Polyaniline-Supported Cobalt Catalyst: A Three-Component Condensation Route to β-Amino Acid Derivatives

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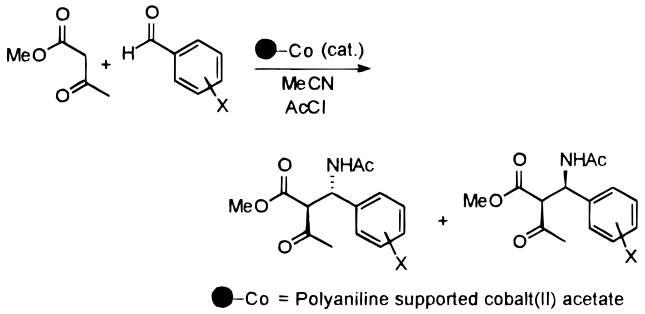
Polymer-supported metal catalysts are increasingly becoming prominent[1] in the repertoire of new synthetic methodology. This prominence stems from the fact that reactions carried out under the aegis of a polymer-supported metal framework render a high level of selectivity during bond formation and offer high economical prospects in developing reusable catalysts. Their use also permits a nonaqueous workup for the reactions yielding water-sensitive and -soluble products. The role of polymer-supported metal-catalyzed organic transformations can be made more attractive in reactions whose yields are quantitative, as such a protocol would circumvent the purification process by column chromatography or solvent extraction procedures and permit isolation of products by merely filtering the catalyst. These features would be highly useful in the domain of combinatorial synthesis[2] of libraries of small molecules required for new drug discovery. A promising beginning[3] has already been made in achieving these objectives, and polymer-supported metal-catalyzed synthesis of organic molecules is attracting the attention of organic chemists engaged in generating libraries of small druglike molecules by a combinatorial approach.

In an earlier study, we have shown that cobalt(II) chloride catalyzes[4] the coupling between a ketone or ketoester, an aldehyde, and acetonitrile in the presence of acetyl chloride to provide a general route to β-acetamido carbonyl compounds. This transformation, however, is influenced by the presence of molecular oxygen, which causes the formation of α,β-unsaturated carbonyl compounds (Knoevenagel product) along with the expected β-acetamido ketones. On the other hand, a moderate to good yield of β-acetamido ketones was obtained under a nitrogen atmosphere, which suppressed the formation of the α,β-unsaturated carbonyl compounds to a large extent as only traces of the latter were observed in the crude reaction mixture. To broaden the synthetic scope of this reaction, we have explored the possibility of developing this reaction via a combinatorial approach leading to a general synthesis of β-amino acid derivatives by applying a polymer-supported cobalt-catalyzed three-component coupling protocol. We have recently demonstrated[5] that polyaniline-supported cobalt(II) acetate or cobalt(II) salen functions as an efficient catalyst in promoting the epoxidation of alkenes and their subsequent opening by anilines or its derivatives. We now demonstrate that polyaniline-supported cobalt(II) acetate catalyzes the coupling between methyl acetoacetate, an aldehyde, and acetonitrile to provide a general synthetic route to β-amino acid derivatives (Scheme 1). The advantage of this reaction over the homogeneously catalyzed one is the operationally simple nonaqueous workup procedure and better diastereoselectivity.

Scheme 1



The reaction of methyl acetoacetate with benzaldehyde, *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, methyl salicyaldehyde, *o*-hydroxybenzaldehyde, isovanillin, and 3-methylbutanal in the presence of polyaniline-supported[6] cobalt (II) acetate afforded the corresponding β-acetamido esters **1a**−**g**, respectively, in good yields (Table 1). *The isolation of these products can be achieved without chromatography by merely washing the crude reaction mixture with hexane*−*carbon tetrachloride, which removes the unreacted starting materials and affords the β-amino acid derivatives in high purity*. The phenolic groups of *o*-hydroxybenzaldehyde and isovanillin were also acetylated during this transformation (Table 1, entries 5 and 6). These compounds were obtained as a mixture of syn and anti diastereomers in which the anti diastereomer was found to be the major (>7:1) product. An analysis of the reaction mixture indicated the presence of a small amount (5%) of the α,β-unsaturated carbonyl compounds (Knoevenagel product). The α-substituted ketones also react with aromatic aldehydes under these conditions to afford the corresponding β-acetamido ketones in a diastereoselective manner. Thus, the reaction of propiophenone with vanillin under the previously defined reaction conditions yielded the anti β-acetamido ketone **1i** in which the phenolic group was also acetylated during the reaction (eq 1). Similarly, 2-butanone reacted with benzaldehyde in a regioselective manner to afford the corresponding compound **1j** under the above-defined reaction protocol (eq 2). In both of these reactions, the

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(3) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977.

