A Convenient Method for the *N*-Acylation and Esterification of Hindered Amino Acids: Synthesis of Ultra Short Acting Opioid Agonist, Remifentanil

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Abstract: A general method has been devised for the one step preparation of *N*-acylamino acid esters of type **7** from the corresponding α-amino acids in high yield under mild conditions and a probable mechanism is proposed.

Key words: acylation, esterification, amino acids

Opiate analgesics of the 4-acylanilinopiperidine type are important adjuncts for anaesthesia. Fentanyl (**1**) is the prototype of the series but many analogues have been prepared, including the more potent carboxylate derivative, carfentanil (**2**). Recently the development by Glaxo Wellcome of the ultra short acting opioid agonist, remifentanil (**3**)[1], has led us to re-evaluate synthetic approaches to 4-carboxypiperidine esters (Figure 1).

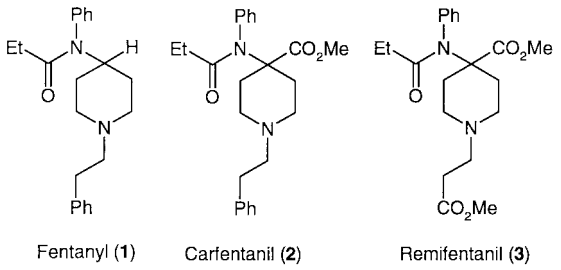
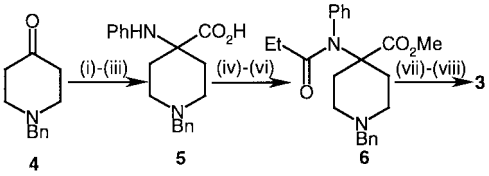


Figure 1

The reported syntheses[2] of the piperidine amino acid class of opiate agonists are based on a classical Strecker reaction of *N*-benzyl-4-piperidone (**4**) leading via stepwise hydrolysis of the nitrile and amide functions to the acid **5** (Scheme 1). Both the 4-carboxylate and the 4-anilino groups at the piperidine quaternary carbon of **5** are relatively unreactive, probably due to a combination of steric and electronic factors. Conventional acid catalysed esterification is very slow[3] and acylation of the aniline requires drastic conditions[4]. Generation of the propion amide **6** was initially achieved by alkylation of the sodium salt of **5** with methyl iodide, followed by acylation in neat propionic anhydride at reflux (Scheme 1). In the development of a practical process for the manufacture of remifentanil improvements to existing reaction conditions provided us with a satisfactory process for both the early and final steps of the synthesis but a new approach to the conversion of **5** into **6** was required.



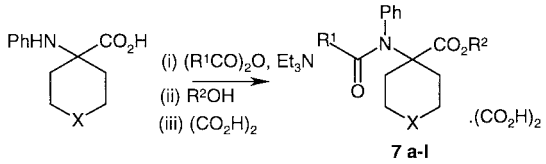
Reagents: (i) KCN, $PhNH_2$; (ii) aq H_2SO_4; (iii) aq HCl; (iv) NaOH; (v) MeI; (vi) $(EtCO)_2O$; (vii) Pd/C, H_2; (viii) methyl acrylate

Scheme 1

The reaction of **5** with aliphatic anhydrides to activate the carboxylate function towards nucleophilic attack by alcohols[5] produced *N*-acylated products even at room temperature. Treatment of the hydrochloride salt of **5** with excess propionic anhydride in the presence of triethylamine in ethyl acetate at reflux followed by the addition of methanol gave the desired 4-propionylaminopiperidine-4-carboxylate ester **6** in high yield. These mild conditions were extended to a range of acids, anhydrides and alcohols and the results of these investigations are summarised in the Table[6].

In most cases yields of the 4-acylaminopiperidine-4-carboxylate esters **7** were high, the acylation and esterification reactions were rapid (ca. 1h and 2h respectively at reflux in ethyl acetate) and the products were conveniently isolated as oxalate salts. The intermediate acid **7a-l** was

Table Preparation of *N*-acylamino acid esters **7**



7	R^1	R^2	X	Yield (%th)
a	CH_3	CH_3	$PhCH_2N$	87
b	CH_3CH_2	CH_3	$PhCH_2N$	92
c	$(CH_3)_2CH$	CH_3	$PhCH_2N$	93
d	$CH_3(CH_2)_2$	CH_3	$PhCH_2N$	82
e	$CH_3CH{=}C(CH_3)$ (*E*)	CH_3	$PhCH_2N$	40
f	$CH_3CH_2CH(CH_3)$	CH_3	$PhCH_2N$	87
g	Ph	CH_3	$PhCH_2N$	59
h	CH_3CH_2	CH_3CH_2	$PhCH_2N$	89
i	CH_3CH_2	$(CH_3)_2CH$	$PhCH_2N$	85
j	CH_3CH_2	$(CH_3)_3C$	$PhCH_2N$	83
k	CH_3CH_2	CH_3	CH_2	75
l	CH_3CH_2	H	$PhCH_2N$	79

isolated in 79% yield by quenching the acylation reaction mixture with water instead of an alcohol.

Attempts to prepare the trifluoromethyl compound **8** using trifluoroacetic anhydride gave instead the oxazolidone **9** in 80% yield (Figure 2). The structure of **9** was confirmed by the single crystal X-ray analysis of its oxalate salt. The desired amide **8** was prepared by treatment of the methyl ester of **5** with trifluoroacetic anhydride in toluene at reflux.

