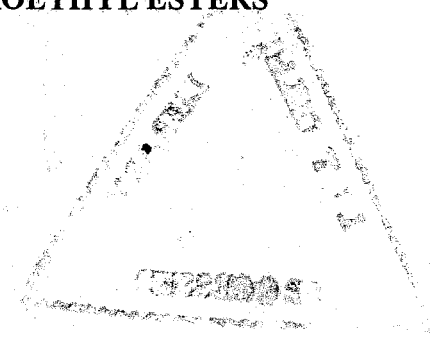
SOME CHEMOSELECTIVE ESTERIFICATION METHODS AND COPPER(I) PROMOTED REARRANGEMENT OF 2,2,2-TRICHLOROETHYL ESTERS



BY

NABIN KUMAR MEHER

Thesis submitted in fulfilment

of

the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

Department of Chemistry

INDIAN INSTITUTE OF TECHNOLOGY, DELHI

JULY, 2002

Dedicated to My Parents

CERTIFICATE

This is to certify that the thesis entitled "Some Chemoselective Esterification Methods and Copper(I) Promoted Rearrangement of 2,2,2-Trichloroethyl esters", being submitted by Mr. Nabin Kumar Meher, 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 out by him. Mr. Nabin Kumar Meher 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 in full, to her University or Institute for the award of any degree or diploma.

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Lastly and most importantly, I take this opportunity to express my heartfelt affection, love and thanks towards my family members.

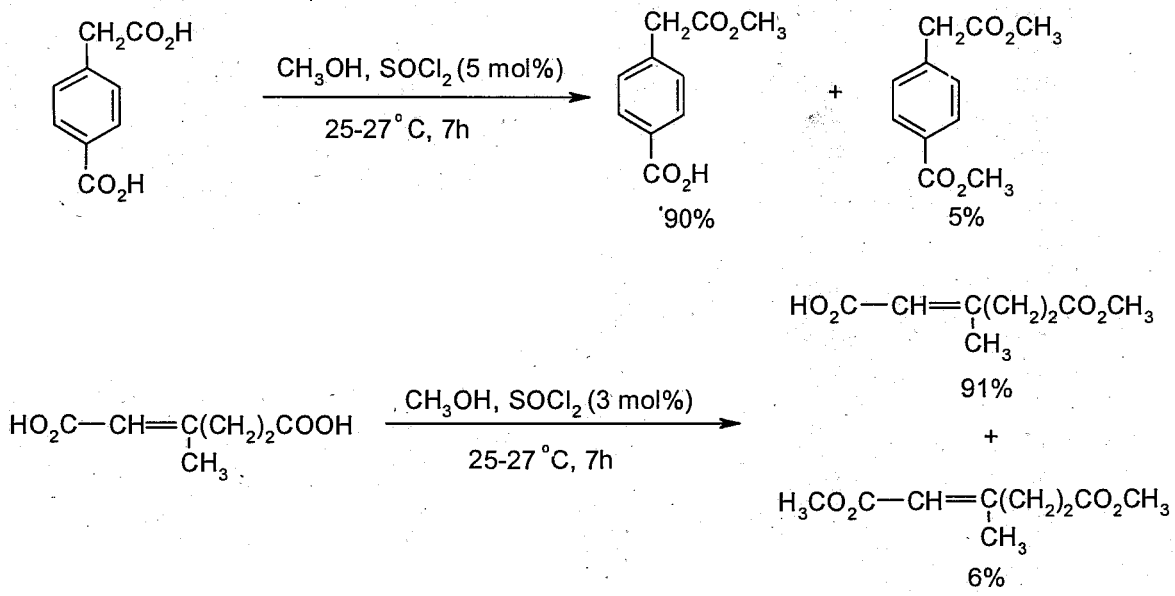
Meher 25/07/2002

Nabin Kumar Meher

Abstract

The thesis is concerned with some chemoselective esterification methods and CuCl/bpy promoted dechlorinative-rearrangement of 2,2,2,-trichloroethyl carboxylates. One of the chemoselective esterification methods describes the selective esterification of non-conjugated carboxy group in the presence of conjugated or aromatic carboxy group in dicarboxylic acids with methanol in the presence of a catalytic amount of thionyl chloride. The other esterification method describes selective formylation of alcohols in the presence of phenols with chloral in the presence of anhydrous potassium carbonate. The last part of the thesis describes a radical rearrangement of 2,2,2-trichloroethyl esters involving CuCl/bpy promoted migration of acyloxy group accompanied by dechlorination to give 1-chloroalkenyl esters.

