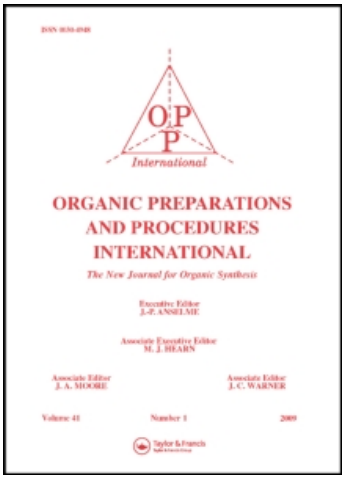

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SELECTIVE ELECTROPHILIC AROMATIC SUBSTITUTIONS *VIA* POSITIONAL PROTECTIVE GROUPS: A REVIEW

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SELECTIVE ELECTROPHILIC AROMATIC SUBSTITUTIONS VIA POSITIONAL PROTECTIVE GROUPS. A REVIEW

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SELECTIVE ELECTROPHILIC AROMATIC SUBSTITUTIONS VIA POSITIONAL PROTECTIVE GROUPS: A REVIEW

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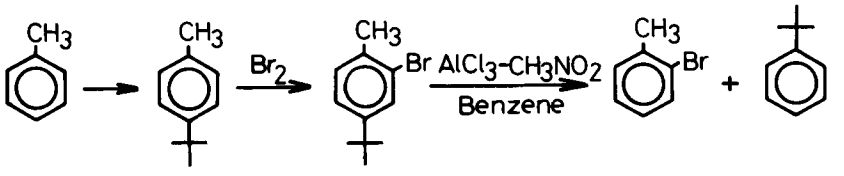
INTRODUCTION

The importance of electrophilic aromatic substitution reactions in organic synthesis needs no emphasis. However, there still remain some problems in the selective introduction of functional groups in order to obtain compounds with the desired orientation. The desired orientation may be achieved by blocking the most reactive site, then carrying out the desired substitution followed finally by removal of the protective group. The following positional protective groups have been used up to now: carbonyl, nitro, sulfonic acid, amino, iodo, bromo, chloro, t-butyl and isopropyl.[1] For example, since electrophilic bromination of toluene yields



(1)

I II III IVa

predominantly p-bromotoluene, the para position may first be blocked by t-butylation[2] followed by bromination and removal of the blocking t-butyl group by transalkylation.[3]

Recently we have extended the positional protective method to prepare some alkyl- and halophenols, hydroxydiphenylmethanes and hydroxydiphenyls using benzyl, t-butyl, iodo, bromo and chloro groups as a positional protective groups for the selective synthesis of aromatic compounds. The present review will summarize recent investigations carried out in our laboratory and by the others during the past 2 years; the literature has been covered up to 1975.

I. SELECTIVE PREPARATION OF HALOPHENOLS

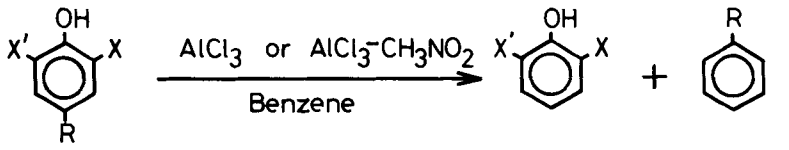
1. Benzyl and t-Butyl as a Positional Protective Groups[4]

It has been previously reported[5-8] that the benzyl group in diphenylmethnaes was easily transferred to aromatic compounds such as benzene, toluene and chlorobenzene under the influence of Friedel-Crafts catalysts. These results strongly suggested that the benzyl as well as t-butyl group might serve as a posiiotnal protective group in aromatic electrophilic substitution reactions.

Indeed, the transalkylation of halophenols which were easily prepared by the halogenation of the corresponding alkylphenols afforded the desired halophenols in good yields respectively (Table 1).

However, in addition to the expected products the transalkylation of Va, Vb and Vc with $AlCl_3$ as the catalyst gave by-products resulting from the transbromination of the desired

products (VIa - VIb); indeed treatment of Va with $AlCl_3$ under the same experimental conditions afforded 2-bromophenol (VIh) and bromobenzene.

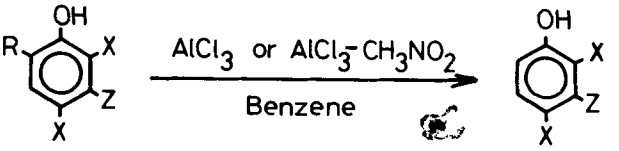


V VI IV (2)

	R	X	X'
a)	benzyl	Br	Br
b)	t-butyl	Br	Br
c)	t-butyl	Br	Cl
d)	benzyl	Cl	Cl
g)	t-butyl	Cl	Cl
j)	t-butyl	Br	H
h)	t-butyl	Cl	H

a) X = X' = Br
b) X = Br, X' = Cl
c) X = X' = Cl
h) X = Br, X' = H
i) X = Cl, X' = H

a) R = benzyl
b) R = t-butyl



V VI + IV (3)

