Intramolecular Nucleophilic Substitution at the C-4 Position of Functionalized Oxetanes: A Ring Expansion for the Construction of Various Heterocycles†

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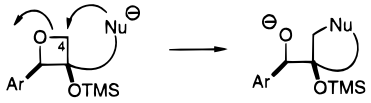
The intramolecular ring opening of epoxides by heteroatom nucleophiles has been frequently exploited for the construction of five- and six-membered heterocycles.[1,2] Depending on the substitution pattern, the reaction conditions, and the length of the side chain the nucleophilic attack occurs in an *exo*[1] or *endo*[2] fashion. Contrary to that, similar ring expansion reactions of oxetanes have been rarely observed. Monosubstituted oxetanes can be ring-opened intramolecularly by carbon nucleophiles.[3] A Lewis acid-mediated intramolecular ring opening of monosubstituted oxetanes has also been reported.[4] In systems in which the stereochemical array enables a facile approach S_N2-type reactions of oxygen nucleophiles have been described.[5] An S_N1-type substitution has been achieved at the higher substituted position of an oxetane.[6] Moreover, 2-oxetanones (β-lactones) have been used extensively for ring expansions.[7] In this case the β-cleavage is facilitated by the acyloxy leaving group.

We have recently shown that 2-aryl-3-(silyloxy)oxetanes are readily obtained in diastereomerically pure form by the photocycloaddition of silyl enol ethers and aromatic aldehydes.[8] Our plan was to use these products as substrates for ring expansion reactions, and we speculated that the preferred site of attack for a strong nucleophile should be the least crowded carbon atom C-4 (Scheme 1).

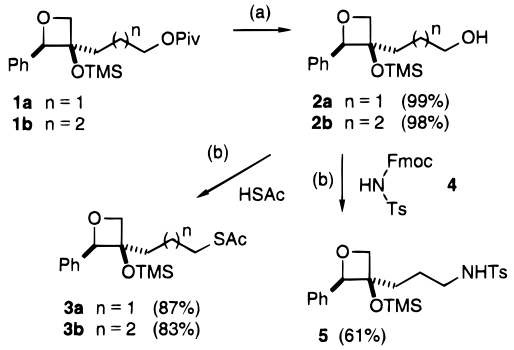
The known oxetanes **1a**[8b] and **1b**[9] already bear a side chain with a latent oxygen nucleophile and served as a versatile entry for other substrates. The pivaloyl protective group (Piv) can be readily removed upon treatment with MeLi in Et_2O at ambient temperature to yield the alcohols **2a** and **2b**, which in turn were converted to the oxetanes **3** and **5** (Scheme 2), which carry sulfur- and nitrogen-based nucleophiles. The Mitsunobu reaction with thiolacetic acid proceeded cleanly according to the modified procedure of Volante.[10] For the construction of oxetane **5** we initially used the *tert*-butyloxycarbonyl (Boc)-protected *p*-toluenesulfonamide (HNBocTs) described by Weinreb et al.[11] to introduce the amide. Cleavage of the Boc-group in the presence of the (silyloxy)oxetane moiety proved difficult, however. Only the thermal deprotection[12] (185 °C, 30 min, Ar) gave the desired compound **5**. Unfortunately, this method proved to be not very reliable for this particular example as the yields varied considerably (55% at best) and the isolation of pure material was complicated by several byproducts. A better solution was found by employing the 9-fluorenylmethyloxycarbonyl (Fmoc)-protected amide **4**.[13] To our surprise, its reaction with alcohol **2a** gave directly the desired oxetane **5**. Although we have not yet made an effort to elucidate what causes the cleavage of the Fmoc-group under Mitsunobu conditions, the amide **4** appears to be a generally useful substitute for $TsNH_2$.

The ring-opening experiments were conducted upon *in situ* generation of the corresponding heteroatom anion. In the case of oxetanes **1** and **3** the acyl protective group was removed with MeLi in dimethoxyethane (DME), and the reaction mixture was subsequently heated to induce the nucleophilic substitution.[14] As Table 1 reveals, the best result was obtained with a sulfur nucleophile forming a six-membered ring (Table 1, entry 3). The corresponding thiotetrahydropyran **7a** (91%) was isolated in diastereomerically pure form (Scheme 3). In none of the described experiments was an epimerization to be detected. Starting from compound **1a** the analogously liberated oxygen nucleophile yielded tetrahydropyran **6a**.

