COPPER(I) CHLORIDE/2,2'-BIPYRIDINE-PROMOTED RADICAL REACTIONS OF ARYL TRICHLOROACETATES, TRICHLOROMETHYL CARBINOL ESTERS AND TRICHLOROMETHYL KETONES

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, DELHI
SEPTEMBER, 2010

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BY

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DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

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Dedicated to my parents

Certificate

This is to certified that the thesis entitled "Copper(I) chloride/2,2'-bipyridine-promoted radical reactions of aryl trichloroacetates, trichloromethyl carbinol esters and trichloromethyl ketones", being submitted by Mr. Ram Kumar Tittal, to the Indian Institute of Technology, Delhi, for the award of the degree of "Doctor of Philosophy" in chemistry is a record of bonafide research carried our by him. Mr. Ram Kumar Tittal has worked under my guidance and supervision, and has fulfilled the requirements for the submission of this thesis which to my knowledge has reached the requisite standard.

The results embodied in this dissertation have not been submitted in part or full, to any other University or Institute for the award of any degree or diploma.

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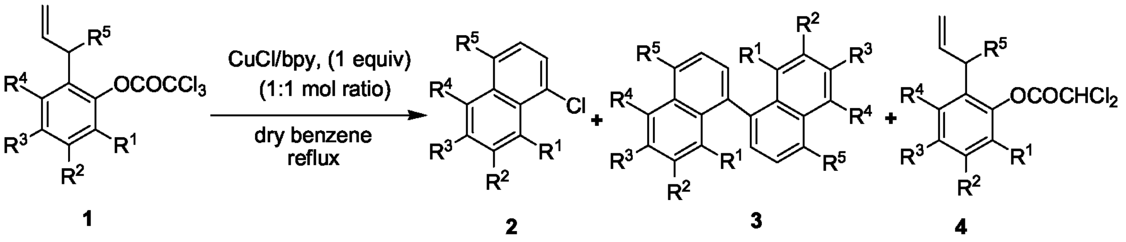
Ram Kumar Tittal

ABSTRACT

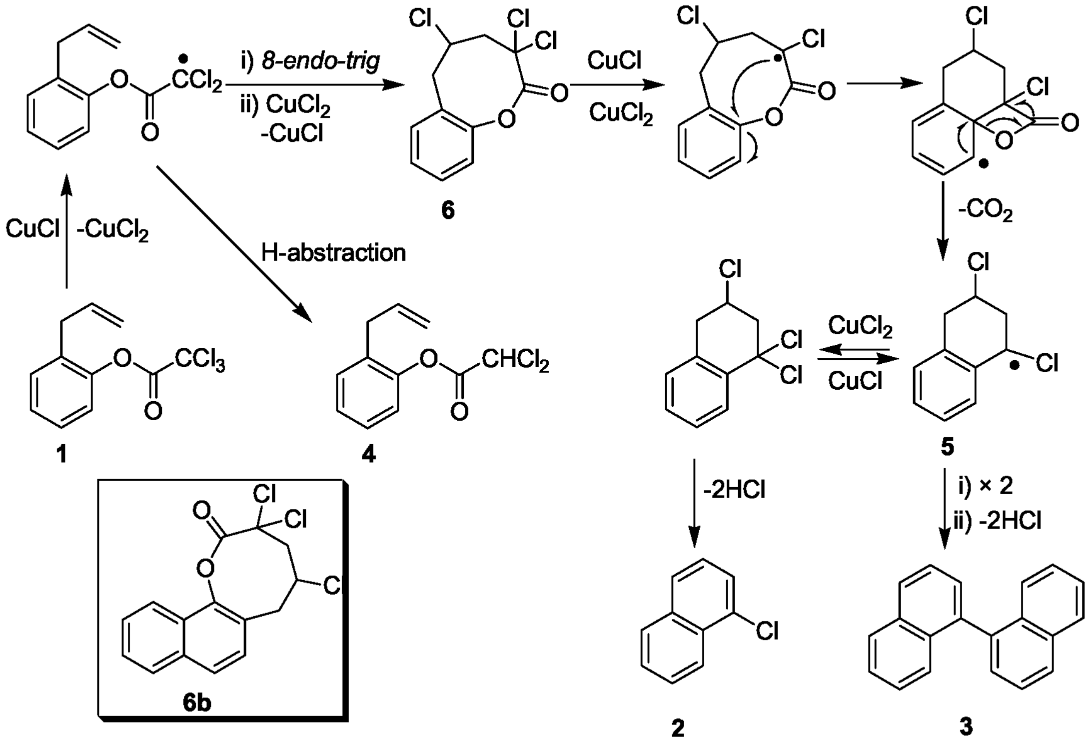
The introductory chapter 1 of the thesis describes some free radical reactions relevant to the present work. The subsequent chapters of the thesis present studies on the mechanistic and synthetic aspects of CuCl/2,2'-bipyridine (bpy)-promoted reactions of some trichloromethyl compounds. Chapter 2 describes an unusual benzannulation of 2-allylaryl trichloroacetates. With a simple idea to synthesize benzene ring fused medium size lactones, 2-allylaryl trichloroacetates **1** (**Scheme 1**) were treated with 1 equiv each of CuCl and bpy in benzene or DCE at reflux under a nitrogen atmosphere for 1-1.5 h. The expected *7-exo* or *8-endo* cyclization products were not isolated. Rather, small amounts of the chloroarenes **2**, biaryls **3** and varying amounts of the reductive dechlorination products **4** were isolated.



