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Cobalt-Mediated Alkylation of (4*R*) and (4*S*)-3-Acetoacetyl-4-benzyloxazolidin-2-ones. Preparation of Enantiopure Diphenylmethyl-, 9-Fluorenyl- and (1-Adamantyl)glycines

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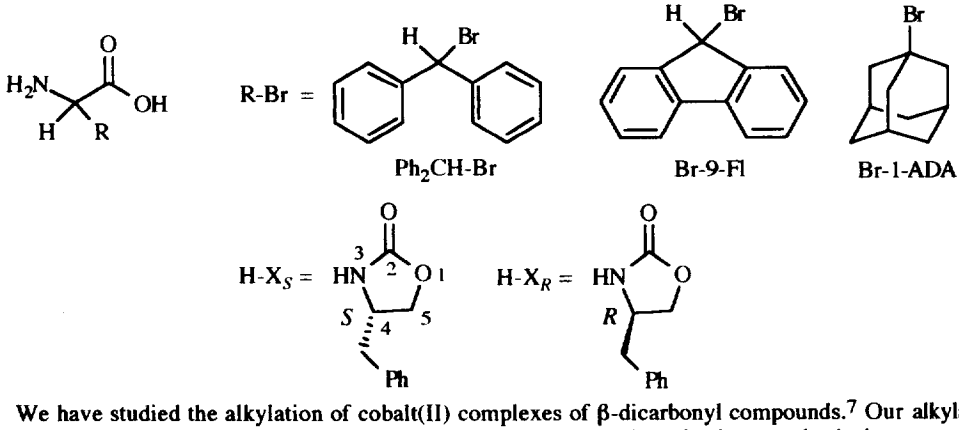
Abstract: The Co(II) complexes of (4*R*) and (4*S*)-3-acetoacetyl-4-benzyloxazolidin-2-ones are alkylated diastereoselectively with diphenylmethyl, 9-fluorenyl, and 1-adamantyl bromide. The resulting products are converted into enantiopure α-substituted glycines. Similar results are obtained by alkylation of the free acetoacetyloxazolidinones under Co(II)-catalysis.

The preparation of α-amino acids enantiomerically pure is a matter of current interest.[1] Substituted glycines featuring bulky substituents confer decreased conformational mobility to artificial peptides being useful for studying peptide-receptor interactions.[2] Racemic (diphenylmethyl)glycine (R = Ph_2CH-) has been incorporated into angiotensin II analogs.[2a] Enantiopure (diphenylmethyl)glycines have been prepared by alkylation of a Oppolzer's sultam derivative of glycine,[2b] and incorporated into substance P analogs.[3] Other preparations are based on the azidation of an enantiopure *N*-(3,3-diphenylpropionyl)oxazolidinone,[4] and on modification of L-serine.[5] (9-Fluorenyl)glycine (R = 9-Fl) has been also prepared in enantiopure forms[2b] and incorporated into substance P analogs.[3] Both enantiomers of (1-adamantyl)glycine (R = 1-ADA) have been prepared by resolution of the racemic.[6] It seems that this amino acid has not been incorporated into peptides.

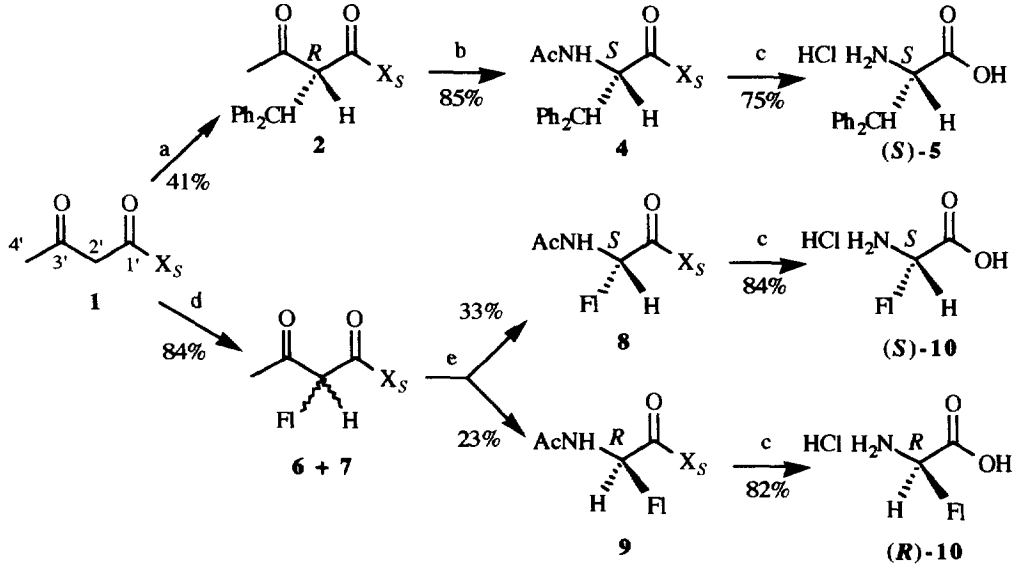


We have studied the alkylation of cobalt(II) complexes of β-dicarbonyl compounds.[7] Our alkylation method is suitable for alkyl halides prone to react through radical-based mechanisms, and substituents such as Ph_2CH,[8] 9-Fl,[9] and 1-ADA[10] are efficiently introduced at the intercarbonylic position. We have reported also

