Three-carbon ring-enlargement of ethereal oxonium ylides—a viable synthesis of medium-sized cyclic ketoethers

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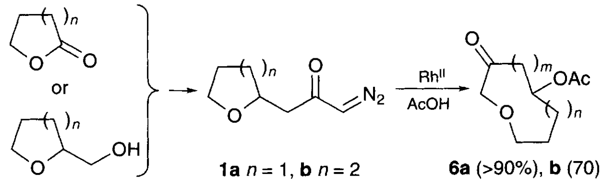
Eight- to eleven-membered cyclic ketoethers are synthesized in a single-step by rhodium(II)-catalysed three-carbon ring-enlargement of diazoacetonyl-substituted cyclic ethers *via* bicyclic ethereal oxonium ylide intermediates.

Ethereal oxygen atoms undergo ligand exchange reactions with carbenes in the presence of a nucleophile. While ethereal oxonium ylides, which have been proposed as plausible intermediates of carbene reactions in ethereal media,[1] still remain the target of spectroscopic identification,[2] they are of synthetic use.[3] For cyclic ethers such as oxetane,[1a] THF and THP,[4] three-component coupling reactions of the type [carbene–cyclic ether–nucleophile] have been reported. Although intermolecular formation of oxonium ylides may not be as effective as those of other heteroatom onium ylides, we expected that the coupling reaction would become more efficient when at least two components of the three are built in a molecule.[5] Based on this we designed the synthesis of medium-sized cyclic ketoethers which have been regarded as laborious to prepare by conventional means.[6] The present report deals with an efficient single-step synthesis of eight- to eleven-membered cyclic ketoethers by a three-carbon ring-enlargement of 2-(diazoacetonyl)-substituted cyclic ethers.

Diazoketones **1** were used as the typical starting molecules.[7] When **1a** ($m = n = 1$) was treated with a catalytic amount of $Rh_2(OAc)_4$ in the presence of a protic nucleophile (NuH), eight-membered cyclic ketoether **6a** was formed (>90%) [eqn. (1)].

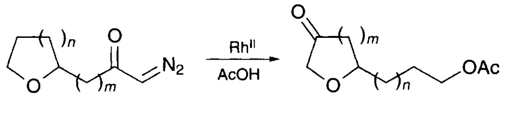


(1)

1a $n = 1$, **b** $n = 2$
c $n = 3$, **d** $n = 4$

6a (>90%), **b** (70)
c (70), **d** (75)

The product composition varied depending on the nucleophiles used,[†] among which acetic acid (pK_a 4.8) was the most appropriate (yield of **6a** >90%). With other nucleophiles such as PhOH (pK_a 10) and CF_3CH_2OH (12), the yields of **6a** decreased to 61 and 5%, respectively. With diazoketones **2**, bearing a sidechain longer than three carbons ($m > 1$), the ring-switched product **11** was obtained [eqn. (2)].[8] For example, the reactions of **2a** ($m = 2$, $n = 1$) with MeOH, PhOH and AcOH gave **11a** ($m = 2$, $n = 1$) in 6, 30 and 65% yield, respectively.



(2)

2 $m = 2$, $n = 1$
1b $m = 1$, $n = 2$

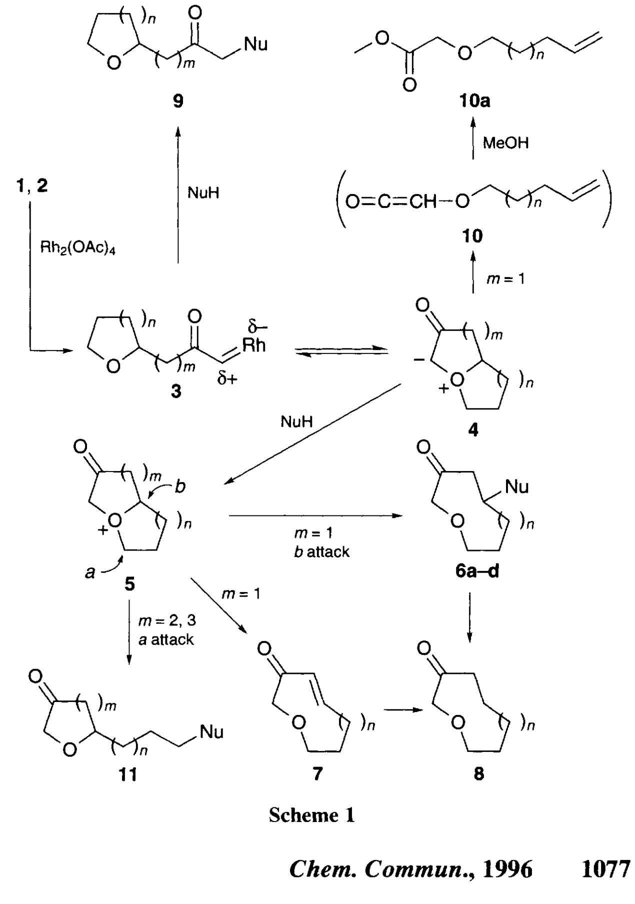
11 (65%)
11b (30%) + **6b**

Adopting the preferred structural parameter ($m = 1$) and the choice of nucleophile (AcOH), the dominating factors for the ring-enlargement pathway, the reaction can be extended to other series **1b-d** ($n = 2$–4) for the synthesis of nine-, ten- and eleven-membered cyclic ketoethers **6b-d**.