	R	X	Z
e)	t-butyl	Br	H
f)	t-butyl	Cl	H
h)	t-butyl	Br	Me
j)	t-butyl	Cl	Me

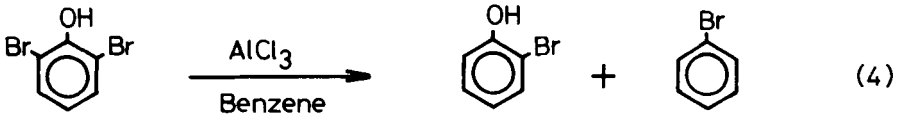
d) X = Br, Z = H
e) X = Cl, Z = H
f) X = Br, Z = Me
g) X = Cl, Z = Me

Table 1. The Transalkylation of Haloalkylphenols (V) in Benzene ($AlCl_3$ or $AlCl_3$-CH_3NO_2 Catalysts)[a]

		Product (%)			
Run	V	VI	VI	X-C_6H_4OH	PhBr
1[e]	a	a (58)	a (100)	2-Br- (24)	(28)
2[c,i]	a	a (70)	a (88)	2-Br- (14)	(16)
3[e]	b	a (78)	b (72)	2-Br- (25)	(23)
4[c]	b	a (79)	b (81)	2-Br- (9)	(9)
5[b,e]	b	a (15)	b (13)	—	—
6[b,i]	b	a (74)	b (85)	—	—
7[c]	c	b (97)	b (97)	2-Cl- (4)	(5)
8[b,i]	c	b (19)	b (27)	—	—
9[f]	d	c (78)	a (83)	—	—
10	e	d (64)	b (73)	2-Br- (15) 4-Br- (7)	(18)
11[b,i]	e	d (42)	b (49)	—	—
12[g]	f	e (52)	a (62)	—	—
13[d]	f	e (89)	a (82)	—	—
14	g	c (80)	b (70)	—	—
15[b,j]	h	f (95)	b (93)	—	—
16[b,h,k]	h	f (46)	b (45)	—	—
17	i	g (74)	b (52)	—	—
18[b]	j	—	b (81)	2-Br- (82)	—
19[b]	k	—	b (69)	2-Cl- (72)	—

a) Benzene/V = 30 moles/1 mole; catalyst/V = 1.2 mole/1 mole; catalyst is $AlCl_3$; temperature is 50° and time is 2 hrs unless otherwise indicated. b) $AlCl_3$-CH_3NO_2 catalyst. c) Temp.: 30°. d) Temp.: 80°. e) Time: 1 hr. f) Time: 3 hrs. g) Time: 5 hrs. h) Time: 6 hrs. i) Time: 10 hrs. j) VII ($C_{14}H_{10}Br_4O_2$) obtained 7% yield. k) VII obtained 16% yield.

However, the transbromination reaction was repressed to some extent at lower reaction temperature (runs 2,4,7).



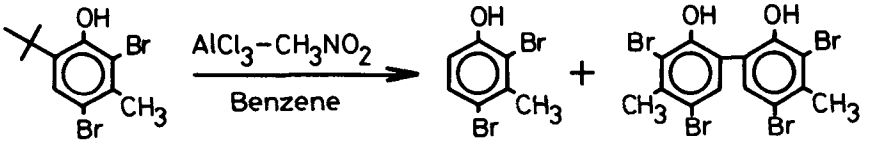
(4)

VIa VIh

In no case was transchlorination observed with $AlCl_3$ as catalyst. These results seem to suggest that the bromo group of phenols might serve as a positional protective group in the preparation of certain chlorophenols which will be discussed in more detail later.

It should be also noted that in contrast with $AlCl_3$, the $AlCl_3$-CH_3NO_2 catalyst[4,6,7] which is known to be inactive in the transbenzylation reaction of diphenylmethanes, proved to be an excellent catalyst for the transalkylation of t-butylhalophenols as well as t-butylphenols[8] but not for transbromination and transbenzylation. This result apparently suggests that the $AlCl_3$-CH_3NO_2 catalyst would be most suitable for the preparation of bromophenols by using t-butyl group as the positional protective group.

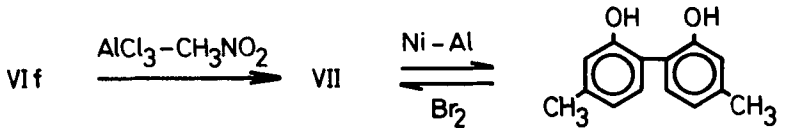
Although the $AlCl_3$-CH_3NO_2 catalyzed transalkylation of Vh afforded the expected VIf in good yield, small amount of by-product VII was obtained. The yield of VII increased with reaction time, while that of VIf decreased (runs 15 and 16 of Table 1); VII was also formed by the treatment of VIf with $AlCl_3$-CH_3NO_2 catalyst under the same conditions as those used



(5)

Vh VIf VII

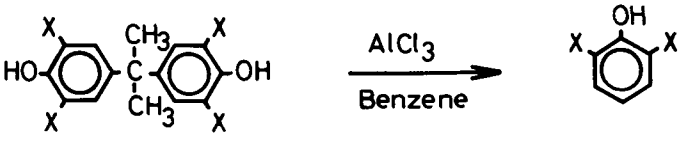
for the transalkylation of Vh. VII was easily reduced by Raney Ni-Al alloy in 10% sodium hydroxide solution to the debrominated compound VIII which could be brominated with bromine in acetic acid to VII in good yield.