a catalytic version of this procedure.[11] Introduction of these substituents through the Co(II) complexes of enantiopure derivatives of acetoacetic acid or, alternatively, by means of the Co-catalyzed alkylation of the free ligands occurs with diastereoselection and further transformation of the acetyl group of the resulting products into acetylamino group (Schmidt rearrangement) and deprotection completes the preparation of enantiopure substituted glycines. Two problems had to be solved beforehand: 1) the introduction of a metal into enantiopure acetoacetates requires the metal in soluble form in organic solvents,[12] and 2) use of sodium azide in chlorinated solvents usual in Schmidt rearrangement is unsafe and alternative solvents had to be tested.[13] On the other hand the success of our approach depends on the stability of the substituted intercarbonyl positions to epimerization. Although the stability was suspected to be low, the bulk of the substituents introduced militated in favour of our purposes and, in fact, diastereoisomerically pure compounds related to enantiopure derivatives of acetoacetic and similar ketoacids have been prepared by alkylation[14] and by other methods.[15]

(4*S*)-*N*-Acetoacetyl-4-benzyloxazolidin-2-one, **1**,[12] was converted into a mixture (82:18) of isomers (4*S*,2'*R*), **2**, (mp 127-128°C, X-ray diffraction) and (4*S*,2'*S*), **3**, (mp 171-173°C) in a diastereoselective Co(II)-catalyzed alkylation[11] with benzhydryl bromide (Scheme 1). Schmidt rearrangement[13b] on **2** afforded acetamide **4** (mp 205-208°C) which was hydrolized in two steps with recovery of the chiral auxiliary to give (*S*)-(diphenylmethyl)glycine hydrochloride, (*S*)-**5** (mp 184-186°C; $[\alpha]_D$ = + 61.3 (MeOH, c = 1.05), lit[4] $[\alpha]_D$ = + 63.8 (MeOH, c = 1.0)).

A similar approach from 9-bromofluorene led to a mixture of the easily epimerizable **6** and **7** (Scheme 1). Schmidt rearrangement[13b] on the mixture followed by chromatographic separation afforded acetamides (4*S*,2'*S*), **8**, (mp 131-132°C) and (4*S*,2'*R*), **9**, (mp 91-95°C). Both diastereoisomeric acetamides were converted into enantioisomeric (*S*)- and (*R*)-(9-fluorenyl)glycine hydrochlorides, (*S*)-**10** (mp 241-244°C; $[\alpha]_D$ = - 15.1 (1M HCl, c = 0.53)) and (*R*)-**10** (mp 242-244°C, $[\alpha]_D$ = + 15.5 (1M HCl, c = 0.51)).



a.- i: K_2CO_3, $[CoCl_4]^{2-}$ $2[PhCH_2NMe_3]^+$, Ph_2CHBr, $HCCl_3$, 50°; ii: chromatography

b.- NaN_3, H_2SO_4, DME, -30° to rt

c.- i: LiOH, THF-H_2O; ii: Refl 6-7 N HCl

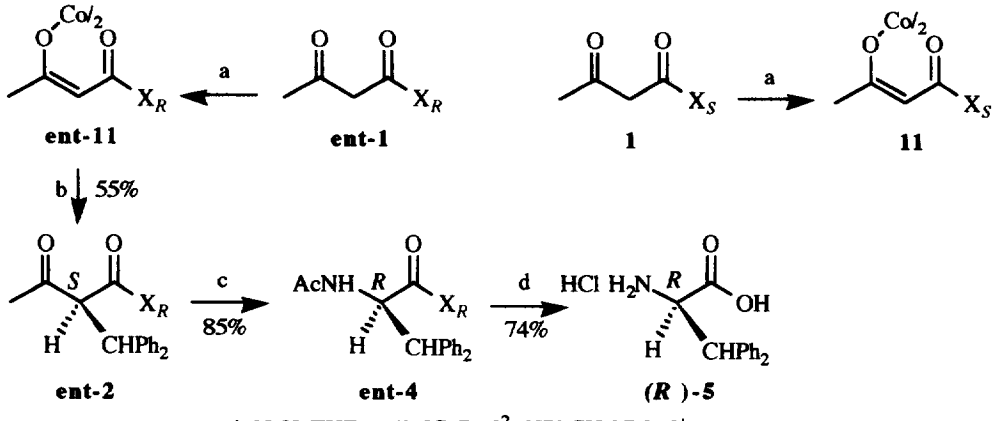
d.- K_2CO_3, $[CoCl_4]^{2-}$ $2[PhCH_2NMe_3]^+$, Br-9-Fl, $HCCl_3$, 50°

