Aroma Chemicals from Alkyl Halides

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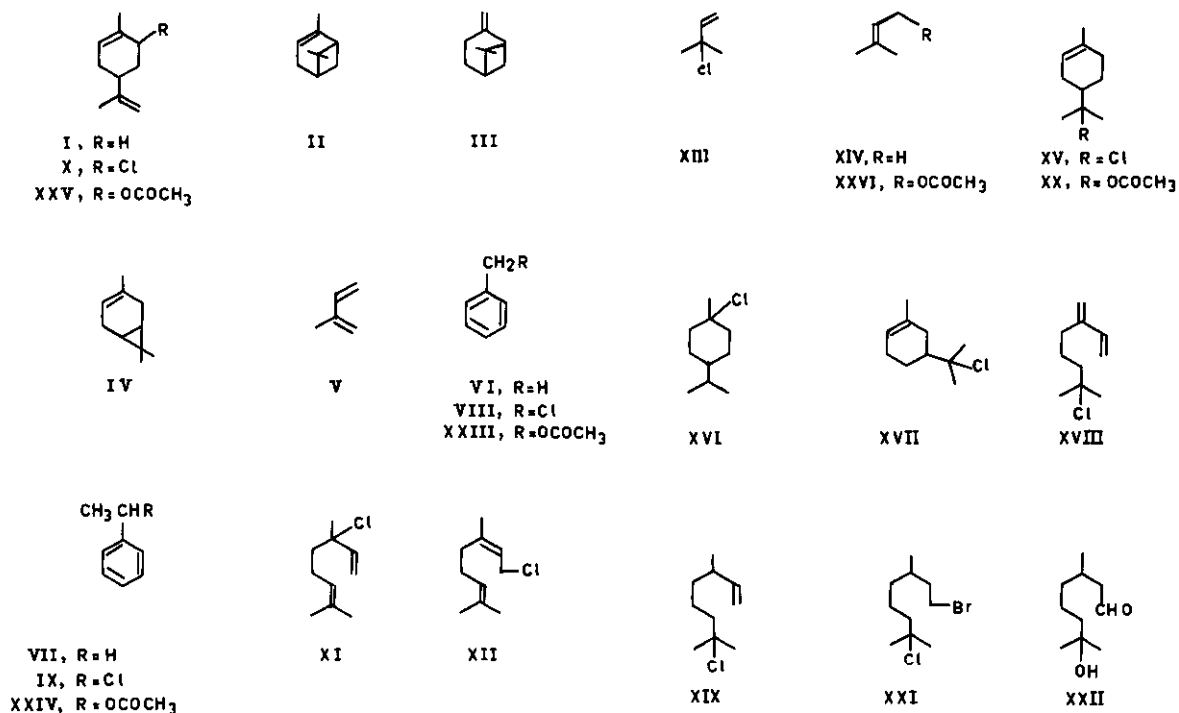
During the last quarter century, the aroma chemical industry has grown into a multibillion-dollar activity. Unprecedented growth in world population naturally increased the demand for newer food products, cosmetics and toiletries, both qualitatively and quantitatively. This, in turn, led to the search for new and abundant raw materials and development of more efficient methods of their conversion to aroma chemicals, which are indispensable constituents of flavour and perfumery compositions. New technologies based on developments in synthetic organic chemistry have contributed significantly to the phenomenal growth of the aroma chemical industry.

Raw Materials for Aroma Chemicals

A large number of flavour and perfumery chemicals in use are based on oxygenated functional groups—alcohols, esters, ethers, carbonyl compounds—and occasionally their sulfur analogs. Compared to the corresponding hydrocarbons, these functionalised derivatives are relatively stable, soluble in water-based foods and have desirable flavour characteristics.