(6)

VIII

When bisphenol A (IX) was treated with $AlCl_3$ in benzene, phenol was obtained in good yield.[8] This result also suggests that IX as well as 4-t-butylphenol might be a starting compound to prepare VIa and VIc . 3,3',5,5'-Tetrabromo (Xa) and 3,3',5,5'-tetrachloro-bisphenol A (Xb) treated with $AlCl_3$ at 50° for 5 hrs, gave the expected VIa and VIc in 57 and 86% yield respectively.[9]



(7)

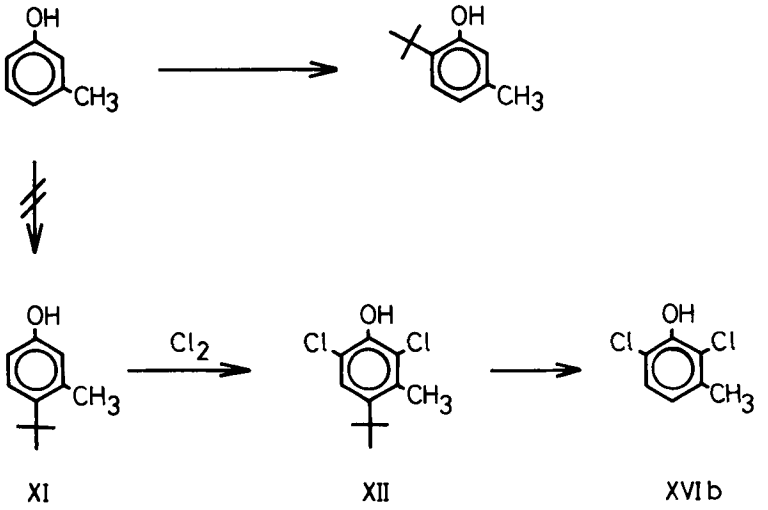
X VI

a : X = Br
b : X = Cl

However, in the case of Xa, by-products resulting from transbromination of VIa were isolated in 6 and 5% yield as described previously in the transalkylation of Va-c.

2. Bromine as a Protective Group[10]

As described in the above section, the bromo group appeared promising as a positional protective group in the preparation of chlorophenols. The preparation of 2,6-dichloro-3-methylphenol (XVIb) from 4-t-butyl-2,6-dichloro-3-methylphenol (XII) by the transalkylation method was not practical because the starting compound 3-methyl-4-t-butylphenol (XI) could not be obtained by the Friedel-Crafts t-butylation of m-cresol.

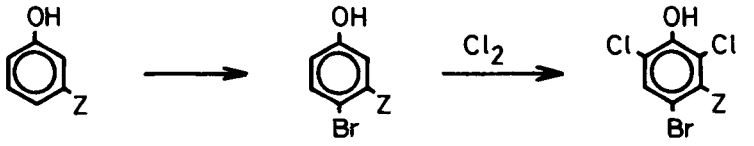


(8)

XI XII XVIb

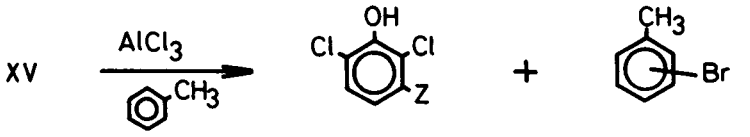
However, XVIb was prepared by the transbromination of XVb, obtained from m-cresol (XIIIb) through the bromination then chlorination, XVIa was obtained by the same method.

Although benzene could be used in place of toluene as a solvent and acceptor of bromo group, the yields of the products were lower than those obtained with toluene used as solvent and acceptor.



XIII XIV XV (9)

a: Z = H, b: Z = Me

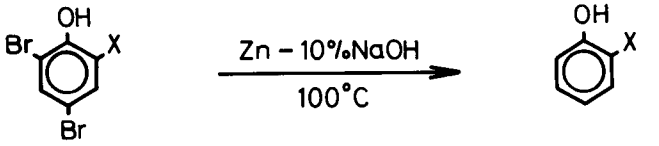


XVI XVII

a: 78%, b: 70%

3. By Selective Reduction of Halophenols[11]

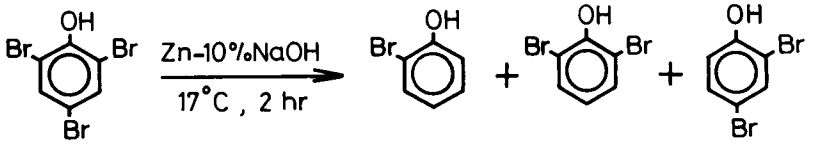
It is well known that some halophenols can be dehalogenated to the corresponding phenols with suitable reducing agents.[4,12-14] This suggests that halo groups might be used as positional protective group with suitable reducting agents. Investigation of the reduction of halophenols under various conditions showed that zinc powder-10% HCl-EtOH and zinc powder-10% NaOH could be used to selectively dehalogenate halophenols. For example,



