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Review Article

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Intermolecular (4+3) cycloaddition reactions: Anthracene and its derivatives as dienes

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ABSTRACT

The (4+3)cycloaddition reactions of allylic cations to dienes is a powerful method for the direct synthesis of seven-membered rings which are occurrence in many of natural products have biological activity. (4+3) cycloadditions reactions between oxyallyl cations and anthracene or 9-substituted anthracene have not yet been studied extensively. Although these compounds have great importance, where 9,10-dihydro-9,10-propano-anthraceness can be used as key step in the medicinal synthesis. For this reason In this review article we will emphasis on the reactions between anthracene and its derivatives as dienes with α,α'-dihaloketones and α,α,α',α'-tetrahaloketones as oxyallyl cations.

Keywords: oxyallyl cations, dienes, (4+3) cycloaddition, seven-membered rings, anthracene.

INTRODUCTION

Before the discovery of the (4+3) cycloaddition reaction, many methods for preparation of seven-membered rings are available in literatures which are limited to the expansion to seven-membered rings and some cyclization reactions. [1, 2] (4+3) cycloaddition reaction is a reaction between an allylic cations and a diene. This reaction is one of the most powerful and straightforward methods for the synthesis of seven-membered rings from simple starting materials. [3] Seven-membered rings comprise a large family of biologically active natural products. For this reason, the (4+3) cycloaddition reactions have a particular interest to many synthetic organic chemists. Unlike the Diels-Alder reaction, (4+3) cycloaddition have been investigated but it's not as widely as with Diels-Alder reaction. These investigations have led to the presence of two types of (4+3) cycloaddition reaction, namely intermolecular of the (4+3) cycloaddition reaction [4, 5] and intramolecular of (4+3) cycloaddition. [6, 7] Electronically, intermolecular (4+3) cycloaddition is similar to the Diels-Alder reaction and can be viewed as a [4π (4C) + 2π (3C)] combination in which an allyl cation participates as the reactive dienophile for the formation of a seven-membered ring as shown in **(Figure 1)**. [8]

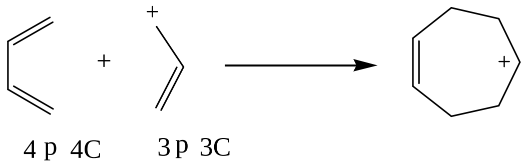


Figure 1: Generic (4+3) Cycloaddition Reaction between an Allylic Cation and Diene

However, (4+3) cycloaddition reaction is more complex than the Diels-Alder reaction, the main reason is that the configuration of the allyl cation intermediate has several alternatives (three possible structures) respectively the W form, the sickle form and U form, the as shown in **(Figure 2)**, and also seven-membered rings are more difficult from six-membered rings to prepare due to increased ring strain and entropy. [9]

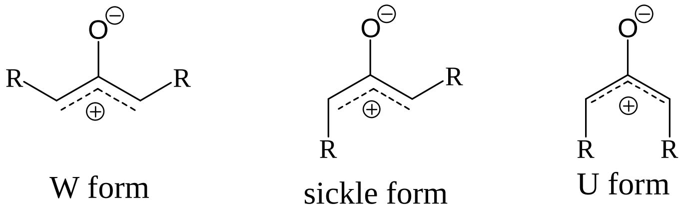


Figure 2: Possible Structures for Cationic Dienophile

Frontier orbital theory analyses and interacting molecular orbital's for (4+3) cycloaddition, allowed by the Woodward-Hoffmann rules, show the diene HOMO and the oxyallyl LUMO as with the Diels-Alder reaction, but the extent of regioselection is normally less pronounced for (4+3) processes, because the regioselectivity which is subject to control by frontier molecular orbital. Nevertheless, several examples have been reported in which excellent selectivity was achieved through the use of chiral substituent on the diene or oxyallyl component. [10]

Classification And Reaction Mechanisms Of Oxyallyl Cations With 1, 3-Dienes:

Hoffmann et al [11] have found that it is useful to divide reactions of allyl cations with 1,3-dienes into three categories based on mechanistic considerations with presenting much of the analyses, semantics and interpretations and also predicted results for this reaction. Theoretical studies suggest that both Type (A) and also Type (B) concerted and stepwise mechanisms are possible that lead to Bridged seven-membered rings or (4+3) cycloadducts. Type (C) processes do not give cycloadducts but lead to products derived from electrophilic addition reactions. These types are shown in **(Figure 3)**. However, type (C) reactions are not of our interest for this study. [7]