The hydrocarbons, on the other hand, have quite the opposite properties and, when they co-occur in nature along with the oxygenated compounds (as in, for example, terpenes in citrus oils), they are profitably removed. But, for some reason, nature found it fit to accumulate more hydrocarbons. Thus, the citrus oils, mentioned above, generally contain 80-98% of terpenic hydrocarbons, mainly d-limonene (I). Turpentine as a source for α-pinene (II) and β-pinene (III) is well known; 3-carene (IV) is the major constituent of Indian turpentine. Isoprene (V), the building block of terpenoids, is available in large quantities from the petrochemical industry. The petrochemical industry is also the source of sev-

I , R = H
X , R = Cl
XXV, R = OCOCH₃

$I, R=H$
$X, R=Cl$
$XXV, R=OCOCH_3$

II

III

XIII

XIV, R = H
XXVI, R = OCOCH₃

$XIV, R=H$
$XXVI, R=OCOCH_3$

XV, R = Cl
XX, R = OCOCH₃

$XV, R=Cl$
$XX, R=OCOCH_3$

IV

V

CH₂R

CH_2R

VI, R = H
VIII, R = Cl
XXIII, R = OCOCH₃

$VI, R=H$
$VIII, R=Cl$
$XXIII, R=OCOCH_3$

XVI

XVII

XVIII

CH₃CHR

CH_3CHR

VII, R = H
IX, R = Cl
XXIV, R = OCOCH₃

$VII, R=H$
$IX, R=Cl$
$XXIV, R=OCOCH_3$

XI

XII

XIX

XXI

XXII

eral other industrially important aliphatic and aromatic hydrocarbons such as ethylene, propylene, toluene (VI) and ethylbenzene (VII).

These hydrocarbons are looked upon as the raw materials for the manufacture of a large number of aroma chemicals. The processes by which the monoterpenic hydrocarbons, namely, the pinenes, 3-carene and d-limonene, are converted into a variety of aroma chemicals are too well known to need elaboration here.[1,4] The chemical reactions that are normally used for functionalisation of hydrocarbons include:

—direct oxidation (aereal, photochemical or catalytic)
—oxidation by a variety of inorganic oxidizing agents
—hydration or solvation
—epoxidation followed by further reactions of the epoxides
—halogenation followed by substitution of the alkyl halides
—miscellaneous reactions involving metallation, hydroboration, and others.

Among these, the strategy of halogenation and substitution of the halogen appears most economical and dependable with respect to the product composition.

Preparation of Alkyl Halides: Intermediates for Aroma Chemicals

Halogenation of hydrocarbons can be achieved in a number of ways. Reaction of unsaturated hydrocarbons with halogens often leads to addition products; in the case of aromatic hydrocarbons, however, this reaction may give rise to substitution at the benzylic carbon. Thus, benzyl chloride (VIII) and α-methylbenzyl chloride (IX) are obtainable by monochlorination[5] of toluene and ethylbenzene respectively.

Benzylic and allylic protons can also be readily substituted by t-butyl hypochlorite, but this reaction has not been popular as most terpenes yield complex mixtures of products. We have recently demonstrated that limonene reacts with t-butyl hypochlorite at ambient temperature yielding carvyl chloride (X) as the predominant product.[6]

The most important halogenation reaction in the manufacture of aroma chemicals, however, is addition of hydrogen halides to unsaturated hydrocarbons. Cuprous ion-catalysed hydrochlorination of myrcene to yield linalyl chlorides (XI) and geranyl chloride (XII) is very well known to the industry.[7] Similarly, hydrochlorination of isoprene yields 1,1-dimethylallyl chloride (XIII) which readily rearranges to 3,3-dimethylallyl chloride (XIV).[8] Several other hydrochlorination

Table I. Reaction of Allyl, Benzyl and Tertiary Alkyl Halides with Zinc Oxide in Acetic Acid (14)

