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Mini-Account

Studies on regioselective addition of benzylic organometallics to α-oxoketene dithioacetals in our aromatic annelation protocol

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Dedicated to Professor Jean Normant on the occasion of his 65th birthday

Abstract

The α-oxoketene dithioacetals derived from various acyclic and cyclic active methylene ketones are shown to undergo either 1,2- or sequential 1,4- and 1,2-addition with various substituted benzylic Grignard reagents (or benzyl lithium) and 1-/2-(naphthylmethyl) Grignard reagents to give carbinol adducts which on facile $BF_3.Et_2O$ induced cycloaromatization afford a variety of substituted naphthalenes, phenanthrenes and other condensed aromatics. This methodology has emerged as a versatile tool for the regioselective construction of aromatic ring via [3 + 3] annulation from readily available acyclic precursors. The various substituted benzylic Grignard reagents (or benzyl lithium) and the corresponding 1- and 2-(naphthylmethyl) reagents display diverse regioselectivity in these reactions via either 1,2-addition or sequential 1,4- and 1,2-addition depending on the substituents in the benzylic moiety, nature of the metal and the substrate oxoketene dithioacetals. The benzylic organocopper reagents undergo regioselective conjugate addition-displacement to give β-benzyl-β-methylthiomethylene ketones while the corresponding alkoxy substituted benzyl organocopper reagents gave unexpected results under these conditions. An attempt has been made to generalize some of these observations in terms of charge control 1,2- and orbital control 1,4-addition, although theoretical studies are needed to throw further light for better understanding of these results.

Keywords: α-Oxoketene dithioacetals; Naphthoannelation; Benzylic Grignard reagents; Condensed aromatics

1. Introduction

Development of efficient methods for the synthesis of substituted aromatic compounds has attracted interest of organic chemists since the beginning of the last century. Classical approaches to aromatic compounds generally involve readily accessible benzene derivatives or their condensed derivatives through their electrophilic and nucleophilic substitution reactions. Important modern methods for the synthesis of substituted aromatic compounds involve highly convergent annulation routes in which aromatic system is assembled from acyclic precursors in a single step. Particularly noteworthy aromatic annulation reactions [1] developed in recent years include methods based on Diels Alder chemistry [2], carbonyl condensation [3], Robinson annelation reactions [4], ring expansion of cyclobutenones [5], transition metal mediated Fischer carbene complexes [6] and cobalt mediated [2 + 2 + 2] cycloadditions [7], etc.

We first reported [8] in 1984 the reaction of allylmagnesium chloride with α-oxoketene dithioacetals of the general formula **1** (Scheme 1) to afford the corresponding carbinol acetals **2** in highly regioselective manner. These carbinol acetals were shown to undergo facile $BF_3.Et_2O$ assisted cycloaromatization to furnish the corresponding benzoannelated products **3** in high yields. This new method of constructing benzene ring from open chain three-carbon precursors, each with