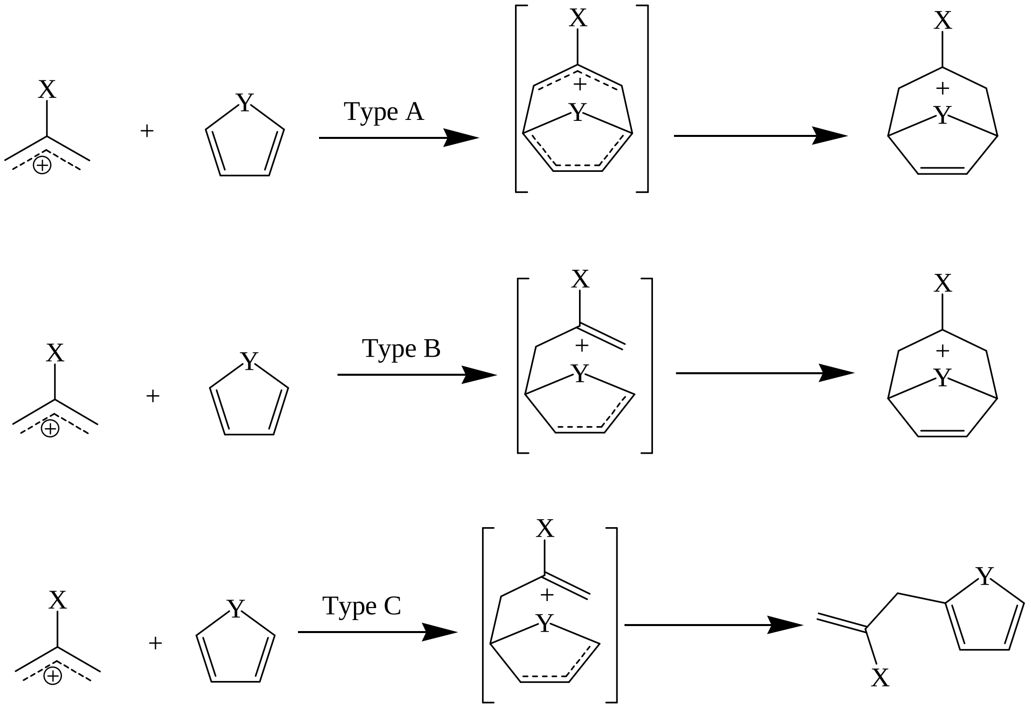
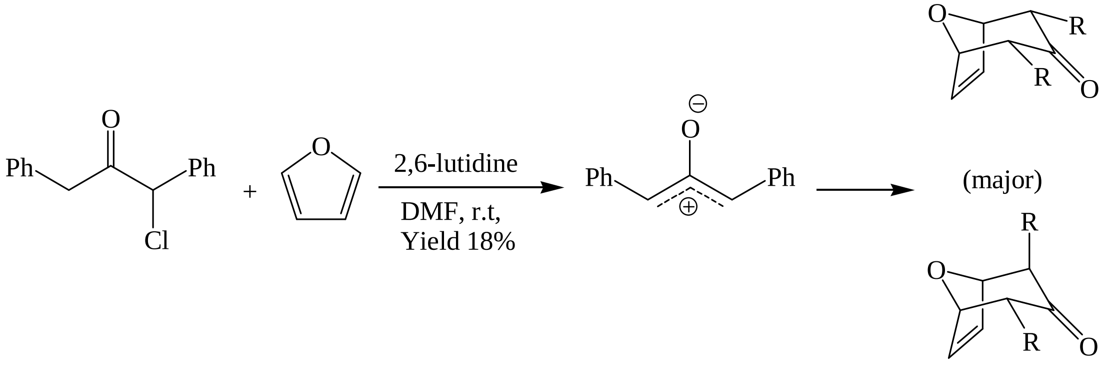


Figure 3: Mechanism Proposed by Hoffmann

Several features of this reaction are noteworthy **(Figure 3)** such as the product formed from the reaction depends on the nature of the (X and Y) groups. Typically, the (X) group is oxygen functionality whereas the (Y) group can be an oxygen, nitrogen or sulfur atom or methylene. [12]

Formation of Oxyallyl Cations From α,α-Dihaloketones and $\alpha, \alpha, \alpha', \alpha$-Tetrahaloketones:

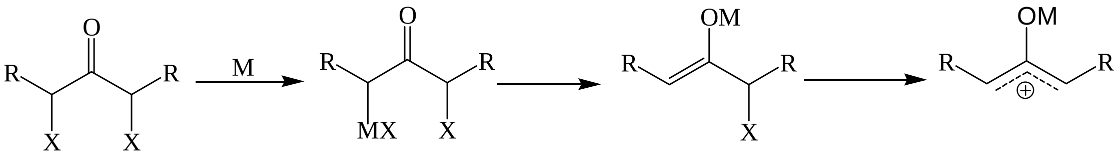
Oxyallyl cations have been known as intermediates in organic chemistry since first proposed by Favorskii in 1894, thereafter it has named Favorskii reaction or Favorskii rearrangement. [13, 14] Since that time, oxyallyl cations have been used by organic chemists as intermediate in syntheses a variety of natural product across a wide range of unique applications. One such application that has enjoyed a great deal of success and studied on extensively in this area is (4+3) cycloaddition reaction to form seven-membered rings. The first evidence for the existence of oxyallyl cations was reported by Fort in 1962, probably unwillingly, when he treated chloro-dibenzyl ketone with 2,6-lutidine in the presence of furan at room temperature. After a couple of days, he isolated the first (4+3) cycloadduct as shown in **(Scheme 1)**. [15-17]



Scheme 1: The First (4+3) Cycloaddition Reactions

Later, Cookson et al [18] developed another, more efficient procedure for the formation of oxabicyclic by treating α, α'-dibromoketone with sodium iodide in the presence of furan as shown in. In this case, it was observed that the formation of large amounts of resulting from the reaction of electrophilic substitution between the cation furan and oxyallyl generated in situ. Reaction of α, α'-dibromoketone with cyclopentadiene afforded the cycloadducts. At a later time, Cookson et al [19] experimented of this reaction with cyclopentadiene and N-methylpyrrole to assess the generality on (4+3) cycloaddition reaction. In the case of cyclopentadiene compounds was isolated, but in the case of N-methylpyrrole just the product of electrophilic substitution was isolated. The works of Fort and Cookson are the foundation on formation of seven- members through cycloaddition (4+3). These works are caught the attention of a number of chemists in this area to the development of several useful synthetic methods to generate appropriate oxyallyl cations. Among the most common ways of generating oxyallyl cations is the reduction of α-haloketones, α,α'-dihaloketones and α,α,α',α'-tetrahaloketones. Contributions of Hoffmann [9, 11, 20, 21], Noyori [22-24], Harmata [7, 25, 26], Fohlisch [27-30], Mann and Barbosa [31-38] were the most important contributions in this area which has been covered in many papers, reviews, etc.

