Tetrahedron Letters, Vol. 34, No. 2, pp. 211-214, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

An Efficient Synthesis and Acylation of α-Amino-β-Keto-Esters: Versatile Intermediates in the Synthesis of Peptide Mimetics.

Jasbir Singh*, Thomas D. Gordon, William G. Earley and Barry A. Morgan,
Medicinal Chemistry Department, Sterling Winthrop Pharmaceutical Research Division, Rensselaer, New York 12144.

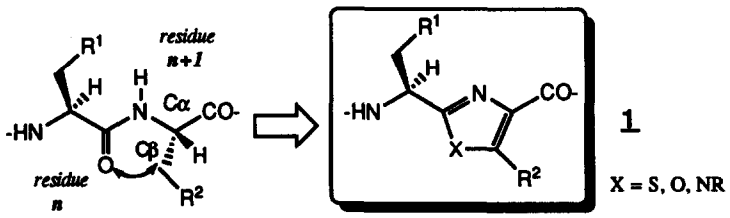
Key Words: α-Amino-β-Keto-Esters; β-Oxo Dipeptides; Schiff Base; C- Acylation; Peptide Mimetics

Abstract: *A flexible and high yield synthesis of α-amino-β-keto esters has been developed via acylation of the ketimine derivatives of α-amino esters. These α-amino-β-keto-esters were acylated with chiral amino acid derivatives in 36-95% yields.*

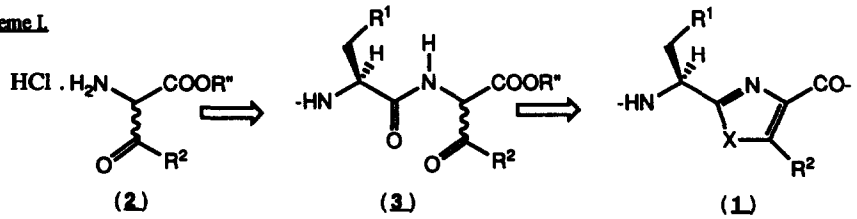
Synthesis and incorporation of novel conformationally constrained dipeptide mimetics[1] is an active area of research in the design and synthesis of biologically useful peptide analogs. We have explored the synthesis and biological effects of novel, conformationally constrained dipeptide mimetics, **1**, in which the carbonyl group of residue 'n' and N, Cα and Cβ of residue 'n+1' are formally represented in a 5-membered heterocycle, Fig. 1.

Our synthetic strategy, as shown in scheme (I), required an efficient method for the preparation of the key intermediate α-amino-β-keto-esters **2**. A search of the literature revealed that α-amino-β-keto-esters such as **2** were prepared rather laboriously via hydrolysis of oxazoles following the method of Suzuki et.al.[2] This method gives reasonable yields of α-amino-β-keto-esters when R^2 is an aromatic group (R^2 = Ph, **2a**, 90%); however, yields suffer dramatically when R^2 is an aliphatic group (R^2 = iPr, **2b**, 13-15%). Therefore, we have developed an efficient, "one pot", high-yield synthesis of α-amino-β-keto-esters **2** by acylation of the anion of the α-amino-ester Schiff base **6**. Here we wish to report this general and practical method for the preparation and subsequent acylation of α-amino-β-keto-esters **2**.

Fig. (I)



Scheme I.

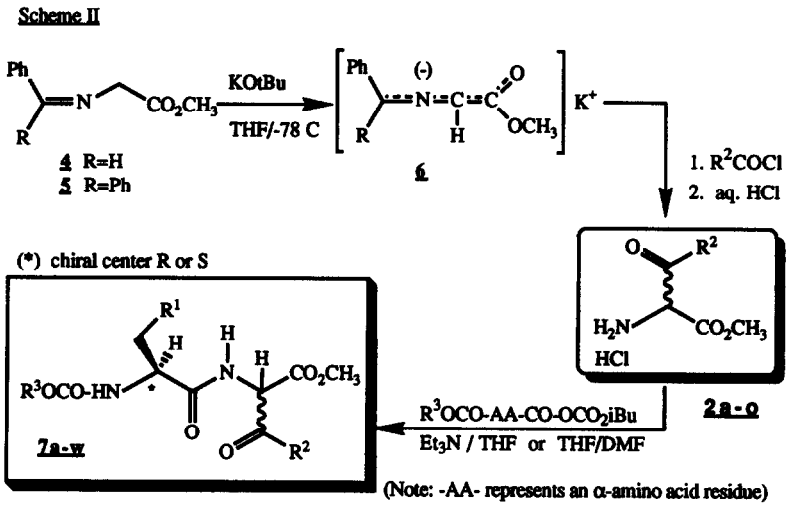


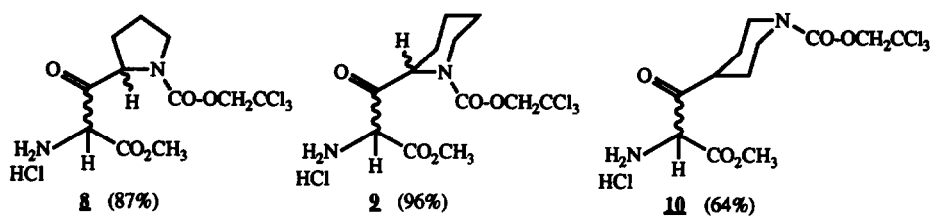
(2) (3) (1)

