Pergamon

Tetrahedron, Vol. 53, No. 29, pp. 9913-9920, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00336-0

The Non-Reaction of Methylene with the Carbon-Carbon Bond

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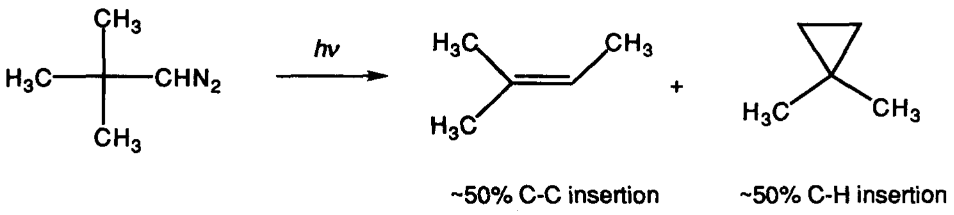
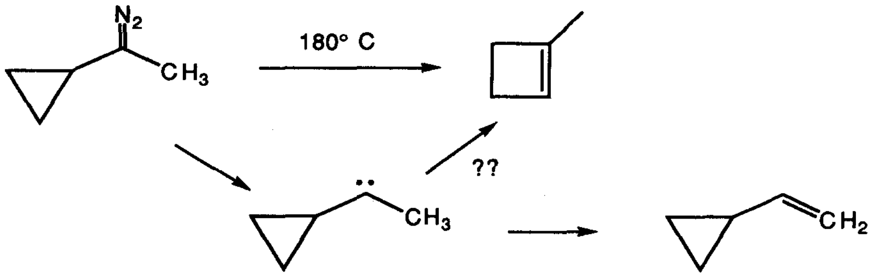
Abstract: Methylene has been shown not to react with the carbon-carbon bonds of spiropentane and spiro[3.3]heptane. © 1997 Elsevier Science Ltd.

The history of the insertion of methylene into the carbon-hydrogen bond goes back to the work of Meerwein, Rathjen, and Werner, who, in 1942, found that a solution of diazomethane in diethyl ether was decolorized by Bavarian sunshine to give small amounts of ethyl propyl ether and ethyl isopropyl ether.[1] Labeling experiments established that the reaction was the result of carbon-hydrogen, not carbon-oxygen insertion.[2,3] Nor was an oxygen atom even necessary; methylene was later found to insert into the available carbon-hydrogen bonds of hydrocarbons in statistical fashion.[4,5] Indeed it was these experiments that led to the famous description of methylene as "the most indiscriminate reagent known in organic chemistry."[4]

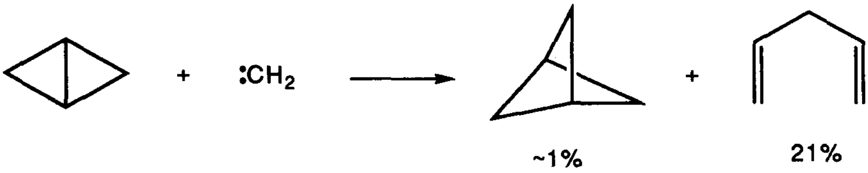
This same work[4] reported that cyclopentane gave no detectable amounts of cyclohexane (< 0.1%), and concluded that "within much increased limits...methylene does not react with the carbon-carbon bond." One may surely be pardoned for wondering why not, especially as a naive bond strength analysis would argue in the other direction. Moreover, this kind of observation has always served as a challenge in organic chemistry, and one is provoked to seek out systems in which carbon-carbon insertion might be found. Indeed, over the last forty years a few examples of carbon-carbon insertion have appeared. For instance, it might seem that intramolecular versions of the carbon-carbon insertion reaction are quite common. Irradiation of *tert*-butyl diazomethane or *tert*-butyl diazirine leads to about 50% of 2-methyl-2-butene, for example.[6]