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) MeLi, 25 °C (Et_2O); (b) PPh_3, DEAD, 25 °C (THF).

† This paper is dedicated to Professor Rolf Gleiter on the occasion of his 60th birthday.

(1) Some selected examples of an *exo* ring opening by heteroatom nucleophiles follow. (a) N-Nucleophiles: Kozikowski, A. P.; Schmiesing, R. *J. Chem. Soc., Chem. Commun.* **1979**, 106. Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1985**, *26*, 3883. McIntosh, J. M.; Matassa, L. C. *J. Org. Chem.* **1988**, *53*, 4452. Pearson, W. H.; Bergmeier, S. C. *ibid.* **1991**, *56*, 1976. (b) O-Nucleophiles: Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252. Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171. Paterson, I.; Craw, P. A. *Ibid.* **1989**, *30*, 5799.

(2) Some selected examples of an *endo* ring opening by heteroatom nucleophiles follow. (a) N-Nucleophiles: Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617. Ratovelomanana, V.; Vidal, L.; Royer, J.; Husson, H.-P. *Heterocycles* **1991**, *32*, 879. (b) O-Nucleophiles: Chmielewski, M.; Guzik, P. *Heterocycles* **1984**, *22*, 7. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

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(7) (a) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991. (b) Mead, K. T.; Lu, J. *Tetrahedron Lett.* **1994**, *35*, 8947.

(8) (a) Bach, T.; Jödicke, K. *Chem. Ber.* **1993**, *126*, 2457. (b) Bach, T. *Liebigs Ann.* **1995**, 855 and references cited therein.

(9) Kather, K. Ph.D. thesis, University of Münster, 1996. Starting from ethyl 5-oxohexanoate the procedure is identical to the one employed for the construction of oxetane **1a** (cf. ref 8b).

(10) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

(11) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(12) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

(13) The amide **4** was prepared from TsNCO and 9-fluorenylmethanol (solvent: toluene; 93% yield) in full analogy to a previously described procedure (cf. ref 11).

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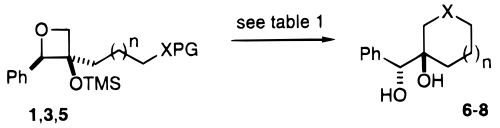
Table 1. Ring Opening of Oxetanes with Various Intramolecular Nucleophiles

entry	oxetane	*n*	X	PG	reagent	time[a] (h)	product	yield[b] (%)
1	**1a**	1	O	Piv	MeLi	6	**6a**	54
2	**1b**	2	O	Piv	MeLi	5	**6b**	
3	**3a**	1	S	Ac	MeLi	4	**7a**	91
4	**3b**	2	S	Ac	MeMgBr	5	**7b**	54
5	**5**	1	NTs	H	MeMgBr	5	**8**	52

[a] Time required for complete conversion at reflux in DME (cf. typical procedure[14]). [b] Refers to isolated yield of analytically pure product.

Scheme 3

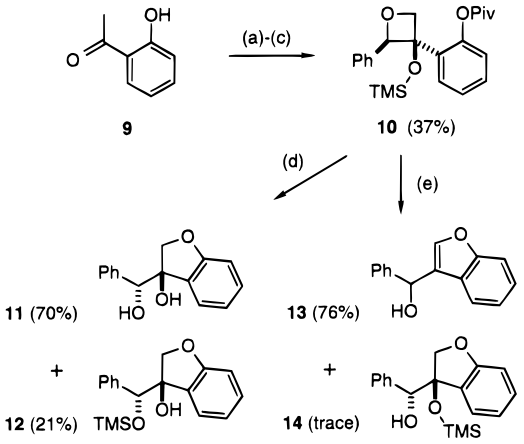


If oxetane **1b** was used as precursor the reaction failed and the seven-membered ring was not formed. Prolonged heating gave decomposition products that arise most likely from oxetane fragmentation. Nitrogen nucleophiles were generated from oxetane **5** by deprotonation. The choice of the counterion appears to be crucial for the success of the ring opening. Whereas lithium (MeLi in DME) and sodium (NaH in DMF) failed to induce a reaction the magnesium amide generated with MeMgBr in DME yielded the desired piperidine **8** (Table 1, entry 5).[15] Obviously, the magnesium ion activates the ether bond by complexation to the oxetane oxygen. The same effect was advantageously employed in the case of the seven-membered thiepane **7b**, which was formed in low yield (16%) by treating compound **3b** with MeLi in DME and subsequent reflux. Repeating the procedure with MeMgBr as reagent gave the desired heterocycle in 54% yield (Table 1, entry 4).

