I–III in acetonitrile at 25 °C. The dependence of k_0 on the initially added concentration ($[CE]_0$) of crown ethers I–III is illustrated in Figure 1. From the curves for the dependence of k_0 on $[CE]_0$, the pseudo-first-order rate constant (k_0^{sp}) observed in the absence of the added crown ethers and the limiting value of the pseudo-first-order rate constant (k_0^{CE}) observed in the presence of a sufficient amount of a crown ether can be estimated.

The data illustrated in Figure 1 indicate that k_0^{CE} is attained when $[CE]_0$ is similar to the concentration of the added sodium salt of B. The data of Figure 1 indicate k_0^{sp} of 8.7×10^{-2} s^{-1} and k_0^{CE} of 5.5×10^{-2} s^{-1} (for I), 4.8×10^{-2} s^{-1} (for II), and 3.3×10^{-2} s^{-1} (for III). Thus, k_0^{CE}/k_0^{sp} is 0.63 for I, 0.55 for II, and 0.38 for III. Crown ethers I–III considerably retard the rate of the reaction of A with B. Furthermore, the inhibitory effect increases in the order of I < II < III. In this sequence, the size of the countercation increases and the corresponding charge density decreases.[1]

If the inhibitory effects of the crown ethers originates mainly from the electrostatic effects, the kinetic data may be taken to suggest that the density of negative charge in the transition state is greater than that in anion B.

Whether the negative charge is more dispersed in the ground state or in the transition state would be correlated with the mechanism of the reaction. Either in the addition–elimination mechanism or in the S_N2-type concerted mechanism, three oxygen atoms are attached to the carbonyl carbon atom of A and bear negative charges in the transition state. In an extreme mechanism, the transition state would resemble the tetrahedral intermediate very closely. In the other extreme case, the transition state might have a "exploded" structure with small bond order between the carbonyl carbon atom and the two phenolate oxygen atoms of both the leaving group and the nucleophile. The exact structure of the rate-determining transition state would depend on the reaction path, which in turn would be governed by several factors including the structures of the ester and the nucleophile. The inhibitory effects of the crown ethers observed in the present study is compatible with the less dispersed negative charge in the transition state compared with the ground state.

In acetonitrile, both anion B and the anionic transition state would be present as aggregates with the countercations. Upon complexation with crown ethers, the countercation becomes bulkier, affecting the relative stability of the ground state and the transition state. The anionic centers in the transition states for both the stepwise and the concerted mechanisms are more crowded than that in B. Thus, an increase in the size of the countercation can retard the reaction regardless of the mechanism, if only the steric effects are considered.

In this regard, however, it is noteworthy that the aliphatic S_N2 reaction between cyanide anion and alkyl halides in acetonitrile is remarkably accelerated by the addition of crown ethers.[2c] In this reaction, the negative charge density is more dispersed in the transition state compared with the ground state,[6] and crown ethers are expected to accelerate the reaction if only electrostatic effects are considered. On the other hand, the anionic center becomes more crowded in the transition state, and crown ethers can retard the reaction on the basis of the steric effects. The electrostatic effects, therefore, predominate over the steric effects in the action of crown ethers on the S_N2 reaction of cyanide ion.

(5) Anionic nucleophile B (8×10^{-4} M) was generated by mixing 1×10^{-3} M *m*-methoxyphenol with 8×10^{-4} M sodium ethoxide.[1]

(6) Jones, R. A. Y. In *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984; Chapter 7.

Experimental Section

Compound A was prepared according to the literature,[7] mp 166–167 °C (lit.[7] mp 166–167 °C). Purification of other materials and kinetic measurements were carried out as reported previously.[1]

Acknowledgment. This work was supported by a grant from the Basic Science Research Program (1989), Korean Ministry of Education.

Registry No. I, 33100-27-5; II, 17455-13-9; III, 16069-36-6; *p*-nitrophenyl acetate, 830-03-5; sodium of *m*-methoxyphenolate, 51113-99-6.

Supplementary Material Available: Table including the kinetic data (1 page). Ordering information is given on any current masthead page.