e.- i: NaN_3, H_2SO_4, DME, -30° to rt, then 60°; ii: chromatography

SCHEME 1

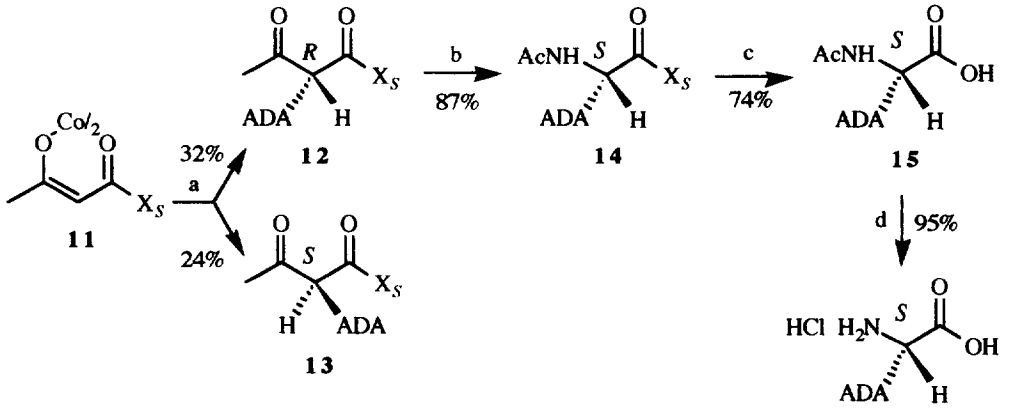
Attempts to alkylate **1** with 1-bromoadamantane under Co(II) catalysis[11] failed. Then we turned to the alkylation of complexes **11** (mp 169-172°C, dec) and **ent-11** (mp 190-192°C, dec) prepared by the general method previously reported[12] (Scheme 2). Reaction of **ent-11** with benzhydryl bromide gave a mixture (78:22) of **ent-2** (mp 127-128°C) and **ent-3** (mp 170-171°C) which was resolved chromatographically

(Scheme 2).[16] Compound **ent-2** was converted into (*R*)-**5** (mp 186-187°C; $[\alpha]_D$ = - 60.0 (MeOH, c = 1.00), lit[4] $[\alpha]_D$ = - 63.7 (MeOH, c = 1.0), lit[5] $[\alpha]_D$ = - 61.0 (MeOH, c = 0.4)) as above for its enantioisomer.



a.- i: NaH, THF, rt; ii: $[CoBr_4]^{2-}$ $2[PhCH_2NMe_3]^+$
b.- i: [Co]=0.8M, Ph_2CHBr, $HCCl_3$, 50°; ii: chromatography
c.- NaN_3, H_2SO_4, DME, -30° to rt.
d.- i: LiOH, THF-H_2O; ii: Refl 6 N HCl

SCHEME 2



a.- i: Br-1-ADA, $CoCl_2(PPh_3)_2$, $LaBr_3.6\ H_2O$, $HCCl_3$, 140°; ii: chromatography
b.- NaN_3, H_2SO_4, DME, -30° to rt
c.- LiOH-H_2O_2, THF-H_2O
d.- Refl 7 N HCl

SCHEME 3

After some experimentation we found that the alkylation of complex **11** with 1-bromoadamantane gave better results when performed as indicated in Scheme 3. Studies are in course to understand the role of each cocatalyst. After chromatographic separation, diastereoisomers (4*S*,2'*R*), **12**, (mp 89-90°C) and (4*S*,2'*S*), **13**, (mp 161-162°C) were obtained.[17] Schmidt rearrangement[13b] on **12** afforded acetamide **14** (mp 166-167°C) from which **15** (mp 234-240°C) and (*S*)-(1-adamantyl)glycine hydrochloride, (*S*)-**16**, (mp 236-240°C; $[\alpha]_D$ = + 16.0 (MeOH, c = 0.50), lit[6] $[\alpha]_D$ = + 14.0 (MeOH-aq HCl, c = 0.80)) were prepared.

Assignment of absolute configuration to enantioisomers **5** rests upon X-ray diffraction of compound **2** and on the coincidence of $[\alpha]_D$ values with those previously reported. Configurations to fluorenylglycines **10**

were assigned by comparison of the Cotton effects with those of isomers **5** and behaviour reported for similar compounds. Amino acids of the L series (*S* for our compounds in the nomenclature system of Cahn-Ingold-Prelog) having an aromatic chromophore in β position show positive Cotton effect in the region around 220 nm.[18] This is the case for (*S*)-**5** (Δε max. (water, 22.3°C) = + 7.63 (211 nm), + 5.74 (221 nm)). The fluorenylglycine formed from the major acetamide **8** has also positive Cotton effect and therefore formula (**S**)-**10** is assigned to it (Δε max. (water, 22.3°C) = + 1.43 (222 nm), + 3.61 (229 nm)). The *S* configuration is assigned to the obtained (1-adamantyl)glycine by comparison with the $[\alpha]_D$ value reported by Belokon and coworkers.[6] Note finally that our results have internal consistency, always amino acids of *S* configuration being obtained from the major alkylation product obtained from the *S*-oxazolidinone.

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