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FORMAL ACTIVATION OF C-H BONDS TOWARD CARBENE BY CAPTO-DATIVE SUBSTITUENTS

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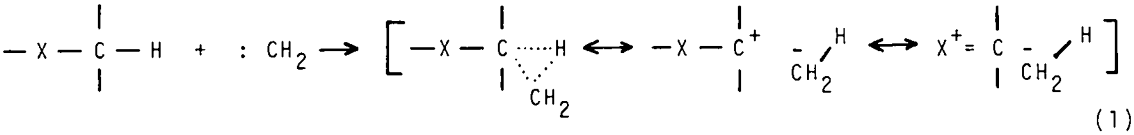
Abstract: The C-H bonds interposed by amine nitrogen and electron withdrawing group were found to be highly activated toward carbene.

Insertion reaction of carbene especially into C-H bonds has been attracting much attention since its first discovery by Meerwein, Rathjen, and Werner[1] and a great number of studies have been devoted[2-4] not only to elucidate the mechanism of the reaction but also to develope the synthetic aspect of the reactions. Although the reaction being known as the most characteristic one of carbene can be considered to be a potentially versatile way of forming a new C-C bond in synthetic chemistry, several drawbacks, e.g., low yield, low selectivity and so forth, still remain unsolved and limit the general applicability of the reaction.

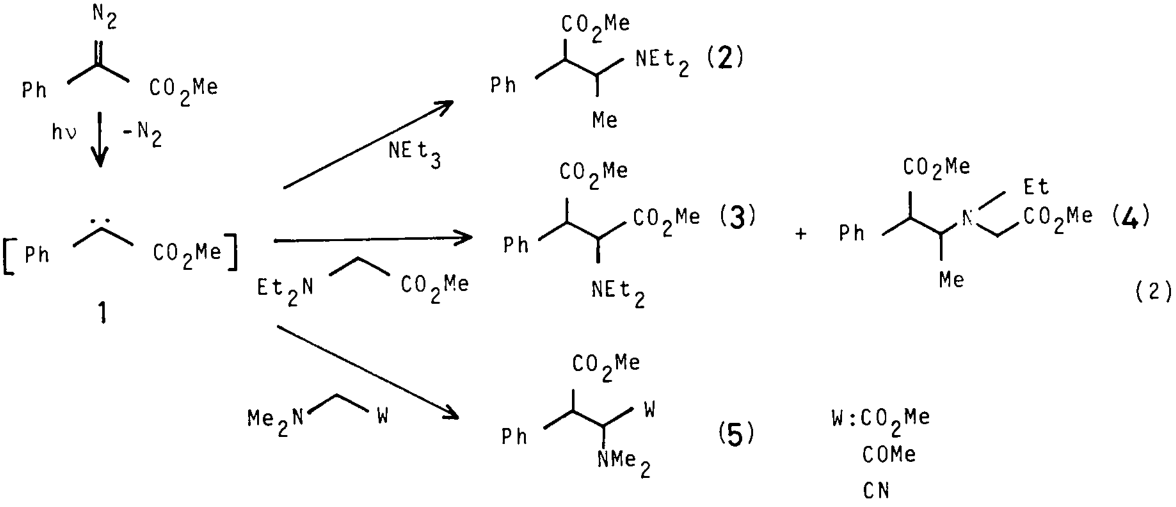
It has been generally recognized[2a] that the insertion of carbene into C-H bonds of hetero atom compounds e.g., ethers and amines, proceeds with small preference for insertion into the α-CH bonds to the hetero atom. For example, methyl β-ethoxybutyrate and γ-ethoxybutyrate were produced in the ratio of 4:1 when methyl diazoacetate was photolyzed in diethyl ether. These results are usually rationalized in terms of polar resonance structure of the transition state as a result of electrophilic nature of carbene attack on C-H bonds (eq 1). In accordance with expectation based on this concept, we found that the photolytic generation of methoxycarbonylphenylcarbene (**1**) from the corresponding diazo precursor in triethylamine afforded 1-methoxycarbonyl-2-diethylamino-1-phenylpropane (**2**) presumably as a result of insertion of **1** into α-CH bond of trietylamine as a sole isolable product in 60 % yield. However, when we generated **1** in N,N-diethylglycine methyl ester, we obtained succinate (**3**, 42.0%) as a major product along with a small amount of phenylpropane (**4**, 13.8%). This is rather unexpected since C-H bonds of CH_2 group adjacent to electron-withdrawing CO_2Me should be more electron deficient compared to those of N-ethyl group. More surprisingly, the reaction of **1** with N,N-dimethylglycine ester resulted in the exclusive formation of 5 (W=CO_2Me, 81.0%), no C-H insertion into N-ethyl group being detected.



(1)

Similar reaction of **1** with other amines bearing electronwithdrawing β-substituent W (COMe, CN) also afforded the less favored C-H insertion products (**5**, W=COMe, 80.5%; W=CN, 68.4%) almost exclusively (eq 2).

