Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2267–2270

TETRAHEDRON: *ASYMMETRY*

Asymmetric Friedel–Crafts alkylation using chiral α-acyl-α-chloromethylsulphides

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Received 27 April 2000; accepted 10 May 2000

Abstract

Lewis acid catalysed stereoselective Friedel–Crafts alkylation of aromatic compounds with α-(–)-menthyloxycarbonyl-α-(phenylthio)methyl chloride and α-(–)-8-phenylmenthyloxycarbonyl-α-(phenylthio)methyl chloride is described.

Acylmethylation of aromatic nuclei using Friedel–Crafts reactions directly with acylmethyl halides such as ethyl chloroacetate and chloro acetone is rather difficult. However, α-acyl-α-chloromethylsulphides[1,2] have been reported to undergo a facile Friedel–Crafts reaction with aromatic compounds and olefins.[3] In continuation of our earlier studies[4] on the asymmetric synthesis, we report here asymmetric Friedel–Crafts alkylations for the synthesis of useful non-racemic synthons[5] using chiral α-acyl-α-chloromethylsulphides employing cyclohexyl based chiral auxiliaries.[6,7] The highest levels of stereochemical control in asymmetric synthesis using these chiral auxiliaries have so far been reported for nucleophilic addition reactions with chiral glyoxylates and acrylate esters.[8] The majority of these reactions employ Grignard reagents or an alkene as a nucleophile.

We studied the reaction of chiral α-acyl-α-(phenylthio)methyl chloride **4**(**a**,**b**), prepared using chiral auxiliaries (1*R*,2*S*,5*R*)-(–)-menthol and (1*R*,2*S*,5*R*)-(–)-8-phenylmenthol, with aromatic compounds catalysed by Lewis acids (Scheme 1). (–)-8-Phenylmenthyloxycarbonyl-α-(phenylthio)methyl chloride **4b** has been found to react in a highly stereoselective manner as compared to (–)-menthyloxycarbonyl-α-(phenylthio)methyl chloride **4a**.

Starting compounds **3**(**a**,**b**) were prepared by esterification of phenylthioacetic acid with (1*R*,2*S*,5*R*)-(–)-menthol and (1*R*,2*S*,5*R*)-(–)-8-phenylmenthol, respectively. Esterification of **1** using DCC in the presence of catalytic amount of DMAP in methylene chloride at 0°C gave poor yields. However, the reaction of acid chloride **2** with these chiral auxiliaries in the presence of

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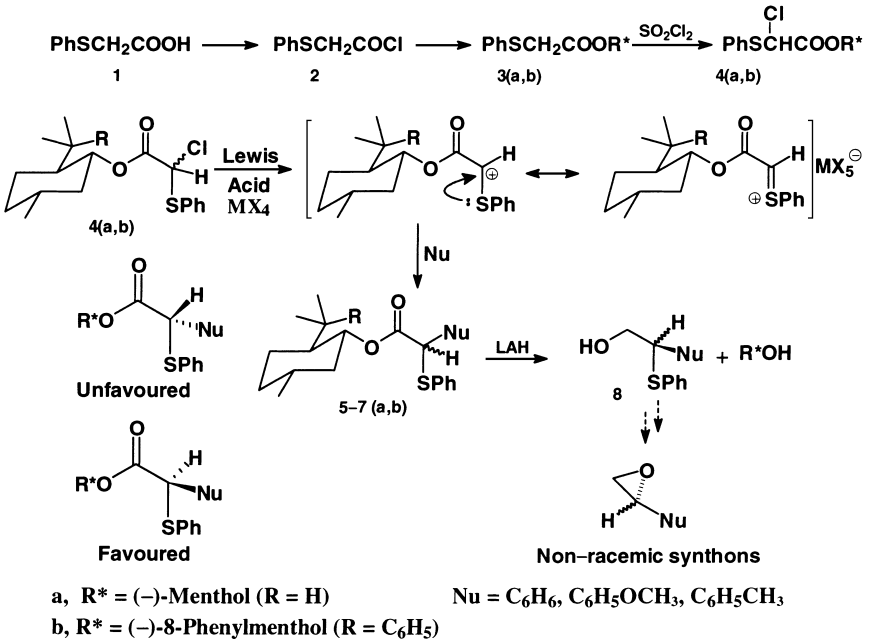
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00186-5



