Pergamon

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Functionalised Pyrrolidinones by Conjugate Addition of Stabilised Enolates and Reformatsky Reagents

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Abstract: The α,β-unsaturated lactam **1b** has been found to readily undergo conjugate addition reactions with a range of stabilised carbon nucleophiles and Reformatsky reagents under mild conditions in good yield with high diastereoselectivity. This method provides a simple and versatile approach to highly functionalised pyrrolidinones.
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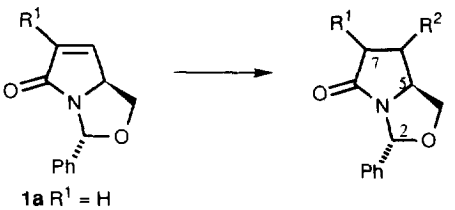
The development of methodology for the preparation of highly functionalised pyrrolidines has attracted considerable interest recently, principally because of the wide ranging biological activity of this class of compounds.[1-3] Our interest in this area has been in the development of more flexible and versatile methodology for the preparation of highly functionalised pyrrolidinones, which permits the introduction of substituents around the heterocyclic ring in a stereocontrolled manner.[4, 5] We report here an approach which makes use of conjugate addition to an activated enone derived from (*S*)-pyroglutamic acid; this compound has been previously shown to undergo facile cycloaddition reactions.[6] Conjugate additions to α,β-unsaturated lactams have been reported to be difficult,[7] and are generally successful only on systems with nitrogen protecting groups which are electron withdrawing, or which possess other activating groups,[8-16] although there are some reports of organometallic additions to unactivated systems.[17-19] However, similar reactions for lactones are better known.[20-22]

Initial investigations of enone **1a**[4a] indicated that conjugate addition of dimethyl malonate under basic conditions ($NaNH_2$, DMPU, THF) was particularly facile, but that reactions with other nucleophiles (derived from methyl thiophenylacetate, Meldrum's acid, and t-butyl acetate) were unsuccessful.[4b] Believing this to be due to the unreactivity of the lactam **1a**, we turned our attention to the activated compound **1b**, whose synthesis has been reported,[6] in conjugate additions. This compound has been found to readily undergo 1,4-additions of stabilised enolates under anhydrous or phase transfer[23] conditions in moderate to good yield (Scheme and Table).[24] While dimethyl malonate and triethyl methanetricarboxylate gave the products **2b,c** as single diastereomers (the relative stereochemistry was assigned using n.O.e. difference spectroscopy, with significant enhancements for **2c** shown in the Figure, since analysis using the relevant coupling constants did not give unequivocal results), the cyanoacetate and acetoacetate adducts **2d,e** were obtained as inseparable mixtures of diastereomers as shown by high field ^1H nmr spectroscopic analysis. The enolates derived from methyl thiophenylacetate and t-butyl acetate using LDA, however, did not give synthetically useful yields of the conjugate adducts. However, the synthetic utility of the compounds **2** was compromised by a facile retro-conjugate addition; thus, an attempt to obtain the product from a tandem addition-coupling procedure using dimethyl malonate and benzyl bromide gave only the alkylated product **3**[25] in low yield, as did an attempted alkylation of **2c** with sodium hydride/benzyl bromide.

Other nucleophiles were therefore investigated which would not participate so readily in the reverse reaction, and Reformatsky reagents were found to add in good yield under mild conditions with excellent

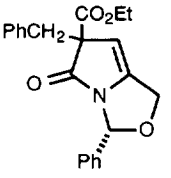
diastereoselectivity. Thus, the Reformatsky reagents derived from bromoesters **5a-d** (Table), generated in THF using ultrasonic irradiation, when treated with enone **1b**, gave the products **2f-i**;[26] these were generally obtained as predominantly one diastereomer, with minor amounts of the other diastereomers. Although this process was found to be particularly facile, each case required separate optimisation, and the different reaction conditions reflect the differing reactivites of the respective Reformatsky reagents. The yields of the reaction were found to be highly solvent dependent, and in the case of the Reformatsky reagent derived from **5b**, the best solvents were THF and diglyme (50 and 52% respectively), with dioxane and toluene giving significantly lower yields (22 and 39%). The best yield, of 73%, was obtained in a DMPU and THF solvent mixture. However, a competing dimerisation reaction, leading to adduct **4**, was observed when formation of the Reformatsky reagent was attempted *in situ* in the presence of the enone **1b** (similar dimerisations, by conjugate additions in a related system have recently been reported[27]); thus pre-formation of the Reformatsky reagent was essential. Attempted equilibration under a variety of basic conditions of the mixture of isomers **2g** obtained from the reaction did not lead to a change in the diastereoisomer ratio, consistent with the fact that the product formation is operating under thermodynamic control. In the one case amenable to ^{1}H n.O.e. analysis (compound **2g**, for which the requisite n.O.e. results were obtained by using a mixed $CDCl_3$:C_6D_6 (1:1.7) solvent, in which H-4_{endo}, H-5, H-6 and H-7 were resolved), the major isomer was shown to possess the relative stereochemistry arising from *exo*- attack by the organometallic reagent at C-6 followed by *exo*-protonation, giving the *trans*- C-6,7 relative stereochemistry, as expected on steric grounds (Figure). It is expected that the diastereoselectivity of the other cases would be similar, although this has not been proven. Surprisingly, a search of the literature revealed few applications of Reformatsky reagents for conjugate additions,[28-30] and those which are reported have generally been performed on α,β-unsaturated ketones with variable regioselectivity. The stereoselective control of conjugate addition reactions has recently been reviewed, but unlike alkylzinc reagents, Reformatsky reactions have generally not previously been found to be useful.[31] Elaboration of the adducts of **1b** derived using this Reformatsky reagent approach would provide access to substituted pyrrolidinones, and therefore complements existing routes to C-3 substituted proline derivatives, which involve alkylation of 4-oxoprolines,[32] or their corresponding enamines,[33, 34] or radical addition to $\Delta^{3,4}$ prolines.[35]



