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De-*tert*-butylation of Substituted Arenes

Sadiq A. Saleh and Hasan I. Tashtoush*

Department of Chemistry, Yarmouk University, Irbid, Jordan

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1. Introduction

The *tert*-butyl group is often employed in the field of synthetic organic chemistry. It has found wide use as a protecting and/or blocking group, and its applications in these regards have been the subject of numerous reports.[1-5] Thus, the *tert*-butyl group was used as a useful positional protecting group for the selective preparation of 2-substituted phenolic compounds such as halophenols,[1,2] 2,2 -dihydroxyphenols[3], alkylphenols[4] and hydroxydiarylmethanes.[5] In addition, the *tert*-butyl group was used as the C-terminal protecting group in the synthesis of peptides,[6-15] and to block the alcoholic hydroxyl groups of the main hydroxyl-L-amino acids.[16-18] The suitability of the *tert*-butyl group for alcohol protection is due to the fact the *tert*-butyl ethers are stable to alkali but conveniently cleaved by acids. The *tert*-butyl group was also used successfully to protect the amino group in the synthesis of primary sulfamides, [19-21] and thiols.[22-27]

* *E-mail: yaserhaj@hotmail.com.* Fax (000962)2274-725

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The introduction of the *tert*-butyl group can be achieved either via direct *tert*-butylation of a substrate or chemical modification of *tert*-butylated compounds. Thus, tri-*tert*-butylnitrobenzene was prepared in high yield by the nitration of tri-*tert*-butulbenzene, but not by the *tert*-butylation of nitrobenzene.[28,29] However, 2,4,6-tri-*tert*-butylphenol was easily obtained by *tert*-butylation of phenols.[30] Recently, much attention has been paid to the removal reactions of this *tert*-butyl substituent.

This review covers the reagents most frequently used for the de- *tert*-butylation involving carbon-carbon bond rupture. De- *tert*-butylation involving carbon-heteroatom cleavage namely carbon-oxygen, carbon-nitrogen or carbon-sulfur bonds, will be mentioned only briefly.

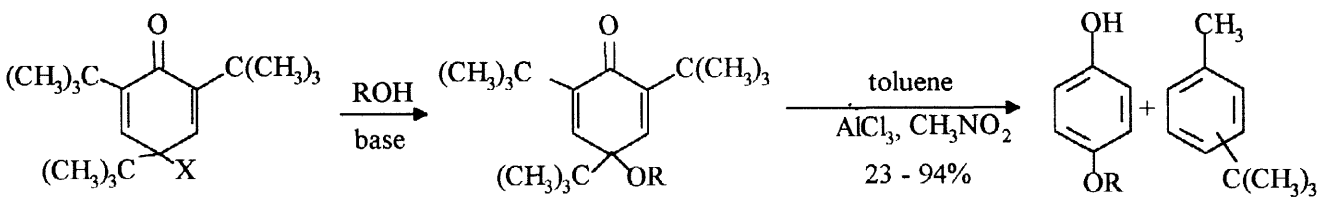
Due to the wide range of functionalities that can be prepared through *tert*-butylation-de-*tert*-butylation reaction sequence, this review is classified according to the catalyst used for the deprotection. It is worth noting that some of the material for this review appears as patents. However, the review covers all the related literature including the patents; but the experimental details for the patented material is limited.

2. Lewis Acid Catalyzed De-*tert*-butylation

Lewis acids have been widely used to remove the *tert*-butyl group from aromatic substrates. The reaction needs an aromatic compound such as benzene or toluene to act as an acceptor for the detached *tert*-butyl substituent. This approach has been used for the synthesis of a variety of aromatic compounds.[4,32-39] Among the different Lewis acid catalysts, aluminum chloride ($AlCl_3$) was found to be the catalyst of choice for its effectiveness and convenience, especially during work-up.

4-Hydroxyphenyl ether **3** was prepared from the reaction of 4-alkoxy-2,4,6-tri- *tert*-butylcyclohexadien-2-one **2** with toluene in the presence of $AlCl_3$-CH_3NO_2 . Compound **2** was readily obtained from the reaction of the corresponding 4-halocyclohexadiene derivatives **1** with alcohols, Scheme 1. [31,32]

Scheme 1

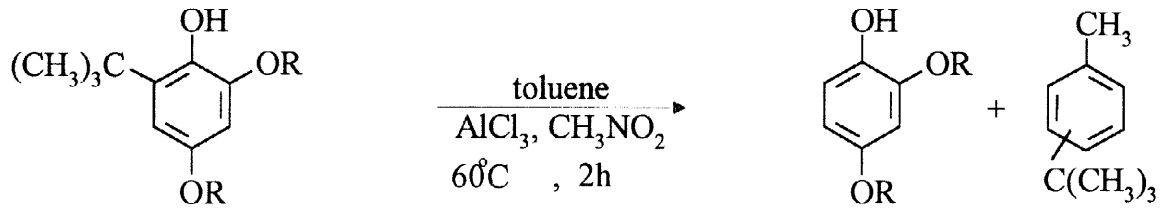


1 **2** **3**

X = Br, Cl R = CH_3, C_2H_5, n-C_3H_7

Similarly, 2,4-dialkoxy-6-*tert*-butylpenols **4** gave phenols **5** when treated with toluene and $AlCl_3$-CH_3NO_2, Scheme 2. It is worth mentioning that the treatment of compound **2** with conc. HCl in methanol led to

Scheme 2

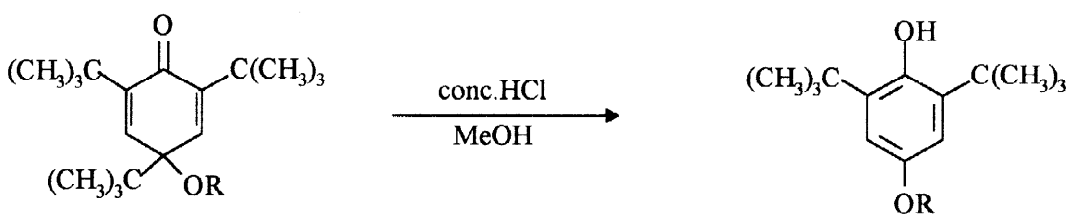


4 **5**

R = CH_3 (68%), C_2H_5 (72%), n–C_3H_7 (76%)

partial de-*tert*-butylphenols to afford the corresponding 4-alkoxy-2,6-di-*tert*-butylphenols **6** in good yields, Scheme 3.[32]

Scheme 3

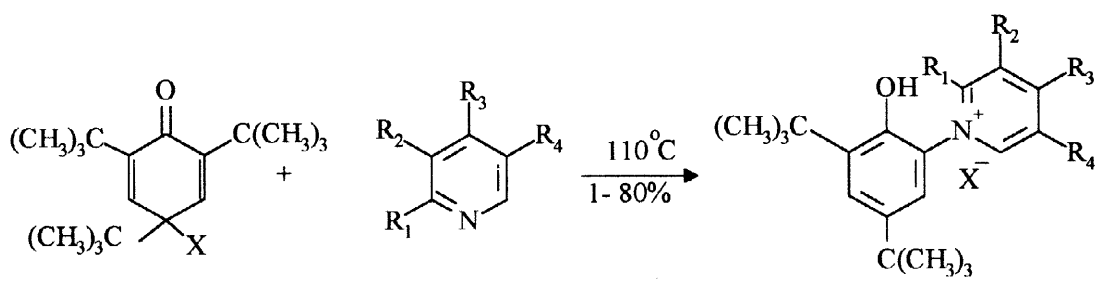


2 **6**

R = CH_3 (97%), C_2H_5 (94%), n–C_3H_7 (81%), i–C_3H_7 (96%), $CH_2C_6H_5$ (87%).

