

A NOVEL ROUTE TO ALDEHYDIC ENOL ETHERS AND ENAMINES¹

J.C. Gilbert* and U. Weerasooriya

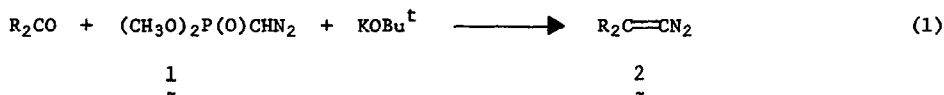
Department of Chemistry

The University of Texas at Austin

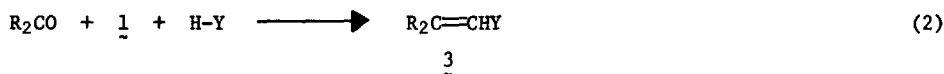
Austin, Texas 78712

Abstract. Base-promoted reaction of dimethyl diazomethylphosphonate (1) with dialkyl and cyclic ketones in the presence of alcohols and of amines affords aldehydic enol ethers and enamines, respectively.

A previous communication² outlined evidence for the proposition that a Wittig reaction between ketones and dimethyl diazomethylphosphonate (1) produced diazoethenes [2, equation(1)]. In this report, we summarize initial results of studies designed to elucidate the consequences of producing 2, or the carbene or carbenoid arising from it, in the presence of nucleophiles.



The net transformation that occurs, as illustrated in equation (2), is the conversion of dialkyl and cyclic ketones to aldehydic enol ethers (3, Y=OR) and enamines (3, Y=NR₂).



Stimulus for the present line of research was the observation that attempts to produce 2-methyl-1-diazopropene [2, R₂=(CH₃)₂] by reaction of acetone with 1.1 eq. each of 1 and potassium *t*-butoxide in anhydrous THF gave the enol ether 4 (Figure) in 15% yield.³ A mechanistic rationale for the formation of 4, via either thermal (path A) or solvent-assisted (path B) decomposition of the diazo compound 2 [R₂=(CH₃)₂] suggested that diazoethenes could serve as common precursors to various aldehyde derivatives, depending on the nature of nucleophiles present in the reaction mixture.

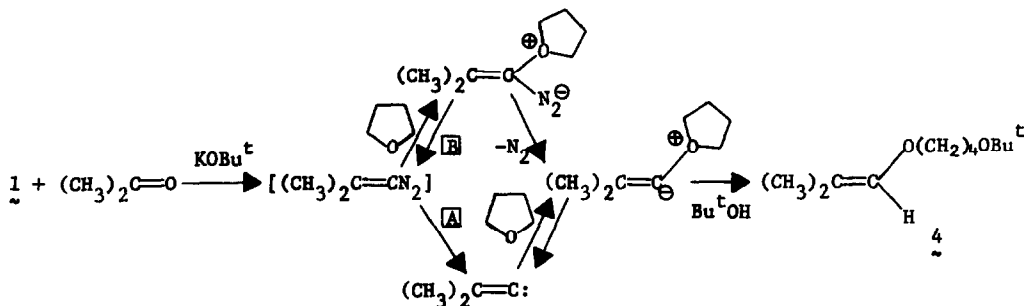


Figure. Possible Pathways to Enol Ether 4.

Confirmation of this expectation is shown by the data collected in the Table. Entries 1-6 demonstrate application of the method to the synthesis of enol ethers, and 7-13 extend the approach to enamines. Although cyclohexanone has been the principal substrate examined thus far, acyclic ketones, including the sterically hindered 3,3-dimethyl-2-butanone, can be successfully transformed (entries 6, 12, and 13). The reaction, however, is unsuccessful when either an aldehyde or an aryl ketone is used as the carbonyl substrate (entries 14-16). This failure presumably is the consequence of the high migratory aptitudes to carbenic centers of hydrogen and aryl relative to alkyl.

Although reaction conditions have not been optimized, overall yields are moderate to good. Improvement in yield is noted, however, when an excess of the phosphonate 1 (entries 2 and 7) or of the ketone (entry 2) is used. This is possibly associated with a kinetic competition between decomposition of the anion of 1 versus its addition to the carbonyl group.⁵ With regard to the production of simple enol ethers, our method appears to give yields superior to that using Horner-Wittig reaction of α -methoxymethyldiphenylphosphine oxide.⁶ The phosphonate reagents reported by Kluge,⁷ in contrast, afford better yields of somewhat more complex enol ethers. Nevertheless, our technique has synthetic utility in that it not only offers the potential of producing a spectrum of enol ethers from a single phosphonate reagent, as reflected in entries 3 and 5, but also has the conveniences of shorter reaction times and of operating at ambient temperatures and involves use of a less basic⁸ and less sterically encumbered phosphorus-stabilized anion than the other methods.

