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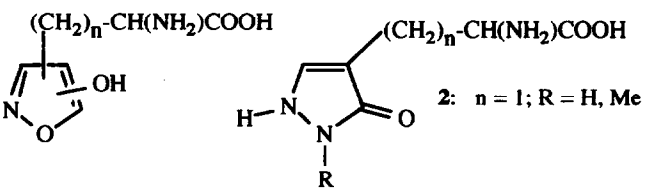
A Radical-Organometallic Glycine Synthon. Preparation of Homochiral Heterocyclic α-Amino Acids

María E. Lloris and Marcial Moreno-Mañas*

Department of Chemistry. Universitat Autònoma de Barcelona. Bellaterra. 08193-Barcelona. Spain

Abstract: $Co(Acac)_2$ reacts with (l) and (d)-menthyl *N*-BOC-2-bromoglycinates to give (l)- and (d)-menthyl *N*-BOC-3-acetylnorvalinates, which are converted into homochiral 2-(3,5-dimethyl-4-pyrazolyl)glycine and 2-(3,5-dimethyl)-4-isoxazolylglycine.

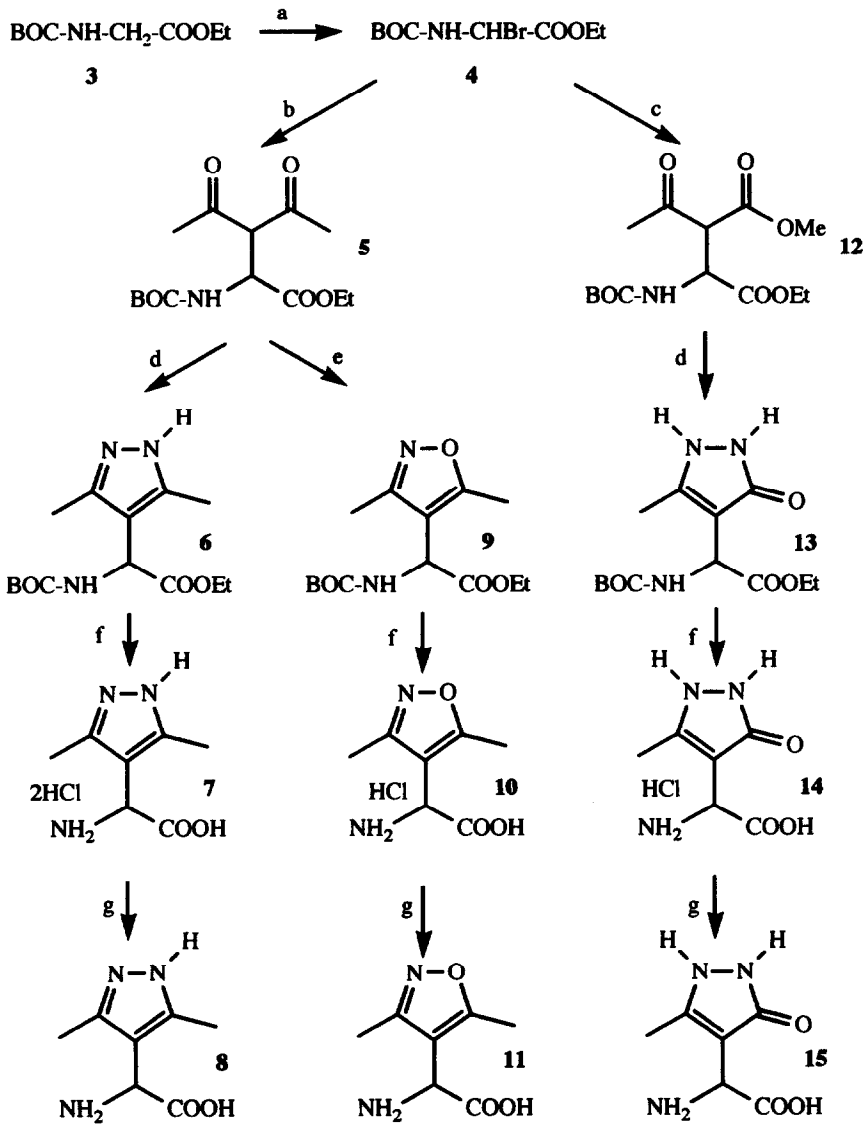
Amino acids[1] bearing 5-hydroxyisoxazole (**1**, n=0,[2a] n=1, [2a,b,c] n=2,[2a,c]), 3-hydroxyisoxazole (**1**, n=0,[3a,b,c] n=1,[3c,d,e,f,g] n=2,[3e] n=3,[3e]) and 5-pyrazolone (**2**[2b]) rings are active in neurotransmission.[4]