Alkyl Halide	Reaction Temperature (°C)	Reaction Time (hr)	Product	Yield (%)
t-Butyl chloride	15	0.50	t-Butyl acetate	96
1-Menthanyl chloride	40	2.00	1-Methanyl acetate	65
1,1-Dimethylallyl chloride	15	0.25	3,3-Dimethylallyl acetate	98
3,3-Dimethylallyl chloride	15	0.50	3,3-Dimethylallyl acetate	98
(+) trans-Carvyl chloride	25	2.00	(+) Carvyl acetate (cis/trans 1:3)	96
Benzyl chloride	75	6.00	Benzyl acetate	86
Benzyl bromide	75	1.00	Benzyl acetate	85
Styrallyl chloride	25	1.50	Styrallyl acetate	95

reactions and their utility in the preparation of fragrance chemicals have been recently reviewed.[9]

Substitution of Allylic and Tertiary Alkyl Halides

Though well-recognized, the full potential of the hydrochlorination reaction has not been realized for two reasons. First, the allylic and benzylic halides described above generally react with alkali metal carboxylates to yield esters, but the main drawback of this procedure is that the reaction occurs only at elevated temperatures. The temperature of the reaction mixture needs to be carefully controlled since elimination of hydrogen chloride is also competitive at higher temperatures.

Secondly, several of the abundantly available terpenic hydrocarbons have trisubstituted or 1,1-disubstituted double bonds and these yield tertiary alkyl halides by Markownikoff addition of the hydrogen halide. Thus, limonene (I) yields α-terpinyl chloride (XV) almost quantitatively and dihydrolimonene gives 1-menthanyl chloride (XVI). 3-Carene gives a mixture of α-terpinyl chloride and sylvestryl chloride (XVII) by opening-up of the cyclopropane ring. Lewis-acid catalysed hydrochlorination of myrcene yields myrcenyl chloride (XVIII) and dihydromyrcene (obtainable by pyrolysis of pinane) gives rise to dihydromyrcenyl chloride (XIX).[9] Replacement of the halogen in these compounds (XIII to XIX) by hydroxy, alkoxy or acyloxy groups would lead to a wide range of highly valued aroma chemicals. But this would involve nucleophilic substitution at a tertiary center, which is very difficult.

Nucleophilic substitution at a tertiary carbon has been the subject of detailed investigation by a number of workers and the following generalizations could be made.

—Substitution of tertiary alkyl halides is more facile under solvolytic conditions; under nonsolvolytic conditions, elimination of hydrogen halide generally predominates[10]

—Solvolysis of tertiary alkyl halides in highly polar media such as water and methanol yields alcohols and methyl ethers in moderate yields but elimination is the major reaction when the solvolysis is carried out in less polar solvents such as ethanol or acetic acid[11]

—Even in polar solvents, the yield of the substitution products decreases sharply with increase in the size of the substituents on the α-carbon atom.

Thus, while t-butyl chloride yields up to 60% of t-butanol on hydrolysis, 3-chloro-3-methylpentane undergoes elimination to the extent of 90% under the same conditions.[12]

Reaction of Zinc Salts with Alkyl Halides

From the preceding discussion, it is apparent that tertiary alkyl halides readily lose elements of hydrogen halide to yield olefins under most conditions. Thus, it is not surprising that there are no preparative methods of substitution at the tertiary center. In this connection, the recent discovery in the author's laboratory that tertiary alkyl and other S_N1-active halides such as allylic and benzylic halides can be smoothly substituted by zinc salts under mild conditions should be of immense practical value.

The discovery was made accidentally when tertiary alkyl acetates invariably formed during the attempted reduction of certain tertiary alkyl halides by zinc and acetic acid. The acetates must have formed by reaction of the tertiary alkyl halide with zinc acetate which, in turn, must

have formed by the reaction of zinc with acetic acid. Indeed, α-terpinyl chloride (XV), when reacted with zinc acetate in acetic acid at ambient temperature, yielded α-terpinyl acetate (XX) almost quantitatively. The enormous potential of this reaction was immediately obtainable by hydrochlorination of appropriate hydrocarbons and the corresponding acetates are highly valued as aroma chemicals. In view of its importance, the scope and limitations of the reaction were studied in detail and the versatility of its applications are briefly discussed here.

