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# Partial Asymmetric Synthesis in the Simmons-Smith Reaction. III. A Modification of the Reaction[1]

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A modification of the Simmons-Smith reaction, which involves a prior reaction of ethyl iodide with zinc copper couple followed by addition of methylene iodide and olefins, was proposed. The improved yields of cyclopropane products were obtained with various olefin substrates. It is likely that the operating species in the present modification is ethyliodomethylzinc.

Simmons and Simth[2,3] have developed a stereospecific synthesis of cyclopropanes which involves the treatment of olefins with methylene iodide and zinc copper couple. The active organozinc intermediate was generated also by Wittig[4] through the addition of diazomethane solution to zinc iodide in ether. The operating species in this reaction has been looked upon as being iodomethylzinc iodide[2,4,5] (III) or its dimer, bis-iodomethylzinc (II), although unequivocal evidence for this has not yet been presented.

Recently, Furukawa and his coworkers[6] have modified this reaction by replacing zinc copper couple with commercial diethylzinc and claimed remarkable improvement in the yield of cyclopropane compounds from olefins. This modification was featured in particular by its excellent performance even with cation-sensitive olefins such as vinyl ethers, in which with the conventional reagent, the competitive polymerization of olefins caused by the Lewis acid catalysis of zinc iodide in the medium outweighed the formation of desired cyclopropanes.

The following two organomagnesium compounds are relevant to this problem: methylene dimagnesium diiodide[7] which was prepared by the treatment

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[1] Previous papers of this series: a) S. Sawada and Y. Inouye, *J. Org. Chem.*, **33**, 1767 (1968); b) S. Sawada and Y. Inouye, *ibid.*, **33**, 2141 (1968).

[2] H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959); E. P. Blanchard and H. E. Simmons, *ibid.*, **86**, 1337 (1964); H. E. Simmons, E. P. Blanchard and R. D. Smith, *ibid.*, **86**, 1347 (1964).

[3] See also H. Hoberg, *Ann.*, **656**, 1 (1962), *ibid.*, **695**, 1 (1965); E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

[4] G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961); G. Wittig and F. Wingler, *Ber.*, **97**, 2139 (1964).

[5] B. Rickborn and J. H. H. Chan, *J. Org. Chem.*, **32**, 3576 (1967).

[6] J. Furukawa, N. Kawabata and J. Nishimura, *Tetrahedron Letters*, **1966**, 3353; *ibid.*, **1968**, 3495; *Tetrahedron*, **24**, 53 (1968).

[7] D. A. Fidler, J. R. Jones, S. L. Clark and H. Stange, *J. Am. Chem. Soc.*, **77**, 6634 (1955); C. Fauveaur, Y. Gault and F. G. Gault, *Tetrahedron Letters*, **1967**, 3149.

of magnesium with methylene iodide, and α-halomethyl Grignard reagent[8] obtained by substitution of isopropylmagnesium chloride with methylene dihalide at dry-ice temperature. Although both organomagnesium compounds were inactive for methylene-transfer to olefins under the corresponding conditions, iodomethylmagnesium iodide reacted at −70°C with cyclohexene to give norcarane in the presence of equimolar zinc iodide or cadmium iodide (8 or 5% yield respectively).

Wittig[9] described recently that bis-benzoxymethylzinc, which was obtained by the exchange of iodomethyl ligands in the dimeric form of the Simmons-Smith reagent with benzoxymethyl groups having a similar nucleophilicity, successfully transferred methylene to cyclohexene to give norcarane in good yields, and this was achieved only in the presence of zinc iodide.