Such partial de-*tert*-butylation was also accomplished by treating compound **1** with base such as pyridine or β-picoline.[33] The reaction gave better yields in the presence of ethylene glycol. Thus, treatment of **1** with pyridine gave product **7** among other phenolic products, Scheme 4.

Scheme 4

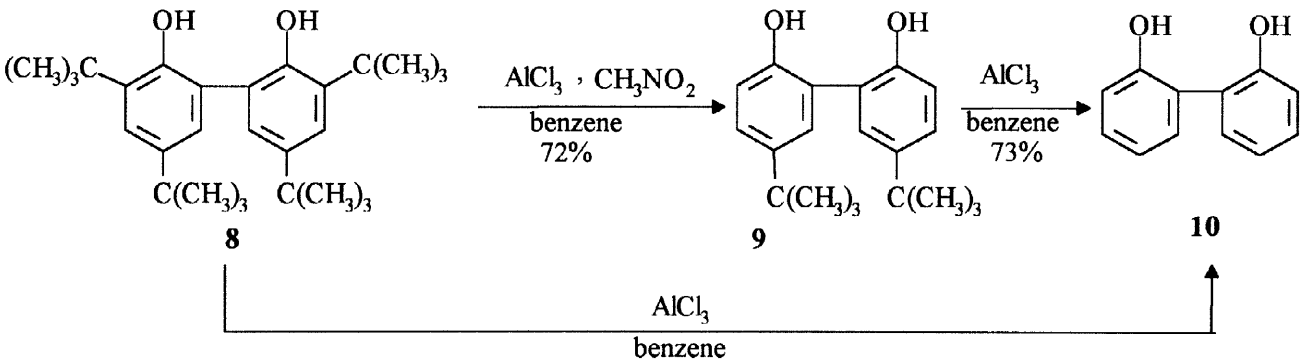


1 **7**

$R_1 = R_2 = R_3 = R_4 = H, CH_3$; X = Br , Cl

Substituted phenols,[4,34] dihydroxybiphenyls[35-38] and oligo[hydroxy-1,3-phenylene]methylenes[39] were prepared using de-*tert*-butylation as a key step. Treatment of 3,3′,5,5′-tetra-*tert*-butyl-2,2′-dihydroxybiphenyl **8** and 5,5′-di-*tert*-butyl-2-2′-dihydroxybiphenyl **9** with $AlCl_3$ in benzene gave 2,2′-dihydroxybiphenyl **10**, Scheme5. $AlCl_3$-CH_3NO_2 in benzene converted **8** to **9** through partial de-*tert*-butylation, Scheme 5.

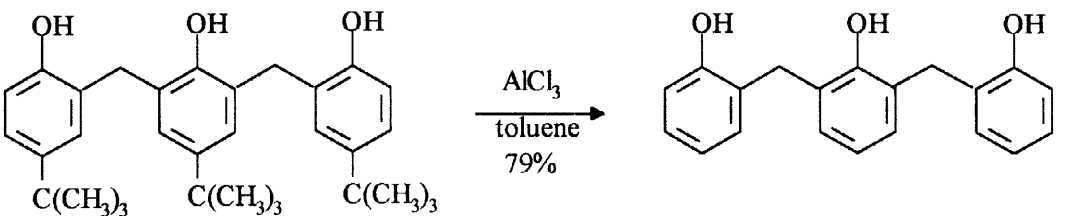
Scheme 5



8 **9** **10**

$AlCl_3$ in toluene has effectively catalyzed the de-*tert*-butylation of oligo[hydroxy-1,3-phenylene]methylenes **11** to the corresponding products **12**, Scheme 6.[39]

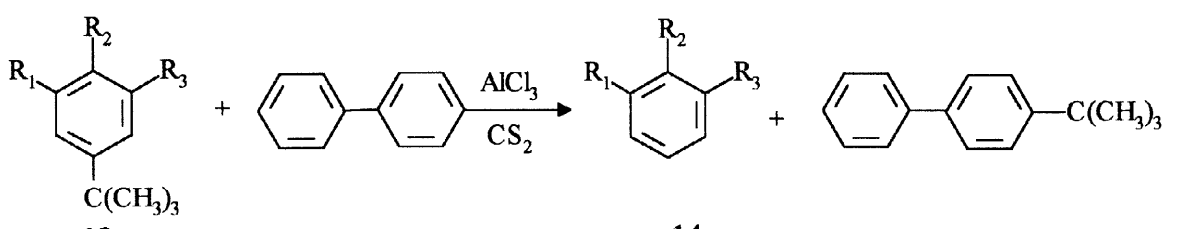
Scheme 6



11 **12**

It has been reported[40,41] that the reaction of 2,3,6-trichloro-4-*tert*-butyltoluene in benzene or toluene with $AlCl_3$ afforded 2,3,6-trichlorotoluene in high yield (97%). Similarly, 1,2,3-trisubstituted benzenes **14** were prepared by Lewis acid catalyzed de-*tert*-butylation of the corresponding *tert*-butyl derivatives **13** with biphenyl being added as an acceptor for the *tert*-butyl group, Scheme 7.[42]

