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New methodology for the [4+3] cycloaddition reactions: generation of oxyallyl cations from α,α′-diiodoketones under sonochemical or thermal conditions

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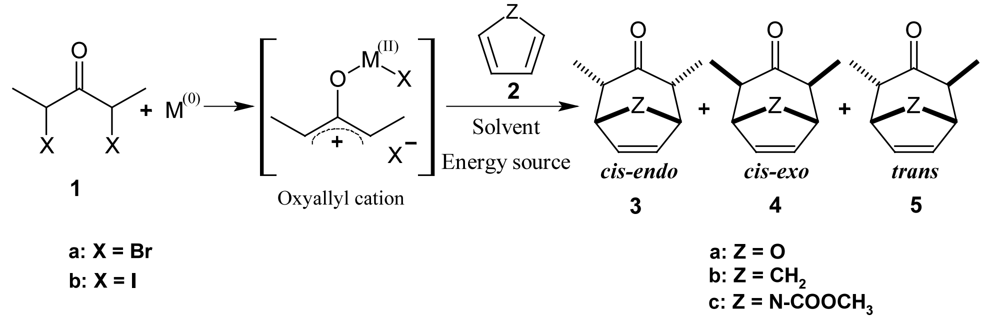
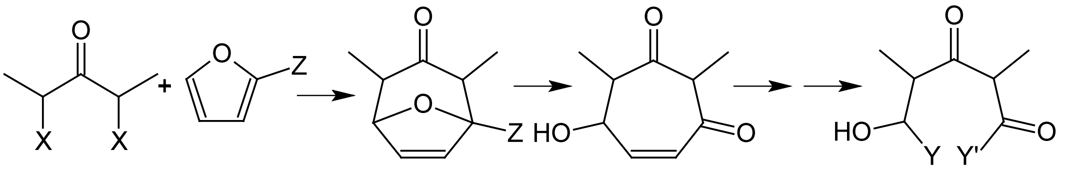
Abstract—A new methodology to perform [4+3] cycloaddition reactions of suitable dienes and 1,3-dimethyl-2-oxyallyl cations is presented. The reaction is carried out starting from commercially available dienes and easy-handling α,α′-diiodoketones, which are reduced by the Zn/Cu couple to generate the oxyallyl cation as intermediate. The reaction is carried out under mild thermal or sonochemical conditions at low temperatures (from 0 to −44°C) and for short reaction times (<15 min). This methodology represents a good alternative respect to the actual procedures based on other reducing agents or starting from more elaborate precursors of the oxyallyl cations. © 2001 Elsevier Science Ltd. All rights reserved.

The work presented deals with the development of a new methodology for the [4C(4π)+3C(2π)] cycloaddition reaction[1] of dienes with oxyallyl cations, generated in situ from dihaloketones in the presence of reducing metals (Scheme 1). This work is a part of a wider study that we are carrying out in our laboratory on the [4+3] cycloaddition reaction of heterocyclic dienes[2–4] and 1,3-dimethyl-2-oxy-allyl cation, in order to synthesize polyfunctionalized cycloheptanes (Scheme 2). These molecules are important precursors of both versatile linear and cyclic synthons[5] for the preparation of biologically active natural products.[6,7]



Scheme 1. Diastereomeric products resulting from the [4+3] cycloaddition reaction of dienes and 1,3-dimethyl-2-oxy-allyl cation.



Scheme 2. Synthetic applications of the [4C(4π)+3C(2π)] cycloadducts.

Keywords: [4+3] cycloaddition; oxyallyl cation; diiodoketone; Zn–Cu couple; sonochemistry.

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In the development of this study we considered the necessity to carry out the reaction under mild conditions to improve the chemical selectivity and also the stereoselectivity of the cycloaddition reaction. For this purpose, the reaction was carried out under such conditions that the generation of the oxyallyl cation should be performed by using selective reagents (compatible with a wide variety of functional groups), which would also improve the general applicability and versatility of this important reaction, and at low temperatures to improve the diastereoselectivity of the process.

Some of the known [4+3] cycloaddition methodologies frequently used to generate allyl cations, unstable and lachrymatory α,α′-dibromoketones, which in the reaction medium are reduced by $Fe_2(CO)_9$ (in benzene at 80°C, for 18 h)[8] or by Cu^0/NaI (in acetonitrile at 60°C, for 4 h).[9]

The alternatives found in the literature to prepare allyl cations at low temperatures, even though clever and meritorious, lack versatility because their application is restricted to certain structural models and start from very elaborate non-commercial precursors (for example: the generation of allyl cations by the reaction of α-chloro-silyl-enol ethers,[10] α-chloro-enamines,[11] α-chloro-imines[12] or α-chloroalkyl-enol ethers[13] with Ag^+ salts, and also starting from the α,α-dialkoxy-silyl-enol ethers,[14] α-bromoalkyl-enol ethers,[15] α-bromo-silyl-enol ethers,[16] α-sulfono-alkyl-enol ethers[17] or α-carbonyl-silyl-enol ethers[18] in the presence of Lewis acids).

