Table I. Relative Rates of S_N2 Reactions of Alkyl Bromides with Iodide Ions, Azide Ions, and 9-Methylfluorenyl Ions in Strongly Dipolar Nonhydroxylic Solvents

alkyl bromide	$I^-(Me_2CO)$[a] (60 °C)	$N_3^-(DMF)$[c] (25 °C)	9-MeFl$^-$(Me_2SO)[d] (25 °C)	2,7-Br_2-9-MeFl$^-$ (Me_2SO, 25 °C)
n-BuBr	3000[b]	200	56[e]	97
i-BuBr	230	10	8.5[f]	
i-PrBr	40	40	6[g]	10
c-C_6H_{11}Br	(1.0)	(1.0)	(1.0)[h,i]	(1.0)[j]

[a] Schotsman, L; Fierens, P. J. C. *Bull. Soc. Chim. Belg.* **1959**, *68*, 580-598. [b] For *n*-PrBr. [c] Alexander, R.; Ko, E. C. F.; Parker, A. J.; Broxton, T. *J. J. Am. Chem. Soc.* **1968**, *90*, 5049-5069. [d] Product studies were carried out, unless otherwise noted, by reacting equimolar quantities of 9-G-Fl$^-$ and RBr at room temperature for several days. The percent of 9-G-FlH in the crude solid product (NMR analysis) was used to estimate the amount of elimination. Satisfactory C and H and mass spectral analyses were obtained on the purified substitution products. [e] Reference 4. [f] 9-$PhCH_2$-9-*i*-BuFlH (85%), mp 85.5-87 °C, was obtained (10% elimination). [g] Reaction with excess *i*-PrBr gave 83% 9-Me-9-*i*-Pr-FlH, mp 39-41 °C. [h] 9-Me-9-c-C_6H_{11}FlH (80%), mp 171-172 °C, was obtained (15% elimination); 9-$PhCH_2$-9-c-C_6H_{11}FlH (85%), mp 107.5-108.5 °C, was obtained (15% elimination). [i] The rates were determined by the method described previously;[3] k = 0.280 ± 0.008 M^{-1} s^{-1}. [j] k = 0.0290 ± 0.001 M^{-1} s^{-1}. The pK_a values for 9-MeFlH and 2,7-Br_2-9-MeFlH are 22.3 and 17.7, respectively.

in alkyl bromides is brought out further in Table I by rate comparisons with I^- and N_3^- ions, which are powerful nucleophiles. We see that the 9-MeFl$^-$ ion, despite its large size and seemingly less accessible reaction site, appears to be actually *less* sensitive to structural effects in RBr that retard S_N2 reactions for steric reasons than are I^- or N_3^- ions. Whereas β-methyl branching (*i*-BuBr vs. *n*-Br) retards the rate of reaction with I^- by 13-fold and that with N_3^- ion by 20-fold, the retarding effect for 9-MeFl$^-$ ion is only 6.5-fold. For α-methyl branching (*i*-PrBr vs. *n*-BuBr) the retarding effects are 75-fold for I^-, 5-fold for N_3^-, and 9-fold for 9-MeFl$^-$. Finally, the retarding effect for c-C_6H_{11}Br is 3000-fold for I^-, 200-fold for N_3^-, and 56-fold for 9-MeFl$^-$.

The variation in sensitivities of 9-MeFl$^-$, N_3^-, and I^- to changes in alkyl bromide structure (Table I) once again emphasizes the importance of the nature of the donor atom in determining anion reactivities.[3] It is necessary to try to make comparisons of anion reactivities of the same basicity, however, before drawing conclusions concerning the reasons for this variation. Each substrate has a different sensitivity to changes in basicity as defined by the Brønsted β. For example, for reactions of 9-MeFl$^-$ anions with *n*-BuBr, *i*-PrBr, and c-C_6H_{11}Br, the β values are 0.365, 0.38, and 0.42, respectively. The appreciable difference in β values for *n*-BuBr and c-C_6H_{11}Br causes the *n*-BuBr/c-C_6H_{11}Br rate ratio to change from 56/1 for 9-MeFl$^-$ to 97/1 for 2,7-Br_2-9-MeFl$^-$, which is 4.6 pK units less basic (Table I). If we use these β values to extrapolate the *n*-BuBr/c-C_6H_{11}Br rate ratio for reactions with 9-MeFl$^-$ down to a basicity equal to that of the conjugate acid of N_3^- in Me_2SO (7.7), the ratio increases from 56 to about 350. Further extrapolation down to a basicity equal to that of the conjugate acid of I^- in Me_2SO (~0) causes the ratio to increase to about 1000. This suggests that although the data at first glance indicate a lesser sensitivity of 9-MeFl$^-$ than I^- or N_3^- ions to the retarding effects of α- and β-alkyl branching, these anions are probably all responding in a similar manner. We conclude that size and extent of delocalization are not important factors in determining the sensitivities of anions to the retarding effects of α branching in alkyl bromides on S_N2 reactions.

