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ORGANIC REACTIONS AT HIGH PRESSURE. A MILD METHOD FOR THE PLACEMENT OF PROTECTING GROUPS ON HINDERED AND SENSITIVE ALCOHOLS[1]

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Abstract: A series of hindered and/or labile alcohols has been derivatized with a variety of acylating and silylating agents using pyridine in methylene chloride at 15 kbar (1.5 GPa) pressure to afford excellent yields of protected alcohols at 20 °C, largely without the need for added DMAP. Methoxyethoxymethyl chloride reacted in moderate yield using N,N-diisopropylethylamine under the high pressure conditions.

As synthetic organic chemists aim at increasingly complex targets, the ability to selectively protect sensitive functionality has become of crucial importance. Many acylating and alkylating agents for the protection of the alcohol function, however, are relatively bulky and thereby limited to use on unhindered sites. The discovery of catalysts such as 4-dimethylaminopyridine (DMAP) has greatly expanded the capabilities of these reactions[3,4] but for tertiary alcohols possessing other labile groupings which preclude the use of heat, the attachment of blocking groups remains a problem.[5]

In the course of several ongoing synthetic studies in this laboratory, a number of sterically demanding and heat-sensitive alcohols were encountered which resisted acylation, silylation and alkylation despite the activation provided by added DMAP. At room temperature, these compounds were relatively inert while more forcing conditions often resulted in significant amounts of elimination, ring opening or decarbonylation. The present study describes the successful application of high pressure methodology to the protection of a number of recalcitrant substrates (see Table 1).

The reactions were performed at 20 °C in sealed Teflon® tubes containing a 3.0:1.5:1.0 molar ratio of pyridine (or amine)/blocking agent/alcohol in methylene chloride. The tubes were pressurized[6] at 15 kbar (1.5 GPa) hydrostatic pressure for the indicated times, then depressurized. Each reaction mixture was concentrated under reduced pressure at 20 °C and subjected to flash chromatography on a 25 cm x 1 cm silica gel column (20-25% ether in hexane) to afford the desired alcohol derivatives in analytical purity.

The observation that the majority of cases did not require the use of DMAP likely derives from the ease with which amines quaternize under high pressure.[7,8] The general nucleophilic catalysis mechanism[4] operating in DMAP promoted esterification and etherification reactions

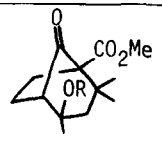
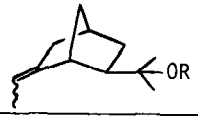
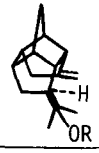
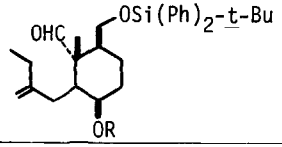
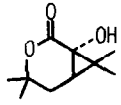
necessitates the formation of a quaternized pyridinium complex. The enhanced nucleophilicity[4] of DMAP over pyridine attributed to the electron donating effect of the 4-dimethylamino group, thereby assists quaternization at ambient pressure. However, this quaternization process is accompanied by a large volume contraction (ΔV = -30 to -50 cm^3 mol^{-1})[7] and consequently is accelerated at elevated pressures even in the absence of the 4-dimethylamino substituent. Therefore, the need for DMAP catalyst is diminished.

A survey of a variety of protecting agents (Table 1) reveals that high pressure most effectively increases the rates of ester and silyl ether formation over 1 bar DMAP controls.[9] As shown by entries 1-3, the rates of product formation at 20 °C, 24-36 h and 15 kbar pressure were dramatically greater in comparison to their 1 bar control experiments performed at 45 °C and 1 bar pressure for several days. This rate enhancement at high pressure and ambient temperature is critical for the protection of sterically congested and labile alcohol substrates, i.e., entries 4-6. In contrast to the ease of protection at 15 kbar pressure, the corresponding 1 bar control experiments (entries 4-6) revealed that the alcohol substrates were labile to the protection conditions employed, such that the reduced rate of formation at 1 bar pressure afforded limited amounts of the protected alcohols and also reduced quantities of recovered alcohol starting materials. Although both pyridine and triethylamine can be employed successfully as bases in all of these high pressure transformations, pyridine generally affords superior results. Reactions of the less sterically demanding methoxyethoxymethyl (MEM) chloride fail in the presence of pyridine and provide only ca 60% yields of MEM ethers when used in conjunction with N,N-diisopropylethylamine at 15 kbar pressure. These conditions, therefore, offer little advantage over the standard protocol[10] for etherification with this reagent.

