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A β-Lactam Approach to γ-Amino-β-Keto Acid Derivatives.

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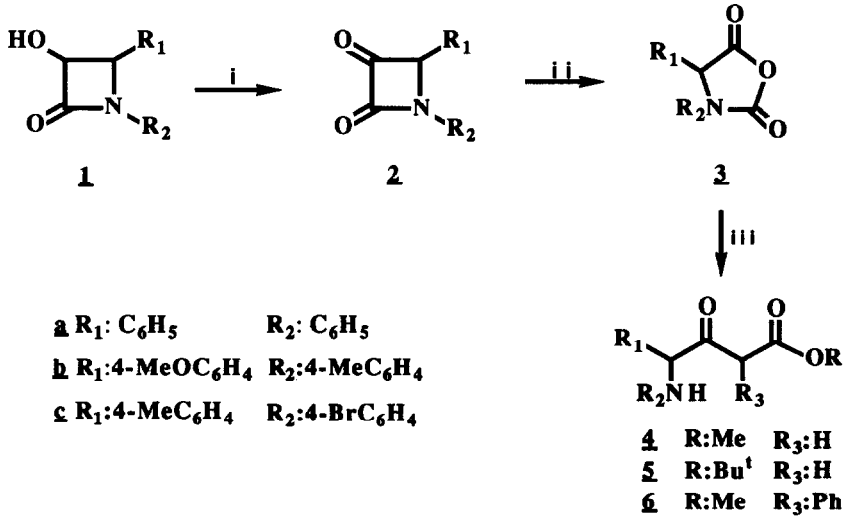
Abstract: Formation of γ-amino-β-keto acid derivatives by enolate acylation with N-carboxyanhydrides previously formed from α-keto β-lactams is described.

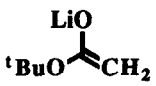
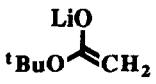
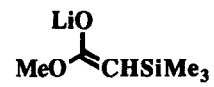
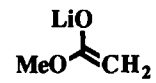
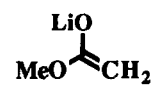
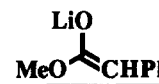
Several groups have demonstrated the utility of γ-amino-β-keto acids as precursors of γ-amino-β-hydroxy acids[1], an important class of compounds because of their occurrence in many natural products[2]. As a consequence, the development of new methodologies, providing an expedient approach to γ-amino-β-keto acids or derivatives continues an active area of investigation[3]. Recent findings from our laboratory have demonstrated the utility of α-keto β-lactams for the production of α-amino acids[4] and β-amino-α-hydroxy acids[5]. As an extension of our work we decided to explore the utility of our methodology to construct γ-amino-β-keto acids from β-lactams. Our general approach, Scheme 1, to these compounds involved prior formation of a N-carboxyanhydride **3** from an azetidine-2,3-dione **2** followed by an ester enolate acylation protocol. To test our intended methodology some selected racemic azetidine-2,3-diones **2** were prepared from α-hydroxy β-lactams **1** according to our established procedure[6] and subjected to the previously reported C_2-C_3 bond cleavage[4].



Scheme 1. Reagents and Conditions: i, Br_2SMe_2, NEt_3, CH_2Cl_2, -20°C → 0°C. ii, m-CPBA, CH_2Cl_2, -20°C, 60 min. iii, $R_3CH_2CO_2R$, LDA, -78°C.

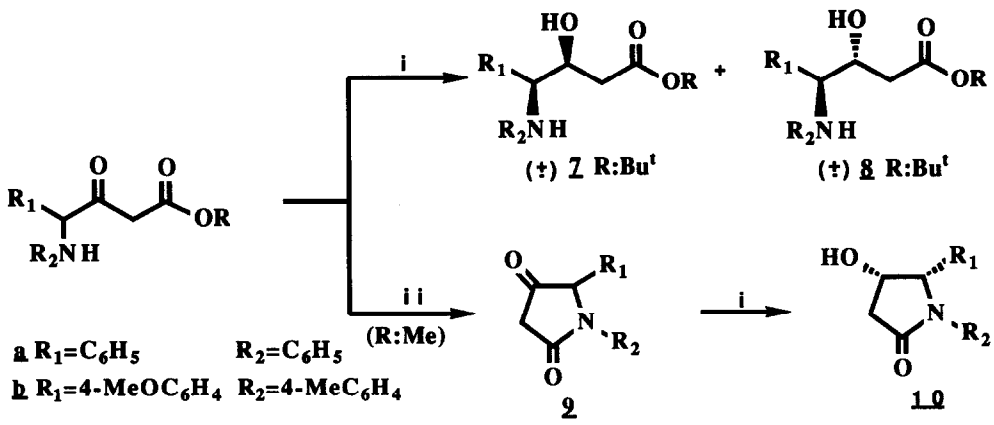
For example, compound **2a** on treatment with m-chloroperbenzoic acid (MCPBA) (1.3 equiv.) in methylene chloride as solvent at -20°C for 1h produced the N-carboxyanhydride (NCA) **3a** in 75% isolated yield. Similarly, when compounds **2b** and **2c** were subjected to treatment with MCPBA under the same conditions as above the corresponding NCA's **3b** and **3c** were obtained in 85% and 75% isolated yields respectively[7]. Although C-acylation of an ester enolate anion with NCA's seems to be of little synthetic utility because of their tendence to polymerization[8], we found that N-aryl substituted N-carboxyanhydrides efficiently reacted with lithium ester enolates under usual conditions, to afford γ-amino-β-keto esters in excellent yields.

