TRANSITION METAL MEDIATED HALOGEN ATOM TRANSFER RADICAL CYCLISATION IN FURAN SYNTHESIS, CHEMOSELECTIVE ESTERIFICATION AND AMINE OXIDATION

by

I. CHARLES

DEPARTMENT OF CHEMISTRY

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to the

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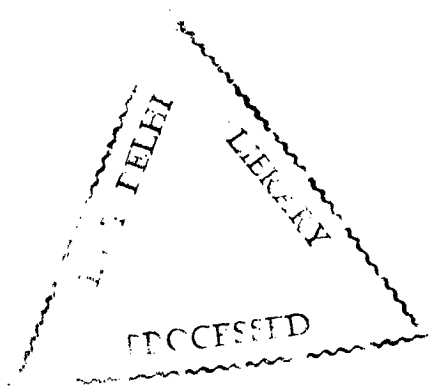
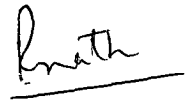


Dedicated to My Parents

CERTIFICATE

This is to certify that the thesis entitled "Transition Metal Mediated Halogen Atom Transfer Radical Cyclisation in Furan Synthesis, Chemoselective Esterification and Amine Oxidation", being submitted by Mr. I. Charles, 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. I. Charles 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 any other University or Institute for the award of any degree or diploma.



(Ram N. Ram)
Thesis Supervisor
Associate Professor
Department of Chemistry
Indian Institute of Technology, Delhi
New Delhi- 110 016
India.

I. I. T. Delhi
23, June 2000

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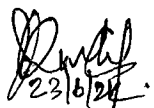
Lastly and most importantly, I take this opportunity to express my heartfelt affection, love and thanks towards my family members. I acknowledge the showers of blessings and love of my respected parents and their unrelenting moral support in the times when I needed them the most, without which it would have been an impossible task to arrive at this high point of my career. I also acknowledge and thank my brothers, sisters, brother-in-laws and sister-in-laws for their affection and moral support.



(I. Charles)

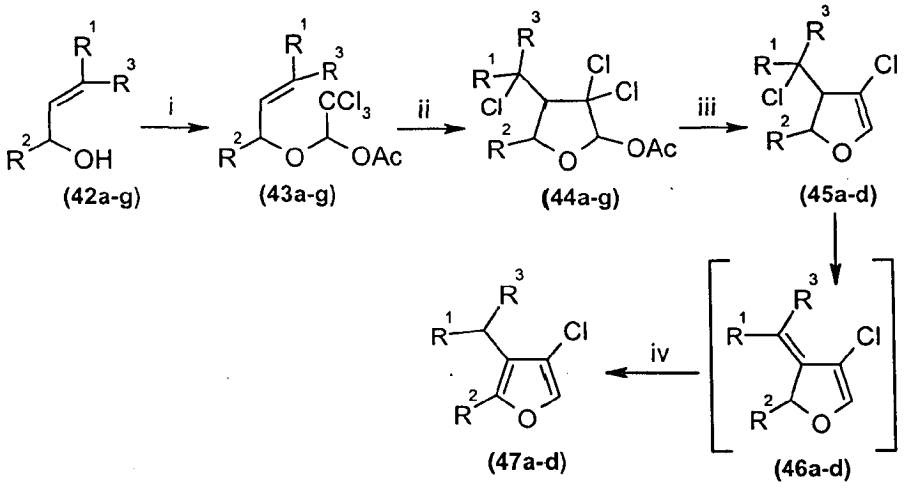
Abstract

The thesis is primarily concerned with the application of CuCl/bipy catalysed intramolecular halogen atom transfer radical cyclisation to the synthesis of some new and difficult to prepare 3-substituted-4-chlorofurans and 2,3-disubstituted-4-chlorofurans. It also describes two new reactions. One of them is $NiCl_2.6H_2O$ catalysed chemoselective esterification of non-conjugated carboxylic acids in the presence of conjugated or aromatic carboxylic acids. The other is about an unusual formation of α-ethylcinnamaldehydes by the reaction of aromatic aldehydes with *n*-Bu_3N in the presence of $TiCl_4$.