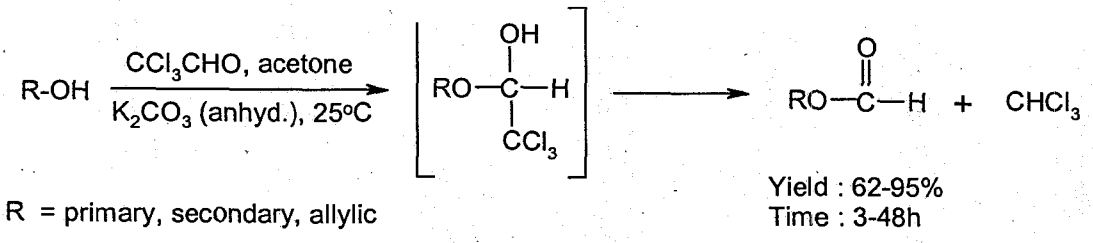
Thionyl chloride in the presence of methanol produces anhydrous hydrochloric acid which catalyses the selective monoesterification of dicarboxylic acids. It has been found that a catalytic amount of thionyl chloride (3-5 mol%) selectively esterifies non-conjugated carboxy group in the presence of conjugated or aromatic carboxy group at room temperatures. The representative examples are shown in Scheme 1.



Scheme 1

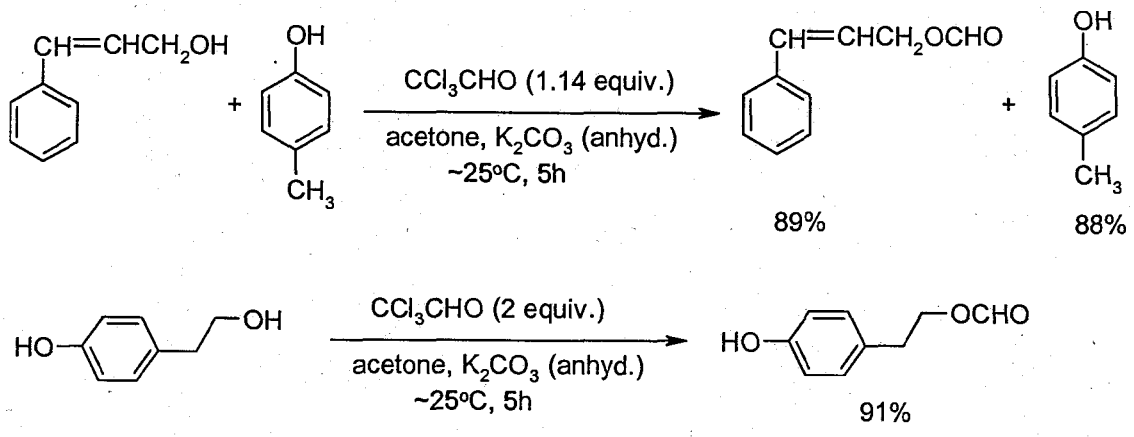
This method was not found to be successful for the formation of ethyl esters. $TiCl_4$ as catalyst also showed the same type of selectivity under similar conditions, but titanium isopropoxide was found to be ineffective.

Chloral forms stable hemiacetals with alcohols easily at room temperatures. It was thought that a weak base might cleave the hemiacetal to give chloroform and a formate. Since chloral is not known to form hemiacetals with phenols, this might constitute a method for selective formylation of an alcoholic group in the presence of a phenolic group. This was realised when hemiacetal of chloral with cinnamyl alcohol was stirred with anhydrous potassium carbonate in acetone at ambient temperatures for four hours to give cinnamyl formate in 93% yield. It was subsequently found that the whole transformation could be done in a single step by mixing the alcohol, chloral and anhydrous potassium carbonate together in acetone and stirring at ambient temperatures. Taking cinnamyl alcohol as a test case, the reaction was examined in various solvents such as acetone, THF, CH_2Cl_2, EtOAc, MeCN, C_6H_6 and bases such as potassium carbonate and triethylamine. The most effective solvent-base combinations were found to be acetone-potassium carbonate and acetonitrile-potassium carbonate. The generality of this reaction was shown by taking various types of primary and secondary alcohols and stirring them with chloral in the presence of anhydrous potassium carbonate in acetone at ambient temperature (Scheme 2).