Halogenated allylic cations, particularly oxyallylic cations such as α,α'-dibromoketones or α,α'-diiodoketones and α,α,α',α'-tetrabromoketones which are most common or α,α,α',α'-tetrachloroketones are also used. As was mentioned earlier, this categories offer some unique opportunities that can be synthetically useful for (4+3) cycloaddition. Many reagents have been used to generate oxyallyl cations from α,α'-dihaloketones and α,α,α',α'-tetrahaloketones. Generally, the simplified mechanism for these reactions initially involves the attack of a metal on the halogens. The metal itself complexed with solvent and other ligands interacts with the carbonyl and assists in the removal of a halide by forming the corresponding cation oxyallyl, as shown in **(Scheme 2)**. [39]



R= alkyl **or** aryl **or** halogene
X= Br **or** Cl **or** I

M= Zn/Cu, THF, -10^oC. **or** $Fe_2(CO)_9$, benzene, 25^oC.

M= $ZnEt_2$, benzene, 25^oC. **or** THF, reflux.

M= NaI, acetonitrile. **or** NaI/Cu, acetonitrile.

M= Zn/Cu, ultrasound, 5-10^oC, dioxane. **or** Zn/Cu, Me_3SiCl, 0^oC.

M= Et_3N, methanol, 25^oC. **or** Et_3N, CF_3CH_2OH.

Scheme 2: The General Mechanism and Reagents Used to Generate Oxyallyl Cations from α,α'-Dihaloketones and α,α,α',α'-Tetrahaloketones

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(4+3) Cycloaddition Reactions Of Dienes And Oxyallyl Cations:
The dienes in (4+3) cycloadditions was also similar to the Diels-Alder reaction in terms of the requirement of an s-cis conformation. Many examples have been mentioned in the intermolecular (4+3) cycloaddition reaction between oxyallyl cations as dienophiles and different dienes such as furan, substituted furan, cyclopentadiene, substituted pyrrole anthracene and substituted anthracene.

The course of (4+3) cycloaddition depends greatly on the choice of the reducing agent. The most widely used reducing agents for the cycloaddition of α,α'-dibromoketones, and α,α,α',α'-tetrahaloketones are iron tricarbonyl $Fe(CO)_3$, [40] diiron carbonyl $Fe_2(CO)_9$, [41-43] diethyl zinc Et_2Zn, [35, 44] triethyl borate with zinc dust $(EtO)_3B$, Zn, Zn-Cu couple in dioxane and sonication, [45] Zn/Cu, copper and sodium iodide Cu/ NaI). [46, 47]

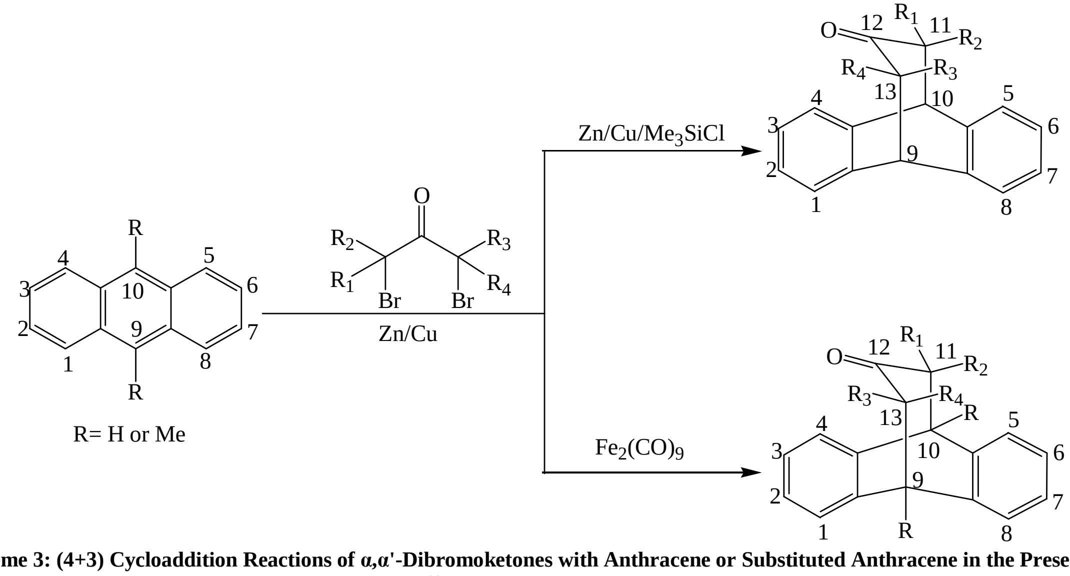
$Fe_2(CO)_9$ is one of the most widely used reducing agents for the cycloaddition of α,α'-dibromoketones, and α,α,α',α'-tetrahaloketones but this reducing agent which is very expensive and toxic. [48]

Among various intermolecular (4+3) cycloaddition reactions of an oxyallyl cation with furan or its derivatives and cyclopentadiene are the compounds which studied widely in this area and also it reacts with different reducing reagents under several conditions to providing the corresponding cycloadduct. [40, 49]