Scheme 7

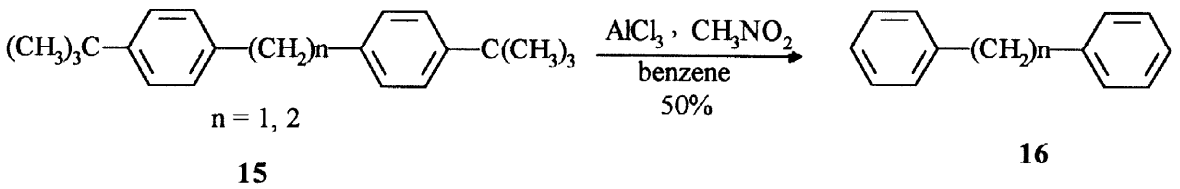


13 **14**

R_1 = H, CH_3 ; R_2 = CH_3 ; C_2H_5 ; R_3 = CH_3

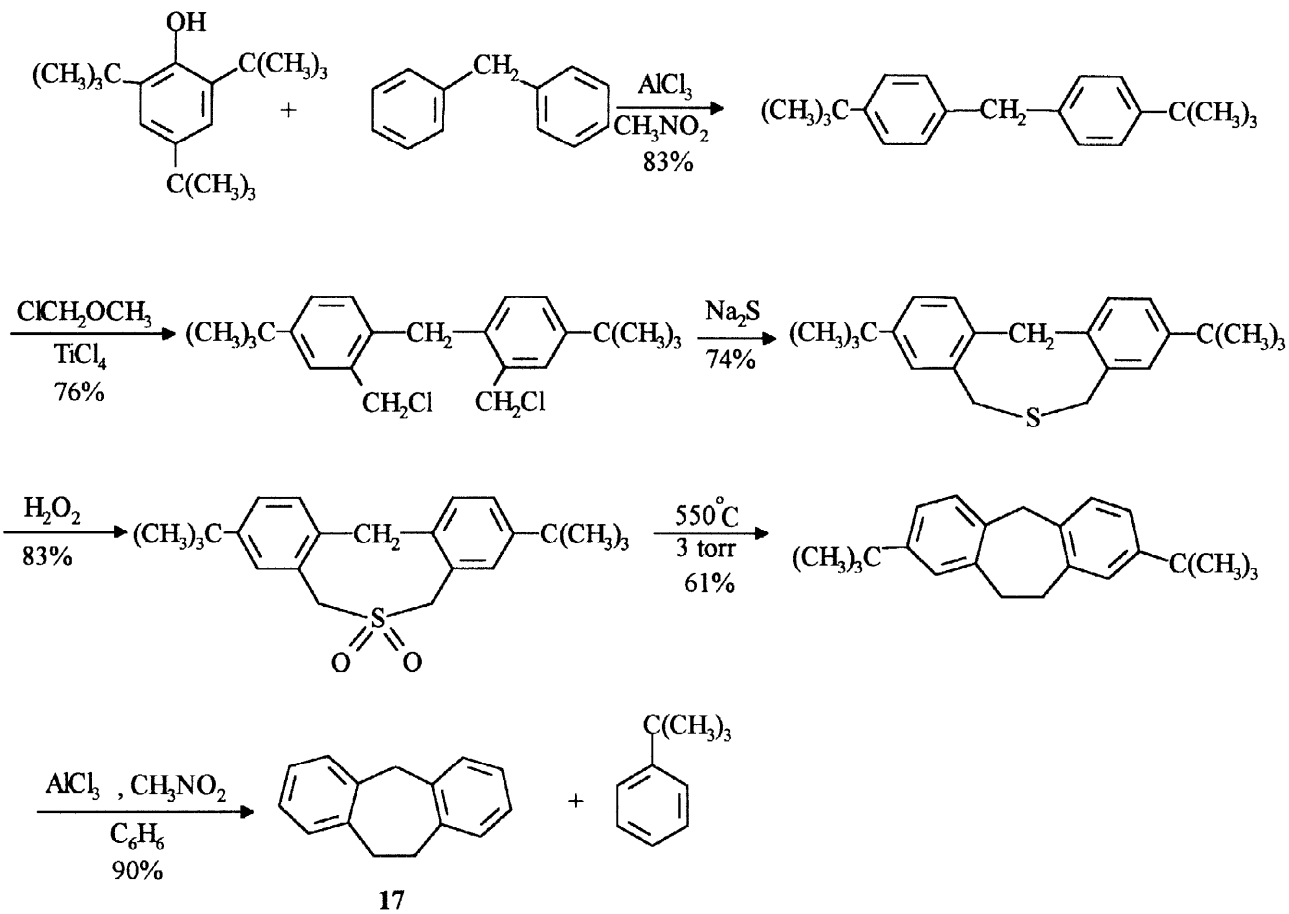
tert-Butyldiphenylmethanes and ethanes **15** underwent de-*tert*-butylation when catalyzed by $AlCl_3$ in benzene to give substituted diphenylmethanes **16**, Scheme 8.[43]

Scheme 8



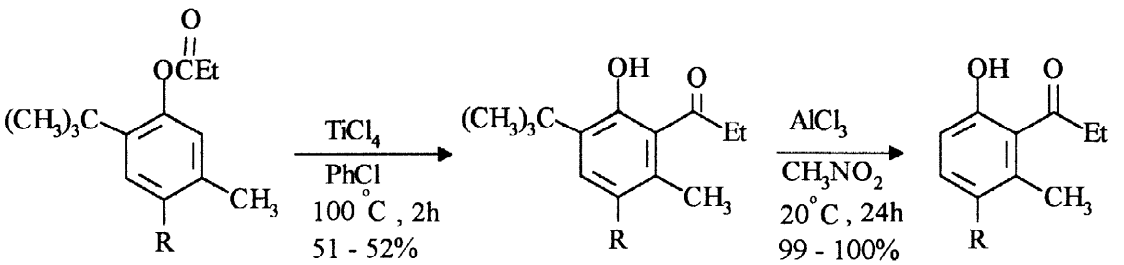
Tashiro and coworkers established a convenient route for the synthesis of 10,11-dihydro-5*H*-dibenzo[a,d]cycloheptane **17** in which de-*tert*-butylation was achieved with $AlCl_3$ as the catalyst, Scheme 9.[44]

Scheme 9



The ketone **20** was prepared by titanium tetrachloride catalyzed Fries rearrangement of 6-*tert*-butylaryl ester **18** to give product **19**, followed by the use of $AlCl_3$ to induce the cleavage of the *tert*-butyl group, Scheme 10.[46]

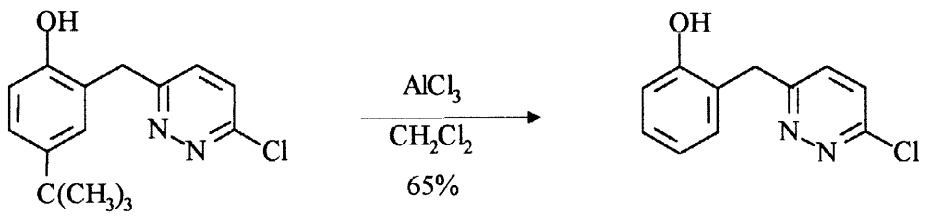
Scheme 10



18 **19** **20**

Recently, Lewis and Morgan reported a facile method for de-*tert*-butylation of phenols under mild reaction conditions. The method utilized $AlCl_3$ in dichloromethane without using a *tert*-butyl acceptor. Thus, treatment of phenol **21** with $AlCl_3/CH_2Cl_2$ gave phenol **22** as the sole product, Scheme 11.[47]

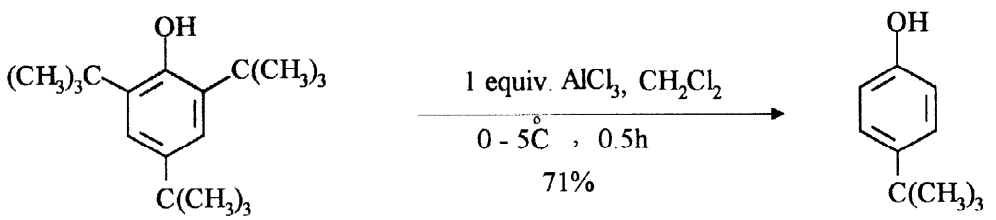
Scheme 11



21 **22**

With careful choice of reaction conditions, it was possible to achieve selective *ortho*-de-*tert*-butylation.[47] Thus, phenol **24** was prepared in reasonably good yield from 2,4,6-tri-*tert*-butylphenol **23**, Scheme 12. The