Acetates from S_N1-Active Halides

A systematic study of the reaction of α-terpinyl chloride with different metal acetates in acetic acid has shown that while the acetates of copper, silver and zinc yield α-terpinyl acetate in good yields, the reaction is fastest and the yield of the desired product the highest, with zinc salt.[14] The zinc salt is preferable for several other reasons also: low cost, clean reaction and easy isolation of the product, and the possibility of substituting zinc acetate by zinc oxide, which forms the salt in *in situ* on reaction with acetic acid. The last-mentioned feature made it possible to extend the reaction to the preparation of several other esters and ethers by substituting acetic acid by appropriate protic solvents. It also made it possible to regenerate and recycle the reagent (zinc oxide), if desired.

In a typical procedure, suitable for large-scale operation,[15] zinc oxide (2 mol) is stirred with acetic acid (15 mol) for 0.5 hour. (About 10% of acetic anhydride may be added to acetic acid to suppress the formation of the tertiary alcohol.) α-Terpinyl chloride (3 mol) is then added and the mixture stirred for two hours, when most of the zinc salt dissolves. Water (about 1 litre) is then added and the mixture stirred for 5 minutes before separating off the lower aqueous layer (Fraction A). The organic phase is washed with saturated aqueous sodium bicarbonate and then fractionated to obtain pure α-terpinyl acetate (75-90%).

The aqueous fraction (A), obtained above, may be distilled to remove the dilute acetic acid and the residue treated with sodium hydroxide (3 mol) to precipitate zinc hydroxide. The precipitate is heated at about 700°C for an hour to recover zinc oxide almost quantitatively.

Apart from the low cost of the reagents, simple and convenient reaction conditions and high yield of the product, the attractive feature of the reaction is its applicability to the substitution of tertiary alkyl halides. Interestingly, primary and secondary alkyl halides such as 1-butyl, 2-butyl,

Table II. Reaction of alpha-Terpinyl Chloride (XV) and 1-Menthanyl Chloride (XVI) with Zinc Oxide and Different Protic Solvents (13, 14)

Halide	Solvent	Reaction Temperature (°C)	Reaction Time (hr)	Product	Yield (%)
alpha-Terpinyl chloride	Acetone, 80%	60	6	alpha-Terpineol	85
alpha-Terpinyl chloride	Formic acid	15	2	alpha-Terpinyl formate	95
alpha-Terpinyl chloride	Acetic acid	25	2	alpha-Terpinyl acetate	90
alpha-Terpinyl chloride	Propionic acid	40	2	alpha-Terpinyl propionate	70
alpha-Terpinyl chloride	Butyric acid	45	2	alpha-Terpinyl butyrate	65
alpha-Terpinyl chloride	Methanol	65	6	alpha-Terpinyl methyl ether	95
alpha-Terpinyl chloride	Ethanol	80	6	alpha-Terpinyl ethyl ether	85
alpha-Terpinyl chloride	Propanol	100	6	alpha-Terpinyl propyl ether	60
1-Menthanyl chloride	Formic acid	15	2	1-Menthanyl formate	70
1-Menthanyl chloride	Acetic acid	35	2	1-Menthanyl acetate	65

menthyl and bornyl chlorides do not react under the conditions described above. The method is thus useful for partial substitution of dihalides such as XXI,[16] which is a key intermediate in the synthesis of hydroxycitronellol (XXII). Primary and secondary alkyl halides can be substituted by zinc salts under mild conditions if they are allylic or benzylic. Thus, benzyl, styrallyl and carvyl chlorides readily yield the corresponding acetates XXIII, XXIV and XXV. Both 1,1-dimethylallyl and 3,3,-dimethylallyl chlorides (XIII and XIV) react with zinc acetate to yield essentially 3,3-dimethylallyl acetate (XXVI). The allylic and benzylic halides react with the zinc salts at much lower temperatures than with the alkali metal salts and the yields are superior. The reactivity of zinc acetates in acetic acid with representative examples of alkyl halides with different structural features are summarised in Table I. The mechanism of the reaction, which explains the unusual reactivity of the alkyl halides with zinc salts, has been discussed elsewhere.[14]

