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A general protocol for the regio high yielding opening of different glycidol derivatives

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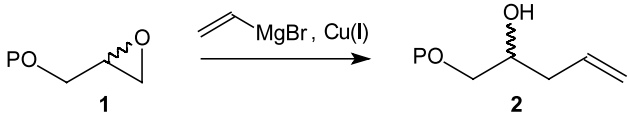
Abstract—Differently protected glycidol derivatives (with Bn, TBDPS, TBS and MPM groups) have been tested for regioselective ring opening with vinylmagnesium bromide in order to obtain useful five-carbon functionalised homoallylic alcohols. Careful choice of the reagents and experimental conditions allowed a general access to important chiral synthons for asymmetric synthesis.

Chiral glycidol derivatives such as **1** (Scheme 1) which can be easily obtained,[1] or are commercially available in both racemic or optically pure forms,[2] are particularly useful starting material for asymmetric synthesis of enantiomerically enriched compounds. The choice of the hydroxyl protecting group is particularly important in synthetic applications and therefore most of the common protecting groups have been used. The more straightforward access to glycidol derivatives is probably the regioselective opening of the oxirane ring in order to get compounds of type **2**. Epoxide opening with vinylmagnesium halides was strongly investigated to prepare chiral homoallylic alcohols and recently, these ring openings have been performed with different protecting groups such as benzyl,[3] MPM[4] or TBDPS[5] in different experimental conditions and with results from good to excellent.

During our studies on the synthesis of polyhydroxylic natural products we had to prepare compounds similar to **2**, and therefore we tried the different reported procedures and also different protecting groups to open type **1** oxirane. However we found, frequently, difficult to reproduce[6] the reported results, specially because the final compound **2** was often contaminated with minor by-products impossible to separate by standard chromatography. Furthermore in the reported procedures, the effect of factors such as temperature, reaction time and order of reagents addition, were never investigated as well as a protecting group as TBS.



Scheme 1.

We report in this paper a careful and extensive study on this opening reaction, in order to find a general protocol for the most useful protected glycidol derivatives **1a–d**. Our results are shown in Scheme 2 and Table 1, and a general procedure with vinylmagnesium bromide in THF at −20°C is described.[7] Since performing the same reactions with vinylmagnesium chloride we found the reaction proceeded in very low overall yields with several by-products, these unsuccessful results have not been reported in Table 1.

All the reactions tested afforded, as the main product, the expected homoallylic alcohol **2a–d** and we found that the conditions in entries 1, 3, 6 and 7 in Table 1 were satisfactory for the conversion and for the homoallylic alcohol yields. Of particular importance is the reaction on glycidol **1c** (Table 1, entries 5 and 6) where a very common protecting group TBS is used. In this case the use of CuBr leads to a quantitative ring opening with an overall 98% yield of the final product in contrast with CuI.

Keywords: glycidol; vinylmagnesium bromide; cuprate; ring opening.
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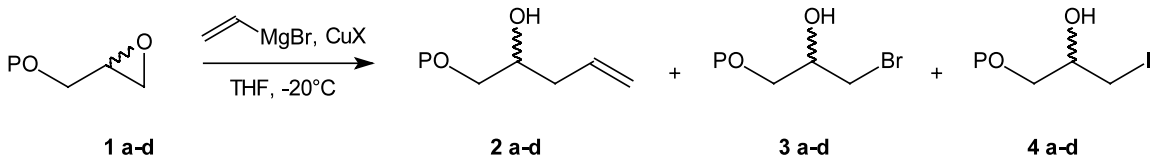


1 a-d **2 a-d** **3 a-d** **4 a-d**

Scheme 2.

Table 1.

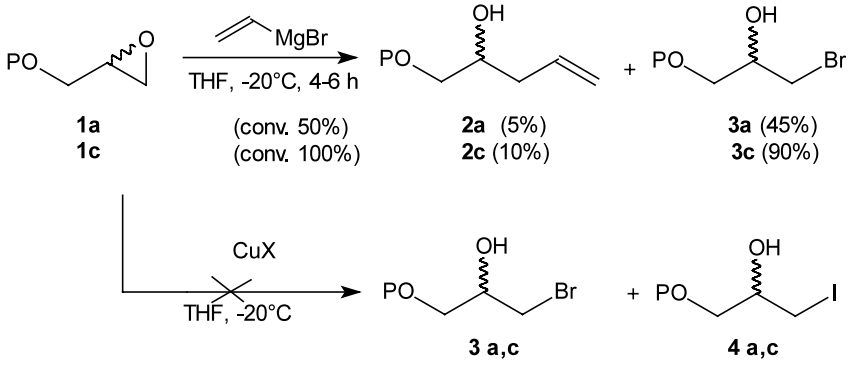
Entry	Glycidol	P	CuI (equiv.)	CuBr (equiv.)	Time (min)	Conv. (%) (yield%)[a]	**2**[b]	**3**[b]	**4**[b]
1	**1a**	Bn	1		60	100 (100)[c]	91	9	–
2	**1a**			0.4	20	100 (100)[c]	84	16	–
3	**1b**	MPM	1		20	100 (90)	91	9	–
4	**1b**			0.8	20	97 (79)	82	18	–
5	**1c**	TBS	1		60	95 (–)[d]	88	5	7
6	**1c**			0.5	20	100 (–)[d]	98	2	–
7	**1d**	TBDPS	1		45	100 (91)	93	0.5	6.5
8	**1d**			1	20	42[e] (39)	93	7	–

