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Effect of Varying the Anionic Component of a Copper(I) Catalyst on Homologation of Arylacetylenes to Allenes by the Mannich Reaction

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The effect of varying the anionic component of a copper(I) catalyst in the homologation of terminal arylacetylenes to allenes by the Mannich reaction was investigated. Varying amounts of allenes, Mannich bases and dimers were obtained depending on the nature of the anionic component of the copper catalyst. On the other hand, Eglinton–Glaser dimerizations were achieved in high yields with 0.5 equiv. of triethylamine.

Introduction

The two cumulated double bonds of allenes represent a versatile functional group that can be utilized in a variety of synthetic transformations, leading to complex structures that are useful for constructing natural and nonnatural products.[1] The versatility and synthetic utility of the allene moiety in organic chemistry have been extensively documented in the recent literature. For instance, allenes participate in a variety of cycloaddition and electrocyclic reactions affording products such as sterpurenes that are not easily accessible by other synthetic methods.[2,3] In addition, the allene moiety can be transformed into a variety of other functional groups such as olefins, α,β-unsaturated carbonyl compounds and alkynes.[4] Moreover, allene axial chirality has been used to transfer asymmetry in cycloaddition reactions.[5]

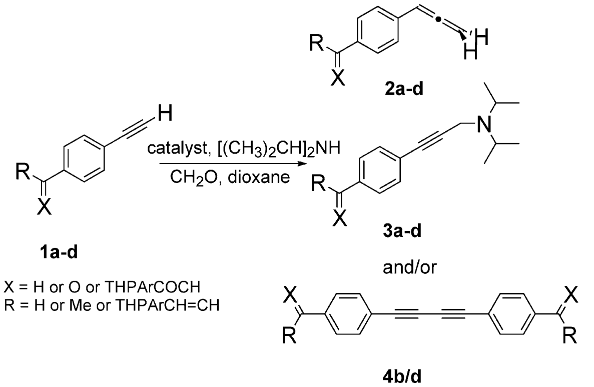
Allenes have also received considerable attention due to the discovery of interesting biological properties[6,7] as well as to the development of improved synthetic methods.

Homologation of acetylenes to allenes by the Mannich reaction has been previously reported.[8–13] However, these reports have only addressed a limited range of acetylene systems. In addition, effects of the nature of aryl substituents as well as variation of the catalyst component on the pattern of product and yield distribution have to date not been investigated.

Results and Discussion

Our interest in the synthesis of biologically active aryl acetylenic Mannich bases led us to explore the homologation of aryl acetylenes to allenes. In this letter, we report the effect of varying the anionic component of the copper(I) catalyst and the nature of the aryl substituent on the product and yield distribution.

The synthesis of allenes from terminal alkynes was attempted by employing various sources of copper(I) catalyst with different anionic components. Initially, the arylacetylenes **1a**, **1b**, **1c**, and **1d** were treated with diisopropylamine and paraformaldehyde in the presence of Cu^IBr under modified reaction conditions described by Crabbe and coworkers to afford the allenes **2a**–**d**, the Mannich bases **3a**–**d** and homocoupling products **4b** and **4d** (Scheme 1). The results are presented in Table 1.



Scheme 1. Cu^I-catalyst-mediated reaction of arylacetylene **1a**–**1d** with paraformaldehyde, *N*,*N*-diisopropylamine in dry dioxane.

The reactions were repeated in the presence of $Cu^{II}Cl$ as a source of Cu^I. A similar product and yield distribution as those with Cu^IBr were obtained. When the source of Cu^I

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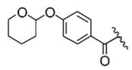
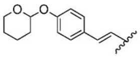
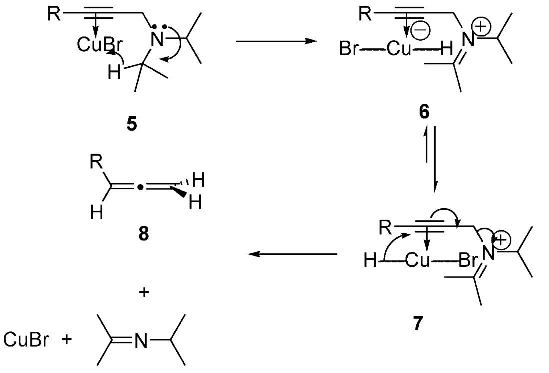
Table 1. $Cu^IBr/Cu^{II}Cl/Cu^{II}OAc$-catalyzed reaction of **1a**–**d** with diisopropylamine and paraformaldehyde.

