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New building blocks for peptide and depsipeptide synthesis: hexafluoroacetone protected L-homoisoserine and D,L-homoisocysteine derivatives☆

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Dedicated to Professor Dr. Lothar Beyer on the occasion of his 65th birthday

Abstract—Efficient syntheses of L-homoisoserine and D,L-homoisocysteine derivatives starting from L-malic and D,L-thiomalic acid using hexafluoroacetone as protecting and activating agent are described. The new compounds are interesting building blocks for the preparation of non-natural peptides and depsipeptides as well as for the construction of new GABA derivatives. © 2003 Elsevier Science Ltd. All rights reserved.

Homoisoserine (2-hydroxy-4-aminobutyric acid) is a constituent of numerous antibiotics, like arbekacin,[2] amikacin[3] and butirosin.[4] Furthermore, it was identified as subunit of phytosiderophores, e.g. in distichonic, avenic and mugineic acid. Phytosiderophores are responsible for iron up-take and iron-transport in plants like wheat and oats.[5] Homoisoserine acts as inhibitor for GABA up-take and exhibits antitumor activity.[6] Therefore, numerous syntheses have been developed, starting from 4-amino-2-oxobutyric acid,[7] *Z*-β-alanine,[6] isoxazolidin-5-carboxylate,[8] malic acid amide,[9] L-2,4-diamino-butyric acid,[10] and 2-pyrrolidone.[11]

In contrast, homoisocysteine (2-mercapto-4-aminobutyric acid) has not been found in nature, to the best of our knowledge. Although, the first publication on homoisocysteine appeared already in 1963,[12] there is no information available about its chemistry.

Recently, we demonstrated that a new protection/activation concept, developed for regioselective functionalization of multifunctional α-amino acids like aspartic acid,[13] can also be applied to α-hydroxy-α,ω-dicarboxylates[14] and their thioanalogues.[15] The syntheses of L-isoserine[16] and D,L-isocysteine[17] represent the first examples of the application of this new synthetic approach to multifunctional α-hydroxy and α-mercapto acids. We now report on the synthesis of L-homoisoserine and D,L-homoisocysteine derivatives and their incorporation into peptidomimetics using hexafluoroacetone as protecting and activating agent.

α-Hydroxy and α-mercapto acids react with hexafluoroacetone in dimethyl sulfoxide at room temperature to give 2,2-bis(trifluoromethyl)-1,3-dioxolan-4-ones (**3**)[18] and 2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones (**4**),[15] in excellent yields (85–90%). In one step, protection of the α-hydroxy and the α-mercapto as well as the adjacent carboxy group can be achieved. Concomitantly, the α-carboxy group is activated toward nucleophiles and can be regioselectively functionalized.[14] A variety of functional groups in the side-chain are tolerated, e.g. an ω-carboxy group remains unaffected and can be selectively activated and derivatized in a consecutive step. On heating with an excess of thionyl chloride compounds **3** and **4** are converted into acid chlorides **5** and **6** in high yields (80–85%). Compounds **5** and **6** are dielectrophiles, and the ω-function is more reactive than the α one (Scheme 1).

Compounds **5** and **6** exhibit the typical reaction pattern of acid chlorides. Diazoketones **7** and **8** are formed in very good yields (90%) on treatment with an excess of

