Tetrahedron Letters,Vol.29,No.19,pp 2315-2318,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE CARBENE COMPLEX ROUTE TO DONOR-ACCEPTOR-SUBSTITUTED CYCLOPROPANES

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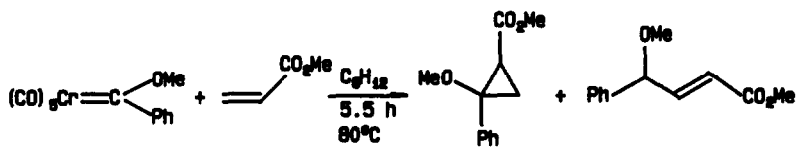
Summary: A variety of donor-acceptor-substituted cyclopropanes can be synthesized starting from electron deficient olefins in preparatively usefull yields employing Fischer carbene complexes as donor-carbene source.

In 1970/72 Fischer and Dötz reported that carbene complex 1 is able to transfer methoxy-(phenyl)carbene to α,β-unsaturated esters giving cyclopropane derivatives.[1] Only few esters have been studied and these were used in large excess in this notable [2+1]-cycloaddition.[2] Since, in the meantime, donor-acceptor-substituted cyclopropanes have gained considerable synthetic importance [3], we explored scope and limitations of the potentially versatile and supplementary entry to this type of activated cyclopropanes. We were also looking for an insight into the mechanism of this carbene-transfer process.[4]

Reaction of equimolar amounts of carbene complex 1 and methyl acrylate in cyclohexane (5.5h, 80°C) affords methyl cyclopropanecarboxylate 2 [5] in good yield (cis:trans = 45:55). As second organic compound we could identify the acyclic "insertion product" 3 (4%, Eq. 1).[6] Approximately 50% of the chromium could be recovered as $Cr(CO)_6$, which is the principal by-product of the reaction. This experiment demonstrates that an olefin excess is not a prerogative for obtaining cyclopropanes in preparatively useful yields. On the contrary, results are less satisfying if 10 equivalents of alkene are used, probably due to the more difficult separation of the product from polymers.

Eq. 1

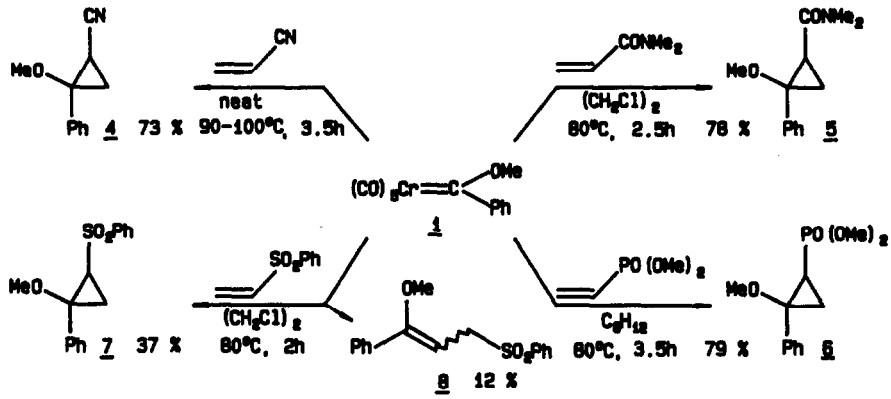


1 2 71 % 3 4 %

(cis : trans = 45 : 55)