Pyrroles have not been used as often as furan or cyclopentadiene as dienes in the (4+3) cycloaddition because of its high nucleophilicity. N-methylpyrrole failed to react in (4+3) cycloadditions. However, N-acetylpyrrole and N-carbomethoxypyrrole could be induced to engage in (4+3) cycloadditions by changing the nitrogen protection to electron withdrawing groups. [50]

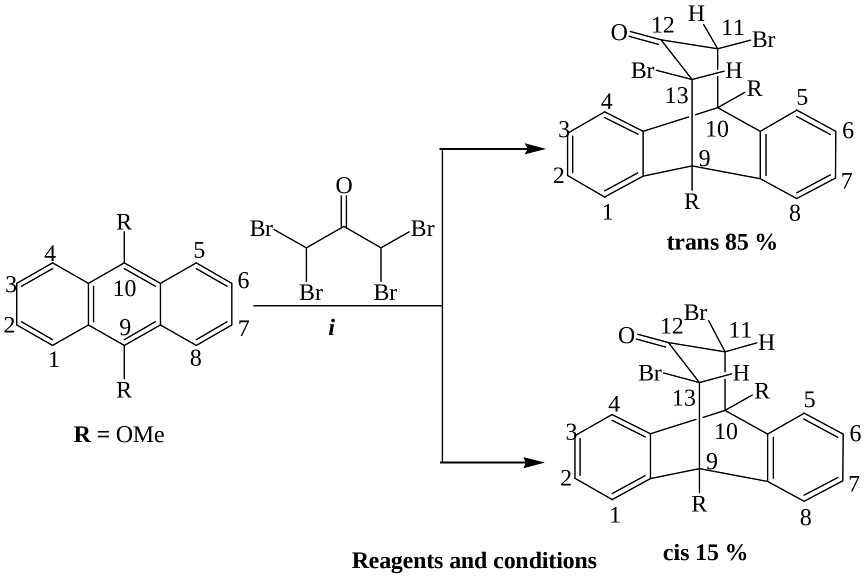
Anthracene and substituted anthracene such as alkyl anthracene methoxyanthracene, phenylanthracene and alkenylanthracenes have also been used as dienes in (4+3) cycloaddition reaction with α,α'-dibromoketones or α,α,α',α'-tetrabromoketones such as 1.3-dibromoacetone or 1.1.3.3-tetrabromoacetone as oxyallyl cations in the presence of reducing agents under different sets of conditions which afforded the cycloadducts in good yields. In the literature, there are a few examples of intermolecular (4+3) cycloaddition of anthracene and/or its derivatives with α,α'-dibromoketones or α,α,α',α'-tetrabromoketones.

Here are, we will address most important of these examples in this area for provide a more complete picture anthracene and its derivatives so that researchers need not scan too many sources to attain a good knowledge of the area. Hoffmann pioneered the use of anthracene and substituted anthracene as dienes for reaction with difference α,α'-dibromoketones and α,α,α',α'-tetrabromoketones in the presence of different reaction condition as shown in **(Scheme 3)** [11, 51]



Scheme 3: (4+3) Cycloaddition Reactions of α,α'-Dibromoketones with Anthracene or Substituted Anthracene in the Presence of Different Reaction Conditions

Another example serves to Hoffmann achievements by reaction of 9,10-dimethoxyanthracene with α,α,α',α'-tetrabromoketones in the presence of different reaction condition **(Scheme 4)** [52]

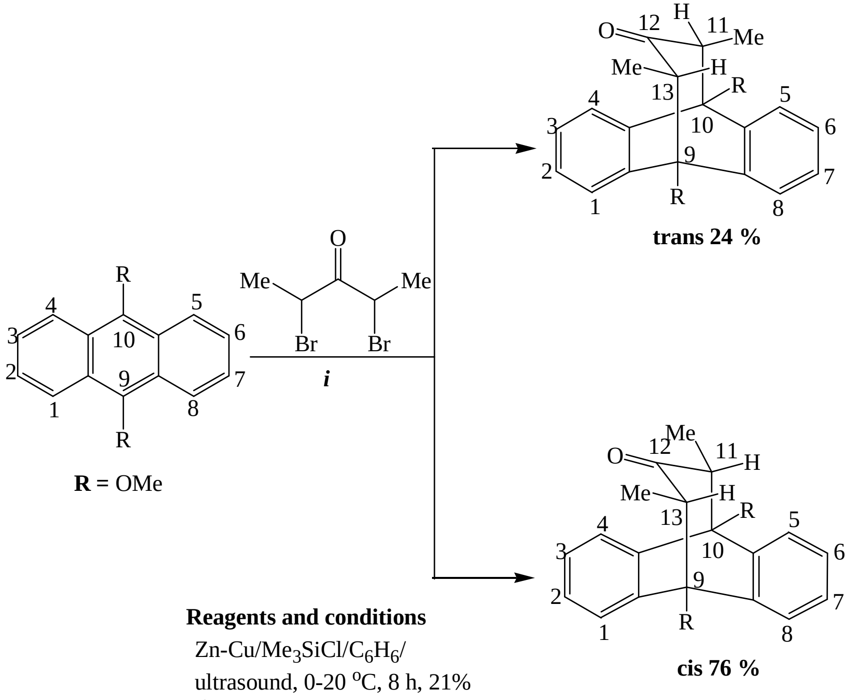


Reagents and conditions

i = Zn-Cu/1,4-dioxane/Me_3SiCl or Zn-Cu/1,4-dioxane/ultrasound, 10-20 ^oC;

Scheme 4: (4+3) Cycloaddition Reactions of α, α, α', α'-Tetrabromoketones with 9,10-Dimethoxyanthracene in the Presence of Different Reaction Conditions