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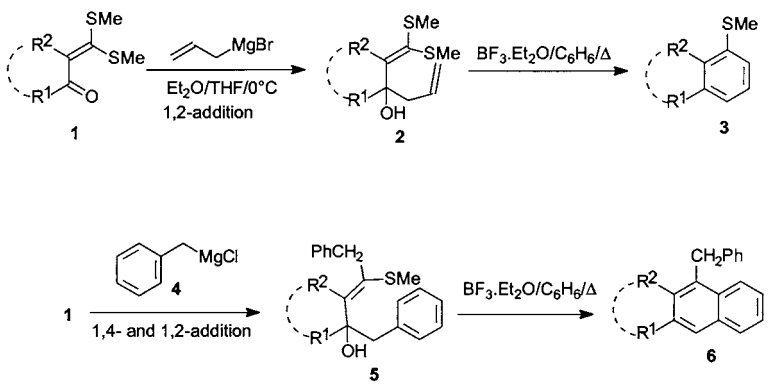
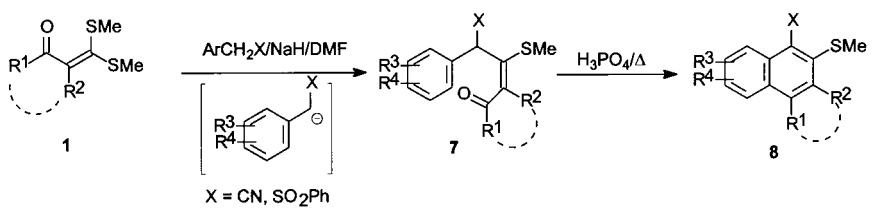
matching 1,3-bielectrophilic and binucleophilic sites proved to be highly versatile for benzoannelation of active methylene ketones via α-oxoketene dithioacetals. The reaction is first of its kind along with those reported by Tius [9] and others [10] in which a benzene ring is efficiently constructed via intramolecular cationic cyclization of an acyclic carbinol precursor. The method has been extensively investigated in our laboratory [11] to establish its generality encompassing a wide structural variants of both allyl anions and α-oxoketene dithioacetals **1** which are being added continuously to enrich the scope of the method. The methodology is equally facile for the regiocontrolled synthesis of heteroaromatics where we can use easily accessible preconstructed five or six membered heterocycles over which we can annelate the benzene ring or its condensed variants [12]. This can be achieved either by employing α-oxoketene dithioacetals (1,3-bielectrophilic components) derived from heterocyclic ketones or the corresponding heterocyclic analogs of benzylic anions (1,3-binucleophilic components) in aromatic annelation protocol as the case may be [12]. Interestingly different allyl anions displayed different regiocontrolled addition pattern with **1** yielding either 1,2-adducts or sequential 1,4- followed by 1,2-addition or exclusively 1,4-addition elimination products. Thus the allyl anions generally followed 1,2-addition to **1** to afford the corresponding carbinol acetals **2** in quantitative yields [8], while the benzylmagnesium halide **4** followed sequential 1,4- and 1,2- addition mode yielding the corresponding benzyl substituted carbinols **5** [13]. Both the carbinol acetals **2** and **5** underwent a facile $BF_3.Et_2O$ assisted cyclization to afford either the methylthio- (**3**) or benzyl- (**6**) substituted aromatics in high yields [8,13]. The third category of regiocontrolled addition was the reaction of benzylcopper reagents with **1** which yielded exclusively conjugate addition-displacement products **50** in excellent yields (Scheme 8) [14a]. Also the stabilized benzyl carbanions derived from arylacetonitriles or benzyl phenyl sulphones also reacted with **1** to afford only conjugate addition-displacement products **7** in quantitative yields (Scheme 2). Some of these intermediates are shown to undergo facile acid promoted cyclization to afford corresponding naphthalenes and their condensed variants **8** [15]. We have thus observed interesting regioselectivity profile of various benzylic and the corresponding 1- and 2-(naphthylmethyl) anions with **1** furnishing addition products, all of which are precursors to the respective aromatic systems. In the present article we give a brief account of this investigation.