Scheme 1.

pyridine in benzene at 0°C gave an almost quantitative yield of esters **3(a,b)** which were purified by column chromatography. The ^{1}H NMR spectra of these esters showed well separated signals for α-methylene protons (-SCH_2-) and C1′-H of the cyclohexane ring at δ 3.62, 4.65 and δ 2.85, 4.82 for **3a** and **3b**, respectively. Treatment of **3(a,b)** with one equivalent of SO_2Cl_2 in methylene chloride at 0°C yielded a mixture of two diastereomeric chlorosulphides **4(a,b)** in quantitative yield.[9] The signal for methine protons in two diastereomers of **4a** appeared downfield at δ 5.51 and 5.52 as two singlets integrating for 1*H* giving diastereomeric excess (de) 20%. In **4b**, the two separate singlets for the methine proton appeared at δ 4.35 and 4.74 giving de 33%.

Initial studies were carried out by reacting benzene with chlorosulphides **4a** and **4b** in the presence of one equivalent of Lewis acid.[10] The reaction proceeds quite rapidly at –78 to 0°C in dry methylene chloride. Reactions are generally complete within one hour and the products are easily isolated and purified by column chromatography.

The diastereomeric excess (de) of the various products **5–7(a,b)** using benzene, toluene and anisole as nucleophiles was easily determined by 300 MHz ^{1}H NMR spectroscopy (Table 1). The ^{1}H NMR spectrum of the product **5a** obtained using benzene as nucleophile and (–)-menthol as auxiliary showed the presence of both diastereomers giving de 8% as evident from the integration of α-hydrogen to the ester carbonyl. Using benzene as a nucleophile as well as solvent in this reaction, the de increased to 14%.

However, an impressive enhancement in diastereoselectivity was observed for product **5b** obtained by using benzene as nucleophile and (–)-8-phenylmenthol as auxiliary. Analysis by ^{1}H NMR spectroscopy showed the presence of both the diastereomers (de 48%) using $SnCl_4$ as Lewis acid whereas only one diastereomer was formed using $TiCl_4$ as Lewis acid. Considering the NMR detection limit of <1% from the ^{13}C–H satellites, de in this reaction is of the order of >98% (Table 2). The same trend in diastereoselectivity is observed for other nucleophiles such as anisole

Table 1
Diastereomeric excess of the products **5a**–**7a** using (–)-menthol as auxiliary

Entry	Product No.	Lewis Acid	Reaction Time(min.)	Solvent	Nuc.	de (%)	Yield* (%)	Temp.
1.	**5a**	$TiCl_4$	50	CH_2Cl_2	C_6H_6	0	40	0°
2.	**5a**	$SnCl_4$	50	CH_2Cl_2	C_6H_6	8	38	–78°
3.	**5a**	$TiCl_4$	50	C_6H_6	C_6H_6	14	56	0°
4.	**6a**	$TiCl_4$	50	CH_2Cl_2	$C_6H_5OCH_3$	13	70	–5°
5.	**6a**	$SnCl_4$	45	CH_2Cl_2	$C_6H_5OCH_3$	12	55	–78°
6.	**6a**	$SnCl_4$	60	CCl_4	$C_6H_5OCH_3$	50	66	0°
7.	**7a**	$TiCl_4$	50	$CHCl_3$	$C_6H_5CH_3$	11	42	–5°
8.	**7a**	$SnCl_4$	60	CH_2Cl_2	$C_6H_5CH_3$	21	46	–78°
9.	**7a**	$SnCl_4$	120	n-hexane	$C_6H_5CH_3$	28	62	–5°