(4) (a) Bhatia, B.; Reddy, M. M.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1994**, 713. (b) Reddy, M. M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1995**, *36*, 4877. (c) Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083. (d) For related three-component coupling, see: Armstrong, R. W.; Combs, A. W.; Templest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123 and ref 2b.

(5) (a) Das, B. C.; Iqbal. J. *Tetrahedron Lett.* **1997**, *38*, 1235. (b) Das, B. C.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083. (c) Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 2903.

(6) (a) Polyaniline-supported cobalt(II) acetate was prepared according to ref 5a. (b) This catalyst was not reusable.

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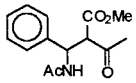
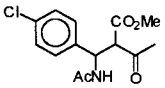
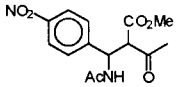
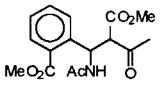
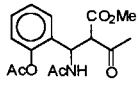
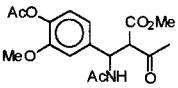
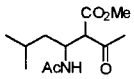
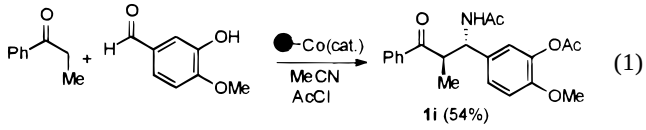
Table 1. Polyaniline-Supported Cobalt and Cobalt(II) Chloride Catalyzed Synthesis of β-Amino Acid Derivatives: A Comparative Study

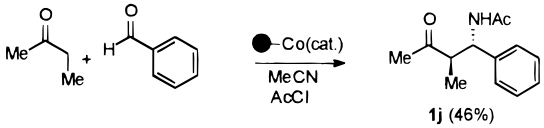
Entry	β-Amino acid derivatives	Yield (%) obtained from ●-Co catalyzed reaction[a,b]	Yield (%) obtained from $CoCl_2$ catalyzed reaction[c,d]	M.P.[e]
1	 **1a**	62	48	129-31 °C
2	 **1b**	68	41	130-32 °C
3	 **1c**	53	31	149-51 °C
4	 **1d**	51	41	145-46 °C
5	 **1e**	58	41	-[f]
6	 **1f**	51	43	173-75 °C
7	 **1g**	55	52	-[f]

[a] Yield of the product purified by carbon tetrachloride−hexane was. [b] Trans diastereomer is obtained as the predominant product (cis/trans = 1:>7). [c] Yield of the product obtained by aqueous workup and column chromatography. [d] The product is obtained as a 3:1 mixture of diastereomer. [e] Melting point of the trans diastereomer. [f] This compound was obtained as a gum.

corresponding anti diastereomers were isolated by column chromatography as the major products along with minor amounts (~10−15%) of the syn diastereomers. A



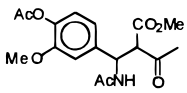
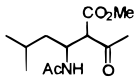
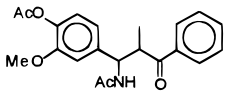
(1)



(2)

comparison between polyaniline-supported cobalt(II) acetate and cobalt(II) chloride catalyzed reactions indicates that the yield and stereoselectivity for the former reaction is better than the latter one (Table 1). It is noteworthy that the anti selectivity in polyaniline-supported cobalt(II) acetate catalyzed reaction is much higher (Table 2), and the product isolation can be done by circumventing the column chromatography. These advantages are not associated with cobalt(II) chloride catalyzed reactions,

Table 2. Comparison of Diastereoselectivity in Polyaniline-Supported Cobalt and Cobalt(II) Chloride Catalyzed Synthesis of β-Acetamido Carbonyl Compounds

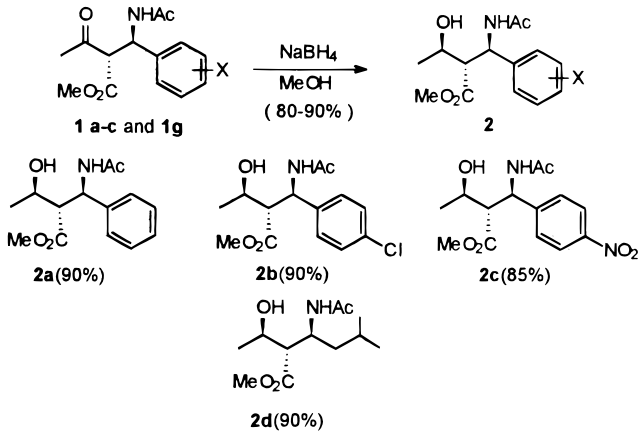
β-Acetamido ketone	Syn : Anti[a] ●-Co catalyzed reaction	Syn : Anti[a] $CoCl_2$ catalyzed reaction
 **1f**	7.5 : 1	3 : 1
 **1g**	>10 : 1	3 : 1
 **1h**	7.5 :1	3 : 1

[a] Ratio obtained from HPLC of the crude mixture.

and therefore, the polyaniline-supported cobalt-catalyzed protocol is amenable to the synthesis of β-amino acid derivatives by a combinatorial approach.