2. Addition of benzylic and 1-/2-(naphthylmethyl) Grignard reagents and benzyl lithium to α-oxoketene dithioacetals

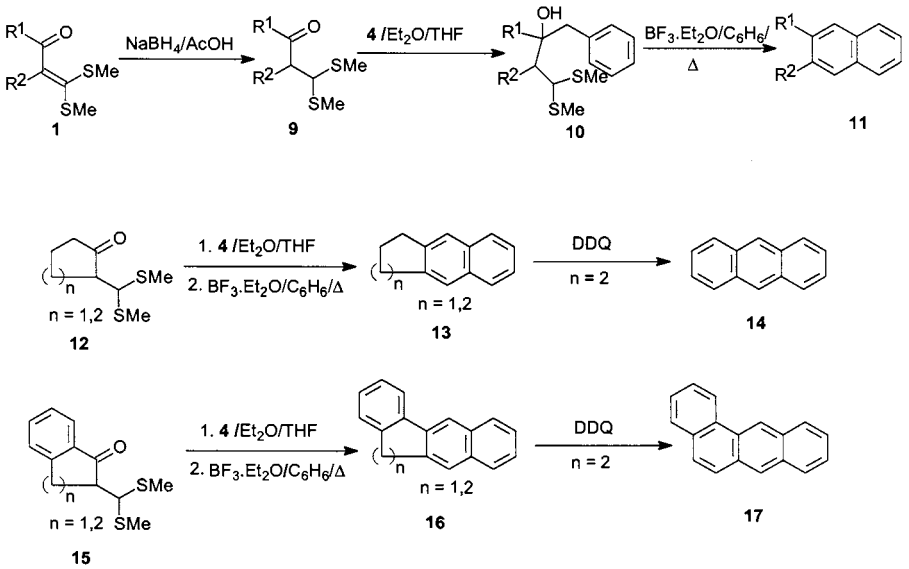
A few representative α-oxoketene dithioacetals derived from acyclic and cyclic ketones employed in these studies are shown in Chart 1. It was generally observed that the benzylic Grignard reagent followed sequential 1,4- and 1,2-addition mode when reacted with **1** (Scheme 1) [13]. The initial 1,4-addition step was attributed in terms of hard-soft matching principle of participating 1,3-bielectrophilic (α-oxoketene dithioac-



Scheme 1.



Scheme 2.



Scheme 3.

etals) and 1,3-binucleophilic (benzyl anions) components. Thus the reaction of benzylmagnesium chloride **4** with **1** generally yielded the corresponding benzyl substituted naphthalenes **6** and their condensed variants depending on the nature of **1**. This problem was circumvented by reacting benzyl Grignard reagents **4** with the β-oxodithioacetals **9** to afford the respective carbinols **10** which were cyclized in the presence of lewis acid to afford the corresponding substituted naphthalenes **11** and their condensed variants without unwanted benzyl group (Scheme 3) [16]. Also the product naphthalenes did not contain the methylthio group and the yields of theses naphthalenes were generally high. The required β-oxodithioacetals **9** were conveniently prepared in good yields by subjecting **1** to reduction in the presence of $NaBH_4$ in AcOH according to the procedure developed in our laboratory [17]. Making use of this alternative method, the polycyclic hydrocarbons such as anthracene **14**, benzo[*a*]anthracene **17** and a number of other variants of these aromatic hydrocarbons were prepared (Scheme 3) [16].

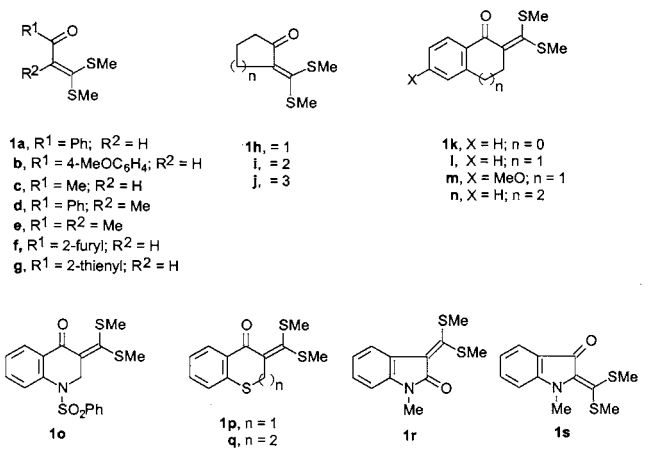
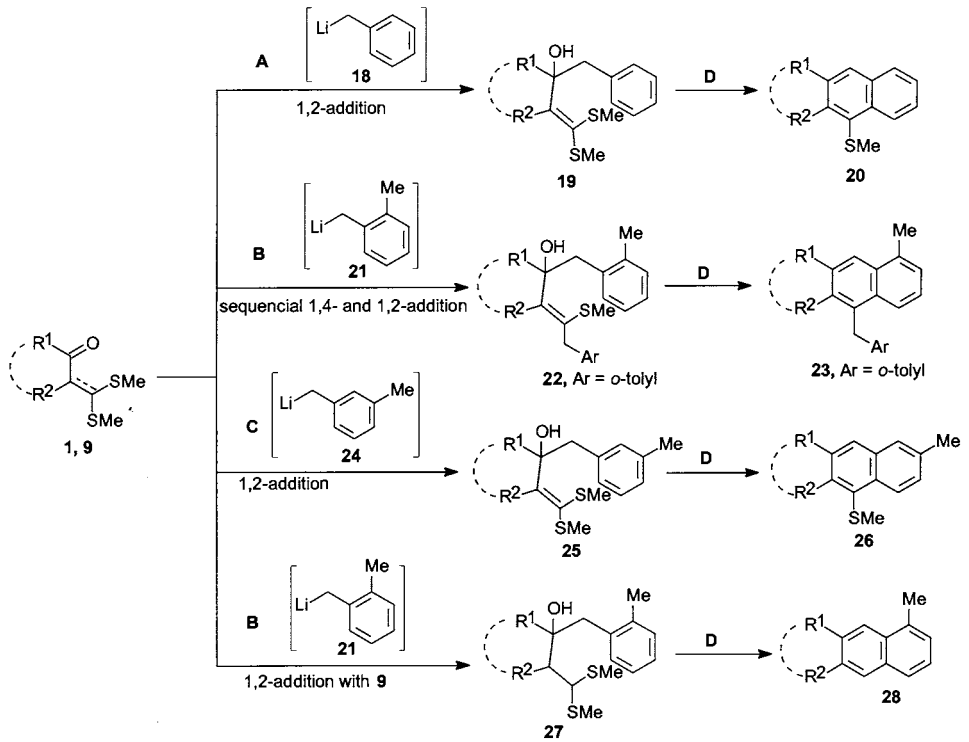


