aqueous acetic acid, yielded (54%) 5-acetamido-6-amino-4,5-dihydro-5-methyl-2(3*H*)-thiopyrimidin-4-one (**3**): mp 243 °C dec (recrystallized from H_2O); UV λ_{max} (EtOH) 261 nm (ϵ 8250), 317 (ϵ 6600); ^1H NMR ($(CD_3)_2SO$, Me_4Si, D_2O) δ 1.44 (s, 3, 5-CH_3), 1.85 (s, 3, $COCH_3$); MS *m/e* (rel abundance; 10 eV) 214 (M^+, 100), 155 (M^+ − NHCS, 30).[5] The ^{13}C NMR spectrum is consistent with structure **3**: four signals between 168 and 188 ppm correspond to C-2, C-4, C-6, and the acetyl carbonyl carbon; signals at 21.5 and 24.2 ppm are due to the two methyl groups; and the crucial resonance at 54.4 ppm establishes the presence of the tetrasubstituted C-5. Concentration of the filtrate yielded additional **3** (12%) and another component (6%), subsequently identified as 6,8-dimethyl-2(1*H*)-thioimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**4**), mp 241–242 °C dec. The isolation and characterization of this byproduct provided the first indication of tetrasubstituted carbon bond cleavage and rearrangement.

A more efficient procedure for the closure of the imidazo ring, along with 4,5-bond cleavage and rearrangement with reclosure to create the triazine ring,[6] was based upon the work of Vorbrüggen involving the amination of *O*-trimethylsilylated heterocycles.[7] Treatment of **3** in pyridine with 2 molar equiv of chlorotrimethylsilane and excess hexamethyldisilazane at reflux for 4 h under nitrogen yielded **4** (83%) after ethanolic treatment at 5 °C: UV λ_{max} (EtOH) 264 nm (sh) (ϵ 9800), 289 (ϵ 13 800); MS *m/e* (10 eV) 196 (M^+, 100), no loss of CH_3, 153 (M^+ − HNCO, 9), 137 (M^+ − HNCS, 26). The ^1H NMR

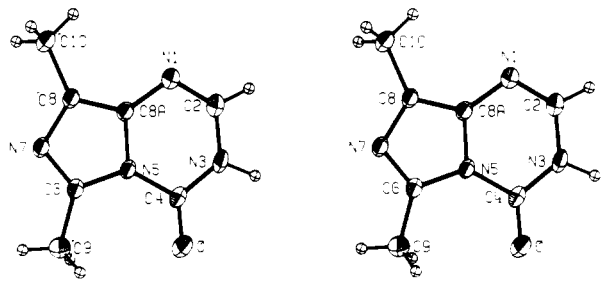

Figure 1.

spectrum showed δ values for two different C_{ar}-CH_3's (2.1, 2.5 overlaps with $(CH_3)_2SO$), and the ^{13}C NMR spectrum confirmed the absence of a tetrasubstituted carbon.

Desulfurization of **4** with Raney nickel in aqueous ammonia yielded (53%) 6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**1a**): mp 269–270 °C dec; MS *m/e* (10 eV) 164 (M^+, 100), 137 (M^+ − HCN, 59), 136 (M^+ − HCNH, 7); ^1H NMR δ 7.42 (s, 1, 2-H). A single crystal of suitable dimensions for X-ray analysis was obtained by slow crystallization from 2-propanol: $C_7H_8N_4O$ molecular weight 164.2; monoclinic, a = 7.320 (1), b = 7.310 (1), c = 14.509 (2) Å, β = 102.05 (2)°, V = 759.3 Å^3, Z = 4, ρ_c = 1.44 g/cm^3, μ(Mo Kα) = 1.1 cm^{-1}, F(000) = 344, systematic absences for $0k0$, $k = 2n + 1$ and $h0l$, $l = 2n + 1$ establish the space group as $P2_1/c$. Of the total 2225 unique reflections collected, 1523 were considered to be observed using a 2σ criterion based on counting statistics. The data were corrected for Lorentz and polarization effects but not for absorption.

The structure (Figure 1) was solved by direct methods using the programs supplied by Syntex.[8] The hydrogens were located from difference maps. Full-matrix least-squares refinement of positional and anisotropic thermal parameters for the nonhydrogen atoms and of positional and isotropic thermal parameters for the hydrogen atoms converged with values for R and $R\omega$ of 0.049 and 0.051, respectively.[9] The final value of $[\Sigma\omega(|F_{obsd}| - |F_{calcd}|)^2/(m - n)]^{1/2}$, where m is the number of observations (1523) and n is the number of variables (141), was 1.60. The neutral scattering factor curves were taken from the analytical expression used in the "International Tables for X-Ray Crystallography".[10] A final difference map showed no peak higher than 42% of an average hydrogen. Of special interest is the intermolecular hydrogen-bonding pattern:

$$N3\overset{0.92\ (3)}{\text{———}}H3\cdots\overset{1.98\ (2)}{\cdots\cdots}N7$$

with the NHN angle = 159 (2)° and the N3–N7 distance = 2.856 Å. The deviation of N5 from the plane of C4, C6, C8a is −0.0113 (13) Å, and the vertical distance between stacked planes is 3.394 Å (average). The crystal structure of imidazo[1,2-*b*]-1,2,4-triazine similarly indicates that the molecules are planar within the limits of accuracy and that their planes are 3.36 Å apart.[11]

With the structures of **1a** and **4** established, the structures of the following were also confirmed by interconversions and by analogous transformations: 2-amino-6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**1b**), mp 220 °C dec, by rearrangement–cyclization of the product of guanidine with **2**; 3,6,8-trimethylimidazo[1,5,*a*]-1,3,5-triazin-4-one (**1f**), mp 130–132 °C, by methylation of **1a** with 1,1-dimethoxytrimethylamine;[12] and, by starting the sequence with ethyl 2-cyano-2-formamidopropionate in place of **2**, 8-methyl-2(1*H*)-thioimidazo[1,5,*a*]-1,3,5-triazin-4(3*H*)-one (**1c**), mp 242 °C dec, 8-methylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**1d**), mp 240 °C dec, 2-amino-8-methylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**1e**), mp 220 °C dec, and 3,8-di-

methylimidazo[1,5-a]-1,3,5-triazin-4-one (**1g**), mp 192 °C dec.