Preparation of Esters, Ethers and Alcohols

The scope of the reaction is extended further by simply replacing the acetic acid in the above procedure by different carboxylic acids or other protic solvents such as alcohols and water, to obtain esters, ethers and alcohols. The yield of the oxyderivatives, however, decreases with the increasing molecular weight of the protic solvent or by increased branching at the α-carbon atom. Nevertheless, a large number of esters and ethers are obtainable by this procedure. They include formates, propionates, butyrates, methyl and ethyl ethers, alcohols and others. These are illustrated in Table II, using α-terpinyl and 1-menthanyl chlorides as examples. The 1-men-

thanyl esters mentioned in Table II are hitherto unreported. These compounds have a very pleasant floral aroma; organoleptically, they should blend well with tobacco flavours.

Esters of Solid Carboxylic Acids

The solvolytic procedure described above is naturally limited in its application to the preparation of the derivatives of low molecular weight alcohols and carboxylic acids which, being liquids at ambient temperature, can be used as solvents. However, there are several prized aroma chemicals such as benzoates, cinnamates and phenyl-acetates, which are derived from solid carboxylic acids. Some reagents, even if liquids, may be too expensive or inconvenient to use as solvents, e.g., thiols and thiolcarboxylic acids (see below). Therefore, it would be avantageous to develop a method for use under nonsolvolytic conditions, so that the proton-active substance could be used as a reagent rather than as a solvent. However, as already mentioned, nucleophilic substitution at a tertiary center is even more difficult under nonsolvolytic conditions than under solvolytic conditions.

After several experiments, the results of which have been discussed elsewhere,[17] a procedure has been developed to effect substitution of allylic, benzylic and tertiary alkyl halides using the appropriate zinc salts under nonsolvolytic conditions. The reaction is carried out in a nonpolar aprotic solvent such as benzene, toluene, chloroform or dichloromethane. One equivalent of a tertiary base (e.g., pyridine or triethylamine) is added to the reaction mixture to prevent the zinc chloride formed from acting as a Lewis acid and causing complications such as dehydrohalogenation of the alkyl halide and polymerisation. The preparation of the zinc salt and

Table III. Reaction of Tertiary Alkyl and Allylic Halides with Zinc Oxide and Carboxylic Acids in Benzene-Pyridine (17, 19)

Halide	Carboxylic Acid	Reaction Time (hr)	Product	Yield(a) (%)
alpha-Terpinyl chloride	Benzoic acid	20	alpha-Terpinyl benzoate	71
alpha-Terpinyl chloride	Cinnamic acid	24	alpha-Terpinyl cinnamate	78
alpha-Terpinyl chloride	Phenoxyacetic acid	8	alpha-Terpinyl phenoxyacetate	85
alpha-Terpinyl chloride	Phenylacetic acid	24	alpha-Terpinyl phenylacetate	93
t-Butyl bromide	Benzoic acid	12	t-Butyl benzoate	91
t-Butyl bromide	Cinnamic acid	10	t-Butyl cinnamate	95
t-Butyl bromide	Phenoxyacetic acid	9	t-Butyl phenoxyacetate	95
t-Butyl bromide	Phenylacetic acid	12	t-Butyl phenylacetate	93
Carvyl chloride	Benzoic acid	12	Carvyl benzoate(b)	72
Carvyl chloride	Cinnamic acid	8	Carvyl cinnamate(b)	83
Carvyl chloride	Phenoxyacetic acid	15	Carvyl phenoxyacetate(b)	82
Carvyl chloride	Phenylacetic acid	12	Carvyl phenylacetate(b)	76

(a) Based on carboxylic acid consumed.
(b) Mixture of cis and trans esters, approximately 1:3.