9,10-dimethoxyanthracene has also been used in (4+3) cycloaddition reactions with α,α'-dibromoketones under similar reaction conditions as shown in **(Scheme 5)** [52]

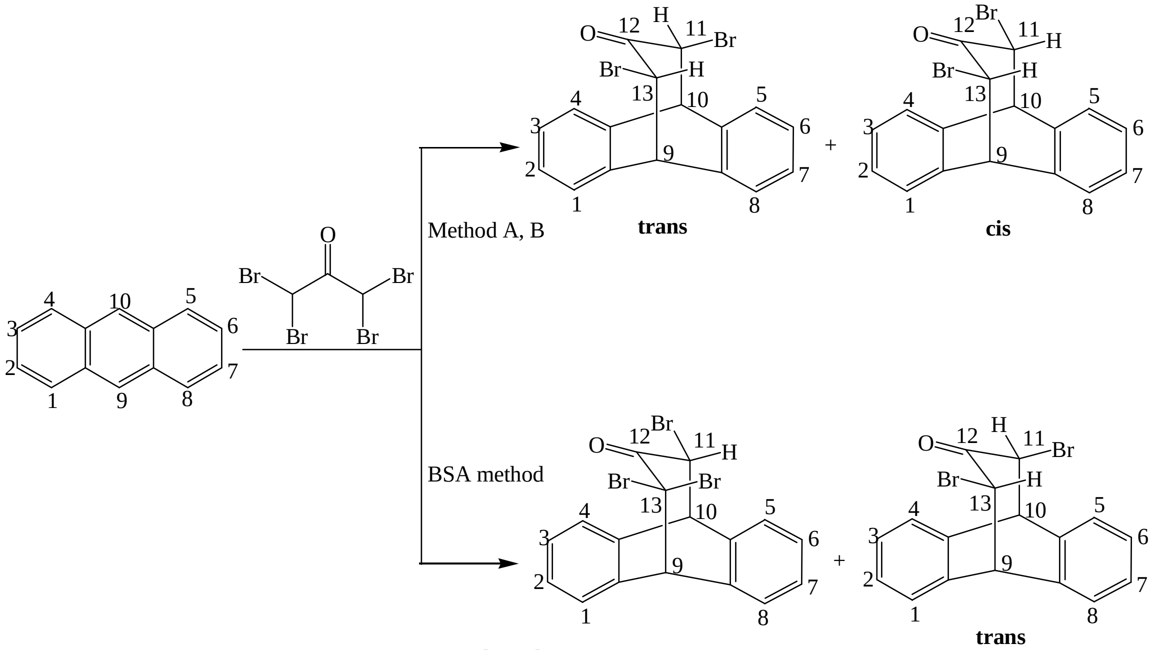


Reagents and conditions

Zn-Cu/Me_3SiCl/C_6H_6/
ultrasound, 0-20 ^oC, 8 h, 21%

Scheme 5: (4+3) Cycloaddition Reactions of α, α-Dibromoketones with 9,10-Dimethoxyanthracene in the Presence of Different Reaction Conditions

Hoffmann students such as Abd El-Wareth was studied this reaction by use different substituted anthracene and other reagents **(Scheme 6)** [53]

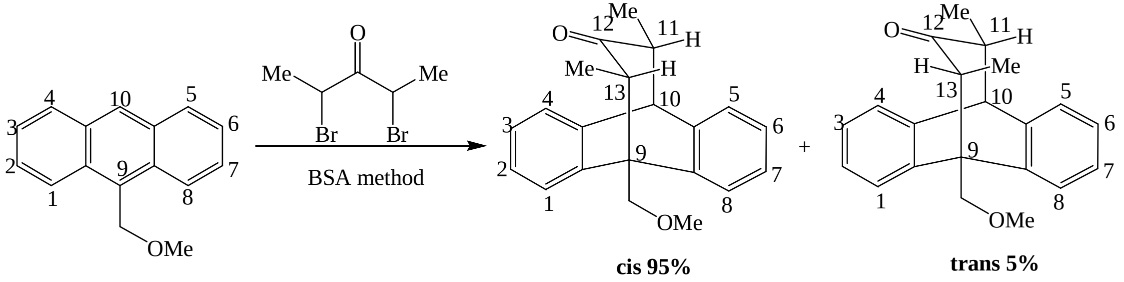


Reagents and conditions

Method A: Zn/Cu, Me,SiCI, dioxane, 80°C, 20 h, 15%.
Method B: Zn/Cu, dioxane, ultrasound, 10-20°C, 8 h, 28%.
BSA method: Zn/CuCl, benzene, ultrasonic bath, 10°C,
N,O-bis(trimethylsily1)acetamide. 42 % and trans 5 %.

