Tetrahedron: Asymmetry Vol. 3, No. 5, pp. 587-590, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

ASYMMETRIC MICHAEL ADDITIONS OF GRIGNARD REAGENTS TO CINNAMAMIDES DERIVING FROM N-ALKYL (R)-(-)-2-AMINOBUTAN-1-OL

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(*Received* 20 *March* 1992)

Abstract : Reaction of cinnamoyl chloride with various N-alkyl derivatives of (R)-(-)-2-aminobutan-1-ol (a readily available reagent) afforded the corresponding cinnamamides. Michael additions of Grignard reagents to the latter, followed by acidic hydrolysis, yielded optically active β-phenylalkanoic acids whose ee most generally were in the range 72-100%.

The enantioselective Michael addition of organometallic reagents to chiral α,β-unsaturated esters[1-4] oxazolines[5,6], amides[7,8] and imides[9] has attracted much interest in the past years. For instance, Mukaiyama and Iwasawa[8] prepared the crotonamide and cinnamamide deriving from (1R, 2S)-(-)-ephedrine, and they observed that addition of various Grignard reagents to the latter, followed by acidic hydrolysis, afforded the corresponding β-methyl and β-phenylalkanoic acids having high enantiomeric purities.

In this case, as well as in most others, the chirality transfer reagents have at least two asymmetric centres, and are often easily obtained in only one enantiomeric form. For this reason, we considered using simple N-alkyl derivatives of (R)-(-) or (S)-(+)-2-aminobutan-1-ol **1** as new chirality transfer reagents. Indeed racemic 2-aminobutan-1-ol **1** is a cheap compound which can readily be resolved into both its enantiomers on the industriel scale.[10]

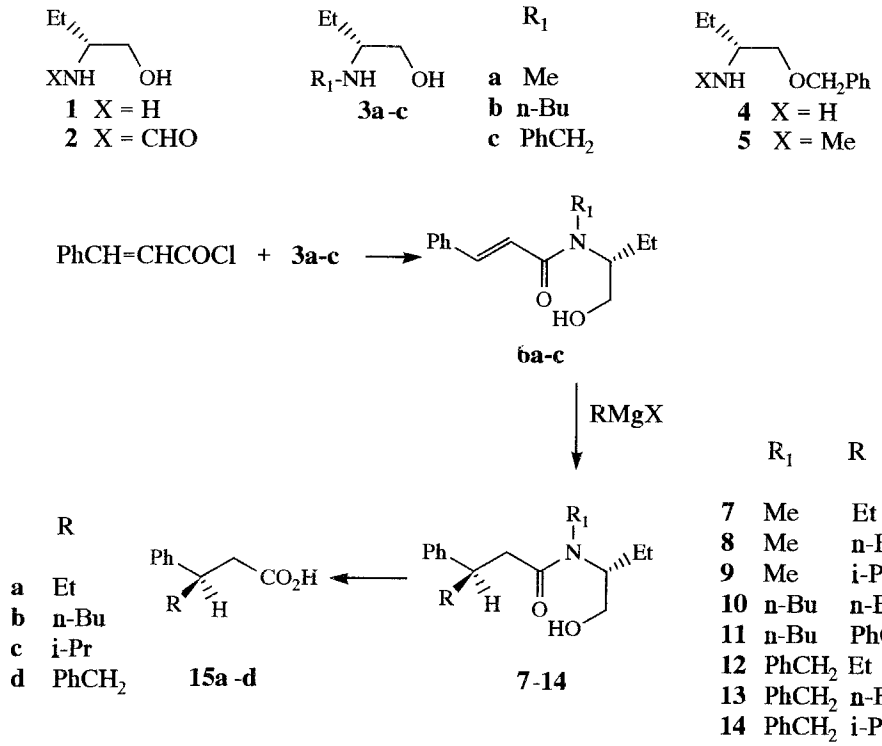
The enantioselective Michael additions of Grignard reagents, to various cinnamamides deriving from (R)-(-)-**1**, are reported in this communication.

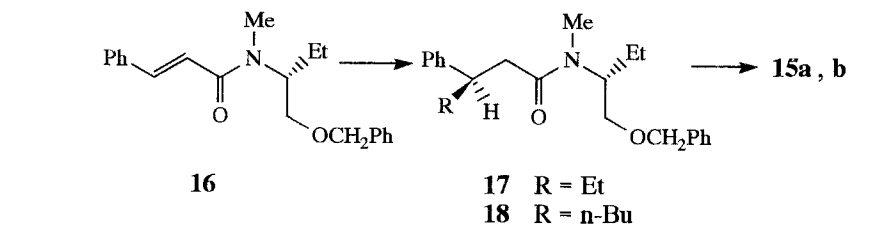
Treatment of (R)-(-)-**1** with excess ethyl formate, followed by reduction of the intermediate formamide **2** with $LiAlH_4$ in a THF/Et_2O mixture, yielded the N-methylamine (R)-(-)-**3a**. The O-benzyl N-methyl derivative (R)-(-)-**5**[11] was similarly prepared from the corresponding primary amine (R)-(-)-**4**[12] (see Scheme).