The β values are also important in determining the effect of a change in basicity of the anion on the E2/S_N2 rate ratio. For ArS^- ions reacting with c-C_6H_{11}Br in EtOH the β values for E2 and S_N2 reactions are 0.36 and 0.32, respectively,[13] and for ArO^- ions reacting with 4-bromoheptane in EtOH they are 0.39 and 0.27, respectively.[14] If the E2 reactions for sodium enolate ions reacting with alkyl halides in polyether solvents have larger β values than the S_N2 reacitons, this would explain, in part, the sharp increase in the percentage of eliminatin with increasing enolate ion basicity.[5,15]

Acknowledgment. This work was supported by the National Science Foundation.

Registry No. 9-$PhCH_2Fl^-$, 53629-11-1; 9-MeFl$^-$, 31468-21-0; 2,7-Br_2-9-MeFl$^-$, 73872-46-5; *n*-BuBr, 109-65-9; *i*-BuBr, 78-77-3; *i*-PrBr, 75-26-3; C-C_6H_{11}Br, 108-85-0; 9-$PhCH_2$-9-*i*-BuFlH, 82571-46-8; 9-Me-9-*i*-PrFlH, 57645-03-1; 9-Me-9-c-C_6H_{11}FlH, 82571-47-9; 9-$PhCH_2$-9-c-C_6H_{11}FlH, 82571-48-0; PhC(ONa)=CHPh, 82571-49-1; PhC(ONa)=CHEt, 17003-51-9.

(13) McLennan, D. J. *J. Chem. Soc. B* **1966**, 705-708.

(14) Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1964**, 5-15.

(15) For *i*-PrBr, changing the base from PhC(ONa)=CHPh to PhC(ONa)=CHEt caused the percentage of elimination to increase from 7% to 88% in the polyether solvent.[5] The basicity increase for the ion pairs (or ion aggregates) was estimated to be 2.5 units. In Me_2SO, where free enolate ions are involved, the change would be about 7 pK units.[16] Differences in steric and ion pairing effects, as well as basicity, may of course also influence the percentage of elimination.

(16) Unpublished results of U. E. Wiersum and of F. J. Cornforth (Ph.D. Dissertation, Northwestern University, Evanston, IL, 1976).

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On the Addition of Allyltrimethylsilane to Glycal Acetates

Summary: A highly stereoselective route to C_1 allylated glycosides bearing C_2–C_3 unsaturation has been developed.

Sir: Recently a very simple entry to 5,6-dihydro-γ-pyrones (1) was found.[1-4] By this methodology the relative configurations about C_5 and C_6 of the heterocycle[5] and even C_7 of a pendant side chain are subject to considerable control.[3-4] The resultant pyrones are readily converted in a stereoselective way to glycals of the type **2**.[6] Through

(1) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(2) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1597.

(3) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.

(4) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981.

(5) Danishefsky, S.; Larson, E.; Askin, D., manuscript submitted.

0022-3263/82/1947-3803$01.25/0

this strategy there can be achieved the de novo synthesis of a variety of unusual sugars,[1,2] and other natural products derivable[3,4] from such systems.

Of course, the extensive investigations into the chemistry of carbohydrates conducted over the last century have provided us with a great deal of methodology for manipulating pyranose systems. Indeed, such transformations have found elegant application in the synthesis of a wide variety of natural products.[7,8] We have been embarked on an effort to develop new methods for the synthesis of C-branched pyranose derivatives with particular emphasis on using substrates now readily available through our cyclocondensation reactions.