Scheme 6: (4+3) Cycloaddition Reactions of α, α, α', α'-Tetrabromoketones with Anthracene in the Presence of Different Reaction Conditions

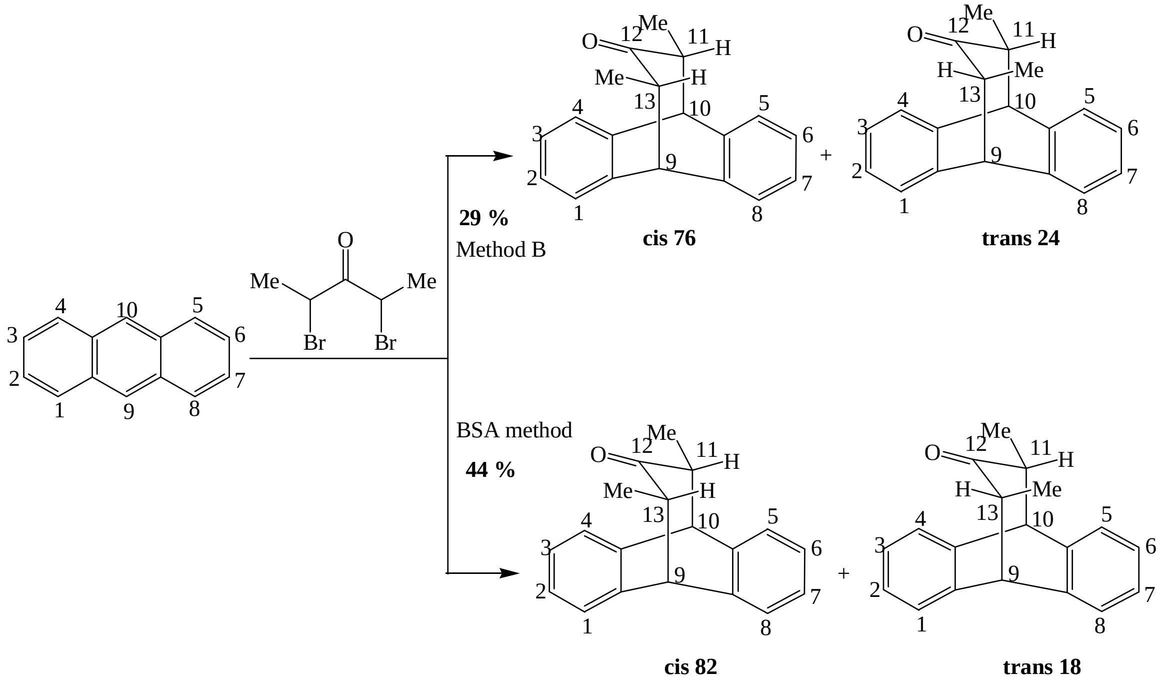
The cycloaddition reactions of 9-methoxymethyl-anthracene with α,α-dibromoketones the cycloadducts in the presence of reaction conditions itself with variable yields **(Scheme 7)**. [53]



BSA method: Zn/CuCl, benzene, ultrasonic bath, 10°C,
N,O-bis(trimethylsily1)acetamide.

Scheme 7: (4+3) Cycloaddition Reactions of 9-Methoxymethyl-anthracene with α, α-Dibromoketones

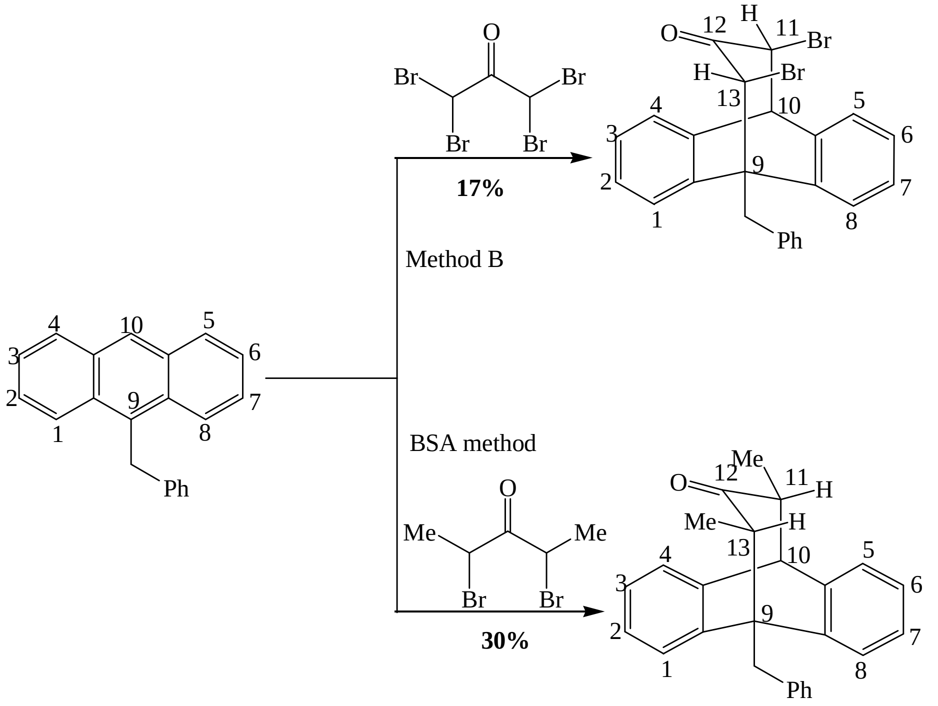
Under similar reaction conditions anthracene **(Scheme 8)** and 9-benzyl-anthracene **(Scheme 9)** underwent (4+3) cycloaddition with α, α-dibromoketones and α, α, α', α'-Tetrabromoketones to give cycloadducts with different yields. [53]



Reagents and conditions

Method B: Zn/Cu, dioxane, ultrasound, 10-20°C.
BSA method: Zn/CuCl, benzene, ultrasonic bath, 10°C, N,O-bis(trimethylsily1)acetamide.