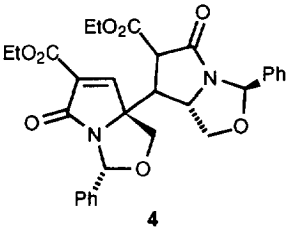
1a R^1 = H
1b R^1 = CO_2Et

2a R^1=H; R^2 = $CH(CO_2Me)_2$
2b R^1=CO_2Et; R^2 = $CH(CO_2Me)_2$
2c R^1=CO_2Et; R^2 = $C(CO_2Et)_3$
2d R^1=CO_2Et; R^2 = $CH(CN)CO_2Me$
2e R^1=CO_2Et; R^2 = $CH(C(O)Me)CO_2Et$
2f R^1=CO_2Et; R^2 = CH_2CO_2Et
2g R^1=CO_2Et; R^2 = CH_2CO_2tBu
2h R^1=CO_2Et; R^2 = $CH(Me)CO_2Me$
2i R^1=CO_2Et; R^2 = $CH(Ph)CO_2Me$

Scheme



3

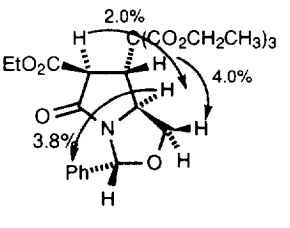


4

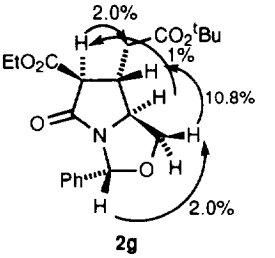
Table: Conjugate Additions to **1b**

Nucleophile	Conditions[a]	Product	Diastereomer Ratio[d]	Major Diastereomer	Yield(%)
$CH_2(CO_2Me)_2$	A	**2b**	1[b]	(6R,7S)	30
$CH_2(CO_2Me)_2$	B	**2b**	1[b]	(6R,7S)	66
$CH(CO_2Et)_3$	C	**2c**	1[b]	(6R,7S)	60
$CH_2(CN)CO_2Me$	A	**2d**	1:1	c	54
$CH_2(C(O)Me)CO_2Et$	D	**2e**	1:1:4.5:4.5	c	72
$BrCH_2CO_2Et$ **5a**	E	**2f**	c	c	27
$BrCH_2CO_2tBu$ **5b**	F	**2g**	1:5.5:43.5	(6S,7S)	73
$BrCH(Me)CO_2Me$ **5c**	G	**2h**	1:5:9:35	c	56
$BrCH(Ph)CO_2Me$ **5d**	G	**2i**	1:15:16:68	c	67

[a] A = $NaNH_2$ (1 eq.), DMPU, THF; B = $NaNH_2$ (13mol%), DMPU, THF; C = K_2CO_3, $Bu_4N\ HSO_4$; D = $Ba(OH)_2$ (10mol%), EtOH; E = Zn, ultrasound, dioxane, 35°C; F = Zn, ultrasound, THF, DMPU (9%v/v), 30-35°C; G = Zn, ultrasound, THF, -10°C; [b] One diastereomer only obtained; [c] Not determined; [d] After purification



2c



2g

Figure

Thus, the conjugate addition of a variety of nucleophiles to α,β-unsaturated lactams under mild conditions is a synthetically viable process, leading to carboxyethyl substituted pyrrolidine ring systems with excellent diasterocontrol, and the application of this approach to the synthesis of natural products and their analogues is under active investigation.

Acknowledgements

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23. A typical procedure is as follows: The methane tricarboxylate, enone **1b**, tetrabutylammonium hydrogen sulphate, potassium carbonate and toluene were mixed and stirred at 60°C for 3h. The mixture was cooled to room temperature, diluted with water and extracted with ether. The resulting oil was purified by flash chromatography.
24. All new compounds gave satisfactory spectroscopic and high resolution mass spectrometric or analytical data.
25. Spectroscopic Data for **3**: δ_H (500MHz, $CDCl_3$) 1.27 (3H, t, *J* 7Hz, $C\underline{H}_3$), 3.38-3.39 (2H, m, $C\underline{H}_2Ph$), 4.18-4.26 (2H, m, $C\underline{H}_2CH_3$), 4.33 (1H, dd, J_1 13.5Hz, J_2 2Hz, C(4)-$\underline{H}$), 4.54 (1H, dd, J_1 13.5Hz, J_2 2Hz, C(4)-$\underline{H}$), 5.03 (1H, t, *J* 2Hz, C(6)-$\underline{H}$), 5.89 (1H, s, C(2)-$\underline{H}$), 7.19-7.30 (6H, m, Ar$\underline{H}$), 7.37-7.44 (4H, m, Ar$\underline{H}$); m/z (Probe CI(NH_3)) 364 (MH^+, 100%). The regioselectivity of this addition is given by the 2Hz allylic coupling constant observed between H-4 and H-6.
26. A typical procedure is as follows: Zinc powder (activated by shaking with sat. NH_4Cl for 3 min., followed by washing with water, ethanol, ether, and drying under high vacuum at room temperature), iodine and the solvent were mixed under N_2 atmosphere and stirred until the solution decolourises. The bromo ester is added in one portion, and the mixture sonicated for 5 min at the stated temperature, and the lactam **1b** added and stirred for 10-30 min. The reaction is quenched with ice/water, then sat. NH_4Cl, and the solution extracted with dichloromethane. The products were obtained by flash chromatography.
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