All the reactions were conducted with 4 equiv. of vinylmagnesium bromide and 1 equiv. of racemic epoxides (0.15 M in THF) at −20°C.
[a] The conversion was evaluated by GC–MS on the starting consuming epoxide and the yield after column chromatography.
[b] The ratio of the products was in percent and was calculated by GC–MS.
[c] The mixture of products was found unseparable by column chromatography.
[d] The products were unstable on silica gel column.
[e] At higher conversion grade larger amounts of bromohydrin and other by-products were produced.
Bn = benzyl, MPM = methoxyphenylmethyl, TBS = *t*-butyl dimethyl silyl, TBDPS = *t*-butyl diphenyl silyl.

The reactions were accompanied by variable amounts of the corresponding halohydrins, which is due to the known ability of metal halides to open simple and functionalised epoxides.[8] The characterisation of these by-products, which have never been isolated or mentioned in earlier experiments,[3–5] is particularly important. Probably these halohydrins have never been detected or separated and the main product was used without purification in the next step of the synthesis. However in our experiments we have found the best reaction conditions in order to minimise the halohydrins formation and to obtain a high yielding reaction.

The bromohydrin formation is probably due to the degradation of vinylmagnesium bromide. In order to verify this hypothesis we carried out reaction of epoxides **1a**,**c** with vinylmagnesium bromide and CuX respectively (Scheme 3). We found that, while Cu(I) salts alone did not open oxiranes **1a**,**c**, the Grignard reagent alone afforded in large amount the corresponding bromohydrins **3** (together with the opening product **2**), a much longer reaction time (4–6 h) was however required for a substantial conversion of the epoxides.

In conclusion, in this epoxide opening reaction, we found that glycidols of type **1** gave the homoallylic alcohols as the main product, in presence of CuI and in excellent yields. The epoxide with a TBDPS protecting group was found to give the lowest percentage of conversion (using CuI the corresponding homoallylic alcohol **2d** was obtained in 45 min instead of 20 min but with an excellent conversion, Table 1, entry 7). The simple experimental conditions and the rapidity of the reactions on different glycidols make this protocol a reliable method to access to functionalised five-carbon chain products, as useful chiral precursor for synthesis of more complex molecules.



1a **1c** (conv. 50%) (conv. 100%) **2a** (5%) **2c** (10%) **3a** (45%) **3c** (90%)

3 a,c **4 a,c**

Scheme 3.

Acknowledgements

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References

1. (a) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1998**, *63*, 5696–5699; (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437–475. For some examples of applications, see: (c) O'Brien, M.; Taylor, N. H.; Thomas, E. J. *Tetrahedron Lett.* **2002**, *43*, 5491–5494; (d) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; Konig, W. A.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487–7495; (e) Dorling, E. K.; Ohler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323–6326.
2. Racemic glycidols, as the corresponding benzyl- and TBS-glycidols, were all purchased from Aldrich.
3. (a) Huang, H.; Mao, C.; Jan, S.-T.; Uckun, F. M. *Tetrahedron Lett.* **2000**, *41*, 1699–1702; (b) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3143–3155; (c) Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192–194.
4. (a) Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233–2235; (b) Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 877–880; (c) Byun, H.-S.; Sadlofsky, J. A.; Bittman, R. *J. Org. Chem.* **1998**, *63*, 2560–2563.
5. Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085.
6. With careful repetition of the other methods reported in literature we had never obtained the same ratio between the alkylated products and the halohydrins. By performing the ring opening with vinyl magnesium bromide slowly added to a solution of Cu(I) salts in THF at −10°C and then a solution of the **1a–d** epoxides we have often found the halohydrins **3a–d** and **4a–d** as the main products of the reaction with variable amounts of the homoallylic alcohols **2a–d**. The homoallylic alcohol/halohydrin mixture was found difficult to separate by standard column chromatography because often compounds **2a–d** and **3a–d** showed similar or identical R_f.
7. *General procedure for the opening reaction of **1a–d***: all reactions were carried out in oven- or flame-dried glass ware under argon atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon before use. The copper salts were all simply flame-dried and cooled in vacuum before use. Vinylmagnesium bromide was purchased from Fluka. A 1 M solution of vinylmagnesium bromide in THF (4 equiv.) was quickly added to a solution 0.15 M in THF of epoxide **1** (1 equiv.) and CuX (for the equivalent ratio see Table 1) at −20°C. The reaction was monitored by TLC and after completion a saturated aqueous solution of NH_4Cl was added. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuum affording a yellow oil. The crude product was analysed by GC–MS.
8. (a) Bonini, C.; Righi, G. *Synthesis* **1994**, 225–238; (b) Righi, G.; Bonini, C. In *Targets in Heterocyclic Systems, Chemistry and Properties*; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Roma, 2001; Vol. IV, p. 139.