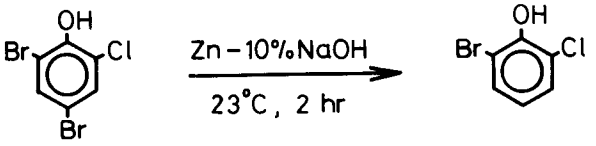
XVIII VI (10)

a : X = Br h : 85.5%
b : X = Cl i : 60.5%

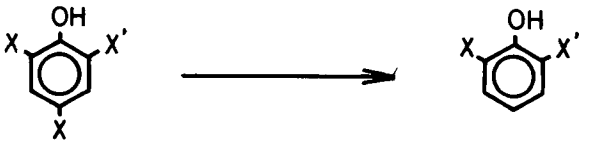
It should be noted that in zinc powder-10% NaOH system, iodo and bromo groups in the para position of halophenols could selectively be dehalogenated to give the corresponding halophenols. However, in the case of XVIIIa, 2,6-dibromophenol was not obtained but 2-bromophenol (VIh) was selectively formed under the conditions used. While at much lower temperature, XVIIIa afforded VIa, VId and VIh. In contrast, XVIIIb gave only VIb in good yield;



XVIIIa VIh 17% VIa 56% VId 3% (11)



XVIIIb VIb 85% (12)

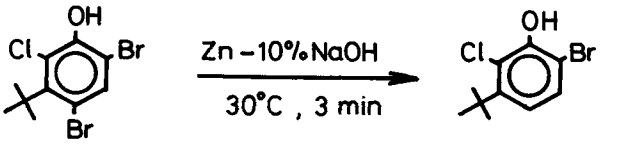


(13)

XIX XX

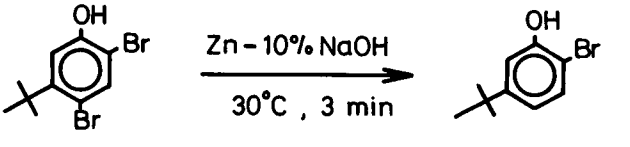
a: X = I, X' = Cl
b: X = Br, X' = Cl
c: X = I, X' = Br

a: X' = Cl 80-83%
b: X' = Br 87%



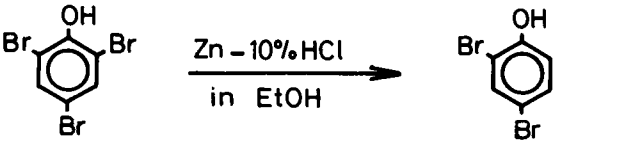
(14)

XXI XXII
84%



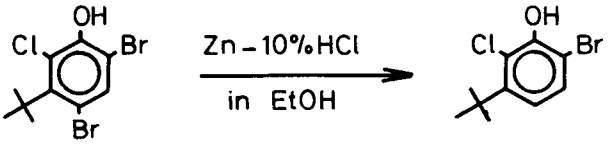
(15)

XXIII XXIV
83%



(16)

XVIIIa VId
96%



XXV XXVI

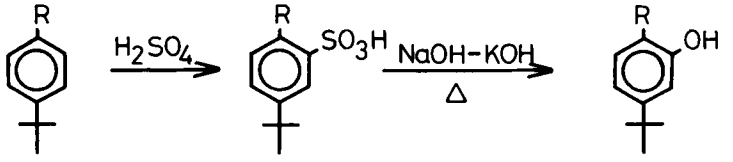
91%

(17)

The Zn-HCl reductive system gave only 2,4-dibromophenol (VId). However, in the reductive debromination of XXV, the bromo group of para position of XXV was selectively removed to give XXVI in good yield.

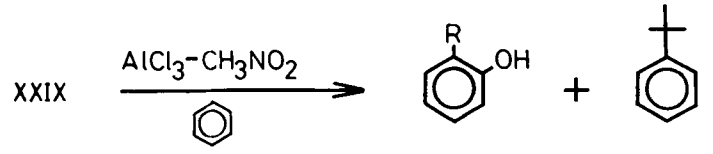
II. SELECTIVE PREPARATION OF ALKYLPHENOLS WITH t-BUTYL AS A PROTECTIVE GROUP[15]

In our laboratory, a new preparative method of some alkylphenols was recently developed by using t-butyl function as a positional protective group as shown in the following scheme.



