One Pot Synthesis of Cyclobutanols by Ring Expansion of Oxaspiropentanes Induced by Grignard Reagents

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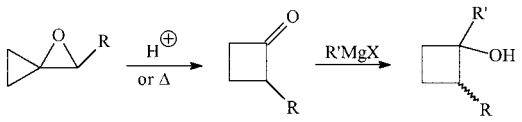
Received 4 February 1998

Abstract : Aromatic, aliphatic and vinylic Grignard reagents efficiently catalyze the ring expansion of oxaspiropentanes **2a,b** to give, in one pot, good yields of cyclobutanols **3a, 3b-7b**. Benzyl magnesium chloride gives a mixture of cyclobutanols and the cyclopropanol **8**, probably coming from a direct nucleophilic attack on the epoxide part of the oxaspiropentane.

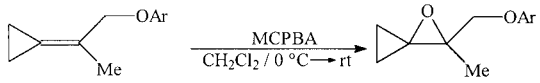
Cyclobutanols are important intermediates in the synthesis of interesting target molecules and can undergo many useful transformations. Their synthesis is carried out mainly by two different reaction protocols : a) through cyclobutanones by reduction with various hydrides or enzymes,[1] or by reaction with organometallic[1, 2] reagents. b) by [2 + 2] photoaddition of enol ethers with olefins.[3] Among these methods the direct reaction of cyclobutanones with organometallic reagents leads to the very interesting tertiary cyclobutanols,[1] that have been used in the synthesis of biologically important products. In this way an amino acid antimetabolite present in an unidentified Streptomyces species X-1029 was prepared from an α-dibenzylaminocyclobutanone,[4] and, through an anionic oxy-Cope rearrangement of vinyl cyclobutanols, the synthesis of AB taxoid models has been reported.[5] On the other hand cyclobutanones[1] are frequently obtained by ring expansion of oxaspiropentanes with acidic reagents like protonic acids or lithium or europium salts [6] or by thermal treatment.[7] Following this synthetic approach, the overall sequence for preparing cyclobutanols implies a two step synthesis as indicated in Scheme 1.



Scheme 1

In this paper we report that the synthesis of cyclobutanols **3a, 3b-7b** can be carried out, in one pot, by reaction of the oxaspiropentanes **2a,b** with Grignard reagents.

As a matter of fact the oxaspiropentanes **2a,b**, prepared by oxidation[8] of the already reported 2-cyclopropylidene-aryloxypropanes[9] **1a,b** (Scheme 2) react very smoothly with a set of Grignard reagents at low temperature to give good yields of cyclobutanols **3a, 3b-7b**, as mixtures of diastereoisomers separable by column chromatography.[10] In the case of **4b** only the **(E)-4b** was isolated from the reaction mixture while the diastereoisomer **(Z)-4b** was isolated always as an enriched mixture, from which the proton NMR data were worked out. The separation of **(E)-7b** from its diastereoisomer **(Z)-7b** was better carried out from a mixture obtained from the reaction of the cyclobutanone **9b** with benzylmagnesium chloride in the same experimental conditions. As it can be seen from Scheme 3 and from the data reported in the Table, aromatic, aliphatic and vinylic Grignard reagents give cyclobutanols, whereas the reaction with benzyl magnesium chloride leads to a 60 :40 mixture of cylobutanols (diastereoisomeric ratio 6 : 4) and the cyclopropanol **8**, probably coming from a nucleophilic attack on the epoxide ring of the oxaspiropentane. We believe that due to their electrophilic character on the metallic atom, the Grignard reagents can coordinate with the oxygen atoms of the epoxide and of the aryl ether group. In this way they can trigger the ring expansion of the oxaspiropentane to the corresponding cyclobutanones **9a, b** that, reacting with the Grignard reagent give the final cyclobutanols. (Scheme 4)