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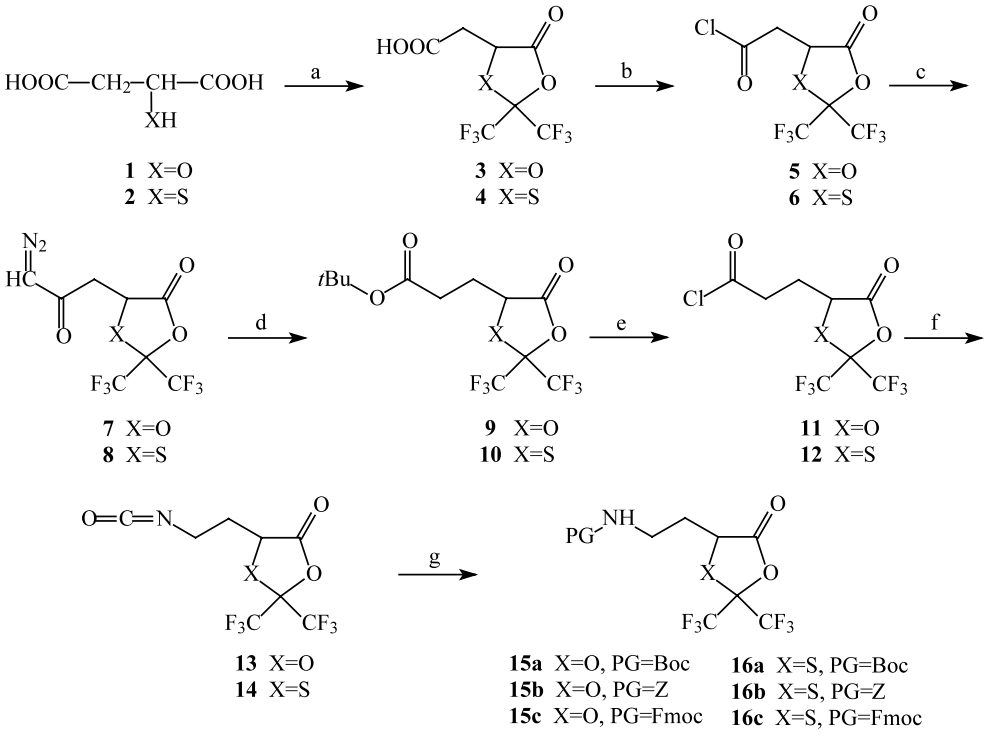


Scheme 1. *Reagents and conditions*: (a) HFA/DMSO/rt; (b) $SOCl_2$/reflux/4 h; (c) >2 equiv. CH_2N_2/Et_2O/−78°C to rt/12 h; (d) *t*BuOH/reflux/$PhCO_2Ag$/X = O: 10 min, X = S: 2 h; (e) $SOCl_2$/reflux/4 h; (f) 1.1 equiv. TMS–N_3/toluene/80–90°C/24 h; (g) 1.1 equiv. ROH/$CHCl_3$/reflux/12 h.

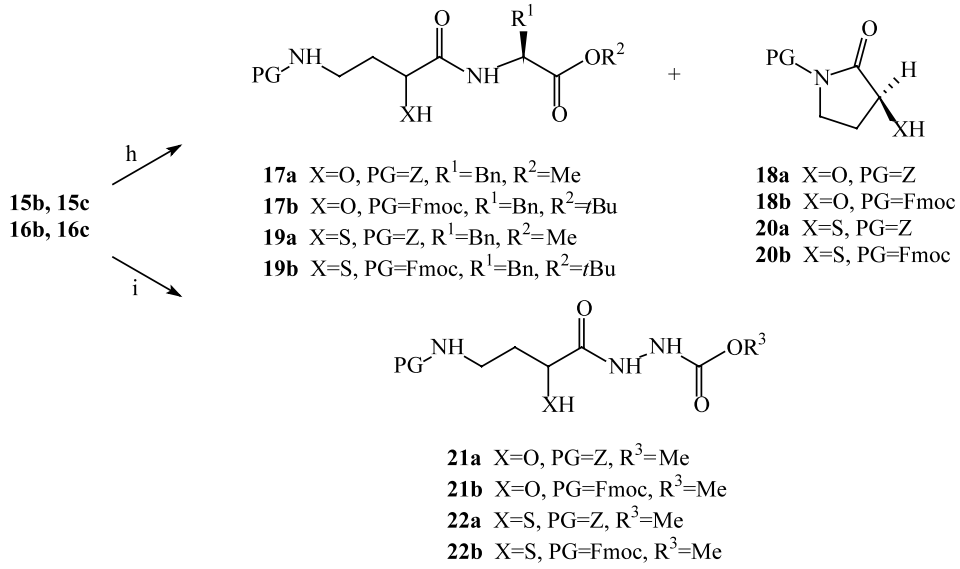
diazomethane (>2 equiv.:1 equiv. is necessary for trapping the HCl formed during the reaction), which can be easily purified by column chromatography (eluent: DCM). Wolff rearrangement[19] was accomplished on heating of compounds **7** and **8** in dry *tert*-butanol in the presence of catalytic amounts of silver benzoate. The ketene formed first is trapped by *tert*-butanol. The *tert*-butyl esters (**9**, **10**) are directly transformed into acid chlorides (**11**, **12**) on heating with thionyl chloride. Alternatively, chain elongation can be achieved, however in lower yields, via Photo–Wolff rearrangement in aqueous dioxane to give the corresponding α-hydroxy and α-mercapto glutaric acid derivatives, which are directly subjected to treatment with thionyl chloride to form acid chlorides **11** and **12**, which can be purified by distillation in vacuo. For the introduction of the γ-amino group, acyl azides are synthesized on reaction with trimethylsilyl azide, which are subjected to a Curtius rearrangement[20] to give the isocyanates **13** and **14** on heating. Compounds **13** and **14** are dielectrophiles. As expected, the isocyanate moiety is the more reactive center towards nucleophiles. This strategy offers an elegant and efficient route for regioselective functionalization of trifunctional compounds with a minimum of steps.