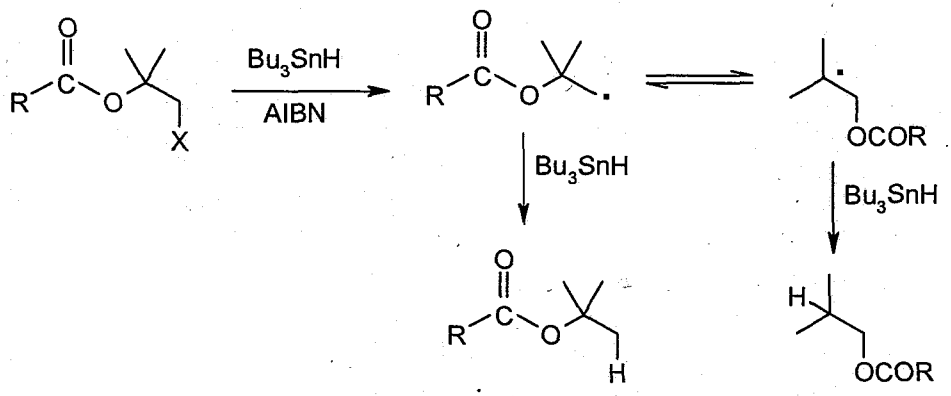
Scheme 2

The reaction was found to be selective for alcohols in the presence of phenols. The selectivity was demonstrated by carrying out competition experiments by taking equimolar mixtures of an alcohol and a phenol, as well as by taking compounds having both alcoholic and phenolic groups. The representative examples are shown in Scheme 3.



Scheme 3

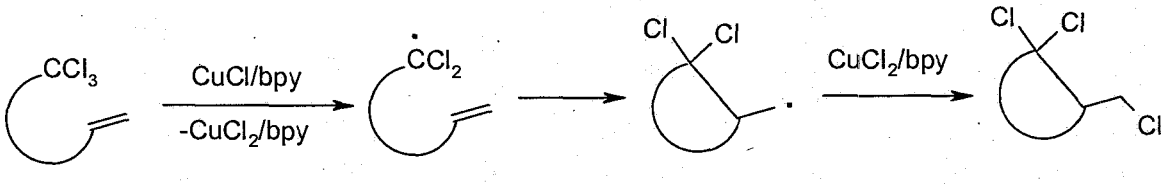
1,2-Migration of acyloxy group in β-(acyloxy)alkyl radicals, known as Surzur-Tanner rearrangement has considerable synthetic potential. It is generally carried out by treating β-(acyloxy)alkyl halides with Bu_3SnH in the presence of a catalytic amount of AIBN (Scheme 4). Under these conditions, the synthetic utility of this rearrangement reaction is severely limited because reduction of the initially generated β-(acyloxy)alkyl