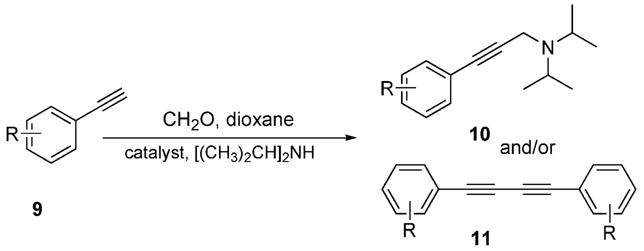
	R	X	Catalyst source	Products (% yield)
1a	H	O	Cu(I)Br	**2a** (14) **3a** (58) –
			Cu(II)Cl	**2a** (16) **3a** (51) –
			Cu(II)OAc	**3a** (63) –
1b	Me	O	Cu(I)Br	**2b** (35) **3b** (24) **4b** (11)
			Cu(II)Cl	**2b** (29) **3b** (27) **4b** (7)
			Cu(II)OAc	**3b** (36) **4b** (21)
1c	H		Cu(I)Br	**2c** (30) **3c** (20) –
			Cu(II)Cl	**2c** (34) **3c** (18) –
			Cu(II)OAc	**3c** (97) –
1d		O	Cu(I)Br	**2d** (12) **3d** (36) **4d** (13)
			Cu(II)Cl	**2d** (20) **d** (47) **4d** (8)
			Cu(II)OAc	**3d** (42) **4d** (30)

was substituted by $Cu^{II}OAc$, only the Mannich bases **3a**–**d** and homocoupling products **4b** and **4d** were obtained as products. From the results in Table 1, it is clear that the product and yield distribution are influenced by both the anionic component of the catalyst and the nature of the aryl substituent. Comparable yields are obtained for catalysts [(CuBr and $Cu^{II}Cl$)] which gave same product composition. The different behaviour of aldehyde **1a** and ketone **1b** was somewhat surprising with the former not giving any dimerization product. The stronger electron-withdrawing effect of the aldehyde carbonyl in **1a** may lead to weaker complexation with the Cu^I ion and hence a slower rate of dimerization due to a decrease in nucleophilicity of the intermediate acetylide ion. This is contrast to **1b** in which the possible existence of the ketone in enolic form under the reaction conditions may lead to stronger complexation with the Cu^I ion. The absence of allenes from copper(II)-acetate-catalyzed reactions may be explained by considering the mechanism for the formation of allenes from Mannich bases. The mechanism involves an intramolecular transfer of an α-hydrogen atom in an *N*-alkyl group of the intermediate Mannich base, to the carbon terminus of the allene. First, the copper(I) forms a 1:1 π complex **5** with the Mannich base in which the hydrogen is well positioned to be lost from the α-position of an isopropyl group (Scheme 2). Hydride ion shift occurs to give a hydridocopper(I) complex **6** which is similar to the cuprate complex as postulated by Pasto and co-workers for the reaction of a lithium cuprate with prop-2-ynylic halides.[14] Then, rotation of the copper atom takes place making the hydrogen available for transfer to the R-substituted terminus of the alkyne and electronic shifts to the allene **8**, thus releasing the diisopropylimine and the catalyst. Formation of **7** (Scheme 2) may not have occurred due to structural reasons (steric effects) when the acetate ion is the anionic component of the copper(I) catalyst generated in situ. The bulky carboxylate ion may have prevented rotation of the copper atom from delivering the hydrogen in a favorable position for transfer to the R-substituted terminus of the alkyne. On the other hand the absence of homocoupling products when the aryl acetylenic component is attached to the β-carbon of the α,β-unsaturated carbonyl system may be explained on electronic grounds. In studies carried out by Bohlmann et al.[15] on the rate of dimerization as influenced by the electronic nature of conjugated acetylenes, they found that more acidic acetylenes underwent more rapid dimerization under alkaline conditions, which was consistent with results obtained by Klebansky et al.[16] However, under acidic conditions, an inverse relationship was observed, and addition of a copper(I) salt became necessary. This is also in a agreement with the recent results obtained by Balcioglu et al.[17]



Scheme 2. Mechanism of allene formation in CuBr-catalyzed reactions.

