α-Methoxyketone Synthesis *via* Ketone Homologation: $ZrCl_4$-Mediated Hydroxy Sulfone Rearrangements

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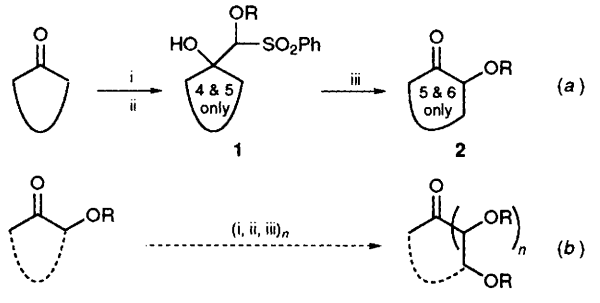
The adducts between ketones and the anion derived from [(methoxymethyl)sulfonyl]benzene undergo efficient, regioselective rearrangement to give α-methoxyketones when treated with $ZrCl_4$ and $HfCl_4$; this new procedure allows the sulfone-mediated homologation methodology to be applied to monocyclic and acyclic ketones.

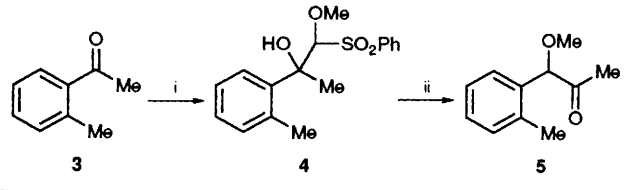
There is widespread interest in the development of new synthetic routes for the preparation of polyoxygenated carbon frameworks for use in natural product synthesis.[1] In principle the alkoxymethylene homologation methodology [Scheme 1(*a*)] introduced by Trost *et al.*,[2] and utilised in prostaglandin synthesis,[3] constitutes a powerful method in this arena. This procedure involves the generation of hydroxy sulfone **1** using α-sulfonyl anion chemistry as shown, followed by a one carbon ring expansion initiated by aluminium-based Lewis acids to give **2**. In practice, however, the ring expansion reaction was shown to be limited to cyclobutanones and cyclopentanones and all of the successful examples were bicyclic systems.[2,3]† We were keen to expand the scope of this methodology to include monocyclic and larger ring systems and acyclic substrates, and to investigate its use as an iterative method [Scheme 1(*b*)]. It seemed likely that the strain inherent in the bicyclic ketones previously studied provided a major driving force for homologation, but it was hoped that by variation of the reaction conditions, particularly the choice of the Lewis acid, homologation would be possible.

Initial investigations confirmed the published observations;[2,3] using the acyclic adducts **4**,[4] prepared as a mixture of diastereoisomers by treatment of substituted acetophenone **3** with the anion derived from [(methoxymethyl)sulfonyl]benzene as a test case (Scheme 2), the aluminium-based Lewis acids favoured in earlier studies[2,3] gave conversion to a complex mixture of products. A wide range of Lewis acids were then screened‡ and after considerable experimentation it was found that treatment of **4** with an excess of $ZrCl_4$ in CH_2Cl_2 at room temp. gave an almost quantitative yield of the required homologated product **5** in an extremely clean reaction. This Lewis acid has not received extensive attention,[5] but it proved to be of great value in this particular example, where the efficiency and complete regioselectivity (with exclusive migration of the aryl group)[6] of the process are noteworthy.