XXVII XXVIII XXIX

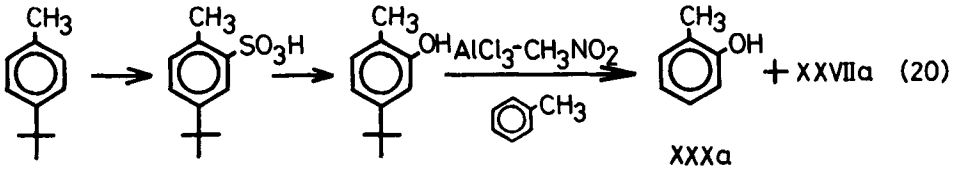
(18)



a: R = CH_3, C_2H_5, n-C_3H_7 XXX IVb

(19)

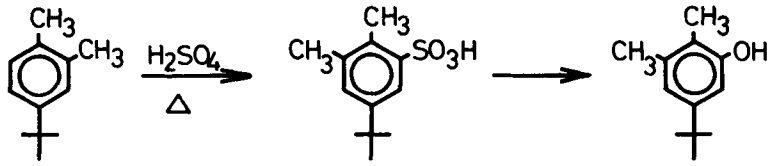
These reactions could be recycled as shown in equation (20).



(20)

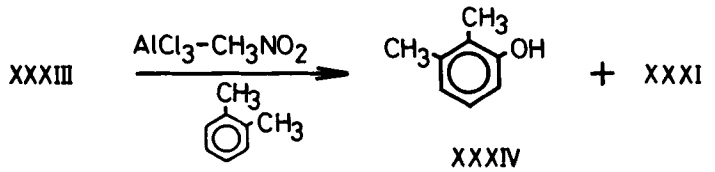
XXVIIa XXVIIIa XXIXa XXXa

Also xylenols were prepared selectively in the same way.

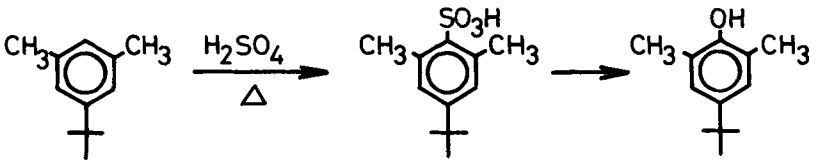


XXXI XXXII XXXIII

(21)

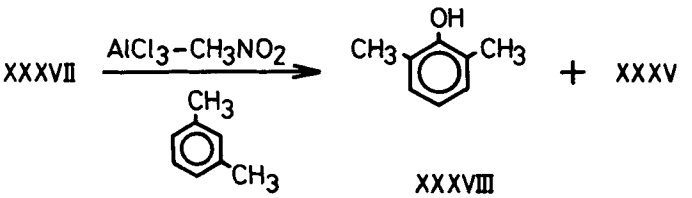


XXXIV



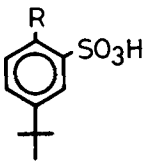
XXXV XXXVI XXXVII

(22)

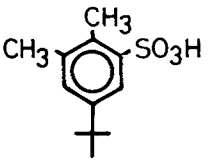


XXXVIII

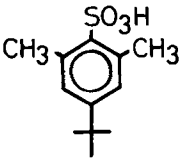
The starting materials XXXI and XXXV were regenerated in the last reaction. It was also found that they can very easily be obtained from o-xylene and m-xylene by using transalkylation of 2,6-di(t-butyl)-p-cresol.[2] Attempts to transalkylate of sulfonic acids XXVIII, XXXII and XXXVI was unsuccesful and only the starting materials were recovered.



XXVIII



XXXII



XXXVI

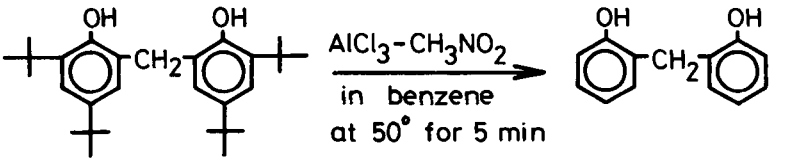
III. SELECTIVE PREPARATION OF HYDROXY DIPHENYLMETHANES

1. Using t-Butyl Group[16]

As was mentioned in section II, the t-butyl group of t-butylphenols and t-butylhalophenols is easily transferred to benzene used as a solvent and acceptor to give the corresponding phenols and halophenols under the infulence of a mild catalyst such as $AlCl_3$-CH_3NO_2 which did not catalyze the transbenzylation reaction of diphenylmethanes. These results seemed to suggest strongly that t-butyl group might serve as a protective group in the preparation of some diphenylmethanes.

Indeed, 2,2'-dihydroxy- (XL), 2,2'-dihydroxy-5,5'-di(t-butyl)- (XLI), 2,2'-dihydroxy-5,5'-dimethyl- (XLII), and 2,2'-

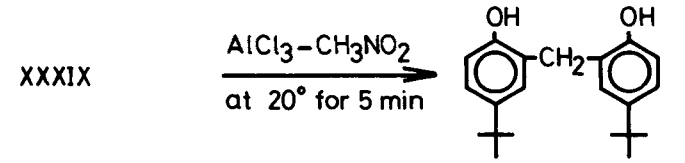
dihydroxy-3,3'-dibromodiphenylmethane (XLVII) were prepared by the transalkylation of the corresponding t-butyl derivatives[17] in the presence of $AlCl_3$-CH_3NO_2 catalyst in benzene solution.