Alkylation of the Schiff base of an α-amino-ester, either via a pre-formed anion[3] or under phase transfer conditions,[4] has been shown to provide good to excellent yields of the α-alkyl amino acids. However, the acylation of these anions has not been reported. We have found that this acylation was best accomplished by addition of the potassium salt of Schiff base **8** to a pre-cooled solution of an acyl chloride at -78°C followed by *in-situ* hydrolysis of the Schiff base with aqueous hydrochloric acid. After removal of solvents at 30°C under reduced pressure, benzophenone could be extracted with ether and the hydrochloride salts of the α-amino-β-keto-ester **2a-o** isolated as crystalline solids, generally from methanol/ether or tetrahydrofuran/ether.[6]

The Schiff base **5**, derived from diphenylketimine and glycine methyl ester[5] consistently gave better yields of **2a**, compared with a similar acylation reaction with the Schiff base **4** [see entries *1* vs. *2*, Table 1]. The inverse addition of the anion consistently produced better yields.

Scheme II





As shown in Table 1, one could obtain good to excellent yields of the ketone **2**, bearing a wide variety of substituents at R^2, including aliphatic, aromatic (entries 2, 5 and 6), heteroaromatic (entry 7), as well as substituents containing heteroatoms (entry 16). Our method is not sensitive to steric bulk in the acylating agent, as is evident from entries 8 to 11 in Table 1. One can also carry out the acylation reaction using more complex acylating agents: for example, ketones **8**, **9** and **10** were prepared in overall excellent yields.

Table (1). Synthesis of α-Amino-β-Keto Esters[9]

Entry No.	Compd No.	R^2	Yield(%) [i,ii]
1	2a	Ph	32 [iii]
2	2a	Ph	95
3	2b	i-Pr	95
4	2c	Bn	86
5	2d	1-Naphthyl	46
6	2e	2-Naphthyl	91
7	2f	3-Pyridinyl	(iv)
8	2g	tert-Bu	95
9	2h	α-Me, cyclo-Hexyl	63
10	2i	Adamantyl	56
11	2j	$CH(CH_2CH_3)_2$	58
12	2k	cyclo-Pentyl	71
13	2l	cylco-Hexyl	93
14	2m	cyclo-Heptyl	45
15	2n	cyclo-Octyl	54
16	2o	CH_2SCH_3	57

(i) Yields are not optimized and are reported for isolated products; (ii) Schiff base 5 was used except for entry (1); (iii) Schiff base 4 was used; (iv) The crude product was used directly for the next step (see entry 6 in Table 2).

Table (2). Synthesis of β-Keto Dipeptides[9]

Entry No.	Comd No.	R^3OCO-AA-CO	R^2	Yield (%) [i]
1	7a	(S) Z-Phe	Ph	71
2	7b	(S) BOC-Phe	Me	78
3	7c	(S) Z-Phe	Bn	64
4	7d	(S) BOC-Phe	1-Naphthyl	80
5	7e	(S) BOC-Phe	2-Naphthyl	87
6	7f	(S) BOC-Phe	3-Pyridinyl	37 [ii]
7	7g	(S) Z-Phe	iPr	74
8	7h	(S) Z-Phe	tert-Bu	95
9	7i	(S) Z-Phe	$CH(CH_2CH_3)_2$	83
10	7j	(S) Z-Phe	cyclo-pentyl	97
11	7k	(S) Z-Phe	cylco-hexyl	82
12	7l	(S) Z-His(Z)-	"	73
13	7m	(S) Z-Ser(OtBu)	"	95
14	7n	(S) Z-hPhe [iii]	"	36
15	7o	(S) Z-Trp	"	82
16	7p	(R,S) Z-α-Allylglycyl	"	76
17	7q	(R,S) Z-β-Nal [iv]	"	63
18	7r	(R,S) Z-4-Pal [v]	"	42
19	7s	(S) Z-Pro	"	90
20	7t	(S) Z-Met	"	67
21	7u	(S) Z-Phe	cyclo-heptyl	69
22	7v	(S) Z-Tyr(Bn)	$CH(CH_2CH_3)_2$	56
23	7w	(S) Z-Tyr(Bn)	CH_2SCH_3	58