In order to investigate the generality of our initial observations, the reactions were investigated with a diverse range of simple substituted aryl acetylenes. The reaction of the acetylenes **9** with paraformaldehyde and diisopropylamine in the presence of Cu^IBr as catalyst in refluxing dry dioxane led to the exclusive formation of the corresponding Mannich adducts with no traces of the homologated product or allenes as evidenced by their crude ^1H and ^{13}C spectroscopic data (Scheme 3). Similar trends in yields as well as the product distribution were observed using $Cu^{II}Cl$ as catalyst (Table 2).



R = H, *p*-CH_3, *p*-Br, *p*-OCH_3, *o*-OCH_3, *p*-CN, *o*-NO_2

Scheme 3. Cu^I-catalyst-mediated reaction of arylacetylene **9a**–**9g** with paraformaldehyde, *N*,*N*-diisopropylamine in dry dioxane.

However, when the above reactions were carried out using $Cu(OAc)_2$, formation of Mannich adducts was accompanied by concomitant homologation (Scheme 3). The product distribution depended upon the nature of the substituent on the aromatic ring of aryl acetylenes with the better yields of the homologated adducts being obtained with the introduction of electron-donating substituents (Table 3).

Table 2. Cu^IBr- and $Cu^{II}Cl$-catalyzed reaction of **9a**–**g** with diisopropylamine and paraformaldehyde.

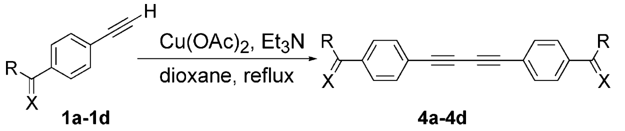
	R	Products (% yield) Cu^IBr	$Cu^{II}Cl$
9a	H	**10a** (82)	**10a** (80)
9b	p-CH_3	**10b** (86)	**10b** (78)
9c	Br	**10c** (73)	**10c** (74)
9d	p-OCH_3	**10d** (78)	**10d** (71)
9e	o-OCH_3	**10e** (75)	**10e** (69)
9f	o-NO_2	**10f** (68)	**10f** (71)
9g	p-CN	**10g** (69)	**10g** (65)

Table 3. $Cu(OAc)_2$-catalyzed reaction of **9a**–**g** with diisopropylamine and paraformaldehyde.

Compd.	R	Products (% yield)	
9a	H	**10a** (57)	**11a** (21)
9b	p-CH_3	**10b** (61)	**11b** (19)
9c	p-Br	**10c** (60)	**11c** (16)
9d	o-OCH_3	**10d** (54)	**11d** (26)
9e	p-OCH_3	**10e** (51)	**11e** (23)
9f	o-NO_2	**10f** (64)	**11f** (12)
9g	p-CN	**10g** (62)	**11g** (13)

Because the mechanism (Scheme 2) involves the formation of a π complex between Cu^I ion and the triple bond, thus activating the alkyne toward deprotonation by the amine to generate a copper acetylide, the low yields in the experiments involving electron-withdrawing groups may be due to the low nucleophilicity of the generated acetylides. The rate of reaction of substrates with electron-withdrawing groups attached to the aryl acetylenic component was slower than those with electron-donating groups. Because dimerization reactions were competing with Mannich base formation, the yields of homocoupling adducts were usually lower than for the corresponding Mannich base adducts. The absence of allene formation in these reactions is supported by earlier observations reported by Crabbé and coworkers in the homologation reactions of alk-1-ynes to allenes.[18] A remarkable decrease in the reactivity of alkynes with the introduction of phenyl substituent was reported. The reaction time had to be increased to 30 h in the conversion of phenyl acetylene to phenyl allene.