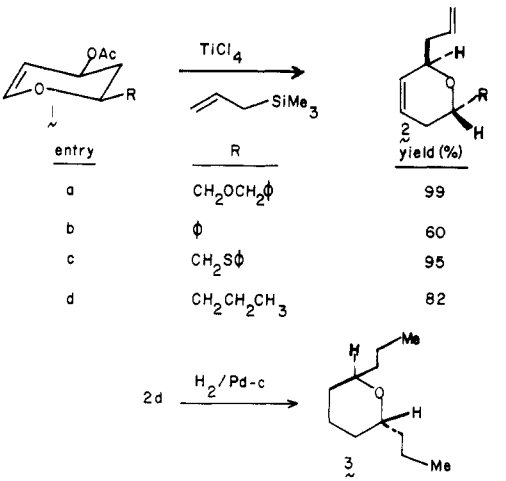
The tendency for leaving groups at C_3 of glycals to be displaced by heteronucleophiles with allylic transposition is well-known.[9,10] It was of interest to investigate analogous reactions with carbon nucleophiles.[11] In this connection, we examined the reaction of glycal acetates with allyltrimethylsilane (ATMS).[12a-c]

The nucleophilic tendencies of such silanes toward Lewis acid activated electrophilic centers have been broadly demonstrated. The regio- and stereoselective synthesis of C_1-branched glycosides through this process is described below.[13]

We first examined the reactions of the parent ATMS with 4-deoxy glycal acetates,[14] which are available by our methodology in three steps from the corresponding aldehyde R'CHO. Reactions were carried out in methylene chloride at −78 °C for 20 min, using 1.5 equiv of ATMS and 1 equiv of $TiCl_4$. After the reaction was quenched with aqueous sodium bicarbonate solution, extraction with ether and flash chromatography[15] afforded the *C*-allyl glycosides (**2**) in homogeneous states in the indicated yields.

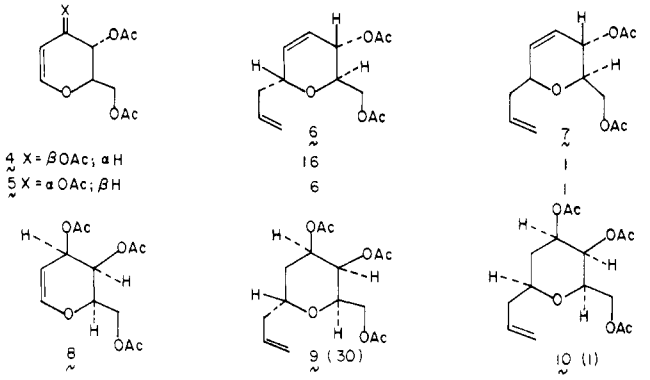
In each case the only regioisomer observed was the one arising from entry of the nucleophile at C_1, with transposition of the double bond to C_2–C_3. The results are shown below. The stereochemistry for entries a–c is provisionally assigned by analogy with the recent finding of Fraser-Reid.[11] The relative configuration shown in structure **2d** was demonstrated after reduction to its tetrahydro derivative, **3**. The trans relationship of the two propyl groups in **3** was established by variable-temperature NMR measurements at 270 MHz.

At room temperature (C_7D_8) the methine protons at positions 1 and 5 give rise to a single unresolved multiplet (δ 3.6). At −85 °C these protons appear as two broad signals δ 3.6–4.0 and 2.9–3.2, undoubtedly reflecting conformational interconversions. It may safely be assumed



that in the hypothetical cis version of **3**, equivalence of these protons would have been maintained.

