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IODODESTANNYLATION: AN IMPROVED SYNTHESIS OF [^{125}I]IODOPROXYFAN, A SPECIFIC RADIOLIGAND OF THE HISTAMINE H_3 RECEPTOR

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Summary

[^{125}I]Iodoproxyfan, a specific radioligand of histamine H_3 receptors, was synthesized in 60% yield under very mild conditions from a tributylstannyl precursor. The arylstannane, which was obtained in a palladium-catalyzed reaction of arylbromide and hexabutylditin, smoothly underwent radioiodination with [^{125}I]sodium iodide and chloramine-T to give tritylated [^{125}I]iodoproxyfan. Final detritylation was achieved with formic acid 90% at room temperature. Compared to the original copper(I)-mediated halogen exchange this procedure has major advantages in terms of cost and ease of use.

Key Words: Iodine-125, iododestannylation, [^{125}I]iodoproxyfan, histamine H_3 receptor antagonist.

Introduction

Cerebral histamine H_3 receptors modulate not only histamine synthesis and release but also the release of several other important neurotransmitters [1] and are thus supposed to play a key role in the general regulation of neurotransmission in brain [2]. As H_3 receptors appear less abundant than other aminergic receptors, [^{125}I]iodinated radioligands allow a more sensitive detection than tritiated ones [3,4]. Because of its high selectivity and *in vitro* affinity to histamine H_3 receptors the *para*-iodinated benzylic ether derivative of 3-(1*H*-imidazol-4-yl)propanol, named iodoproxyfan (1), was recently selected for radiolabeling from a series of aliphatic and aromatic imidazolylalkyl ethers [5]. In a binding assay using (*R*)-α-[^{3}H]methylhistamine at H_3 receptors from rat brain membranes, 1 exhibited a particular $-\log K_i$ value of 9.0 and thus appeared to be a reliable probe for autoradiographic visualization of cerebral histamine H_3 receptors [3].

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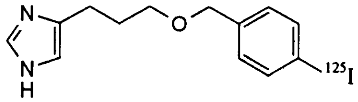
The original synthesis of 1 in its radioiodinated form was achieved by copper(I)-mediated halogen exchange of the corresponding bromo precursor 6 with [^{125}I]sodium iodide, but unfortunately this procedure required high temperatures of 120 °C for 45 min [5]. Accordingly the need for security against radioactivity increased, and the cost of the radioligand 1 went up. Therefore a more economical route was required that could be carried out efficiently at ambient temperature.



[^{125}I]Iodoproxyfan (1)

The synthesis of radiochemicals has been improved in recent years using organometallics as key intermediates, and by preference group 14 metals have been applied extensively. In particular, organostannanes appeared to be most suitable [6] because they are more reactive than silanes and more affordable than germanes [7]. It has thus been the main goal of the present study to synthesize 1 via iododestannylation (Chart).

Results and Discussion

The tritylated 4-bromobenzyl imidazolylpropyl ether 5 was obtained either by borontrifluoride-catalyzed alkylation of imidazolylpropanol (2) with 4-bromobenzyl trichloroacetimidate (3) [8] or by classical Williamson reaction with 4-bromobenzylchloride (4) [5]. Each method afforded a 60% yield of the tritylated 4-bromobenzyl ether 5, which was then conveniently converted to the corresponding tributyltin analogue 7 in a palladium-catalyzed reaction with hexabutylditin using tetrakis(triphenylphosphine)palladium as catalyst in refluxing dioxane [9].

The stable arylstannane 7 turned out to be an appropriate precursor for the following electrophilic iodination which was smoothly achieved with [^{125}I]sodium iodide and chloramine-T at room temperature to give tritylated [^{125}I]iodoproxyfan 8 in 60% yield [10]. In contrast to standard deprotection in refluxing 2 N HCl, final detritylation of 8 was readily accomplished with formic acid 90% over night at room temperature [11] to provide the title compound 1 in a quantitative yield.