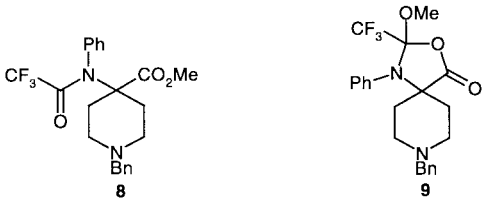
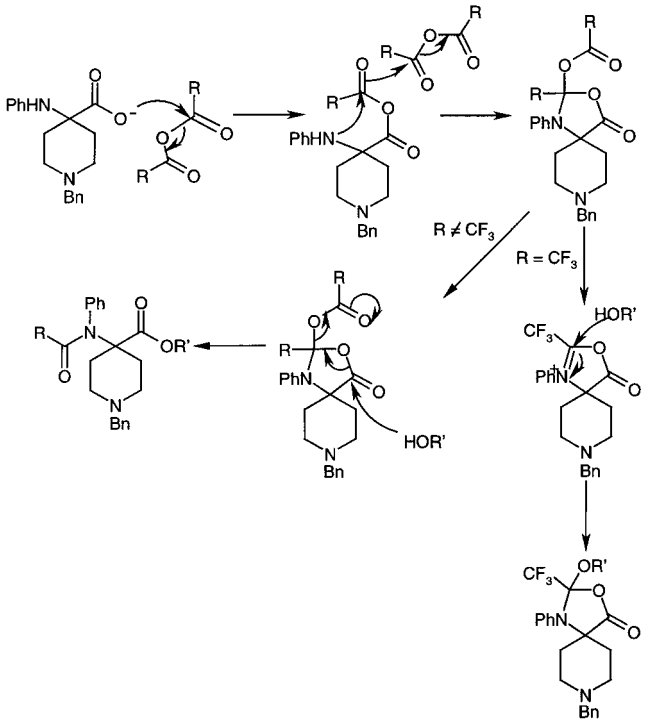


Figure 2

A possible mechanism for the *N*-acylation and esterification reactions is depicted in Scheme 2. The mild conditions of the *N*-acylation step compared with those required to acylate the esters of **5** suggest that the reaction is intramolecular[4]. A related *N*-O intramolecular transposition has been proposed by Colapret[2b] in the preparation of 4-acyloxypiperidines related to fentanyl. Support for a spiro intermediate is also provided by the structure **9**. In this case the electronegativity of the trifluoromethyl group favours attack by methanol at C2 of the oxazolinium ion. The related 2-hydroxy-2-trifluoromethyl-5,5-diphenyl-4-oxazolidone has been reported by Ketcha[7] and this compound was converted via an oxazolinone into the corresponding 2-ethoxy compound by heating in anhydrous ethanol.

In conclusion this easily performed sequence provides a convenient method for the preparation of *N*-acylamino acid esters of type **7** from α-amino acids in high yields under mild conditions.



Scheme 2

Acknowledgement

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References and Notes

(1) Feldman P. L.; James M. K.; Brakeen M. F.; Bilotta J. M.; Schuster S. V.; Lahey A. P.; Lutz M. W.; Johnson M. R. and Leighton H. J. *J. Med. Chem*. **1991**, *34*, 2202.

(2) For recent examples see: a) Janssens F.; Torremans J. and Janssen P. *J. Med. Chem.* **1986**, *29*, 2290. b) Colapret J. A.; Diamantidis G.; Spencer H. K.; Spalding T.C. and Rudo F. G. *J. Med. Chem*. **1989**, *32*, 968. c) Feldman P.L. and Brakeen M. F. *J. Org. Chem.,*. **1990**, *55*, 4207 and references cited therein.

(3) Taber D.F. and Rahimizadeh M. *J. Org. Chem*. **1992**, *57*, 4037.

(4) Van Deale P. G.; De Bruyn M. F.; Boey J M.; Agten J. T. and Janssen P. A. *Arzneim.-Forsch. Drug Res.* **1976**, *26*, 1521.

(5) Parish R. C. and Stock L. M. *J. Org. Chem*. **1965**, *30*, 927.

(6) **General procedure for the preparation of *N*-acylamino esters of type 7:** Triethylamine (0.3 mol, 41.8 mL) was added slowly to a stirred suspension of the acid **5** (0.1 mol, 34.7 g) and propionic anhydride (0.7 mol, 89.8 mL) in ethyl acetate (260 mL) at reflux and the resulting solution was heated at reflux for 1 h. The reaction mixture was cooled to 70°C, methanol (70 mL) added, the reaction heated at reflux for a further 2 h, cooled to room temperature and then basified with 5 M aqueous sodium hydroxide. The biphasic mixture was separated and the aqueous extracted with ethyl acetate, the combined ethyl acetate solution was washed with 2M aqueous sodium hydroxide and water. Water was then added followed by aqueous phosphoric acid (2.5 M) until the pH of the aqueous reached 6. The layers were separated and a solution of oxalic acid dihydrate (0.1 mol, 12.6 g) in methanol (34.7 mL) was added to the organic layer. The resulting solid was isolated by filtration and washed with ethyl acetate and dried in vacuo at 40°C to afford the product **7b** (43.5 g, 92%).

(7) Ketcha D. M.; Abou-Gharbia M.; Smith F. X. and Swern D. *Tetrahedron Lett.* **1983**, *24*, 2811.

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