On the other hand, there are methodologies that use strong reaction conditions (i.e. the generation of allyl cations by reaction of chloroketones in an alkaline medium),[19a–d] which make these procedures incompatible with a wide variety of organic functions attached to the diene. On the basis of these precedents we developed a methodology starting from non-volatile and non-lachrymatory α,α′-diiodoketones, that afforded cycloadducts in high yield (up to 90%), at low temperatures (from 0 to −44°C) and in very short reaction times (<15 min).

Table 1. Experimental factors that were modified and parameters that were analyzed in the study of the reactivity of the system furan/1,3-dimethyl-2-oxy-allyl cation

Experimental variable factors	Type of dihaloketone Type of reducing agent (nature and morphology): $Fe_2(CO)_9$, Cu (powder, bronze, submicron), Zn, Zn–Cu pair Reaction activator: NaI, LiI, TMSCl Temperature: reflux of solvent, rt, 0°C, −20°C, −44°C, −78°C Source of energy: heating, sonication Type of solvent: polar, non-polar, protic, aprotic Concentration of reagents Stoichiometry
Parameters analyzed	Reaction time (up to total or constant conversion) Conversion of starting materials Yield *cis–trans* diastereoselectivity *endo–exo* diastereoselectivity

To analyze the factors that condition the reduction of dihaloketones in the [4+3] cycloaddition reaction we carried out an exhaustive study on all experimental parameters affecting the reaction (see Table 1). In these experiments, each parameter was independently modified, which made it possible to analyze its influence on the reaction results (conversion, yield and diastereoselectivity). In this way, we made important observations that helped us to better understand the reactivity of these systems and to design new and optimized reaction conditions for the [4+3] cycloaddition reaction procedure.

From this study it is possible to draw the following conclusions (see Table 2):

(1) The use of α,α′-diiodoketones as precursors of the oxyallyl cation instead of α,α′-dibromoketones (with the other reaction factors constant) considerably increases the reaction rate, in such a way that it is possible to get complete conversion and high yield at reaction temperatures as low as −44°C, which is much lower than the usual reaction temperatures reported for these processes, and affording cycloadducts in a reaction time also much shorter (10–30 min instead of 4–18 h).

(2) From the operational and safety points of view, to work with diiodoketones, which are non-volatile (in same cases they are solids) and non-lachrymatory, is easier and safer than working with the corresponding dibromo derivatives that are relatively volatile and very lachyrmatory. Even though dibromoketones are usually stored in the freezer, after a while they decompose and every time you need to use them, it is necessary to filter them through a pad of neutral alumina in order to remove Br_2 and HBr formed, or it can even be necessary to redistil them. However, diiodoketones, when stored in the freezer and protected from light, crystallize and they are stable for long periods of time.

(3) The use of reducing agents based on Zn[20] (Zn powder and Zn–Cu pairs), improves the reactivity of the system, affording cycloadducts at lower temperatures and shorter reaction times than in the case of using copper powder as the reducing agent. At the same time, the use of Zn-based reductors allows the reaction to be run without activators such as NaI or TMSCl, which, on the other hand, facilitate the formation of polymers and/or electrophilic addition products to the detriment of [4+3] cycloadducts.

(4) The use of ultrasound (generated by a high-frequency immersion sonication probe) considerably accelerates the kinetics of the reaction.[21] This increase of the reaction rate allows the cycloaddition reaction to be carried out with similar yields, at a lower temperature (−44°C) than the one (0°C) necessary under stirring.

Table 2. Comparative results, from [4+3] cycloaddition selected experiments with several dienes, between standard and newly designed reaction conditions

Entry	**1**[a]	**2**[b]	Reducing agent	Additional reagent	Energy source[c]	Temp. (°C)	Time (min)	Conv.[d] (%)	Yield[e] (%)	DS[f] (*cis*:*trans*) (%)	DS[f] (*endo*:*exo*) (%)
1	**1a**	**2a**	Cu	NaI	Therm.	60	240	100	63	100:0	90:10
2	**1a**	**2a**	$Fe_2(CO)_9$	–	Therm.	80	960	100	90	46:54	100:0
3	**1a**	**2a**	Zn(Cu)	–	Sonic	−44	150	100	83	100:0	80:20
4	**1a**	**2a**	Zn(Cu)	NaI	Sonic	−44	90	100	78	100:0	90:10
5	**1b**	**2a**	Zn(Cu)	–	Sonic	−44	15	100	90	100:0	91:9
6	**1b**	**2a**	Zn(Cu)	NaI	Sonic	−44	7	100	58	100:0	94:6
7	**1b**	**2a**	Zn(Cu)	–	Sonic	0	10	100	70	100:0	90:10
8	**1b**	**2a**	Zn(Cu)	–	Stirr.	0	30	100	75	100:0	90:10
9	**1b**	2b	Zn(Cu)	–	Stirr.	0	60	100	71	100:0	66:34
10	**1b**	2c	Zn(Cu)	–	Stirr.	0	30	100	42	100:0	51:49

[a] **1** = Dihaloketone.