a: R^1= H, R^2= H, R^3 R^4= CH=CH-CH=CH, R^5= H
b: R^1 R^2= CH=CH-CH=CH, R^3= H, R^4= H, R^5= H
c: R^1= H, R^2= H, R^3= Cl, R^4= H, R^5= H
d: R^1= H, R^2= H,R^3= Cl, R^4= H, R^5= Ph
e: R^1=H, R^2= H, R^3=Me, R^4=H, R^5= H
f: R^1= H, R^2= Me, R^3= H, R^4= H, R^5= H
g: R^1= H, R^2= H, R^3= H,R^4= Me, R^5= H
h: R^1= OMe, R^2= H, R^3= H, R^4= H, R^5= H

Scheme 1

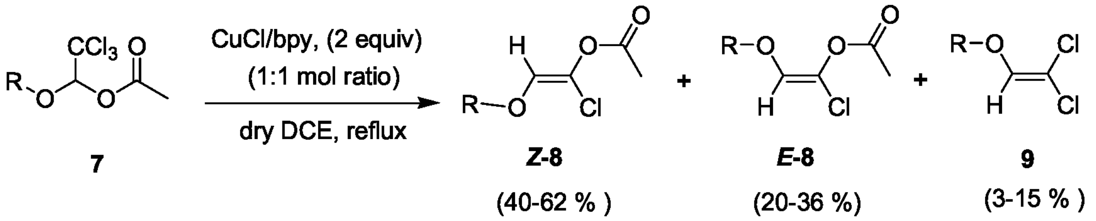
The lactone **6** (**Scheme 2**) was isolated when the reaction of 2-allylnaphthalen-1-yl trichloroacetate **1b** in benzene was interrupted after 15 minutes. The formation and isolation of the 8-member lactone **6** revealed that the mechanism of the reaction as shown in **Scheme 2** involved *8-endo-trig* radical cyclization reaction followed by decarboxylation and dehydrochlorination. Better yields of the biaryls were recorded in benzene as the solvent as compared to DCE probably because the transfer of a chlorine atom in heterogeneous benzene



Scheme 2

medium from the sparingly soluble $CuCl_2$/bpy to the radical intermediate **5** was less favorable, thus promoting the dimerization of the radical intermediate **5**.