The anti β-acetamido esters **1** were reduced stereoselectively with sodium borohydride to give the corresponding α-hydroxyethyl β-amino acid derivatives (β-aryl homoisothreonine) **2a**−**d**, respectively, mainly as 1,3-*syn*-amino alcohol diastereomers in good yields (Scheme 2).

Scheme 2



The corresponding anti diastereomers were obtained in ~10% yield in all cases. This diastereoselectivity may be arising due to the reduction of the chelated cyclic six-membered intermediate, which will result in a 1,3-stereocontrol. The 1,3-syn stereochemistry is assigned on the basis of the ^1H NMR, where the large coupling constant between the methine protons at C-2 and C-3 is indicative of anti stereochemistry between the hydroxy/acetamide and methoxycarbonyl groups.

The products derived from *o*-benzaldehydes, i.e., **1d** and **1e** can be cyclized intramolecularly to afford interesting heterocycles. Similarly, the β-aryl homoisothreonine derivatives **2a**−**d** may be useful building blocks for the peptidomimetic compounds used as novel enzyme inhibitors.

In conclusion, we have developed an efficient polymer-supported cobalt-catalyzed three-component coupling

protocol for the synthesis of β-amino acid derivatives that can be manipulated to useful building blocks required for the synthesis of the peptidomimetic compounds.

Experimental Section

Preparation of Polyaniline. Freshly distilled aniline 10 mL (109.5 mmol) was dissolved in 125 mL of 1.5 M HCl, and a solution of ammoniumpersulfate (54.8 mmol) in 1.5 M HCl (125 mL) was added to it at 0 °C. Since aniline polymerization is strongly exothermic, the oxidant must be added slowly over a period of 1 h. After the addition of the oxidant, the reaction was stirred further for 4 h. The polyaniline hydrochloride precipitate was separated by filtration and washed consecutively with water (3 × 30 mL), methanol (2 × 25 mL), and diethyl ether (2 × 15 mL) to remove the oligomers and the reaction side products. The polymer was then vacuum-dried until constant mass. Deprotonation of polyaniline hydrochloride was achieved with aqueous ammonia (3 wt %). Deprotonated polymer was again washed with water, methanol, and diethyl ether and dried until constant mass.

Preparation of Polyaniline-Supported Cobalt(II) Acetate. Cobaltous acetate (200 mg) and polyaniline (200 mg) were added to a solution of acetic acid (25 mL) in acetonitrile (25 mL) and stirred at ambient temperature for 36 h. The resultant catalyst was filtered off and washed first with acetic acid (3 × 10 mL) and then thoroughly with acetonitrile until the filtrate was colorless. The resulting residue was dried in an air oven at 100 °C for 2 h to afford the black catalyst.

General Procedure for the Synthesis and Isolation of β-Ketoamides (1). Polyaniline-supported cobalt(II) acetate (5 mg) was added to a solution of methyl acetoacetate/ketone (5 mmol), aldehyde (5 mmol), and acetyl chloride (15 mmol)[7] in acetonitrile (15 mL) at ambient temperature. The reaction mixture was heated under nitrogen atmosphere at 80 °C for 8−10 h, and at the completion of reaction, the catalyst was removed by filtration through a sintered glass funnel. The filtrate was evaporated to afford a residue that was washed repeatedly with CCl_4−hexane solvent mixture (1:2) to afford an yellow powder. The solid was further washed thoroughly with CCl_4 and dried under vacuum to yield the β-ketoamides **1** in moderate to good yields (50−70%) and high purity (HPLC 95−100%).

General Procedure for the Synthesis of β-Aryl Homoisothreonines (2). Sodium borohydride (5 mmol) was added in portions to a solution of β-acetamido ketone (5 mmol) in methanol (7.5 mL) with constant stirring at 0−5 °C for 1.5 h. The reaction was quenched with a saturated solution of NH_4Cl, and the solvent was evaporated in vacuuo. The residue was taken in ethyl acetate (25 mL), and the organic layer was washed successively with water (3 × 10 mL) and brine (1 × 10 mL). Drying (Na_2SO_4) and evaporation of solvent gave the crude product, which was purified by column chromatography (silica gel) to afford the corresponding alcohols **2a**−**d** in good yields (85−90%).

