Communications

Cyclobutene Derivatives as Isoprene Equivalents in Terpene Synthesis. The Metathesis of 1-Methylcyclobutene

Summary: The metathesis of 1-methylcyclobutene leads to head-to-tail isoprenoid homologation and can convert the monoterpene geraniol acetate into the sesquiterpene farnesol acetate.

Sir: As part of a general program of natural products synthesis, a portion of our efforts are directed toward uncovering *fundamentally new approaches* to terpene synthesis. This is a difficult task, since terpene chemistry is a mature science and the head-to-tail linking of isoprene units has long been an objective of organic synthesis.[1,2] A new and potentially quite general approach to terpenoid synthesis involves the use of 1-methylcyclobutene (1) as an isoprene synthon. This molecule contains the five carbons required for an isoprene unit as well as ~26-kcal/mol strain energy[4] to drive reactions to completion.[5] We have recently described[3] the synthesis of terpenoid 1,3-dienes using cyclobutenes as reactive isoprene synthons. Since 1,5-dienes are more common (geraniol, farnesol, squalene, etc.), we now disclose a method for "insertion" of an isoprene unit into an unactivated double bond, resulting in the head-to-tail linking of isoprene units.

The olefin metathesis reaction[6] has been the object of a flurry of recent activity, with only limited application to natural products synthesis.[7] Since Dall'Asta had reported the metathetical polymerization of cyclobutenes to 1,5-dienes[8a] (eq 1), *we felt that this unique reaction might have application* to terpene chemistry.

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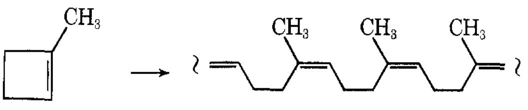

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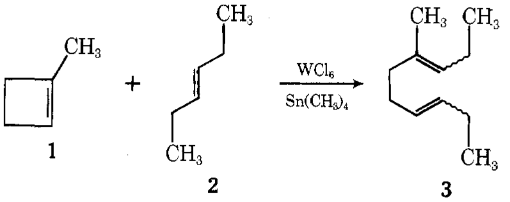
(2)

1-Methylcyclobutene (1) reacts exothermically[9] with the metathesis catalyst $WCl_6/Sn(CH_3)_4$[10] giving a polymer (eq 2) whose gross structure is that of polyisoprene (natural rubber).[8b] After this work was completed, a detailed examination of the metathetical polymerization of 1-methylcyclobutene was published.[11] The polymer produced is 84–87% *Z* and more importantly 10.1/1 head-to-tail, the regioisomerism crucial for the production of terpenoid products. Based on the currently accepted mechanism,[6a] the selectivity is a consequence of factors which favor a more highly substituted metallocarbene.[12]

At the outset a model system was investigated which avoids regioisomer problems. The crossed metathesis of 1-methylcyclobutene (1) with excess 3-hexene (2) in chlorobenzene gives compound 3 in 20–30% yields[13,14] (eq 3). Compound 3 (a mixture of *E*/*Z* isomers) was prepared by an independent route shown in eq 4. Wittig reaction of methyl levulinate gives the unsaturated ester 5 which was converted to 3 via the aldehyde. The materials were identical from the two pathways.[15]



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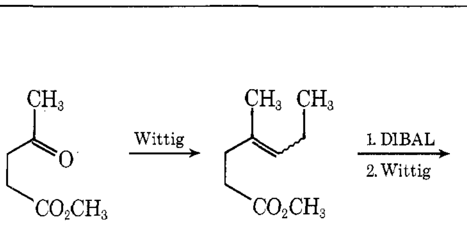

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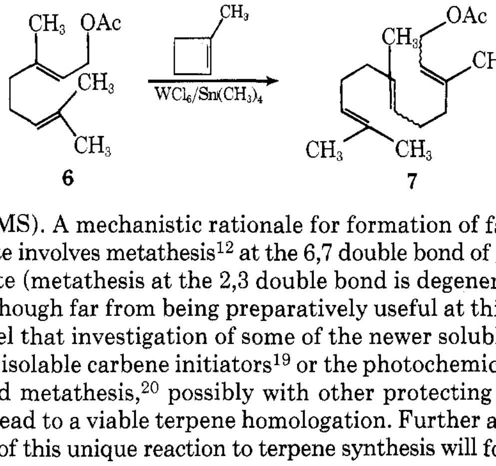
(4)

The interconversion of terpenes was then attempted. There are few reports in the literature concerning the metathesis of trisubstituted olefins.[16] Presumably because of steric hindrance they react much slower. In addition, there seems to be no systematic study of the effect of functional groups on the metathesis reaction.[17] Since alcohols quench the metathesis catalyst the corresponding acetates were used, and appear to be compatible.[18] When geraniol acetate (6) and excess 1 were reacted [$WCl_6/Sn(CH_3)_4$ in chlorobenzene] for prolonged periods and the polymer was precipitated with methanol, 1–2% farnesol acetate (7) (*E*/*Z* isomers) could be detected (GC/MS). A mechanistic rationale for formation of farnesol acetate involves metathesis[12] at the 6,7 double bond of geranyl acetate (metathesis at the 2,3 double bond is degenerate.)



