β-Lithiated Enol Ethers as Enolate Equivalents. Application to *N*-Substituted Pyrrolidin-3-ones

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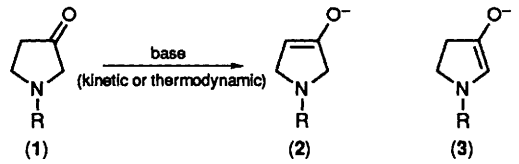
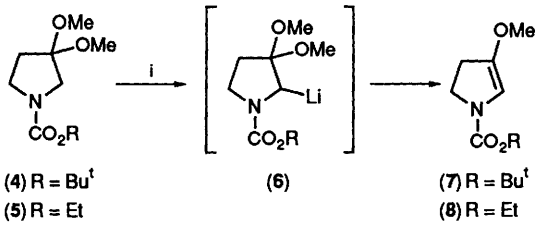
Lithiation of the isomerically pure enol ethers (**7**) and (**8**) provides the organolithium derivatives (**9**) and (**13**) which were trapped with aldehydes and shown to function as synthetic equivalents of the pyrrolidin-3-one enolate (**3**); aldehyde adducts (**10**) also react with Bu^tMe_2SiCl to give the 2-substituted-3-methoxypyrroles (**12**).

α-Lithiated enol ethers, which can be prepared by a number of different routes, have established themselves as synthetic equivalents of regiospecific ketone enolates.[1] This concept becomes particularly useful if the enol ether is not synthesised directly from the ketone as it then becomes possible to obtain an organolithium derivative that corresponds to an enolate isomer that is inaccessible by conventional means.

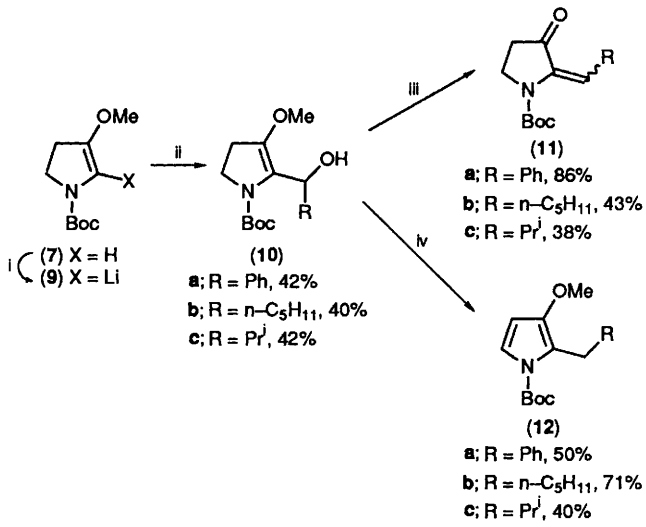
Our interest in this area has focused on the chemistry of heterocyclic-based ketone enolates and in earlier work[2] we established the use of a β-lithiated enol ether as an equivalent



Scheme 1



Scheme 2. *Reagents and conditions*: i, Bu^{t}Li, tetrahydrofuran (THF), −78 °C or LDA, THF, −78 °C (see text).

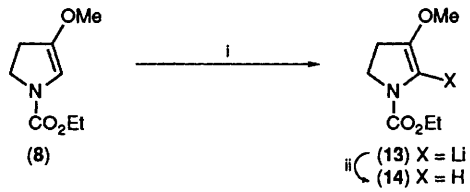


Scheme 3. *Reagents and conditions*: i, Bu^{t}Li, THF, −78 °C; ii, RCHO; iii, 1 M $(CO_2H)_2$, MeOH, room temperature, 15 h; iv, Me_2Bu^tSiCl, CH_2Cl_2, room temperature, 2 h.

of the enolate isomer disfavoured under the usual kinetic and thermodynamically controlled enolization of tetrahydropyran-3-ones.[3] Similar problems of regioselectivity are encountered with other heterocyclic ketones, such as the *N*-substituted pyrrolidin-3-ones (**1**), which also show a marked tendency to enolize away from the ring-constrained heteroatom leading to enolate (**2**) (Scheme 1).[4] Access to the isomeric species (**3**) is therefore limited and for this reason we have examined the use of β-lithiated enol ethers as equivalents of enolate (**3**) and the results of this study are outlined in this paper.

The synthesis of the requisite enol ethers (Scheme 2) is based on the generation and fragmentation of a dipole-stabilized organolithium (**6**) derived from either the *N*-t-butoxycarbonyl- (Boc) or *N*-ethoxycarbonyl-protected pyrrolidines (**4**) and (**5**) respectively. The Boc group was initially chosen as both a readily removable and an efficient directing group[5] and reaction of the Boc-protected dimethoxyketal (**4**)† with Bu^{t}Li induced a smooth elimination of methanol to give the isomerically pure enol ether (**7**) in 68% yield (m.p. 82.5—83.5 °C).‡ Lithiation of (**7**) was then achieved by addition of a second equivalent of Bu^{t}Li and the resulting β-lithiated enol ether (**9**) was trapped by aldehydes to give adducts (**10**) in moderate yields (Scheme 3).

The equivalence of anion (**9**) to the regiospecific enolate (**3**) was then readily exposed as shown in Scheme 3. Mild acid hydrolysis of adducts (**10**) gave the corresponding enones (**11**) in good to moderate yields, without loss of the Boc residue.§



Scheme 4. *Reagents and conditions*: i, LDA, THF, −78 °C; ii, MeI (71%).

In addition to giving enones (**11**), adducts (**10**) underwent another unexpected fragmentation. Attempts to silylate the allylic hydroxy function of (**10**) led smoothly to 2-alkyl-3-methoxypyrroles (**12**). This represents a novel synthesis of these unusually substituted heterocycles;[7] however, it is not clear what factors control the two pathways shown in Scheme 3.

The use of the Boc-protected alkenyl-lithium (**9**) as an enolate equivalent is limited since all our efforts to alkylate this species using a wide range of solvents and additives failed. In an attempt to overcome this problem an alternative derivative was examined. The *N*-ethoxycarbonyl enol ether (**8**) was prepared in 63% yield using the methodology shown in Scheme 2. In this case fragmentation of ketal (**5**) and subsequent lithiation of enol ether (**8**) was efficiently carried out using lithium di-isopropylamide (LDA) rather than Bu^{t}Li. Anion (**13**) exhibited a similar pattern of reactivity towards aldehydes to that of the Boc derivative (**7**) but methylation of this organolithium to give (**14**) was achieved in 71% yield using iodomethane (Scheme 4). However, we were unable to trap this species with other alkyl or allyl halides.

In summary, β-lithiated enol ethers (**9**) and (**13**) can serve as equivalents of the pyrrolidin-3-one-derived enolate (**3**). Their use in this regard is, however, limited by the range of electrophiles that they are reactive towards and efforts are continuing to develop a more efficient and general solution to this enolate problem.

† Ketal (**4**) was prepared from carbamate (**1**, R = CO_2Et)[6,7a] by treatment with methanol/TsOH, followed by $Ba(OH)_2/H_2O$ and then $(Boc)_2O$. Ketal (**5**) was prepared by treatment of carbamate (**1**, R = CO_2Et) with methanol/TsOH (Ts = *p*-$MeC_6H_4SO_2$).

‡ A related fragmentation involving a dithioketal derivative related to (**6**) has been observed by Meyers and co-workers (Professor A. I. Meyers, personal communication).

§ The corresponding β-hydroxyketones, the formal aldol adducts, were not observed and are probably not involved as intermediates in the cleavage of (**10**) to (**11**).[1]

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