3-Substituted and 2,3-disubstituted 4-chlorofurans were synthesised from readily available allyl alcohols. The method involves CuCl/ bipy catalysed regioselective chlorine atom transfer radical cyclisation of 1-acetoxy-2,2,2-trichloroethyl allyl ethers **(43a-g)** as the key step (Scheme 1). The allyl ethers **(43a-g)** were prepared by simple mixing of chloral with allyl alcohols **(42a-g)** followed by protection of the hemiacetals thus formed by acetylation with Ac_2O/DMAP in pyridine. The regioselectivity of the cyclisation was excellent in that only the five-membered ring was formed. Though the ring size was established by further reaction of the tetrahydrofurans **(44)** to 2,3-dihydrofurans **(45)** and 4-chlorofurans (47), both DQF COSY spectrum of **(44a)** and spin decoupling experiments supported the formation of the five membered ring. Attempts to cyclise the unprotected hemiacetal was unsuccessful under the same conditions.

The dechlorodeacetoxylation of **(44a-d)** with zinc dust in THF furnished 2,3-dihydrofurans in good yields. Dehydrochlorination of **(47a-d)** with KOH/EtOH followed by isomerisation of the crude isofurans with catalytic amounts of conc. H_2SO_4 furnished the 4-chlorofurans **(47a-d)** in 31-65% overall yields (starting from

the allyl alcohols). When the dehydrochlorination was done with t-BuOK/ 18-Crown-6/THF, tandem isomerisation of isofurans was observed, giving the 4-chlorofurans (**47a-d**) in better overall yields (51-74%).

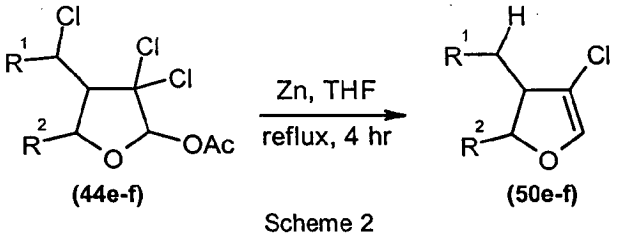


R^1, R^2, R^3 = *n*-C_3H_7, H, H; H, Ph, H; H, *n*-C_5H_{11}, H; CH_3, Ph, H; Ph, H, H; Ph, CH_3, H; CH_3, H. CH_3

Reagents and conditions i). (a) CCl_3CHO, 2 hr, then Ac_2O, Pyridine, DMAP (30 mol%), room temp., overnight; ii) 30 mol% of CuCl/bipy (1:1 mixture), 1,2-dichloroethane, reflux, 2 hr, N_2 atmosphere; iii) Zn, THF, reflux, 4 hr; iv) *Method A*: (a) KOH, EtOH, reflux; (b) conc. H_2SO_4 (cat.), room temp., overnight (in the case of **(45a)** and **(45c)**) or (a) KOH, EtOH, reflux(in the case of **(45b)** and **(45d)**); *Method B*: *t*-BuOK, 18-Crown-6, THF, reflux, 10 hr.

Scheme 1

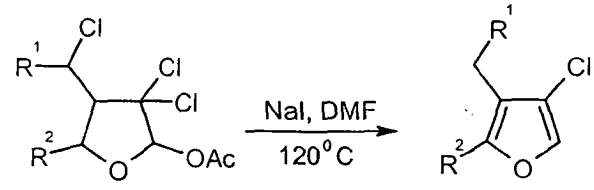
Dechlorodeacetoxylation of **(44e)** and **(44f)** gave 2,3-dihydrofuran **(50e)** and **(50f)** respectively with concomitant reductive cleavage of the benzylic chloro group (Scheme 2).



Scheme 2

After some unsuccessful attempts to tide over the problem of reductive cleavage of benzylic C-Cl bond in the dechlorodeacetoxylation step, it was observed

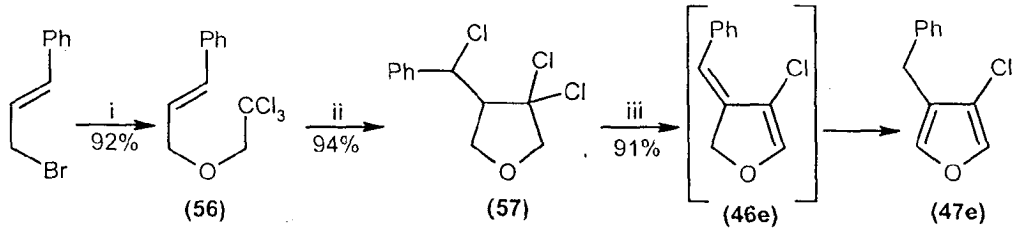
that the tetrahydrofurans (**44b, c, e, f**) not only underwent dechlorodeacetoxylation but also dehydrochlorination and aromatisation all in one step on heating with NaI in DMF at 120°C to give the 4-chlorofurans (**47b, c, e, f**) in 25-40% overall yields (starting from allyl alcohols)(Scheme 3).