We were disappointed in the outcome of our efforts to prepare 2-methoxyethyl enol ethers (entry 5) owing to the somewhat surprising participation of both the alcoholic and ethereal oxygen atoms of 2-methoxyethanol. Some enhancement in selectivity for the desired enol ether could be achieved by use of 1,2-dimethoxyethane as co-solvent, but the overall yield was only moderate.⁹

The elaboration of ketones to aldehydic enamines occurs with secondary amines having nitrogens in a variety of steric environments (*cf.* entries 7-9). This is of interest owing to the observation of Curphey, *et al.*, regarding the importance of steric factors in optimizing yields in the alkylation of such enamines.¹¹ Of considerably greater significance is our success in generating the widely utilized pyrrolidine enamine (entries 9, 11, and 13) in yields that are comparable to, or better than, those claimed when various aminomethylphosphonates are used.¹² Preliminary data (entry 7) suggest that better yields are obtained when an excess of 1 is used and the reaction is performed at low temperatures.

The flexibility of having a single phosphonate reagent, 1, that allows generation of a variety of aldehydic enol ethers and enamines from aliphatic ketones has obvious merit from the practical synthetic standpoint.¹³ Studies designed to extend the transformation to other aldehydic derivatives, *e.g.*, allyl and propargyl enol ethers and enamines, are currently in progress.

Table. Enol Ethers and Enamines from Diazoethenes^a

Entry	Substrate R ₁ COR ₂		Solvent(s)	R ₁ R ₂ C=CH-Y ^b	% Yield ^c
	R ₁	R ₂		Y	
1	-(CH ₂) ₅ -		CH ₃ OH	CH ₃ O	50(58) ^d
2	-(CH ₂) ₅ -		CH ₃ OH	CH ₃ O	70 ^e (75) ^f
3	-(CH ₂) ₅ -		(CH ₃) ₃ COH	(CH ₃) ₃ CO	56
4	-(CH ₂) ₄ -		CH ₃ OH	CH ₃ O	30(30) ^{d,e,g}
5	-(CH ₂) ₅		CH ₃ O(CH ₂) ₂ OH	CH ₃ O(CH ₂) ₂ O CH ₃ O	34(37) ^h 34(3) ^h
6	CH ₃	(CH ₃) ₃ C	CH ₃ OH	CH ₃ O	37 ^d
7	-(CH ₂) ₅ -		(C ₂ H ₅) ₂ NH/(CH ₂) ₄ O ⁱ	(C ₂ H ₅) ₂ N	35(53) ^d (69) ^{d,k}
8	-(CH ₂) ₅ -		[(CH ₃) ₂ CH] ₂ NH	[(CH ₃) ₂ CH] ₂ N	50 ^d
9	-(CH ₂) ₅ -		(CH ₂) ₄ NH/(CH ₂) ₄ O ⁱ	Pyrrolidinyl	66 ^d
10	-(CH ₂) ₄		(C ₂ H ₅) ₂ NH/(CH ₂) ₄ O ⁱ	(C ₂ H ₅) ₂ N	50 ^d
11	-(CH ₂) ₇ -		(CH ₂) ₄ NH/(CH ₂) ₄ O ⁱ	Pyrrolidinyl	55 ^d
12	CH ₃	(CH ₃) ₃ C	(C ₂ H ₅) ₂ NH/(CH ₂) ₄ O ⁱ	(C ₂ H ₅) ₂ N	50 ^{d,f}
13	CH ₃ (CH ₂) ₃	CH ₃ (CH ₂) ₃	(CH ₂) ₄ NH/(CH ₂) ₄ O	Pyrrolidinyl	60 ^{d,j}
14	P-O ₂ NC ₆ H ₄	H	CH ₃ OH	P-NO ₂ C ₆ H ₄ C≡CH	80
15	C ₆ H ₅ CH ₂	H	CH ₃ OH	C ₆ H ₅ -CH ₂ C≡CH	69
16	C ₆ H ₅	C ₆ H ₅	(C ₂ H ₅) ₂ NH/(CH ₂) ₄ O ⁱ	C ₆ H ₅ C≡CC ₆ H ₅	97 ^k

^a Conditions (unless noted otherwise): Reaction of equivalent amounts of 1 and carbonyl substrate with 1.1 eq of KOBu^t at RT for 2 h; mixture quenched with water, and organic products extracted into pentane or dichloromethane, and solvents removed by rotary evaporation to leave desired product which was contaminated in some cases with unchanged carbonyl compound.