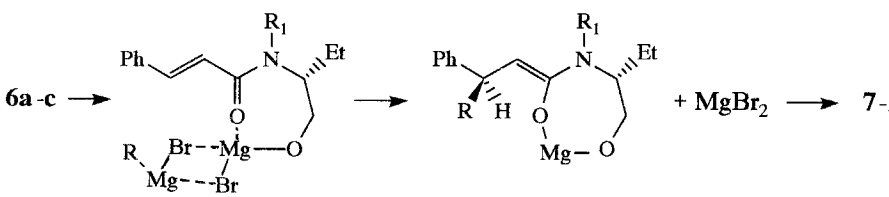
The secondary bases (R)-(-)-**3b** and (R)-(-)-**3c** were prepared from (R)-(-)-**1** as previously described.[13]

The secondary amines (R)-(-)-**3a-c** were next treated with cinnamoyl chloride in CH_2Cl_2 and in the presence of aqueous Na_2CO_3 at room temperature. This afforded the required cinnamamides (R)-(+)-**6a-c** in high yields,[14] undesirable ester formation being negligible under these conditions. The liquid amides (R)-(+)-**6a** and **6b** were purified by column chromatography over silica gel using Et_2O/cyclohexane 8:2 as an eluent. The amide **6c** is crystalline.

The Michael adducts **7-14** were obtained by reaction of the cinnamamides **6a-c** with a sixfold


Et
XNH OH
1 X = H
2 X = CHO
Et
R1-NH OH
3a-c
R1
a Me
b n-Bu
c PhCH2
Et
XNH OCH2Ph
4 X = H
5 X = Me
PhCH=CHCOCl + 3a-c
Ph
N
Et
O
HO
6a-c
RMgX
R1 R
7 Me Et
8 Me n-Bu
9 Me i-Pr
10 n-Bu n-Bu
11 n-Bu PhCH2
12 PhCH2 Et
13 PhCH2 n-Bu
14 PhCH2 i-Pr
R
a Et
b n-Bu
c i-Pr
d PhCH2
CO2H
15a-d
7-14


Me
Ph
N
Et
O
OCH2Ph
16
17 R = Et
18 R = n-Bu
15a, b


6a-c
Ph
N
Et
O
R
Br
Mg
O
Mg
Br
+ MgBr2
7-14

Scheme

excess of an appropriate Grignard reagent (RMgX) in Et_2O at 0°C for 3 hrs, which is somewhat simpler than the conditions used by Mukaiyama and Iwasawa (-40°C for 48 hours).[8] In RMgX, R is Et, i-Pr, n-Bu or $PhCH_2$. The liquid adducts **7-14** were isolated in yields ranging from 45 to 90% after column chromatography using Et_2O/cyclohexane as an eluent (see Table).

Entry	Michael adducts **7-14**, **17**, **18**					Resulting acids **15a-d**				
		R1	R	Yield (%) [a]	$[\alpha]_D$ [b]		Yield (%) [c]	$[\alpha]$ [d] observed	Lit. $[\alpha]$ (Ref.) [d]	ee (%)
1	**7**	Me	Et	76	-16	**15a**	71	-42.4	-49.96 (8)	85
2	**8**	Me	n-Bu	72	-14	**15b**	80	-33.2	+37.05 (8)	90
3	**9**	Me	i-Pr	71	-22 3	**15c**	81	-31.8	-41.05 (16)	78.5
4	**10**	n-Bu	n-Bu	60	-19.5	**15b**	80	-31.8	+37.05 (8)	85
5	**11**	n-Bu	$PhCH_2$	70	+15.5	**15d**	57	+39	-60 (2)	65
6	**12**	$PhCH_2$	Et	90	-1.3	**15a**	70	-46	-49.96 (8)	92
7	**12** e)	$PhCH_2$	Et	64	-4.2	**15a**	48	-46	-49.96 (8)	92
8	**13**	$PhCH_2$	n-Bu	50	-2.75	**15b**	80	-37	+37.05 (8)	100
9	**14**	$PhCH_2$	i-Pr	52	-6.8	**15c**	85	-29.8	-41.5 (16)	72
10	**17**	Me	Et	40	+10	**15a**	80	-38.2	-49.96 (8)	76
11	**17** e)	Me	Et	57	-5	**15a**	80	-45	-49.96 (8)	90
12	**18**	Me	n-Bu	50	+4.1	**15b**	80	-20.75	+37.05 (8)	56

a) Yield after chromatography. - b) Taken in PhH as a solvent. - c) Yield after distillation. - d) Specific rotations were taken at 22°C in PhH, at 589 nm except for **15b** whose $[\alpha]$ was recorded at 578 nm. - e) Michael addition carried out in the presence of ZnI_2.

