Photochemistry of 3,6-Dihydro-1,2-Oxazines (1) a Mechanistic Study for Pyrrole Cyclization

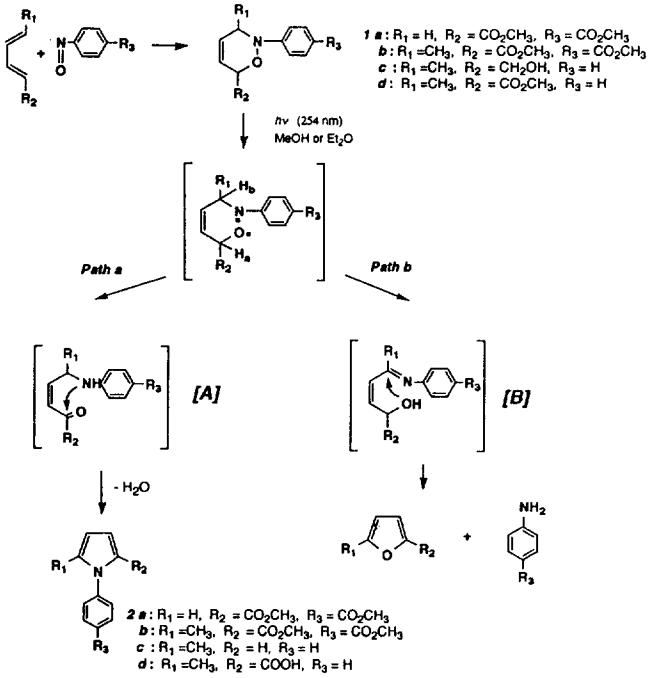
Young Hee Lee and Dong Joon Choo*

Department of Chemistry, Kyung Hee University, Seoul 130-701

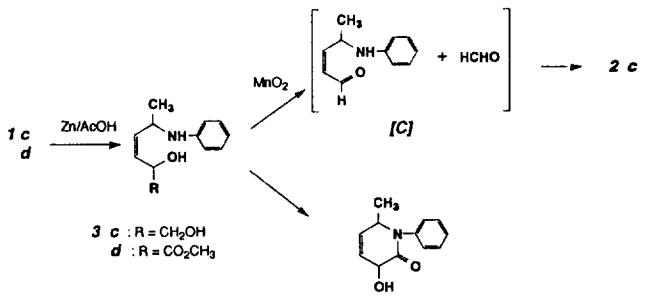
Received February 27, 1993

Even though the pyrrole ring is an integral part of many biologically significant compounds, there are few general synthetic routes to substituted pyrroles, especially the 3-substituted derivatives.[1,2] The acid and base sensitivity of pyrrole has made the synthesis of substituted heterocycles of this class often difficult to realize. One of the more general methods for the pyrrole synthesis which requires only mild reagents during the pyrrole forming step has been reported.[3,4] In this method, 3,6-dihydro-1,2-oxazine (**1**), which can be conveniently prepared by [4+2] cycloaddition reaction from an aryl nitroso compound and a diene, is irradiated with 254 nm UV. An extrusion of a H_2O molecule from the dihydrooxazine upon UV exposure results in the formation of a pyrrole ring. The regiochemistry of [4+2] cycloaddition reaction is erased during the photochemical step because either regioisomeric dihydrooxazine results in the same pyrrole. We have confirmed this general method for **1a, b** where irradiation of **1a, b** with 254 nm UV affords the pyrroles **2a** and **b** in 27% and 61% yield respectively along with a small amount of azoxybenzene[5] (Scheme 1).

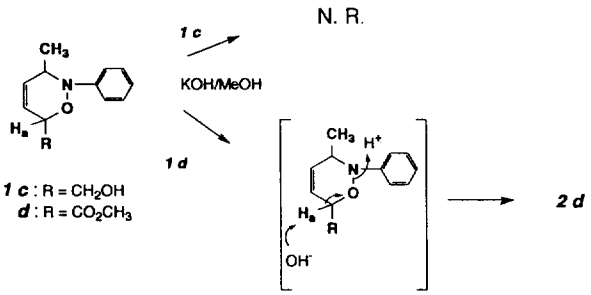
Although not firmly established, the mechanism of photochemical transformation of the dihydrooxazine **1** to pyrroles, shown in Scheme 1, has been suggested previously.[3] In this mechanistic scheme, homolytic cleavage of N-O bond of dihydrooxazine and subsequent abstraction of hydrogen H_a by



Scheme 1.