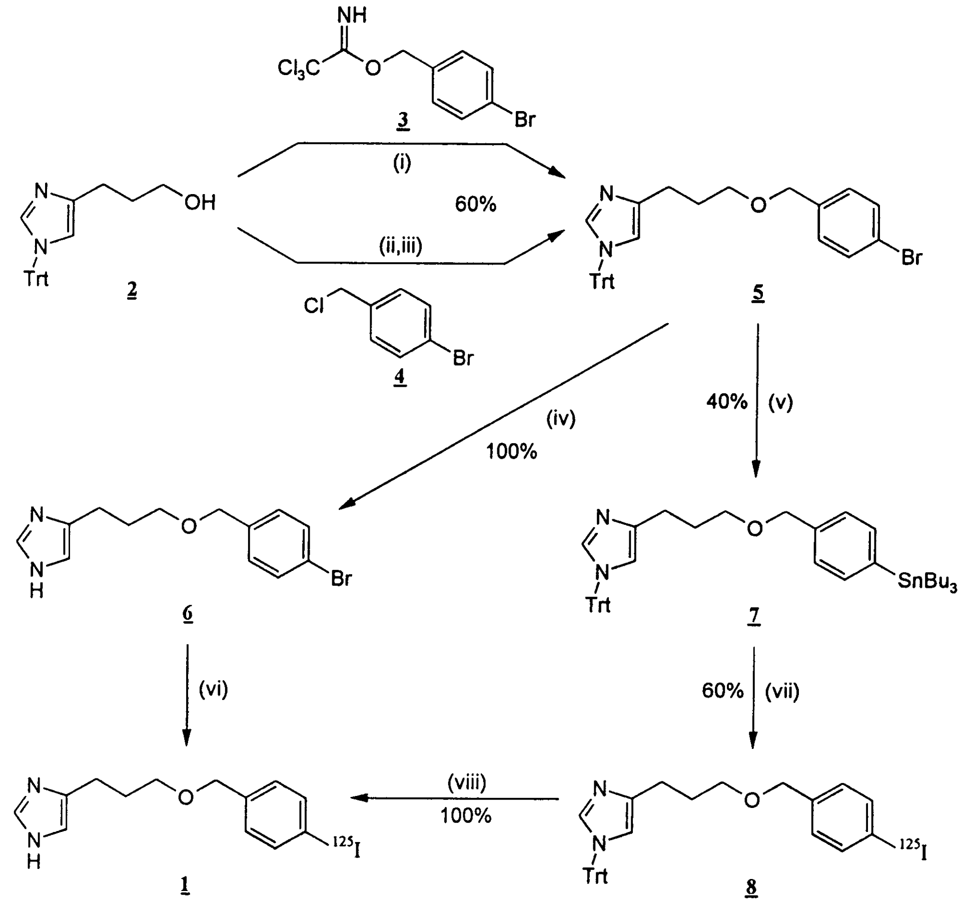


Chart: Synthesis of [^{125}I]Iodoproxyfan (1) via Iododestannylation. Key: (i) $BF_3{\cdot}Et_2O$, cyclohexane, CH_2Cl_2, argon, 70 °C, 18 h; (ii) NaH, toluene, 60–70 °C, 2 h; (iii) TBAI, 15-crown-5, toluene, 80 °C, 24 h; (iv) 2 N HCl, EtOH, 70 °C, 2 h; (v) Sn_2Bu_6, $Pd(PPh_3)_4$, dioxane, argon, reflux, 15 h; (vi) [^{125}I]NaI, $CuSO_4$, $SnSO_4$, 2,5-dihydroxybenzoic acid, citric acid, H_2O, 120 °C, 45 min; (vii) [^{125}I]NaI, H_2O, AcONa, chloramine-T, MeOH, argon, room temperature, 30 min; (viii) HCOOH 90%, room temperature, 24 h.

However, we were not only able to prepare the cold non-radioactive compound in this fashion, but we also found this approach reliable for the production of the radiolabeled compound.

In summary, the synthesis of 1 presented in article has major advantages in terms of cost and ease of use compared to the original copper(I)-mediated halogen exchange, as the critical steps during the radiolabeling procedure could be carried out at ambient temperature.

Experimental

Melting points were determined on an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC 300 (300 MHz) spectrometer using the solvent indicated. Chemical shifts are expressed in ppm downfield from internal Me_4Si as reference. ^{1}H-NMR data are reported in order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; qui, quintet; m, multiplet), number of protons, and approximate coupling constants in Hertz. A Finnigan MATCH/A (EI) and a Finnigan MAT CH5DF mass spectrometer (FAB$^+$) were used, respectively. Elemental analyses (C, H, N) were measured on Perkin-Elmer 240 C instrument and were within ±0.4% of the theoretical values unless otherwise indicated. Analytical TLC was performed on silica gel F_{254} plates (Merck). Preparative column chromatography was carried out using silica gel 63–200 μm (Merck).