We have developed a method for alkylation of β-dicarbonyl compounds based on the reactions of their Co(II)[5] and Cu(II)[6] complexes with alkylating agents, X-R, that are precursors of stabilized free radicals. These reactions require an initiation in which the carbon-based radical, R• is formed[7] and a propagation in which organometallic intermediates (acac)CoXR and $(acac)_2CoR$ (for acetylacetone) play a key role. Therefore, alkyl halides forming stabilized captodative radicals[8] ought to be good alkylating agents.[7b]

Glycine derivatives both electrophilic and nucleophilic at the central carbon atom are broadly used for amino acids preparation.[1] However, radical synthons in the form of α-halogenoglycine derivatives, precursors of captodative radicals, have been seldom used.[9,10] As far as we know no organometallic synthons of glycine have been used in the preparation of open chain amino acids.

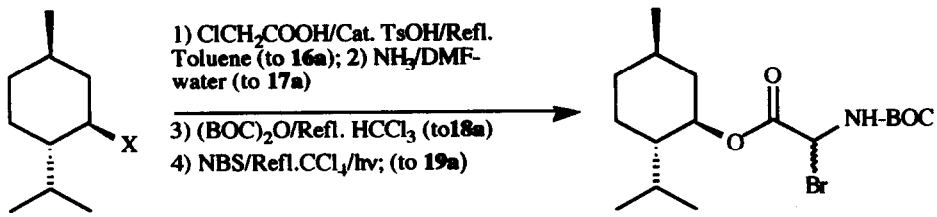
We report here the use of 2-bromoglycine derivatives as a source of radical and organometallic species in the preparation of amino acids by reaction with Co(II) complexes of β-dicarbonyl compounds. Thus, ethyl 2-bromo-*N*-t-BOCglycinate, **4**[11] was reacted with cobalt(II) bis(pentane-2,4-dionate) to afford ethyl *N*-t-BOC-3-acetyl-4-oxonorvalinate, **5** (57%, mp 70-71°C) (Scheme I). Reactions of **5** with hydrazine and with hydroxylamine afforded respectively ethyl *N*-t-BOC-2-(3,5-dimethyl-4-pyrazolyl)glycinate, **6** (95%, foam) and ethyl *N*-t-BOC-2-(3,5-dimethyl-4-isoxazolyl)glycinate, **9** (98%, mp 90-93°C). Deprotections of **6** and **9** by refluxing in 6N HCl gave 2-(3,5-dimethyl-4-pyrazolyl)glycine dihydrochloride, **7** (94%, mp >180°C (dec)) and 2-(3,5-dimethyl-4-isoxazolyl)glycine hydrochloride, **10** (86%, mp 187-188°C). The free aminoacids **8** (mp 244-245°C) and **11** (mp 229-231°C) were prepared in 86 and 87% yield by treating the hydrochlorides with propylene oxide in ethanol. Similarly, treatment of **4** with the cobalt(II) complex of methyl acetoacetate afforded ethyl *N*-t-BOC-3-methoxycarbonyl-4-oxonorvalinate, **12** (53%, oil). Reaction of **12** with hydrazine gave ethyl *N*-t-BOC-2-(3-methyl-5-oxo-3-pyrazolin-4-yl)glycinate, **13** (40%, mp 175-176°C) that upon



a.- NBS, refl. CCl_4, hv; b.- $Co(acac)_2$, $HCCl_3$; c.- $Co(CH_3COCHCOOMe)_2$, $HCCl_3$
d.- $NH_2NH_2 \cdot H_2SO_4$, $NaHCO_3$, refl. EtOH; e.- $NH_2OH \cdot HCl$, $NaHCO_3$, refl. EtOH;
f.- Refl. 6N HCl; g.- Propylene oxide, EtOH, rt.

