SYNTHESIS OF σ-TRIS-HOMOAZEPINE SKELETON

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Addition of dichlorocarbene in aqueous medium (phase transfer method) to N-ethoxycarbonyl-1(1H)-azepine gave all-trans-N-ethoxycarbonyl-1(1H)-σ-tris-homoazepine derivative in a highly stereospecific manner.

Previously, we have described that electrophilic addition reactions of iodine azide to medium-membered ring unsaturated compounds are to be stereospecific and regiospecific.[1]

Recently much interest has arisen in the chemistry of σ-tris-homobenzene derivatives.[2] We have investigated carbene reactions to medium-membered ring unsaturated compounds for one step syntheses of σ-tris and σ-tetrakis-homobenzenoid skeleton from a standpoint of the molecular design for preparing a new carbon skeleton.[3]

Now we wish to report similar carbene addition reactions to azepine and homoazepine for synthesis of σ-tris-homoazepine skeleton.

The reaction of N-ethoxycarbonyl-1(1H)-azepine (1) with a tenfold molar excess of dichlorocarbene (DCC) prepared at room temperature from chloroform in the presence of 50% aqueous sodium hydroxide-benzene with triethylbenzylammonium chloride as a catalyst afforded a 1:3 adduct (2), mp 178-180°, $C_{12}H_{11}O_2NCl_6$, λ_{max}^{EtOH} end absorption,

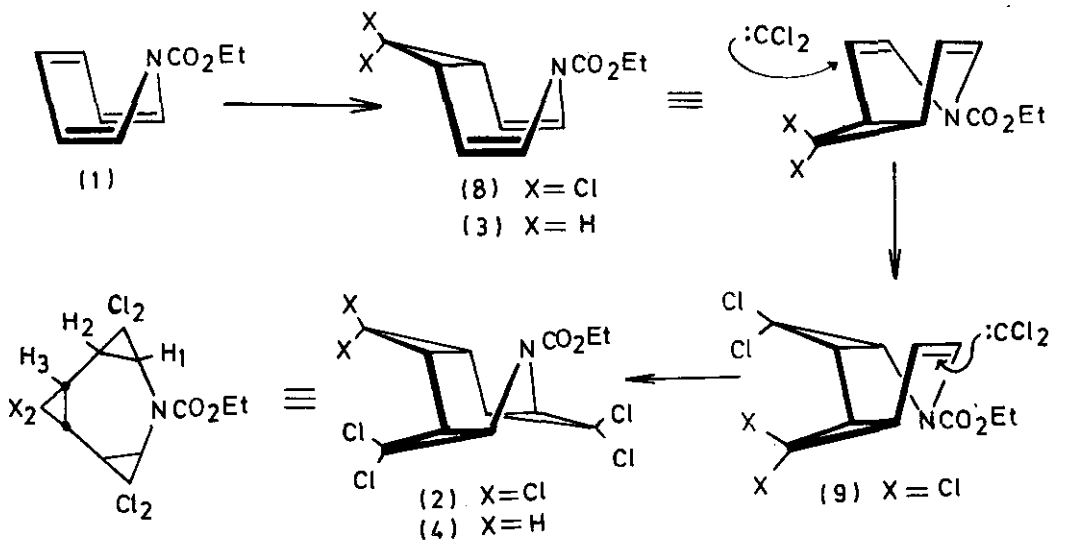
as colorless needles in 35% yield. The nmr spectrum of 2 in $CDCl_3$ showed a symmetrical pattern at δ 4.25(q, J= 7.2 Hz, $OC\underline{H}_2CH_3$), 3.10 (d, J= 9.0 Hz, H_1), 2.08 (s, H_3), 2.05 (d, J= 9.0 Hz, H_2) and 1.38 (t, J= 7.2 Hz, $OCH_2C\underline{H}_3$). Since the dihedral angle between H_2 and H_3 is estimated to be approximately 100° from molecular models of 2, the all-trans configuration to 2 could be determined from the magnitude of $J_{2,3}$. Similar treatment of N-ethoxycarbonyl-1(1H)-4,5-homoazepine (3) gave a 1:2 adduct, mp 112-114°, $C_{12}H_{13}O_2NCl_4$, as colorless needles in 65% yield. The nature of the adduct (4) was also confirmed by the nmr spectrum to be all-trans isomer ($J_{1,2}$= 9.0 Hz, $J_{2,3}$ = 0 Hz). By contrast, similar DCC addition to 2,3-homoazepine (5) gave a mixture of 6 (mp 92- 93°, $C_{12}H_{13}O_2NCl_4$) and 7 (mp 128-129°, $C_{12}H_{13}O_2NCl_4$) in 52 and 5% yields. The analyses of 6 and 7 indicated both to be σ-trishomoazepine derivatives. The nmr spectrum of a major product (6) in $CDCl_3$ showed signals at δ 3.12 (d, $J_{1,2}$= 9.0 Hz, H_1), 2.55 (sextet, J= 6.8 and 4.5 Hz, H_6), 2.07 (d, $J_{1,2}$= 9.0 Hz, H_2) and 1.94 (s, H_3 and H_4). The appearance of a signal at δ 1.94 as a singlet ($J_{2,3}$= 0 Hz) suggested that 6 was also all-trans-σ-trishomoazepine derivative. Only from the nmr spectrum of the minor product (7), however, it is difficult to determine the configuration of the cyclopropane ring, because of the complex signals centered at δ 2.05 (H_2, H_3 and H_4).