(4-Bromophenyl)methyl 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl ether (5)

Method A: A solution of tritylated 2-(1*H*-imidazol-4-yl)propanol (2; 5 mmol, 1.84 g) and *t*-butyl 2,2,2-trichloroacetimidate (3; 10.5 mmol, 2.29 g) in 10 mL C_6H_{12} and 5 mL CH_2Cl_2 was stirred for 18 h at 60–70 °C in an argon atmosphere, on addition of $BF_3{\cdot}Et_2O$ (600 μL) through a septum. Working up involved filtration of the reaction mixture to remove precipitated 2,2,2-trichloroacetamide and removal of the solvent. The resulting oil was finally subjected to column chromatography [eluent: CH_2Cl_2 (90%), MeOH (10%)] to afford an oil (yield, 56%); *Method B*: Synthesis according to ref. [5] (yield, 51%); ^{1}H-NMR ($CDCl_3$) δ 7.50–7.07 (m, 20H, 19 Ph-H, Im-2-H), 6.59 (s, 1H, Im-5-H), 4.39 (s, 2H, Ph-CH_2), 3.48 (t, J = 6.1 Hz, 2H, Im-CH_2-CH_2-CH_2), 2.72 (t, J = 7.4 Hz, 2H, Im-CH_2), 1.91 (m, 2H, Im-CH_2-CH_2); FAB$^+$-MS (Xe, DMSO/glycerol), *m/z* (%) 537 (2) [M + H$^+$], 459 (1), 369 (1), 297 (4), 243 (100) [Trt$^+$], 165 (31), 109 (3), 81 (4); ($C_{32}H_{29}BrN_2O$).

[4-(Tributylstannyl)phenyl]methyl 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl ether (7)

A solution of 5 (1.02 mmol, 0.55 g), $Pd(PPh_3)_4$ (0.05 mmol, 0.06 g), and Sn_2Bu_6 (1.53 mmol, 0.89 g) in 5 mL dry dioxane was refluxed for 15 h in a nitrogen atmosphere. Then the solution was filtered and the filtrate was evaporated to leave an oil which was subjected to column chromatography [eluent: CH_2Cl_2 (50%), EtOAc (50%)] to give an oil (yield, 0.30 g, 40%); ^{1}H-NMR ($CDCl_3$) δ 7.42–7.11 (m, 20H, 19 Ph-H, Im-2-H), 6.54 (s, 1H, Im-5-H), 4.43 (s, 2H, Ph-CH_2), 3.50 (t, J = 6.4 Hz, 2H, Im-CH_2-CH_2-CH_2), 2.69 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.95 (m, 2H, Im-CH_2-CH_2), 1.58–1.00 (m, 18H, 3 Sn-$(CH_2)_3$-Me), 0.90 (qui, J = 7.2 Hz, 9H, 3 Me); FAB$^+$-MS (Xe, DMSO/4-nitrobenzylic alcohol; target: Cu), *m/z* (%) 811 (4) [M + Cu$^+$], 749 (1) [M + H$^+$], 691 (1) [M$^+$ – Bu], 569 (1), 447 (2), 400 (2), 243 (100) [Trt$^+$], 177 (50), 165 (63), 121 (21), 109(7), 91 (21), 81 (4); Anal. ($C_{44}H_{56}N_2OSn$) C: calcd. 70.8, found. 70.7; H: calcd. 7.56, found. 7.83; N calcd. 3.75; found. 3.27.

3-(1*H*-Imidazol-4-yl)propyl (4-iodophenyl)methyl ether (1)

To a solution of 7 (0.15 mmol, 0.55 g) in 1 mL MeOH in an argon atmosphere AcONa (0.3 mmol, 0.3 mL 1 M in MeOH), NaI (0.3 mmol, 0.3 mL 1 M in H_2O), and chloramine-T (0.3 mmol, 0.6 mL 0.5 M in MeOH) were added sequentially. The mixture was stirred for 30 min at ambient temperature and then quenched by adding 1 M aqueous $Na_2S_2O_3$. After addition of 10 mL H_2O the aqueous layer was washed with three portions of Et_2O. The combined organic layers were evaporated to yield 8 as an oil which was subsequently stirred in 20 mL HCOOH 90% for 24 h at ambient temperature. The cold non-radioactive product was isolated by column chromatography according to the procedure described for 5 under *Method A* (yield, 60%). The radiolabeled product was isolated by HPLC according to ref. [5]; crystallized from EtOH/Et_2O as hydrogen maleate: mp. 123-124 °C; ^{1}H-NMR (DMSO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.70 (d, J = 8.1 Hz, 2H, Ph-3-H, Ph-5-H), 7.39 (s, 1H, Im-5-H), 7.12 (d, J = 7.9 Hz, Ph-2-H, Ph-6-H), 6.05 (s, 2H, Mal), 4.42 (s, 2H, Ph-CH_2), 3.43 (t, J = 6.0 Hz, 2H, Im-CH_2-CH_2-CH_2), 2.70 (t, J = 7.2 Hz, 2H, Im-CH_2), 1.88 (m, 2H, Im-CH_2-CH_2); MS (70 eV), *m/z* (%) 342 (7) [M$^+$], 217 (30), 125 (56), 110 (55), 95 (33), 82 (100); ($C_{13}H_{15}IN_2O\cdot C_4H_4O_4$).

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