The spectral details of the compounds are given below:

Methyl-2-acetyl-3-acetamido-3-phenylpropionate (1a): ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 10.0 Hz, 1H), 7.34 (s, 5H), 5.84 (dd, J = 12.5, 3.0 Hz, 1H), 4.10 (d, J = 6.0 Hz, 1H), 3.72 (s, 3H), 2.37 (s, 3H), 2.04 (s, 3H); IR (KBr) ν_{max} 3300, 3080,1720, 1680, 1650, 1095, cm^{-1}; MS m/z 263 (M^+), 147, 130, 105.

Methyl-2-acetyl-3-acetamido-3-*p*-chlorophenylpropionate (1b): ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 10.0 Hz, 1H), 7.7−7.1 (m, 5H), 5.70 (dd, J = 10.0 and 5 Hz, 1H), 4.01 (d, J = 6.25 Hz, 1H), 3.58 (s, 3H), 2.30 (s, 3H), 2.02 (s, 3H); IR (KBr) ν_{max} 3300, 1735, 1715, 1650, 1435, 1370, 1095, 820 cm^{-1}; MS m/z 298 (M^+), 182, 165, 140.

Methyl-2-acetyl-3-acetamido-3-*p*-nitrophenylpropionate (1c): ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 9 Hz, 2H), 7.85 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 9 Hz, 2H), 5.90 (dd, J = 12.0, 3 Hz, 1H), 4.14 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H); IR (KBr) ν_{max} 3290, 3050, 1740, 1715, 1675, 1535, 1340, 1100, 850 cm^{-1} ; MS m/z 308 (M^+), 192, 176, 150.

Methyl-2-acetyl-3-acetamido-3-(4′-acetoxy-3′-methoxy)-phenylpropionate (1f): ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 7 Hz, 1H), 6.93 (s, 5H), 5.83 (dd, J = 8.0, 5 Hz, 1H), 4.12 (d, J = 5.0 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 2.37 (s, 3H), 2.27 (s, 3H), 2.03 (s, 1.5H), 1.97 (s, 1.5H); IR (KBr) ν_{max} 3330, 3050, 1740, 1720, 1660, 1535, 1340, 1100, 835 cm^{-1} ; MS m/z 369 (M^+), 352, 235, 192, 148.

2-Methyl-3-acetamido-3(3′-acetoxy-4′-methoxy)phenyl propiophenone (1h): ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 4 Hz, 1H), 7.2 (m, 5H), 6.97−6.73 (m, 3H), 5.62 (dd, J = 7, 5 Hz, 1H), 4.12 (dq, J = 10, 7 Hz, 1H), 3.68 (s, 3H), 2.16 (s, 3H), 1.94 (s, 3H), 1.31 (d, J = 4 Hz, 3H); IR (KBr) ν_{max} 3300, 3030, 1750, 1675, 1305, 1109 cm^{-1}; MS m/z 369 (M^+), 237, 132.

Methyl-2-acetyl-3-acetamido-5-methylhexanoate (1i): ^{1}H NMR ($CDCl_3$) δ 6.50 (d, J = 7.5 Hz, 1H), 4.83 (d.t, J = 11, 5 Hz, 1H), 3.93 (s, 3H), 3.87 (d, J = 3.5 Hz, 1H), 2.53 (s, 1.5H), 2.45 (s, 1.5H), 2.15 (s, 3H), 1.58 (dt, J = 10, 5 Hz, 2H), 1.3 (m, 1H), 1.13 (d, J = 5 Hz, 3H); IR (KBr) ν_{max} 3290, 1750, 1675, 1340, 1100, 850 cm^{-1} ; MS m/z 243 (M^+), 185, 142, 126, 112.

Methyl-3-acetamido-2(1′-hydroxyethyl)-3-*p*-chlorophenylpropionate (2b): ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 4H), 7.16 (d, J = 6 Hz, 1H), 5.63 (dd, J = 10, 3 Hz, 1H), 4.15 (m, 1H), 3.55 (s, 3H), 2.89 (dd, J = 11, 3 Hz, 1H), 2.23 (s, 1.5 H), 2.08 (s, 1.5 H), 1.26 (d, J = 6 Hz, 3 H); IR (KBr) ν_{max} 3350, 3050, 1750, 1655, 1530, 1425 cm^{-1}.

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(7) For aldehydes with a hydroxy group, 5 equiv of acetyl chloride was used.