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Asymmetric reduction of substituted fluorenones with aluminium lithium hydride in the presence of chiral amino alcohols

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Abstract

The enantioselective reduction of substituted fluorenones by aluminium lithium hydride in the presence of different chiral amino alcohols has been investigated. The best conditions found were also assayed with a multi-substituted fluorenone achieving the corresponding fluorenol compound with high enantiomeric excess. Shorter reaction times with high conversion yields were found when compared with borane reductions.

1. Introduction

Synthesis of enantiomerically pure compounds using easily recoverable chiral auxiliaries is still a major focus in organic chemistry, owing to the numerous applications not only in the fields of pharmaceuticals[1] and agrochemicals,[2] but also in new materials science. Chiral aromatic compounds are especially interesting in materials science since they can be used to design chiral monomers. Chiral compounds with mesogenic behaviour can exhibit liquid crystal order with ferroelectric properties of interest in the display device industry.[3] The preparation of a chiral fluorene system as a mesogenic unit, due to its closed structural relationship with the biphenyl unit, which is well known for inducing mesophases,[4] is of interest in the development of a new class of liquid crystal materials. We faced the problem of the introduction of a stereogenic centre on the fluorene ring. One plausible way is the synthesis of chiral alcohols via asymmetric reduction of prochiral ketones. We have reported[5] our previous results on the asymmetric reduction of 1-bromofluorenone by borane in the presence of several chiral amino alcohols. We now focus on chiral modified aluminium lithium hydride as a reduction system.

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2. Results and discussion

We present the asymmetric reduction of substituted fluorenones (Fig. 1) by aluminium lithium hydride in the presence of chiral amino alcohols with different substitution patterns (Fig. 2). Factors such as temperature and the ratio between chiral amino alcohol and aluminium lithium hydride, which affect the course of the reaction, were considered.

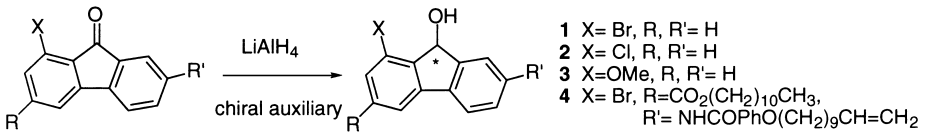

Figure 1. Asymmetric reduction of substituted fluorenones

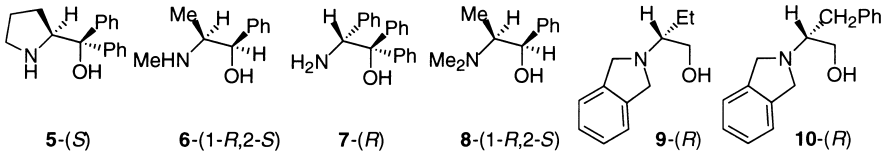

Figure 2. Chiral amino alcohols as chiral modifiers

The reduction study was mainly performed on 1-bromofluorenone.[6] However, the best conditions were also assayed for other fluorenone derivatives (Table 1). 1-Chlorofluorenone was prepared as previously described[6] and 1-methoxyfluorenone was synthesized quantitatively from 1-amino-fluorenone[6] through its diazonium salt. Undecyl 1-bromo-9-oxo-7-(4-(undec-10-enyloxy)-benzoylamino)fluoren-3-carboxylate was synthesized from 2-bromo-4-methyl-8-nitrofluorenone in several steps. Chiral modifier borane reduction performed on this kind of compound gave poor conversion yields and low-to-medium enantiomeric excess. Previous work on reduction of benzophenones with lithium aluminium hydride[7,8] prompted us to study different mixtures of $LiAlH_4$ with amino alcohols at different molar ratios.

