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NOTE

Reaction of (iodomethyl)tin(IV) compounds with (2*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine

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Abstract: Following the Schöllkopf methodology, the reaction of (2*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine **1** with (iodomethyl)trimethylstannane gives (2*S*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-[(trimethylstannyl)methyl]pyrazine **2** in good yields. The obtained compound was characterized by elemental analysis and multinuclear (^{1}H, ^{13}C and ^{119}Sn)-NMR spectroscopy.

Keywords: Schöllkopf reaction; 2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine; stannylmethylation; NMR-spectroscopy.

INTRODUCTION

Among the synthetic methods for the preparation of optically active amino acids, compounds that contain a structural element producing a high asymmetric induction in the alkylation step and that can be separated after the reaction are the most important.[1,2] One of them is the Schöllkopf bis-lactim ether methodology,[3] which has proved to be of enormous utility in the preparation of a wide range of α-substituted and α,α-disubstituted amino acids in both enantiomeric forms. The most popular and extensively studied bis-lactim ether is 2,5-dihydro -2-isopropyl-3,6-dimethoxy-pyrazine **1**, which is derived from valine and glycine and is commercially available in both enantiopure (*R*)- and (*S*)-forms. The metalation of the bis-lactim ether with *n*-butyllithium in THF at a low temperature followed by alkylation with an electrophile proceeds with a high degree of stereoselectivity. The electrophile reacts at the side opposite to the alkyl group at the 2-position of the pyrazine ring.

The Schöllkopf method is widely used for the synthesis of (*R*)- and (*S*)-enantiomers of unnatural amino acids, such as β-(trimethylsilyl)alanine and β-(trimethylgermyl)alanine,[4–6] which due to their C/Si/Ge bioisosterism are of interest as

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precursors of drugs and plant-protective agents. For example, *β*-(trimethylsilyl)-alanine derivatives are used as renin inhibitiors.[7]

Stannylated alanine derivatives of the type $R_3SnCH_2CH(NHCOR')COOR''$ were previously synthesized using different procedures[8–10] but, in all cases, the products were mixtures of stereoisomers. However, the stereoselective reaction of (iodomethyl)tin(IV) compounds with (*S)*-1-(*t*-butoxycarbonyl)-2-*t*-butyl-3-methyl-4-imidazolidinone (Boc-BMI) yielded a pure product, (2*S*,5*R*)-*t*-butyl,2-t-butyl-3-methyl-4-oxo-5-[(trimethylstannyl)-methyl]-1imidaazolidine-carboxylate of high stereoselectivity.[11]

Therefore, it seemed of interest to investigate stereoselectively produced C-stannylated amino acids based on the Schöllkopf procedure. Herein, the reaction of (iodomethyl)trimethylstannane with (2*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine **1** is described.

EXPERIMENTAL

Materials and methods

All operations were performed under dry nitrogen. THF of analytical purity was dried over Na/benzophenone prior to use. (2*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-pyrazine was purchased from Merck. (Iodomethyl)trimethylstannane was obtained as described previously.[12] The elemental microanalyses were realized using a Carlo Erba Elemental Analyzer. All the NMR spectra were recorded in $CDCl_3$ solution by means of a Bruker AC 80, WP 200 or a Varian Unity 500 spectrometer.

*Synthesis of (2S,5S)-2,5-dihydro-2isopropyl-3,6-dimethoxy-5-[(trimethylstannyl)-lmethyl]pyrazine (**2**)*

An equimolar amount of butyl-lithium in hexane (15 mmol, 16.7 ml of a 0.9 M solution in hexane) was added to a stirred solution of (2*S*)-2,5-dihydro -2-isopropyl-3,6-dimethoxy-pyrazine (**1**) (2.5 ml, 13.9 mmol) in dry THF (10 ml) at –70 °C. After stirring for 10 min, a precooled solution (–70 °C) of (iodomethyl)trimethylstannane (4.24 g, 13.9 mmol) in dry THF (10 ml) was added dropwise. After stirring at –70 °C for about 24 h, the reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure, the residue treated with diethyl ether and then extracted with 20 ml water. The aqueous phase was extracted three times with diethyl ether (10 ml). The ether phases were combined and dried over $MgSO_4$. The solvent was removed after filtration and the crude yellow oil was chromatographically separated over silica gel (Merck Kieselgel 60; solvent ligroin:ether 3:1). *Rf*: 0.83 (ligroin/ether 3:1).

RESULTS

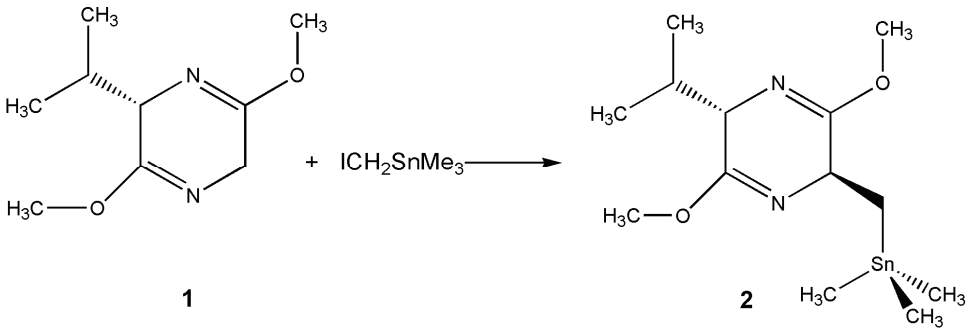
*Analytic and spectral data of the obtained compound **2***