With a successful homologation procedure in hand, we turned our attention to an examination of its scope and

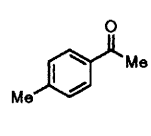
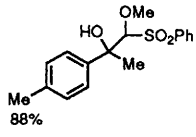
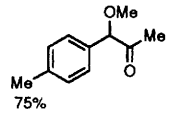
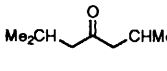
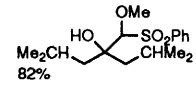
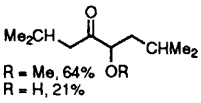
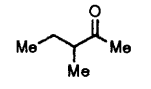
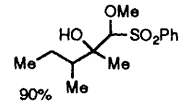
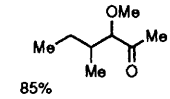
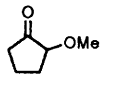
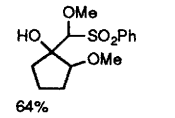
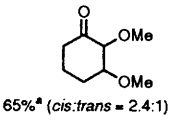
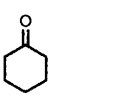
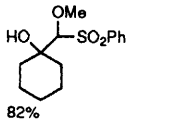
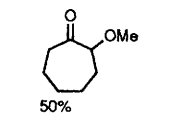
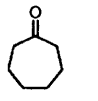
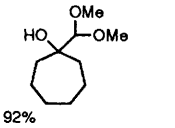
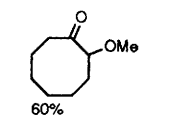
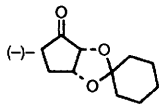
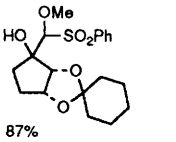
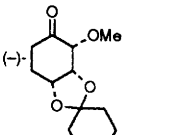
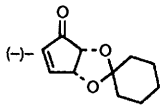
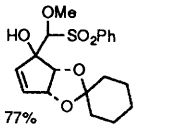


Scheme 1 *Reagents and conditions*: i, $ROCH(Li)SO_2Ph$; ii, H_3O^+; iii, Bu^i_2AlCl



Scheme 2 *Reagents and conditions*: i, $MeOCH_2SO_2Ph$, BuLi, THF, −78 °C (82%); ii, 6 $ZrCl_4$, CH_2Cl_2, room temp. (99%)

Table 1 Conversion of ketones **3** into **4** and **5** according to Scheme 2 (using $ZrCl_4$ for homologation)

	Ketone **3**	Adduct **4**	Homologated product **5**
a		 88%	 75%
b		 82%	 R = Me, 64% OR R = H, 21%
c		 90%	 85%
d		 64%	 65%[a] (*cis*:*trans* = 2.4:1)
e		 82%	 50%
f		 92%	 60%
g		 87%	 51–84%[c]
h		 77%	–[b]

[a] Carried out using $HfCl_4/CH_2Cl_2$ [$ZrCl_4$ gave **5d** in 40% yield]. [b] An extremely complex mixture was obtained from this reaction with little, if any, of **5h** present. Similar results were obtained with the parent cyclopent-2-enone adduct. [c] $[\alpha]_D$ −50.0 (*c* 0.5, CH_2Cl_2); although only one diastereoisomer was formed the stereochemical assignment is tentative at present.

limitations in terms of substrate structure (Table 1). Application of the optimised conditions to 4′-methylacetophenone adducts (entry a) gave a similarly encouraging results with clean formation of **5a**. Whilst we had now succeeded in applying the methodology to acyclic systems, aryl groups are well known to undergo facile migration to an electron deficient centre.[6] Much more significant indications of the generality of this procedure came with the successful homologations of ketones **3b** and **3c**. The migrating group in the rearrangement of **4b** to **5b** is a primary, saturated alkyl chain which offers little stabilisation of the electron-deficient centre in the reaction intermediate. The system also possesses no significant strain to act as a driving force, and yet homologation occurs cleanly in an overall, purified yield of 85% (partial demethylation being observed in this example). The formation of **5c** provided a further example of alkyl group migration; total regioselectivity was observed in this example with the exclusive migration of the secondary centre.[6] The first example of monocyclic ring expansion with the simultaneous incorporation of an α-oxygenated centre was provided by the successful formation of **5d**. Again complete regioselectivity was observed, with the oxygenated centre migrating to the exclusion of the alternative primary migrating group.[6] On this occasion the use of hafnium tetrachloride in dichloromethane was found to give the cleanest ring expansion. The cyclohexanone and cycloheptanone adducts, **4e** and **4f**, also underwent ring expansion giving cycloheptanone **5e** and cyclooctanone **5f**, respectively, in respectable yields for medium size ring formation.