(23)

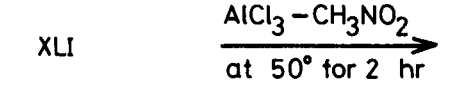
XXXIX

XL 60%

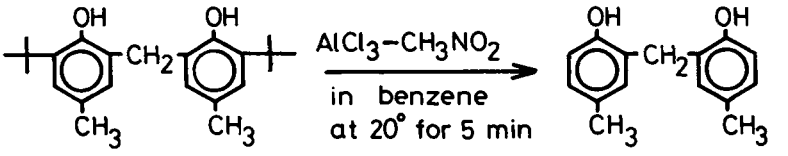


(24)

XLI 80%

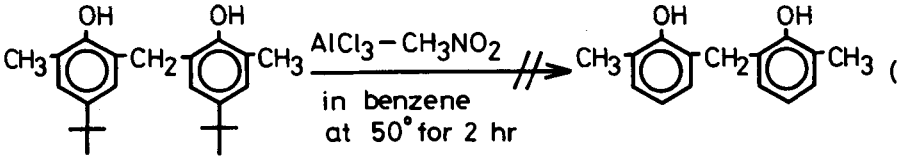


(25)



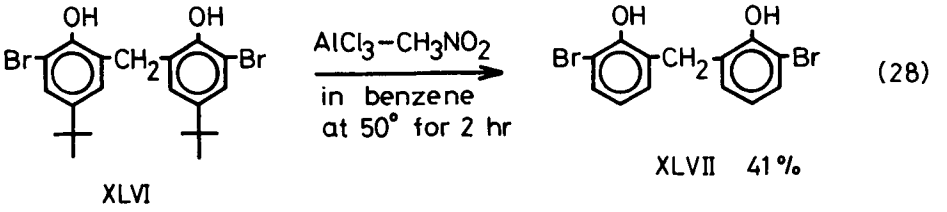
(26)

XLII XLIII 85%



(27)

XLIV XLV



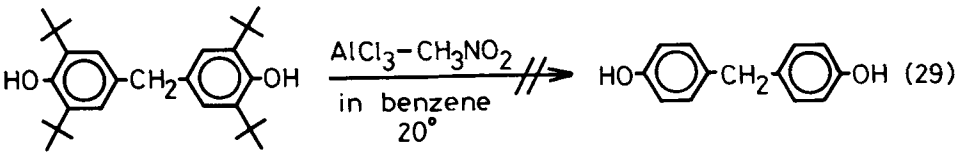
XLVI

XLVII 41%

(28)

However, the transalkylation of XLIV did not give the expected compound XLV but only starting material XLIV was recovered in almost quantative yield. It should be noted that the ortho-t-butyl group of XXXIX could be transferred more easily than the para-t-butyl group.

It was found[18] that in contrast with 2,2'-dihydroxydiphenylmethanes, 4,4'-dihydroxydiphenylmethane (XLIXa) could not easily be prepared by the above method from 3,3',5,5'-tetra(t-butyl)-4,4'-dihydroxydiphenylmethane (XLVIII).



XLVIII

XLIX a

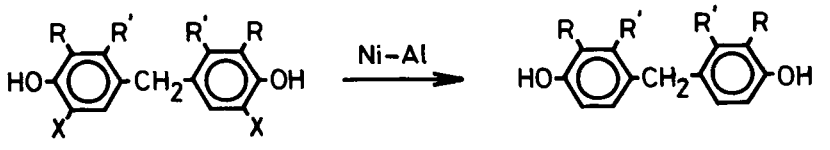
(29)

The expected XLIXa was obtained in only trace amount yield with large amount of resinous material and unidentified compounds.

2. Using Bromine and Chlorine as Positional Group[19,20]

However, the desired 4,4'-dihydroxydiphenylmethanes (XLIXa) could be prepared by using the chloro or bromo groups

as a protective group. The dehalogenation of 3,3',5,5'-tetrabromo- (La), 5,5'-dichloro-3,3'-dimethyl- (Lb), 3,3',5,5'-tetrachloro-2,2'-dimethyl-4,4'-dihydroxydiphenylmethane (Lc) which could be easily prepared from corresponding halophenols and 37% formalin were reduced with Raney-Ni alloy in 10% NaOH solution to give the corresponding XLIXa, XLIXb and XLIXc in good yield.

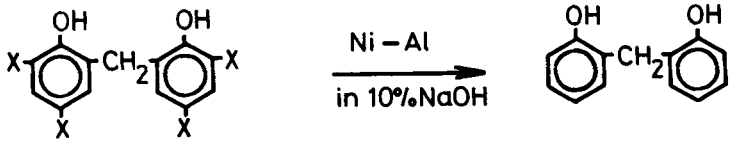


(30)

L XLIX

a: R = X = Br, R' = H	a: R = R' = H	95.5%
b: R = CH_3, X = Cl, R' = H	b: R = CH_3, R' = H	96.0%
c: R = X = Cl, R' = H	c: R = H, R' = CH_3	98.0%

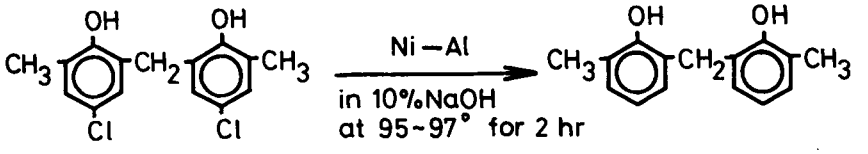
This method was applied to the preparation of 2,2'-dihydroxydiphenylmethanes.