Table 1 collects the results obtained in the reduction process by a standard procedure.[8] When compared the different amino alcohols tested, better yields in the reduction product of compound **1** were obtained with amino alcohol **9**. It should be remarked that amino alcohols **5**, **6** and **7** produce as the major product the same enantiomer when they are used as chiral modifier either with $LiAlH_4$ or with borane,[5] so the reduction with both hydrides might be explained by the same model. The other amino alcohols **8**, **9** and **10** have not been tested with borane. High chemical yields were obtained when a ratio 6:3:1.1 of chiral modifier:$LiAlH_4$:fluorenone compound was used (entry 6). This ratio also gave the best enantiomeric excess (e.e.). A greater ratio of amino alcohol with respect to $LiAlH_4$ did not enhance the enantiomeric excess (entry 7).

A large effect on the e.e. was noted[10] for the reduction with lithium aluminium hydride when ethanol as a secondary modifier was added. However, in our case the addition of 1 equivalent of a secondary modifier, ethanol, did not give a better result (entry 8). The enantioselective reduction of the other 1-substituted fluorenone: 1-chlorofluoren-9-one **2** (entry 9) and 1-methoxyfluoren-9-one **3** (entry 10), were also assayed in the optimal conditions with a ratio of 6:3:1.1 of chiral modifier 9:$LiAlH_4$:fluorenone compound. The presence of a second stereogenic centre in the amino alcohol did not seem to enhance the stereoselectivity (entries 2, 4). All experiments were

Table 1
Reduction of substituted fluorenones with chiral modified $LiAlH_4$

Entry	AA	Comp	Ratio[1]	Temp(°C)	Time(h)	Config.[2]	e.e.	Yield(%)
1	**5**	**1**	1 : 1 :1	-78	2	S	59	7
2	**6**	**1**	3.6:3:1	-16	8	R	14	43
3	**7**	**1**	1 : 1 :1	-16	8	R	5	15
4	**8**	**1**	7.6:3:1	-16	8	R	20	33
5	**10**	**1**	2.5:1:1	-16	6	R	12	7
6	**9**	**1**	6:3:1.1	-16	8	R	42	98
7	**9**	**1**	7.5:3:1	-16	8	R	42	89
8	**9**	**1**	2:1:1[3]	-16	8	R	14	13
9	**9**	**2**	6:3:1.1	-16	8	(+)	20[4]	91
10	**9**	**3**	6:3:1.1	-16	8	(+)	55[4]	61
11	**9**	**4**	6:3:1.1	-16	8	(-)	91[5]	21[5]

[1] Molar ratio of chiral modifier, $LiAlH_4$ and fluorenone compound.
[2] The configuration of 1-bromofluorenol was related to the sign of its optical rotation as described elsewhere.[9]
[3] 1 equimolar ethanol was added respect to the fluorenone compound.
[4] $[\alpha]_D$=+4.2 (c=0.48, $CHCl_3$) for a solution of 20% of e.e. of 1-Chlorofluoren-9-ol. $[\alpha]_D$=+11.6 (c= 0.56, $CHCl_3$) for a solution of 55% of e.e. of 1-Methoxyfluoren-9-ol.
[5] The yield and enantiomeric excess given are referred to the acylation product **12** of the resulting fluorenol from the reduction process, $[\alpha]_D$=-12.5 (c =0.4,$CHCl_3$) for 91% e.e.

performed at low temperature (–16°C), because only the debromination product was detected at room temperature. At low temperature the reduction was compatible with the presence of different organic functions. Polysubstituted fluorenone **4** (entry 11) was reduced quantitatively to the fluorenol compound without altering the other functionalities. The low yield reported in Table 1 is attributed to the acylation product **12** of the resulting fluorenol, which is hard to prepare because of steric hindrance. The fluorenol **11**, quantitatively produced according to thin layer chromatography analysis, was converted to **12** by treatment with acetyl chloride in the presence of *N*,*N*-dimethylaniline directly without further purification.

It has been pointed out[11] that the stereoselectivity of the reduction with derived chiral aluminium hydride complexes decreased due to a desproportionation process resulting in the regeneration of $LiALH_4$. For 1-substituted fluorenones shorter reaction times with high conversion yields were found when using chiral aluminium hydride complexes than with chiral borane reductors.[5] The medium to acceptable enantiomeric excesses obtained in the reduction of monosubstituted and polysubstituted 1-bromofluorenones open a way to the synthesis of chiral polysubstituted fluorenols, where the bromo substitution can be easily removed after the chiral reduction.

