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PREPARATIVE SYNTHESES OF OPTICALLY PURE ORTHO-SUBSTITUTED BENZHYDROLS BY ASYMMETRIC REDUCTIONS OF THE CORRESPONDING BENZOPHENONES

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Abstract : Lithium aluminium hydride previously treated with 2.5 equivalents of (S)-(+) or (R)-(-)-2 -(2-iso-indolinyl)butan-1-ol **3** (readily available reagents) reduced the five ortho-substituted benzophenones **4-6**, **8** and **10** into the corresponding optically active benzhydrols with nearly 100% enantiomeric excesses. Other examples of asymmetric reductions of prochiral benzophenones are given.

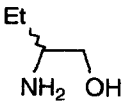
Racemic 2-aminobutan-1-ol **1** is a cheap chemical which can be easily resolved into both its enantiomers on the industrial scale.[1] This is why we considered using simple derivatives of (R)-(-) and (S)-(+)-**1** as new chirality transfer reagents. In a previous study,[2] we described the asymmetric reductions of prochiral ketones with ethereal solutions of $LiAlH_4$ partially decomposed with various *N*, *N*- disubstituted derivatives of (R)-(-)-**1**. In all cases, the best results were obtained with $LiAlH_4$ previously treated with 2 equivalents of a given optically active aminoalcohol ROH, which corresponds to the gross formula $LiAl(OR)_2H_2$ for the reducing complex thus formed. Indeed, markedly lower enantiomeric excesses were observed when using $LiAlH_4$ previously treated with 1 or 3 equivalents of the same aminoalcohol. (R)-(-)-*N*-Benzyl-*N*-methyl-2-aminobutan-1-ol (R)-(-)-**2** and (R)-(-)-2-(2-iso-indolinyl) butan-1-ol (R)-(-)-**3** are the aminoalcohols which gave the best results. Thus, the chiral reagent deriving from $LiAlH_4$ and (R)-(-)-**3** reduced 2-chloro and 2,4-dimethyl benzophenones into the corresponding benzhydrols with 100% enantiomeric excesses. However, asymmetric reductions of meta-substituted benzophenones, as well as acetophenone, α-tetralone and 2-acetylfuran, with the same reagent gave markedly lower enantiomeric excesses.

The above results prompted us to study more thoroughly the asymmetric reductions of various ortho-substituted benzophenones using the same aminoalcohol (R)-(-)-**3**. Thus, the nine optically active benzhydrols **13-21** were obtained from the corresponding benzophenones **4-12**, respectively (see Scheme).

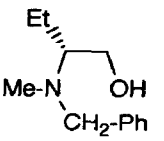
Preparations of the benzophenones

Ortho-trifluoromethyl benzophenone **8** is commercially available. The other benzophenones were synthesized as follows. 2-Methylbenzoyl chloride was treated with excess benzene as the solvent, in the presence of $AlCl_3$ for 3 hrs 30 min at room temperature, and afforded 2-methylbenzophenone **4**.[3] The α-halobenzophenones **6**[3,4] and **7**[3, 5] were similarly prepared from the corresponding α-halobenzoyl chlorides respectively. In the case of 2-iodobenzophenone **6**, the Friedel-Crafts reaction was carried out at 0°C in order to avoid iodine elimination. Treatment of 2-bromobenzaldehyde with phenylmagnesium bromide in refluxing ether for 2 hrs afforded (±)-**14**.[3, 6] Oxidation of the latter, using pyridinium chlorochromate in CH_2Cl_2 at 0°C gave 2-bromobenzophenone **5**.[3, 7]

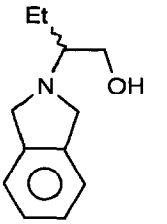
2,4-Dichlorobenzoyl chloride **22** was treated with excess benzene as the solvent and in the presence of



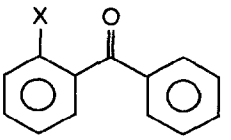
(R)-(-)-**1**, α-Et
(S)-(+)-**1**, β-Et



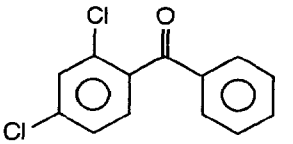
(R)-(-)-**2**



(R)-(-)-**3**, α-Et
(S)-(+)-**3**, β-Et



4 X = Me
5 X = Br
6 X = I
7 X = F
8 X = CF_3



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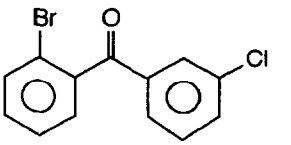

