Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 5051-5054, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00934-1

Michael-Type Addition of Phthalimide Salts to Chiral α,β-Unsaturated Imides

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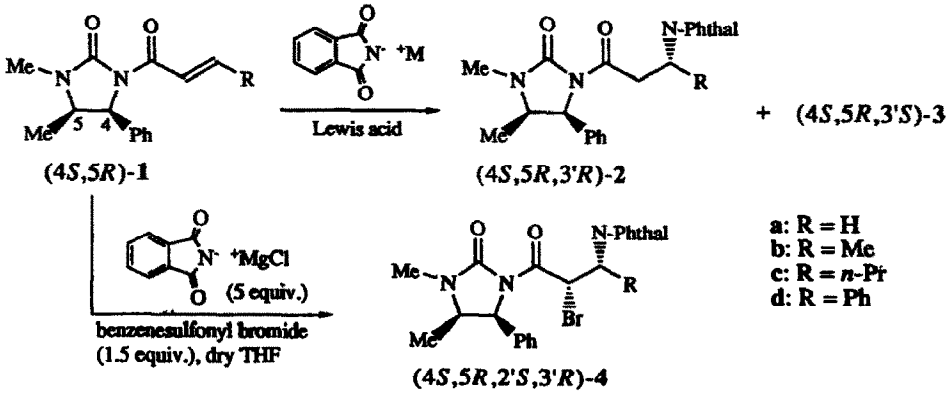
Abstract : The synthesis of (*R*)-(-)-3-aminobutanoic acid starting from chiral α,β-unsaturated imide **1b** is described, by means of the nucleophilic attack of several phthalimido derivatives in the presence of a Lewis acid. The reaction was studied in some details and chloromagnesium phthalimide afforded the better results with 95:5 diastereomeric ratio and 90% yield. Furthermore the resulting enolate was trapped performing the reaction in the presence of benzenesulfonyl bromide and the 2-bromo-3-phthalimido derivative **4** was obtained in good yield and high diastereoselectivity and successively transformed into the corresponding 2-azido-3-phthalimido derivative **6** by displacement of the bromide with sodium azide.

Recently many efforts have been focussed on the synthesis of β-amino acids as useful intermediates in the preparation of biological active compounds.[1] In this field we have previously reported the asymmetric synthesis of β-amino acids through 1,4 addition of O-benzylhydroxylamine mediated by Lewis acids on chiral unsaturated imides.[2]

In order to define the best nucleophile to introduce a carbon-nitrogen bond, several phthalimide salts were screened. We describe here the successful synthesis of (*R*)-(-)-3-aminobutanoic acid by the 1,4 conjugate addition [3] of phthalimido derivatives to the prochiral α,β-unsaturated imides **1** (Scheme 1). Moreover the Michael-like addition followed by electrophilic bromination with benzenesulfonyl bromide results in a highly stereoselective reaction, useful to introduce the two new chiral centres preferentially in the *syn* configuration. The stereoselectivity is controlled by (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one as chiral auxiliary.[4]



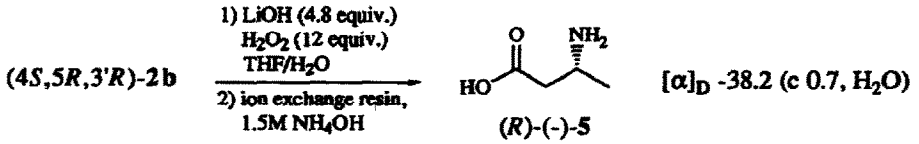
Scheme 1.

As a first approach to the carbon-nitrogen bond formation in the β position we added lithium phthalimide to the unsaturated imide **1b** in dry THF (Table 1). Under these conditions no reaction occurred. On the other hand, when the addition was performed in the presence of 1.2 equivalents of $(CH_3)_2AlCl$ as chelant in dry CH_2Cl_2, the adducts (4*S*,5*R*,3'*R*)-**2b** and (4*S*,5*R*,3'*S*)-**3b** were obtained in good yield, with a 70:30 diastereomeric ratio. Better results have been achieved when phthalimide-DBU salt was added to the imide **1b** in dry CH_2Cl_2 in the presence of 1.2 equivalents of $(CH_3)_2AlCl$.

Table 1. Addition of various phthalimido derivatives to imide **1b**.

