Pergamon

Tetrahedron Letters 41 (2000) 7387–7390

TETRAHEDRON LETTERS

The importance of A-strain in the stereochemical control of ring opening of tetrahydropyrans

John M. Mellor* and Afaf H. El-Sagheer

Department of Chemistry, University of Southampton, Southampton SO17 1BJ, UK

Received 9 June 2000; revised 14 July 2000; accepted 20 July 2000

Abstract

Readily available cyclic β-alkoxy-α,β-unsaturated trifluoromethylketones react with excess phenyl magnesium bromide by initial 1,4-addition, followed by ring opening to give a variety of products. Both the major products, unsaturated diols, and the minor products, as shown by X-ray diffraction studies, are generated with high stereoselectivity, which is attributed to $A^{1,3}$-strain. © 2000 Published by Elsevier Science Ltd.

Keywords: allylic strain; Grignard reagents; tetrahydropyrans.

$A^{1,3}$-strain has been recognised[1] as a major factor determining the stereochemical pathway of reactions in both cyclic and acyclic systems. In epoxidations,[2] hydroborations,[3] dihydroxylations[4] and in other[4,5] addition reactions, $A^{1,3}$-strain has been recognised as a dominant control. However, the observed selectivity has also been attributed[6] to stereoelectronic as well as simple steric factors. In cyclic systems, $A^{1,3}$-strain was first proposed to account for the course of additions[7] to 2-substituted methylenecyclohexanes, the reactions of enamines[8] and then the alkylation and protonation of enolate anions of 1-acyl and 1-nitrocyclohexanes.[1] However, the general importance of $A^{1,3}$-strain in elimination reactions has not been demonstrated. We describe here examples of elimination reactions, where the stereochemical pathway is determined by $A^{1,3}$-strain. In the previous letter[9] we have described the addition of organometallic reagents to the ketone (**1**). Alkyl and aryl Grignard reagents undergo 1,4-addition but benzyl and allyl Grignard reagents undergo 1,2-addition to the ketone (**1**) permitting a route to trifluoromethyl aromatics to be established. We now report the different course of addition of Grignard reagents to the ketones (**2**) and (**3**), where ring opening affords products thus exposing a stereochemical control of $A^{1,3}$-strain.

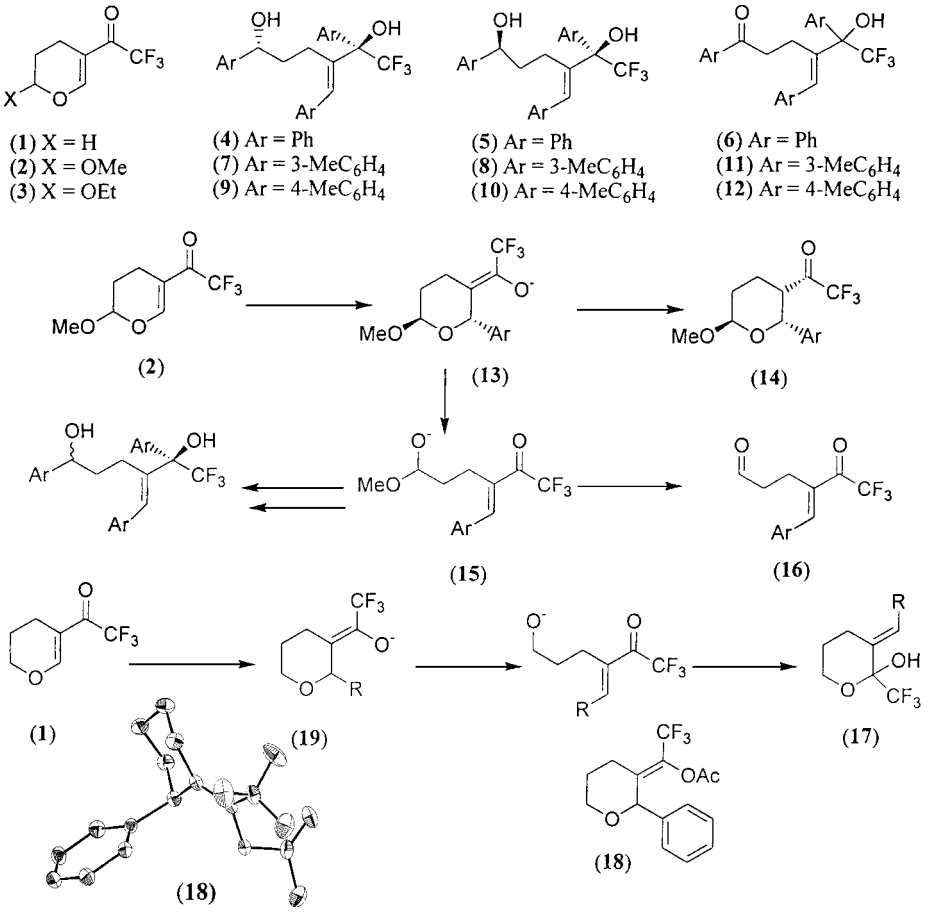
Reaction of ketone (**3**) with phenyl magnesium bromide gave the two diols (**4**) and (**5**)[10] in 35 and 57% yields, respectively. Similarly ketone (**2**) afforded the same diols in comparable yields.