(7) Galatis, L. C. *J. Am. Chem. Soc.* **1947**, *69*, 2062.

Wittig Rearrangement of Aromatic Acetals and Ketals Induced by Reductive Electron Transfer

Ugo Azzena,* Teresa Denurra, Giovanni Melloni, and Anna Maria Piroddi

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

Received January 23, 1990

The [1,2]-Wittig rearrangement, i.e., the migration of groups from oxygen to carbon in benzyl and related ethers promoted by alkyl- or aryllithium derivatives to afford alkoxides, is well known. Much effort has been devoted to the study of both its mechanistic aspects[1] and synthetic usefulness.[2] It is generally accepted[1-7] that the reaction proceeds through the formation of an intermediate benzylic carbanion, which subsequently rearranges via a nonconcerted radical cleavage–recombination mechanism (Scheme I). This view is supported by the migratory aptitude of substituents R (allyl ≅ benzyl > methyl > ethyl > phenyl), which parallels the order of free radical stabilities,[8,9] and by the fact that optically active precursors usually lead to partial racemization.[1,10] Far less studied is the related rearrangement of aromatic acetals or ketals promoted by electron transfer from alkali metals. To the best of our knowledge, nothing further has appeared in the literature since the early report of Schlenk and Bergmann[11] on the

(1) Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763.
(2) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(3) Eichinger, P. C. H.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 497.
(4) Eichinger, P. C. H.; Bowie, J. H.; Blumenthal, T. *J. Org. Chem.* **1986**, *51*, 5078.
(5) D'Orchymont, H.; Goeldner, M. P.; Biellmann, J. F. *Tetrahedron Lett.* **1982**, *23*, 1727.
(6) Davies, S.G.; Holman, N. J.; Laughton, C. A.; Mobbs, B. E. *J. Chem. Soc., Chem. Commun.* **1983**, 1316.
(7) Landsbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78.
(8) Hauser, C. R.; Kantor, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 1437.
(9) Cast, J.; Stevens, T. S.; Holmes, J. *J. Chem. Soc.* **1960**, 3521.
(10) Schollkopf, U.; Fabian, W. *Justus Liebigs Ann. Chem.* **1961**, *642*, 1.
(11) Schlenk, W.; Bergmann, E. *Justus Liebigs Ann. Chem.* **1928**, *464*, 1.

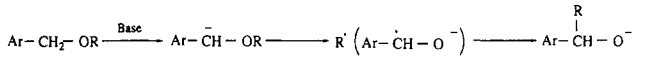
0022-3263/90/1955-5532$02.50/0

Table I. Reductive Rearrangement of Aromatic Acetals and Ketals

entry	substrate	metal	solvent	T, °C	product, yield,[a] % 2	3
1	**1a**	Li	THF	20	**2a**, 70	–
2	**1a**	Li	THF	66	**2a**, 68	–
3	**1a**	Na	THF	20	**2a**, –	–
4	**1a**	Na	THF	66	**2a**, 20	–
5	**1a**	K	THF	20	**2a**, 75	–
6	**1a**	Li	Et_2O	20	**2a**, 13	–
7	**1a**	Li	isooctane	20	**2a**, –	–
8	**1b**	Li	THF	20	**2b**, 72	–
9	**1c**	Li	THF	20	**2c**, 78	–
10	**1d**	Li	THF	20	**2d**, 73	–
11	**1e**	Li	THF	20	**2e**, 75	–
12	**1f**	Li	THF	20	**2f**, 41	33
13	**1f**	Li	THF	66	**2f**, 40	36
14	**1f**	Na	THF	20	**2f**, –	–
15	**1f**	K	THF	20	**2f**, 42	31
16	**1g**	K	THF	20	**2g**, 42	29
17	**1h**	Li	THF	20	**2h**, 65	21
18	**1h**	K	THF	20	**2h**, 70	15

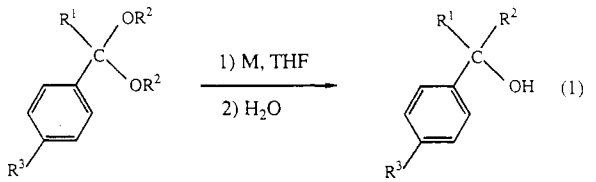
[a] Determined by GLC.