Yield: 60 %; Anal. Calcd. for $C_{13}H_{26}N_2O_2Sn$: C, 43.25; H, 7.26; N, 7.76 %. Found: C, 43.27, H, 7.42, N, 7.81 %; ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C, δ / ppm): 0.05 (9H, *s*, ^2J (^{119}Sn, C^{1}H) = 54.0 Hz, $SnMe_3$), 0.66 (3H, *d*, ^3J = 7.0 Hz, $CH(C\mathbf{H}_3)_2$), 1.00 (3H, *d*, ^3J = 7.0 Hz, $CH(C\mathbf{H}_3)_2$), 1.13 (1H, *dd*, ^2J (H_A, H_B) = = –12.77 Hz, ^3J (H_A, H-5) = 9.22 Hz, $SnCH_A$), 1.42 (1H, *dd*, ^2J (H_B, H_A) =

= –12.77 Hz, ^3J (H_B, H-5) = 5.96 Hz, $SnCH_B$), 2.17–2.25 (1H, *m*, C**H**$(CH_3)_2$), 3.62 (3H, *s*, OCH_3), 3.65 (3H, *s*, OCH_3), 3.92 (1H, *t*, ^5J (C^2H, H-5) = 3.55 Hz, H-2), 4.03–4.13 (1H, *sept*, ^3J (^{119}Sn, C^1H) = 55.0 Hz, ^3J ($SnCH_A$, H-5) = 9.22 Hz, ^3J ($SnCH_B$, H-5) = 5.96 Hz, ^5J (H-2, H-5) = 3.55 Hz, H-5); ^{13}C-NMR (125.7 MHz, $CDCl_3$, 30 °C, δ / ppm): –9.17 (^1J (^{119}Sn, ^{13}C) = 334.3 Hz, $Sn(CH_3)_3$), 16.7 ($CH(\mathbf{C}H_3)_2$), 19.0 ($CH(\mathbf{C}H_3)_2$), 19.25 (^1J (^{119}Sn, ^{13}C) = 368.9 Hz, $SnCH_2$), 31.8 ($\mathbf{C}(CH_3)_2$), 52.27 (OCH_3), 52.29 (OCH_3), 54.2 (^2J (^{119}Sn, ^{13}C) = 21.9 Hz, C-5), 61.1 (C-2), 162.97 (C-3), 165.59 (^3J (^{119}Sn ^{13}C) = 18.5 Hz, C-6); ^{119}Sn--NMR ($CDCl_3$, ^{1}H decoupled, internal standard $(CH_3)_4Sn$, δ / ppm): –6.3.

DISCUSSION

Following the standard reaction conditions (Experimental part), 2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-[(trimethylstannyl)methyl]pyrazine was formed in 60 % yield (Scheme 1). Analysis of the crude reaction mixture by ^{119}Sn-NMR spectroscopy revealed the presence of two signals at –6.3 and –5.6 ppm in a ratio of 10:1, corresponding to the (2*S*,5*S*)- and the (2*S*,5*R*)-derivatives, **2** and **3**, respectively; both identified by ^{1}H-NMR spectroscopy of the raw product.



Scheme 1. Reaction of (2*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine **1** with (iodomethyl)trimethylstannane.

The mixture was separated by column chromatography on silica gel yielding **2** as diastereomerically pure and colorless oil soluble in common organic solvents such as diethyl ether, chloroform and methanol. Attempts to prepare the stannylated alanine by hydrolysis of **2**, analogously to the preparation of *β*-(trimethylsilyl)alanine ethyl ester,[4] failed. Under the acidic reaction conditions, Sn–C bond cleavage was observed. Compound **2** was studied in detail by multinuclear NMR spectroscopy. The δ^{119}Sn at –6.3 ppm is situated in the region for tetramethyl tin compounds,[13] indicating tetra coordination at the tin atom. The non-equivalence of both protons of the $SnCH_2$ group in the neighbourhood of the C^5H proton leads to an AMX spin system in which the X-part becomes still more complicated because of the higher order coupling to the homoallylic standing C^2H proton atom. This long range coupling constant through five bonds was used

to determine the orientation of the protons at C^2 and C^5, and to serve thereby for differentiation of the diastereomers. The determination of the configuration of the diastereomer **2** was based on the specific ^5J coupling constants in the ^{1}H-NMR spectra, which corresponds very well with literature data.[14] The configuration of **2** can also be explained based on the accepted model for the alkylation reactions of the Schöllkopf reagent,[3] verified by a large number of examples.

CONCLUSIONS

Following the Schöllkopf methodology, the reaction of (2*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine **1** with (iodomethyl)trimethylstannane gives (2*S*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-[(trimethylstannyl)methyl]pyrazine **2** in good yields. Compound **2** was studied in detail by multinuclear NMR spectroscopy. The determination of the configuration of **2** was based on the specific ^5J coupling constants between protons at C^2 and C^5, which correspond very well with literature data.[14] The configuration can also be explained based on the accepted model for the alkylation reaction of the Schöllkopf reagent.[3]

ИЗВОД

РЕАКЦИЈА ЈЕДИЊЕЊА (ЈОДМЕТИЛ)КАЛАЈА(IV) И (2*S*)-2,5-ДИХИДРО-2--ИЗОПРОПИЛ-3,6-ДИМЕТОКСИ-ПИРАЗИНА

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Пратећи методологију Schöllkopf-a реакцијом (2*S*)-2,5-дихидро-2-изопропил-3,6-диметокси-пиразина **1** и (јодметил)триметилстанана добијен је (2*S*,5*S*)-2,5-дихидро-2-изопропил-3,6-диметокси-5-[(триметилстанил)метил]пиразин **2** у добром приносу. Производ је окарактерисан елементалном анализом и (^{1}H, ^{13}C и ^{119}Sn)-NMR спектроскопијом.

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