(44b, c, e, f) (47b, c, e, f)

Scheme 3

The 4-chlorofuran (**47e**) was also prepared in 81% overall yield by a simple modification involving preparation of trichloroethyl cinnamyl ether (**56**) by the reaction of trichlorethanol with cinnamyl bromide followed successively by CuCl/bipy catalysed chlorine atom transfer radical cyclisation of the ether thus obtained and dehydrochlorination of the cyclised product with DBU (Scheme 4). Though this scheme seems to be more attractive than Scheme 1, both in the number of steps and overall yields, attempts to prepare trichloroethyl ethers derived from secondary allylic halides were unsuccessful.



(56) (57) (46e) (47e)

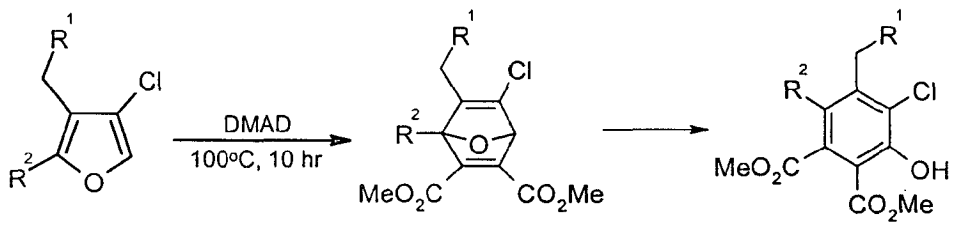
Reagents and conditions i) CCl_3CH_2OH, K_2CO_3, acetone, reflux, 6 hr; ii) 30 mol% of CuCl/bipy(1:1 mixture), $ClCH_2CH_2Cl$, reflux, 2.5 hr, N_2 atmosphere; iii) DBU, benzene, reflux, 3 hr.

Scheme 4

The 2,3-dihydrofurans and chlorofurans are fairly stable in hydrocarbon solvents, especially in dilute solutions. But they tend to deteriorate in chlorinated or

oxygenated solvents and the decomposition is faster when they are stored as neat liquids.

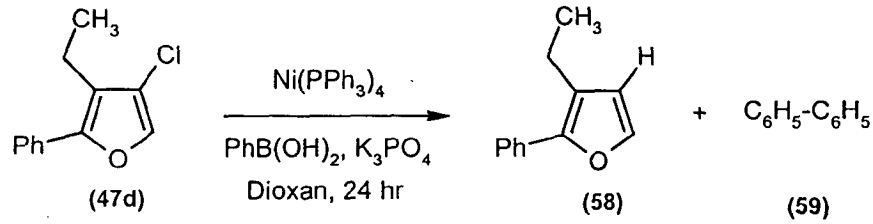
The Diels-Alder reaction of 4-chlorofurans **(47a-e)** with dimethyl acetylenedicarboxylate under solvent free conditions gave the corresponding adducts **(48a, d, e)** or the phenols **(49b, c)**. The latter was formed probably by isomerisation of the adducts (Scheme 5). In the case of the chlorofuran **(47c)** a mixture of the adduct **(48c)** and the phenol **(49c)** was obtained which got completely converted into the phenol **(49c)** on slight warming with $BF_3.OEt_2$.



