β-Ketoester Dianions as Regiospecific Enolate Equivalents for *N*-Substituted Pyrrolidin-3-ones

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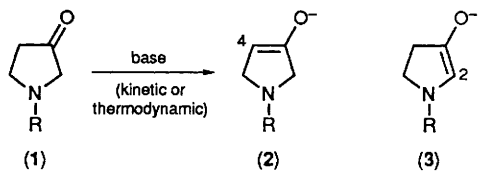
Double deprotonation of β-ketoester (**6**) gives dianion (**7**) which serves as a synthetic equivalent of the regiospecific ketone enolate (**3**), providing a synthetic entry to 2-substituted pyrrolidin-3-ones (**9**) and (**10**).

The synthetic utility of enolates derived from heterocyclic ketones such as pyrrolidin-3-ones is limited by the level of regiocontrol that can be exercised in the enolization step. In a comprehensive study, Garst and co-workers showed that the preferred mode of enolization of *N*-substituted pyrrolidin-3-ones (**1**), under conditions of both kinetic and thermodynamic control, is away from the ring-constrained heteroatom leading to the C-4 enolate (**2**).[1] These workers were able to generate the C-2 enolate (**3**, R=CO_2Et), but at best as a 1:1 mixture with the C-4 enolate (**2**, R=CO_2Et). This poor level of regioselectivity dramatically limits the synthetic value of enolate (**3**) but, despite its relative inaccessibility, this enolate offers considerable potential to the synthetic chemist in the construction of, for example, alkaloids containing a 2-substituted-3-hydroxypyrrolidine subunit.[2]

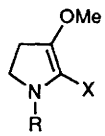
We recently described the synthesis of the isomerically pure enol ether (**4**) which undergoes facile lithiation to give the β-lithiated enol ether (**5**).[3] This organolithium derivative can function as a synthetic equivalent of enolate (**3**); however, this chemistry suffers from a number of problems that limit the use of (**5**) as a synthon for the synthesis of 2-substituted pyrrolidin-3-ones.

We have now developed a more general solution to the problem of generating an equivalent of enolate (**3**) which is based on the use of a β-ketoester dianion[4] derived from (**6**), readily accessible *via* a Dieckmann cyclisation reaction.[5]

Deprotonation of (**6**) with lithium diisopropylamide (LDA) (2 equiv.) proceeded smoothly at −78 °C and the resulting dianion (**7**) was trapped by a range of electrophiles to give adducts (**8a—h**) in good yields, as a mixture of diastereoisomers and enol tautomers. This alkylation step proceeded most efficiently when a co-solvent, such as dimethylpropyleneurea (DMPU) or hexamethylphosphoramide (HMPA), was employed (Scheme 1).†

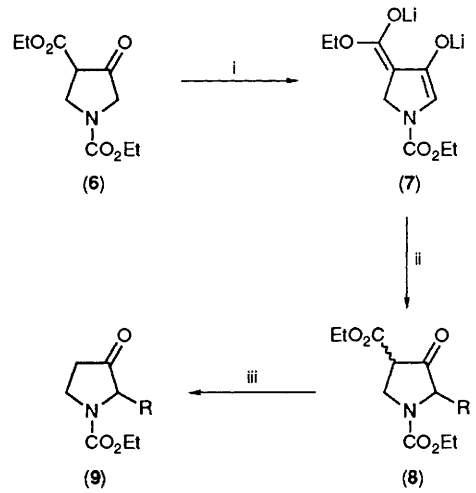


(**1**) (**2**) (**3**)



(**4**) X = H, R = CO_2Bu^t or CO_2Et
(**5**) X = Li, R = CO_2Bu^t or CO_2Et

† Early work was carried out using HMPA as co-solvent to solubilise dianion (**7**) but we subsequently found that DMPU, which is a much more generally acceptable additive,[6] was equally effective. A wide range of other solvent systems were also investigated but without success.



Scheme 1. *Reagents and conditions*: i, LDA (2 equiv.), DMPU or HMPA, THF, −78 °C; ii, electrophile (see Table 1); iii, $(CO_2H)_2$, H_2O, dioxane, 100 °C or NaCl, wet DMSO, 130 °C.

Table 1. Yields of adducts (**8a—h**) and (**9a—g**).