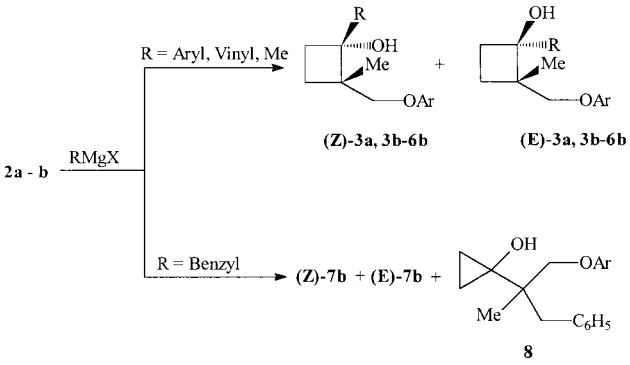


1a,b **2a,b**

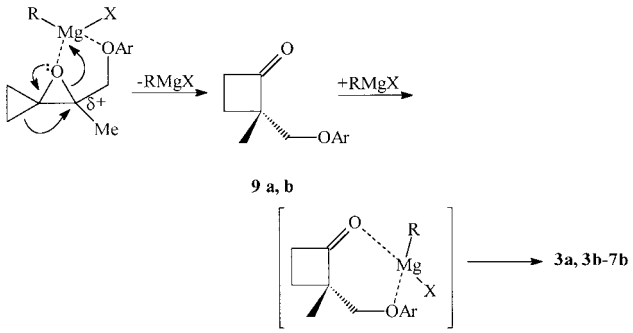
a : Ar = *p*-MeO-C_6H_4

b : Ar = C_6H_5

Scheme 2



Scheme 3

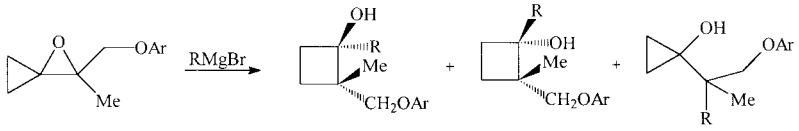


Scheme 4

This hypothesis is supported by the fact that cyclobutanols **3b**, **6b** and **7b** are also obtained, in the same diastereoisomeric ratio, by reaction of cyclobutanone **9b** with the corresponding Grignard reagents.

We can say nothing about the stereoselectivity of the ring expansion, while the attack of the intermediate cyclobutanone is occurring with moderate diastereoselectivity, probably as a consequence of a chelation of the magnesium with the oxygen atom of the ether group. This chelation leads to a preferential attack of the cyclobutanone, from the same side of the ether group, to give the cyclobutanols with the *E* geometry, except in the case of methyl magnesium iodide, that gives the corresponding cyclobutanols **3b** with practically no selectivity. The

Table . Reaction of oxaspiropentanes **2a,b** with Grignard reagents



2a,b			(E)-3a, 3b-7b	(Z)-3a, 3b-7b	8			
entry	**R**	**X**	**React. Condition**	**Ar**	**Derivatives 3a, 3b-7b**	**Cyclobut. : cycloprop.**	**(E) / (Z) ratio**	**Yields**
1	C_6H_5	Br	Ethyl Ether/THF	*p*-MeO-C_6H_4	**3a**	100 :0	80 :20	90
2	C_6H_5	Br	Ethyl Ether/THF	C_6H_5	**3b**	100 :0	75 :25	75
3	*p*-Me-C_6H_4	Br	Ethyl Ether/THF	C_6H_5	**4b**	100 :0	80 :20	84
4	$CH{=}CH_2$	Br	THF	C_6H_5	**5b**	100 :0	68 :32	90
5	CH_3	I	Ethyl Ether/THF	C_6H_5	**6b**	100 :0	45 :55	80
6	$C_6H_5CH_2$	Cl	Ethyl Ether/THF	C_6H_5	**7b**	60 :40	60 :40	90

stereochemical assignments have been made on the basis of the different chemical shifts of the methyl and the methylene hydrogens of the geometric isomers of the cyclobutanols. As a matter of fact, it is well known that a phenyl group exerts shielding effects on groups *cis* to such a phenyl group in four-membered rings while a hydroxy group is expected to exert an opposite effect.[11]

In conclusion we have reported a new way of inducing the ring expansion of some oxaspiropentanes by using Grignard reagents as electrophilic catalysts. This reaction is very useful as it allows the synthesis of tertiary cyclobutanol derivatives saving one step compared to the other methods involving the use of oxaspiropentanes. Further studies are in progress for the assessment of the general character and the stereoselectivity of this interesting transformation.

Acknowledgments. Financial support from CNR (Rome) and Murst is gratefully acknowledged.

References

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(8) Occasionally variable amounts of cyclobutanone **9b** are sometimes obtained if an excess of MCPBA is used. **9b** has also been prepared, in 84% yield, by treating the oxaspiropentane**2b** with TsOH in CH_2Cl_2 at reflux temperature for 24h.