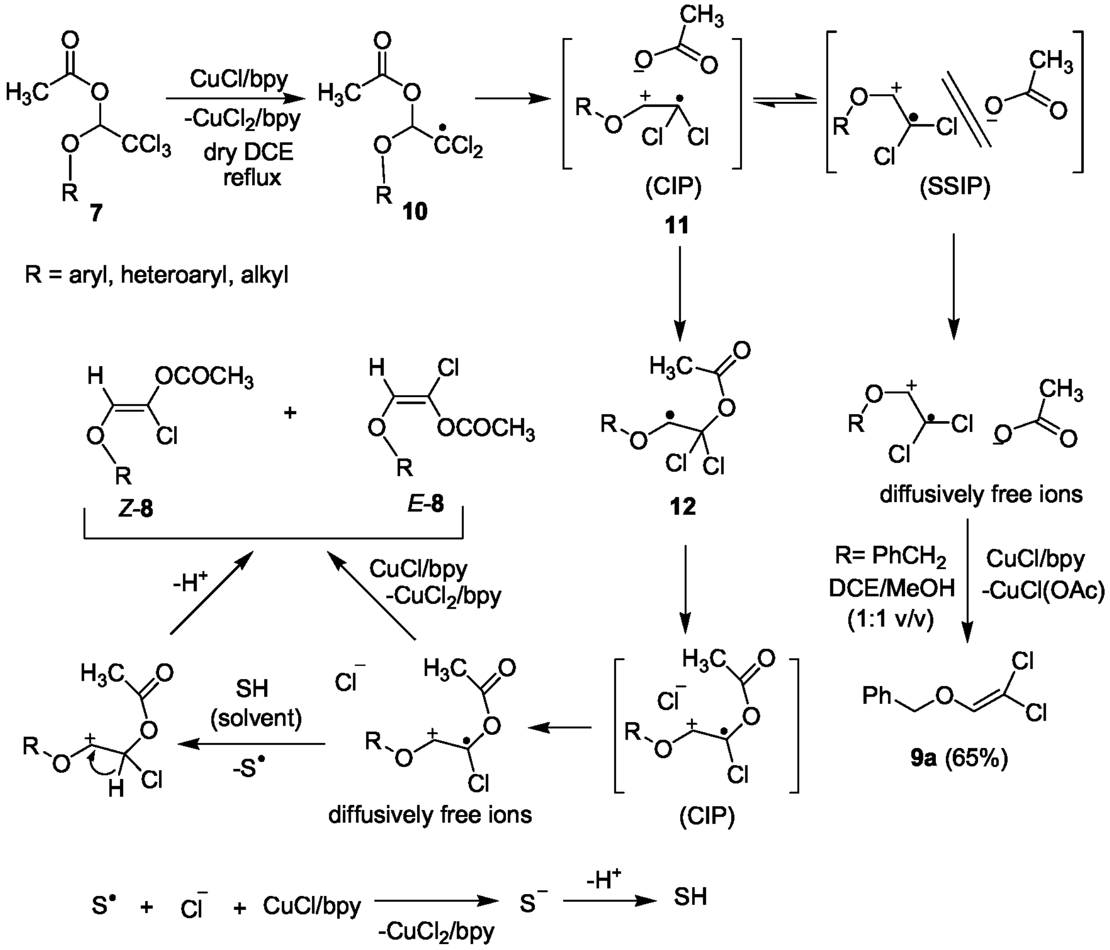
The reaction of the 1-alkoxy-2,2,2-trichloroethyl acetates **7** (**Scheme 3**) with 2 mol equiv each of CuCl and bpy in refluxing DCE under a nitrogen atmosphere has been described in chapter 3. The reaction furnished the trisubstituted alkenes *Z*-**8** in 40-62 % and *E*-**8** in 20-36 % yields by dechlorinative 1,2-acetoxy migration together with 1-alkoxy-2,2-dichloroalkenes **9** in 3-15 % yields by dechlorodeacetoxylation. The stereochemistry of the trisubstituted alkenes were assigned by the uniform pattern of the chemical shift values of some relevant signals in ^{1}H NMR and ^{13}C NMR spectra and by X-ray diffraction spectroscopy of *Z*-1-chloro-2-(4-nitrobenzyloxy)vinyl acetate *Z*-**8g**, which was the only solid product obtained.



