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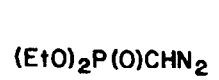
3-PYRROL-2-ONES FROM PYRUVAMIDES: MECHANISTIC AND SYNTHETIC ASPECTS

John C. Gilbert* and Brent K. Blackburn
Department of Chemistry
The University of Texas at Austin
Austin, TX 78712

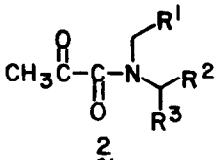
SUMMARY: 3-Pyrrol-2-ones, 4, and 2-butynamides, 5, are formed by reaction of N,N-dialkylated pyruvamides, 2, with diethyl (diazomethyl)phosphonate (1). The selectivity of the C-H insertion reaction to give 4 and the basis for it are discussed.

The mechanistic and synthetic aspects associated with the formation of five-membered rings by intramolecular insertions of carbenes and carbenoids into carbon-hydrogen bonds has drawn considerable attention.[1-3] The present communication describes studies of the formation of heterocycles by way of such an insertion process involving an alkylidenecarbene, $R_2C{=}C{:}$.[4]

Reaction of diethyl (diazomethyl)phosphonate (DAMP, 1)[5] with a variety of substituted pyruvamides, 2,[6] under basic reaction conditions affords two major types of products in high overall yield.[7,8] The predominant type of product formed is the 3-pyrrol-2-one, 4, the result of the anticipated[1,3] 1,5-C-H insertion of the alkylidenecarbene, 3, derived from the pyruvamide, but it is always accompanied by the 2-butynamide, 5, originating from a 1,2-shift of 3.[9] A summary of some typical results obtained in the reaction between 1 and 2 is contained in the Table.



1



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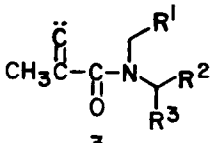

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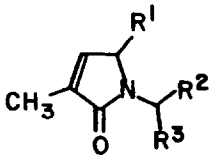
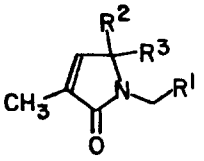
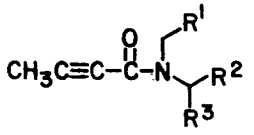


4a



4b



5

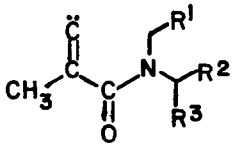
Several of the recorded observations merit comment. In no case was a product observed, even in crude reaction mixtures, that involved incorporation of methanol, the solvent for the reaction. The preference for occurrence of intramolecular C-H insertion to the exclusion of intermolecular O-H insertion is unprecedented in our experience[1k,10] and denotes an important role of the heteroatom in the reaction (vide infra).[11,12]

Table

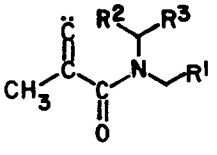
Entry	2			4[a]	4a:4b	5a	4a:4b[b]
	R^1	R^2	R^3				
1	H	H	H	50	--	23	--
2	H	n-propyl	H	67(43)[c]	70:30	32(20)[c]	1.5:1.0
3	H	phenyl	H	60(56)[c]	80:20	35(16)[c]	2.6:1.0
4	CH_3	CH_3	H	67	--	31	--
5	$-(CH_2)_3-$		H	67	--	32	--
6	$-(CH_2)_3-$		CH_3	67(63)[c]	50:50	32(26)[c]	1.0:1.2

[a] Yield (%) as determined by PMR analysis. [b] Statistically corrected ratio. [c] Isolated yield (%)

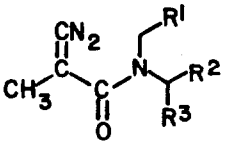
Entries 1-3 illustrate the fact that the insertion readily occurs into 1° C-H bonds. This is in sharp contrast to the results observed with all-carbon analogs of 3 generated by reaction of 1 with aliphatic ketones, wherein no reaction with such bonds was observed.[1k] Moreover, entries 2 and 3 demonstrate that the normal trend in relative reactivities of C-H bonds toward alkylidenecarbenes, viz., 3° 2° (benzylic) 2° 1°,[1a,i,k] is not seen with 3; in fact, the results, taken at face value, would seem to suggest that 1° C-H bonds are the most reactive. We believe that the apparent preference is the result of conformational factors, that is, a consequence of which of the alkyl substitutents on the nitrogen atom is syn to the diazoalkenyl moiety in 6 at the moment of birth of 3 from it. It seems likely that the hindered rotation associated with the amido group would preclude interconversion of 3a and 3b during the lifetime of the alkylidenecarbene 3; if this is true, the results are consistent with an argument that the selectivity of the insertion depends on the relative energies of the two conformers, 6a and 6b, and that the amido oxygen is sterically less bulky than the diazoalkenyl moiety.