Scheme 8: (4+3) Cycloaddition Reactions of Anthracene with α, α-Dibromoketones under Different Reaction Conditions

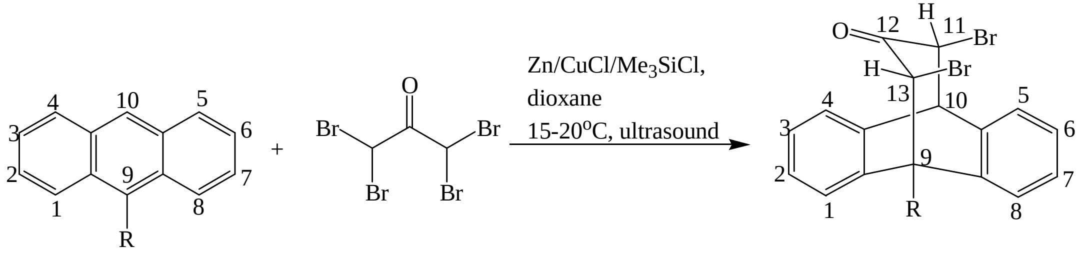


Reagents and conditions

Method B: Zn/Cu, dioxane, ultrasound, 10-20°C.
BSA method: Zn/CuCl, benzene, ultrasonic bath, 10°C, N,O-bis(trimethylsily1)acetamide.

Scheme 9: (4+3) Cycloaddition Reactions of 9-Benzyl-anthracene with α, α-Dibromoketones and α, α, α', α'-Tetrabromoketones Under Different Reaction Conditions

Usama Karama and Hoffmann [54-57] was also studies the (4+3) cycloaddition reactions of some substituted anthracene such as 9-alkenylanthracene with α,α,α',α'-tetrabromoketones as shown in **(Scheme 10)**. Some of these compounds have great importance, where 9,10-dihydro-9,10-propano-anthraceness can be used as key step in the synthesis of a homologues of antidepressants and anti-anxiety.

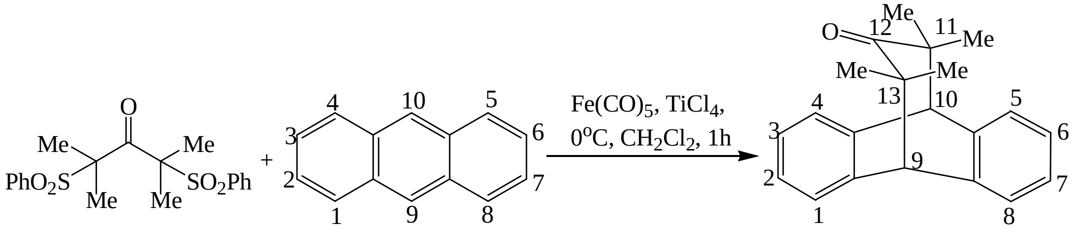


R= H
CH$_3$
CH$_2$=CH
CH$_2$-CH=CH$_2$
CH$_2$=CH-CH-CH$_2$
OCH$_3$

R= CH$_3$, 71%
CH$_2$=CH, 71%
CH$_2$-CH=CH$_2$, 67%
CH$_2$=CH-CH-CH$_2$, 71%
OCH$_3$, 64%

Scheme 10: (4+3) Cycloaddition Reactions of α, α, α', α'-Tetrabromoketones with Anthracene and substituted anthracene in the Presence of same Reaction Conditions

Hardinger reported [58, 59], that the reactions of α,α'-bis(sulfonyl) ketones with iron pentacarbonyl and TiCl$_4$ in the presence of anthracene gave Hardinger reported, that the reactions of α,α'-bis(sulfonyl) ketones with iron pentacarbonyl and TiCl$_4$ in the presence of anthracene gave the expected (4+3) cycloadducts in good yields as shown in **(Scheme 11)**.



yield: 86%

Scheme 11: Cycloaddition Reactions of α,α'-Bis(sulfonyl) Ketones with Anthracene in the Presence of Iron Pentacarbonyl

CONCLUSION

In this review article, we described the intermolecular (4+3) cycloaddition reactions between anthracene and/ or its derivatives and oxyallyl cations particularly of α,α'-dihaloketones and α,α,α',α'-tetrahaloketones to synthesis of seven-membered rings. It also gives advantages and disadvantage reducing agents and reaction conditions, along with some examples for cycloaddition reactions of anthracene and its derivatives.

REFERENCES

[1] T Takahashi; WH Sun; Z Duan; B Shen, *Org. Lett.*, **20002**, (9), 1197-1199.
[2] EJ Kantorowski, MJ Kurth, *Tetrahedron.*, **2000**, (56), 4317-4353.
[3] D T Craft; BW Gung, *Tetrahedron Lett.*, **2008**, 49(41), 5931-5934.
[4] R Aspiotis, *University of Toronto, National Library of Canada*, **1997** 10-14.
[5] R B Owoarie, *King's College London*, **2003** 21-24.
[6] RS Grainger; RB Owoare; P Tisselli; JW Steedl, *J. Org. Chem.*, **2003**, (68), 7899-7902.
[7] M Harmata, *Tetrahedron.*, **1997**, 53(18), 6235-6280.
[8] JH Rigby; FC Pigge, *Org. React.*, **1998**, (51), 351-478.
[9] H.MR Hoffmann, *Angew Chem. Int. Edit.*, **1973**, 12(10), 819-835.
[10] TK Lo Brian, *The University of Hong Kong, The HKU Scholars Hub.*, **2011**, 1-24.
[11] HMR Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **1984**, 23(1), 1-19.
[12] CJ Stephen; A Bayle, *University of Glasgow.*, **2011**, (2), 91-94.
[13] MNV Wal; AK Dilger; DWC MacMillan, *Chem. Sci.*, **2013**, (4), 3075-3079.
[14] C Rappe; K Andersson, *Acta. Chemica Scandinavica.*, **1969**, (23), 2839-2847.
[15] AW Fort, *J. Am. Chem. Soc.*, **1962**, (84), 2620-2625.
[16] AW Fort, *J. Am. Chem. Soc.*, **1962**, (84), 4979-4981.