Entry	Lewis acid (equiv.)	Nucleophile (equiv.)	Solvent	Temp. (°C)	Time (h)	Diastereomeric ratio **2b** : **3b**	Yield (%)
1	-	Phthal-Li (1)	THF	0 - rt	70	-	-
2	$AlMe_2Cl$ (1.2)	Phthal-Li (2)	CH_2Cl_2/THF	-78 - rt	24	70 : 30	60
3	$AlMe_2Cl$ (1.2)	Phthal-DBU (1.5)	CH_2Cl_2	-78 - rt	72	83 : 17	90
4	Phthal-MgCl (2)		THF	0 - rt	24	95 : 5	30
5	Phthal-MgCl (5)		THF	0 - rt	24	95 : 5	90

Best results were obtained utilising chloromagnesium phthalimide (5 equiv.),[5] in which case the reaction occurred in 90% yield and with a 95:5 diastereomeric ratio (entry 5). The absolute stereochemistry of the newly introduced stereogenic centre of the major isomer (4*S*,5*R*,3'*R*)-**2b** was established by the characterisation of the (*R*)-(-)-β-aminobutanoic acid **5** [6] obtained by total hydrolysis with an excess of LiOH in the presence of H_2O_2 [7] followed by purification on BIORAD AG 50 W-X_2 resin (1.5M NH_4OH as eluant) (Scheme 2).



Scheme 2.

This result shows that the Michael-type addition occurs by *re*-face of the Lewis acid-imide complex (Figure 1) and it implies that the chloromagnesium phthalimide acts both as Lewis acid and as nucleophile. In fact when 2 equivalents are utilised (entry 4), the reaction proceeds in 95:5 diastereomeric ratio but in low yield.

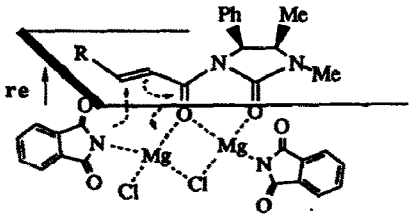


Figure 1.

When the reaction of imides **1** with chloromagnesium phthalimide was carried out in the presence of benzenesulfonyl bromide, the intermediate magnesium enolates were trapped and the corresponding 2-bromo-

3-phthalimidoimides 4 were obtained in high yield and good diastereomeric ratio.[8] In contrast for R = Ph no addition occurred (Table 2).

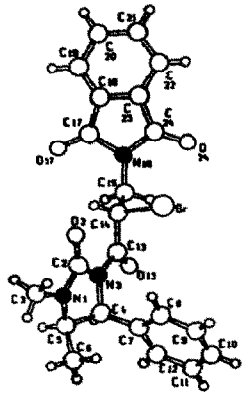
Table 2. Addition of chloromagnesium phthalimide to imides 1 in the presence of benzenesulfonyl bromide.

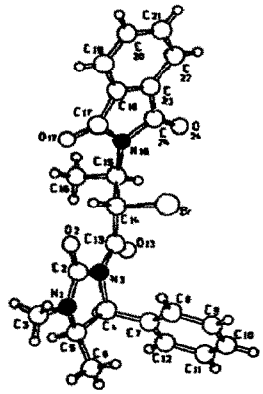
R	Major product	Temp. (°C)	Time (h)	Diastereomeric ratio	Yield (%)
H	4a	0	3	3 : 2	98
Me	4b	0 - rt	48	7 : 1 : 1[a]	95
n-Pr	4c	0 - rt	72	8 : 1 : 1[a]	98
Ph	4d	0 - rt	72	-	-

[a] Only three isomers were observed.

HPLC analysis [9] and the ^{1}H NMR spectroscopy were utilised to evaluate the diastereoselectivity of the bromination reaction [10] and the absolute stereochemistry of the major isomers 4a and 4b [11] was assigned by an X-ray study.[12] These results show that the magnesium enolate delivers preferentially the *syn* adduct as a consequence of the directing effect of the C-4 phenyl group on the chiral auxiliary.

4a

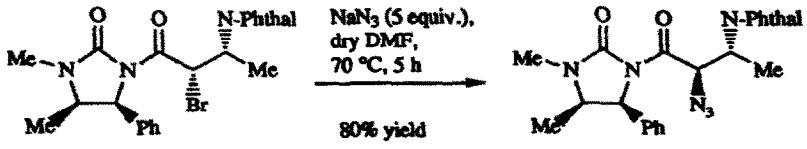




4b

Figure 2. X-Ray molecular structures of compounds 4a and 4b.

Finally, S_N2 displacement of the pure 4b by NaN_3 gave the corresponding azido derivative 6 [13] (Scheme 3) in high yield and without racemisation, as shown by ^{1}H NMR of the crude reaction mixture.



(4*S*,5*R*,2'*S*,3'*R*)-4b (4*S*,5*R*,2'*R*,3'*R*)-6

Scheme 3.

In summary the new methodology described herein represents a good method that delivers precursors of optically pure β-amino acids and α-bromo-β-amino acids, useful intermediates for biological active

compounds. In particular, the latest ones have been obtained through the highly stereoselective one-pot Michael-type addition of phthalimide salts and electrophilic bromination. Furthermore through the displacement of the bromine with sodium azide the synthesis of optically pure α,β-diamino acids can be achieved.

