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Synthesis of chiral α-(tetrazol-1-yl)-substituted carboxylic acids

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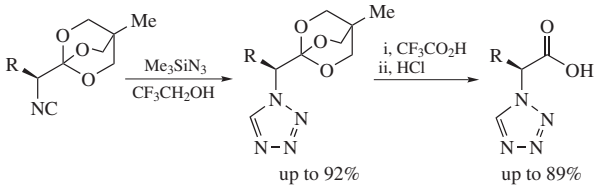
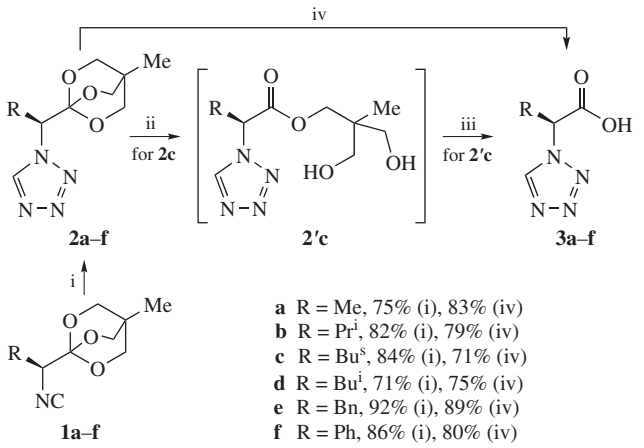
Optically active α-(tetrazol-1-yl)-substituted carboxylic acid OBO-esters were synthesized from the corresponding α-isocyano OBO-esters and trimethylsilyl azide in up to 92% yield. Subsequent acidic hydrolysis proceeds without epimerization and makes it possible to prepare enantiomerically pure α-(tetrazol-1-yl)-substituted carboxylic acids in up to 89% yield.



The development of tetrazole chemistry is related to a wide application of tetrazoles in various fields of modern medicinal chemistry.[1] 1,5-Disubstituted tetrazoles are bioisosteres of the *cis*-amide group, however, they possess higher metabolic stability.[2] Synthetic strategies based on the replacement of carboxylate groups by tetrazole moiety in biologically active molecules are of special interest in modern pharmaceutical industry. The ability of tetrazoles to participate in the formation of stable complexes with cations of different metals has also found broad applications.[3,4]

This article describes the synthesis of chiral α-(tetrazol-1-yl)-substituted carboxylic acids which are very attractive small molecules.[5] These compounds are interesting building blocks to construct other tetrazole-containing molecules and can also be used as chiral bidentate ligands for coordination chemistry. The reaction between isocyanides and hydrazoic acid (HN_3) is a valuable method to prepare 1-substituted tetrazoles.[6] We used enantiomerically pure 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (OBO)-esters of α-isocyano carboxylic acids as chiral starting materials due to their stability towards epimerization.[7] Whereas alkyl esters of these acids are prone to racemize in the presence of even weak bases, ortho esters, in particular convenient bicyclic OBO ones of type **1** (Scheme 1), do not contain mobile hydrogen atom and are base-resistant,[8] which made them useful in our recent studies as well.[9] Despite the apparent simplicity of chosen approach, application of dangerous HN_3 is required.[10] We decided to use trimethylsilyl azide as a safe source of hydrazoic acid.[11] To find optimal conditions for this reaction, (*S*)-phenylalanine derived OBO-isocyanide **1e** was chosen as a model reactant. Various solvents (MeOH, EtOH, Pr^iOH, CF_3CH_2OH), acidic catalysts ($ZnCl_2$, HCl–MeOH, HCl–H_2O) were tested. Compound **2e** was not found in the reaction mixture when acidic catalysis was tried. The influence of temperature and reagent ratio on the yield of **2e** was also investigated. The reaction in alkanols (except for trifluoroethanol) even with a large excess of $TMSN_3$ proceeded very slowly, and yields of **2e** did not exceed 20% within one week. Extremely low reaction rate was also observed at room temperature. However, the reaction at 70 °C in CF_3CH_2OH as a solvent led to the target product **2e** in high yield (92%). Most probably high effectiveness of trifluoroethanol can be explained by its greater acidity (pK_a = 12.4) in comparison with other alcohols. In this manner, various 1-substituted tetrazoles **2a–f** were prepared in high yields within reasonable reaction time (see Scheme 1, step i) and readily isolated by flash chromatography.

Next, libertation of tetrazol acids **3** by deprotection of OBO-esters **2** was studied. Standard removal of OBO group can be performed in two steps (see Scheme 1, steps ii and iii): acidic hydrolysis to obtain the corresponding diol ester followed by basic saponification. To optimize such a transformation, isoleucine OBO-ester derivative **2c** was chosen as a model compound since it contains additional stereo center resistant to the deprotection conditions. We found that on using the standard procedure (trifluoroacetic acid–dioxane followed by treatment with 2 M NaOH solution) product **3c** was isolated in good yield. However, its ^{1}H NMR spectrum contained two sets of signals of two diastereomers to indicate total epimerization of the sample in the presence of sodium hydroxide. Therefore, we decided to try acidic removal of the OBO-group. Reflux of compound **2c** in 6 M HCl resulted in formation of complex reaction mixture. To our delight, treatment of OBO-tetrazole **2c** with trifluoroacetic acid in dioxane for 1–2 h followed by heating the mixture at 90 °C in 6 M HCl for 20 h gave the target compound **3c** in 71% yield. Luckily, no epimerization occurred and the product



a R = Me, 75% (i), 83% (iv)
b R = Pr^i, 82% (i), 79% (iv)
c R = Bu^s, 84% (i), 71% (iv)
d R = Bu^i, 71% (i), 75% (iv)
e R = Bn, 92% (i), 89% (iv)
f R = Ph, 86% (i), 80% (iv)

Scheme 1 *Reagents and conditions:* i, Me_3SiN_3, CF_3CH_2OH, 70 °C, 1–2 days; ii, CF_3CO_2H, dioxane; iii, 2 M aq. NaOH, then H_3O^+; iv, CF_3CO_2H, dioxane, H_2O, 1 day, then HCl, 90 °C, 1 day.

was a single diastereomer. This procedure was extended towards preparation of the set of enantiomerically pure tetrazolyl-substituted carboxylic acids **3a**–**f** (see Scheme 1, step iv).

In conclusion, the reaction of chiral OBO isocyano derivatives **1** with azidotrimethylsilane was investigated. Trifluoroethanol was found the solvent of choice affecting the cycloaddition to afford the target tetrazoles in up to 92% yield. Subsequent acidic hydrolysis (TFA–HCl) leads to chiral α-(tetrazol-1-yl)-substituted carboxylic acids in up to 89% yield.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.007.

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