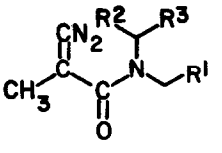
3a



3b



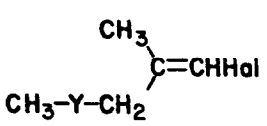
6a



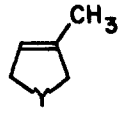
6b

The ratio of alkyne to 1,5-C-H insertion product is essentially constant throughout the series of pyruvamides examined. A common precursor for the two types of products is thus indicated, and this is most reasonably 3. Because alkyl groups are loathe to migrate in alkylidenecarbenes,[9] it is thought that 1,2-shift of the formamido moiety is occurring instead; unambiguous determination of this awaits the results of an appropriate labeling experiment, however.

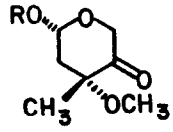
The activating effect of a heteroatom on the lability of a C-H bond to it toward insertion by an alkylidenecarbene, as reported here, is consistent with the observations of others. For example, Bottini and Walsh[3a] noted formation of 8, among other products, upon reaction of 7 with KOBu^t and Hauske, et al., have produced the erythromycin A derivative 10 by base-promoted reaction of DAMP (1) with the ketone 9.[3b] Although it is possible that the mechanism for activation involves some sort of complexation between the heteroatom and the carbenic carbon atom, our present working hypothesis is that the effect arises from stabilization of the transition state for insertion by development of orbital interaction between the non-bonding electrons of the heteroatom and the carbon atom undergoing the reaction.



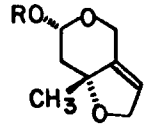
7 (Y = O, NR)



8



9



10

As a synthetic method for formation of 3-pyrrol-2-ones, the reaction described herein is best suited for use when the nitrogen atom of the pyruvamide is symmetrically substituted. The production of the 2-butynamides as by-products is vexing, but preliminary results indicate that the ratio of 4:5 is dependent on the selection of solvent and that the amount of 5 produced can be dramatically suppressed.[14]

ACKNOWLEDGMENTS. The generous support of our research by the Robert A. Welch Foundation (F-815) and the National Institutes of Health (GM 29972) is appreciated.

FOOTNOTES AND REFERENCES

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7. All compounds were characterized by their ^{1}H NMR, ^{13}C NMR, MS, HRMS, and IR spectra.
8. The general procedure for reaction between 1 and 2 is as follows: To a solution of 1 mmole of pyruvamide 2, 2 mmoles of DAMP (1), and 2 mL of methanol at -40°C (anisole, dry ice) is added a solution of 2.7 mmole (0.3 g) of potassium tert-butoxide in 2 mL of methanol. After 2 min the reaction mixture is allowed to warm slowly to 0°C, at which point the solution is stirred for an additional 2 hr. The mixture is then brought to room temperature, quenched with 10 mL of water, and extracted with five 15-mL portions of ethyl acetate. The combined organic extracts are dried over $MgSO_4$, filtered and concentrated in vacuo to yield the crude products. Purification is achieved by distillation (Kugelrohr) followed by HPLC.
9. Gilbert, J.C., Weerasooriya, U. J. Org. Chem. 1982, 47, 1837, and references cited therein.
10. Gilbert, J.C.; Weerasooriya, U. Tetrahedron Lett. 1980, 2041; b. Gilbert, J.C.; Weerasooriya, U. ibid, 1980, 5003; c. Gilbert, J.C.; Weerasooriya, U. J. Org. Chem. 1983, 48, 448.
11. Hauske and coworkers reported that the cyclization of 9 proceeds without alteration in the presence of a large excess of allyl alcohol.[3b]
12. Interestingly, reaction of ethyl pyruvate with 1 under the prescribed conditions[8] gives no intramolecular insertion product; only the product of insertion into methanol is observed.[13]
13. Unpublished results of M. Jones and E. Valencia, UT-Austin.
14. Unpublished results of B.K. Blackburn.

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