As postulated in Scheme 1, the intermediate bicyclo[(m + 2).(n + 2).0]oxonium ylide **4** must play a central role in product formation.[‡] In the presence of an appropriate protic nucleophile (NuH), ylide **4** is protonated to form oxonium ion **5**. However, when the acidity of NuH is as low as that of MeOH, **4** ($m = 1$) is hardly protonated and it collapses to produce 4-pentenyloxyketene **10**, which was identified in the form of the methyl ester **10a**.[§]

In the presence of a more acidic NuH than MeOH, **4** is protonated to form the oxonium ion **5** followed by nucleophilic attack by the conjugate base Nu^- on the bridgehead position *b* to give ring-enlargement product **6**. The regioselectivity for one of the positions *a* or *b* is apparently controlled by both the release of strain energy and the S_N mechanism. When $m = 1$, the largest strain can be released by cleaving the central bond of the bicyclo[(n + 2).3.0] system **5**.

For **2** ($m = 2$), the bicyclo[4.3.0] ring system of the oxonium ion **5**, produced by protonation, is attacked by a nucleophile on the less hindered position *a* to give the ring-switched product



Scheme 1

11. The reason for this switch is because the ring-strain for *m* = 2 is smaller than that for *m* = 1, thus inducing an S_N2 type substitution on position *a*. In this system (*m* = 2), the non-rearranged O–H insertion product **9** of methanol was also formed due to reversible formation of **3** from **4**.[2]

With moderately acidic NuH, **4** can be protonated to form the bicyclo[(*m* + 2).(*n* + 2).0]oxonium ion **5** faster than its rearrangement. When *m* = 1, **5** undergoes nucleophilic attack by the conjugate base Nu^- mainly at the bridgehead position *b* where a relatively large charge seems to be localized due to the bond weakening by strain at the central bond. Consequently, the reaction results in the formation of three-carbon ring-enlargement products **6** and **7**, which are precursors of parent ketoether **8**. On the other hand, when *m* > 1, the strain is small and, therefore, an S_N2-type attack at the less-crowded position *a* becomes favourable to produce ring-switched product **11**.

Acidity of NuH in conjunction with its nucleophilicity also modulates the product formation. With methanol, protonation of ylide **4** to generate **5** can not surpass its rearrangement to **10**. On the other extreme, acids stronger than trifluoroacetic acid can protonate diazoketone **1** to generate the diazonium ion surpassing the carbenoid formation even in the presence of Rh^{II} catalyst. In fact, the reaction of **1a** or **2a** with MeOH in the presence of a catalytic amount of CF_3SO_3H or $BF_3{\cdot}Et_2O$, but in the absence of Rh^{II} catalyst, gave the corresponding **6a** or **11** in moderate yields (52 or 44%, respectively). This is in marked contrast to the fact that with **1a** and a mixture of MeOH and AcOH the reaction did not take place in the absence of the catalyst.

With moderately acidic nucleophiles such as phenols, cyclic enones **7** were formed together with the phenoxy derivatives of **6** at the expense of the latter. We presume that with phenols the conjugate base phenoxide ion may be acting equally as a base and a nucleophile.¶ Consequently, acetic acid seems so far the best and well-balanced protic nucleophile for the preparation of **6**.

The present method of ring-enlargement can be utilized as a tandem [*p* + 6] ring-expansion method where *p* is the initial ring-size, an example of which is shown in eqn. (3).

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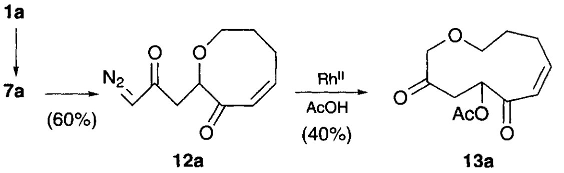

(3)

Footnotes

† MeOH, CF_3CH_2OH, PhOH, *p*-$NO_2C_6H_4OH$, AcOH, HCN, CF_3CO_2H and TsOH were examined.

‡ Ylide **4** did not undergo the Stevens-type rearrangement, which is general to our knowledge for other heteroatom ylides, see refs. 3 and 5.

§ In the presence of MeOH **10a** was exclusively formed. This is a hitherto unknown type of skeletal rearrangement.

¶ Enone **7** may be formed *via* the E2-type elimination of **5** in which the conjugate base Nu^- acts as the base, rather than the intramolecular proton-transfer from 4- to 2-position of **4**.

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