Scheme 4

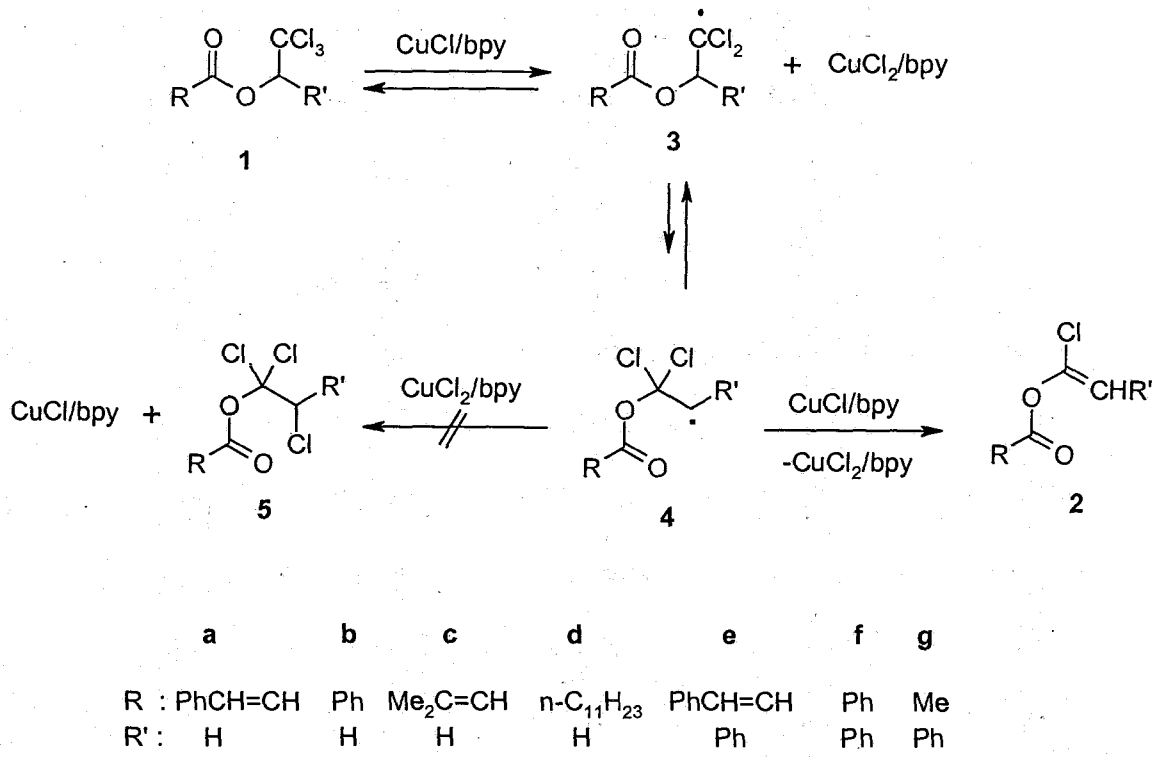
radical with Bu_3SnH is a serious side reaction. Further, the rearrangement is a reductive process, in which the rearranged radical is stabilised by hydrogen abstraction from Bu_3SnH and thus the valuable halogen functionality is lost.

CuCl/bpy is known to be an efficient catalyst in HATR addition or cyclisation reactions. In these reactions, CuCl/bpy abstracts a chlorine atom from a reactive halogen compound such as the one having a trichloromethyl group to produce a dichloromethyl radical. This radical adds to a carbon-carbon double bond inter- or intramolecularly and the $CuCl_2$/bpy produced in the first step, being a good halogen transfer reagent, transfers the chlorine atom to the adduct radical to complete the addition (Scheme 5).



Scheme 5

It is therefore considered worthwhile to use CuCl/bpy in Surzur-Tanner rearrangement in place of Bu_3SnH. It was expected that this modification would remove both the limitations of Surzur-Tanner rearrangement. Moreover, CuCl/bpy or $CuCl_2$/bpy being Lewis acids may catalyse the reaction, which is known to be prone to acid catalysis. It was found that when trichloroethyl carboxylates (**1**) (Scheme 6) were heated with CuCl/bpy (1:1 molar ratio) in 1,2-dichloroethane at reflux under nitrogen atmosphere, 1-chloroalkenyl carboxylates (**2**) were formed in high yields, apparently by migration of the acyloxy group followed by elimination of a chlorine atom. Transfer of chlorine to the rearranged radical to give (**5**) was not observed.