These results clearly indicated that the carbene underwent insertion preferentialy into the C-H bonds of apparently less electron rich side of CH_2 groups i.e., CH_2 interposed by electron donating amine group and withdrawing W group.



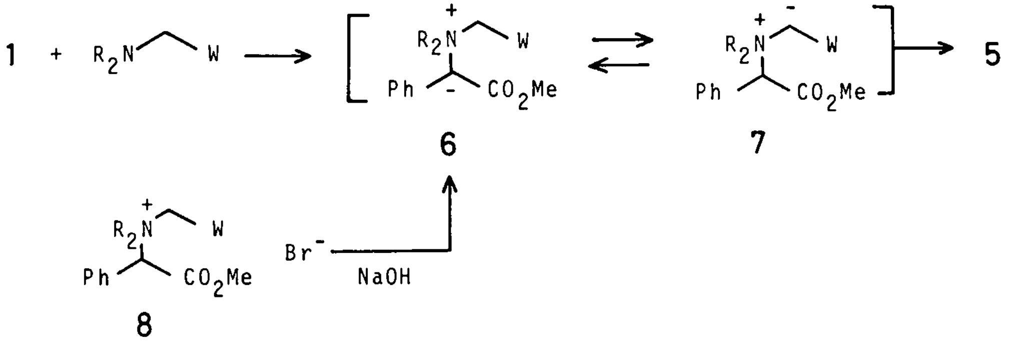
In order to estimate the reactivities of the C-H bonds of these amines toward carbene more quantitatively, we carried out the competition experiments using methanol as a standard substrate. Thus, the carbene was generated in a binary mixture of methanol and appropriate amines and the relative reactivities were calculated by means of the well-established equation of Doering and Henderson[7] using the fraction of products and substrates and were listed in the Table. The relative reactivities of simple amines, i.e., triethylamine as well as N,N,N',N'-tetramethyldiaminomethane were also recorded in the Table for comparison purpose. Inspection of the results in the Table clearly indicates that the C-H bonds of N-CH_2-W are obviously more reactive than the O-H bond of methanol, while that of simple amine, i.e., triethylamine are less reactive. This is rather surprising since the O-H bond of methanol is a highly efficient trapping reagent for singlet carbene while C-H bonds of simple hydrocarbons are usually believed to be least reactive center toward carbenes. For example, the absolute rate constant determined for the reaction of

Table 1. The reactivities of amines toward carbene **1** relative to methanol.

Amines	k_{Amine}/k_{MeOH}
$Me_2NCH_2CO_2Me$	2.69
Me_2NCH_2CN	1.80
Me_2NCH_2COMe	1.01
Et_3N	0.63
$Me_2NCH_2NMe_2$	0.58

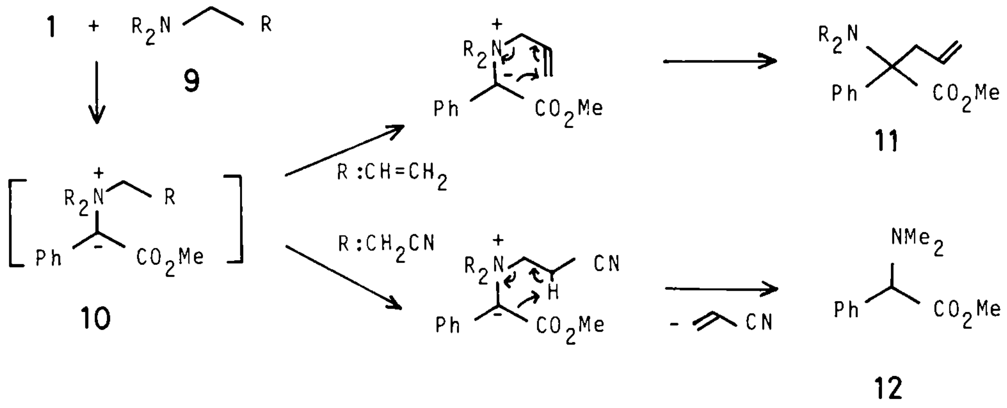
fluorenylidene with methanol[8] was $8.9\times10^{-8}M^{-1}s^{-1}$, while that with cyclohexane[9] was $8.3\times10^{-7}M^{-1}s^{-1}$. The findings that $N\text{-}CH_2\text{-}W$ showed increased reactivities than $N\text{-}CH_2\text{-}CH_3$ clearly suggested that the electron withdrawing substituent W plays an important role in activating the CH bonds toward carbenes.