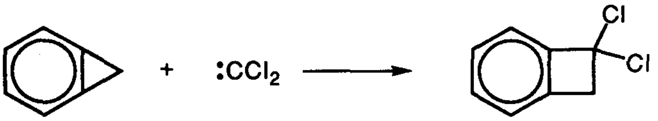
However, it quickly became clear that something was awry, because, as noted by Frey and his collaborators very early on,[7] and explicitly recognized by Shechter,[6] the thermal decompositions of these precursors gave the same two products in a very different ratio (~10:90). It is now clear that the products of "carbon-carbon insertion" formed through intramolecular reactions in simple photolyses of diazo compounds owe their existence mainly to reactions of photo-excited diazo compounds.[6-10] Still, in the case shown above, about 10% of the product apparently comes from a genuine carbon-carbon insertion. Other intramolecular insertions have undergone a similar transformation, and are no longer thought to be carbene reactions. For example, the typical reaction of cyclopropylcarbenes has long been thought to be ring expansion - a carbon-carbon insertion - to give cyclobutenes.[11] It is now known that much - perhaps all - of the cyclobutenes are also the result of ring expansions in precursor molecules, not carbenes.[12,13] Still other intramolecular carbon-carbon insertions, such as the ring contraction of cyclobutylidenes to methylenecyclopropanes, and the ring opening of cyclopropylidenes to allenes, await reinvestigation.



In special cases, even intermolecular carbon-carbon insertions can be found. Bicyclo[1.1.0]butanes commonly undergo the reaction. In fact, there are two different kinds of carbon-carbon insertion in such molecules. The first involves the rare formations of bicyclo[1.1.1]pentanes through insertion into the zero bridge. The parent compound gives at most about 1% bicyclopentane on reaction with methylene,[14,15] but some substituted bicyclobutanes yield substantial amounts of dichlorobicyclopentanes on reaction with dichlorocarbene.[16] In most bicyclobutanes, however, the major product comes from a double carbon-carbon insertion to give 1,4-pentadienes. There is now strong evidence that the 1,4-pentadienes are formed in a concerted process in which the central bond and a side bond are cleaved simultaneously.[17]

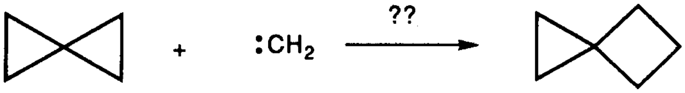


Another special case involves benzocyclopropenes. In at least two cases, these are known to undergo ring expansion, a formal carbon-carbon insertion, to give benzocyclobutenes.[18,19] The mechanism of this process is by no means clear, and it may well not involve carbene chemistry.

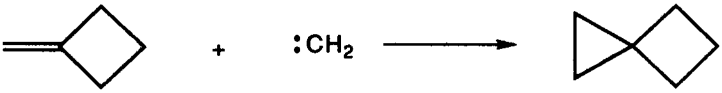


Theory agrees that carbon-carbon insertion should be difficult. For example, insertion of methylene into the carbon-carbon bond of ethane is calculated [MP4/6-31G(d)//6-31G(d)] to require the overcoming of an activation barrier of 46 kcal/mol.[20,21] Strikingly, this paper goes on to calculate that the barrier drops precipitously as strain appears. Thus, the transformation of cyclopropane into cyclobutane is estimated to require a mere 2.3 kcal/mol.[20] The reaction of methylene with cyclopropane had been investigated, of course, and no cyclobutane found.[22] Naturally, this remarkable prediction[20] led to a rapid reinvestigation. Once again, no cyclobutane was found, and an upper limit of 40,000:1 was reported for the methylcyclopropane/cyclobutane ratio.[22] Although this result effectively shows that ring expansion in cyclopropane does not occur, we thought it appropriate to report our earlier work on related systems, as well as some new experiments on the subject.

We have examined the reaction of methylene with spiropentane, in which the strain energy has been increased and in which every carbon-carbon insertion would lead to the same product, spirohexane.

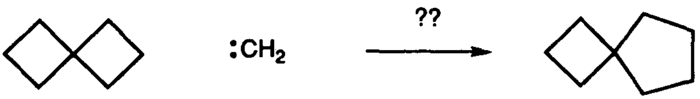


Spiropentane was produced by Applequist's modification of Murray and Stevenson's treatment of pentaerythrityl tetrabromide with zinc dust.[23,24] Unfortunately, even Applequist's improvements do not suffice to remove the last traces of methylenecyclobutane from the product mixture. Of course methylenecyclobutane is lethal to our proposed experiment as it will inevitably lead to spirohexane through addition to the double bond.