R = **a.** $PhCH_2$, **b.** $Ph(CH_2)_2$, **c.** $n\text{-}C_8H_{17}$, **d.** $C_2H_5OCH_2CH_2$, **e.** $CH_3CH(CH_3)CH_2CH_2$, **f.** $p\text{-}MeO\text{-}C_6H_4CH_2$, **g.** $p\text{-}NO_2C_6H_4CH_2$, **h.** $p\text{-}BrC_6H_4CH_2$, **i.** $m\text{-}CH_3COO\text{-}C_6H_4CH_2$, **j.** $C_5H_4NCH_2$

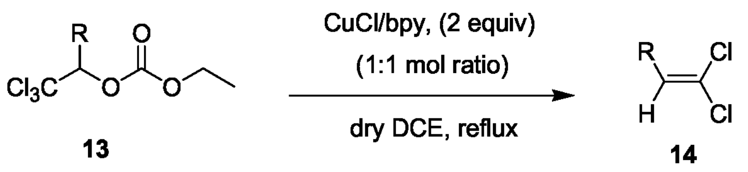
Scheme 3

A mechanism involving the intermediacy of the contact alkene radical cation/carboxylate anion pair **11** (**Scheme 4**) has been proposed for the reaction. Collapse of the contact ion pair **11** in the solvent cage would give the rearranged radical **12**, which being a β-chloroalkyl radical having a good chlorine atom leaving group at the β-position would dissociate to the alkene radical cation chloride ion contact pair. Diffusion out of the solvent cage to the diffusively free solvated ions through the solvent separated ion pair (SSIP) and direct or solvent-mediated electron-transfer to the alkene radical cation from another equivalent of CuCl/bpy would then furnish the chloroenol ethers *Z*-**8** and *E*-**8**. The preponderance of the *Z*-**8** alkene might be attributed to its arguably higher thermodynamic stability. Similarly, diffusion of the contact ion pair **11** out of the solvent cage and direct or solvent mediated electron-transfer to the alkene radical cation from CuCl/bpy would yield the dichloroalkene **9**. Since the acetate ion is a poorer leaving group than chloride ion, the dichloroalkenes **9** would be expected to be minor products of the reaction. The mechanism was supported by the formation of 1-benzyloxy-2,2-dichloroalkenes **9a** on reaction of 1-benzyloxy-2,2,2-trichloroethyl acetate **7a** with 2 mol equiv each of CuCl and 2,2'-bipyridine in higher yield (65 %) in more polar DCE/MeOH (1:1 v/v) solvent.

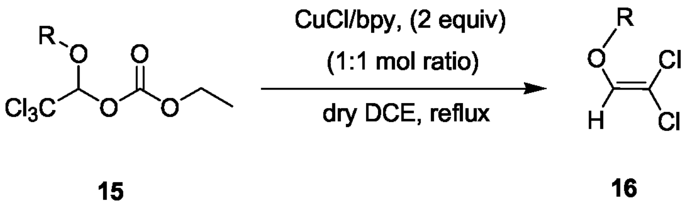


Scheme 4

The work described in chapter 4 is based on the expectation that being a better nucleofugal group, a β-alkoxycarbonyloxy group (carbonate group), which is missing in the spectrum of the reported migrating groups in rearrangements of β-(ester)alkyl radicals would promote the fragmentation of the dichlorocarbo radical initially formed to the alkene radical cation-carbonate anion pair and therefore it would be possible to trap the radical cation for exploiting it in synthesis. Thus, on treatment of ethyl 1-substituted 2,2,2-trichloroethyl carbonates **13** and **15** (**Scheme 5**) with CuCl and 2,2'-bipyridine in dry DCE at reflux under a nitrogen atmosphere afforded the 1,1-dichloroalkenes **14** and **16** in excellent yields without



R = **a.** C_6H_5, **b.** *o*-MeC_6H_4, **c.** *p*-MeC_6H_4, **d.** *o*-$MeOC_6H_4$, **e.** *p*-$MeOC_6H_4$,
f. *o*-ClC_6H_4, **g.** *p*-ClC_6H_4, **h.** *m*-ClC_6H_4, **i.** *p*-BrC_6H_4, **j.** *m*-BrC_6H_4,
k. *p*-$O_2NC_6H_4$, **l.** *p*-$Me_2NC_6H_4$, **m.** 2-pyridyl, **n.** 2-furanyl, **o.** cinnamyl,
p. $C_6H_5CH(CH_3)$, **q.** C_7H_{15}, **r.** *o*-$EtO_2COC_6H_4$, **s.** *o*-$(CH_2{=}CHCH_2O)C_6H_4$,
t. *o*-$(BrCH_2CHBrCH_2O)C_6H_4$.