Chart 1.

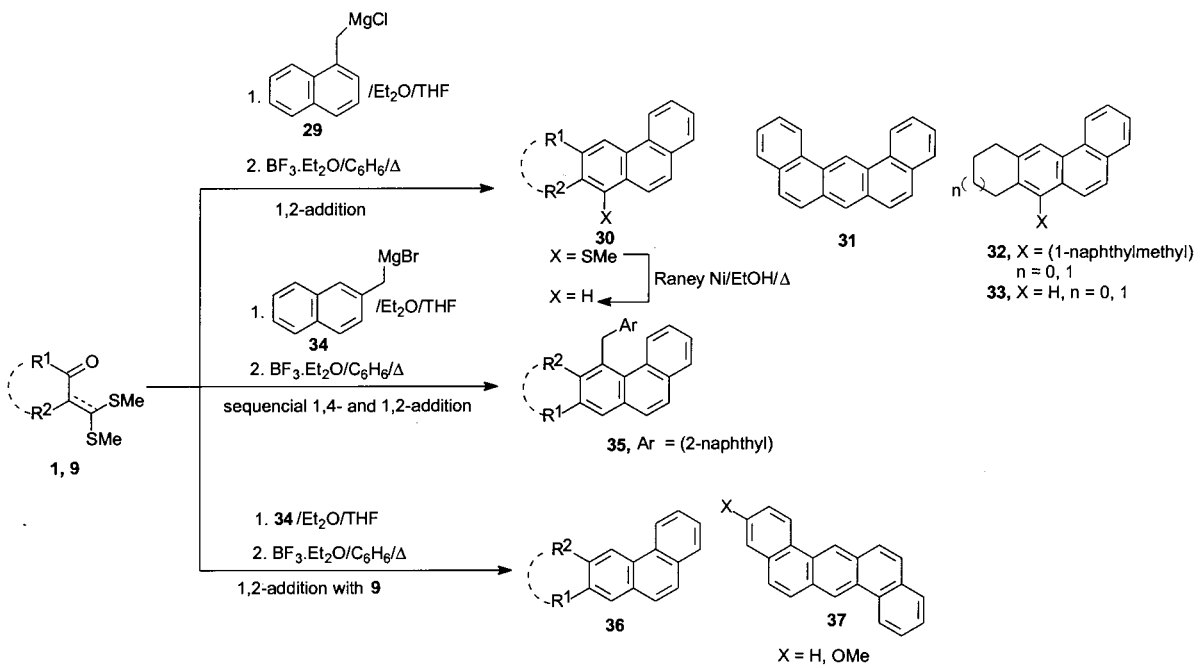
When lithiomethylbenzene **18** instead of benzylmagnesium chloride was reacted with **1**, surprisingly, the reaction followed exclusively 1,2-addition mode to afford the carbinol acetals **19** in high yields [18]. These acetals when cyclized as described above, yielded the corresponding methylthionaphthalenes **20** in good yields (Scheme 4). This selectivity was observed with many systems with a few exceptions [18b]. However the cycloaromatization of *o*-xylyllithium **21** with **1** afforded the corresponding *o*-xylyl substituted naphthalenes **23** following sequential 1,4- and 1,2-addition mode [18]. On the other hand, metallated *m*-xylene **24** followed exclusive 1,2-addition to afford the corresponding methylthionaphthalene **26** through carbinol acetals **25** [18]. Similarly the methylthio free naphthalenes **28** were obtained when the anion **21** from *o*-xylene was reacted with the corresponding β-oxodithioacetals **9** (Scheme 4) [18].