Table. Preparation of γamino-β-keto esters **4-6** [a]

enolate	compound	R'	R_2	R_3	R	Yield, % [b]	mp °C (solvent)[e]
	**4 a**	C_6H_5	C_6H_5	H	^{t}Bu	92	95-96 (hexane)
	**4 b**	4-$MeOC_6H_4$	4-MeC_6H_4	H	^{t}Bu	87	89-91 (hexane)
	**5 a**	C_6H_5	C_6H_5	H	Me	50[c]	72-73 (Et_2O-hexane)
	**5 a**	C_6H_5	C_6H_5	H	Me	85	- - -
	**5 c**	4-MeC_6H_4	4-BrC_6H_4	C_6H_5	Me	89	72-74 (Et_2O-hexane)
	**6 a**	C_6H_5	C_6H_5	C_6H_5	C_6H_5	84[d]	- - -

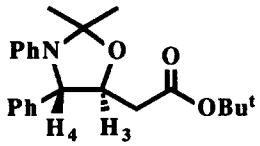
[a]Reaction conducted at -70°C, by using an enolate: NCA ratio of 1.6:1. [b]Yields based on weight of isolated product. [c]Only desilylated product was obtained. [d]Produced as an equimolar mixture of diastereomers. [e]Crystallization solvent.

The reaction was examined with some representative enolates and the results are summarized in the Table. With the exception of the enolate derived from methyl trimethylsilylacetate the yields, after isolation of the products by column chromatography, were high. Unfortunately, reaction between the lithium enolate of methyl phenylacetate and **3a** furnished the desired compound **6a** in high yield but without any stereoselectivity. Production of functionalized N-aryl amino derivatives, whose preparation by arylation of the parent free amino group is not obvious, constitutes an additional feature of our approach.

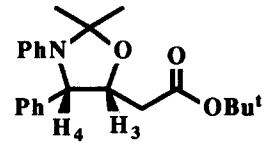


Scheme 2. Reagents and conditions: i, $NaBH_4$, MeOH, 0°C, 30 min. ii, toluene, reflux, 12-20 h.

The next question which we explored was the reduction of these N-aryl-γ-amino-β-keto esters **5** to the corresponding γ-amino-β-hydroxy derivatives as shown in Scheme 2. For this purpose we selected $NaBH_4$-MeOH system, wich is known to afford the best results in terms of chemical yields and stereoselectivity[9]. When the γ-amino-β-keto ester **5a** was treated with $NaBH_4$ at 0°C in methanol as solvent the expected γ-amino-β-hydroxy ester **7a** was obtained together with its diastereomer **8a** in a ratio 68:32 respectively. Under similar conditions **5b** furnished a 64:36 mixture of **7b** and **8b** in nearly quantitative yield. The relative stereochemistry of the epimeric mixture of diastereomers **7a** and **8a** was determined by conversion into their corresponding oxazolidines **11** and **12** respectively and determining the coupling constant between H_3 and H_4 protons in both diastereomers[10]. Interestingly, cyclisization of γ-amino-β-keto ester **4a** in refluxing toluene provided the γ-lactam **9a** (m.p. 152-153°C, 80%) which upon borohydride reduction of the carbonyl group afforded the hydroxy derivative **10a** in quantitative yield as single cis-isomer[11,12]. The β-hydroxy γ-lactam **10a** could be transformed into the γ-amino-β-hydroxy ester **7a** whose relative stereochemistry at C_3-C_4 positions is the same that those found in some natural renin inhibitors[13].



11 $J_{3,4}$= 6.5 Hz



12 $J_{3,4}$= 8.6 Hz

Particularly noteworthy is that the presently described methodology constitutes a tactically and conceptually new approach to γ-amino-β-keto esters and hence β-keto pyrrolidinones and related compounds. Further studies to the synthesis of natural γ-amino-β-hydroxy acids and derivatives from optically active azetidine-2,3-diones are now underway in our laboratory.

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7.-Some representative data: **3a**: m.p. 133-134°C ($CHCl_3$/hexane); IR (KBr, υ cm^{-1}): 1850, 1760 (C=O); ^{1}H-NMR ($CDCl_3$, δ ppm): 7.54-7.12 (m, 10H, arom), 5.65 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$, δ ppm): 165.6 (C_5), 149.7 (C_2), 134.7-113.6 (Arom), 64.4 (C_4). **3b**: m.p. 92-93°C ($CHCl_3$/hexane); IR (KBr, υ cm^{-1}): 1850, 1760 (C=O); ^{1}H-NMR ($CDCl_3$, δ ppm): 7.58-6.87 (m, 8H, arom); 5.68 (s, 1H, CH), 3.80 (s, 3H, O CH_3), 2.32 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, δ ppm): 166.3 (C_5), 149.5 (C_2), 132.1-114.7 (Arom), 64.2 (C_4), 55.2 (O CH_3). **3c**: m.p.135-136°C (Et_2O/hexane); IR (KBr, υ cm^{-1}): 1860, 1770 (C=O); ^{1}H-NMR ($CDCl_3$, δ ppm): 7.45-7.30 (m, 4H, arom); 7.19 (s_b, 4H, arom), 5.65 (s, 1H, CH), 2.35 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, δ ppm): 165.4 (C_5), 149.7 (C_2), 133.9-119.2 (Arom), 64.2 (C_4), 21.2 (CH_3).

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