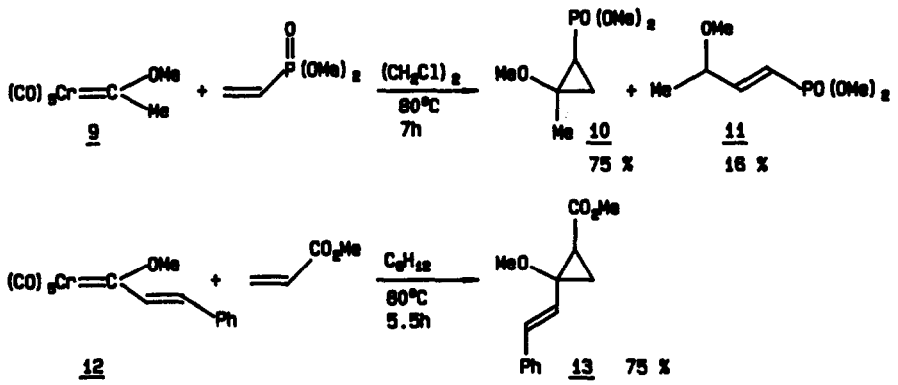
The [2+1]-cycloaddition is not restricted to α,β-unsaturated esters. Acrylonitrile, dimethyl acrylamide, dimethyl vinylphosphonate, and phenyl vinyl sulfone provide cyclopropanes 4 [7], 5, 6, and 7, respectively, in good yield (Scheme I). Sulfone 7 is accompanied by a relatively high amount of the enol ether 8 (E/Z-mixture). In all examples the cis/trans ratio is near to 1:1.

Scheme I:



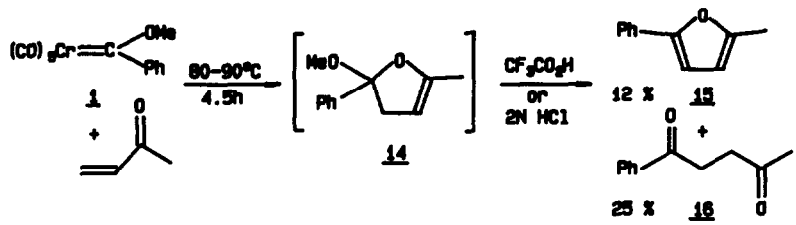
Scheme II shows that methyl(methoxy)carbene complex 9 and styryl-substituted carbene complex 12 [8] are also suitable precursors for cyclopropanes. Together with compound 10 the acyclic product 11 is formed in 16% yield. Vinylcyclopropanes of type 13 are trifunctional systems and should therefore have high synthetic potential.[3]

Scheme II:



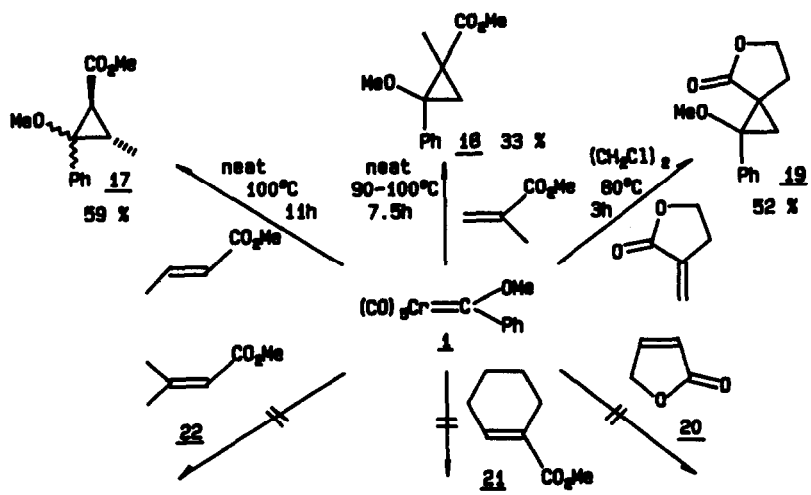
Fumarodinitrile, 2-nitropropene, phenyl vinyl sulfoxide, styrene, crotonaldehyde, or cyclohexanone as olefinic components do not afford cyclopropanes with 1 but give unidentified product mixtures. The nitro compound and the sulfoxide oxidize the carbene complex to give methyl benzoate.[9] However, methyl vinyl ketone provides a formal [4+1]-cycloaddition product 14 which could be detected in the crude reaction mixture (Eq. 2). Treatment of this unstable dihydrofuran derivative with acid leads to elimination and ring cleavage, respectively, producing a mixture of 2-methyl-5-phenylfuran 15 [10] and 1,4-diketone 16 [11] in relatively low isolated yield.