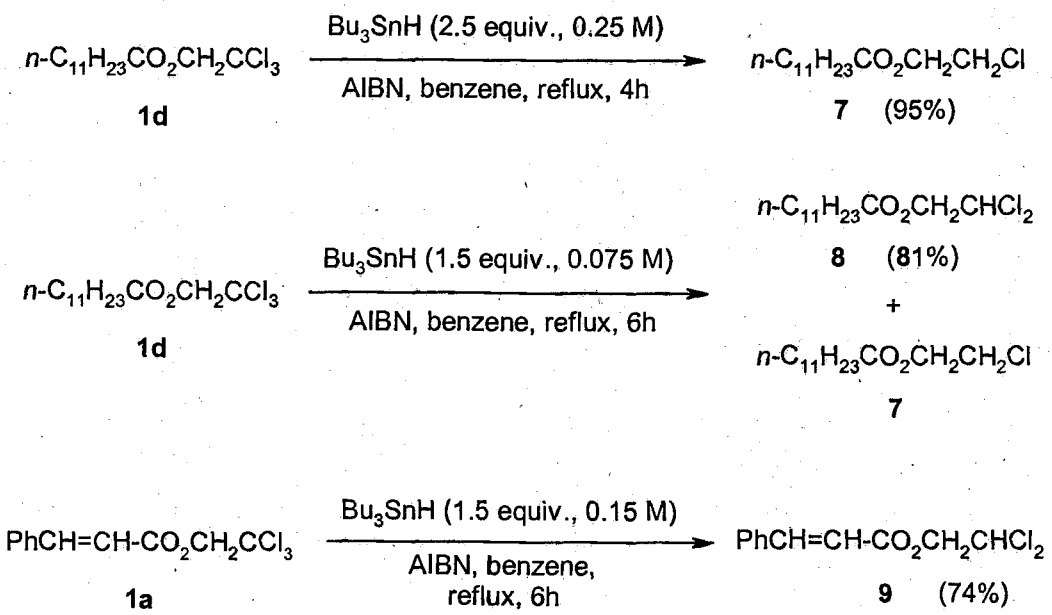
Scheme 6

The reaction required two equivalents of the CuCl/bpy reagent for completion. Though the expected formation of (**5**) by transfer of a chlorine atom to the rearranged radical (**4**) from $CuCl_2$/bpy was not observed, it was not disappointing in view of the fact that a new carbon-carbon double bond functionality was created providing greater latitude for further manipulation. The observed elimination of a chlorine atom after the rearrangement suggested that the elimination in the rearranged radical was faster than chlorine atom abstraction probably due, among other factors, to the relief in steric strain. The reaction is comparatively faster than many reported 2-acyloxyalkyl radical rearrangements. The yields of the products were high and side products were not observed. An additional interesting feature of the rearrangement is that a more stable radical (**3**, R'= H) rearranges to a less stable radical (**4**, R' = H). Also phenyl migration in the case of (**1e-g**) and chlorine scrambling were not detected. It is also noteworthy that the favoured 5-*exo-trig* radical cyclisation, so well known in tributyltin-mediated and HATR

reactions was not observed in the cases of (**1a, c, e**). The rearrangement also proceeded in other solvents such as benzene, toluene, THF, however, it did not go to completion in comparable amounts of time.

Cross-over experiment on a mixture of (**1d**) and (**1e**) gave only (**2d**) and (**2e**) without any detectable cross-over products suggesting that the reaction is intramolecular. The reaction of (**1a**) was not inhibited by radical inhibitor 4-*t*-butylcatechol, as observed for other Cu(I)-catalysed HATR reactions. The reaction of (**1b**) with dibenzoylperoxide or AIBN in benzene at reflux under nitrogen atmosphere gave a mixture of unidentified products. 2,2-Dichloroethy benzoate was found to be inert under the same reaction conditions. Plausibly, the $-CHCl_2$ group is not reactive enough to generate the initial radical under these reaction conditions.

. In order to compare the reactivity of 2,2,2-trichloroethyl carboxylates towards CuCl/bpy with that towards Bu_3SnH/AIBN, the trichloroethyl dodecanoate (**1d**) (1 mmol, 0.1 M in benzene) was treated at reflux with tributyltin hydride (2.5 mmol, 0.125 M in benzene), the latter being added slowly through a syringe for 1.5 hour. In this reaction mostly 2-chloroethyl dodecanoate (**7**) was obtained without formation of any rearranged product (Scheme 7). Then, (**1a**) and (**1d**) (1 mmol, 0.04 M) were treated with tributyltin hydride (1.5 mmol, 0.075 M) under more dilute conditions with longer addition time (4 hours). In these reactions also only reduction products 2,2-dichloroethyl cinnamate (**9**) and 2,2-dichloroethyl dodecanoate (**8**) respectively were obtained. This showed that the hydrogen abstraction by the initial radical formed is faster than the rearrangement.



Scheme 7

Reaction of (**1a**) with CuCl/bpy (2 equiv.) in the presence of Bu_3SnH (1.5 equiv.) in benzene at reflux gave rearranged product (**2a**) and the reduction product 2,2-dichloroethyl cinnamate (**9**) in a ratio of nearly 4:1. A small amount of unreacted starting compound was also detected. This experiment showed that the rearrangement in the presence of copper complex is faster than the abstraction of hydrogen by the initially formed radical. It has been speculated that the difference in the reactivity of trichloroethyl esters under CuCl/bpy and Bu_3SnH/AIBN conditions may probably be due to the formation of copper complexed radical and /or due to Lewis acid catalysis by CuCl/bpy / $CuCl_2$/bpy in the copper promoted reactions which might favour rearrangement.

CONTENTS