(i) Yields are not optimized and are shown for isolated products; (ii) Yield based on nicotinoyl chloride (i.e. for two steps); (iii) homophenylalanyl; (iv) b-naphthylalanyl; (v) 4-pyridylalanyl

The α-amino group of the keto ester **2** could be readily protected by acylation with di-tert-butyldicarbonate or benzyl chloroformate, affording BOC and Z protected amino ketones, respectively.[7] However, efficient acylation with an activated amino acid derivative could only be achieved under very strict reaction conditions. BOC- or Z- protected amino acid was activated as the mixed anhydride using isobutyl chloroformate at -20°C , to which the hydrochloride salt **2a-o**, as a solid, or in a solution of DMF, was added followed by addition of an equimolar amount of tertiary base, Et_3N. This procedure gave the β-oxo-dipeptide derivatives[8] **7a-w**, in good to excellent yields [Table 2].

All of the β-oxo dipeptides **7** exist as the keto form in non-polar solvents (^1H- and ^{13}C-NMR in $CDCl_3$). Method for the transformation of the β-oxo-dipeptide intermediates **7** to the dipeptide mimetics **1** will be reported elsewhere.

References and Notes:

1. Morgan, B. A. and Gainor, J. A. *Annual Reports of Medicinal Chemistry*, Allen, R.C. (ED) Academic Press Inc., Orlando; **1989**; vol. 24 pp. 243-247.
2. Suzuki, M.; Iwasaki, T.; Matsumoto, K. and Okumura, K. *Syn. Comm.* **1972**, *2*, 237-242 .
3. (a) Stork, G.; Leung, A.Y.W. and Touzin, A. *J. Org. Chem.* **1976**, *41*, 3491-3493; (b) Rich, D.H.; Singh, J.; Gardner, J.H. *J. Org Chem.*, **1983**, *48*, 431-434.
4. O'Donnell, M.J. and Eckrich. T.M. *Tetrahedron Lett.*, **1978**, *47*, 4625-4628
5. We have succesfully prepared and used Schiff bases from ethyl, benzyl and tert-butyl esters as well. For the preparation of the Schiff base **5** see: O'Donnell, M. J. and Polt, R. L. *J. Org. Chem.*; **1982**, *47*,. 2663-2666.
6. Typical synthesis of α-amino-β-keto-ester hydrochloride salt: Synthesis of **2l** - A solution of KO^tBu (88.6g, 0.79 mole) in anhydrous THF (600 mL) was cooled under argon to -70°C, and a solution of the Schiff base **5** (200g, 0.79 mole) in THF (300 mL) added while maintaining the reaction temp. at -70°C. After 30 min., this red solution of the Schiff base anion **6**, was added via cannula to a mechanically stirred solution of the cyclohexanecabonyl chloride (105.6 mL, 0.79 mole) in anhydrous THF (200 mL) maintained at -70°C. Half an hour after completion of addition, the reaction mixture was quenched with 3N HCl solution (800 mL), the cold bath removed, and the reaction mixture concentrated to dryness under reduced pressure (<40°C). The residue taken in water (500 mL) and benzophenone extracted with ether (2 X 400 mL). The aqueous solution was concentrated to dryness under reduced pressure, stripped twice from methanol, the residue re-dissolved in anhydrous methanol and the white solid (57.5g, 97% of KCl) removed by filtration. The clear filtrate was concentrated and the residue crystallized from THF/Et_2O to give the keto ester **2l** as a white solid (162.9g first crop, 11.3g second crop); total yield 174.2 g, 93%).
7. For example: BOC-of **2a** was prepared using $(BOC)_2O$ in pyridine at 0°C in 67% yield, Z- derivative of **2l** was prepared using Z-Cl and 2 eq. of Et_3N in 10% aq HOAc in 87% yield.
8. Typical conditions for acylation of α-amino-β-keto-ester: Synthesis of **7k** - Z-Phe-OH (38g, 0.127 mole) was dissolved in anhydrous THF (500 mL), N-methyl morpholine (14 mL, 0.127 mole) added, and the solution cooled to - 20°C under argon. iBuOCOCl (16.5 mL, 0.127 mole) was added while maintaining the reaction mixture at - 20°C. After 15 min., solid **2l**, followed by second eq. of NMM were added, and the reaction mixture stirred at - 20°C for a further 30 min. Solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 (1L) and water. The organic layer was dried over anhydrous Na_2SO_4, and the crude product purified by flash chromatography on silica gel using 2:1:1 hexane:EtOAc:CH_2Cl_2 as eluent. The fractions containing product were pooled, concentrated under reduced pressure and the residue crystallized from EtOAc and hexane to yield 50g (82%) of the β-oxo-dipeptide **7k** as a white solid.
9. All new compounds were characterized using TLC, ^1H-NMR, elemental analysis and /or MS.

(Received in USA 4 September 1992; accepted 7 October 1992)