Scheme I



formation of 1,1-diphenylethanol on treatment of benzophenone dimethyl ketal with Na metal in the absence of solvent. The reactivity of the same ketone derivative was later investigated by Wittig and Happe,[12] who established that the rearrangement also proceeded with Li and K in ethereal solvents. Subsequent to these findings, the reaction was virtually forgotten; indeed, it was not mentioned either in reviews on the Wittig rearrangement[1,2] or in reviews concerning the cleavage of C–O bonds under reductive electron-transfer conditions.[13,14] On the other hand, it is known that the reduction of aromatic acetals and ketals with alkali metals in liquid ammonia, with or without the addition of proton donors, leads to the nearly quantitative formation of the corresponding arenes.[14,15]

Due to our interest in the reductive dealkoxylation of aromatic substrates,[17] we undertook a study concerning the action of alkali metals on various aromatic acetals and ketals **1** in THF. The reductive rearrangement of **1** affords carbinols **2** according to eq 1.

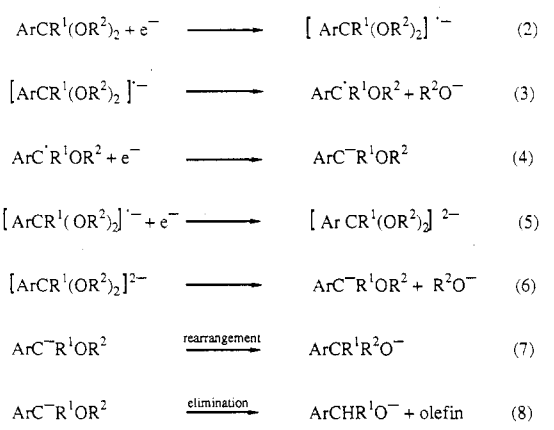


1 **2**

1a, **2a**: $R^1 = R^3 = H$, $R^2 = CH_3$; **1b**, **2b**: $R^1 = H$, $R^2 = R^3 = CH_3$; **1c**, **2c**: $R^1 = H$, $R^2 = CH_3$, $R^3 = OCH_3$; **1d**, **2d**: $R^1 = R^2 = CH_3$, $R^3 = H$; **1e**, **2e**: $R^1 = C_4H_9$, $R^2 = CH_3$, $R^3 = H$; **1f**, **2f**: $R^1 = R^3 = H$, $R^2 = C_2H_5$; **1g**, **2g**: $R^1 = R^3 = H$, $R^2 = C_4H_9$; **1h**, **2h**: $R^1 = R^3 = H$, $R^2 = CH(CH_3)C_2H_5$

M = Li, Na, or K

Scheme II



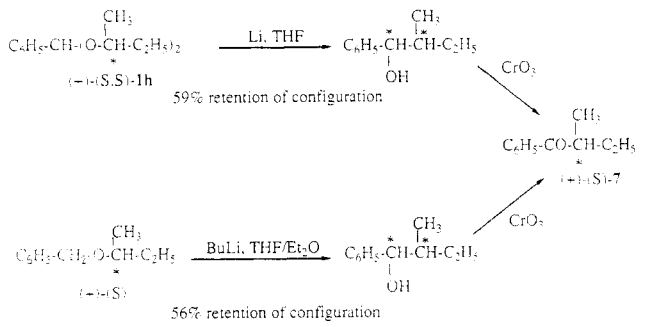
The reactions were conducted on a 5-mmol scale under argon with 3 equiv of freshly cut alkali metal for 24 h. THF was used as solvent in most experiments due to its ability to aid the Wittig rearrangement of α-metallated benzyl ethers;[12] for comparison purposes, some experiments were also run in Et_2O and in isooctane. The most significant of the results obtained are reported in Table I.