In connection with the above-mentioned reactions and also with our asymmetric syntheses[1] in this type of reaction, we wish to report a further modification of the Simmons-Smith reaction. The present procedure consists of the reaction of ethyl iodide with zinc copper couple which gives ethylzinc iodide probably in an equilibrium with diethylzinc plus zinc iodide,[10] and subsequent introduction of methylene iodide and olefin substrates. A mild reaction took place upon the addition of methylene iodide and olefin under stirring at room temperature and after a period of 0.5—5.0 hr, the reaction mixture was treated in the usual way[1-3] to give the corresponding cyclopropane products. In Tables 1 and 2 are summarized the yields of cyclopropane products obtained by the present procedure in comparison with those by the Simmons-Smith reagent and by the Furukawa modification.[6] The present modification offers the advantage of enabling one to eliminate explosion hazards which are so frequently encountered on handling diethylzinc and even to ensure much improved yields of cyclopropanes.

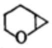
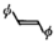
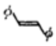
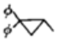
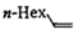
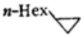
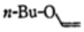
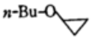
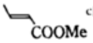
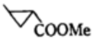
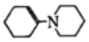
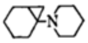
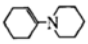
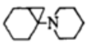
An equilibrium as schemed below is conceivable for the present system and the operating species responsible for methylene-transfer may be either ethyliodomethylzinc (I), bis-iodomethylzinc (II) or iodomethylzinc iodide (III).

$$\mathrm{EtZnI} \rightleftarrows \mathrm{Et_2Zn}+\mathrm{ZnI_2} \xrightarrow{\mathrm{CH_2I_2}} \underset{\text{(I)}}{\mathrm{EtZnCH_2I}}+\mathrm{ZnI_2}+\mathrm{EtI}$$

$$\underset{\text{(I)}}{2\,\mathrm{EtZnCH_2I}} \rightleftarrows \mathrm{Et_2Zn}+\underset{\text{(II)}}{\mathrm{Zn(CH_2I)_2}} \rightleftarrows \mathrm{Et_2Zn}+\underset{\text{(III)}}{2\,\mathrm{ICH_2ZnI}}$$

Both the reactivity and reaction yield in the present modification surpassed those in the conventional Simmons-Smith reaction, and compared well with those in the Furukawa modification except that the

TABLE 1. YIELDS OF CYCLOPROPANES BY THE PRESENT PROCEDURE IN COMPARISON WITH THOSE BY THE SIMMONS-SMITH REACTION AND THE FURUKAWA MODIFICATION

| Run | Olefin[a] | Cyclopropane product | Reaction period (hr) | % Yield by Present work | Simmons-Smith | Furukawa[i] |
|---|---|---|---|---|---|---|
| 1 |  |  | 2 | 92 | 61[e] | 79 |
| 2 |  |  | 1 | 80 | 65[f] | |
| 3 |  |  | 3 | 78 | 32[f] | 76 |
| 4 |  |  | 3 | 68 | 54[f] | |
| 5 |  |  | 3 | 13 | | |
| 6 |  [b] |  | 3 | 48 | 18[g] | |
| 7 |  |  | 3 | 45 | 17[g] | |
| 8 |  |  | 3 | 77 | 70[f] | 60 |
| 9 |  |  | 1 | 15 | | 92 |
| 10 |  [c] |  | 3 | 24 | 9[f] | |
| 11 |  |  | 1 | 15 | (8)[h] | |
| 12 |  [d] |  | 1 | 28 | | |

a) mol ratio of olefin : $CH_2I_2$ : EtZnI=1 : 1 : 2 in all runs except 6,10 and 12.
b) mol rtatio=1 : 3 : 6.
c) mol ratio=1 : 2 : 2.
d) solvent composition: ether : tetrahydrofuran=1 : 1
e) Ref. 3 f) Ref. 2 g) Ref. 1
h) yield of the pyrrolidine analog. Ref. 11
i) by glpc-analysis. Ref. 6

