(5) Other acetals which are commonly used as protecting groups for alcohols are the tetrahydropyranyl ether (ref 4, p 104), ethoxyethyl ether (S. Chladek and J. Smrt, *Chem. Ind.* (*London*), 1719 (1964)), 2-methoxyisopropyl ether (ref 4, p 107), and 4-methoxytetrahydropyranyl ether (ref 4, p 108). Removal of all of these groups can be accomplished with dilute, aqueous acid. They are prepared from the corresponding vinyl ether with *acid catalysis*. The methoxymethyl ether,[1] as well as our *tert*-butoxymethyl ether, is prepared from the chloro ether with *base catalysis*.

(6) See, for example, (a) the synthesis of chloromethyl methyl ether: C. S. Marvel and P. K. Porter, "Organic Synthesis", Collect. Vol. I, 2nd ed, A. H. Blatt, Ed., Wiley, New York, N.Y., 1941, p 377; (b) the preparation of methoxyethyl chloromethyl ether: E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976); and (c) a review on α-halo ethers: L. Summers, *Chem. Rev.*, **55**, 301 (1955).

(7) Ethers are halogenated on the α carbon: M. L. Poutsma in "Methods in Free Radical Chemistry", Vol. 1, E. S. Huyser, Ed., Marcel Dekker, New York, N.Y., 1969, p 137.

(8) Methods for the free-radical halogenation of organic compounds have been reviewed: E. S. Huyser, *Synthesis*, 7 (1970).

(9) Sulfuryl chloride has been used to chlorinate tetrahydrofuran (THF): C. G. Kruse, N. L. J. M. Broekhof, and A. van der Gen, *Tetrahedron Lett.*, 1725 (1976).

(10) All attempts to isolate the chloro ether by concentration have led to decomposition.

(11) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932).

(12) There is no reaction at 0 °C after 4 h but a satisfactory reaction rate is obtained at room temperature. The water bath is used for cooling purposes only.

(13) The ^1H NMR spectra of the *tert*-butoxymethyl ethers show singlets at δ 4.1–4.7 (2 H) and 1.2–1.25 (9 H). The corresponding ^{13}C NMR spectra are also consistent with the proposed structures. For example, the acetal and quaternary carbons are found at δ 89.248 and 74.251, respectively, for the benzyl alcohol acetal and δ 90.038 and 74.068, respectively, for the 1-hexanol acetal.

Desiccant Efficiency in Solvent Drying. 3. Dipolar Aprotic Solvents[1,2]

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Received May 2, 1978

It is generally acknowledged that dipolar aprotic solvents are the media of choice in some reactions and are unique in facilitating others.[3] The special solvent effects of molecules such as DMF and Me_2SO are attributable to their large dielectric constants coupled with the absence of solvation by hydrogen bonding and typically manifest themselves in properties such as poor anion solvation, voracious cation solvation, and a marked hydrophilicity. For the chemist, this latter feature is unfortunate since small amounts of water in these systems can diminish[3,4] their nucleophilicity and may even be hazardous to some operations.[5] The drying of these solvents is thus of paramount importance, but in these cases, as previously,[1] the chemical literature contains little reliable quantitative data.

We have recently developed a method of solvent water assay which utilizes a tritiated water tracer for the determination of water content.[6] The method circumvents many of the problems encountered in other assay methods and has provided some new correlations on the efficiency of desiccants.[1,2] For example, it has been shown that, rather surprisingly, the efficiency of a given desiccant is strongly dependent upon the solvent type,[1] and there is thus much uncertainty in extrapolating generalizations from one solvent type to another.

The method has now been applied to the desiccation of the dipolar aprotics acetone, DMF, Me_2SO, and HMPT. Since the dielectric constants of these solvents range between 20.7 (acetone) and 46.7 (Me_2SO), their rigorous desiccation is expected to be difficult.