The e.e. of the resulting 1-substituted fluorenols from the corresponding fluorenones **1**–**3** were determined by HPLC on a bonded cellulose-derived chiral stationary phase.[12] In the case of compound **4**, the enantiomeric excess was obtained by the determination of the e.e. of the acylated product **12** of the resulting fluorenol by using ^1H NMR in the presence of the $Eu(hfc)_3$. ^1H NMR spectra of compound **12** in the presence of $Eu(hfc)_3$, in a molar ratio of 0.64 respect to the fluorenol derivative, showed two signals at 2.66 and 2.78 ppm of methyl hydrogens of the acetyl moiety of the two enantiomers respectively.

3. Experimental

3.1. 1-Methoxyfluoren-9-ol

^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.60 (s, 1H, OH), 3.96 (s, 3H, OMe), 5.80 (s, 1H, OCH), 6.83 (d, J = 8.1 Hz, 1H, Ar), 7.33 (7.28–7.38) (m, 4H, Ar) and 7.64 (7.62–7.66) (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz, δ, ppm): 55.9 (1 OCH_3), 74.1 (1 HOCH), 110.4, 113.4, 120.7, 125.7, 128.4, 129.3 and 131.3 (7 ArCH), 132.4, 140.6, 142.5, 145.5 and 157.4 (5 ArC). MS (EI), m/z (%): 212 (M^+, 25), 211 (M^+–1, 15), 210 (M^+–2, 27), 181 (88), 153 (36), 152 (100), 151 (38), 150 (25), and 121 (38). EA (calcd): C: 79.04 (79.22), H: 5.78 (5.70), O: 15.18 (15.08).

3.2. Undecyl 1-bromo-9-acetoxy-7-(4-(undec-10-enyloxy)benzoylamino)-fluoren-3-carboxylate

^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 0.88 (t, 3H, J = 6.4 Hz, Me), 1.27 (s, 14H, 7CH_2), 1.32 (s, 10H, 5CH_2), 1.38 (m, 4H, 2×CH_2), 1.78 (m, 4H, 2×CH_2), 2.05 (m, 2H, CH_2), 2.21 (s, 3H, MeCO), 4.00 (t, 2H, J = 6.4 Hz, O-CH_2), 4.36 (t, 2H, J = 6.6 Hz, O-CH_2), 4.96 (m, 2H, =CH_2), 5.82 (5.72–5.92) (m, 1H, =CH), 6.82 (s, 1H, Ar–CH(OAc)–Ar), 6.95 (d, 2H, J = 8.8 Hz, ArH), 7.66 (d, 1H, J = 8.0 Hz, ArH), 7.68 (d, 1H, J = 2.4 Hz, ArH), 7.84 (d, 2H, J = 8.8 Hz, ArH), 7.98 (dd, 1H, J = 8.0 and 2.0 Hz, ArH), 8.00 (s, 1H, Ac–NHCO), 8.05 (d, 1H, J = 1.2 Hz, ArH) and 8.16 (d, 1H, J = 1.0 Hz, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz, δ, ppm): 14.2 (Me), 20.8 (Me), 22.7, 26.0 (2), 28.7, 28.9, 29.1 (2), 29.30, 29.36 (2) 29.42, 29.51, 29.54, 29.62 (2), 31.9, and 33.8 (17 CH_2), 65.8 (O–CH_2), 68.2 (Ar–O–CH_2), 74.6 (O–CH), 114.1 (=CH_2), 114.4 (2), 117.7, 119.4, 121.4, 121.6, 128.9 (2), 131.8 and 139.1 (9 ArCH and 1 =CH), 120.1, 126.2, 133.7 (2), 135.0, 142.8 (2), 143.3 and 144.7 (9 ArC), 162.1 (Ar–CONH), 165.1 (O–C=O), and 171.1 (MeC=O). EA (calcd): C: 67.61 (68.52), H: 7.64 (7.41), N: 1.82 (1.78), Br: 10.04 (10.13), O: 12.89 (13.13).

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