Interestingly when **1** was subjected to addition cycloaromatization with 1-(naphthylmethyl) Grignard reagent **29**, the formation of only methylthio substituted phenanthrene **30** was observed thus demonstrating exclusively 1,2-addition mode in the first addition step (Scheme 5) [16]. A number of α-oxoketene dithioacetals were reacted with this reagent which followed exclusively 1,2-addition mode and the condensed polycyclic aromatic systems such as dibenz[*a*,*j*]-anthracene **31** were prepared by this method [16,19]. However 1-(naphthylmethyl) Grignard reagent **29** followed sequential 1,4- and 1,2-addition mode when added to α-oxoketene dithioacetals **1h** and **1i** derived from cyclopentanone and cyclohexanone respectively (Chart 1) to afford only the corresponding (1-naphthylmethyl) substituted-2,3-cycloalkanophenanthrenes **32** in good yields [16]. Again this problem was circumvented

by reacting the required 1-(naphthylmethyl) Grignard reagent **29** with β-oxodithioacetals **9** derived from cyclopentanone and cyclohexanone to afford unsubstituted 2,3-cycloalknophenanthrenes **33** in good yields (Scheme 5) [16,19]. Cycloaromatization of 2-(naphthylmethyl) Grignard reagent **34** with **1**, on the other hand



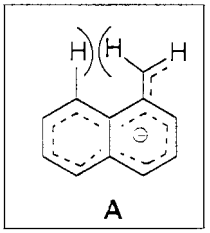
Scheme 4. Reaction conditions: A = Toluene/*n*-BuLi/TMEDA/110°C; B = *o*-Xylene/*n*-BuLi/TMEDA/THF/110°C; C = *m*-Xylene/*n*-BuLi/TMEDA/THF/110°C; D = $BF_3{\cdot}Et_2O/C_6H_6/\Delta$.



Scheme 5.