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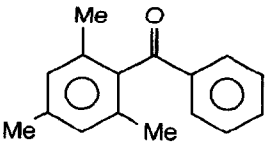

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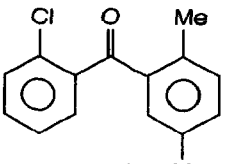

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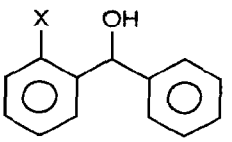
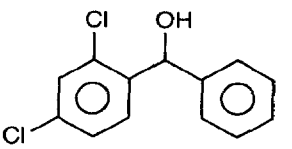


13 X = Me
14 X = Br
15 X = I
16 X = F
17 X = CF_3



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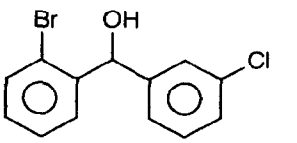

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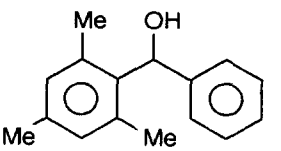

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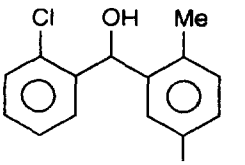

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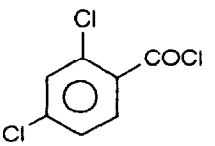

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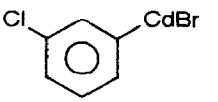

23

SCHEME

$AlCl_3$ (reflux, 30 min) and yielded 2, 4-dichlorobenzophenone **9**.[3, 8] 2-Bromo-3'-chlorobenzophenone **10**[3] was prepared according to the literature,[9] by treatement of the organocadmium reagent **23** (deriving from 1-bromo-3-chlorobenzene) with 2-bromobenzoylchloride in toluene (reflux 1 hr). Reaction of benzoyl chloride with excess mesitylene as the solvent, and in the presence of $AlCl_3$ for 1 hr at room temperature, furnished the trimethylbenzophenone **11**.[3, 10, 11] Finally, 2-chlorobenzoyl chloride was treated with p-xylene in excess ($AlCl_3$, 2hrs at room temperature) and yielded the benzophenone **12**.[3, 5]

Asymmetric reductions of the benzophenones

Approximately molar, commercial, $LiAlH_4$ solutions in ether were used.[12] Their $LiAlH_4$ content was estimated by means of fluorenone as we previously described.[13] The benzophenones **4-12** (5 mmol) were reduced with $LiAlH_4$ (6 mmol) in ether, previously treated with 2 or 2.5 equivalents of the aminoalcohol (R)-(-)-**3**.[2] Surprisingly, the highest enantiomeric excesses were obtained with $LiAlH_4$ previously treated with 2.5 equivalents (15 mmol) of (R)-(-)-**3**, which corresponds to the gross formula $LiAl(OR)_{2.5}H_{1.5}$ for the reducing species in solution (see Table).

The enantiomeric excess of each optically active benzhydrol **13-21** thus obtained was determined by examination of the signal of its carbinolic proton, in the ^1H NMR spectrum (400 MHz) run in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium3[Eu(hfc)$_3$].

Benzhydrol	Substituents	ee (%)
(-)-**13**[3, 11, 14]	2-Me	> 95 (73) [a]
(+)-**14**[3, 6]	2-Br	> 95
(+)-**15**[3]	2-I	> 95
(-)-**16**[3, 15]	2-F	88 (84) [a]
(+)-**17**[3]	2-CF_3	> 95 (37) [a]
(+)-**18**[3]	2-Cl; 4-Cl	89 (87) [a]
(+)-**19**[3, 9]	2-Br; 3'-Cl	> 95
(+)-**20**[3, 10, 11]	2-Me; 4-Me; 6-Me	44
(+)-**21**[3]	2-Cl; 2'-Me; 5'-Me	12

a) Values in brackets refer to reductions carried out with the reagent $LiAl(OR)_2H_2$ deriving from (R)-(-)-**3**.

TABLE - Enantiomeric excesses (ee, %) of the benzhydrols **13-21** obtained by reduction of the benzophenones **4-12**, respectively, with the chiral reagent $LiAl(OR)_{2.5}H_{1.5}$ deriving from the aminoalcohol ROH (R)-(-)**3**.