Results and Discussion

Drying of Hexamethylphosphoric Triamide (HMPT). *Caution! HMPT is a suspected carcinogen.* Although in recent years the favored desiccant for HMPT appeared to be calcium hydride,[7] drying has also been previously accomplished with alkali metals,[5,8] alkali metal earth oxides,[8] and 4A[9a] and 13X[9b] molecular sieves.

The results with the siccatives summarized in Table I are largely self-evident, but the following points are worth noting. The extreme resistance to desiccation is demonstrated by the impossibility of obtaining *super-dry*[10] HMPT under any of the conditions used here. Even sequential drying,[11] which was previously found to be effective with acetonitrile,[2] falls short in this case. The use of sodium–potassium alloy as a drying agent seems questionable in view of the thermal instability of solutions of alkali metals in solvents of this type.[12]

Since phosphorus pentoxide causes loss of material through side reactions, the best procedure for drying HMPT appears to be distillation from calcium hydride followed by storage over molecular sieves.

Drying of Dimethylformamide One source[8] observes that it is doubtful whether distillation alone can remove water from this solvent and recommends a chemical method for the elimination of protonic impurities. 4A molecular sieves, alumina, potassium hydroxide, and calcium hydride have all been endorsed as siccatives[8] for DMF.

The results in Table II indicate the powerful hydrophilicity of this solvent, although sequential drying with 3A sieves almost achieves *super-dryness.* Interestingly, and contrary to an earlier suggestion,[13] while some of the basic dessiccants investigated are totally inept, e.g., alumina and potassium carbonate, others such as calcium hydride and potassium hydroxide achieve quite reasonable drying levels. Also, although seldom advocated for use in this circumstance, phosphorus pentoxide is a commendable desiccant. For DMF, however, barring impurities other than water, by far the

Table I. Efficiency of Desiccants in the Drying[a] of HMPT[b]

desiccant	residual solvent water content, ppm				
	6 h	24 h	72 h	144 h	other conditions
P_2O_5	1840[c]				22[d]
CaH_2	1750	857	347	248	80[d]
B_2O_3					190[e]
3A molecular sieves	1380	595	307	239	
4A molecular sieves	1167	610	344	269	29[f]
KOH (powdered)	1380	840	404		321[f]
Na–K					1620[d,g]
BaO	2190	1540	1040		
CaO	2360	2034	1890	1380	
$CaSO_4$	2080				
Al_2O_3	2134				

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2620 ppm (0.262% w/w). [c] Strongly colored solution. [d] Distilled sample. [e] Stirring for 24 h followed by distillation. [f] Sequentially dried sample, 72 h. [g] Significant quantities of dimethylamine are released on distillation.

Table II. Efficiency of Desiccants in the Drying[a] of DMF[b]

desiccant	residual solvent water content, ppm			
	6 h	24 h	72 h	other conditions
3A molecular sieves	500	167	98	1.5[c]
P_2O_5	879	105		2[d]
CaH_2	641	227	102	94[d]
4A molecular sieves	454	134	108	
KOH (powdered)	1360	1110		303[d]
B_2O_3				890[e]
BaO	2060	1520	1140	
CaO	2090			
Al_2O_3	1970			
$CaSO_4$	2310	2030	1420	
K_2CO_3	2500			

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2860 ppm (0.286% w/w). [c] Sequentially dried sample, 72 h. [d] Distilled Sample. [e] Stirring for 24 h followed by distillation.

simplest and most effective method is sequential drying with 3A molecular sieves.

Drying of Dimethyl Sulfoxide (Me_2SO). Although calcium hydride[14a] and molecular sieves[14b] appear to be approved desiccants, the drying of Me_2SO has also been accomplished with a large variety of other siccatives.[8] Calcium sulfate, alkali earth metal oxides, alkali metal hydroxides, alumina, and, surprisingly perhaps, fractional distillation alone[15] have all been utilized.