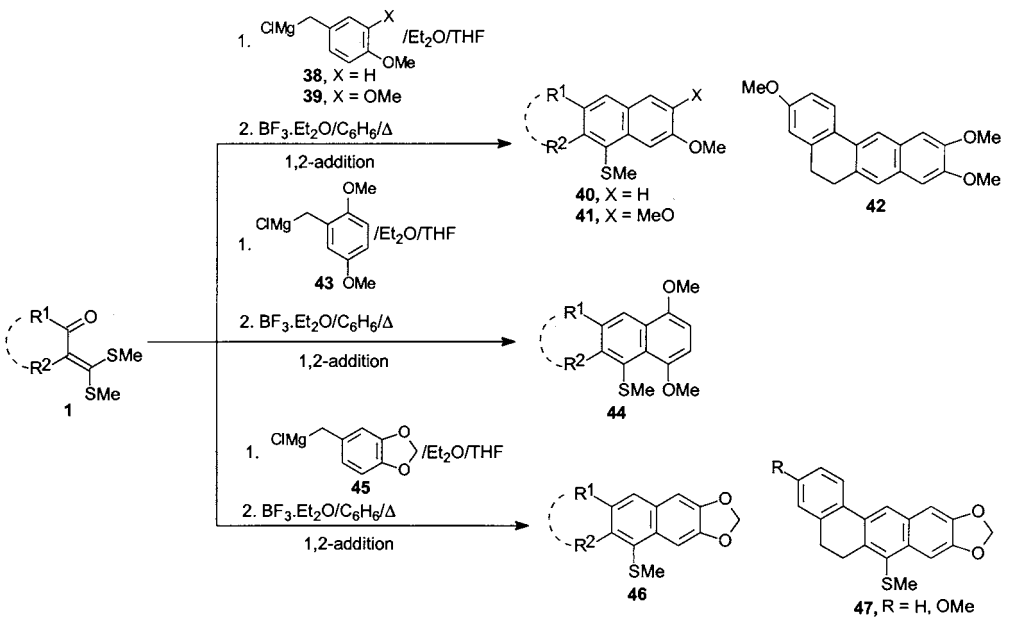
followed exclusive 1,4- and 1,2-addition sequence with both acyclic and cyclic ketene dithioacetals with a few exceptions thus furnishing only (2-naphthylmethyl) substituted phenanthrenes **35** and no trace of 1,2-addition products were detected in these reactions (Scheme 5) [16]. Here again the corresponding 2-(naphthylmethyl) free phenanthrenes **36** were obtained by reacting Grignard reagent **32** with β-oxodithioacetals **9**. Polycyclic hydrocarbons such as dibenzo[*a*,*h*]anthracene **37** and the related condensed aromatics were prepared using this approach (Scheme 5) [16,19].

It is necessary to understand these reaction modes. Unlike benzylic Grignard reagent the lithiomethylbenzene **18** follows exclusive 1,2-addition mode that appears to be due to tightly held lithiobenzylic anion supporting the charge controlled 1,2-addition mode. Alternatively the observed regioselectivity in the addition of **18** may possibly be due to complexation between lithium and the carbonyl group of oxoketene dithioacetals thus leading to exclusive 1,2-addition. however this binding protocol appears to be disturbed due to steric reasons in the case of *o*-xylyllithium **21** which follows sequential 1,4- and 1,2-addition mode. The anions in the absence of such steric factors as in *m*-xylyllithium **24** followed 1,2-addition with **1** to afford the corresponding methylthionaphthalenes **26** (Scheme 4). Similarly, the delocalization of charge over aromatic ring in 1-(naphthylmethyl) Grignard reagent **29** will push the two exocyclic methylene hydrogen atoms in the plane of the naphthalene ring, which is resisted by the *peri* hydrogen due to steric interaction (Structure **A**) [16].

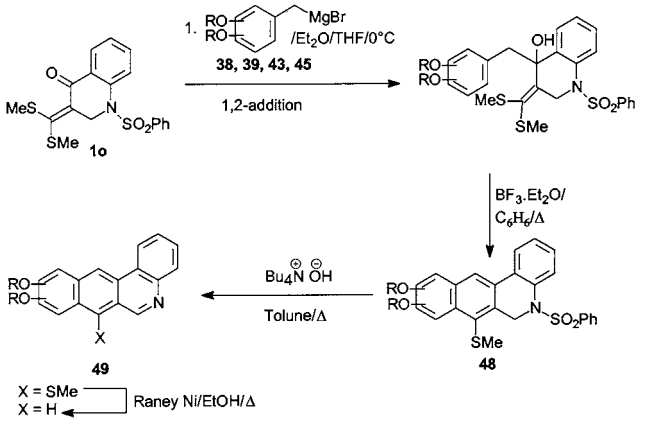


Therefore the charge in 1-(naphthylmethyl) Grignard reagent **29** is likely to stay largely on exocyclic methylene carbon atom facilitating charge control 1,2-addition mode thus accounting for the formation of methylthio substituted phenanthrenes **30** (Scheme 5) [20]. The reaction of **29** with other α-oxoketene dithioacetals also followed the same 1,2-addition mode with only a few exceptions. It was then considered logical to examine the reactivity of 2-(naphthylmethyl) Grignard reagent **34** with **1** which in the absence of steric constraints such as in **29** follows sequential 1,4- and 1,2-addition mode to afford the corresponding phenanthrenes **35** and any of its condensed variants with 2-(naphthylmethyl) substituents in place of methylthio group (Scheme 5). This was again in accordance with the soft nucleophilic interaction of **34** due to unhindered resonance interaction of the charge on exocyclic methylene carbon with the naphthalene ring (Scheme 5) [16].