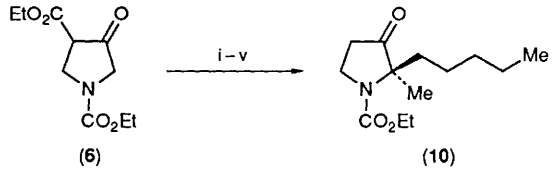
Electrophile	R =	(**8**) yield[a,b]	(**9**) yield[c,d]
MeI	Me	(**8a**) 73%[a], 62%[b]	(**9a**) 81%[c]
n-$C_5H_{11}Br$	n-C_5H_{11}	(**8b**) 56%[a], 45%[b]	(**9b**) 77%[c], 76%[d]
$PhCH_2Br$	CH_2Ph	(**8c**) 51%[b]	(**9c**) 88%[c]
$H_2C{=}CHCH_2Br$	$CH_2CH{=}CH_2$	(**8d**) 56%[a], 54%[b]	(**9d**) 67%[c,e]
$PhCH_2O(CH_2)_3I$	$(CH_2)_3OCH_2Ph$	(**8e**) 70%[b]	(**9e**) 89%[c]
Me_2CHCHO	$CH(OH)CHMe_2$	(**8f**) 88%[a]	(**9f**) 91%[d]
n-$C_5H_{11}CHO$	$CH(OH)C_5H_{11}$	(**8g**) 71%[a]	(**9g**) 55%[c], 77%[d]
PhCHO	CH(OH)Ph	(**8h**) 87%[a]	see text

[a] Using DMPU as co-solvent. [b] Using HMPA as co-solvent. [c] Aqueous oxalic acid. [d] NaCl–wet DMSO. [e] Ketone (**9d**) has previously been prepared using a highly selective Claisen rearrangement.[8]

Removal of the superfluous ethoxycarbonyl residue from adducts (**8**) was then achieved in one of two ways. Conventional acid hydrolysis and decarboxylation, using aqueous oxalic acid in dioxane, proceeded well for the 2-alkylated adducts (**8a—e**) and the corresponding 2-substituted pyrrolidin-3-ones (**9a—e**)‡ were obtained in good overall yield (see Table 1). However, low yields were obtained when this decarboxylation method was applied to the aldehyde adducts (**8f—h**). Nevertheless, efficient cleavage of the CO_2Et moiety from (**8f**) and (**8g**) was accomplished using NaCl in wet dimethyl sulphoxide (DMSO) at 130 °C[7] and good yields of the aldol products (**9f**) and (**9g**) were obtained. This procedure proved to be less successful in the case of the benzaldehyde adduct (**8h**)§, but did work well for the decarboxylation of the alkylated adducts, as illustrated by the conversion of (**8b**) to (**9b**).

‡ Adducts (**8**), (**9**), and (**10**) gave satisfactory spectral data (IR, ^1H and ^{13}C NMR) and (**9a—g**) and (**10**) were further characterised by elemental analysis and/or high resolution mass measurement; all yields refer to isolated material, homogeneous by TLC.

§ For reasons that are not clear, adduct (**8h**) was sensitive towards retroaldol fragmentation. Aldol (**9h**) was observed (^1H NMR) when decarboxylation was carried using either aqueous oxalic acid (method c) or NaCl–DMSO (method d) but only as an inseparable mixture (1—3:1 ratio) together with *N*-ethoxycarbonyl-pyrrolidin-3-one (**1**; R = CO_2Et). An alternative procedure for removal of the ethoxycarbonyl residue, based on the use of propane-1,2-diol and base,[9] resulted in cleavage of the *N*-ethoxycarbonyl moiety.



Scheme 2. *Reagents and conditions*: i, LDA, 2 equiv., THF, DMPU, −78 °C; ii, MeI; iii, LDA, 0 °C; iv, $C_5H_{11}Br$ (60% overall yield); v, NaCl, wet DMSO, 130 °C (83% yield).

Dialkylation of β-ketoester (**6**) was also straightforward (Scheme 2). Alkylation of dianion (**7**) using iodomethane followed by addition of another equivalent of LDA and then bromopentane was efficiently carried out in a one-pot procedure to give, after decarboxylation, the 2,2-disubstituted derivative (**10**) in 50% overall yield from β-ketoester (**6**).

As a synthetic equivalent of the regiospecific enolate (**3**), dianion (**7**) offers a number of advantages over the alternative reagent, β-lithiated enol ether (**5**),[3] that are worthy of comment. Dianion (**6**) reacted with a wide range of electrophiles and while anion (**5**) was trapped by aldehydes, the capacity of this species to react with alkyl halides was limited. Access to 2,2-dialkylated pyrrolidin-3-ones such as (**10**) is also precluded by the use of anion (**5**). When dianion (**6**) was trapped by aldehydes the aldol products were stable; with reactions involving anion (**5**) and aldehydes, it was only possible to isolate the corresponding enones.

The diastereoselectivity available in aldol reactions involving dianion (**7**) is also of interest with regard to the application of this methodology to the synthesis of more complex heterocycles. These and related processes are currently under investigation.

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