Scheme 12

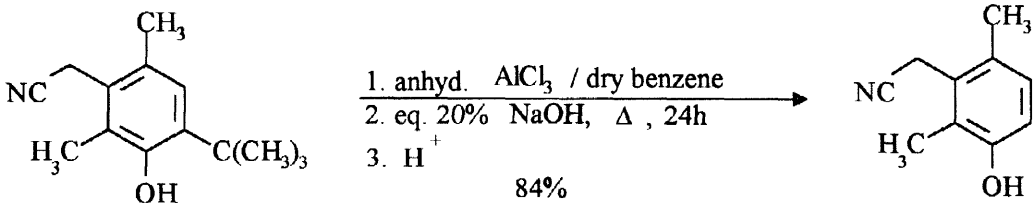


23 **24**

method was found to be quite general and gave better yields under milder reaction conditions than the use of trifluoroacetic acid.[48,49] Similar results were obtained in the de-*tert*-butylation of alkyl quinol ethers.

De-tert-butylation utilizing $AlCl_3$ was used as a key step in the synthesis of the phenylacetic acid **26** from compound **25** using benzene as a *tert*-butyl acceptor, Scheme 13.[50]

Scheme 13



25 **26**

$AlCl_3$ catalyzed de-*tert*-butylation was effectively used in a simple recycling process for the preparation of various *ortho*-bromo substituted benzenes in high yields and high purity.[51]

The macrocyclic compounds, calixarenes, were synthesized via base-induced condensation of *para*-substituted phenols, especially, *tert*-butylphenols. A key step in their synthesis was the de-*tert*-butylation. This was mostly carried out using $AlCl_3$-catalyzed retro-Friedel Crafts reactions.[52-60]

3. Metal Oxide Catalyzed De-*tert*-butylation

The removal of *tert*-butyl group utilizing $AlCl_3$ may be complicated by the fact that the thermodynamic equilibrium may retard complete removal. It has been established that gas-phase de-*tert*-butylation is more efficient and practical than the transalkylation in the liquid phase. Silica-alumina was found to be an effective catalyst for de-*tert*-butylation in the vapour phase.[61-66] The gas phase de-*tert*-butylation of *p*-alkylated-*tert*-butylbenzenes, *p*-halogenated *tert*-butylbenzenes and *p*-alkylated-*tert*-butylanisole were efficiently carried out over commercially obtained silica-alumina catalyst.[63-65] Most of the subst*tert*-butylbenzenes decomposed to the corresponding substituted benzenes, but *p*-*tert*-butylbromobenzene decomposed via complicated networks.[66,67] Similarly alkylbenzenes, including *tert*-butylbenzenes, were readily dealkylated by passing over Cu-Chromite in the presence of oxygen.[68,69] $Ni/Al_2O_3/Cr_2O_3$ was used to dealkylate alkyl adamantanes at high temperatures. The reaction proceeds by a stepwise mechanism successive loss of methyl groups.[70]

α- And β-*tert*-butylnaphthalenes were pyrolyzed in a flow reaction over Al_2O_3-SiO_2 catalyst at 330-490°. De-*tert*-butylation prevailed as the major reaction affording naphthalene in a 32-76% yield; the yield of naphthalene product increased with increasing temperature.[71]

In several cases the catalytic effect of alumina-silica was modified by adding zeolites.[72-73] Thus, the effect of acid strength on selectivity in the decomposition of *p*-*tert*-butylcumene and *tert*-butylbromobenzene, after poisoning of the alumina-silica and zeolites catalysts by pyridine, was investigated.[72] The poisoned catalyst was found to be favourable for the de-*tert*-butylation of halogenated *tert*-butylbenzene. In addition, silica-alumina and HY type zeolite were studied as catalysts in the liquid phase decomposition of *tert*-butyl derivatives of benzenes; a comparison was made in the vapour phase.[74] The decomposition coefficients in the liquid phase were 10 to 100

times as large as in the vapour phase in the de-*tert*-butylation of *tert*-butylbenzenes. The activaton energies for the action of the phenolic derivatives were nearly the same as that for the vapour phase de-*tert*-butylation.

In a recent report, a new process of gaseous-phase dealkylation of alkylphenols by heterogeneous catalysis ($NiSO_4/Al_2O_3$) through a tubular reactor has been described. As a model, the de- *tert*-butylation reaction of 4- *tert*-butyl-2,6-dimethylpenol gave the corresponding de- *tert*-butylated product in 98% conversion and 100% selectivity.[75]

4. Mineral Acid Catalyzed De-*tert*-butylation

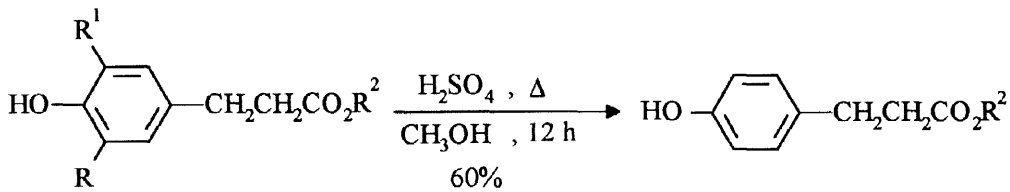
Mineral acids had been employed extensively as catalysts to remove the *tert*-butyl substituent from *tert*-butylated phenols. Several examples of such phenols with varying degrees of substitution have been reported.[76-79] Some aromatic diethers gave similar reactions regarding de-*tert*-butylation compared to hydroquinone and pyrocatechol monoethers in which the aromatic hydrogen atoms are hindered towards electrophilic substitution by *tert*-butyl groups. Such ethers were eventually transformed to the corresponding *para*-benzoquinones and alcohols with catalytic nitrous acid. This method is being notable for its mild conditions, which makes it of potential value for compounds with the appropriate substitution pattern.[76]

2,4, 2,6 and 3,4-di-*tert*-butylphenols, as a mixture, were heated at 200-240 °C with H_2SO_4 catalyst and afforded predominantly *p-tert*-butyl-phenol, which in turm at higher temperatures gave mainly phenol.[77]

The relative degrees of de-*tert*-butylation at 190°C for 4-*tert*-butylphenols, *p-tert*-octylphenol, 2-pheyl-2-(4-hydroxyphenyl)propane and 2,2-bis(4-hydroxyphenyl)propane have been checked and gave 3.7%, 80.6%, 42.9% and 72.0% respectively.[78] The mutual interconversions of *o*-and *p-tert*-butylphenols have been studied at different temperatures with H_2SO_4 being used as the catalyst. It was found that the rates of the total conversion and de-*tert*-butylation of the *para*-isomer were 30 and 10 times greater than for the *ortho*-isomer.[79]

Sulphuric acid was used in the de-*tert*-butylation of some mono- and di-*tert*-butylated aromatic esters and acids to afford 4-hydroxyphenyl propionic acids which are expected to be of potential use as intermediates for prospective drugs and antioxidants. Scheme 14.[80]