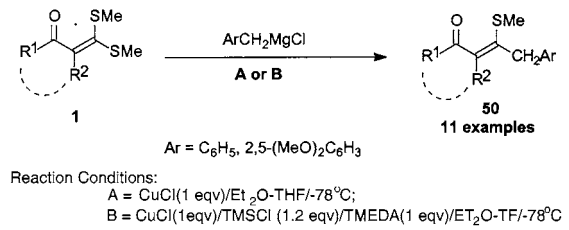
These results led us to further investigate the problem of regioselectivity by selecting benzylic Grignard reagents with strong electron donating substituents such as alkoxy groups which will resist resonance charge distribution from the exocyclic benzylic carbon into the ring and should facilitate charge controlled 1,2-addition mode to afford the corresponding alkoxy



Scheme 6.



Scheme 7.



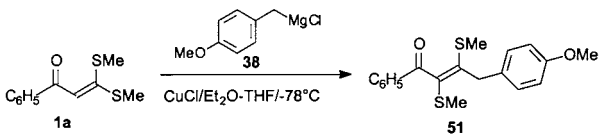
Scheme 8. Reaction conditions: A = CuCl (1 equiv.)/Et_2O–THF/ − 78°C; B = CuCl (1 equiv.)/TMSCl (1.2 equiv.)/TMEDA (1 equiv.)/ Et_2O–THF/ − 78°C.

substituted naphthalenes and their condensed variants. Thus the addition of 4-methoxybenzyl Grignard reagent **38** with **1** followed exclusively 1,2-addition mode yielding the corresponding methoxy substituted methylthionaphthalenes **40** in good yields (Scheme 6) [21]. The 3,4-dimethoxybenzyl Grignard reagent **39** also followed 1,2-addition mode and reacted with various α-oxoketene dithioacetals such as derived from 6-methoxytetralone to give the benzo[*a*]dihydroanthracene **42** in good yield (Scheme 6) [21]. The trend of these reactions was uniform with 1,2-addition mode when other dioxygenated benzyl Grignard reagents were reacted with **1**. Thus 2,5-dimethoxy benzyl Grignard reagent **43** reacted with various α-oxoketene dithioacetals **1** to afford the corresponding 1,4-dimethoxynaphthalenes **44** in excellent yields (Scheme 6) [22]. Similarly the 3,4-methylenedioxybenzyl Grignard reagent **45** also followed the same trend furnishing the corresponding linearly dioxygenated naphthalenes **46** and its condensed variants **47** in excellent yields [21]. This 1,2-addition and cycloaromatization methodology mediated by alkoxybenzyl Grignard reagents provides a facile regiocontrolled synthesis of substituted and condensed alkoxynaphthalenes which constitute structural frameworks of many naturally occuring compounds such as lignans, naphthoquinone and anthracyclines, etc.

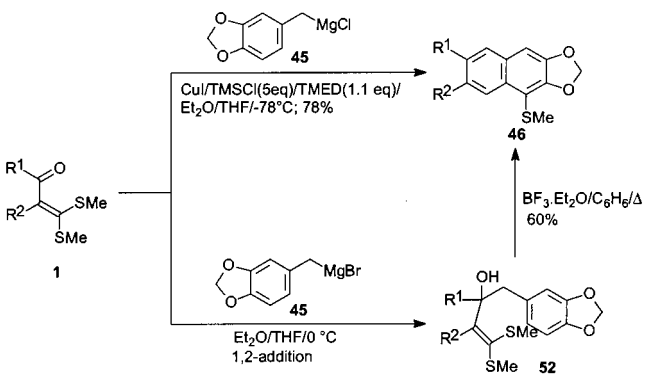
The methodology could further be extended for an efficient synthesis of a variety of benzo[*j*]phenanthridines **49** by addition of oxygenated benzyl Grignard reagents to α-oxoketene dithioacetal **1o** derived from *N*-benzylsulphonyl-1,2,3,4-tetrahydroquinolin-4-one in an exclusively 1,2-addition mode followed by subsequent cycloaromatization (Scheme 7) [23].

