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An Improved Synthesis of Valsartan

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Supporting Information

ABSTRACT: Biphenyltetrazole group, an important component of sartans, is usually formed in excellent yield by the reaction of 4′-alkylbiphenyl-2-carbonitrile with excessive organotin azide. However, it is restricted in industrial scale because of the difficult post-treatment. In this article, an improved synthetic method for valsartan and the quantitative recovery of tri-*n*-butyltin chloride are reported. During this process, the tetrazole−Sn complex and excessive organotin azide were decomposed by HCl to furnish tri–*n*-butyltin chloride, and then reacted with NaF to lead to filterable polymer tributyltin fluoride which was converted again to tributyltin chloride by HCl in ethyl acetate. This approach is facile for the efficient manufacture of sartans using organotin azide to form the tetrazole group and is valuable for industry readers.

1. INTRODUCTION

Since losartan, an angiotensin II receptor inhibitor, came into the market in 1994, scientists modified its mother molecular structure via chemical reactions in order to increase the anti-hypertensive effects and reduce its side effects.[1] These impelled the development of such drugs and led to the formation of the sartans family.

With the development of molecular biology and biochemistry, research on the angiotensin II (Ang II) receptor inhibitor has gained significant breakthrough in recent years. Ang II receptor inhibitors can be divided into two types according to the structure, one of which comprises biphenyltetrazoles such as losartan, irbesartan, candesartan, tasosartan, valsartan, and olmesartan.The other type is non-biphenyltetrazole which comprises eprosartan, telmisartan, etc. During recent decades, there have been some reports on the synthesis of biphenyltetrazole sartan drugs, in which converting the cyano group to the tetrazole ring is the key step. One of the classical methods for the synthesis of the tetrazole group adopted the reaction of carbonitrile with sodium azide in the presence of a Lewis acid.[2−7] The acidity of tetrazoles ($pK_a = 4.89$) is close to that of acetic acid ($pK_a = 4.76$) due to the high chemical activity of the *H*-atom in the tetrazole group. After protection by trityl group, the methyl of biphenyl was brominated by *N*-bromosuccinimide in cyclohexane using 2,2′-azo-bis-isobutyronitrile (AIBN) as the radical starter to afford 4′-bromomethyl-2-(*N*-trityl-1*H*-tetrazol-5-yl)-biphenyl.[8,9] Various amine derivatives were combined, and then the protective group was decomposed to provide a series of sartans. This synthetic route has been adopted in industrial scale even though it has lower total yield. The other important method for the preparation of the tetrazole group, which adopted the reaction of carbonitrile with organotin azide in excellent conversion, has difficult post-treatment and recovery of excessive organotin reagent. This may restrict its application in industry.

Calling attention to the synthesis of the tetrazole group in the second method, we report here a facile project wherein the above problems were solved. The recovery of tributyltin chloride released during the workup of compound **3** is based on the formation of filterable polymer tributyltin fluoride, which is then converted again to tributyltin chloride by treatment with hydrochloric acid. Mitchell and co-workers[10] reported the recovery of organotin halides from organotin fluorides which is performed under complete water-free conditions in THF with sodium chloride or sodium bromide without releasing hydrofluoric acid, and the yield for the conversion of tributyltin fluoride to tributyltin chloride is only 65%, requiring 3 days reaction time. In this contribution, we report this conversion under an aqueous solution of hydrochloric acid leading to the recovery of tributyltin chloride; the reaction time was greatly shortened (10 h), and the yield was nearly quantitative (99.6%). During the conversion, a PTFE-flask was used to deal with the formation of hydrofluoric acid. The recovered tri-*n*-butyltin chloride can be reused for the formation of the tetrazole group. This method would help to reduce the manufacturing cost of sartans and make possible its application in industrial scale.

The synthetic route being adopted in this article can be shown in Scheme 1.

2. EXPERIMENTAL SECTION

Main chemicals were purchased from Sigma-Aldrich and Alfa-Aesar chemical companies and used without further purification. Melting points were determined on a X-4 microscope melting-point testing apparatus (Shanghai) and are uncorrected. Yields refer to isolated pure products. IR spectra were recorded on a Bruker spectrum VECTOR22 (FT) instrument. Mass spectrum was measured on a Finnigan LCQ spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance III 400 spectrometer, and the chemical shifts were reported as δ values in parts per million relative to TMS as an internal standard. HPLC and GC were performed on Agilent 1200 and Agilent 7890A, respectively. Ee values were determined on Breeze-2 (Waters).