Scheme 2.



Scheme 3.

nitrogen radical to form intermediate [*A*] would occur at either excited singlet or triplet state manifold depending on the substitution patterns of aryl group in the dihydrooxazine.[4] In our case, dihydrooxzine **1b** which has *p*-carbomethoxy substituent on the N-aryl group undergoes the transformation by acetophenone sensitization, while dihydrooxazine **1c** is reactive only under the direct irradiation condition.[6] The key step in the transformation of dihydrooxazine to pyrrole is then the nucleophilic attack of nitrogen to the carbonyl carbon of the α,β-unsaturated ketoamine [*A*], followed by the extrusion of H_2O molecule at the ground state with the typical product yield of 60% for dihydrooxazine **1b** (Path *a* in Scheme 1). On the other hand, abstraction of hydrogen H_b by oxygen radical would result in the formation of intermediate [**B**], which is then cyclized to form a furan and aniline derivative (Path *b* in Scheme 1). In our study of photochemical transformation of dihydrooxazine, a small amount of furan derivative (in case of **1b** : 2%), together with aniline (in case of **1b** : 24%), has always been produced. This suggests the contribution of the minor pathway *b* to the pyrrole formation. To further confirm the mechanistic aspect of intermediate cyclization that the N-arylamino group nucleophilically attacks the carbonyl carbon, dihydrooxazine **1c** has been prepared from nitrosobenzene and *trans, trans*-2,4-hexadien-1-ol. Dihydrooxazine **1c** is then reduced by zinc/acetic acid to obtain an allylic aminoalcohol **3**. Upon oxidation of the alcohol **3c** by MnO_2, the only product confirmed was pyrrole **2c** in 13% isolated yield, which presumably has been cyclized *via* an intermediate [**C**] (Scheme 2). Supporting this mechanistic pathway is a report that when dihydrooxazine **1d** was reduced by the same manner as the dihydrooxazine **1c**, not the pyrrole derivative but an azinone was produced (Scheme 2).[7]

We have further studied the ground state chemistry of dihydrooxazines **1c** and **1d**. While heating **1c** in the KOH/MeOH solution to reflux for 4 days has resulted in no reac-

tion on the starting material, dihydrooxazine **1d** has been reported to be converted to pyrrole **2d** in 93% yield under the same reaction condition.[8] It is quite understandable that dihydrooxazine **1c** does not afford the desired pyrrole. Unlike **1d**, the proton at the 6-position (H_a in Scheme 3) of dihydrooxazine **1c** is much more weakly acidic than that of **1d** thus would prevent the formation of carbonyl group to be attacked by the N-phenylamino group in the intermediate for cyclization (Scheme 3).[9]

Acknowledgement. This work was supported in part by the Korea Research Foundation through Non Directed Research Fund, 1990.

References

1. (a) R. A. Jones and G. P. Bean "The Chemistry of Pyrroles" Vol. 34 in "Organic Chemistry: A series of Monographs", A. T. Blomquist and H. H. Wasserman, ed., Academic Press (1977) Chap. 3; (b) J. M. Patterson, *Synthesis*, 281 (1976).
2. L. A. Paquette, "Modern Heterocyclic Chemistry" W. A. Benjamin, Inc., (1968) Chap. 4.
3. P. Sheiner, O. L. Chapman, and V. D. Lassila, *J. Org. Chem.*, **34**, 813 (1969).
4. R. S. Givens, D. J. Choo, S. Merchant, R. Stitt, and B. Matuszewski, *Tet. Lett.*, 1327 (1982).
5. Synthetic and structure determination methods will be described in full paper. The NMR (^{13}C and ^{1}H), IR, and mass spectra of the compounds reported here were all consistent with the assigned structures. All products were recrystallized and reported yields are purified yields.
6. Irradiations were carried out in the Rayonet Photochemical Reactor. Standard photochemical experimental procedures were employed for this study.
7. J. Firl and G. Kresze, *Chem. Ber.*, **99**, 3695 (1965).
8. G. Kresze and J. Firl, *Ang. Chem. Int. Ed. Engl.*, **3**, 382 (1964).
9. T. Sasaki, S. Eguchi, T. Ishii, and H. Yamada, *J. Org. Chem.*, **35**, 4273 (1970).

