

Allylic Amination Promoted by Copper

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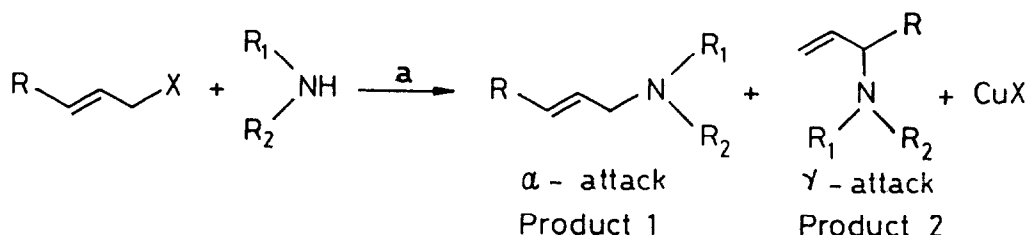
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Abstract: A mild method for the synthesis of allylic amines by using a mixture of copper(II) perchlorate and copper metal is described.

Allylic amines are important compounds found in many naturally occurring compounds such as gabaculin,¹ oryzoxymycin,² cytosinine.³ Development of easier and selective methods for synthesis of allylic amines merits thorough investigation,⁴ since direct reaction of allylic chlorides and amines require rather drastic conditions.¹⁰ Transition metal complexes of palladium are found to be most effective for selective processes, although complexes of iron,⁶ nickel,⁷ copper⁸ are also used for allylic amination. In our efforts to study the copper promoted allylic nucleophilic substitution⁹ we observed that a mixture of copper(II) perchlorate and copper metal powder can be used as a reagent for converting allylic halides to allylic amines. The copper promoted reactions proceeded under extremely mild conditions, and there were significant differences in the product ratios of the isomeric products formed when compared to other allylic aminations, making it unique.

When a mixture of an allylic halide and an amine is added to a mixture of copper(II) perchlorate hexahydrate and copper metal powder suspended in ether the corresponding allylic amine is formed and simultaneous precipitation of CuX occurs. The reaction is shown in scheme I. The order of the addition of the amine to copper(II) and copper(0) mixture plays an important role in the reaction. If the amine is first added to the copper(II) and copper(0) mixture and the allylic halide is added later, the reaction is inhibited completely due to formation of a stable Cu(II) complex of the amine. If the

allylic chloride is added in the absence of the amine to copper(II) and copper(0), the allylic alcohol along with the corresponding diallyl ether are formed.^{9a}



a = Cu(0)/Cu(ClO₄)₂·6H₂O, ether as a solvent.

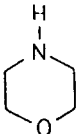

X = Cl, Br. R, R¹, R² as specified in table 1.

Scheme 1

The results of the amination are presented in table I. Both 1-chloro-2-butene and 3-chloro-1-butene react independently with diphenylamine under these reaction conditions to give identical product ratios. This seems to indicate that there is a common intermediate with which the amine reacts. When one compares the reactions of aniline, N-methylaniline, diphenylamine with crotyl chloride in the presence of copper(II)perchlorate and copper metal (entries 4,5,6) the ratios of the products showed that as the size of the nucleophile is increased, the regiochemical discrimination of the nucleophile increases and it tends to attack the less hindered site. However there is an overriding electronic factor which determines the site of attack in cases where an electron withdrawing substituent is present. Thus a carbomethoxy group on the allylic substituent directs the incoming groups towards the unsubstituted end (entries 9,10).

Leaving groups other than halides are less effectively activated toward substitution. Allylic acetates reacted with amines in the presence of copper(II) perchlorate and copper(0) to give allylic