(47a-e) **(48a-e)** **(49b, c)**

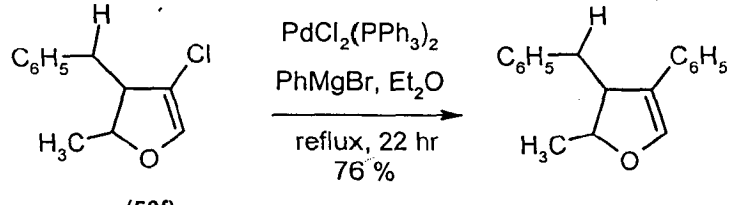
Scheme 5

In view of the current interest in the replacement of chloro group of aryl and vinylic chlorides, attempts were made to replace the same in the dihydrofurans and furans. The classical Wurtz-Fittig cross-coupling reaction, palladium and nickel catalysed Suzuki coupling reactions and Negishi coupling on the chlorofuran **(47d)** gave either complicated mixtures or the starting material. But the Suzuki coupling of the 4-chlorofuran **(47d)** in the presence of one equivalent of $Ni(PPh_3)_4$ generated by *in situ* reduction of $NiCl_2(PPh_3)_2$ with BuLi gave a mixture of the reduced chlorine free furan **(58)** and biphenyl **(59)** (Scheme 6). This reaction mixture was difficult to separate by chromatography. In an attempt to separate them chemically, the mixture was heated with DMAD to 100°C for 10 hr. However, it gave only biphenyl and unreacted DMAD, the furan got completely decomposed.



Scheme 6

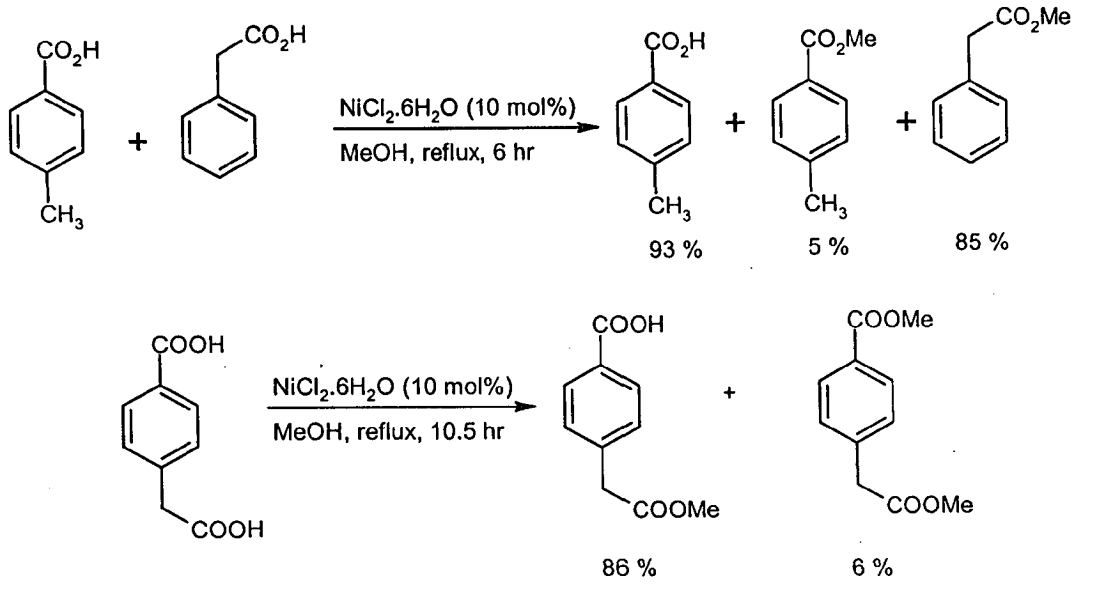
However, palladium catalysed cross coupling reaction of 4-chloro-2,3-dihydrofuran **(50f)** with phenylmagnesium bromide gave the phenyl substituted 2,3-dihydrofuran **(60)** in 76% yield (Scheme 7).



Scheme 7

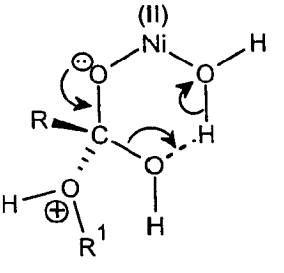
Since metal ions are milder acids than protons, they are expected to show selectivity in acid catalysed reactions such as esterification. It was expected that Ni (II) might serve as a mild and selective catalyst for the esterification of aliphatic non-conjugated acids in the presence of relatively less reactive aromatic or conjugated carboxylic acids owing to a suitable balance between its hard and soft acidities. Thus, a solution of carboxylic acid (0.01 mol) and alcohol (10 ml) was heated at reflux with $NiCl_2.6H_2O$ (0.001 mol, 10 mol%) to give the ester in high yields after a simple work up involving evaporation of the solvent and extraction with ether or dichloromethane. The reaction was observed to be selective for aliphatic non-conjugated acids. The aromatic or conjugated acids and hindered acids were found to be far less reactive. The selectivity was found to be better than that observed with the same molar proportion (10 mol%) of proton as catalyst in proton catalysed reaction. The selectivity was demonstrated by carrying out esterification of mixtures of two types of

carboxylic acids as well as of dicarboxylic acids having both the types of carboxyl groups. The representative examples are shown in the Scheme 8.