Experimental procedure. (Chloromagnesium phthalimide) To a solution of phthalimide (0.56 g, 3.8 mmol) in dry THF, isopropyl magnesium chloride (2M sol. in THF, 1.9 mL, 3.8 mmol) was added at 0 °C. The mixture was stirred for 30 min., then a solution of 1,5-dimethyl-3-butenoyl-4-phenyl-imidazolidin-2-one **1b** (0.2 g, 0.76 mmol) in dry THF was added slowly, then warmed to 25 °C and stirred for 24 h. After the 1,4-addition was complete (by t.l.c.), the reaction was quenched with 1M aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were washed with distilled water, brine, dried over $MgSO_4$ and concentrated in vacuo. The diastereoselectivity of the 1,4 addition was evaluated by ^1H NMR spectroscopy (300 MHz) and HPLC analysis [9] and the isomers were obtained pure after silica gel chromatography and recrystallisation from ethanol.

Acknowledgement: We thank Italian C.N.R. (Progetto Finalizzato 'Chimica Fine II') and M.U.R.S.T. (Fondi 40%) for financial support and Miss Micaela Fabbri for HPLC analysis.

References and Notes

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9. Column: SPHERI-5 RP-18 5 micron 250x4.6 mm; flow: 1.5 mL/min; solvent A: CH_3CN/H_2O 9/1; solvent B: H_2O; A/B ratio 10:90 to 100:0 in 25 min; wavelength: 214 nm.
10. **4a**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, 3H, J = 6.6 Hz, C_5-CH_3), 2.81 (s, 3H, N-CH_3), 3.94 (dq, 1H, J = 6.6 Hz, J = 8.8 Hz, C_5-H), 4.21 (dd, 1H, J = 5.5 Hz, J = 14.6 Hz, C*H*H-Phtal), 4.39 (dd, J = 8.4 Hz, J = 14.6 Hz, CH*H*-Phtal), 5.34 (d, 1H, J = 8.8 Hz, C_4-H), 6.32 (dd, 1H, J = 5.5 Hz, J = 8.4 Hz, CHBr), 7.19-7.92 (m, 9H, Ph); $[\alpha]_D$ +45.5 (c 0.6, $CHCl_3$). **4b**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, 3H, J = 6.6 Hz, C_5-CH_3), 1.55 (d, 3H, J = 6.9 Hz, CHPhtal-C*H*$_3$), 2.85 (s, 3H, N-CH_3), 3.90 (dq, 1H, J = 6.6 Hz, J = 8.8 Hz, C_5-H), 4.71 (dq, 1H, J = 6.9 Hz, J = 10.4 Hz, C*H*-Phtal), 5.24 (d, 1H, J = 8.8 Hz, C_4-H), 6.32 (d, 1H, J = 10.4 Hz, CHBr), 6.63-6.90 (m, 4H, Ph), 7.62-7.92 (m, 5H, Ph); $[\alpha]_D$ +32.0 (c 0.5, $CHCl_3$).
11. The absolute configuration of **4c** was deduced by comparison with the ^1H NMR spectra of **4b** and **4c**.
12. Crystal data. **4a**: $C_{22}H_{20}BrN_3O_4$, a=10.299(9), b=13.107(7), c=16.003(3) Å, V=2160.2 Å^3, orthorhombic, $P2_12_12_1$, Z=4; **4b**: $C_{23}H_{22}BrN_3O_4$, a=32.297(9), b=7.764(4), c=8.885(4) Å, V=2227.9 Å^3, orthorhombic, $P2_12_12$, Z=4. Data collected at 293K by the ω/2θ scan technique to a 2θ max. of 50°. Both crystal structures were solved by direct methods and refined isotropically, except for the Br atoms [SHELX system of programs]. The final cycle of full matrix least-square refinement was based on 871 observed reflections (I>2σI) and 126 variables giving an R index of 0.061 for **4a** and on 1017 observed reflections and 130 variables giving R=0.052 for **4b**. The X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.
13. **6**: IR (film) 2100, 1735, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, 3H, J = 6.7 Hz, C_5-CH_3), 1.57 (d, 3H, J = 6.9 Hz, CHPhtal-C*H*$_3$), 2.87 (s, 3H, N-CH_3), 3.92 (dq, 1H, J = 6.7 Hz, J = 8.8 Hz, C_5-H), 4.73 (dq, 1H, J = 6.9 Hz, J = 10.4 Hz, C*H*-Phtal), 5.26 (d, 1H, J = 8.8 Hz, C_4-H), 6.34 (d, 1H, J = 10.4 Hz, CH-N_3), 6.65-6.94 (m, 4H, Ph), 7.67-7.94 (m, 5H, Ph).

(*Received in UK* 31 *March* 1994; *revised* 14 *April* 1994; *accepted* 12 *May* 1994)