Special attention is warranted to the preparation of silyl ethers at high pressure. The results in Table 1 (entries 1-3 and 6) demonstrate that silylation of these hindered alcohols is not achieved at 1 bar pressure but is effected only by using the ambient temperature, high pressure procedure. Furthermore, a 15 kbar experiment performed with linalool and t-butyldimethylsilyl chloride in the absence of base remarkably gave silylation in similar yield to that obtained with pyridine present. In pressure dependent runs at 6-9 kbar for 3-6 days, silylations of entries 1-3 could not be effected. However, under these conditions the corresponding esterifications with acetic anhydride occurred in comparable yields to their 15 kbar runs.

Our results demonstrate the potential of elevated pressures in promoting ester and ether formation for the protection of valuable synthetic intermediates. While all of the entries (Table 1) illustrate the increased rates of ester and silyl ether formation at 15 kbar pressure, several cases also establish the mildness of the method, entry 6 undergoing facile ring opening and entry 5 readily decarbonylating under the requisite forcing conditions. Finally, formation of silyl ethers from hindered alcohols can only be accomplished by using elevated pressure. High pressure, thus, constitutes an unusually powerful technique for affixing a variety of blocking groups on hindered and labile alcohols which could not otherwise be protected.

Table 1. Protection of Tertiary Alcohols Promoted by High Pressure

Entry	Alcohol (R = H)	Protecting Agent[a]	Product	Yield[b]	Controls[c]		
					T(°C)	t(h)	Yield[b,d]
1		a) Ac_2O, pyr, 24 h	a) R = Ac	98	20	14	80[e]
		b) Bz_2O, DMAP, pyr, 24 h	b) R = Bz	98	45	96	86(12)
		c) t-Bu$(Me)_2$SiCl, pyr, 24 h	c) R = Si$(Me)_2$-t-Bu	97	45	24	<5
		d) t-Bu$(Ph)_2$SiCl, pyr, 24 h	d) R = Si$(Ph)_2$-t-Bu	91	45	24	0
		e) MEMCl, (i-Pr)$_2$NEt, 36 h	e) R = MEM	62	45	36	88(9)
2		a) Ac_2O, pyr, 24 h	a) R = Ac	93	45	96	81(10)
		b) Bz_2O, DMAP, pyr, 24 h	b) R = Bz	83	45	96	77(16)
		c) t-Bu$(Me)_2$SiCl, pyr, 36 h	c) R = Si$(Me)_2$-t-Bu	74	45	36	0
		d) MEMCl, (i-Pr)$_2$NEt, 36 h	d) R = MEM	60	45	36	73(9)
3		a) Ac_2O, pyr, 24 h	a) R = Ac	79	45	44	48(52)
		b) Bz_2O, DMAP, pyr, 36 h	b) R = Bz	95	45	72	49(51)
		c) t-Bu$(Me)_2$SiCl, pyr, 36 h	c) R = Si$(Me)_2$-t-Bu	98	45	44	0
4		a) Ac_2O, pyr, 24 h	a) R = Ac	96	20	48	50(22)
5		a) Ac_2O, pyr, 36 h	a) R = Ac	84	60	36	28(0)
6		a) Ac_2O, pyr, 48 h	a) R = Ac	94	20	36	75(0)
		b) Bz_2O, DMAP, pyr, 36 h	b) R = Bz	97	20	72	58(0)
		c) t-Bu$(Me)_2$SiCl, pyr, 48 h	c) R = Si$(Me)_2$-t-Bu	92	45	18	0

[a]All reactions were run at 20 °C using a 3.0:1.5:1.0 molar ratio of base/protecting agent/alcohol in CH_2Cl_2 at 15 kbar pressure; [b]Isolated, purified yields. All new compounds gave satisfactory spectral and analytical data; [c]Controls were run at 1 bar pressure using the identical ratio of reagents plus 1.0-1.5 eq DMAP; [d]The yield of recovered alcohol starting material is shown in parentheses; [e]Höfle, G.; Steglich, W. Synthesis 1972, 619.