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Table IV. Reaction of Alkyl Halides (RBr) with Zinc Thiolates (Zinc Oxide and Thiols, R'SH) in Benzene-Pyridine (20)

R	R'	Reaction time (hr)	Product	Yield (%)
$PhCH_2$	$PhCH_2$	4	$PhCH_2SCH_2Ph$	97
$CH_2=CHCH_2$	$PhCH_2$	6	$CH_2=CHCH_2SCH_2Ph$	93
$MeCH_2CH_2CH_2$	$PhCH_2$	8	$MeCH_2CH_2CH_2SCH_2Ph$	97
$MeCH_2CH(Me)$	$PhCH_2$	46	$MeCH_2CH(Me)SCH_2Ph$	92
Me_3C	$PhCH_2$	7	$(Me)_3CSCH_2Ph$	88
Me_3C	$CH_2=CHCH_2$	26	$(Me)_3CSCH_2CH=CH_2$	53
Me_3C	Ph	8	$(Me)_3CSPh$	85
Me_3C	$MeCH_2CH_2CH_2$	22	$(Me)_3CSCH_2CH_2CH_2CH_3$	73
Me_3C	$MeCH_2CH(Me)$	24	$(Me)_3CSCH(CH)_3CH_2CH_3$	55
Me_3C	Me_3C	20	$(Me)_3CSC(CH_3)_3$	65
Me_3C	$MeCO$	14	$(Me)_3CSC(O)CH_3$	53
$MeCH_2CH(Me)$	$MeCO$	32	$MeCH_2CH(Me)SC(O)Me$	49
$MeCH_2CH_2CH_2$	$MeCO$	26	$MeCH_2CH_2CH_2SC(O)Me$	81
$CH_2=CHCH_2$	$MeCO$	5	$CH_2=CHCH_2SC(O)Me$	52
$PhCH_2$	$MeCO$	10	$PhCH_2SC(O)Me$	61

its further reaction with the alkyl halide is carried out in a one-pot procedure exemplified below for the preparation of α-terpinyl benzoate.[18]

Benzoic acid (1 mol) is stirred under reflux with zinc oxide (or zinc carbonate, 0.5 mol) in benzene (1 lit) in a flask equipped with Dean-Stark apparatus to remove water as it is formed. After two hours, pyridine (1 mol) and α-terpinyl chloride (1 mol) are added and stirring and refluxing continued for about 20 hours, until TLC (or GC) shows disappearance of α-terpinyl chloride. The mixture is extracted with aqueous sodium bicarbonate to recover unreacted benzoic acid (0.65 mol). It is then washed with dilute hydrochloric acid to remove pyridine and again with aqueous sodium bicarbonate. Removal of solvent

and fractionation yields hydrocarbons (0.75 mol) and α-terpinyl benzoate (0.25 mol). While the recovered benzoic acid can be reused as such, the hydrocarbons (consisting essentially of limonene and terpinolene) may be fractionated, hydrochlorinated and reused. The yield of α-terpinyl benzoate, based on the benzoic acid consumed, is 70%. α-Terpinyl esters of several other carboxylic acids, viz., cinnamate, phenoxyacetate and phenylacetate) are prepared in a similar manner (Table III). The reaction is particularly useful for the preparation of t-butyl esters of carboxylic acids; these esters are used as flavorants and as alkali-stable protective groups in organic synthesis.

Interestingly, primary and secondary alkyl halides do not react even under the nonsolvolytic conditions unless they are allylic or benzylic. The ready availability of carvyl chloride (from limonene and t-butyl hypochlorite[6]) and the facile substitution of allylic halides by zinc carboxylates have been utilised for the preparation of several novel esters of carveol, namely, the benzoate, cinnamate, phenoxyacetate and phenylacetate (Table III).[19] By the nature of the zinc-salt reaction, these esters are racemic mixtures of cis and trans derivatives (in the ratio 1:3, approximately), irrespective of the stereochemistry and optical purity of the starting carvyl chloride.

