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Water-Promoted Reactions : Generation of Oxyallyl Intermediates and their [4+3] Cycloadditions with Furan and Cyclopentadiene. Facile Access to Bridged-cycloheptenones.

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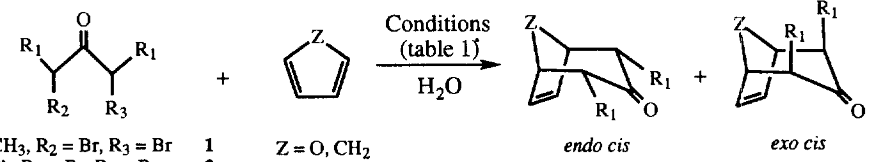
Abstract : α,α'-dibromo ketones in the presence of iron powder, or α-chloro ketones in the presence of triethylamine, have been shown to react very easily with furan or cyclopentadiene when water was used as solvent. © 1997 Published by Elsevier Science Ltd.

Seven-membered carbocycles are an important class of organic compounds which are useful precursors for preparing natural products or pharmacologically active compounds. One of the major access to this class of compounds are the (4+3) cycloaddition reactions which have been actively studied during the last three decades. In 1962, Fort[1] first reported the preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-one by reacting α-chlorodibenzylketone with furan (2.5 eq) in the presence of 2,6-lutidine (4 eq) (DMF, 4 days at 25°C, 18%). Soon afterward, Cookson and Nye[2] in 1963, treated the corresponding α,α'-dibromoketone with sodium iodide, zinc-copper couple or with mercury in order to generate the same postulated oxyallyl cation intermediate which adds to furan or cyclopentadiene when used in a large excess (*ca.*70 eq). Later on, these reactions were actively studied by Hoffman[3], Noyori[4] and Mann[5] who have shown the synthetic utility of oxyallyl cations as intermediates to a wide range of organic frameworks. In the majority of these earlier investigations, all reactions were conducted using sophisticated promotors under an atmosphere of nitrogen in often anhydrous organic solvents. Following our studies on the use of water as a solvent for organic reactions[6], we describe the first [4+3] cycloaddition in water as a simple and efficient access to the oxabicyclo[3.2.1]octene skeleton.

Oxyallyl cations had been generated starting from α,α'-dibromoketones with several reducing reagents such as Cu/NaI in acetonitrile,[7] Zn-B(OEt)$_3$ in THF,[8] Zn/Cu in acetone or DME,[9] Fe/graphite in THF,[10] CeCl$_3$ -SnCl$_2$ in THF[11] etc... . The most popular method was introduced in the very beginning by Noyori using Fe$_2$(CO)$_9$ in benzene[12] but a major drawback was the use of the highly toxic and expensive diiron nonacarbonyl. These oxyallyl cations were trapped with various 1,3-dienes such as furan, cyclopentadiene in an inter- or intramolecular manner. The (4+3) cycloadditions proceed via compact (endo cis) or extended (exo cis) modes in the transition state. The stereochemical outcome in the reaction depends of the reducing agent and has been linked to the relative electrophilicity of the oxyallylcation.[3-5] In organic solvents, the compact mode is favoured when NaI/Cu is employed and the extended mode becomes more favorable as the oxyallyl cation becomes more electrophilic (using Fe$_2$(CO)$_9$).

In fact, oxyallyl cations can be generated at room temperature from α,α'-dibromoketones using simple commercially available iron powder in water and trapped with furan in excellent yields (table 1, entry 1).



$R_1 = CH_3, R_2 = Br, R_3 = Br$ **1**
$R_1 = Ph, R_2 = Br, R_3 = Br$ **2**
$R_1 = CH_3, R_2 = Cl, R_3 = H$ **3**

$Z = O, CH_2$

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Alternatively, a mixture of copper powder with sodium iodide promoted the reaction as well under the same conditions (88%, table 1, entry 2). In both cases, a mixture of diastereoisomers was obtained in which the endo cis compound is largely predominant. The only side reaction is the competitive solvolytic reaction leading to hydroxypentanone which can be avoided by using an excess of furan (2 eq). The same reaction conditions when conducted in any organic solvent yielded very low yields of cycloadducts (<30%) showing the specific effect of water as solvent. In the case of the less reactive cyclopentadiene, the cycloadducts were obtained in 60% yields using either iron powder or the mixture Cu/NaI as promotors. The dibenzylketone **2** could also be used. In this case, the reaction led, although in lower yields, exclusively to the endo cis diastereomer as expected from the steric interaction between the phenyl substituents and the bridge group.

Following the pionnering work of Fort, the cycloaddition of monohalogenoketones with furan has been extensively studied by Föhlisch and coworkers. Thus 2-chloro pentan-3-one (**3**) adds to furan under a variety of basic conditions with a reaction time varying from one day[13] (sodium trifluoroethoxide in trifluoroethanol) to 69 days[14] (Et$_3$N in hexafluoropropan-2-ol). The reaction could be accelerated (6h) in the presence of lithium perchlorate in ether.[15] Alternatively, and starting from 2-bromo pentan-3-one, the reaction required 16-20 hrs using sodium 2,2,3,3-tetrafluoropropoxide in 2,2,3,3-tetrafluoropropanol.[16] These very weakly nucleophilic fluorosolvents have been used because the reaction in methanol led to 2-methoxy pentan-3-one as by-product.[14, 17, 19]

In contrast, we found that in water, the reaction is faster and more efficient (88% isolated yield with 2 eq furan) in 5 h at room temperature in the presence of 1 eq of Et$_3$N. The reaction with the less reactive cyclopentadiene gave under the same conditions, but in 12 hrs, a satisfactory 76% yield with a slight increase of the solvolytic reaction.

Table 1. Condensation of mono- and dihalogenoketones with furan (2 eq) and cyclopentadiene (2 eq) in water.

Entry	ketones (1.5 M)	Diene	Conditions	Yield (%)[a]	*endo : exo*[b]
1	**1**[18]	Z= O	Fe[c] (2 eq), 20° C, 34h	82	89 : 11
2	**1**	Z= O	NaI (2 eq), Cu[c] (3 eq), 20° C, 48h	88	84 : 16
3	**1**	Z= CH$_2$	Fe (2 eq), 20° C, 13h or NaI (2 eq), Cu (3 eq), 20° C, 16h	60	67 : 33
4	**2**[18]	Z= O	NaI (2 eq), Cu (3 eq), 50°C, 12h	60	100 : 0
5	**2**	Z= CH$_2$	NaI (2 eq), Cu (3 eq), 50°C, 12h	31	100 : 0
6	**3**[19]	Z= O	Et$_3$N (1 eq), 20°C, 5 h	88	90 : 10
7	**3**	Z= CH$_2$	Et$_3$N (1 eq), 20°C, 12 h	76	70 : 30

[a] Isolated yield after flash chromatography. All compounds are identical with those described in the literature[7, 9, 20]

[b] *Endo : exo* ratio was determined by ^{1}H NMR spectroscopy. [c] from Prolabo, Fe : 98%, 40-160μm, Cu : 98,5%, 50μm.

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