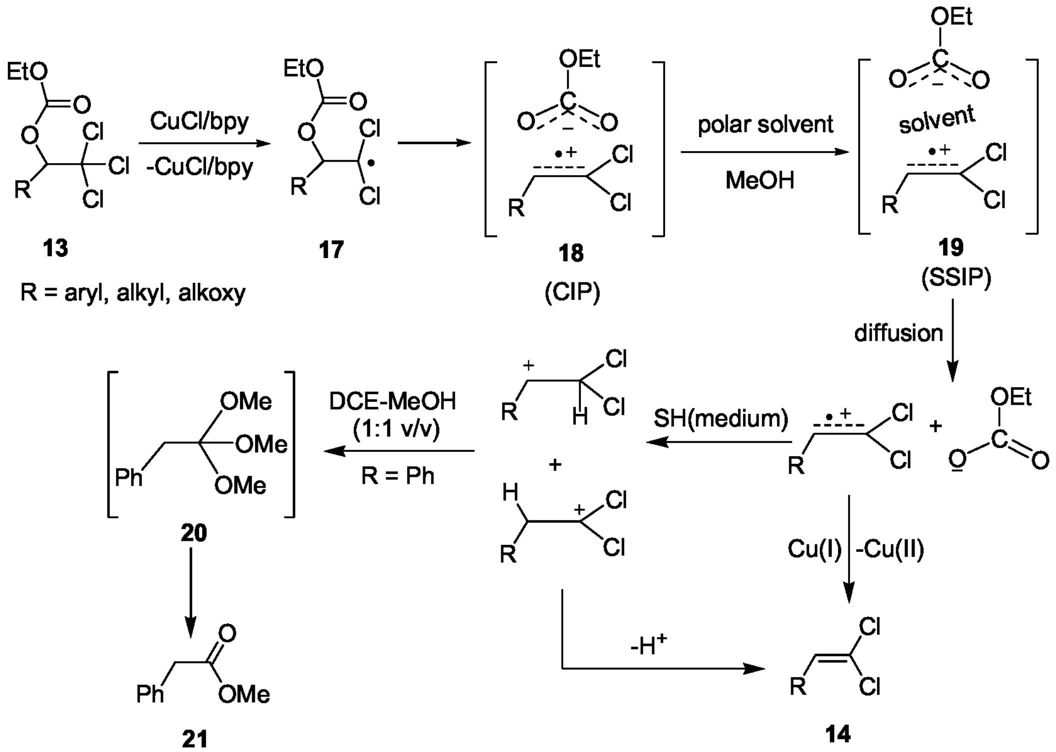


R = **a.** $C_6H_5CH_2$, **b.** *p*-$BrC_6H_4CH_2$, **c.** *p*-$O_2NC_6H_4CH_2$, **d.** $C_6H_5CH_2CH_2$,
e. $C_5H_4NCH_2$, **f.** *o*-$ClC_6H_4CH_2$, **g.** *p*-$ClC_6H_4(CH_3)CH$,
h.:$C_6H_5CH(CH_2CH{=}CH_2)$, **i.** *n*-C_8H_{17}

Scheme 5

forming the rearrangement products. The reaction required 2 mol equiv each of CuCl and 2,2'-bipyridine for completion. Under similar reaction conditions, the ethyl 1-alkoxy-2,2,2-trichloroethyl carbonates also underwent a similar elimination reaction to furnish the 1-alkoxy-2,2-dichloroethenes in good to excellent yields.