Thioethers and Thiolesters

The above procedure is convenient not only for the preparation of the derivatives of solid carboxylic acids but also for those of several other protic reagents which are inconvenient to handle as solvents, e.g., benzyl alcohol and phenol for the preparation of benzyl ethers and phenyl ethers.[17] More interestingly, the reaction becomes readily extendable to the preparation of unsymmetrical sulphides (thioethers) some of which are constituents of allium, asafetida, coffee and meat flavours. For this purpose, the appropriate thiol is reacted with zinc oxide in the same manner as described above for benzoates and the zinc thiolate is treated with alkyl halides, preferably bromides.[20]

Substitution of the thiol by a thiolcarboxylic acid gives the corresponding thiolesters. These are illustrated in Table IV. Again, there are no suitable methods in literature to prepare the tertiary alkyl thioethers and thiolesters. As can be seen from the table, thioethers and thiolesters can be obtained from saturated primary and secondary alkyl halides also; the reason for their reactivity in this case is apparently the superior nucleophilicity of the thiolate ion.

Conclusion

The substitution of alkyl halides by zinc salts thus constitutes a very useful synthetic reaction for the preparation of alcohols, ethers, esters, thioethers and thiolesters both under solvolytic and nonsolvolytic conditions. Using this versatile reaction, a large number of allyl, benzyl and tertiary alkyl derivatives, which are widely used in the perfumery and flavour industry, can be obtained. Among these, mention must be made of α-terpinyl, 1-menthanyl, myrcenyl, dihydromyrcenyl, benzyl, styrallyl 3,3-dimethylallyl and carvyl esters, ethers and alcohols. The inexpensive reagents, convenient reaction conditions and suitability for large-scale operation are attractive features of the method.

References

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1. H. R. Ansari, Flavour Ind., 1, 252, 1970
2. J. M. Derfer, Perf. Flavor., 3(1), 45, 1978
3. J. Verghese, Perf. Flavor., 4(4), 23, 1979
4. B. Ravindranath, J. Sci. Industr. Res., 43, 82, 1983
5. W. E. Faith, D. P. Keyes, and R. L. Clark, Industrial Chemicals, 4th Ed. Wiley, New York, 1975, pp. 145-148
6. B. Ravindranath and P. Srinivas, Indian J. Chem., (In Press), Indian Pat. Appl. 1982
7. R. Weiss, U.S. Pat. 2,822,323, 1959
8. A. J. Ultee, J. Chem. Soc. 530, 1948
9. J. Verghese, Perf. Flavor., 8(6), 9, 1983
10. J. E. Shaw, D. C. Kunerth and J. J. Sherry, Tetrahedron Letters, 689, 1973
11. M. Cocivera and S. Winstein, J. Am. Chem. Soc. 85, 1702, 1963
12. H. C. Brown and R. S. Fletcher, J. Am. Chem. Soc. 71, 1845, 1949 and 72 1223, 1950
13. S. Anandaraman, K. N. Gurudutt, C. P. Natarajan and B. Ravindranath, Tetrahedron Letters, 21, 2198, 1980
14. K. N. Gurudutt, B. Ravindranath and P. Srinivas, Tetrahedron, 38, 1843, 1982
15. S. Anandaraman, K. N. Gurudutt, C. P. Natarajan and B. Ravindranath, Indian Pat., 146632, 1979
16. J. P. Bain, U.S. Pat. 3,005,845, 1961 and U.S. Pat. 3,060,237, 1962
17. B. Ravindranath and P. Srinivas, Tetrahedron, 40, 1623, 1984
18. B. Ravindranath and P. Srinivas, Indian Pat. Appl. 1984
19. B. Ravindranath and P. Srinivas, Indian J. Chem. (In Press)
20. B. Rajanikanth and B. Ravindranath, Indian J. Chem. (In Press); Indian Pat. Appl. 1983