Scheme 14

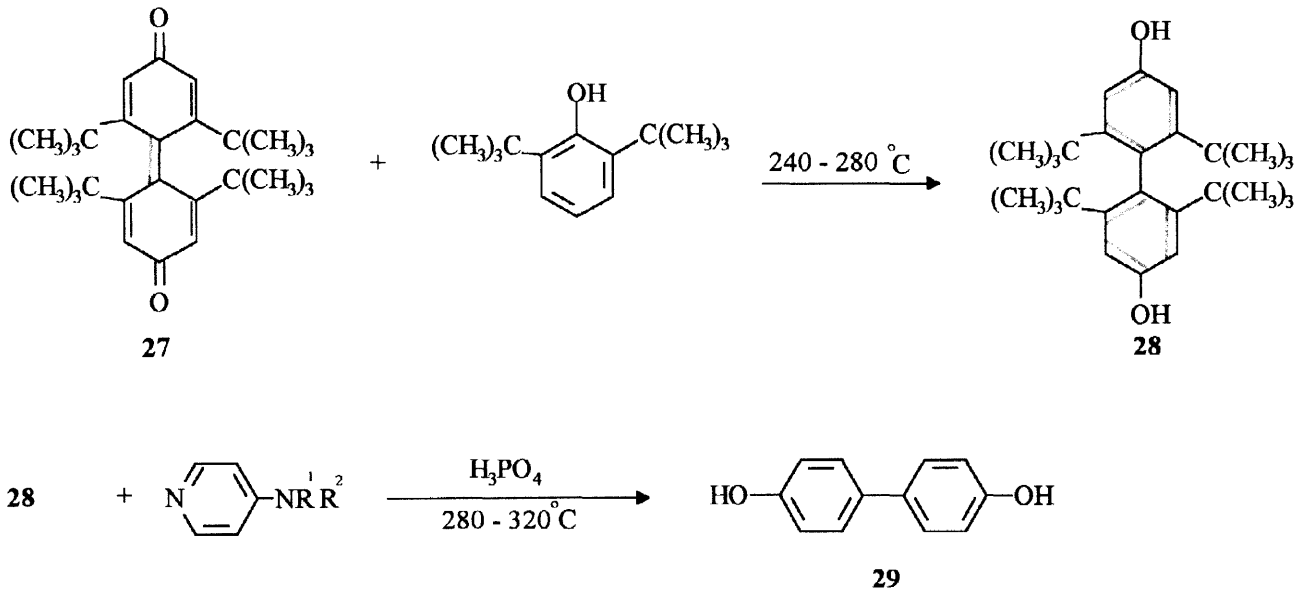


$R = H,\ R^1 = C(CH_3)_3$; $R = R^1 = C(CH_3)_3$; $R^2 = H,\ CH_3$

Treatment of 3,6-di-*tert*-butyl-*o*-benzoquinone with sulphuric acid in a variety of solvents, such as ether, methanol, hexane, carbon tetrachloride and benzene afforded partial and complete de-*tert*-butylation products of pyrocatechol in high yields.[81] Similar results were obtained upon de-*tert*-butylation of 2-methyl-4,6-di-*tert*-butylresorcinol.[82]

Phosphoric acid had been used as an effective catalyst for the de-*tert*-butylation of alkylated phenol.s[83] Recent work confirmed its widespread utility. Thus, 3,3′,5,5′-tetra- *tert*-butyldiphenoquinone **27** was reduced to the corresponding dihydroxybiphenyl, **28**, using 2,6-di-*tert*-butylphenol at 240-280 °C. This dihydroxy compound, without being isolated, was reacted with 4-dialkylaminopyridine in the presence of phosphoric acid at 280-320°C and gave 4,4′-dihydroxybiphenyl **29**, Scheme 15.[84]

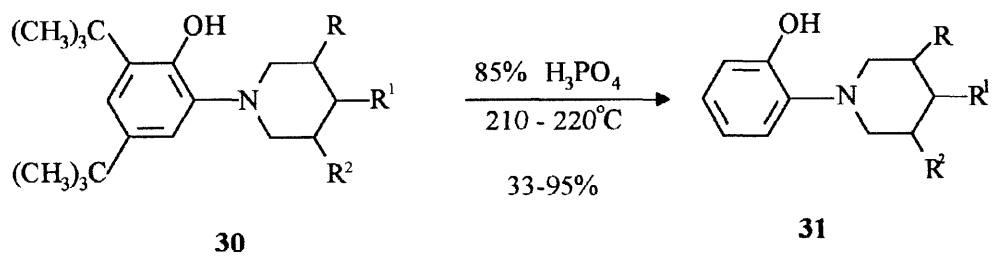
Scheme 15



R^1, R^2 = alkyl

2,4,-Di-*tert*-butyl-6-(2′,3′,4′-trialkylpiperidine)phenol **30** was de-*tert*-butylated and gave *ortho*-trialkylatedpiperidinophenols, **31**, Scheme 16.[85]

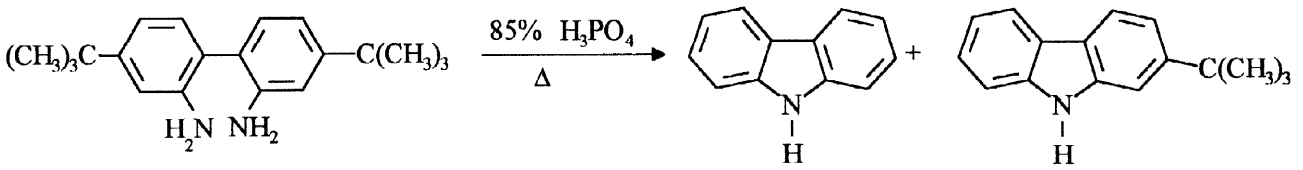
Scheme 16



R, R_1, R_2 = Me, H, Me; H, H, H; Me, H, H; H, Me, H

Carbazole **33** was obtained in a good yield by the thermal de-*tert*-butylation of compound **32** using phosphoric acid as a catalyst, Scheme 17.[86]

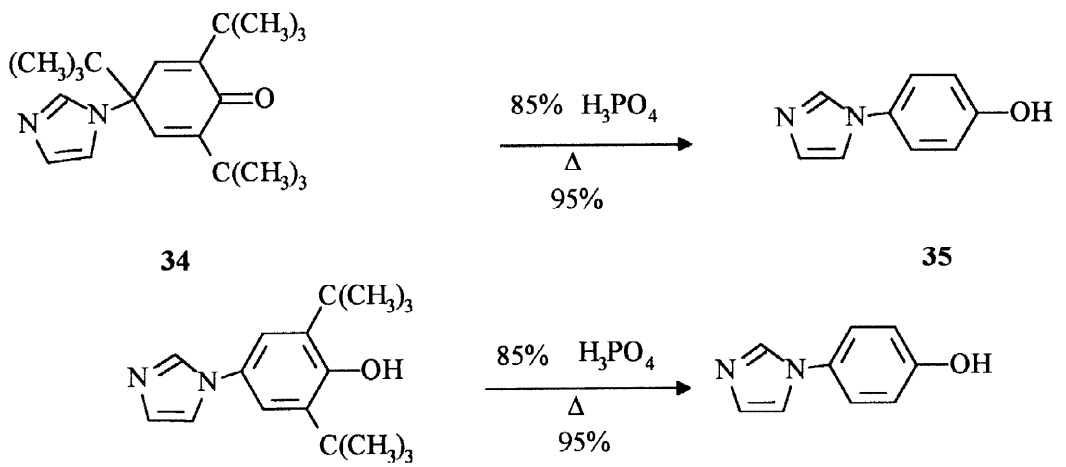
Scheme 17



32 **33**

The de-*tert*-butylation of compounds **34**, and **36** gave the products **35**, Scheme 18.[87]