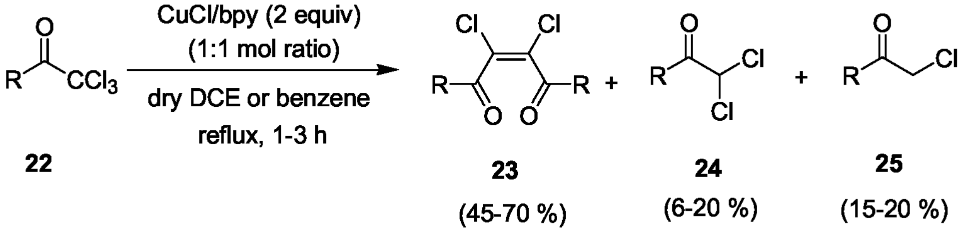
The probable mechanism of the reaction may be considered to involve fragmentation of the radical intermediate **17** (**Scheme 6**) to form the alkene radical cation/carbonate anion contact ion pair (CIP) **18** initially. The diffusion out of the solvent cage to the free solvated radical cation and carbonate anion through the solvent separated ion pair (SSIP) may occur subsequently due to higher stability of the carbonate anion. The cation radical may accept an electron from CuCl/bpy directly or through the intermediacy of the solvent to form the observed 1,1-dichloroalkene products. The diffusion to free ions appears to be considerably fast even in less polar solvents, such as DCE and benzene to preclude any rearrangement.



Scheme 6

Partial decarboxylation of the carbonate group was revealed by the evolution of carbon dioxide during the reaction. The formation of the orthoester **20** and ester **21** in the reaction of ethyl (2,2,2-trichloro-1-phenylethyl) carbonate **13a** with 2 equiv of each CuCl and bpy in more polar solvent methanol or in a mixture of DCE/MeOH (1:1 v/v) supported the intermediacy of the alkene radical cation in the reaction. However, several attempts to intercept the radical cation by tandem radical cyclization-nucleophilic trapping in methanol failed, suggesting that the heterolysis of the C-O bond in the initially produced radical **17** required an activation energy which probably lies between that of pure *5-exo* radical cyclization and *6-exo* or *7-endo* radical cyclization.

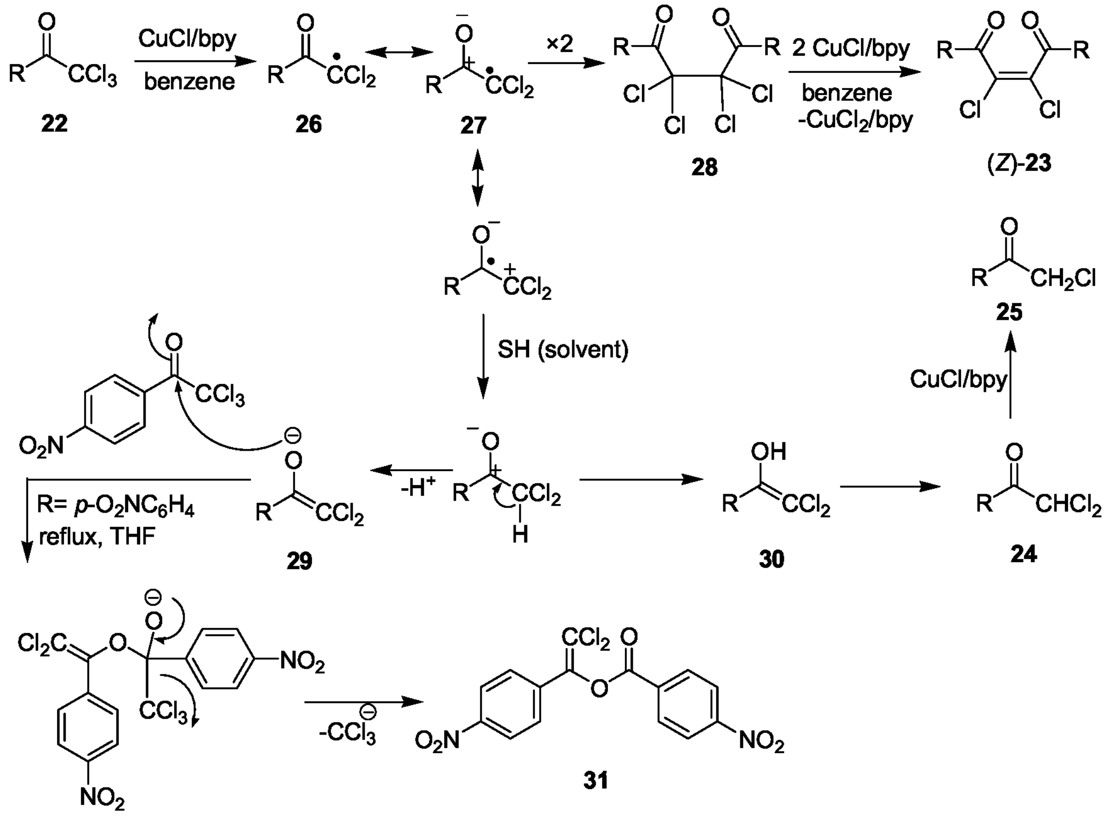
In the last chapter (chapter 5) dechlorinative dimerization of trichloromethyl ketones on reaction with CuCl and 2,2'-bipyridine has been described. The reaction of the trichloromethyl ketones **22** (**Scheme 7**) with 2 mol equiv each of CuCl and 2,2'-bipyridine in refluxing DCE under a nitrogen atmosphere afforded stereoselectively the *Z*-2,3-dichloro-1,4-diphenylbut-2-ene-1,4-diones **23** in acceptable to good yields (45-70 %). Small amounts of the dichloromethyl ketones **24** or monochloromethyl ketones **25** were also isolated as a result of reduction of the CCl_3 group. The proportion of the reduction products decreased when the reaction was performed in relatively poorer hydrogen atom donor solvent benzene.