References and Notes

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2. National Institutes of Health Postdoctoral Fellow, 1981-1983. Present address: Department of Chemistry, Oklahoma State University, Stillwater, OK 74078.

3. The first reports of the use of 4-dialkylaminopyridine catalysts were: a) Steglich, W.; Höfle, G. Angew. Chem. Int. Ed. Eng. 1969, 8, 981; b) Litvinenko, L. M.; Kirichenko, A. I. Dolk. Akad. Nauk. SSSR, Ser. Khim. 1967, 167, 97.

4. The use of 4-dialkylaminopyridine catalysts is reviewed in: a) Höfle, G.; Steglich, W.; Vorbrueggen, H. Angew. Chem. Int. Ed. Eng. 1968, 17, 569; b) Reilly Reports: DMAP Update, published in 1982 by Reilly Tar and Chemical Corporation, 1510 Market Square, 151 N. Delaware St., Indianapolis, Indiana 46204.

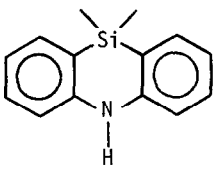
5. Other methods for carboxy group activation in ester formations are reported in: a) Staab, H. A. Angew. Chem. Int. Ed. Eng. 1962, 1, 351; b) Dharmaratne, H. R. W.; Gunatilaka, A. A. L.; Sotheeswaran, S. Indian J. Chem. 1982, 21B, 39; c) Mohacsi, E. Synth. Commun. 1982, 12, 453; d) Chandrasekaran, S.; Turner, J. V. Synth. Commun. 1982, 12, 727. Other methods for preparing hindered silyl ethers are reported in: e) Klebe, J. F.; Finkbeiner, H.; White, D. M. J. Am. Chem. Soc. 1966, 88, 3390; f) Galbraith, M. N.; Horn, D. H. S.; Middleton, E. J.; Hackney, R. J. Chem. Commun. 1968, 466; g) Veysoglu, T.; Mitscher, L. A. Tetrahedron Lett. 1981, 22, 1299, 1303.

6. The basic high pressure apparatus employed in the present study has been described in Dauben, W. G.; Krabbenhoft, H. O. J. Org. Chem. 1977, 42, 282. More detailed plans were submitted as supplementary material.

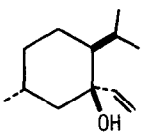
7. a) Isaacs, N. S. "Liquid Phase High Pressure Chemistry," Wiley Interscience, New York, 1981, p. 338; b) LeNoble, W. J.; Ogo, Y. Tetrahedron 1970, 26, 4119; c) LeNoble, W. J.; Asano, T. J. Am. Chem. Soc. 1975, 97, 1778; d) Asano, T.; LeNoble, W. J. Chem. Rev. 1978, 78, 407.

8. Matsumoto, K. Angew. Chem. Int. Ed. Eng. 1982, 21, 922.

9. During the course of the present work, two examples were found which failed to acylate under the 15 kbar conditions. Compound i, generously provided by Professor Gideon Fraenkel (The Ohio State University), resisted esterification even at 15 kbar, 40 °C, 48 h with 1.0 eq of added DMAP. The inertness of this compound has been attributed to through-bond and through space p to d backbonding of the nitrogen lone pair to the silicon. Interestingly the carbon analogue, 10,10-dimethylacridane acylates without any trouble.



i



ii

Compound ii, sent by Professor David Hart (The Ohio State University), was also unreactive to high pressure acylation even with added DMAP. A rationale for this observation eludes us since this compound readily undergoes propionylation at ambient pressures.

10. Corey, E. J.; Gras, J.-L.; Ulrich, P. Tetrahedron Lett. 1976, 809.

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