The reactivity of benzaldehyde dimethyl acetal (**1a**), taken as a model substrate, was tested under various reaction conditions. The reductive rearrangement was achieved with Li or K in THF both at room and reflux temperatures. Sodium was much less effective under the same conditions (entries 3 and 4). Low conversion was obtained in Et_2O (entry 6), and no reaction was observed in a hydrocarbon solvent (entry 7). Extension of the reaction to dimethyl acetals of substituted benzaldehydes **1b** and **1c**, as well as to aromatic dimethyl ketals **1d** and **1e** with Li in THF, afforded good yields of the corresponding carbinols **2b–e** (entries 8–11).

Extension of the reaction to other acetals of benzaldehyde gave more complex results. The reductive rearrangement of diethyl, dibutyl, and di-2-butyl acetals of benzaldehyde **1f**, **1g**, and **1h** with Li or K in THF afforded, in addition to the expected carbinols **2f–h**, significant amounts of benzyl alcohol (**3**) (entries 12, 13, 15–18). For these reactions, there was no apparent effect of temperature on the distribution of products. As in the case of **1a**, no reaction occurred with Na at room temperature (entry 14).

(12) Wittig, G.; Happe, W. *Justus Liebigs Ann. Chem.* **1947**, *557*, 205.
(13) Maerker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.
(14) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
(15) Kaiser, E. M. *Synthesis* **1972**, 391.
(16) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35.
(17) Azzena, U.; Denurra, T.; Fenude, E.; Melloni, G.; Rassu, G. *Synthesis* **1989**, 28. Azzena, U.; Cossu, S.; Denurra, T.; Melloni, G.; Piroddi, A. M. *Tetrahedron Lett.* **1989**, *30*, 1689. Azzena, U.; Cossu, S; Denurra, T.; Melloni, G.; Piroddi, A. M. *Synthesis* **1990**, 313.

Scheme III



An interpretation of these results is shown in Scheme II. As in the case of aryl[13,18,19] and benzyl ethers,[13,19] the reductive cleavage of a benzylic C–O bond by electron transfer from an alkali metal is a multistep process, starting with the formation of a radical anion by electron transfer from the alkali metal (eq 2).

The radical anion then fragments to an alkoxide anion and a benzyl radical (eq 3), which is further reduced to the α-metalated benzyl ether (eq 4). Alternatively, the radical anion is further reduced to the dianion, mainly through disproportionation (eq 5).[18] Cleavage of the latter affords the benzyl anion (eq 6), which undergoes a [1,2] Wittig rearrangement (eq 7). The formation of an intermediate benzyl anion is supported by the formation of **3** as a by-product in the reduction of compounds **1f–h** (eq 8). It is known that such a product is formed in the Wittig rearrangement of benzyl alkyl ethers when a competitive elimination is possible.[5,7,20,21]

Investigations into the stereochemistry of this process established that this reaction proceeds through a Wittig rearrangement. In fact, according to the nonconcerted radical cleavage–recombination mechanism mentioned above, Wittig rearrangements of optically active alkyl benzyl ethers were shown to occur with partial retention of configuration at the migrating carbon atom.[1,10] We therefore decided to investigate the reductive rearrangement of optically active benzaldehyde (+)-(*S*,*S*)-di-2-butyl acetal ((+)-(*S*,*S*)-**1h**, optical purity 71.5%) with Li in THF at room temperature. Following a procedure described in the literature,[10] the carbinol obtained was oxidized with CrO_3 in CH_3COOH to give (+)-(*S*)-1-phenyl-2-methyl-1-butanone ((+)-(*S*)-**7**, optical purity 13.4%), which showed 59% retention of configuration at the migrating carbon atom. This stereochemical result was in good agreement with that previously obtained in the rearrangement of the corresponding optically active (+)-(*S*)-benzyl 2-butyl ether with BuLi in THF/Et_2O (85:15) at room temperature, which proceeded with 56% retention of configuration[8] (Scheme III).