Perhaps the most unexpected result (Table III) is that fractional distillation, discarding the first 20% of the distillate, affords desiccation of similar magnitude to that obtained with molecular sieves! This result is most surprising in view of the high dielectric constant and hygroscopicity of Me_2SO.

The interpretation of other results for Me_2SO is not so straightforward. For many of the basic desiccants, e.g., calcium hydride and calcium and barium oxides, initial dehydration is followed by an increase in *apparent* water content, and this indicates a base-catalyzed exchange between the acidic α protons of Me_2SO and labeled water. This suggestion is supported by a desiccation experiment with powdered potassium hydroxide which gave very little *apparent* drying. In this case, standing for 2 or 3 h over the desiccant produced yellow solutions, most likely indicating the presence of the dimsyl ion, which would of course lead to labeled solvent through exchange processes.

Although the results with the basic desiccants are therefore not very conclusive, a necessary corollary in the case of calcium hydride is, however, that drying is relatively slow, and perhaps not very efficient. A similar result for this desiccant was noted earlier with acetonitrile.[1]

In summary, although phosphorus pentoxide gave the best drying, it also induced significant decomposition, and the method of choice for Me_2SO would appear to be initial fractional distillation followed by sequential drying with molecular sieves.

Drying of Acetone. Acetone has been dried with a wide spectrum of desiccants.[8] Thus, alumina, calcium chloride, phosphorus pentoxide, and 4A molecular sieves,[16] as well as calcium and (anhydrous) cupric sulfate, have all been used.

Since acetone has the lowest dielectric constant of the solvents investigated here, it might be predicted that its drying should be relatively easy. In fact, in many respects the drying of acetone proved to be the most difficult case. As with Me_2SO, the root of the difficulty is the acidic α protons, which in this case compounds the drying problem not only by inflating *apparent* water content by exchange process but also by providing a pathway to self-condensation through enol intermediates. This facet of acetone chemistry makes the choice of a successful desiccant a delicate process. As Table IV shows, mild siccatives such as calcium sulfate are inept; more potent desiccants such as molecular sieves exhibit a short initial drying action but thereafter actually cause disastrous *increases* in water content by displacement of the condensation equilibrium. This interpretation was confirmed for molecular sieves and other basic desiccants such as barium oxide by gas chromatographic analysis which demonstrated the presence of mesityl oxide in the dried solvent (see Table IV).

In summary, while both cupric sulfate and 3A molecular sieves are clearly at least useful preliminary desiccants, the agent *par excellence* for acetone is powdered boric anhydride. Using stirring and sequential drying conditions, this siccati gave a solvent containing only 18 ppm of water and caused detectable condensation. In fact, the true water content likely to be lower as even with the premise that drying occu considerably faster than other processes, some labeling via t enol surely occurs on preparation of the standard wet sol tion.

In view of the remarkable efficiency of this desiccant acetone and acetonitrile,[1] it is puzzling that boric anhydri is not particularly outstanding for other members of this ser (Tables I–III). This finding emphasizes once more the danger in assuming the existence of any kind of absolute scale in the efficiency of desiccants for solvent drying.

Table III. Efficiency of Desiccants in the Drying[a] of Me_2SO[b]

desiccant	residual solvent water content, ppm				
	6 h	24 h	72 h	144 h	other conditions
4A molecular sieves	978	471	332	318	10[c]
3A molecular sieves	1050	448	269	226	
none					261[d]
P_2O_5					1.4[e,f]
B_2O_3					897[g]
CaH_2	1560		1820	1740	1802[e]
BaO	1450	1330	1770	2251	
CaO	2060		1740	1800	
Al_2O_3	1840	1900	1920		
K_2CO_3	2280	2200			
KOH (powdered)	2130[h]				2190[e]
$CaSO_4$	2140				

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2560 ppm (0.256% w/w). [c] Sequentially dried sample, 72 h. [d] Fractionally distilled sample. [e] Distilled sample. [f] Contaminated by decomposition products. [g] Stirring for 24 h followed by distillation. [h] Yellow colored solutions.