TABLE - Enantioselective syntheses of β-phenylalkanoic acids **15a-d**

The β-phenylalkanoic acids **15a-d** (Scheme) were next obtained by acidic hydrolysis of the corresponding amides **7-14** following the literature procedure.[8] The enantiomeric excess (ee, %) of each acid **15a-d** was determined as the ratio of the specific rotation we observed to that reported for the optically pure compound (see Table). The acids **15a-c** had the (R)-(-) configuration in all cases. The acid **15d** was dextrorotary. The ee of the acids **15a-c** ranged from 72 to 100% (entry 8). When the Michael addition of EtMgBr to the N-benzylcinnamamide **6c** was carried out in the presence of ZnI_2, no improvement was observed in the enantioselectivity of the reaction, whereas the chemical yield was markedlly lower than without ZnI_2 (entries 6 and 7).

In order to assess the importance of a free hydroxyl group on the enantioselectivity of the above Michael addition reactions, the cinnamamide **16**[15] was synthesized in the usual manner, starting from the O-benzyl base (R)-(-)-**5**. The cinnamamide **16** was treated with EtMgBr and n-BuMgBr, thus leading to the liquid Michael adducts **17** and **18** respectively (entries 10 and 12). The ee of the resulting acids **15a** and **15b** were lower than those of the same acids deriving from the cinnamamide **6a**. Addition of 1 equiv. of ZnI_2, in the preparation of the Michael product **17**, resulted in an increase of the optical purity of the final acid **15a** (entry 11), which is in agreement with some earlier findings.[2]

A typical procedure is described for the preparation of (R)-(-)-3-phenylheptanoic acid **15b** (entry 8). The cinnamamide (R)-(+)-**6c** (3.5 g ; 12.5 mmol) in Et_2O (20 mL) was added to a

solution of n-BuMgBr (ca. 90 mmol) in Et_2O (20 mL) at 0°C in 1 hr. After stirring for 3 hrs at 0°C, the mixture was hydrolyzed with a buffer solution (KH_2PO_4/NaOH pH7, (108 mL). The biphasic medium was filtered through celite and the latter was washed with AcOEt. The aqueous phase was extracted with AcOEt, and the organic solutions were pooled, dried ($MgSO_4$), filtered and evaporated. Column chromatography of the oily residue (4.6 g) over silica (using Et_2O/cyclohexane 9/1 for the elution) afforded the Michael adduct (-)-**13** (2.1 g ; 50%), $[\alpha]_D^{20}$ -2.75 (c 2, PhH). The compound (-)-**13** (1.6 g ; 4,36 mmol) was added to AcOH (15 mL) and 6N H_2SO_4 (29 mL) and the mixture was refluxed for 4 hrs. After cooling, the mixture was extracted with Et_2O (3 x 75 mL) and the extract was washed with brine, then with water, and was dried ($MgSO_4$), filtered and evaporated. Distillation of the residue under reduced pressure afforded the acid (R)-(-)-**15b** (0.7 g ; 80%), $[\alpha]_{578}$ -37 (PhH), ee = 100%. Litt.[8] $[\alpha]_{578}$ +37.05 (PhH).

Conclusion

The high values of ee we generally observed for the final β-phenylalkanoic acids **15a-d** (see Table) imply that a high degree of asymmetric induction occurs during the addition of the Grignard reagent to the starting cinnamamide (**6a-c**, **16**). In agreement with Mukaiyama and Iwasawa,[8] it can be assumed that in the presence of excess Grignard reagent, the starting cinnamamide has a rather rigid and planar structure due to magnesium binding both with the carbonyl of the amide group and with the alkoxy group (or benzyl ether group). The Grignard reagent must add to the double bond in a trans manner with regards to the ethyl group carried by the asymmetric carbon, as shown on the Scheme. This indeed accounts for the (R) configuration we observed for the final acids **15a-c**.

From the sole viewpoint of asymmetric synthesis, our method is satisfying inasmuch as we could create a new asymmetric centre starting from a chirality transfer reagent (such as **3a-c**) which contains only one asymmetric centre. Besides, other advantages are that the above chiral reagents are rather cheap and readily available in both enantiomeric forms.

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14. Yields after purification and $[\alpha]_D$ (MeOH) of the cinnamamides. **6a** : 71%, +23.8 ; **6b** : 85%, +4 ; **6c** : 82%, +10.
15. Coumpound **16** : liquid, 80% yield, $[\alpha]_D$ +80 (c 2.8, MeOH).
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