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(10) Typical procedure for the synthesis of cyclobutanols **3a, 3b- 7b :** To a stirred THF (10 ml) solution of the oxaspiropentane **2** (1.6 mmol), prepared under argon in a Schlenk apparatus, a solution of Grignard reagent (2.5 mmol) is added at -70 °C. The solution is allowed to reach room temperature under stirring for 20h, and then is quenched with brine. Extraction with diethyl ether, drying with Na_2SO_4 and evaporation of the solvent leads to an oil that is chromatographed on a silica gel column with light petroleum/ diethyl ether (1 :1).
All new compounds have been fully characterized by ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz). Selected spectral data for compounds **2a,b, 3a,7b, 8, 9b** are given.
2a: ^1H NMR ($CDCl_3$) δ : 0.93-1.10 (m, 4H), 1.60 (s, 3H), 3.76 (s, 3H), 4.07 (s, 2H), 6.80-6.89 (m, 4H). ^{13}C NMR ($CDCl_3$) δ : 1.82, 2.77, 17.75, 55.65, 62.03, 62.86, 72.95, 114.13, 116.25, 152.88, 154.07. **2b:** ^1H NMR ($CDCl_3$) δ : 0.89-1.08 (m, 4H), 1.58 (s, 3H), 4.08 (s, 2H), 6.89-7.29 (m, 5H). ^{13}C NMR ($CDCl_3$) δ : 1.68, 2.62, 17.59, 61.74, 62.63, 71.88, 114.50, 120.90, 129.27, 158.53. **(E)-3a :** ^1H NMR ($CDCl_3$) δ : 1.43 (s, 3H), 1.79-1.87 (m, 2H), 2.09-2.19 (m, 1H), 2.41 (br s, 1H), 2.72-2.81 (m, 1H), 3.20, 3.28 (ABq, 2H, *J* = 9.0 Hz), 3.63 (s, 3H), 6.42-7.40 (m, 9H). ^{13}C NMR ($CDCl_3$) δ : 18.49, 25.03, 30.69, 47.53, 55.47, 74.05, 78.83, 114.25, 115.33, 125.77, 127.22, 127.95, 142.71, 153.24, 153.43. **(Z)-3a :** ^1H NMR ($CDCl_3$) δ : 0.78 (s, 3H), 1.52-1.56 (m, 1H), 2.12-2.35 (m, 2H), 2.75-2.85 (m, 1H), 3.21 (br s, 1H), 3.75 (s,

3H), 3.96, 4.20 (ABq, 2H, *J* = 9.3 Hz), 6.83-7.52 (m, 9H). ^{13}C NMR ($CDCl_3$) δ : 21.81, 25.02, 30.88, 46.99, 55.66, 73.66, 80.62, 114.66, 115.64, 126.15, 127.01, 128.00, 129.41, 143.41, 152.92, 154.01. **(E)-7b :** ^{1}H NMR ($CDCl_3$) δ : 1.27 (s, 3H), 1.50-1.61 (m, 1H), 1.81-2.02 (m, 2H), 2.25-2.30 (m, 1H), 2.35 (br s, 1H), 2.90 (s, 2H), 3.99, 4.11 (ABq, 2H, *J* = 9.0 Hz), 6.89-7.30 (m, 10H). ^{13}C NMR ($CDCl_3$) δ : 19.45, 24.47, 31.43, 42.42, 46.37, 73.06, 76.58, 114.60, 120.88, 126.30, 128.04, 129.39, 130.45, 137.32, 158.89. **(Z)-7b :** ^{1}H NMR ($CDCl_3$) δ : 1.35 (s, 3H), 1.61-1.98 (m, 3H), 1.80 (br s), 2.25-2.32 (m, 1H), 2.92, 3.01 (ABq, 2H, *J* = 13.5 Hz), 3.88, 4.02 (ABq, 2H, *J* = 9.3 Hz), 6.92-7.32 (m, 10H). ^{13}C NMR ($CDCl_3$) δ : 18.80, 24.25, 30.82, 41.47, 46.29, 72.47, 76.68, 114.49, 120.65, 126.36, 128.15, 129.36, 130.33, 137.24, 159.06. **8** (data worked out from an unseparated reaction mixture) **:** ^{1}H NMR ($CDCl_3$) δ : 0.58-0.68 (m, 4H), 0.65 (s, 3H), 2.35 (br s, 1H), 3.08, 3.22 (ABq, 2H, *J* = 13.5 Hz), 3.91, 3.95 (ABq, 2H, *J* = 9.0 Hz), 6.92-7.22 (m, 10H). ^{13}C NMR ($CDCl_3$) : 9.78, 10.62, 18.32, 39.97, 40.89, 60.65, 74.37, 114.54, 121.21, 126.03, 127.85, 129.50, 130.80, 138.14, 158.31. **9b** : ^{1}H NMR ($CDCl_3$) δ : 1.20 (s, 3H), 1.81-1.90 (m, 1H), 2.34-2.44 (m, 1H), 2.99- 3.20 (m,2H), 3.83, 4.04 (ABq, 2H, *J* = 9.0 Hz), 6.78-7.22 (m, 4H). ^{13}C NMR ($CDCl_3$) : 17.85, 21.76, 43.39, 63.80, 70.13, 114.32, 120.85, 129.20, 158.44, 212.83.

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