TABLE 2. YIELDS OF 1-METHYL-2-HYDROXYMETHYLCYCLOPROPANE[a] BY THE REACTION OF CROTYL ALCOHOL AND SODIUM CROTYLATE WITH THE PRESENT AND THE SIMMONS-SMITH REAGENTS

| Run | Olefin | Mol equivalent of Simmons-Smith reagent | Present modif. (as $EtZnCH_2I$) | Reaction period (hr) | % Yield |
|---|---|---|---|---|---|
| 13 | crotyl alc. | 1 | | 5 | 8 |
| 14 | crotyl alc. | 2.5 | | 5 | 65 |
| 15 | Na crotylate | 1 | | 0.5 | 53 |
| 16 | crotyl alc. | | 1 | 0.5 | 27 |
| 17 | Na crotylate | | 1 | 0.5 | 60 |

a) M. Julia., S. Julia and J. A. Chaffaut, *Bull. Soc. Chim. France*, **1960**, 1735; bp 131°C, $n_D^{20}$ 1.4284.

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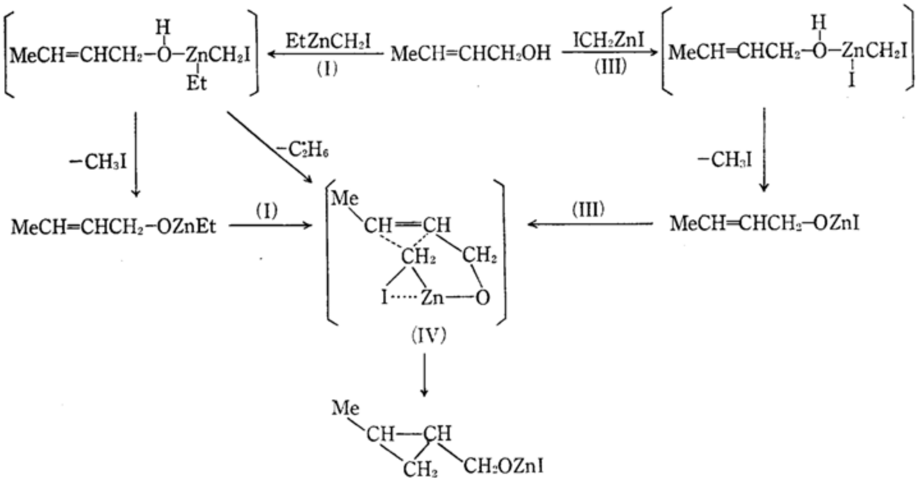
[8] H. Normant and J. Villieras, *Compt. rend.*, **260**, 4535 (1965); J. Villieras, *ibid.*, **260**, 4137 (1965).

[9] G. Wittig and M. Jautelat, *Ann.*, **702**, 24 (1966).

[10] M. H. Abraham and P. H. Polfe, *Chem. Commun.*, **1965**, 325; J. Boersma and J. G. Noltes, *Tetrahedron Letters*, **1966**, 1252.



present modification was accompanied by the undesirable olefin polymerization as was also the case with the conventional procedure (runs 2, 9, 11 and 12). Accordingly, active intermediate may reasonably be looked upon as being ethyliodomethylzinc (I), and thus the reaction mechanism may be essentially the same as that in the Furukawa modification.

The behavior of the present organozinc reagent toward olefinic alcohols is worthy of note. When crotyl alcohol was allowed to react with equimolar iodomethylzinc iodide (III), 1-methyl-2-hydroxymethylcyclopropane was just sparingly produced (8%, run 13), whereas with the use of an excess of the reagent (2.5 mol equivalent, run 14) a much higher yield (65%) of the cyclopropane alcohol was obtained. A similar trend was observed in run 15 where sodium crotylate was employed instead of the free alcohol. This observation suggests that crotyl alcohol coordinates primarily with zinc atom in the reagent to form a zincate complex which in turn dissociates predominantly with elimination of methyl iodide so far as alcoholic hydrogen is available. It seems likely that crotoxyzinc iodide thus formed (or sodium crotylate in run 15) undergoes spontaneous substitution with surplus methylene-transfer reagent to form another zincate (IV), iodomethylzinc crotylate, which decomposes eventually to afford cyclopropane product. Runs 16 and 17 stand for this mechanism proposed.