We have extended this process to glycal derivatives obtained from natural hexoses.[16] Thus, reaction of D-glucal triacetate **4** with ATMS under the same conditions gives rise to an 85% yield of a 16:1 mixture of **6**/**7** from which both epimers were purified by HPLC.[17] When the same reaction was conducted with D-allal triacetate **5**, the same products were produced in 95% yield but now in a 6:1 ratio of **6**/**7**. As before, no indication for "direct" as opposed to allylic displacement was evident. The stereochemistry at C_1 in compounds **6** and **7** was assigned by NOE experiments. Irradiation of the C_5 methine proton (δ 3.70) in compound **7** at 500 MHz (C_6D_6) showed an enhancement of 12–15% in the C_1 methine protone signal at δ 3.92. Likewise, irradiation of the C_1 methine proton showed a similar enhancement of the C_5 methine signal. An NOE experiment performed on compound **6** using the C_1 methine signal (δ 4.27) and the C_5 methine signal (δ 3.95) at 500 MHz ($CDCl_3$) showed no evidence of any enhancement.



Reaction of D-galactal triacetate **8** gave a 93% yield of compounds **9** and **10** in a 30:1 ratio. The stereochemical assignment here is based on analogy with C_1-allyl glycosides **6** and **7**.

In all cases, the principal *C*-glycoside is the one that is produced by apparent axial attack by the allyl "nucleophile". In the most selective cases (see entries for **4** and **8**), axial allylation also results in an *anti* SN_2' displacement. In these terms, the erosion of specificity in the

(6) Refer to ref 1 and 2 for a general approach to compounds of type **2**.

(7) Fraser-Reid, B.; Anderson, R. C. *Fortschr. Chem. Org. Naturst.* **1980**, *39*, 1.

(8) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

(9) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(10) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570.

(11) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. In this paper triacetyl glucal is used as an alkylating agent with respect to the trimethylsilyl enol ether of acetophenone.

(12) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71. (b) Hosomi, A.; Sakurai, H. *Ibid.* **1976**, *17*, 1295. (c) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

(13) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. This paper describes the reactions of ATMS with glycosyl esters under the influence of zinc bromide. The Kozikowski reaction, which occurs under more forcing conditions, is valuable for products with different substitution patterns than those discussed herein.

(14) We have found that 4-deoxy glycals will react without prior acetylation. However, the yields are not as high, the stereospecificity of these processes was not as high, and the configurations of these products were not assigned rigorously. In some of these experiments as well as those of the 4-deoxy glycals, we have detected minor products which we believe to be the corresponding cis isomers.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(16) D-Glucal triacetate was purchased from Aldrich. D-Galactal triacetate was purchased from Raylo Chemicals Limited. D-Allal was prepared from β-D-allose (Sigma Chemical Co.). Refer to Haga, M.; Tijima, S. *Carbohydr. Res.* **1974**, *34*, 214.

(17) This mixture was separated by HPLC on a Waters μ-Porasil column 7.8 mm i.d. by 30 cm, using a 10% ethyl acetate in hexane solution as the elutant.

allal series (see entry 5) could be interpreted as reflecting the opposing tendencies of axial alkylation and anti SN_2' modes of attack.[18]

In any event this highly stereoselective process, conducted under extremely mild conditions, is likely to find application to various synthetic objectives.

Acknowledgment. This research was supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by the NSF Chemistry Division Grant CHE 7916210.

Registry No. 1a, 80127-55-5; **1b**, 82740-79-2; **1c**, 82740-80-5; **1d**, 82740-81-6; **2a**, 82740-82-7; **2b**, 82740-83-8; **2c**, 82740-84-9; **2d**, 82740-85-0; **3**, 82740-86-1; **4**, 2873-29-2; **5**, 52485-06-0; **6**, 82740-87-2; **7**, 82740-88-3; **8**, 4098-06-0; **9**, 82740-89-4; **10**, 82795-64-0; ATMS, 762-72-1.

Supplementary Material Available: Representative experimental procedures for the synthesis of compounds **2a** and **6** as well as spectral characterization of all new compounds (4 pages). Ordering information is given on any current masthead page.

(18) An alternative explanation for the glucal (4) and galactal (8) cases that cannot be rigorously excluded assumes that ionization of the allylic acetate occurs only when it is axially disposed. In that case, the principal products would be arising from an "equatorial" entry, presumably for reasons of steric hindrance. However, this formulation does not appear to embrace the finding in the allal (5) series.

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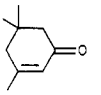
Ultrasound in Organic Synthesis. 2.[1] Formation and Reaction of Organocopper Reagents

Summary: Organocopper reagents can be formed from alkyl and aryl halides under ultrasonic irradiation and reacted in situ with enones to give high yields of β-alkylated ketones.