It is noteworthy that, in the reductive cleavage of aromatic acetals and ketals, a solvent of lower polarity than liquid ammonia, such as THF, suppresses the double dealkoxylation reaction[15,16] and instead promotes the reductive rearrangement. On the other hand, Et_2O, a less polar solvent than THF, reduces the reactivity of such substrates; a solvent of even lower polarity, i.e., isooctane, suppresses any reaction. Such a remarkable solvent effect has already been observed in the reductive cleavage of alkyl aryl ethers.[13,17]

We also wish to point out that alkyl benzyl ethers were found in trace, if any, amounts among the isolated products. This can be taken as evidence that, under the reported reaction conditions, both the Wittig rearrangement and the elimination reaction of benzylic anions are faster processes than the reductive cleavage of compounds **1**, so that benzylic anions do not survive until the final quenching.

As a final remark, our results show no apparent effect of alkoxyl leaving group on the formation of intermediate benzylic anions under our reaction conditions; indeed, the yield of products **2** and **3** are in all cases within the range of 75–85%.

Experimental Section

Boiling points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$, with TMS as internal standard, using a Varian T-60 spectrometer operating at 60 MHz. Mass spectra were recorded on a Perkin-Elmer ion trap detector operating at 70 eV, interfaced with a Perkin-Elmer 8310 gas chromatograph, equipped with a Supelco SP-2100 30-m capillary column (i.d. 0.25 mm). GLC analyses were performed with a Hewlett-Packard Model 5890 gas chromatograph equipped with a similar SP-2100 capillary column; the chromatograms were recorded with a Perkin-Elmer LC 100 integrator. Solvents and starting materials were purified following standard procedures. (+)-(*S*)-2-Butanol, $[\alpha]^{27}_D$ = +10.6° (neat, l = 1), o.p. 78.4,[22] was purchased from Aldrich. Authentic samples of carbinols **2** were prepared by reaction of the appropriate carbonyl compounds with Grignard reagents following standard procedures.

Preparation of Starting Materials. Benzaldehyde dimethyl acetal (**1a**) was a commercial product (Fluka). All other acetals (except (+)-(*S*,*S*)-**1h**) and ketals were prepared according to standard procedures.[23]

Benzaldehyde (+)-(*S*,*S*)-Di-2-butyl Acetal ((+)-(*S*,*S*)-1h). A solution of **1a** (5 g, 33 mmol) and (+)-(*S*)-2-butanol (10 g, 135 mmol) in 50 mL of dry benzene was distilled with fractionation under argon in the presence of NH_4Cl (100 mg, 1.9 mmol) until the azeotrope benzene–methanol was distilled away. The reaction mixture was chilled to 0 °C and triethylamine (1 mL, 7.2 mmol) was added all at once. The reaction mixture was then filtered, washed with saturated $NaHCO_3$ (1 × 50 mL) and water (2 × 50 mL), and dried over anhydrous $CaCl_2$. Evaporation of the solvent and vacuum distillation afforded pure (+)-(*S*,*S*)-**1h** (4.9 g, 21 mmol, 64%): bp 142–143 °C (15 Torr); α^{28}_D = +25.1° (l = 1). The minimal optical purity of (+)-(*S*,*S*)-**1h** was 71.5%, as determined by acid hydrolysis (1 N HCl/Et_2O (1:1), 1 h) and recovery of (+)-(*S*)-2-butanol.

Reductive Rearrangement: General Procedure. In a typical experiment, 5 mmol of compound **1**, dissolved in 5 mL of anhydrous solvent and 1 mL of dodecane (internal standard), were added dropwise under an inert atmosphere (argon) to a vigorously stirred mixture of 3 equiv of alkali metal in 25 mL of anhydrous solvent. After stirring for 24 h at the indicated temperature, the reaction mixture was chilled to 0 °C and quenched by careful dropwise addition of 4 mL of anhydrous EtOH, followed, after complete disappearance of the metal, by addition of 10 mL of H_2O. Following workup, drying over anhydrous $CaCl_2$, and evaporation of the solvent, the reaction mixture was analyzed by GLC (quantitation) and GLC/MS. The carbinol **2** (and, eventually, **3**) was recovered by fractional distillation. The results are summarized in Table I.