Eq. 2



Having established scope and limitations with regard to the activating substituents we screened the substitution pattern suitable for the [2+1]-cycloaddition. As depicted in Scheme III crotonic ester [1], methyl methacrylate, and α-methylene γ-lactone give reasonable yields of the expected cyclopropanes 17 [1a], 18, and 19. Smooth formation of spiro compound 19 is opposed by the failure to convert butenolide 20 to a cyclopropane derivative. Trisubstituted esters 21 and 22 are also unreactive with respect to 1 even under forced reaction conditions. Similar results were obtained with unsaturated nitriles. Apparently, steric hind rance must not be too high for the carbene-transfer process.

Scheme III:



Further experiments show that the solvent influence on the reaction is rather low. With 1 and acrylonitrile cyclopropane 4 is formed in 60-80% yield, together with small quantities of acyclic isomers (0-12%) analogous to 3 or 8, regardless whether no solvent or cyclohexane, benzene, 1,2-dichloroethane, acetonitrile, dimethylformamide, or methanol are employed. Usually the cis/trans ratio is near to 1:1, however, in methanol a 1:2.7 mixture has been obtained. This observation might be relevant in the mechanistic interpretation of the cyclopropanation reaction.

Our results demonstrate that rather different donor-acceptor-substituted cyclopropanes, which are not easily available by other methods, can be prepared using transition metal carbene complexes. Since the three-membered ring can be cleaved by acid [3,12] (e.g. compound 2 gives methyl 4-oxo-4-phenylbutanoate with 2N HCl in THF), the overall process can be regarded as a nucleophilic acylation of the corresponding electrophilic olefin.[13] Further investigations [14] and applications will be reported in due course.[15]

Acknowledgement: We are very grateful for support of this work by the Stiftung Volkswagenwerk, the Fonds der Chemischen Industrie, the Karl-Winnacker-Stiftung (Hoechst AG), and the BASF AG (Ludwigshafen).

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9) Oxidation of carbene complexes can provide the corresponding esters; see ref. 4.

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13) For direct nucleophilic 1,4-acylation see: D. Seyferth, R.C. Hui, J. Am. Chem. Soc. 107(1985) 4551.

14) Reaction of carbene complexes with 1,3-dienes are reported in the succeeding letter.

15) All new compounds provide correct elemental analysis and appropriate spectra; e. g. 18 cis:trans ≈ 47:53, ^{1}H NMR ($CDCl_3$, 300 MHz): cis-18 δ 7.4-7.25 (m, Ph), 3.86 (s, CO_2Me), 3.22 (s, OMe), 2.03 and 1.30 (2d, 6.1Hz, CH_2), 1.06 (s, Me); trans-18 δ 7.4-7.25 (m, Ph), 3.37 (s, CO_2Me), 3.25 (s, OMe), 2.14 and 1.16 (2d, 5.8Hz, CH_2), 1.69 (s, Me); ^{13}C NMR ($CDCl_3$): cis-18 δ 172.8, 51.8 (s, q, CO_2Me), 136.2, 129.5, 128.4, 128.2 (s, 3d, Ph), 72.2 (s, C-2), 55.3 (q, OMe), 33.5 (s, C-1), 22.5 (t, C-3), 17.6 (q, Me); trans-18 δ 172.9, 52.5 (s, q, CO_2Me), 136.5, 129.6, 129.1, 128.6 (s, 3d, Ph), 72.1 (s, C-2), 55.1 (q, OMe), 33.7 (s, C-1), 20.4 (t, C-3), 15.2 (q, Me).

(Received in Germany 7 March 1988)