[b] **2** = Diene.

[c] Energy source: Therm. = thermal (heating and magnetic stirring). Sonic. = ultrasound sonication. Stirr. = magnetic stirring.

[d] Conv. = conversion of raw materials.

[e] Yield = % of raw material reacted that afforded cycloadducts **3**–**5**.

[f] DS = Diastereoselectivity: *cis*/*trans* = **3**+**4**:**5**; *endo*/*exo* = **3**:**4**.

(5) Finally, other experimental modifications like the use of activating agents such as NaI, LiI or TMSCl also accelerate the reaction rate, but decrease the chemical selectivity and then the yield of cycloadducts. So, for example, the use of Zn(Cu)/NaI as a reducing system generates oxyallyl cations (having Na^+ as counter-ion), which when they react with medium or low electron-density dienes afford polymerization products to the detriment of cycloadducts. In the case of using Zn(Cu)/TMSCl, the reduction process is so efficient that a concomitant reduction of some functional groups attached to the diene can happen (for example reduction of sulfoxide groups to thioethers). The use of these activators could be very convenient for certain molecular patterns, but they lack general applicability, due to the aforementioned reasons.

In Table 2 we summarize the most significant results from our study, which comprised almost 300 experiments. In all cases we used as precursor the oxyallyl cation 2,4-dihalo-3-pentanone. As dienes we used three different cyclic dienes (see Scheme 1).

Entries 1 and 2 from Table 2 show the results obtained by using the standard conditions found in the literature.[1,9] Under these conditions good yields and diastereoselectivities are obtained, but the reaction conditions require reflux of solvent (60–80°C) for long periods of time.

When we applied our new cycloaddition methodology with furan as a diene (entries 5, 7 and 8 from Table 2) it is possible to appreciate that the reaction goes faster (10–30 min instead of 240–960 min) and at a much lower reaction temperature (−44°C to 0°C instead of 60–80°C) than in the case of using the Hoffmann or the Noyori methodologies (entries 1 and 2, respectively).[1] On the other hand, in entry 1 the yield is lower (with similar *cis–trans* and *endo–exo* diastereoselectivities) than in our case. Also, in entry 2 the *cis–trans* diastereoselectivity is low (46:54), meanwhile the *endo–exo* diastereoselectivity is complete (100:0). It is worth noting (compare entries 7 and 8) the use of sonication as an energy source, which allows the reaction to be carried out in one third of the reaction time, invariably maintaining the rest of the reaction conditions. The use of NaI as a reaction activator decreases the reaction time to 7 min, but considerably decreases the yield of cycloadducts (favoring the formation of electrophilic addition products on C-2 of dienes), even though the *endo–exo* diastereoselectivity is slightly increased (see entries 5 and 6).

When our cycloaddition methodology was applied to other dienes than furan (entries 8–10), the reaction affords diastereomeric cycloadducts **3**, **4** and **5** with similar yields and diastereoselectivities than those observed in the literature[1] under more drastic standard conditions, but in our case, with much shorter reaction times and at a lower reaction temperature.

Typical reaction procedure: In a 25 mL round bottomed flask, fitted with septa and magnetic stirring and under an argon atmosphere, a Zn–Cu pair (217 mg, 3.32 mmol) was placed (freshly prepared by deposition of Cu^0, from $CuSO_4$, on Zn powder[22]). Dry acetonitrile, 5 mL (in experiments carried out at temperatures lower than the melting point of acetonitrile, −44°C, propionitrile was used instead) was added and the resulting black suspension was stirred for 5 min in a cooling bath until the work temperature was reached (usually 0 or −44°C). Then, the diene (4.24 mmol) was added, at once, under continuous stirring. Afterwards, a solution of 2,4-diiodo-3-pentanone[23,24] (360 mg, 1.06 mmol) in acetonitrile (6 mL) was added dropwise by cannula. The cooled reaction mixture was vigorously stirred for a few minutes (10–30 min, depending on the reaction conditions).

Sonication conditions: For the experiments carried out under ultrasound, a three-necked sonication reactor, fitted with septa and partially immersed in a cooling bath (0°C, −44°C, −78°C), was used. This reactor is a cost efficient piece of glassware and it was designed ad-hoc in our laboratory.[25] A 1/8” sonication probe (from Branson EDP ref. no. 101-148-062) was immersed in the reaction mixture and adapted to obtain a conveniently closed system. This reactor allows us to work with quite different reaction volumes (from 100 down to 4 mL). The reaction was carried out under an inert argon atmosphere and the inner temperature was monitored by a flexible thermo-couple (PT-100).

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