(+)-(*S*)-1-Phenyl-2-methyl-1-butanone ((+)-(*S*)-7). According to the general procedure described above, (+)-(*S*,*S*)-**1h** (3 g, 12.7 mmol) was allowed to react with Li metal (0.27 g, 38.1 mmol) in 60 mL of anhydrous THF at room temperature for 24 h. After the usual workup, the crude reaction product was distilled

(18) Thornton, T. A.; Woolsey, N. F.; Bartak, D. E. *J. Am. Chem. Soc.* **1986**, *53*, 5230 and references therein.
(19) Fish, R. H.; Dupon, J. W. *J. Org. Chem.* **1989**, *53*, 5230.
(20) Wittig, G.; Lohmann, L. *Justus Liebigs Ann. Chem.* **1942**, *550*, 260.
(21) Accordingly, the corresponding alkenes, such as ethene from **1f** and butenes from **1g** and **1h**, should be formed. We have not investigated the formation of gaseous reaction products.
(22) $[\alpha]^{27}_D$max = +13.52° (neat, l = 1). Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1911**, *99*, 45.
(23) Wagner, R. B.; Zook, H. D. *Synthetic Organic Chemistry*; J. Wiley & Sons: New York, 1965; p 261.

in vacuo (bp 110–118 °C, 15 Torr), and 2.1 g of product was collected. The product was dissolved in 5 mL of glacial CH_3COOH and slowly added to a stirred suspension of CrO_3 (2.1 g, 21 mmol) in 15 mL of CH_3COOH. After being stirred for 2 h at room temperature, the reaction mixture was poured into water (50 mL) and extracted with petroleum ether (3 × 30 mL); the organic phase was washed with saturated $NaHSO_3$ (3 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and water (50 mL) and dried over anhydrous $CaCl_2$. Evaporation of the solvent and vacuum distillation afforded the compound (+)-(*S*)-**7** (0.88 g, 5.4 mmol, 42.5%): bp 105–109 °C (15 Torr) (lit.[10] bp 125–127 °C, 24 Torr); $\alpha^{25}_D = +5.3°$ ($l = 1$) (lit.[10] α^{25}_Dmax = +39.6° ($l = 1$)).

Acknowledgment. We acknowledge financial support from M.P.I., Roma (60% and 40% funds), and from the Consiglio Nazionale delle Ricerche, Italy, through the Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, Sassari, under the Special Project "Processi di Trasferimento Monoelettronico". Mrs. Clara Fina (CNR, Sassari) is gratefully acknowledged for technical assistance.

Supplementary Material Available: Characterization data (boiling point, ^1H NMR, and MS) for compounds **1b–h**, **2**, and (+)-(*S*)-**7** (4 pages). Ordering information is given on any current masthead page.

The Synthesis of 3(5)-[(2-Hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide, an Acyclic Analogue of 4-Deoxypyrazofurin

Daryl R. Sauer and Stewart W. Schneller*

Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250

Received March 5, 1990

Pyrazofurin (pyrazomycin) (**1**) (Figure 1), one of the *C*-nucleoside antibiotics,[1] has generated considerable interest due to its marked antiviral[2] and antitumor[3] activities. Syntheses of 4-deoxypyrazofurin (**2**)[4,5] were stimulated by its structural relationship to (i) the parent compound, (ii) the broad spectrum antiviral agent ribavirin (**3**),[2] and (iii) to the antitumor agent tiazofurin (**4**).[6]

A major development in antiviral chemotherapy in recent years has been the recognition that potent antiviral activity is displayed by certain nucleoside analogues in which the ribose moiety is replaced by a truncated riboacyclic residue.[7] Significant examples include 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) (**5**),[8] which is used clinically to treat herpes infections, 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine (DHPG, ganciclovir),[9] which posseses antiherpetic activity, and (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA],[10] which exhibits broad spectrum antiviral activity.