(31)

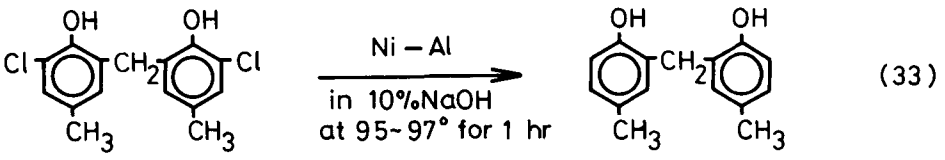
LI XL

a: X = Cl	at 95-97° for 30 min	51%
b: X = Br	at room temperature for 10 min	65%

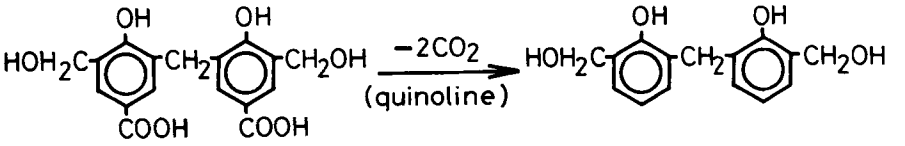


(32)

LII XLV 50%



LIII XLIII 87 % (33)

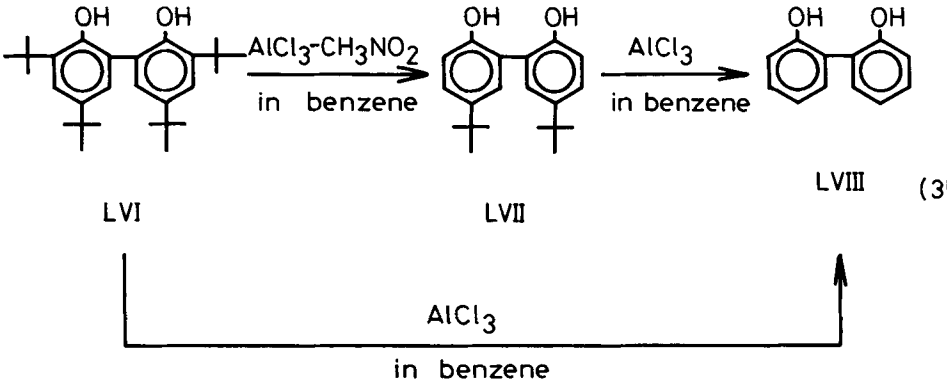


LIV LV (34)

This reductive method seemed to be practical method for the preparation of XLV which could not be obtained by the transalkylation method previously described. Recently, Lotz and Böhmer reported the preparation of LV by the decarbonylation of LIV in quinoline.[21]

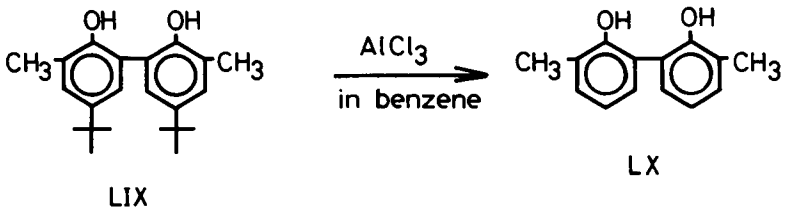
IV. SELECTIVE PREPARATION OF DIHYDROXYDIPHENYLS[22,23]

Some dihydroxydiphenyls were also prepared from the

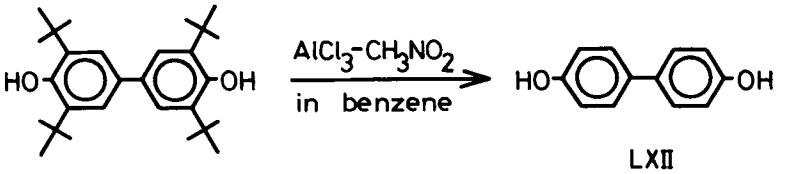


LVI LVII LVIII (35)

corresponding t-butyl derivatives using the transalkylation method.