Sir: Application of organocopper derivatives in synthetic organic chemistry has received considerable attention.[3] The useful SN_2 and SN'_2 reactions of these reagents have been extensively studied,[3,4] and their conjugate addition to α,β-unsaturated carbonyl compounds provides the most versatile methods of effecting reductive alkylations of these substrates.[3,5] The preparation of the copper reagents in most cases requires a separate preparation of the intermediate lithio or magnesio derivatives. Recently, in the course of our effort to develop applications of ultrasonic waves, we discovered[1] that the Barbier reaction[6] can be greatly improved through the physical effects of ultrasonic irradiation. Thus, a variety of organolithium compounds can readily be prepared, and in the presence of ketones and aldehydes, high yields of the desired alcohols are obtained. The efficiency of this method, by comparison with the usual two-step procedure,[1] prompted us to investigate the possibility of forming organocopper species under these conditions and to react them with α-enones. The feasibility of this one-step transformation is demonstrated by the preliminary results reported in this communication.

Table I

enone	halide	method	isolated yield of the β-alkylated ketone	lit. % yield
	n-C_4H_9Br	A B	89 91	82[a]
		A B	76 88	65[b]–95[c]
	t-C_4H_9Br	A B	traces[e] 71	66[d]
	n-$C_7H_{15}Br$	A B	19[e] 88	
	C_6H_5Br	A B	64 67	
		A B	36[e,f] traces[e]	91[d]
		A B	45[g] traces	0[h]

[a] See ref 11. [b] See ref 12. [c] See ref 8. [d] VPC estimation, see ref 11. [e] Enolate polymerization occurs extensively. [f] 22% allylic alcohol isolated. [g] 30% allylic alcohol isolated. [h] See ref 13.

Initially, a Barbier-type reaction resulted on irradiation of a mixture of n-butyl bromide, lithium, and 2-cyclohexenone in the presence of copper iodide, yielding mostly 1-n-butyl-2-cyclohexen-1-ol. Ultrasonic irradiation was performed with a low-intensity generator (80 kHz, 30 W) without temperature control in dry THF. As the reaction of the intermediate RLi species is apparently much faster with the keto group than with the insoluble copper iodide, we attempted to overcome this difficulty through the acceleration of the reaction of RLi with the Cu^I reagent, i.e., through the use of more energetic sonication conditions and/or the use of a soluble copper derivative. Two procedures resulted from these investigations. In the first procedure (method A) an organic halide, lithium sand,[7] CuI, or pentynylcopper–hexamethylphosphorous triamide C_5H_7Cu–2HMP[8] (generally 1.5 mmol each) and an α-enone (1 mmol) at 0 °C in diethyl ether–THF (1:1) under an argon atmosphere are sonicated in a modified ultrasound laboratory cleaner.[9a] Generally, the metallic lithium is rapidly consumed (3–5 min), after which the resultant

(1) Previous paper: Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926. For other recent examples of the use of ultrasound in organic chemistry, see the following: Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 752. Suslick, K. S.; Schubert, P. R.; Goodale, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 7342. Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1679. Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558.

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(3) For an exhaustive literature survey, see: Posner, G. H. "An Introduction to Syntheses Using Organocopper Reagents"; Wiley: New York, 1980. Also see the following: Posner, G. H. *Org. React.* **1975**, *22*, 253. Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236. McDonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740. Trost, B. M.; Klein, T. P. *Ibid.* **1980**, *45*, 4256. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(4) Inter alia see the following: Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783 and references cited. Crabbé, P.; Dollat, J. M.; Gallina, J.; Luche, J. L.; Velarde, E.; Maddox, M. L.; Tokes, L. *J. Chem. Soc., Perkin Trans. 1* **1978**, 730.

(5) Posner, G. H. *Org. React.* **1972**, *19*, 1. House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(6) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

(7) Obtained as a 50% suspension in mineral oil from Alfa.

(8) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(9) (a) The generator provides a 50-kHz, 96-W acoustic wave. For a better temperature control, the electronic system of the generator was separated from the sonication bath. (b) 50 kHz, 130 W.

0022-3263/82/1947-3805$01.25/0