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Cobalt Catalyzed Multiple Component Condensation Route to β-Acetamido Carbonyl Compound Libraries

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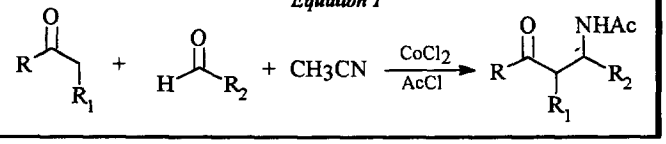
Abstract: A simple and general procedure for the synthesis of various β-acetamido carbonyl compounds by a cobalt catalyzed one pot multiple component condensation reaction involving ketones, aldehydes and acetonitrile is described. A library of twenty discrete β-acetamido carbonyl compounds with two or three functional group variation was prepared.

Incorporation of peptidomimetic surrogates into bioactive molecules has been the focus[1] of intensive research over the last ten years. This technique has been utilized successfully in the design and synthesis of enzyme inhibitors. For example, inhibition of *human immunodeficiency virus* type 1 (**HIV 1**) protease by peptidomimetic core structures has become an attractive strategy in the design of therapeutic agents[2] for the treatment of acquired immunodeficiency syndrome (***AIDS***). Therefore a search for enzyme inhibitors with diverse structural profile has placed great demand on synthetic chemists to produce new compounds in a time and resource effective manner. This demand has led to the development of techniques leading to the generation of large combinatorial libraries[3] of small organic molecules. With this premise, we have developed a cobalt catalyzed general route to β-amino ketones or esters as potential core structures for mechanism based inhibitors for various proteases. These small molecules have been synthesized by ***multiple component condensation*** route involving a ketone, aldehyde and acetonitrile in the presence of cobalt(II) chloride. A similar ***multiple component condensation*** reaction have been applied to the generation of library of compounds using **Ugi**[4] and **Passerini**[5] reaction.

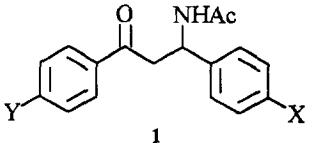
In a preliminary study we have demonstrated[6] that cobalt(II) chloride catalyzes the coupling of ketone or ketoester, aldehyde and acetonitrile in the presence of acetyl chloride to afford a high yield of β-acetamido ketones or esters (**Eq. 1**). In order to create a library of compounds, we have taken a variety of ketones and

Equation 1



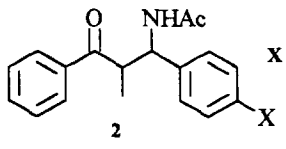
aldehydes for such coupling[7] to afford a diverse set of β-amino ketones or esters. Thus, acetophenone and it's derivatives, propiophenone, diethyl ketone, cyclohexanone and methyl levulinate were reacted with variety of *p*-substituted benzaldehydes to afford the corresponding β-acetamido ketones with (**1-6**) two or three fold functional diversity. A library of ten such compounds was obtained using this protocol (**Scheme 1**) and in general the yields of these products were good to excellent, averaging 60 to 85%. In general the *anti* diastereomer (*anti:syn* ≈ 3:1) was found to be the major product in the case of α-substituted carbonyl compounds. Similarly, methyl acetoacetate or acetyl acetone was reacted with various *p*-substituted benzaldehydes or aliphatic aldehydes to afford a diverse set of β-acetamido esters or ketones in good yields. The versatility of this ***multiple component condensation*** procedure was demonstrated by the preparation of a set of library containing ten distinct β-acetamido carbonyl compounds (**7-11, Scheme 1**) in a yield ranging 60 to 80%. The procedure for the isolation is very simple, as most of these compounds were isolated by crystallization or passing it over a silica gel column. By and large the reaction of methyl acetoacetate with different aldehydes resulted in the formation of *anti:syn* diastereomers in 3:1 ratio. The small molecule library synthesized from methyl acetoacetate and different aldehydes provides direct route to β-aminoacid derivatives, a core structure which on incorporation with an amino acid may provide dipeptide isosteres with better binding properties.

Scheme 1



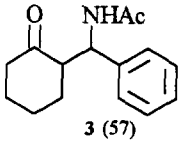
1

X = Cl, **Y** = H, (64), **1a**.
= OAc, = OAc, (69), **1b**.
= H, = OAc, (67), **1c**.
= Cl, = NHAc, (56), **1d**.