^b Spectra (mass, pmr, ir) used for characterization.

^c Determined by pmr analysis; reaction conditions not optimized.

^d Reaction performed at -78°C for 12-24 h and then allowed to warm to RT.

^e Two equivalents of 1 used.

^f Two equivalents of carbonyl substrate used.

^g The reaction failed to give higher yields when attempted at -100°C; cf. reference 5.

^h A molar ratio of 1:3.8 of CH₃O(CH₂)₂OH:(CH₃OCH₂)₂ used.

ⁱ A molar ratio of 1:25:75 of 1:amine:THF used.

^j Five equivalents of 1 used along with a molar ratio of 1:75:225 of 1:amine:THF.

^k Isolated yield.

REFERENCES AND NOTES

1. We acknowledge partial support of this work by the Robert A. Welch Foundation and the University Research Institute.
2. Gilbert, J.C.; Weerasooriya, U.; Giamalva, D., Tetrahedron Lett., 1979, 4619.
3. This unexpected product was characterized by the following spectra: mass: m/e 129: M-(CH₃)₂C=CHO, m/e 127: M-(CH₃)₃CO, m/e 72 (base peak): M-(CH₃)₃CO(CH₂)₂CH=CH₂; ir (CCl₄) 1680 cm⁻¹ (ν_{C=CHO-}); and pmr (CCl₄): δ1.10 s(9H), δ1.40 1.80 m (10H), δ3.30br t (2H), δ3.60 br t (2H), δ5.65 m (1H).
4. Hartzler, H.D. in "Carbenes," Vol. II, Moss, R.A.; Jones, M.J., Jr., ed. New York, J. Wiley and Sons, 1975.
5. Colvin, E.W.; Hamill, B.J. J. Chem. Soc. Perkin I, 1977, 869.
6. (a) Earnshaw, C.; Wallis, C.; Warren, S. J. Chem. Soc. Chem. Commun. 1977, 314. (b) Earnshaw, C.; Wallis, C.; Warren, S. J. Chem. Soc. Perkin I, 1979, 3099.
7. (a) Kluge, A.F. Tetrahedron Lett. 1978, 3629. (b) Kluge, A.F.; Cloudsdale, I.S. J. Org. Chem. 1979, 44, 4847.
8. The pK_a of 1 is unknown. An estimate of the value could be made if the pK_a's of diazomethane and dimethyl methylphosphonate were available; however, we have been unable to discover literature reports for either of these values. The fact that sodium methoxide in methanol and triethyl amine in THF, among other bases, are effective in promoting reaction of 1 with ketones and aldehydes supports a qualitative estimate of the pK_a of 1 as 20 or less.
9. The preference for use of the 2-methoxyethyl (or the tetrahydropyranyl) enol ether instead of the simple methyl enol ether apparently rests in the likely lesser effective basicity, owing to intramolecular cation complexation, of the anion derived from the (2-methoxyethoxy)methylphosphonate used to prepare the enol ether, since the hydrolysis of simple alkyl enol ethers is at least as facile and efficient¹⁰ as that of the more complex species.⁷ Our interest in synthesizing the methoxyethyl species resided in its possible use for the generation of vinyl anions.
10. See, for example, Boeckman, R.K., Jr.; Bruza, K.J. J. Org. Chem. 1979, 44, 4781.
11. Curphey, T.J., et al. J. Org. Chem. 1975, 40, 607.
12. Martin, S.F.; Gompper, R. J. Org. Chem. 1974, 39, 2814; Martin, S.F., et al. J. Org. Chem. 1977, 42, 2520; Broekof, N.; Jonkers, F.; van der Gen, A. Tetrahedron Lett. 1979, 2433.
13. A review that encompasses the methods for the preparation of derivatives of aldehydes from ketones by way of carbon-carbon bond forming reactions has recently appeared: Martin, S.F. Synthesis, 1979, 633.

(Received in USA 13 February 1980)