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Although far from being preparatively useful at this time, we feel that investigation of some of the newer soluble catalysts, isolable carbene initiators[19] or the photochemically initiated metathesis,[20] possibly with other protecting groups may lead to a viable terpene homologation. Further applications of this unique reaction to terpene synthesis will form the basis of subsequent reports.

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References and Notes

(1) A. F. Thomas, "The Total Synthesis of Natural Products", Vol. 2, J. Apsimon, Ed., Wiley, New York, N.Y., 1973.

(2) See, for example, S. R. Wilson, K. M. Jernberg, and D. T. Mao, *J. Org. Chem.*, **41**, 3209 (1976), and ref 3.

(3) S. R. Wilson and L. R. Phillips, *Tetrahedron Lett.*, 3047 (1975).

(4) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *J. Am. Chem. Soc.*, **90**, 4315 (1968).

(5) For example, thermolysis of **1** gives isoprene itself: H. M. Frey, *Trans. Faraday Soc.*, **58**, 957 (1962).

(6) The olefin metathesis reaction has been the subject of a number of major review articles: (a) N. Calderon, E. A. Ofstead, and W. A. Judy, *Angew Chem., Int. Ed. Engl.*, **15**, 401 (1976); (b) R. Streck, *Chem. Ztg.*, **99**, 397 (1975); (c) L. Hocks, *Bull. Soc. Chim. Fr.*, 1893 (1975); (d) R. J. Haines and G. J. Leigh, *Chem. Soc. Rev.*, **4**, 155 (1975); (e) J. C. Mol and J. A. Moulijn, *Adv. Catal.*, **24**, 131 (1975); (f) W. B. Hughes, *Organomet. Chem. Synth.*, **1**, 341 (1972); (g) N. Calderon, *Acc. Chem. Res.*, **5**, 127 (1972); (h) R. L. Banks, *Top. Curr. Chem.*, **25**, 39 (1972); (i) M. L. Khidekel, A. D. Shebaldova, and I. V. Kalechits, *Russ. Chem. Rev.* (*Engl. Transl.*), **40**, 669 (1971); (j) G. C. Bailey, *Catal. Rev.*, **3**, 37 (1969).

(7) (a) L. G. Wideman, *J. Org. Chem.*, **33**, 4541 (1968); (b) F. W. Kuepper and R. Streck, *Chem. Ztg.*, **99**, 464 (1975); (c) R. Rossi, *Chim. Ind.* (*Milan*), **57**, 242 (1975) [*Chem. Abstr.*, **84** 73557f (1976)].

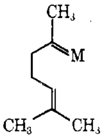
(8) (a) G. Dall'Asta, *J. Polym. Sci., Part A-1*, **6**, 2397 (1968), and references cited therein. (b) Dall'Asta reported the polymerization of 1-methylcyclobutene, but the polymer was largely saturated: G. Dall'Asta and R. Manetti, *Atti Acad. Naz. Lincei Rend. Cl. Sci. Fis. Mat. Nat.*, **41**, 351 (1966) [*Chem. Abstr.*, **67** 33003q (1967).

(9) The metathesis reaction has been capricious in our hands; sometimes the reaction is inexplicably slow.

(10) An astonishing variety of catalyst recipes have been reported.[6] We have chosen the mixture $WCl_6/Sn(CH_3)_4$ because of its reported compatability with esters.[17b]

(11) T. J. Katz, J. McGinnis, and C. Altus, *J. Am. Chem. Soc.*, **98**, 606 (1976).

(12) The reactive (chain carrying) metallocarbene derived from 1-methylcyclobutene is **8**.



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(13) All new compounds possessed spectral and analytical data in accord with the assigned structures.

(14) A cyclobutene/hexene/catalyst ratio of 8/44/1 was used.

(15) Only two isomers could be resolved (mol wt, 152.1558 and 152.1563) by VPC. Materials from the two pathways possessed identical spectral data and retention times on a 200-ft. DB-TCP capillary column. We have not established the configuration about the double bonds.

(16) (a) T. Katz, Abstracts, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 1976, INOR81; (b) C. P. Pinazzi, I. Guilmet, and D. Reyx, *Tetrahedron Lett.*, 989 (1976); (c) R. Rossi, P. Diversi, A. Lucherini, and L. Porri, *ibid.*, 879 (1974); (d) British Patent 1125529 [*Chem. Abstr.*, **69**, 105851f (1968)].