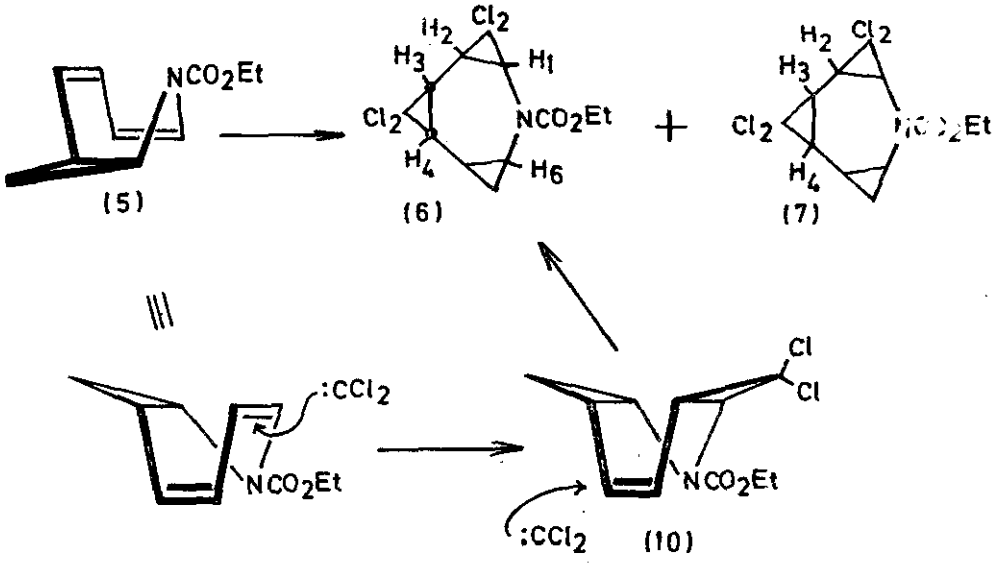
In the addition reaction of N-ethoxycarbonyl-1(1H)-azepine (1), whether the initial DCC addition occurs at the 2,3- or at the 4,5-double bond, the same all-trans-σ-trishomoazepine derivative (2) should be afforded, because the reaction of N-ethoxycarbonyl-1(1H)-2,3- and

4,5-homoazepines with DCC gave all-trans-σ-trishomoazepine derivatives (4) and (6) respectively. While, reactions of N-ethoxycarbonyl-1(1H)-azepine (1) and N-ethoxycarbonyl-1(1H)-2,3-homoazepine (5) with equimolar phenyl(trichloromethyl)mercury gave a mixture of 4,5-homo- (8) and 2,3-4,5-bishomoazepine derivatives (9), and 2,3-6,7-bishomoazepine derivative (10) respectively.

From these results, reaction pathway in the reaction of N-ethoxycarbonyl-1(1H)-azepine with DCC involved electrophilic attack of the reagent at the 4,5-double bond of 1 followed by the generation of the 4,5-homoazepine (8), the second at the 2,3-double bond, and then the third at the 2',3'-double bond of a more favorable conformer of 8 from the less hindered site affording uniquely an all-trans-σ-trishomoazepine (2). Therefore, the addition of DCC to 1 is also stereospecific and regiospecific fashions.

As a conclusion, the generation of DCC by this catalytic method (phase transfer) compared with other methods[4] is quite useful for syntheses of σ-trishomoazepine skeletons.





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