* Corresponding author. E-mail: jmm4@soton.ac.uk

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01256-9

The structure of the crystalline diol (**4**) was determined[11] by single crystal X-ray diffraction studies, but the structure of the non-crystalline major product (**5**) was established, in part spectroscopically and by oxidation with Jones reagent of both diols (**4**) and (**5**), which gave the same ketoalcohol (**6**). The generality of these additions was established by reaction of the ketone (**3**) with 3-tolyl magnesium bromide to give the diols (**7**) and (**8**), in 41 and 43% yields, respectively, and with 4-tolyl magnesium bromide to give the diols (**9**) and (**10**), in 30 and 35% yields, respectively. The relationship of the pairs of diols was established in both cases by oxidations giving the ketoalcohols (**11**) and (**12**).

The likely reaction path to the diols is shown in Scheme 1. An initial 1,4-addition gives possible diastereoisomeric enolate anions, of which the enolate (**13**) is favoured. Formation of the enolate (**13**) shows a preference for *trans*-addition with respect to the alkoxy group and the stereochemistry about the enolate double bond reflects the large size[12] of the trifluoromethyl group. When reaction is conducted with 3 equivalents of 4-tolyl magnesium bromide at –35°C, the ketone (**14**) can be isolated in 76% yield. Comparison NMR data both from the literature[13] and with a series of 1,4-adducts of ketone (**1**) permit the stereochemical detail in ketone (**14**) to be defined. Reaction with an excess of a Grignard reagent affording the diols requires ring opening of the enolate (**13**) to give the hemiacetal anion (**15**). By effecting reaction at 0°C it is possible to



isolate the aldehyde (**16** Ar = 4-MeC_6H_4) in low yield (14%). Hence, the intermediacy of the anion (**15**) is indicated. The subsequent evolution to the diol products requires a 1,2-addition to the unsaturated ketone and the collapse of the hemiacetal to an aldehyde with the addition of a further equivalent of Grignard reagent. Although the timing of these stages is not established, a number of interesting points emerge from Scheme 1. The first 1,4-addition follows the pattern established in the accompanying paper[9] of reaction of the ketone (**1**) with aryl Grignard reagents. The 1,2-addition to the acyclic ketone typifies[14] the behaviour of aryl Grignard reagents with aryl α,β-unsaturated ketones. The final Grignard addition to afford the diols occurs, unsurprisingly, with little selectivity. However, the striking feature of Scheme 1 is the high degree of selectivity, which leads to a single series of geometrical isomers.