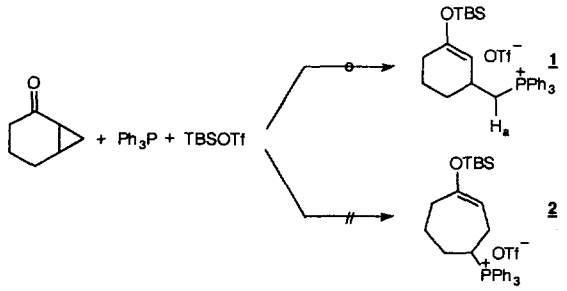
An Efficient Electrophile-Assisted Homoconjugate Addition of Triphenylphosphine to Cyclopropyl Ketone

Phil Ho Lee*, Jong Soon Kim, and In-Sup Han

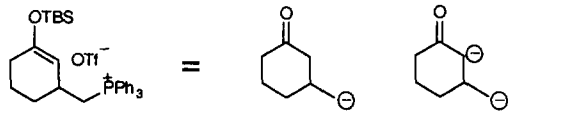
Department of Chemistry, Kangwon National University, Chunchon 200-701

Received March 2, 1993

Recent advances in the formation of three-membered rings have led to the steadily increasing usage of cyclopropyl derivatives as reagents for organic synthesis.[1] In this respect, cyclopropyl ring opening reactions by nucleophiles or electrophiles have received considerable attention over the past years.[2] In contrast to double bonds, which are susceptible to the Michael reaction in the presence of one activating group, comparable homoconjugate additions to monoactivated cyclopropane derivatives are few and normally restricted to highly strained systems, powerful nucleophiles or electrophile-assisted nucleophilic reactions. In connection with our recent of research for the functionalization of α,β-unsaturated carbonyl compounds *via* phosphoniosilylation,[3] we have had an occasion to study ring opening reaction of cyclopropyl ketone and it has been found that TBSOTf assisted homoconjugate addition of triphenylphophine to the fused bicyclic cyclopropyl ketone occurred cleanly to provide 1,5-addition product **1** in which ketone group is protected as silyl enol ether (Eq. 1). Moreover, the silyl enol ether phosphonium salt **1** has a wide potential since further functionalization can be possible at α or γ-position (Eq. 2). As far as we are aware, this is the first example in which trivalent phosphorus compound opened monoactivated cyclopropane.



(1)



(2)

Among the solvent tested in this study, dichloromethane gave the best result, although tetrahydrofuran, diethyl ether and toluene were effective to some extent. Notably, triphenylphosphine by virtue of TBSOTf unlike TMSOTf and BF_3:OEt_2 opened regioselectively the cyclopropane ring to give **1**. This result suggested that geometry-dependant orbital interaction (stereoelectronic effect) appears to control the direction of the cyclopropane ring opening and the bond that cleaves is the one which has the greater overlap with the carbonyl π-system. The structure of **1** was determined by coupling constant for H_a[δ 5.40(ddd, J=18.52, 12.92, 5.60 Hz, 1 Ha)]. In case of cyclopropyl phenyl ketone, ring opening reaction was not effective under the present condition.

As shown in Eq. (3), silyl enol ether of ketone containing alkenyl group at β-position was prepared in one pot procedure from cyclopropyl ketone without any isolation of the intermediate. While such β-alkenyl ketones are generally derivable from the parent enones by copper conjugate addition procedures followed by enolate trapping, the yields which attend such process in case of containing electrophile in transfer ligand are some times low and the requisite organocuprates are difficult to procure.[4] Also, *n*-BuLi in hexane does effect deprotonation of enol phosphonium salt without competing desilylation.

The experimental procedure for the synthesis of 3-[(*Z*)-2′-phenylethenyl]-1-cyclohexenyl *tert*-butyldimethyl silyl ether is as follows. To a solution of triphenylphosphine (203.2 mg,