Table IV. Efficiency of Desiccants in the Drying[a] of Acetone[b]

desiccant	residual solvent water content, ppm 6 h	24 h	72 h	other conditions
B_2O_3				$18^{c,d}$
				$47^{c,e}$
				107^f
3A molecular sieves	115	152	322^g	322^h
$CuSO_4$ (anhydrous)	1920	972	579	1700^h
4A molecular sieves	331	887	1720	
$CaSO_4$	1590	1600		
BaO	1910	1870^i		
P_2O_5	j			1970^f
K_2CO_3	2057	2250		

[a] Static drying modes unless specified otherwise. [b] Desiccant loading 5% w/v; initial water content 2710 ppm (0.271% w/w), unless specified otherwise. [c] Initial water content 2890 ppm (0.289% w/w). [d] Stirred, distilled, and sequentially dried, 24 h. [e] Stirred for 24 h and distilled. [f] Dried for 24 h and then distilled. [g] Contamination (2%) by mesityl oxide. [h] Fractionated sample. [i] Contamination (12%) by mesityl oxide. [j] Brown-black solutions.

Experimental Section

Desiccants. Details of the source, activation, and handling of most of the desiccants have already been described.[1] Reagent grade cupric sulfate was activated by heating at 320 °C for 15 h before use. Barium and calcium oxides were of reagent grade, and a fresh batch was used directly without activation.

Solvents. DMF, Me_2SO, and HMPT were commercial synthetic grades of 99% purity (Merck). Acetone was of analytical grade (M&B). All solvents were rigorously purified by standard methods.[8]

HMPT and Me_2SO were treated by standing over barium oxide overnight, followed by filtration, distillation from calcium hydride, and subsequent storage over 20% w/v 4A molecular sieves. Me_2SO had bp 74.5–75.0 °C at 12 mmHg, and HMPT had bp 89.0–89.5 °C at ~3 mmHg.

Commercial DMF was allowed to stand over 4A molecular sieves overnight and was filtered, distilled from phosphorus pentoxide (bp 55.8–56.0 °C at 20 mmHg), allowed to stand over anhydrous potassium carbonate, and subsequently stored over 4A molecular sieves.

Analytical grade acetone was allowed to stand over anhydrous potassium carbonate for one day and then over 4A molecular sieves overnight. Fractionation gave material, bp 56.2 °C, which was not stored but used immediately. Gas chromatographic analysis of this material showed it to be free of impurities.

Techniques. The procedure used for HMPT serves as an example. A stock solution of HMPT containing 2620 ppm of labeled water was prepared by the addition of 0.50 g of tritiated water, specific activity 0.5 mCi/mL, to the appropriate mass of purified rigorously dried HMPT. Aliquots of the stock solution (15.0 ± 0.1 mL) were syringed directly onto the appropriate desiccant contained in a 25 mL clear-fit round-bottom flask, which was immediately stoppered. Experiments were conducted at ambient temperatures (26–30 °C). Where specified, samples were stirred magnetically. Aliquots (1.00 ± 0.02 mL) were taken at time intervals as specified in Table I and assayed directly by liquid scintillation counting, as previously described.[1,2] Where necessary, viz., in the case of colored solutions or suspected contamination by soluble desiccant residues, samples were distilled before assay. Sequential drying[2] was accomplished by decanting *monosiccated* solvent onto a fresh charge of 5% w/v desiccant. Sampling was then effected at the time intervals given in the table footnotes.

Registry No.—HMPT, 680-31-9; DMF, 68-12-2; Me_2SO, 67-68-5; acetone, 67-64-1.

References and Notes

(1) Part I: D. R. Burfield, K. H. Lee, and R. H. Smithers, *J. Org. Chem.*, **42**, 3060 (1977).