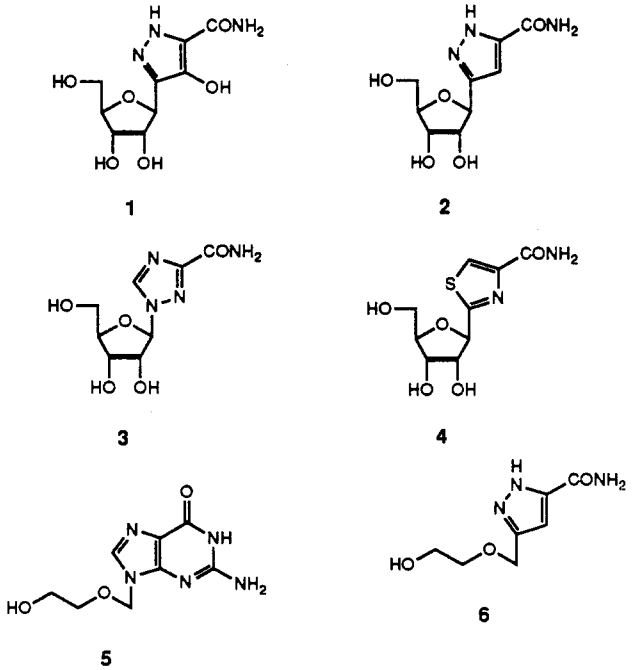


Figure 1.

With these facts in mind, 3(5)-[(2-hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide (**6**) emerges as an interesting target since it combines structural features found in both 4-deoxypyrazofurin (**2**) and acyclovir (**5**). The synthesis of **6** (Scheme I) is described herein from the protected pyrazole ester **7**, which is prepared via the regiospecific[11] 1,3-dipolar cycloaddition of the previously unknown diazoalkane **8** and methyl propiolate. The preparation of **8** became the initial synthetic goal.

The results of previous synthetic efforts in our laboratory,[12] and the laboratories of others,[13] indicated that the diazo functionality of **8** could be readily prepared from the corresponding nitrile. A search of the literature[14,15] revealed that a desirable nitrile precursor (that is, **9** of Scheme I) could be prepared via the Lewis acid catalyzed reaction of cyanotrimethylsilane and 1,3-dioxolane (Scheme I). This was accomplished to give **9** using zinc iodide as the catalyst. Since the trimethylsilyl protecting group was not expected to withstand the subsequent conditions required for preparation of the diazoalkane, it was removed by treatment with citric acid in methanol, and the resultant alcohol **10** was protected as the benzyl ether **11** by treatment with sodium hydride followed by benzyl bromide. The nitrile moiety of **11** was reduced efficiently with lithium aluminum hydride to yield the corresponding amine, which was directly converted to amide **12** with acetic anhydride/triethylamine in diethyl ether. Dinitrogen tetroxide was then utilized to convert amide **12** into its *N*-nitroso derivative **13**. The desired

(1) Buchanan, J. G. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1983; Vol. 44, p 243.
(2) De Clercq, E.; Torrence, P. F. *J. Carbohydr. Nucleosides Nucleotides* **1978**, *5*, 187.
(3) Cadman, E. C.; Dix, D. E.; Handschumacher, R. E. *Cancer Res.* **1978**, *38*, 682.
(4) Buchanan, J. G.; Saxena, N. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2367.
(5) Vanek, T.; Gut, J. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2004.
(6) Robins, R. K.; Srivastava, P. C.; Narayanan, V. L.; Plowman, J.; Paull, K. D. *J. Med. Chem.* **1982**, *25*, 107.
(7) Chu, C. K.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 289.
(8) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
(9) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759.
(10) De Clercq, E.; Descamps, J.; De Somer, P.; Holy, A. *Science* **1978**, *200*, 563.
(11) Regitz, M.; Heydt, H. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, p 393.
(12) Sauer, D. R.; Schneller, S. W. *Nucleosides Nucleotides* **1989**, *8*, 1079.
(13) For example, Acton, E. M.; Ryan, K. J.; Henry, D. W.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1971**, 986.
(14) Kirchmeyer, S.; Mertens, A.; Arvanaghi, M.; Olah, G. A. *Synthesis* **1983**, 498.
(15) Zimmerman, S. C.; Cramer, K. D.; Galan, A. A. *J. Org. Chem.* **1989**, *54*, 1256.

0022-3263/90/1955-5535$02.50/0