Scheme 18

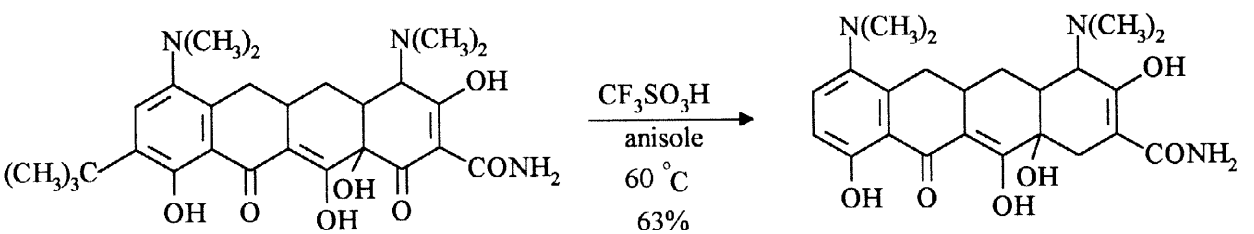


34 **35**

36 **35**

Sulfonic acids have attracted attention as catalysts for de-*tert*-butylation.[88] Thus, trifluoromethanesulfonic acid in anisole effectively catalyzed the de-*tert*-butylation 9-*tert*-butyl-7-dimethylamino-6-deoxytetracycline, **37** to afford product **38** in a convenient yield. The reaction was a part of a regioselective synthesis of minocycline, Scheme 19.[88]

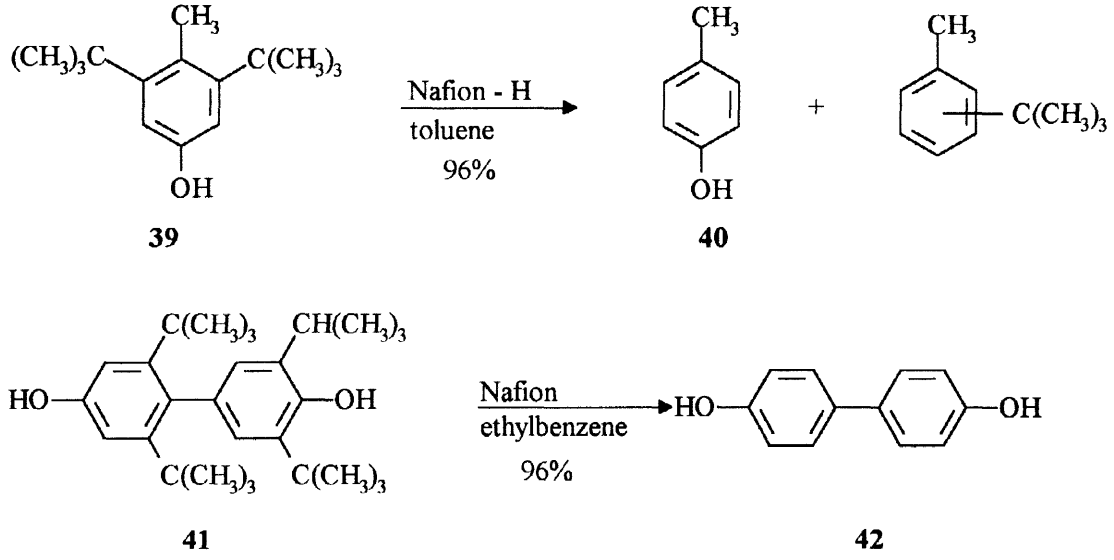
Scheme 19



37 **38**

Perfluoronated resinsulfonic acids (Nafion type) were successfully used to catalyze the de-*tert*-butylation of alkylated phenols. Thus, substituted phenol **39** and biphenyls **41** were effectively de-*tert*-butylated to the corresponding phenol **40** and biphenyl **42**, respectively, Scheme 20.[89,90]

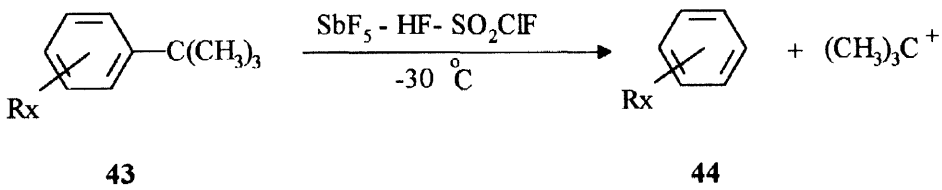
Scheme 20



Para-tert-butylphenol was also de-*tert*-butylated in a 96% yield. This subject had been comprehensively reviewed.[89]

The catalytic effect of fluoroantimonic acid in the de-*tert*-butylation was well established by Olah and coworkers.[91] Thus, several deactivated or sterically crowded *tert*-butylated benzenes **43** were treated with SbF_5-HF-SO_2ClF at –30°C. All substrates, without exception, produced *tert*-butylation and the de-*tert*-butylated product **44** Scheme 21.[91] The same results were obtained by using HF-TaF_5 as the catalyst.[92]