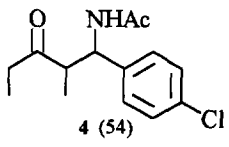


2

X = Cl, (78), **2a**.
= CO_2Me, (64), **2b**.



3 (57)



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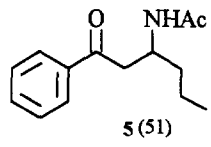
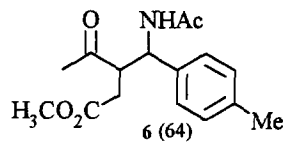
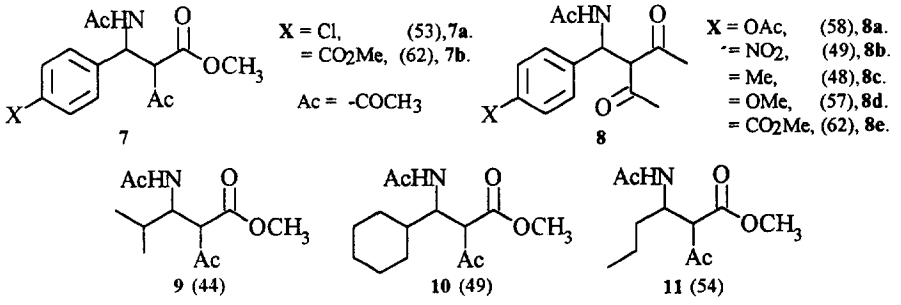


5 (51)



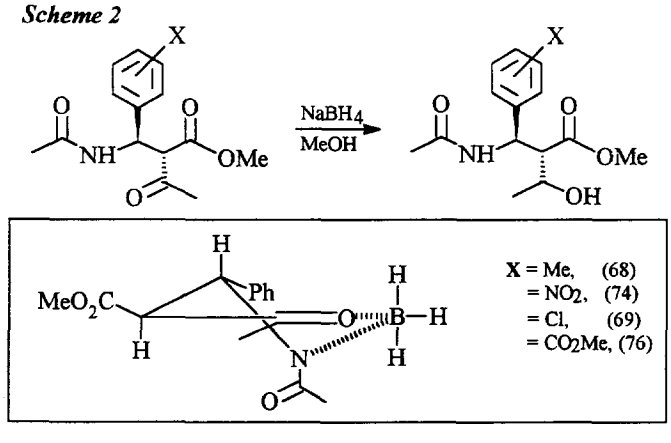
6 (64)

(Scheme 1 continued...)



The β-acetamido esters are also useful precursor to β-aryl homoisothreonine derivatives which can be incorporated in an aminoacid residue to afford the corresponding dipeptide isosteres. Thus $NaBH_4$ reduction of *anti* β-acetamido esters (obtained from coupling of methyl acetoacetate with *p*-methyl, methoxy, nitro and chloro benzaldehydes) in methanol afforded the corresponding α-hydroxyethyl β-aminoacid derivatives (β-aryl homoisothreonine) mainly as a 1,3 *syn* diastereomer in quantitative yields (**Scheme 2**). The stereocontrol during the borohydride reduction may be explained by invoking a six membered transition state resulting due to the formation of chelate between carbonyl group and β-acetamido group. Such a reduction will result in a 1,3 *syn* relationship between hydroxy and acetamido groups (**Scheme 2**).

Scheme 2



In conclusion, we have demonstrated a versatile cobalt catalyzed protocol for the synthesis of β-acetamido carbonyl compounds using a multiple component condensation procedure. This one step procedure has been used to generate a library of twenty discrete compounds which may be potentially useful as peptidomimetic

surrogates. The β-acetamido esters obtained by this procedure are useful precursor to β-aryl homoisothreonine derivatives which promises to be an effective core structure for mechanism based inhibitors of aspartate proteases.

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7. *In a typical experimental procedure*, 1,3-dicarbonyl compound / ketone (5 mmol) and aldehyde (5.5 mmol) were taken in acetonitrile (30 mL) and the mixture was heated under nitrogen balloon at 80°C in the presence of catalytic amount of cobalt(II) chloride (10 mg) and acetyl chloride (10 mmol). The progress of the reaction was monitered by TLC. Removal of acetonitrile followed by bicarbonate workup afforded a residue which on column chromatography yielded the product β-acetamido ketone.

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