The regiochemistry of the ring opening was documented by ^{1}H-NMR studies of the heterocyclic diols in d_6-DMSO. One of the alcohol OH protons appears as a singlet and the other as a doublet. If the ring opening had occurred at C-2 a tertiary (singlet) and a primary (triplet) alcohol would have been expected. In some instances, *O*-silyl-protected products were also obtained in minor amounts. They could be quantitatively converted to the diols by treatment with K_2CO_3 in MeOH.[16]

In order to test a phenolate as intramolecular nucleophile we prepared the diastereomerically pure oxetane **10** from 2-hydroxyacetophenone (**9**).[8a] Due to the *cis*-arrangement of the enolate in the aromatic side chain this substrate seems to be predisposed toward an effective ring expansion. Indeed, treatment of compound **10** with MeLi in DME and subsequent reflux yielded the desired diol **11** in combination with its monosilylated derivative **12**. MS data clearly revealed that the silyl group had migrated and was found at the least hindered position. Contrary to that, the analogous procedure conducted with MeMgBr in DME gave directly the benzofuran **13**. There is no indication that a silyl shift occurs. The only byproduct found is the alcohol **14** in which the tertiary alcohol is still silyl-protected. This observation helps to explain why the elimination in the latter example is so facile. The silyl ether **14** is prone to an elimination by an E_1cB- or an E_2-mechanism, whereas the alkoxide formed from compound **11** or **12** will not be able to react along this pathway. In a control experiment the diol **11** was subjected to the reaction conditions of the MeMgBr-initiated ring opening. No elimination product was observed.

Scheme 4[a]



[a] Reagents and conditions: (a) PivCl, NEt_3, DMAP, 25 °C (CH_2Cl_2); (b) LDA, TMSCl, −78 → 25 °C (THF); (c) PhCHO, *hν*, 30 °C (PhH); (d) MeLi, 25 → 85 °C (DME); (e) MeMgBr, 25 → 85 °C (DME).

In summary, the intramolecular ring opening of diastereomerically pure oxetanes leads to several interesting heterocycles that bear a side chain in the 3-position. In the described cases a diol unit is established at this site. An extension to other functionalized oxetanes is projected. Further studies are directed toward this goal and toward the application of this methodology to the synthesis of biologically relevant compounds.

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Supporting Information Available: Procedures and analytical data (NMR, MS) for compounds **2**, **3**, **5**−**8**, **10**−**13** (14 pages).

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(14) Typical procedure: To a stirred solution of 0.9 mmol of oxetane **3a** (315 mg) in 15 mL of DME was added 1.4 mL of a 1.6 M solution of MeLi (2.3 mmol) in Et_2O by syringe at ambient temperature. The mixture was stirred for 1 h at room temperature and subsequently heated to reflux for 4 h. After that time, 0.3 mL of a saturated NH_4Cl solution was added. Upon dilution with ether (20 mL) Na_2SO_4 was added, and the mixture was filtered. After evaporation of the solvent in vacuo the crude product was treated with 10 mL of a saturated solution of K_2CO_3 in MeOH at room temperature. As soon as the desilylation was complete (1 h), the mixture was diluted with water. Solid NaCl was added until the solution was saturated. After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over Na_2SO_4. Filtration and solvent removal gave 281 mg of crude material, which was purified by flash chromatography (eluent: cyclohexane/ethyl acetate = 85/15). The desired compound **7a** was obtained as a colorless oil (183 mg, 91%). The same procedure was followed while working with MeMgBr as nucleophile/base. A 3.0 M solution in Et_2O was used. If no silylated product was detected by TLC and NMR the desilylation procedure was omitted.

(15) For the biological relevance of closely related compounds, see: Hite, G.; Lokhandwala, M.; Patel, D. B.; Patel, H.; Merker, P. C.; Shafi'ee, A. *J. Pharm. Sci.* **1971**, *60*, 685.

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