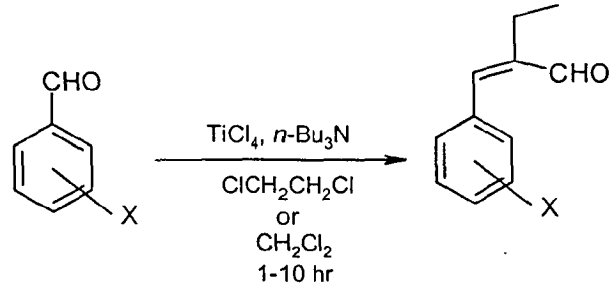
Scheme 8

The method worked well for the preparation of methyl, ethyl and isopropyl esters but was unsatisfactory for *t*-butyl esters. Curiously, anhydrous $NiCl_2$ was found to be less effective than the hydrated salt. Probably, the water of co-ordination facilitates the removal of hydroxyl group from the tetrahedral intermediate by hydrogen bonding as shown in the following structure.



Some of the notable points about the reaction are: (a) strictly dry alcohol is not required. (b) the configuration at the α-carbon is not disturbed as revealed by comparable value of specific rotation of L-dimethyl tartarate obtained from the reaction with the reported value. (c) the reaction is extremely simple to carry out and uses readily available shelf-reagent as the catalyst.

$TiCl_4$ is known to oxidise trialkylamines and the most likely primary oxidation product is expected to be an iminium ion. It was thought that the iminium ion might add to a carbonyl compound under the influence of $TiCl_4$ and excess base to give an aldol condensation product. Thus, when to an equimolar mixture of aromatic aldehydes and $TiCl_4$ in 1,2-dichloroethane or dichloromethane was added two equivalents of *n*-Bu_3N slowly with stirring at room temperature and the solution was stirred for 1-10 hr a complex mixture was obtained after work up from which α-ethylcinnamaldehydes could be isolated in 18-30% yields (Scheme 9). In the case of 4-chlorobenzaldehyde, 19 % of 4-chlorobenzyl alcohol was also isolated. Interestingly, electron-withdrawing groups in the aldehyde impede the reaction.



X = H, 2-Me, 3-Me, 4-Me, 4-Cl, 4-NO_2

Scheme 9

In order to understand the mechanism and improve the yields, the reaction was performed with different proportions and different modes of mixing of the reactants and under N_2 and O_2 atmospheres taking benzaldehyde as a test case. However, no significant change in the yields of the product was observed. The reaction probably involves oxidation of *n*-Bu_3N with $TiCl_4$ to give iminium ion, which is converted to enamine by loss of a proton. Condensation of the enamine with the aldehyde could follow in the usual manner to give the product. It is also possible that the iminium ion undergoes base-promoted titanation at the α-position, and the organotitanium then adds on the aldehyde to give the observed product.

It is to be mentioned that during the course of this investigation, Periasamy and Bharathi have reported a similar observation. However, there are some significant differences between our work and that reported by them as enumerated below.

1. None of the reactions described in the present work has been reported by Periasamy and Bharathi. In fact, only one reaction on aldehyde, which involves benzaldehyde and triethylamine in the presence of $TiCl_4$ to give cinnamaldehyde, has been reported by them.
2. Periasamy and Bharathi have used *n*-Bu_3N in only one reaction i.e., in the reaction with benzophenone whereby they obtained a conjugated dienal ($Ph_2C{=}CH{-}CH{=}CH{-}CHO$). But we observed the formation of α-ethylcinnamaldehyde derivatives in the reactions of *n*-Bu_3N with aldehydes.
3. In the present work, reduction of some aldehydes to alcohols has been observed. Periasamy and Bharathi reported the formation of some unidentified polar compounds in the reaction of benzaldehyde with triethylamine.

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