The mechanism of C-H insertion is then quite important in order to rationalize the observed increased reactivity. It may be possible that the C-H insertion products are formed from triplet state of carbene via H abstraction followed by the recombination of the resulting radical pair. This mechanism explain reasonably the increased reactivities of $N\text{-}CH_2\text{-}W$ in terms of the capto-dative stabilization[10] of the resulting radical, i.e., $N\text{-}\dot{C}H\text{-}W$. However, it has been well-documented[2a] that most carbenes interact efficiently with the lone pair electrons of amine nitrogen atom in its nascent singlet state forming ylide intermediates, which are sometimes detected[11] spectroscopically. Coincidentally, the fact that no cage-escaped by-products expected[12] to be formed in the triplet carbene reaction were detected in the present reaction systems also supported the singlet nature of the CH insertion reaction[14]. Thus, we would like to suggest that the initial step of the reaction must be electrophilic attack of singlet carbene on the amine nitrogen lone pair electrons leading to ylide (**6**). In the ylide intermediate, methylene protons of $N^+\text{-}CH_2\text{-}W$ are highly mobile due to the two adjacent electron deficient substituents and therefore undergo 1,3-shift generating an another ylide (**7**) which then undergoes the Stevens rearrangement[13] producing the formal C-H insertion product (eq 3). The observed high regioselectivity is then ascribable to the increased acidity of methylene protons by the electron withdrawing substituents W and N^+. The validity of the mechanism was gained in the following additional experiments. Thus, the reaction of **1** with allylamine **9** ($R=CHCH_2$) afforded **11** while cyanoethylamine **9** ($R=CH_2CN$) gave **12** almost exclusively (eq **4**). Those products are reasonably explained in terms of the initial formation of ylide **10** followed by the Claisen rearrangement[14] forming **11** or by β-elimination[15] of acrylonitrile giving **12**, respectively. Moreover, the treatment of the ammonium bromide (**8**) with MeONa/MeOH under the Stevens rearrangement conditions actually afforded the C-H insertion products almost quantitatively (eq 3).



(3)

Thus, the present findings suggested that C-H bonds can be activated toward carbenes formally by capto-dative substituents resulting in highly regioselective formation of a new C-C bond. This method can be applied to the other capto-dative methylene group as well and would improve the notorious indiscriminate nature of C-H insertion of carbene.



(4)

References and Notes

1. H. Meerwein, H. Rathjen and H. Werner, Chem. Ber., **75**, 1610 (1942).
2. See for review: a)W. Kirmes, "Carbene Chemistry", 2nd ed., Academic Press, New York, 1971, Chapter 7; b)A. Oku and T. Harada, J. Syn. Org. Chem., Jpn., **44**, 736 (1986).
3. A. Oku and T. Harada, Rep. Asahi Glass Found. Ind. Technol., **49**, 65 (1986).
4. C. D. Gutsche, G. L. Bachman, W. Udell and S. Banerlein, J. Am. Chem. Soc., **93**, 5172 (1971); T. A. Bear and C. D. Gutsche, Ibid., **93**, 5180 (1971).
5. J. E. Basiński, Ph. D. thesis, Yale University, New Haven, Conn., 1961.
6. W. von E. Doering, L. H. Knox and M. Jones, Jr., J. Org. Chem., **24**, 136 (1959).
7. W. von E. Doering and W. A. J. Henderson, J. Am. Chem. Soc., **80**, 5274 (1958).
8. P. B. Grasse, B-E. Brauer, J. J. Zupanic, K. J. Kaufman and G. B. Schuster, J. Am. Chem. Soc., **105**, 6833 (1983).
9. P. C. Wong, D. Griller and J. C. Scaiano, J. Am. Chem. Soc., **103**, 5934 (1981).
10. For review see: H. G. Viehe, R. Merenyi, L. Stella and Z. Janousek, Angew. Chem., **91**, 982 (1979).
11. J. E. Jackson, N. Soundararajon and M. S. Plats, J. Am. Chem. Soc., **110**, 5595 (1988); M. B. Jones, J. E. Jackson, N. Soundararajan and M. S. Platz, Ibid., **110**, 5597 (1988).
12. M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kulczycki, Jr., P. M. Howley, K. M. Hummel and D. S. Malament, J. Am. Chem. Soc., **94**, 7469 (1972).
13. Benzyldimethylamine reacts with carbenes by apparent insertion of the carbene into N-benzyl bond, which arises from a Stevens rearrangement of the initial ylide intermediate: W. R. Banford and T. S. Stevens, J. Chem. Soc., 4675 (1952).
14. W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, H. Yamamoto, I. Imai, S. Nakaido and T. Migita, J. Am. Chem. Soc., **44**, 3870 (1972); Triplet carbenes were believed to be trapped by the double bond of allylamine leading to cyclopropanes, but no cyclopropanes were detected in the reaction of **1** with allylamine.
15. W. Kirmse and H. Arold, Chem. Ber., **101**, 1008 (1968); V. Franzen and H. Kuntze, Ann., **627**, 15 (1959). It should be noted that the elimination products are usually formed only to a minor extent.

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