Recently, we demonstrated that a homologue of **13**-(5*S*)-2,2-bis(trifluoromethyl)-4-oxo-1,3-dioxolan-5-yl]-methyl isocyanate[16] is an excellent reagent for photoaffinity labeling experiments.[21]

Introduction of orthogonal protection groups can be accomplished on heating isocyanates **13** and **14** with alcohols. Treatment with *tert*-butanol, benzyl alcohol and 9-fluorenylmethanol provides access to *N*-Boc-, *N*-*Z*- and *N*-Fmoc-protected 4-amino-2-hydroxybutyric acid and 4-amino-2-mercaptobutyric acid derivatives (**15**, **16**), which represent -XH-protected (X = O, S) and carboxy group activated species. They are stabile compounds and can be stored for months in a fridge on exclusion of moisture (Scheme 2).

Compounds **15** and **16** are ready for direct application in peptide synthesis. On reaction with amino acid derivatives (α-amino acid, β-amino acid and γ-amino acid esters, amides and hydrazides) dipeptides of type **17**,**19** and azapeptides of type **21**,**22** become readily accessible. They represent a class of dipeptide derivatives which are interesting per se, since they are GABA derivatives. Furthermore, they represent new building blocks for peptide and depsipeptide modification. Remarkably, peptide bond formation and deblocking of the α-functionality occur in one-step. The reaction sequence is suitable for the generation of libraries of peptidomimetics.

3-Hydroxy-2-pyrrolidinones **18** can be isolated as minor by-products (up to 10%) of the aminolytic ring opening of **15a–c**. They are the result of a base-induced intramolecular cyclocondensation reaction. The thioderivatives should be handled under inert gas atmo-



Scheme 2. *Reagents and conditions:* (h) 1.2 equiv. HCl×H-Phe-OR^2/DMF/1.2 equiv. NMM/12 h; (i) 1.2 equiv. $H_2NNHCO_2R^3$/DMF/12 h.

sphere to avoid oxidation of the mercapto group. Compounds containing the mercapto or mercaptoacyl moiety often exhibit strong inhibitory effects on metal-containing enzymes (metallozymes),[22] similar to hydroxamic acids.[23]

A growing number of reports focus on structured peptidomimetic compounds built from two or more different types of monomers (peptide hybrids).[24] The use of ω-amino acids in peptide design is a newly emerging area of current research.[25] This is mainly due to the ability of these amino acids to modify the geometry of the peptide backbone,[25d] providing proteolytic resistance to bioactive peptide sequences.[26] Insertion of one or more extra carbon atoms into intramolecular hydrogen bonded, folded structures leads to the creation of unusual turns and novel helical folds.[27,28]

In the case of L-malic acid we proved that all steps of the reaction sequence occur stereoconservatively (NMR analysis).

On further applications of hexafluoroacetone-protected α-functionalized and α,α-difunctionalized β- and γ-amino acids in peptide, depsipeptide and glycopeptide synthesis we report elsewhere.

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