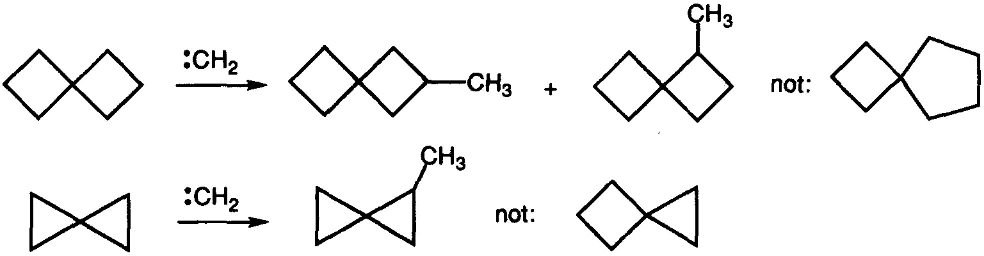


We used preparative gas chromatography to produce spiropentane in which less than 0.1% methylenecyclobutane could have been easily detected. Authentic spirohexane was synthesized through the cyclopropanation of methylenecyclobutane as shown above, and shown to be identical to authentic material.[25] Irradiation of diazomethane in spiropentane leads to methylspiropentane and several other very small peaks, one of which matches spirohexane in retention time. This peak corresponds to 0.1% of the remaining spiropentane and 0.4% of the methylspiropentane product. However, a capillary ^{1}H NMR spectrum of the collected peak shows no signal at δ 2.1 ppm. Thus, it cannot contain substantial amounts of spirohexane, which does show such an absorption. There is essentially no spirohexane produced in the reaction, and therefore, increasing the strain energy further does not open an avenue for carbon-carbon insertion.

Despite the calculations, it might be reasonably argued that the relief in strain in expanding a cyclopropane ring to a cyclobutane is minimal. Given the non-reaction with both cyclopropane and spiropentane, perhaps a better test would be the ring expansion from a cyclobutane to a cyclopentane, in which strain relief should be substantial.



Once again, Becerra and Frey have studied the prototype reaction with cyclobutane and found no carbon-carbon insertion by methylene.[22] We have examined the reaction of spiro-[3.3]heptane, seeking ring expansion to spiro[3.4]octane. Diazomethane generated from *N*-nitroso-*N*-methyl urea was bubbled into spiro[3.3]heptane with a stream of argon and irradiated with a Sylvania 300 w projection bulb. Analysis by GC/MS and analytical GC revealed two major products in exactly the 2:1 ratio expected for the unselective insertion of methylene into the two kinds of available carbon-hydrogen bonds to give a pair of methylated spiro[3.3]heptanes.[4,5] In addition, there was a forest of minor products appearing at longer retention times. Most of these appeared to be the result of two insertion reactions, as they showed a base peak in their mass spectra of 109 (124 - 15). In order to be certain, we synthesized authentic spiro[3.4]octane. Although its retention time placed spiro[3.4]octane among the many C_9 products of diaddition, we were most fortunate to find conditions under which it fell squarely in the only empty region of the chromatogram. We see no trace of this compound in the reaction mixture, and a one-percent yield would have been easily detected. There is no discernable ring expansion.



Experimental Section:

Spiropentane.[23,24] In a three-necked flask equipped with a mechanical stirrer, water condenser, and solids addition device was placed 37 g sodium hydroxide in 64 mL water, 184 g 95% ethanol, 2.6 g sodium iodide, and 107 g disodium dihydrogen ethylenetetraacetate. The condenser led to two traps cooled by Dry-Ice acetone. The mixture was heated to reflux. With nitrogen bubbling through the system, 26.7 g zinc dust was added, followed by 40 g pentaerythrityl tetrabromide added in portions. After the addition was complete, the mixture was allowed to stir at reflux for 1 h. The crude hydrocarbon product (5.5 g) was collected from the traps and analyzed by GC on a 15' x 1/4" column packed with 15% Dow-Corning 550 silicone oil on crushed firebrick (Column A). Analysis revealed only 0.2% methylenecyclobutane, which was removed by preparative GC on column A and a 5' x 1/4" column packed with 1% silver nitrate on crushed firebrick. Reanalysis on column A showed no detectable methylenecyclohexane.

Spirohexane. (a) A mixture of 1 g methylenecyclobutane, 1.96 g methylene iodide, 0.75 g zinc-copper couple, and 5 mL anhydrous ether was refluxed for 9 h. The ether was removed by careful distillation and spirohexane collected by preparative GC on column A. (b) Diazomethane liberated from 20 g *N*-methyl-*N*-nitrosourea was blown by a stream of nitrogen into a mixture of 80% methylenecyclobutane and 20% spiropentane in a water-cooled flask attached to a Dry-Ice/acetone-cooled condenser. Continuous irradiation was provided by one General Electric Sunlamp for 9 h. The ether was removed by distillation and spirohexane collected by preparative GC on column A.[25] For further details see the procedure for the irradiation of diazomethane in spiro[3.3]heptane.