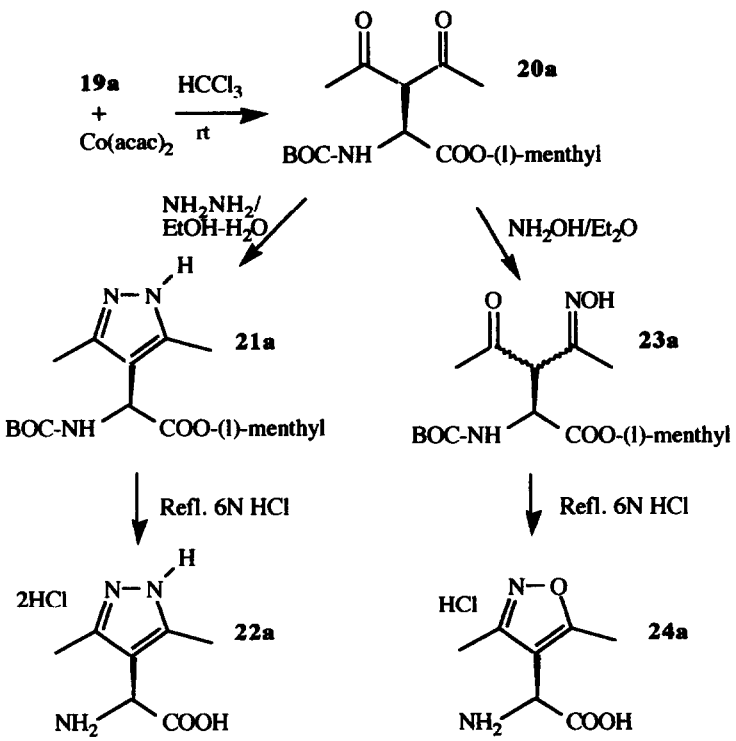
SCHEME I

refluxing in 6N HCl gave 2-(3-methyl-5-oxo-3-pyrazolin-4-yl)glycine hydrochloride, **14** (92%, mp 214-216°C). The free aminoacid **15** [71%, mp >200°C (dec)] was prepared by treating **14** with propylene oxide.



X = OH, (l)-menthol; $OCOCH_2Cl$, **16a**; $OCOCH_2NH_2$, **17a** $OCOCH_2NH$-BOC, **18a**.

19a



SCHEME II

The chiral version is shown in Scheme II. Thus (*l*)-(1*R*,3*R*,4*S*)-menthol was converted into (1*R*,3*R*,4*S*)-menthyl 2-bromo-*N*-*t*-BOC-glycinate, **19a**, which was reacted with cobalt(II) bis(pentane-2,4-dionate) to afford both diastereoisomers of constitution (1*R*,3*R*,4*S*)-menthyl *N*-t-BOC-3-acetyl-4-oxonorvaline, **20** (60%) in a ratio 70:30. The major one crystallized; it was (1*R*,3*R*,4*S*)-menthyl (2*S*)-*N*-t-BOC-3-acetyl-4-oxonorvaline, **20a** (25%, mp 115.5-116.5°C from dichloromethane-hexane, $[\alpha]_D$ = -9.9° (c 1.01, $HCCl_3$)). Its reaction with hydrazine afforded (1*R*,3*R*,4*S*)-menthyl (2*S*)-*N*-*t*-BOC-2-(3,5-dimethyl-4-

pyrazolyl)glycinate, **21a** (mp 62-65°C, $[\alpha]_D$ = +36.1° (c 1.00, $HCCl_3$)) that by refluxing in 6N HCl gave (2*S*)-2-(3,5-dimethyl-4-pyrazolyl)glycine dihydrochloride, **22a** [97%, mp >180°C(dec), $[\alpha]_D$ = +51.9 (c 1.02, water)]. The reaction of **20a** with hydroxylamine gave the monooxime **23a** (94%, crude form, undetermined stereochemistry at C-3) instead of the related isoxazole as had occured in the racemic series. However, cyclization and deprotection was achieved by treating with 6N HCl to yield (2*S*)-2-(3,5-dimethyl-4-isoxazolyl)glycine hydrochloride, **24a** [93%, mp 189-191°C, $[\alpha]_D$ = +58.1 (c 1.05, water)].

The reactions of Scheme II were repeated starting from (*d*)-(1*S*,3*S*,4R)-menthol. Thus, aminoacids **22b** and **24b**, enantioisomers of **22a** and **24a**, were prepared through compounds **16b-21b** and **23b**. Compounds **16b-24b** showed the same spectroscopic properties and mp as compounds **16a-24a** and opposite optical activities.

Arylglycines and related amino acids showing positive Cotton effect pertain to the *S* series and those exhibiting negative Cotton effect pertain to the *R* series.[12] Compounds **22a** and **24a** show positive Cotton effect and *S* configuration is therefore assigned to them whereas *R* configuration is assigned to **22b** and **24b**.

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