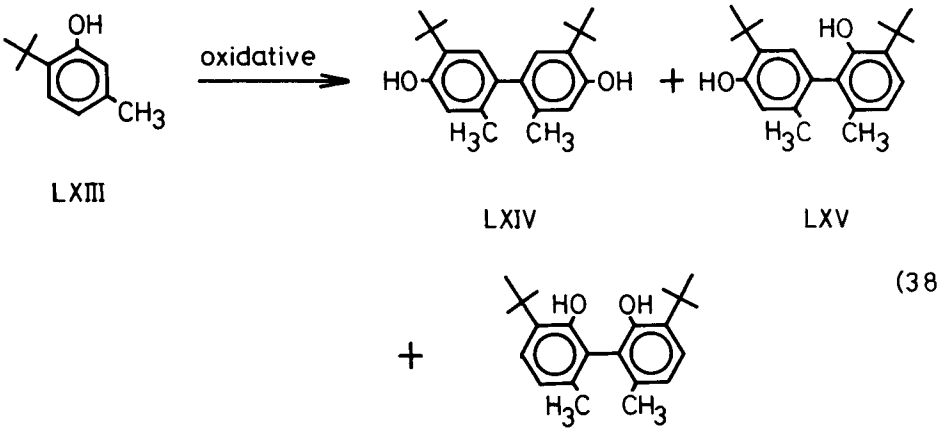


LIX LX (36)

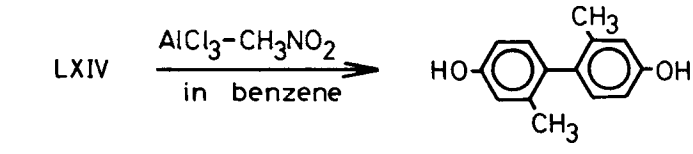


LXI LXII (37)

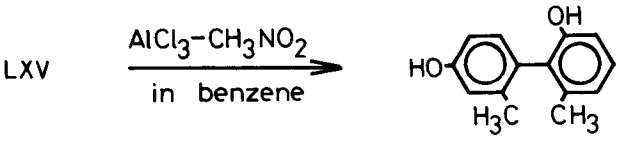
The t-butyl groups of para position in LVI, LVII and LIX could not be transferred by the influence of $AlCl_3$-CH_3NO_2 catalyst. However, in the presence of $AlCl_3$, the expected LVIII from LVI and LVII was obtained. In contrast with 4,4'-dihydroxydiphenylmethane XLIXa, the transalkylation of LXI occurred and afforded the expected LXII in 82% of yield. Also the dimers of oxidative coupling of m-cresol could be prepared by the transalkylation method as shown in the following scheme.



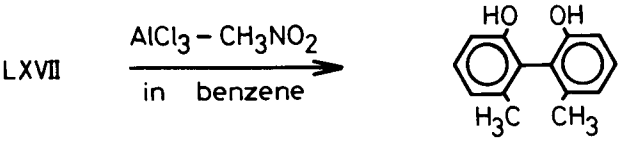
LXIII LXIV LXV LXVI (38)



LXVII (39)



LXVIII (40)



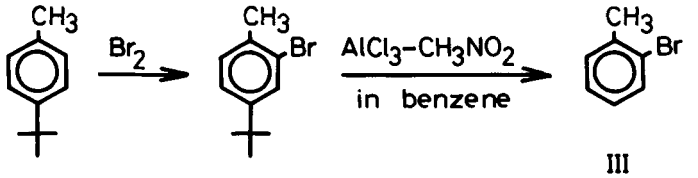
LXIX (41)

V. OTHERS APPLICATION

The transalkylation method was applied for the preparation of diaryl ethers because the ether linkage is not cleaved under the condition which t-butyl group of diaryl ether is easily transferred to benzene used as a solvent and acceptor.[24]

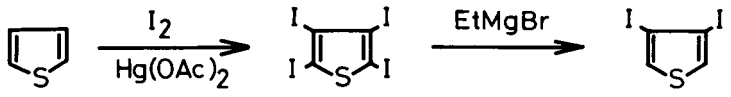
LXX LXXI (42)

Also o-halogenoalkylbenzene could be prepared by using the above transalkylation method as described previously.[3]



I II III (43)

As described previously, t-butyl, chloro, bromo and iodo groups could be used as a positional protective group for the halophenols, alkylphenol, dihydroxydiphenylmethanes and dihydroxydiphenyls. Recently Hori, Kataoka and Yoshimura reported that 3,4-diiodothiophene (LXXIV) was prepared by the reductive deiodonation of 2,3,4,5-tetraiodothiophene (LXXIII) which was prepared by the iodonation of thiophene (LXXII).[25]



LXXII LXXIII LXXIV (44)

These results shows that the iodine could serve as a positional protective group for the preparation of β-substituted thiophene derivatives.

CONCLUSION

The investigations carried out so far indicate that

a) The benzyl group can be used only for the chlorophenols.

b) The t-butyl group is best suited for preparation of the bromophenols, dihydroxydiphenyl and 2,2'-dihydroxydiphenylmethanes but not 4,4'-dihydroxydiphenylmethanes.

c) The transbromination of bromophenols with aluminum chloride in toluene could be applied to the preparation of chlorophenols.

d) Selective reductive dehalogenation could be applied to preparation of some halophenols, alkylhalophenols and thiophenes.

e) The t-butyl group is also suited for the preparation of alkylphenols.

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