Irradiation of Diazomethane in Spiropentane. Diazomethane liberated from 30 g *N*-methyl-*N*-nitrosourea was blown by a gentle stream of nitrogen into 2 mL of pure spiropentane in a water-cooled flask. Continuous irradiation was provided by one General Electric Sunlamp for 9 h. The products were analyzed by GC on column A. The single major product was assumed to be methylspiropentane (NMR), and it was certain that no sign of spirohexane could be found. For further details see the procedure for the irradiation of diazomethane in spiro[3.3]heptane.

Spiro[3.3]heptane. This material was prepared from *tert*-butyl spiro[3.3]heptane-3-peroxycarboxylate through the method of Roberts, Walton, and Maillard.[26]

Spiro[3.4]octane. A mixture of 0.2 g spiro[3.4]octan-5-one,[27] 3 mL ethylene glycol, 0.2 mL 90% hydrazine hydrate and 0.3 g powdered KOH was placed in a 10 mL round-bottomed flask fitted with a reflux condenser. The mixture was warmed slowly until the KOH dissolved and then heated under reflux for 2 h. The mixture was cooled to room temperature and the reflux condenser removed. After the addition of 10 mL water, the solution was steam distilled. The condensate was collected until the temperature of the mixture rose to 175 °C, and was washed with 2 x 5 mL ether. The ether layers were combined, dried over Na_2SO_4, and the ether removed at the water pump to leave residual spiro[3.4]octane.[28]

Irradiation of Diazomethane in Spiro[3.3]heptane. This procedure was modelled on that of Doering and Roth for the catalytic decomposition of diazomethane.[29] In the right-hand side of an efficient fume hood, 0.5 mL spiro[3.3]heptane was placed in a 5 mL pear-shaped flask cooled with a stream of water, and fitted with a Y adapter and a water condenser. A carefully fire-polished Pyrex tube led beneath the surface of the spiroalkane. The entry tube was shielded with aluminum foil and attached through similarly shielded Tygon tubing to the diazomethane generator in the left-hand side of the hood. The light source was aimed directly at the flask and pointed away from the diazomethane generator. The generator consisted of a 100 mL two-necked flask (no ground glass joints) equipped with a magnetic stirring bar and attached through aluminum foil-wrapped Pyrex and Tygon tubing to the flask containing the spiroalkane. A carefully fire-polished Pyrex tube led to the bottom of the generator flask. In the generator was placed 20 mL of a 50% KOH solution and 10 mL decalin. The flask was cooled to 0 °C with an ice-water bath. Both the generator and irradiation flask were placed behind explosion shields, and the hood doors kept closed as much as possible. All manipulations behind the shields were carried out by hands well protected by thick gloves. As argon was slowly bubbled through the system, ca. 0.1 g portions of *N*-nitroso-*N*-methyl urea (NMU) were added to the generator flask with a spatula. When a slight yellow color developed in the spiro[3.3]heptane, the lamp was lighted, and kept on throughout the addition. A total of ca. 8 g of NMU was added over 3 h. After the addition was complete, the contents of the irradiation flask were analyzed directly by GC and GC/MS. The two major products were isolated by preparative GC on a 2 m x 1/4" 10% OV-101 on 80/100 Supelport column operated at 50 °C, and the mixture analyzed by GC on a 30 m x 0.25 mm HP-1701 column (14% cyanopropylphenyl - 86% dimethylsiloxane copolymer) operated at 50 °C.

1-Methylspiro[3.3]heptane. ^{1}H NMR (CDCl$_3$) δ (ppm) 0.97 (d, 3H), 1.30 (m, 1H), 1.66 (m, 2H), 1.83 (m, 6H), 2.06 (m, 2H).

2-Methylspiro[3.3]heptane. ^{1}H NMR (CDCl$_3$) δ (ppm) 1.01 (d, 3H), 1.51 (m, 2H), 1.85 (m, 4H), 1.97 (m, 1H), 2.11 (m, 4H).

CAUTION! In a variant of this procedure in which the water condenser had been replaced by a Dry-Ice-acetone condenser in an attempt to reduce spiroalkane loss, diazomethane apparently was collected on the surface of the condenser. A fierce explosion occurred on warm up.

Acknowledgement: Work at Princeton was supported by the National Science Foundation through grant CHE-9322579.

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(*Received* 21 *November* 1996; *accepted* 11 *March* 1997)