We are currently investigating the use of this methodology for the preparation of cyclitols. As part of this study we have effected the ring expansion of ketone (−)-**3g**,[7] *via* the intermediates **4g**, into (−)-**5g**, the reaction proceeding with complete regio- and diastereo-selectivity in yields up to 84%. The unsaturated analogues **4h**, however, failed to undergo clean homologation, as did the corresponding adducts of cyclopent-2-enone, demonstrating a limitation to this procedure.

In conclusion, the use of zirconium tetrachloride facilitates a high yielding homologation of ketones into α-methoxy ketones *via* the intermediacy of sulfone adducts **4**, which appears to be extremely general and regioselective, and experimentally straightforward.§ The regioselective homologation of α-oxygenated ketones **3d** and **3g** indicates that the process should also be capable of iteration.

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Footnotes

† The corresponding rearrangement to give α-phenylthioketones [**1** → **2**, OR = SPh] does proceed on monocyclic systems, however.[2]

‡ $CeCl_3$ gave no reaction and Bu^i_2AlCl gave a complex product mixture containing no discernible amounts of **5**; other Lewis acids [*e.g.* $BF_3{\cdot}OEt_2$, $MgBr_2$, $ZnCl_2$ and $Hg(OCOCF_3)_2$] gave some **5** along with other products. Small amounts of the α-hydroxy aldehydes formally obtained by hydrolysis of **4** were seen in most reactions.

§ Representative homologation procedure: Zirconium(IV) chloride (1.25 g, 5.36 mmol) was added to a stirred solution of sulfone **4** (300 mg, 0.94 mmol) in dry CH_2Cl_2 (40 ml) at room temp. under N_2. The resulting brown mixture was stirred for 10 min and then a saturated aqueous solution of $NaHCO_3$ (15 ml) was added. The mixture was diluted with ethyl acetate and filtered through a plug of celite. The filtrate was washed with water and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give ketone **5** (165 mg, 99%) as a pale-yellow liquid, R_f (0.61, petrol–Et_2O, 1 : 1); ν_{max} ($CHCl_3$) 1717 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.10 (3H, s, CH_3CO), 2.38 (3H, s, Ar-CH_3), 3.35 (3H, s, -OCH_3), 4.84 (1H, s, CH), 7.16–7.45 (4H, m, Ar-H); δ_C (22.5 MHz, $CDCl_3$) 19.45, 25.3, 57.1, 86.9, 126.4, 127.3, 128.5, 131.0, 134.3, 136.9, 206.25.

References

1 For lead references see D. J. Ager and M. B. East, *Tetrahedron*, 1992, **48**, 2803 and 1993, **49**, 5683; L. Pingli and M. Vandewalle, *Tetrahedron*, 1994, **50**, 7061 and references therein.
2 B. M. Trost and G. K. Mikhail, *J. Am. Chem. Soc.*, 1987, **109**, 4124.
3 H. Finch, A. M. M. Mjalli, J. G. Montana, S. M. Roberts and R. J. K. Taylor, *Tetrahedron*, 1990, **46**, 4925; M. A. Ardakani, G. C. Loftus, A. M. M. Mjalli, R. F. Newton and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1989, 1709.
4 All new compounds gave consistent spectral and analytical/MS data.
5 S. Shimada, Y. Hashimoto and K. Saigo, *J. Org. Chem.*, 1993, **58**, 5226.
6 Section 3.1 (J. R. Hanson), Sections 3.2 and 3.3 (B. Rickborn), and Section 3.4 (D. J. Coveney) in *Comprehensive Organic Synthesis*, vol. 3, eds. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991 and references therein.
7 D. R. Borcherding, S. A. Scholtz and R. T. Borchardt, *J. Org. Chem.*, 1987, **52**, 5457.