The trend in yield distribution was further addressed by embarking on a study of the dimerization reactions. First, the reaction conditions were optimized using **1b** as a model substrate in the presence of $Cu(OAc)_2$ as the catalyst and triethylamine as a base (Scheme 4). It was found that the use of 0.5 equiv. of $Cu(OAc)_2$ and 1.0 equiv. of triethylamine in dioxane effectively mediated formation of dimers even though prolonged reaction times were necessary (Table 4). Attempts to reduce the amount of $Cu(OAc)_2$ resulted in incomplete reactions. This result is worth noting because typical Eglinton–Glaser Cu-mediated reactions require an excess amount (10 equiv.) of $Cu(OAc)_2$ in the absence of dioxygen. The results are summarized in Table 4. As can be seen from Table 4, a similar trend in the yield distribution of homocoupling products was observed as those in Tables 1 and 3. Compounds **1a** and **1c** (with the aryl acetylenic component attached to β-carbon of the α,β-unsaturated carbonyl system) gave low yields compared to their counterparts **1b** and **1d**.



Scheme 4. Homodimerization reaction of **1a**–**1d**.

Table 4. $Cu(OAc)_2$-catalyzed dimerization of **1a**–**d**.

	Product (% yield)
1a	**4a** (32)
1b	**4b** (72)
1c	**4c** (62)
1d	**4d** (99)

Conclusions

In conclusion, the product composition depends on both the nature of the aryl substituent and the anionic component of the catalyst. Low yields of homocoupling products were obtained from substrates with electron-withdrawing groups due to weaker complexation with Cu^I ion which leads to slow formation of the homodimers compared to the Mannich bases. The yields of homocoupling products also decrease as the strength of the electron-withdrawing group increases due to the decrease in the nucleophilicity of the intermediate acetylide ion. On the other hand, the catalyst, $Cu(OAc)_2$, with a bulky nonlinear anionic component does not give allene products presumably because the carboxylate ion prevents rotation of the copper atom from delivering the hydrogen in a favorable position for transfer to the R-substituted terminus of the alkyne. $Cu(OAc)_2$ in the presence of 0.5 equiv. of triethylamine mediated the formation of homodimers in a superior manner to the typical Eglinton–Glaser coupling conditions.

Experimental Section

General Method for the Preparation of Compounds 2a–d, 3a–d, 4b and 4d: A mixture of acetylenic chalcone (1.0 mmol), paraformaldehyde (2.5 mmol), amine (2.0 mmol) and anhydrous cuprous bromide or cupric chloride (0.5 mmol) in dry 1,4-dioxane (5.0 mL) was heated under reflux at 100 °C for 3 h. The reaction mixture was cooled to room temperature and then filtered. The filtrate was poured into water and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated to give a light brown solid residue, which was subjected to column chromatography on silica gel (10% EtOAc/hexane and $MeOH/CHCl_3/17\%\ NH_4OH$, 2:2:1) to afford the title compounds **2a**–**d**, **3a**–**d**, **4b** and **4d**.

General Method for the Preparation of Compounds 10a–g and 11a–g: A mixture of aryl acetylene (1.0 mmol), paraformaldehyde (2.5 mmol), amine (2.0 mmol) and anhydrous cuprous bromide or cupric chloride or $Cu(OAc)_2$ (0.5 mmol) in dry 1,4-dioxane

(5.0 mL) was heated under reflux at 100 °C for 3 h. The reaction mixture was cooled to room temperature and then filtered. The filtrate was poured into water and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated to give a light brown solid residue, which was subjected to column chromatography on silica gel (5% EtOAc/hexane and 10% EtOAc/hexane) to afford the title compounds **10a**–**g** and **11a**–**g**.

Supporting Information (see also the footnote on the first page of this article): Experimental procedure and characterization data of all the compounds have been provided in the supporting information.

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