(17) There are scattered reports of the metathesis of functionalized olefins. (a) Nitrile: G. Foster, *Chem. Abstr.*, **75**, 63172b (1971). (b) Ester: P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *Chem. Commun.*, 1221 (1972); P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *J. Am. Oil Chem. Soc.*, **51**, 389 (1974); W. Ast, G. Rheinwald, and R. Kerber, *Makromol. Chem.*, **177**, 39 (1976). (c) Acids: K. Hummel and Y. Imanoglu, *Colloid Polym. Sci.*, **253**, 225 (1975); *Chem. Abstr.*, **83**, 96094w (1975).

(18) Geraniol acetate is relatively stable in the presence of active metathesis catalyst $WCl_6/Sn(CH_3)_4$. Catalyst activity was checked by injecting aliquots of 2-pentene. Within minutes at room temperature 2-butene and 3-hexene are produced.

(19) J. McGinnis, T. J. Katz, and S. Hurwitz, *J. Am. Chem. Soc.*, **98**, 605 (1976).

(20) (a) P. Krausz, F. Garnier, and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 437 (1975); (b) S. Warwel and W. Laarz, *Chem. Ztg.*, **99**, 502 (1975); (c) A. Agapiou and E. McNelis, *Chem. Commun.*, 187 (1975).

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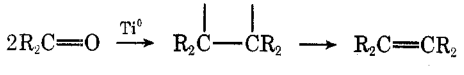
Synthesis of Unsymmetrical Olefins by Titanium(0) Induced Mixed Carbonyl Coupling. Some Comments on the Mechanism of the Pinacol Reaction

Summary: Unsymmetrical olefins can be synthesized in useful yields by titanium induced ketone coupling if one component is used in excess. Mixed coupling is particularly efficient for diaryl ketones, and a mechanism is proposed to account for this.

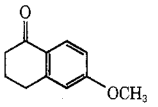
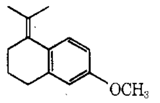
Sir: We recently reported an improved carbonyl coupling procedure employing active titanium(0). Olefins were isolated in high yields.[1] Since the reaction occurs by a two-step pathway involving initial reductive dimerization of the carbonyl to a pinacol, followed by deoxygenation to olefin, one might expect the intermolecular version of this reaction to be limited to the synthesis of symmetrical olefins.



$$2R_2C{=}O \xrightarrow{Ti^0} R_2\overset{O^-}{\overset{|}{C}}{-}\overset{O^-}{\overset{|}{C}}R_2 \longrightarrow R_2C{=}CR_2$$

Pinacol formation is generally presumed to occur by dimerization of anion radicals,[2] and the synthesis of unsymmetrical olefins by our method therefore requires that we be able to carry out mixed pinacol couplings. There is little information in the literature concerning mixed pinacol reactions,[3-6] but the few scattered reports that do exist indicate that one generally obtains a mixture of the three possible pinacols in a nearly statistical ratio. Recently, while this work was in progress, another report appeared describing several mixed pinacol reactions. Again, the mixed products appear to be found in approximately statistical amounts, although complete product analyses were not reported.[7]

Table I. Titanium Induced Mixed Coupling Reactions between Acetone and Other Ketones (Acetone/Ketone, 4:1)

Entry	Ketone	Products	Isolated yield, %[a]
1	Adamantanone	Isopropylideneadamantane	63
		Biadamantylidene	12
2	4-*tert*-Butylcyclohexanone	4-*tert*-Butylisopropylidenecyclohexane	55
		Bi-4-*tert*-butylcyclohexylidene	22
3	3-Cholestanone	3-Isopropylidenecholestane	54
		Bi-3-cholesterylidene	29
4	Cycloheptanone	Isopropylidenecycloheptane	50
		Bicycloheptylidene	26
5	1-Indanone	1-Isopropylideneindan	71
		Bi-1-indanylidene	24
6	Acetophenone	2-Methyl-3-phenyl-2-butene	65
		2,3-Diphenyl-2-butene	16
7	Benzophenone	1,1-Diphenyl-2-methylpropene	94
		Tetraphenylethylene	tr
8	Fluorenone	Isoptropylidenefluorene	84
		Bifluorenylidene	0
9			85
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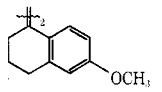
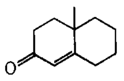
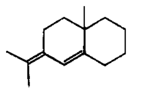
			9
10			67
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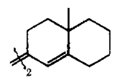
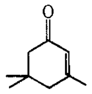
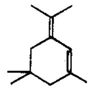
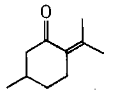
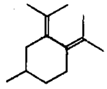
			26
11			63
12			55

[a] The crude product mixtures were purified by column chromatography on silica gel and the products identified by spectral methods (NMR, MS).

We felt, therefore, that our olefin-forming reaction would probably only be synthetically useful in cases where an excess of one inexpensive carbonyl component could be used and where the major olefinic by-product could be easily removed. Acetone is the obvious choice as one component of the reaction since it may be used in excess and its self-coupling product,