TABLE I^{a, b}

Entry No.	Allylic unit or R ^c	Amine or R ^{1 c}	R ^{2 c}	X	Yield (%)	Ratio of 1 and 2 (Diallylation)
1	H	C ₆ H ₅ ,	H	Cl	76 ^d	(49% diallylation)
2	H	C ₆ H ₅ ,	CH ₃	Cl	97	-
3	H	C ₆ H ₅ ,	C ₆ H ₅	Cl	80	-
4	CH ₃	C ₆ H ₅ ,	C ₆ H ₅	Cl	88	84:46
5	CH ₃	C ₆ H ₅ ,	CH ₃	Cl	86	46:54
6	CH ₃	C ₆ H ₅ ,	H	Cl	60 ^d	33:67 (30% diallylation)
7	CH ₃	C ₂ H ₅ ,	C ₂ H ₅	Cl	90	65:35
8	CH ₃			Cl	91	52:48
9	CH ₃ OCO	C ₆ H ₅ ,	CH ₃	Br	94	100:0
10	CH ₃ OCO	C ₆ H ₅ ,	C ₆ H ₅	Br	76	100:0
11		C ₆ H ₅ ,	CH ₃	Br	94	-

a. All compounds are characterised by their IR and NMR spectra and by comparison with the authentic sample. b. Ratio of 1:2 determined by GC and / or NMR spectroscopy. c. Significance of R, R¹, R² as in the scheme 1. d. Combined yield of mono and diallylated products.

amines in poor yield. For example 1-acetoxy-2-butene reacted with N-methyl aniline in the presence of copper(II) and copper(0) only when refluxed with THF for 12 hours, only 14% of the product was obtained, but the ratios of α and γ attack remained the same as that from the reaction of 1-chloro-2-butene with N-methyl aniline (46:64).

Loss of the double bond geometry was observed in the products formed. Thus when a mixture of cis- and trans-1-chloro-2-butene was reacted with diethyl amine or morpholine in the presence of copper(II) and copper(0) only the trans isomer of product 1 is obtained along with product 2. ^{13}C nmr spectroscopic data are given along with references.¹¹ In the case of the palladium catalysed reaction also, loss of the double bond geometry was observed.^{5d} However, in the case of the iron promoted reaction the integrity of the double bond was retained i.e. the trans and cis isomers independently gave the trans and cis products respectively.⁶

It is interesting to compare the regiochemistry of attack by various amines with allylic systems under the influence of different metal catalysts. Nickel⁶ and palladium⁵ catalysed reactions always led to terminal attack (product 1). The iron promoted reaction led to different isomer ratios (1:2) depending on whether the reaction is carried out with η^2 olefinic complexes or η^3 -allylic complexes.⁶ Reaction between morpholine and 1-chloro-2-butene in the presence of copper(II) and copper(0) gave the ratio of products 1:2 as 52:48 whereas the iron promoted 1-acetoxy-2-butene complex led to the ratio of 43:57 when a η^2 complex was involved. The use of a η^3 complex on the other hand resulted in the formation products 1 and 2 in the ratio of 12:88. The copper promoted amination is found to give different ratios of the products from the direct reaction of allylic chloride with the amine. Diethylamine for example reacts with 1-chloro-2-butene to give 1-N-diethylamino-2-butene as the only product in 82% yield after refluxing the reactants for 36 hours.¹⁰ However, the same reaction in the presence of copper(II) proceeds to completion at room temperature in two hours to give 1-N,N-diethylamino-2-butene and 3-N,N-diethylamino-1-butene in the ratio of 65:35. The variations in the product ratios are clearly due to the differences in the nature of intermediates involved in these reactions, and could be used to synthesise the required isomer.

Thus it has been possible to develop a new method for the conversion of allylic halides to allylic amines which complements the existing metal promoted reactions in terms of product distributions and is much milder than most other available procedures.

Experimental

General procedure for preparation of allylic amines:

A mixture of allylic halide (2 mmol) and amine (3 mmol) in ether (2 ml) was added to a well stirred mixture of copper(II) perchlorate hexahydrate (371 mg, 1 mmol) and copper metal powder (76 mg, 1.2 mmol) in 5 ml ether under nitrogen atmosphere. After stirring the reaction mixture at room temperature for two hours, an aqueous solution of potassium cyanide (2 g in 25 ml of water) was added. A clear solution was obtained, this solution was extracted with ether (2 X 50 ml). The combined extracts were dried over anhydrous sodium sulphate and the solvent was removed by distillation. After purification by column chromatography, the allylic amines obtained were characterised by ^1H , ^{13}C NMR and IR spectroscopy and comparison with authentic samples.

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11. ^{13}C NMR (CDCl_3 , TMS as reference).