The step defining the olefin stereochemistry is the ring opening of the enolate anion (**13**) to give the unsaturated ketone (**15**). The possibility that the methoxy substituent has an influence on the course of the ring opening can be eliminated by the observation that in 10 examples of additions of Grignard reagents to the ketone (**1**) minor products (**17**) are observed (see Scheme 1). The structure of (**17** R = 4-MeC_6H_4) has been proven[11] by X-ray analysis showing that the ring opening follows the same stereochemical course observed in the ring opening of the enolate anion (**13**). A factor other than the methoxy substituent must be controlling the pathway of the ring opening. This factor is exposed by a further X-ray analysis[11] of the acetate (**18**), obtained by quenching the enolate anion (**19**) with acetyl chloride, which reveals two interesting stereochemical features. First the large trifluoromethyl group[12] is in the less congested position in the acetate (**18**) and hence we assume in the enolates (**13**) and (**19**). The second interesting stereochemical observation shows that the acetate (**18**) has the aryl substituent in the pseudo-axial position (see Scheme 1). A ring opening of the enolates (**13**) and (**19**) having an axial substituent will lead to the observed olefin stereochemistry in the diol products, in the aldehydes (**16**) from enolate (**13**) and in the alcohols (**17**) from enolate (**19**). The adoption by a substituent of a pseudo-axial conformation in the acetate (**18**) must be attributed to $A^{1,3}$-strain. This strain is present both in the acetate (**18**), as shown by the X-ray analysis, and, we propose, in the enolates (**13**) and (**19**), hence determining the stereochemistry of ring opening. In the case of the enolate (**13**) the conformation adopted in the transition state of ring opening requires not only the aryl substituent to be in the pseudo-axial position, but also requires the methoxy substituent to be placed in a pseudo-equatorial position, counter to an anomeric effect.[15] The observation of stereoselective ring opening requiring this conformation is testimony to the very substantial effect of $A^{1,3}$-strain. The diols shown in Scheme 1 are obtained in over 90% yield without observation of other geometrical isomers. The addition of alcohols to α,β-unsaturated esters[16] is complex, involving both steric and stereoelectronic factors. The outcome of the reverse process, alkoxide elimination from the enolate anion of a β-alkoxy-α,β-unsaturated ketone can be seen from our results to be determined in this instance by $A^{1,3}$-strain. Although the ring opening of pyrans has previously been observed,[17] our results provide the first evidence of a steric control of products via $A^{1,3}$-strain.

Acknowledgements

We thank the Egyptian government for a research studentship (A.H.El-S.) and EPSRC for X-ray facilities.

References

1. Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841.
2. Vedejs, E.; Dent, W. H. *J. Am. Chem. Soc*. **1989**, *111*, 6861; Jackson, R. F. W.; Standen, S. P.; Clegg, W.; McCamley, A. *J. Chem. Soc. Perkin Trans. 1* **1995**, 141; Adam, W; Wirth, T. *Acc. Chem. Res*. **1999**, *32*, 703.
3. Yokoyama, Y.; Kawashima, H.; Masaki, H. *Chem. Lett*. **1989**, 453.
4. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247; Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc*. **1997**, *119*, 8031; Kauppinen, P. M.; Koskinen, A. M. P. *Tetrahedron Lett*. **1997**, *38*, 3103.
5. Dulcere, J. P.; Dumez, E. *Chem. Commun*. **1997**, 971.
6. Crump, R. A. N. C.; Fleming, I.; Hill, J. H. M.; Parker, D.; Reddy, N. L.; Waterson, D. *J. Chem. Soc., Perkin Trans*. 1 **1992**, 3277.
7. Johnson, F. *Chem Rev*. **1968**, *68*, 375.
8. Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta*. **1993**, *76*, 2473.
9. Mellor, J. M.; El-Sagheer, A. H.; Salem, E. M. *Tetrahedron Lett*. **2000**, *41*, 7383.
10. All new compounds were characterised spectroscopically and by high resolution mass spectroscopy, or by combustion analysis.
11. Genge, A. R. J.; Patel, B; Reid, G. personal communication.
12. Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99.
13. Yu, C.-M.; Jung, W.-H.; Choi, H.-S.; Lee, J.; Lee, J. K. *Tetrahedron Lett*. **1995**, *36*, 8255.
14. House, H. O.; Traficante, D. D.; Evans, R. A. *J. Org. Chem*. **1963**, *28*, 348.
15. Booth, H.; Dixon, J. M.; Khedhair, K. A.; Readshaw, S. A. *Tetrahedron* **1990**, *46*, 1625; Booth, H.; Readshaw, S. A. *Tetrahedron* **1990**, *46*, 2097.
16. Mohrig, J. R.; Rosenberg, R. E.; Apostol, J. W.; Bastienaansen, M.; Evans, J. W.; Franklin, S. J.; Frisbie, C. D.; Fu, S. S.; Hamm, M. L.; Hirose, C. B.; Hunstad, D. A.; James, T. L.; King, R. W.; Larson, C. J.; Latham, H. A.; Owen, D. A.; Stein, K. A.; Warnet, R. *J. Am. Chem. Soc*. **1997**, *119*, 479.
17. Gelin, S.; Gelin, R. *Bull. Soc. Chim. France* **1968**, 288; Boring, D. L.; Sindelar, R. D. *J. Org. Chem*. **1988**, *53*, 3617.