(2) For Part 2, see D. R. Burfield, G. H. Gan, and R. H. Smithers, *J. Appl. Chem. Biotechnol.*, **28**, 23 (1978).

(3) See, for example, Heinz Becker et al., "Organicum, Practical Handbook of Organic Chemistry", translated by B. J. Hazzard, Pergamon Press, Braunschweig, 1973, pp 185, 190. See also L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–5, Wiley, New York, N.Y., 1967, 1969, 1972, 1974 and 1975.

(4) For an interesting recent study involving Me_2SO-H_2O mixtures, see L. F. Blackwell and J. L. Woodhead, *J. Chem. Soc., Perkin Trans. 2*, 1218 (1975).

(5) The reaction of sodium hydride with Me_2SO has been reported to sometimes give rise to violent explosions; inter alia, see L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971, p 24. However, in our hands, the same reaction has been carried out a number of times using stringently dried solvent with no untoward effects. While the cause of these accidents remains undetermined, it is noteworthy that the equilibrium water content of Me_2SO is 10%, and it thus seems not unlikely that the origin of these mishaps may lie in the use of insufficiently dried solvents.

(6) D. R. Burfield, *Anal. Chem.*, **48**, 2285 (1976).

(7) See, for example, B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977).

(8) See references contained in J. A. Riddick and W. B. Bunger, "Organic Solvents", 3rd ed., Wiley-Interscience, New York, N.Y., 1970.

(9) (a) F. Tröndlin and C. Rüchardt, *Chem. Ber.*, **110**, 2949 (1977); (b) T. J. Wallace and A. Schriesheim, *Tetrahedron*, **21**, 2271 (1965).

(10) Here, as earlier,[1,2] the term *super-dry* denotes solvents containing less than 1 ppm of water.

(11) See Experimental Section.

(12) C. A. Young and R. R. Dewald, *J. Chem. Soc., Chem. Commun.*, 188 (1977).

(13) See S. S. Pizey, "Synthetic Reagents", Vol. 1, Ellis Horwood Ltd., Chichester, 1974. This author reports that the use of calcium hydride and other basic desiccants in the drying of DMF could produce significant amounts of dimethylamine. However, the presence of this amine would give rise to inflated *apparent* water contents, and the values observed here, both for statically dried and distilled samples, suggest that this side reaction is of minor importance for these desiccants.

(14) (a) D. Martin and H. G. Hauthal, "Dimethyl Sulphoxide", translated by E. S. Halberstadt, Wiley-Halsted, New York, N.Y., 1975. (b) H. E. Baumgarten, Ed., "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, pp 243, 756.

(15) W. H. Smyrl and C. W. Tobias, *J. Electrochem. Soc.*, **115**, 33 (1968).

(16) R. L. Meeker, F. Critchfield, and E. T. Bishop, *Anal. Chem.*, **34**, 1510 (1962).

3,4-Dimethyl-*cis*-bicyclo[3.3.0]-3-octene-2,8-dione: A Potentially Useful Pentalenolactone Synthon

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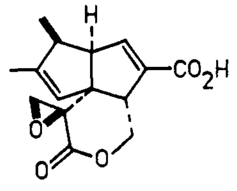
Received March 13, 1978

Pentalenolactone (**1**) is an acidic lipophylic antibiotic isolated from the fermentation broth of *Streptomyces* UC 5319 which exhibits inhibitory activity against nucleic acid synthesis in bacterial cells.[1,2] Both the novel structural nature of pentalenolactone together with its biological activity prompted us to consider possible routes to the synthesis of this molecule.



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Inspection of the literature revealed a number of potential pentalene synthons,[3] the most interesting of which was the pentalenedione **2** reported first by Stetter[4] and more recently by Eaton.[5] The salient feature of both the Stetter and Eaton routes was the base-induced internal Claisen condensation of the ester **3**, which in Eaton's hands gave an excellent yield of the dione **2**. These data inspired us to consider the possi-

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