The treatment of enamine (run 11) with the present organozinc reagent in ether-tetrahydrofuran (1 : 1) resulted in the formation of 1-piperidinobicyclo[4,1,0]heptane without any separation of gelatinous precipitate.[11] (−)-Menthyl crotonate and cinnamate failed to afford the corresponding cyclopropane acids when subjected to the present reaction procedure under the standard conditions.

## Experimental

The cyclopropane product in each run was identified by glpc, IR- and NMR-spectral comparisons with the respective authentic specimen. The yields were estimated by glpc-analysis except in runs 2, 9, 11, 12 and 14 where the products were actually isolated.

**Stock Solution of Ethylzinc Iodide.** Ethyl iodide (156 g, 1 mol) was allowed to react with zinc copper couple (70 g, 1 atom) in absolute ether (900 m*l*), and the mixture was stirred at room temperature overnight. The supernatant liquid was withdrawn free from sludge and stored in a stoppered flask carrying a drying tube. After storage at room temperature for a week, no precipitate was formed and the activity of the solution remained unchanged.

The cyclopropane synthesis in the present modification is exemplified by the typical run with cyclohexene to give norcarane (run 1) and essentially the same procedure except in runs 11 and 12, was followed for other runs in the mol ratio of olefin: $EtZnCH_2I=1:1$.

**Synthesis of Norcarane (Run 1).** Methylene iodide (15 g, 0.055 mol) was added to an aliquot of the stock solution (100 m*l*) containing 2 mol equivalent of active ethylzinc iodide and the reaction mixture was stirred at 30—35°C for 1 hr. To the chilled solution, cyclohexene (4.1 g, 0.05 mol) was added and the mixture was gently refluxed under stirring and after 2 hr, *ca.* 50 m*l* of ether was distilled off. The resulting pale yellow mixture was decomposed with water and dil. HCl, and the organic layer was separated, washed with water, sodium thiosulfate solution and again with water, and dried over anhydrous $MgSO_4$. The solution which contained norcarane in a 92% yield as determined by glpc-analysis was ozonized to remove unreacted cyclohexene and washed with NaOH solution. After drying over anhydrous $MgSO_4$, the solution was distilled to give norcarane boiling at 115—117°C, $n_D^{25}$ 1.4540. The IR- and NMR-spectra were identical with those of the authentic specimen. Yield 2.8 g. Additional amount of norcarane (1 g) was recovered by the rectification of the forerun (bp 70—115°C), totalizing the yield as 3.8 g (88%).

**Synthesis of 1-(1-Piperidino)bicyclo[4.1.0]hep-**

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[11] E. P. Blanchard, H. E. Simmons and J. S. Taylor, *J. Org. Chem.*, **30**, 4321 (1965).

**tane (Run 12).** Methylene iodide (6 g, 0.02 mol) was allowed to react with ethylzinc iodide (40 m*l* of the stock solution, 0.04 mol) and 40 m*l* of absolute tetrahydrofuran was added to the solution. After 1 hr's stirring, 1-(1-piperidino)cyclohexene (bp 120°C/17 mmHg, $n_D^{20}$ 1.5120[11]; 3 g, 0.018 mol) in 10 m*l* of THF was introduced at 30—40°C and the mixture was refluxed for an additional hr. The reaction mixture was hydrolyzed with dil. HCl and then was made alkaline with sodium carbonate. The organic layer, which exhibited a single peak of the product on glpc-analysis and indicated the absence of the parent enamine, was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was distilled to give 1-(1-piperidino)bicyclo-[4.1.0]heptane, bp 115°C/17 mmHg, $n_D^{25}$ 1.4889. Found: C, 80.10; H, 11.93; N, 7.66%: Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81%. Yield 0.9 g (28%).

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12) Z. Eckstein and A. Sacka, *Chem. Abstr.*, **54**, 22637e (1961).