Tetrahedron Letters, Vol. 34, No. 2, pp. 255-256, 1993
Printed in Great Britain

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

Synthesis of Succinate Containing Dipeptide Isosteres via Carbonylation of Enol Triflates.

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Abstract : Pd(0) catalysed carbonylations of enol triflates in the presence of amino acid derivatives yield the corresponding amides.

The Pd(0) catalyzed carbonylation of enol triflates to acrylic acid derivatives is well studied.[2] Depending upon the reaction conditions one obtains esters, amides, or acids. One limitation of the carbonylations is that significant amounts of amine (*ie.* 5-6 equiv) or alcohol (~40 equiv) are employed in the synthesis of amides or esters respectively. If the amine component is expensive and/or of sufficiently large molecular weight that product isolation is difficult, then this approach is less attractive. It was of interest to determine if synthetically useful yields of amides could be obtained with ~1 equiv of a complex amine in the carbonylation.[3] Of more interest was if ~1 equiv of a less nucleophilic α–amino acid derivative would yield its corresponding amide. We are unaware of prior use of α–amino acid derivatives as nucleophilic traps in the carbonylation of enol triflates.

The reaction of triflate **1** with various α–amino acid esters, generated *in situ* from their HCl salts, in the presence of CO are summarized in Table 1. The yields range from modest (~50 %) to good (~70-80 %) and are unoptimized. Simply drying the HCl salts over P_2O_5 can increase yields substantially. This appears to be a facile route into a variety of dipeptide like compounds. The reaction conditions are quite mild and appear to tolerate a wide range of functionality. The reaction appears to be insensitive to steric constraints working very well for proline as well as β -branched amino acids (ie. isoleucine). Presumably even free N-terminal small peptide fragments, if soluble in DMF, will participate in these reactions.

A typical procedure is as follows : A 100 mL Fisher-Porter bottle was charged with 0.5 g (1.57 mmol) crude **1**[4], 11 mg (0.05 mmol) $Pd^{(II)}(OAc)_2$, and 24 mg (0.09 mmol) Ph_3P, in 5 mL DMF. To this was added a mixture of 0.66 mL (4.7 mmol) NEt_3, and 0.4 g (1.73 mmol) of dry L-phenylalanine ethyl ester HCl in 5 mL of

DMF. The reaction was charged with 40 psi of CO and stirred at RT for 2 days. The reaction was concentrated in vacuo and partitioned between ethyl acetate and 5% aqueous citric acid. The organic phase was washed with brine, dried, and concentrated in vacuo to a thick oil. Chromatography on silica gel (30% EA / H) afforded 420 mg (78 %) pure product **5a**.[5]

In summary, this sequence allows for rapid construction of a variety of pepitidomimetic compounds. The chemistry of these dipeptide isosteres, particularly with respect to asymmetric hydrogenation, will be communicated shortly.

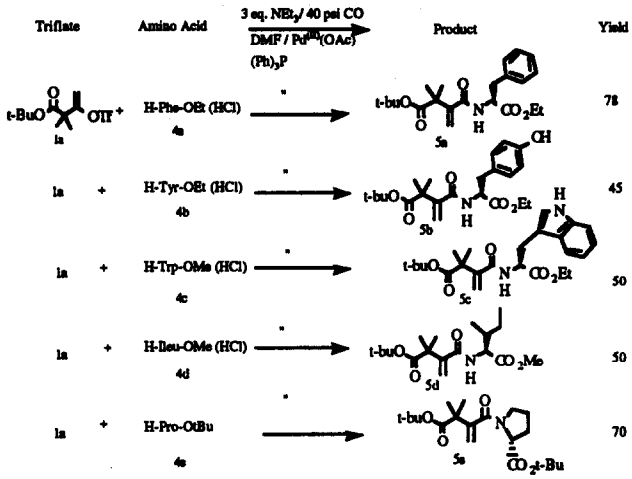

Table 1.

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3. For use of chiral amino alcohols in Pd catalysed carbonylations see: Meyers, A.I.; Robichaud, A.J.; McKennon, M.J. *Tet.Lett.*, 1992, *33*, 1181.
4. Triflate **1a** was prepared via addition of ketone to 1.1 equiv LDA in THF at-78°C. After 10 minutes 1.05 equiv of $PhN(Tf)_2$ was added and reactions were allowed to warm to RT overnight. Reaction workup consisted of conc *in vacuo* followed by partitioning between ethyl acetate and water. The organic phase was washed with excess aqueous base, dried and concd to an oil that was used without further purification. The triflate contained small amounts of PhNH(Tf) byproduct. The triflate is stable to dilute aqueous acid and silica gel chromatography .
5. Structure assignment is consistent with ^{1}H-NMR, ^{13}C-NMR, and high resolution mass spectroscopy.

(Received in USA 18 September 1992; accepted 11 October 1992)