Scheme 21



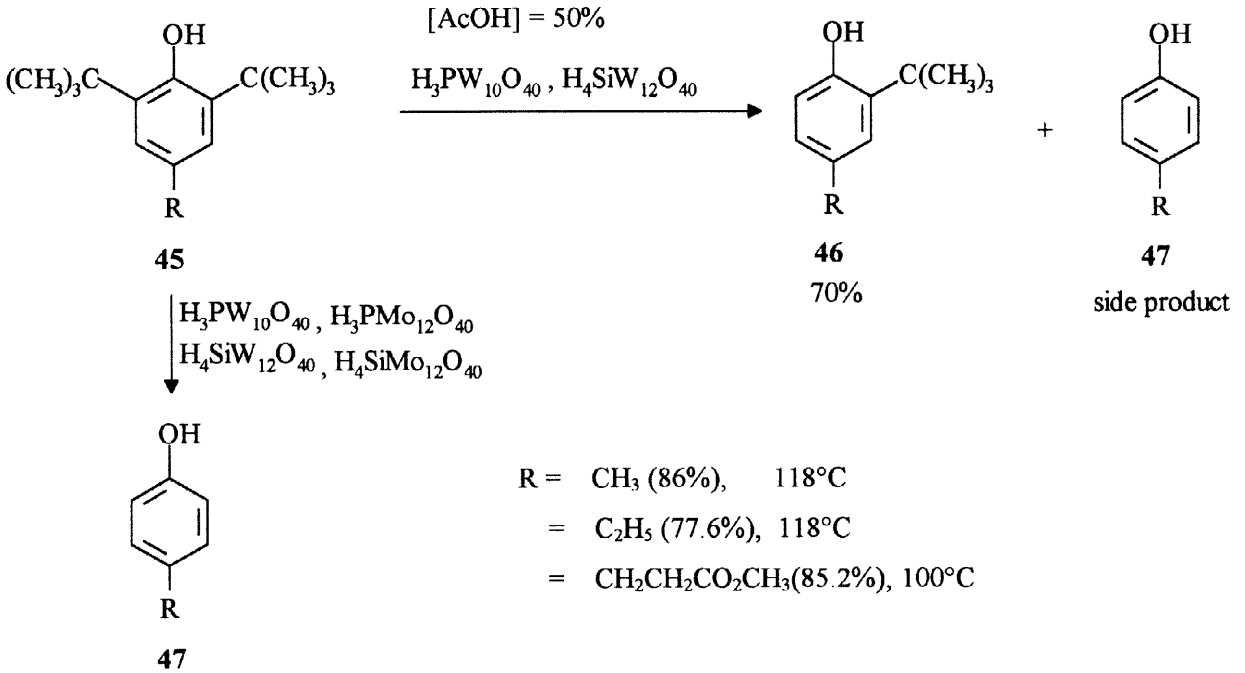
R_X = F_5; *o*-F; *p*-F; *p*-NH_2; *m*-$CONH_2$; *p*-NO_2; *p*-CO_2CH_3; *p*-CO_2H. *o*-, *m*, *p*-*tert*-butyl-;3,5-di-*tert*-butyl-4-nitro-; 3,5-di-*tert*-butyl-4-bromo-2,4,5-and 3,4,5-tri-*tert*-butyl.

5. Miscellaneous Catalysts for De-*tert*-butylation

Varying types of heteropolyacids, such as $H_3PW_{12}O_{40}$ and $H_4SiMo12O40$, were used to detach the *tert*-butyl substituent from butylated phenols.[93-96] Both heteropolyacids, $H_3PW_{10}O_{40}$ and $H_4SiW_{12}O_{40}$ catalyzed the

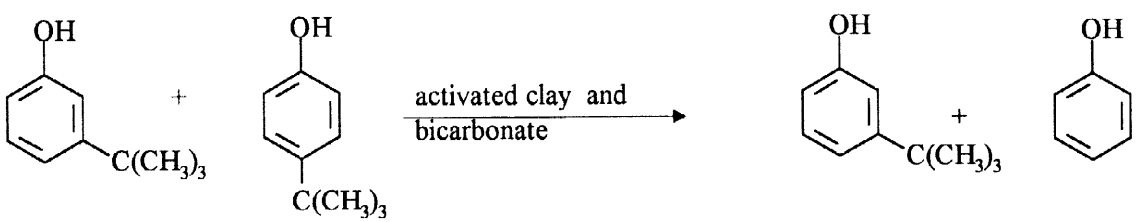
selective removal of one *tert*-butyl group from di-*tert*-butyl-4-alkylphenol **45** to give product **46**.[95] Upon modification of the heteropolyacid complete de-*tert*-butylation had been achieved to give product **47**,Scheme 22.

Scheme 22



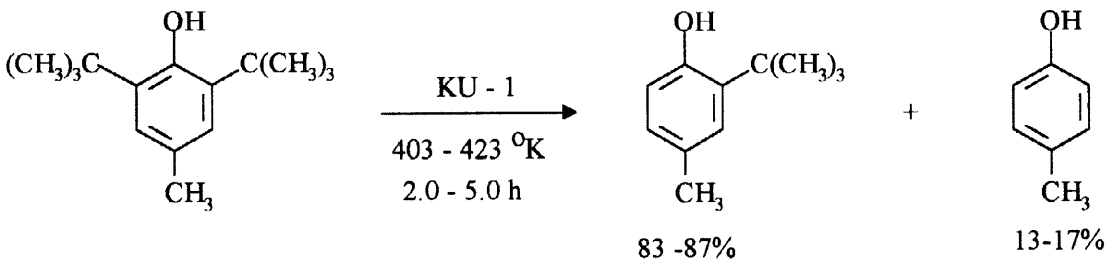
Clays and zeolites were also used to catalyze the de-*tert*-butylation.[97-99] ***m*-*tert*-Butylphenol, 48**, was obtained selectively in a high purity from a mixture of ***m*-*tert*-butylphenol** and ***p*- *tert*-butylphenol 49** using activated clay as the catalyst in the presence of bicarbonate and/or oxides of alkali metals and/or alkali earth metals. The mixture of the isomeric forms was treated with activated clay and potassium carbonate at 190-240°C for ~ 3h to give ~ 9% and ~ 94% ~ de-*tert*-butylation rate for the *meta*- and *para*-isomers, respectively. This is versus ~ 50% and ~ 97% without the carbonate, Scheme 23.[98]

Scheme 23



The cation exchanger of the KU-1 type was effectively used to partially de-*tert*-butylate 2,6-di-*tert*-butyl-4-methylphenol, **50**, to give 2-*tert*-butyl-4-methylphenol, **51** a known antioxidant, Scheme 24.[100]

Scheme 24



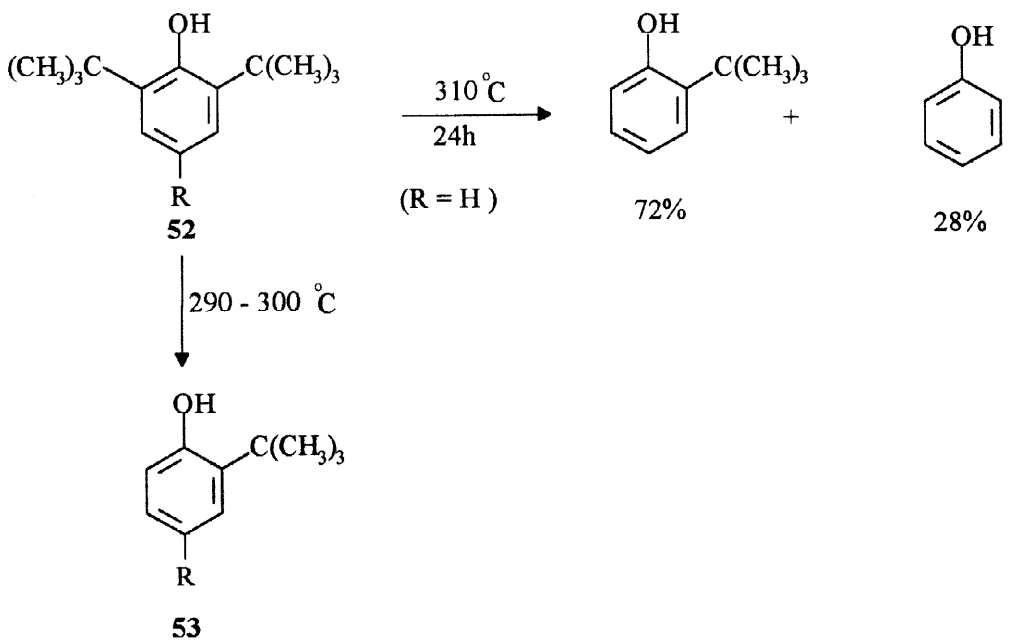
83 -87% 13-17%

50 **51**

Modification of the catalyst KU-2 by the addition of lithium sulfate or potassium perchlorate had efficiently raised the catalytic activity with its selectivity being also tremendously improved.[101-103]

