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

Melvyn Giles,[a] Michael S. Hadley,[b] and Timothy Gallagher[a]

[a] *School of Chemistry, Bath University, Bath BA2 7AY, UK*
[b] *Medicinal Research Centre, SmithKline Beecham Pharmaceuticals, The Pinnacles, Harlow CM19 5AD, UK*

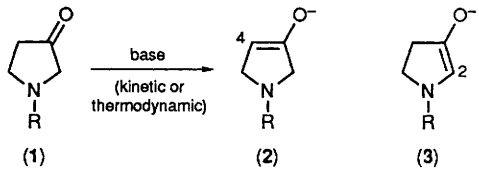
Double deprotonation of β-ketoester (**6**) gives dianion (**7**) which serves as a synthetic equivalent of the regiospecific ketone enolate (**3**), providing a synthetic entry to 2-substituted pyrrolidin-3-ones (**9**) and (**10**).

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]

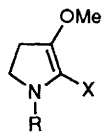
We recently described the synthesis of the isomerically pure enol ether (**4**) which undergoes facile lithiation to give the β-lithiated enol ether (**5**).[3] This organolithium derivative can function as a synthetic equivalent of enolate (**3**); however, this chemistry suffers from a number of problems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

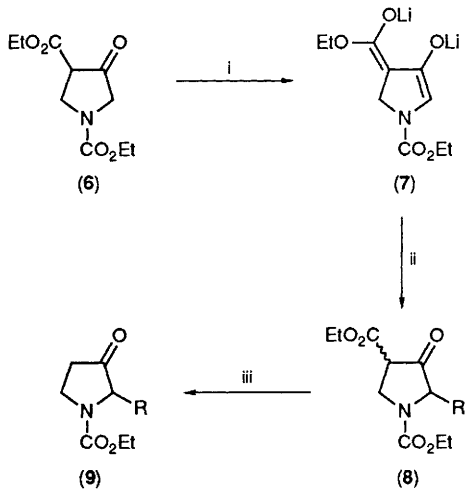


(**1**) (**2**) (**3**)



(**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**).

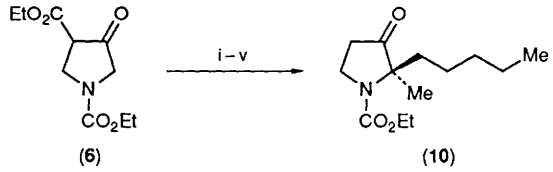
Electrophile	R =	(**8**) yield[a,b]	(**9**) yield[c,d]
MeI	Me	(**8a**) 73%[a], 62%[b]	(**9a**) 81%[c]
n-$C_5H_{11}Br$	n-C_5H_{11}	(**8b**) 56%[a], 45%[b]	(**9b**) 77%[c], 76%[d]
$PhCH_2Br$	CH_2Ph	(**8c**) 51%[b]	(**9c**) 88%[c]
$H_2C{=}CHCH_2Br$	$CH_2CH{=}CH_2$	(**8d**) 56%[a], 54%[b]	(**9d**) 67%[c,e]
$PhCH_2O(CH_2)_3I$	$(CH_2)_3OCH_2Ph$	(**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.

We thank SmithKline Beecham Pharmaceuticals and S.E.R.C. for a CASE award (to M. G.).

Received, 23rd April 1990; Com 0/01796E

References

1 M. Garst, J. N. Bonfiglio, D. A. Grudoski, and J. Marks, *J. Org. Chem.*, 1980, **45**, 2307; M. E. Garst, J. N. Bonfiglio, D. A. Grudoski, and J. Marks, *Tetrahedron Lett.*, 1978, 2671. For attempts to generate enamines of *N*-alkyl pyrrolidin-3-ones see P. A. Zoretic, F. Barcelos, and B. Branchaud, *Org. Prep. Proced. Int.*, 1976, **8**, 211. However, for the synthesis of an enol triflate corresponding to (**3**) see M. R. Peña and J. K. Stille, *Tetrahedron Lett.*, 1987, **28**, 6573.

2 A. D. Elbein and R. J. Molyneux in 'Alkaloids: Chemical and Biological Perspectives,' ed. S. W. Pelletier, Wiley, New York, 1987, vol. 5, pp. 1—54; A. S. Howard and J. P. Michael, *Alkaloids (N.Y.)*, 1986, **28**, 183; F. P. Guengerich and H. P. Bronquist in 'Bioorganic Chemistry,' ed. E. E. van Tamelen, Academic Press, New York, vol. 2, pp. 97—109.

3 M. Giles, M. S. Hadley, and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1990, 831.

4 S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, 1974, **96**, 1082.

5 M. Viscontini and H. Bühler, *Helv. Chim. Acta*, 1967, **50**, 1289 and references therein.

6 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385.

7 A. P. Krapcho, *Synthesis*, 1982, 805.

8 T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, 1983, **48**, 3645. Alkylation of bicyclic aminoketones has also been achieved by a [2,3]sigmatopic rearrangement mechanism involving an ammonium ylide, see W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonth, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1963; S. Mageswaran, W. D. Ollis, D. A. Southam, I. O. Sutherland, and Y. Thebtaranonth, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1969.

9 R. Aneja, W. M. Hollis, A. P. Davies, and G. Eaton, *Tetrahedron Lett.*, 1983, **24**, 4641.