The analogy between C8 substitution in **1d** and **1e**, as examples, and N9 substitution on hypoxanthine and guanine, respectively, suggests further applications of the intriguing cyclization–rearrangement sequence.

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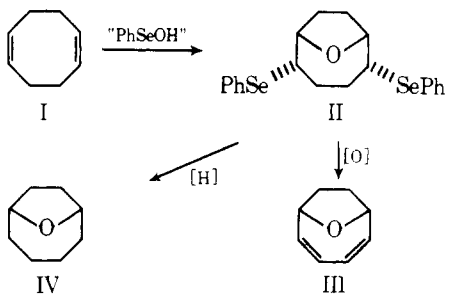
Organoselenium-Induced Ring Closures: Cyclization of Dienes with "PhSeOH" to Form Cyclic Ethers

Summary: "PhSeOH" converts dienes to cyclic ethers; use of the reaction in the synthesis of eucalyptole, (±)-linalool, *cis*-terpin, a "cage" ether, and a prostacyclin analogue is described.

Sir: In connection with our continuing programs[1-4] directed at developing new synthetic methodology employing novel selenium reagents, we have observed that a variety of simple and structurally complex dienes afford cyclic ethers in good to excellent yield when subjected to treatment with "PhSeOH", a new reagent recently independently introduced by Sharpless[5] and Reich.[6,7] This reaction represents a novel and simple procedure for the construction of complex oxygen-containing heterocyclic systems with simultaneous introduction of two phenylseleno (PhSe) groups. The high frequency in which oxygen heterocycles occur in nature and the synthetic potential of the phenylseleno group[8] should make this new cyclization process an extremely powerful synthetic method.

This novel selenium-induced cyclization of dienes is illustrated in Scheme I. Specifically, treatment of 1,5-cyclooctadiene (I) with "PhSeOH"[5] in CH_2Cl_2 at 25 °C afforded the bis(phenylseleno)oxabicyclo[4.2.1]nonane derivative II[9] in

Scheme I

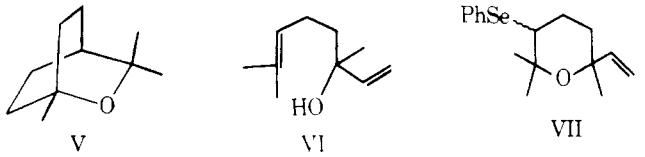


90% yield.[10,11] Subsequent oxidation (O_3, CH_2Cl_2, −78 °C) followed by syn elimination[12] of the derived selenoxide furnished the known bicyclic diene III[13] (73% yield[10]), thus confirming the skeletal structure assigned to II. The stereochemistry of II follows both from mechanistic considerations (vide infra) and the observation of a single resonance in the ^{77}Se NMR spectrum.[14] Finally, reduction of II with *tri*-n-butyltin hydride [$PhCH_3$, 110 °C, traces of azobis(isobutyronitrile)] led to the known saturated tetrahydrofuran derivative IV[15] in 80% yield.

To explore both the generality and utility of this new methodology, a series of dienes was subjected to the cyclization process. As indicated in Table I, good yields of cyclic products were obtained from a wide variety of dienes, thereby clearly demonstrating the potential of this method as a ring-forming reaction.[16] In general, highly substituted dienes and those conformationally fixed enter into this reaction with increased rates and yields, the final products depending on the precise diene substitution as well as the relative stability of the derived products. Such characteristics are beneficial in that selectivity is often observed (see Table I).

The reported cyclization process is presumed to proceed via initial Markownikoff's addition of "PhSeOH" across the more highly substituted olefinic bond to generate a β-hydroxyselenide which subsequently undergoes cyclization with participation of a second molecule of "PhSeOH". The latter reaction is quite reminiscent of the cyclization of unsaturated ethers induced by phenylselenenyl chloride.[1b] In cases where cyclization is not favored, good to excellent yields of mono and/or bis(hydroxyselenides) are obtained.[7]

To demonstrate the utility of this selenium-based methodology for construction of natural and other complex structures, we report here a number of facile approaches to such systems. Thus, reductive removal of the phenylseleno groups (Raney Ni, THF) from **10a**[19] furnished eucalyptole (V) in 80%



V VI VII

yield, which was identical in all respects with an authentic sample. (±)-Linalool (VI) on the other hand was obtained in 45% overall yield from either **8a** or **9a** by: (i) cleavage of the acetate ($LiAlH_4$, THF, 2 h); (ii) elimination of the β-hydroxyphenylselenide functionality (MsCl, Et_3N, CH_2Cl_2);[21] and (iii) reductive cleavage of the derived cyclic ether (VII) (Na–liquid NH_3, 10 min).[22] Facile formation of complex cage-type systems is illustrated by the preparation of VIII in 85% yield via treatment of **12a** with *n*-Bu_3SnH in toluene (110 °C, 2 h) in the presence of trace amounts of azobis(isobutyronitrile).[23] Finally, oxidative (*m*-CPBA, CH_2Cl_2) removal of the phenylseleno groups from **13a** afforded the interesting cage prostacyclin analogue IX[2b,24] in 96% yield.

The ability of "PhSeOH" to functionalize readily available starting materials such as dienes to form cyclic ethers ac-