*All new compounds gave satisfactory CHN analysis and yields quoted are for the isolated products characterised by IR, ^{1}H NMR, ^{13}C NMR and MS.

and toluene. It is anticipated that (–)-8-phenylmenthol favours the formation of product by effectively blocking one diastereoface by its phenyl ring. The product **5b** was easily reduced with LAH in dry ether to afford substituted 2-phenylthioethanol **8**, a chiral synthon, in 89% yield and enantiomerically pure (–)-8-phenylmenthol in almost quantitative yield without any detectable racemisation.

Table 2
Diastereomeric excess of the products (**5**–**7**)**b** using (–)-8-phenylmenthol as auxiliary

Entry	Product No.	Lewis Acid	Reaction Time(min.)	Solvent	Nuc.	de (%)	Yield* (%)	Temp.
1.	**5b**	$SnCl_4$	60	$CHCl_3$	C_6H_6	48	54	–78°
2.	**5b**	$TiCl_4$	60	CH_2Cl_2	C_6H_6	98	64	0°
3.	**6b**	$SnCl_4$	50	CH_2Cl_2	$C_6H_5OCH_3$	50	68	–78°
4.	**6b**	$TiCl_4$	50	CH_2Cl_2	$C_6H_5OCH_3$	96	72	–5°
5.	**7b**	$TiCl_4$	60	CH_2Cl_2	$C_6H_5CH_3$	98	66	0°

*All new compounds gave satisfactory CHN analysis and yields quoted are for the isolated products characterised by IR, ^{1}H NMR, ^{13}C NMR and MS.

Both the enantiomers of (–)-8-phenylmenthol can be easily synthesized[11] and are also available commercially. Also the Friedel–Crafts products of type **5b** are easily transformed to 2-phenylthioethanols **8**, the described methodology is applicable to the preparation of a variety of chiral building blocks of both absolute configurations having high enantiomeric purity. Further studies, to explore the potential of these chiral building blocks, are in progress in our laboratory.

Acknowledgements

The authors gratefully acknowledge the financial support for this research from the Department of Science and Technology (DST), New Delhi, Government of India. We would like to thank Mr. Avtar Singh for skillful NMR experiments, at the Regional Sophisticated Instrumentation Centre (RSIC), Panjab University, Chandigarh.

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10. General procedure for the synthesis of (–)-8-phenylmenthyl 2-(phenylthio)phenylacetate **5b**: To a stirred solution of α-chlorosulphide **4b** (80 mg, 0.2 mmol) and benzene (0.2 mL, 0.22 mmol) in dry methylene chloride (10 mL) at 0°C was added $TiCl_4$ (0.026 mL, 0.23 mmol) rapidly under a nitrogen atmosphere via a syringe and the resulting solution was stirred for an additional 1 h at the same temperature. The reaction mixture was then allowed to warm to rt; quenched with water; extracted with methylene chloride; washed with 5% $NaHCO_3$ solution; dried over anhydrous Na_2SO_4 and then purified using column chromatography (2% EtOAc–hexanes) to furnish **5b** (56 mg, 64%); FTIR ($CHCl_3$): 1728 cm^{-1}; ^1H NMR (excluding methylene protons) ($CDCl_3$) δ: 7.51–7.02 (m, 15H, aromatic), 4.75 (dt, 1H, C1′-H), 4.08 (s, 1H, C2-H), 1.25 (s, 3H, -CH_3), 1.17 (s, 3H, -CH_3), 0.82 (d, 3H, C7′-CH_3); ^{13}C NMR ($CDCl_3$) δ: 167.91, 151.69, 133.19, 132.79, 129.04, 128.87, 128.42, 128.24, 128.07, 125.49, 125.04, 76.77, 57.38, 50.43, 40.99, 39.72, 34.48, 31.27, 27.82, 26.58, 25.13, 21.82.
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