De-*tert*-butylation of *tert*-butylated alkylphenols was accomplished in many cases by just heating the substances at relatively high temperatures without utilizing any catalyst.[104-111] 2- *tert*-Butyl alkylphenols **53** were obtaby heating the corresponding 2,6-dir-*tert*-butyl alkyl-phenols, **52**, at 290-300°C for 12-24h, Scheme 25.[104,105]

Scheme 25



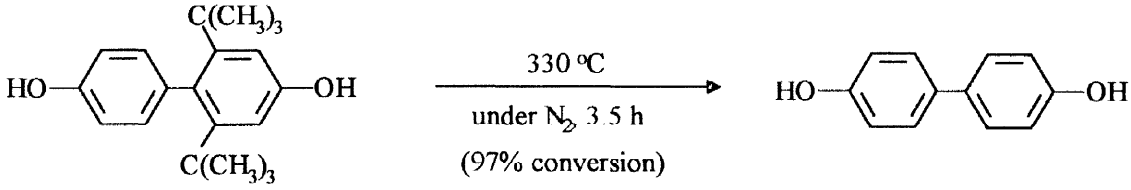
52 72% 28%

53

R = CH_3, C_2H_5, n–C_4H_9, CH_2OH, $(CH_2)_3Cl$

Similar treatment was also applied to 4-*sec*-, 4-*tert*- and 2,4-di-*sec*-butylphenols and gave phenol as the product in 96-99% yields.[107] 4,4′-Dihydroxydiphenyl, **55**, was prepared by the de-*tert*-butylation of 4,4′-bis(2,6-di-*tert*-butylphenol, **54**, in nitrogen atmosphere at 330°, Scheme 26.[109]

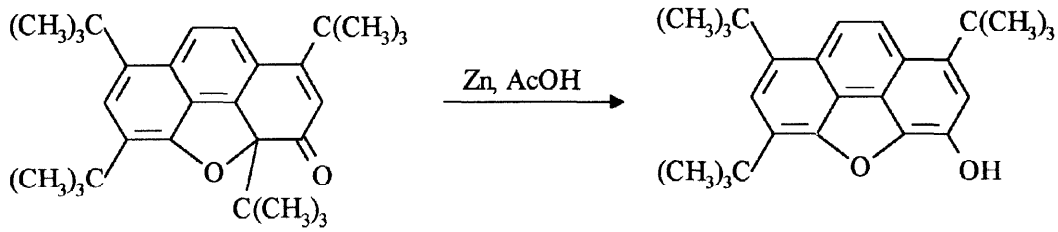
Scheme 26



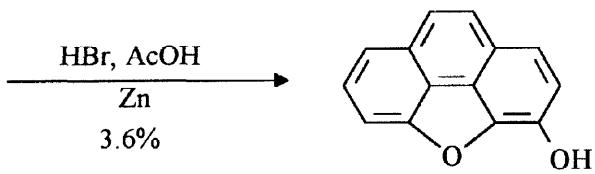
54 **55**

Starting with 2,4-di-*tert*-butyl-5-methylphenol, a multi-step synthesis was developed to prepare 1,3,6,8-tetra-*tert*-butylphenanthrene-4,5-quinone as a short-lived species in solution. This quinone had rapidly rearranged to the dienone, **56** which on de-*tert*-butylation using HBr/acetic acid as catalyst yielded morphenol, **57**. The corresponding 9,10-dihydroquinone crystallized as its oxepine valence isomer Scheme 27.[112]

Scheme 27



56



57

6. Concluding Remarks

From the literature cited in this review, it has been well established that the utility of the *tert*-butyl moiety can be attributed to its ability to protecting some selected positions in aromatic compounds. This has been extended to oxidative coupling of hindered phenols leading to quinol ethers, which on deprotection afforded diphenyl ethers. An aromatic *tert*-butyl substituent can be conveniently introduced and easily abstracted from aromatic substrates even sometimes at ambient temperature, ordinary atmospheric pressure and other relatively mild reaction conditions.

It is also important to note that the products obtained from *tert*-butylation and de- *tert*-butylation processes are of much practical use as antioxidant additives in food, plastics, fuel, greases,oils and several other widespread applications. These products can also form intermediates in the synthesis of biologically important molecules.

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Biographical sketch

Sadiq A. Saleh

Hasan I. Tashtoush

Sadiq A. Saleh was granted both his Bachelor (1960) and Master degrees (1964) in Chemistry from Southern Illinois University, U.S.A. While working for U.S. Industrial Chemicals Company in applied chemical research, he carried on his postgraduate studies. Later he obtained his Ph.D. degree (1974) in Organic Chemistry from Bristol University, United Kingdom, under the supervision of Professor J. F. W. McOmie.

After teaching for two years at Sana'a University, Yemen, as an Assistant Professor, he joined Yarmouk University in 1977 where he is continuing till to date. In 1992 he was promoted to an Associate Professor.

Immediately after earning his Ph.D., he went on a fellowship from University of Zurich, Switzerland. In 1984 he obtained Fulbright grant to spend his first Sabbatical at the University of Kansas, University of California (Berkeley) and Stanford University. Then in 1989, he got the DAAD fellowship which enabled him to carry out fundamental research in association with Professor H. Meier at Mainz University, Germany. His second Sabbatical financed by the Lady Davis Trust as a fellowship was spent at Hebrew University of Jerusalem (1995-96).

His main research interests lie in the synthesis of heterocycles, characterisation of natural products extracted from a variety of plant species, and catalysts employed in de-tert-butylation of butylated aromatic nucleii.

Hasan I. Tashtoush received his B.Sc. in 1976 and his M.Sc. in 1979 from University of Jordan, Amman, Jordan. He received his Ph.D. in 1984 from Iowa State University – USA under the guidance of the late Prof. Glen A. Russell.

In 1984 he was appointed Assistant Professor in the Department of Chemistry at Yarmouk University. He was promoted to Associate Professor in 1989, and to the rank of Professor in 1993. His current research interests focus on the synthesis of some biologically active compounds in addition to the use of free radicals in organic synthesis.

He earned Alexander Von Humboldt Fellowship in 1991, where he spent a year at Essen University, Germany, working in association with Prof. R. Sutsmann. In 1994, he earned Abdel-Hameed Showman Award for Youth Arab Researchers. Currently, he is Chairman of the Chemistry Department at the newly established Al-Hashemite University, Zarka, Jordan.