R = **a.** C_6H_5, **b.** *p*-MeC_6H_4, **c.** *m*-MeC_6H_4, **d.** *o*-MeC_6H_4, **e.** *p*-$MeOC_6H_4$, **f.** *o*-$MeOC_6H_4$, **g.** *p*-Cl-C_6H_4, **h.** *o*-Cl-C_6H_4, **i.** *p*-Br-C_6H_4, **j.** *p*-NO_2-C_6H_4, **k.** C_3H_7,

Scheme 7

The formation of the *Z*-ene-1,4-diones **23** and the reduction products **24** and **25** could be explained by dimerization of the initially formed radical **26** (**Scheme 8**) to **28** and its reduction through hydrogen abstraction from the medium. However, the radical **26** may be considered to be highly polarized as shown in the structure **27** by analogy with the well documented heterolysis of the C-L bond of the radicals having a leaving group L at the β-position. In this context a π bond of the carbonyl group may be regarded as equivalent to an extremely powerful leaving group. The highly polar character of this radical could also explain the formation of the enol ester **31** in the reaction of *p*-nitrophenyl ketone in a good H-atom donor solvent THF in which the concentration of the enolate **29** or the enol **30** would be sufficient for the intermolecular reaction with the unreacted considerably electrophilic *p*-nitrophenyl ketone. The *Z*-selectivity in the formation of the ene-1,4-diones might be due to association of the zwitterionic radical intermediate **27** with the copper complexes present in the medium.



Scheme 8

CONTENTS

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Chapter 2 An unusual decarboxylative benzannulation on copper(I) chloride/2, 2'-bipyridine-promoted halogen atom transfer radical cyclization of 2-allylaryl trichloroacetates

Chapter 3 Copper(I) chloride/2,2'-bipyridine-promoted radical rearrangement of 1-alkoxy-2,2,2-trichloroethyl acetates

Chapter 4 Copper(I) chloride/2,2'-bipyridine-promoted elimination reaction of ethyl 1-substituted 2,2,2-trichloroethyl carbonates to 2-substituted 1,1-dichloroethenes

Chapter 5 Copper(I) chloride/2,2'-bipyridine-promoted stereoselective radical

dimerization of trichloromethyl ketones to (*Z*)-2,3-dichlorobut-2-ene-1,4-diones