[17] AW Fort, *J. Am. Chem. Soc*., **1962**, (84) 2625-2628.
[18] RC Cookson; MJ Nye, *J. Chem. Soc*., **1965**, 2009-2018.
[19] RC Cookson; MJ Nye; G Subrahmanyam, *J. Chem. Soc*., **1967**, (C), 473-479.
[20] HMR Hoffmann; KE Clemens; EA Schmidt; RH Smithers, *J. Am. Chem. Soc*., **1972**, 94 (9), 3201-3204.
[21] HMR Hoffmann; MN Iqbal, *Tetrahedron Lett*., **1975**,16(50), 4487-4490.
[22] R Noyori; Y Baba; S Makino; H Takaya, *Tetrahedron Lett*., **1973**, 1741-1774.
[23] T Sato; R Noyori, *Bulletin of the Chemical Society of Japan*., **1978**, 51(9), 2745-2746.
[24] R Noyori; F Shimizu; Y Hayakawa, *Tetrahedron Lett*., **1978**, 2091-2094.
[25] M Harmata, *Chem. Commun*., **2010**, (46), 8904-8922.
[26] M Harmata, *Chem. Commun*., **2010**, (46), 8886–8903.
[27] G Kreiselmeier; B Föhlisch, *Molbank*., **2004**, M390.
[28] H Meining; B Föhlisch, *Molbank*., **2005**, M409, 1-2.
[29] G Kreiselmeier; S Menner; B Föhlisch, *Molbank*., **2005**, M406, 1-2.
[30] B Föhlisch; S Reiner, *Molecules*., **2004**, (9), 1-10.
[31] J Mann; AA Usmani, *J. Chem. Soc. Chem. Comm*., **1980**, 1119.
[32] J Mann; PD Wilde; MW Finch, *J. Chem. Soc. Chem. Comm*., **1985**, 1543-1544.
[33] J Mann, *Tetrahedron*., **1986**, (42), 4611-4659.
[34] J Mann; HJ Holland, *Tetrahedron*., **1987**, 43 (11), 2533-2542.
[35] J Mann; LCA Barbosa, *J. Chem. Soc, Perkin Trans*., **1992**, (1), 787-790.
[36] LCA Barbosa; AJ Demuner; J Mann; D P Veloso, *J. Chem. Soc*., **1993**, (1), 585-587.
[37] LCA Barbosa; J Mann, *Synthesis*., **1996**, 31-33.
[38] KG Owers; J Mann; AJ Markson, *Journal of Chemical Research. Synopses*., **1986**, (4), 24-425.
[39] AJ Demuner; LCA Barbosa, *Applications Organic Synthesis, New Chemistry*., **1997**, 20(1), 18-29.
[40] H Takaya; S Makino; Y Hayakawa; R Noyori, *J. Am. Chem. Soc*., **1978**, (100), 1765-1777.
[41] R Noyori; S Makino; T Okita; Y Hayakawa, *J. Org. Chem*., **1975**, 40(6), 806-807.
[42] R Noyori; S Makino; Y Baba; Y Hayakawa, *Tetrahedron Letters*., **1974**, (12), 1049-1050.
[43] R Noyori, *Annals New York Academy of Sciences*., **1977**, (295), 225-238.
[44] AJ Demuner; LCA Barbosa; DP Veloso, *J. Agric. Food Chem*., **1998**, (46), 1173-1176.
[45] AOS Abd El-Wareth, *Monatshefte Fut Chemie*., **1999**, (130), 563-572.
[46] LCA Barbosa; LB Nogueira; CRÁ Maltha; RR Teixeira; AA Silva, *Molecules*., **2009**, (14), 160-173.
[47] FC Chaves; LCA Barbosa; AJ Demuner; AA Silva; *Verlag der Zeitschrift fur Naturforschung.*, **2006**, 1287-1294
[48] R Noyori; Y Hayamawa; M Funakura; H Takaya; S Murai, R Kobayashi; S Tsutsumi, *J. Am. Chem. Soc*., **1972**, (94), 7202-7204.
[49] L Yafan, *University of Windsor, Ontario, Canada*., **2001**, 1-6.
[50] G Fierz; R Chidgey; HMR Hoffmann, *Angew. Chem. Int. Ed. Engl*., **1974**, (13), 410-411.
[51] AOS Abd El-Wareth; HMR Hoffmann, *European Journal of Inorganic Chemistry*., **1994**, (127), 1755-1760.
[52] RJ Giguere; DI Rawson; HMR Hoffmann, *Synthesis Stuttg*., **1978**, (12), 902-905.
[53] AOS Abd El-Wareth, *J. Chem. Res*., **1999**, (S), 24-25.
[54] HMR Hoffmann; U Karama, *Chem. Ber*., **1992**, (125), 2803-2807.
[55] U Karama; HMR Hoffmann, *Chem. Ber*., **1992**, (125), 2809-2812.
[56] HMR Hoffmann; U Karama, Chem. Ber., **1992**, (125), 2803-2807.
[57] U Karama; A Al-Saeedi; AR Almansour, *Journal of Chemical Research*., **2010**, 241-242.
[58] SA Hardinger; C Bayne; E Kantorowski; R McClellan, L Larres; N Mary-Ann, *J. Org. Chem*; **1995**, 60(5), 1104-1105.
[59] F Hans-Werner, *Chem. Rev*., **1997**, (97), 523-596.