The results displayed in the Table show that, apart from **20** and **21**, the above benzohydrols have enantiomeric excesses higher than 88%. Furthermore, the five benzhydrols **13-15**, **17** and **19** have been isolated as nearly pure enantiomers (ee > 95%). With the exception of **13** and **20**, none of the above benzhydrols were obtained in optically active form before us. According to Cervinka and coworkers,[11] the benzhydrols (-)-**13** and (+)-**20** belong to the (R) series. This may apply as well to the other benzhydrols (+)-**14**, (+)-**15**, (-)-**16**, (+)-**17**, (+)-**18** and (+)-**19**.

Similar benzophenone reductions were next carried out using the (S)-(+) enantiomer of the aminoalcohol (R)-(-)-**3**. The compound (S)-(+)-**3**, m.p. 61-62°C, $[\alpha]_D$ + 19.4 (c 3.3, EtOH), was obtained by alkylation of (S)-(+)-2-aminobutan-1-ol (S)-(+)-**1** with α, α'-dichloro-ortho-xylene as previously described for the preparation of the enantiomer (R)-(-)-**3**.[2] Reduction of 2-bromobenzophenone **5** with $LiAlH_4$ previously treated with 2.5 equivalents of (S)-(+)-**3** afforded the benzhydrol (-)-**14** with ee > 95%. Similar treatment of 2-iodobenzophenone **6** gave the benzhydrol (-)-**15** with ee = 90%.

As a typical experimental procedure, the asymmetric reduction of 2-bromobenzophenone **5** is described

hereafter. This procedure shows that our method has a practical and preparative value. Commercial $LiAlH_4$ solutions in ether [12] were estimated by means of fluorenone [13] prior to use. Thus, to a solution of $LiAlH_4$ in ether (30 mL; 30 mmol) contained in a 500 mL 3-necked flask kept under argon, a solution of (R)-(-)-2-(2-iso-indolinyl)butan-1-ol (R)-(-)-**3** (14.32 g; 75 mmol), m.p.59-60°C and $[\alpha]_D$ - 19.4 (c 3.0, EtOH), in dry ether (200 mL) was added dropwise in 3 hrs at room temperature and under stirring. After a period of 45 min, the mixture was cooled to - 13°C and a solution of 2-bromobenzophenone **5** (6.52 g; 25 mmol) in anhydrous ether (30 mL) was slowly added (2hrs) under stirring. After a period of 15 min, the reaction mixture was hydrolysed with aqueous 1N NaOH (20 mL). The organic phase was washed successively with aqueous 1N HCl (2 x 100 mL) and 1N NaOH (2 x 100 mL), then with water until neutral, and was finally dried ($MgSO_4$), filtered and evaporated, affording the crude (+)-2-bromobenzhydrol (+)-**14** (6.6 g; 100%), $[\alpha]_D$ + 45.8 (c 1.4, Me_2CO), as a pale yellow oil. Molecular distillation of a fraction (1.0 g) of this oil yielded colourless (+)-**14** (0.95 g), $[\alpha]_D$ + 46.6 (c 1.3, Me_2CO), ee > 95%. IR (film) :3350 (OH) cm^{-1}. ^1H NMR($CDCl_3$) δ (ppm): 2.41 (1H, d, J = 3.7 Hz) OH; 6.19 (1H, d, J = 3.7 Hz) **CH**-OH; 7.15 (1H), 7.27 (1H), 7.33 (3H),7.40 (2H), 7.53 (1H), 7.59 (1H) (aromatic protons). The chiral aminoalcohol (R)-(-)-**3** was easily recovered from the above aqueous extracts.

Conclusion

Both enantiomers of the readily available iso-indolinyl compound **3** are highly efficient chirality transfer reagents for the asymmetric reduction of ortho-substituted benzophenones. Seven benzhydrols (**13-19**) of high enantiomeric purities (ee > 88%) were obtained by the present method, which was also used in a preliminary study [2] for the preparation of (+)-2-chlorobenzhydrol (ee 100%) and (+)-2,4-dimethylbenzhydrol (ee >95%). Including both latter compounds, we therefore obtained a new series of seven ortho-substituted benzhydrols in optically pure form. Since these compounds may be obtained easily on a multigram scale and in both enantiomeric forms, we hope that they will prove to be useful chiral transfer reagents in asymmetric synthesis, such as Diels-Alder reactions for instance.

Aknowledgements

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References and Notes

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