3. Addition of benzylic copper reagents to α-oxoketene dithioacetals

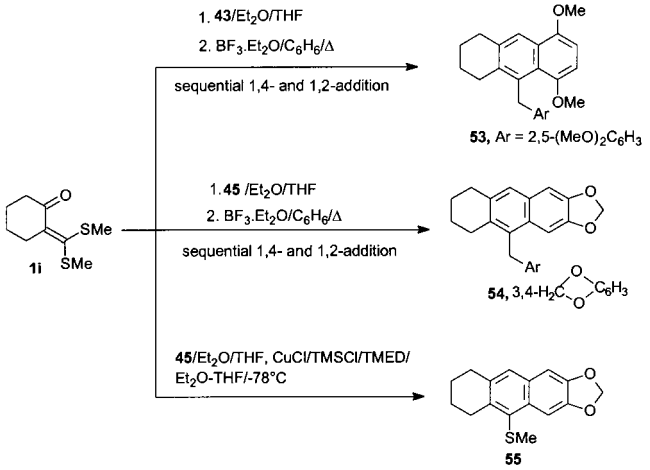
The organocopper reagents derived from benzylic Grignard reagents and Cu(I) halides followed the expected conjugate addition-displacement mode to yield β-benzyl-β-methylthiomethylene ketones **50** in highly regio- and stereoselective fashion (Scheme 8) [14a]. Interestingly the alkoxybenzyl Grignard reagents gave unexpected and diverse results when reacted with **1** in the presence Cu(I) halides. Thus the 2,5-dimethoxybenzyl Grignard reagent **43** in the presence of Cu(I) halide underwent the expected conjugate addition-displacement to afford β-benzyl-β-methylthiomethylene ketones **50** [Ar = 2,5-$(MeO)_2$-C_6H_3], the corresponding 4-methoxybenzyl Grignard reagent **38** on the other hand yielded an unexpected rearranged product **51** with **1a** in the presence of cuprous chloride (Scheme 9) [24]. Surprisingly when 3,4-methylenedioxybenzyl Grignard reagent **45** was reacted with **1** in the presence of Cu(I) halide under the standard reaction conditions, the product isolated was found to be **46** identical with that obtained earlier via two steps 1,2-addition-cycloaromatization with **45** in the absence of Cu(I) salt (Scheme 10) [24]. This unexpected Cu(I) halide promoted one pot addition-cycloaromatization with **45** proved to be gen-



Scheme 9.



Scheme 10.



Scheme 11.

eral with other α-oxoketene dithioacetals studied and furnished naphthoannelated products in good yields (Scheme 10) [24]. Surprisingly α-oxoketene dithioacetal **1i** derived from cyclohexanone which has consistently yielded sequential 1,4- and 1,2-addition products with most of the benzylic and naphthylic Grignard reagents, gave directly the tetrahydromethylenedioxyanthracene **55** via 1,2-addition when reacted with **45** in the presence of Cu(I) iodide. Thus the α-oxoketene dithioacetal **1i** displays some unique properties in these reactions as shown in Scheme 11 [21,22,24].

4. Conclusions

We have described in this short account the diverse regioselectivity profile of the few benzylic organometallics (benzylic, 1-/2-(naphthylmethyl) Grignard reagents, benzyl lithium, benzylic copper reagents) observed in their addition to various α-oxoketene dithioacetals during our cycloaromatization studies with these substrates. An attempt has been made to generalize few of these observations in terms of charge control 1,2- and orbital control 1,4-addition although answer to the diverse reactivities of benzylic organometallics appears to be not straightforward. Theoreticians and more experienced organometallic chemists may throw further light for better understanding of these reactions.

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