2.1. Synthesis of Tri-*n*-butyltin Azide. Tri-*n*-butyltin azide was prepared according to references 11 and 12, with appropriate modifications. A three-neck flask was fitted with tri-*n*-butyltin

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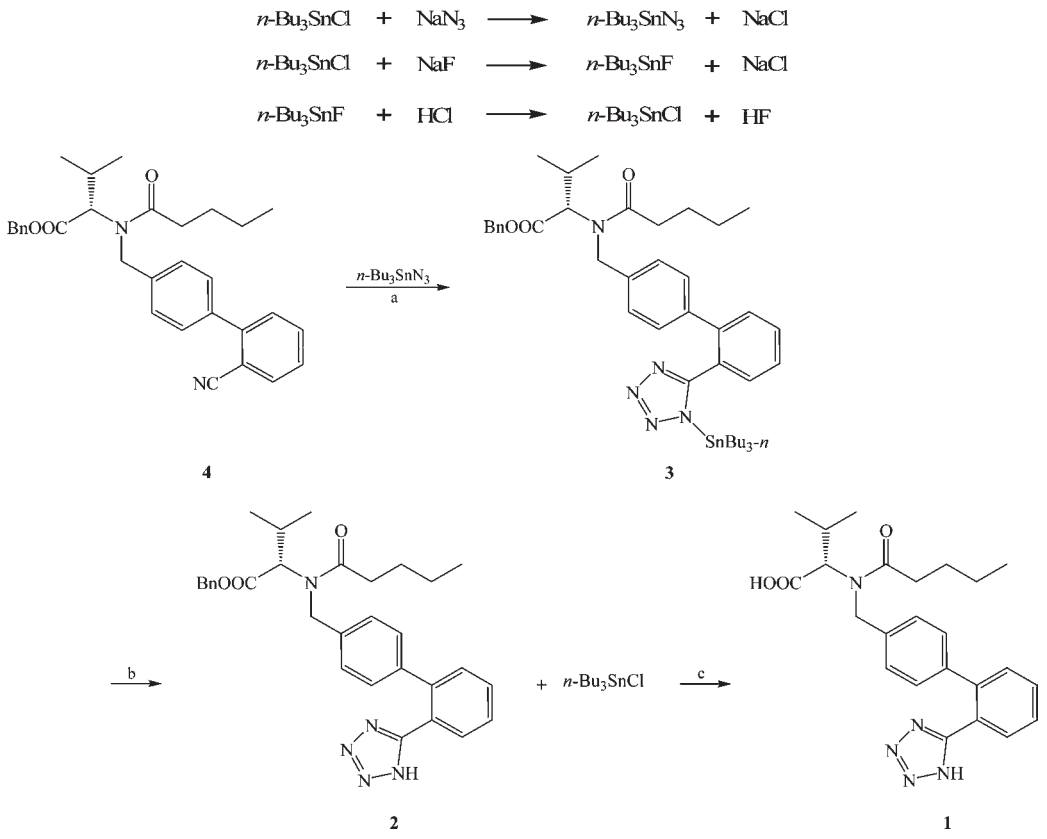
Scheme 1. Preparation of valsartan and recovery of *n*-Bu_3SnCl[a]



[a] Reaction conditions: (a) Xylene, reflux, 24−30 h; (b) HCl, MeOH, reflux; (c) NaF; $NaOH/H_2O$, 60−65 °C; HCl, pH = 2, CH_2Cl_2; diisopropyl ether.

chloride (100.0 g, 0.307 mol). After being cooled to below 0 °C, the saturated sodium azide solution (NaN_3 30.0 g, 0.46 mol; water 70 mL) was added dropwise slowly, and the mixture was kept stirring at 0 °C for another 2 h during which an opaque-like solution was formed gradually. The organic phase was extracted with ethylene chloride, washed with water and brine, dried with sodium sulphate, and kept standing overnight. After the solvent had been recycled at normal conditions, the residue was heated at 90 °C with a rotatory apparatus under reduced pressure for 30 min, and then was distilled. The fraction (118−120 °C/0.2 mm) was collected to give pure product (100.2 g) tri-*n*-butyltin azide as a colorless viscous oil with a yield of 98.6%. IR (KBr) ν_{max}/cm^{-1}: 2957(s), 2930(s), 2871(s), 2855(s), 2075(s), 1462(m), 1416(w), 1377(m), 1340(m), 1275(w), 1180(w), 1154(w), 1076(m), 1023(w), 960(w), 877(m), 697(m), 671(m), 606(w), 515(w).

2.2. New Procedure for the Synthesis of (*S*)-2-[(*N*-Tri-*n*-butyltin-1*H*-tetrazol-5-yl)biphenyl-4- ylmethyl-pentanoyl-amino]-3-methyl-butyric Acid Benzyl Ester (3). (*S*)-2-[(2′-Cyano-biphenyl-4-ylmethyl)pentanoyl-amino]-3-methyl-butyric acid benzyl ester (**4**, prepared according to the work by Beutler and co-workers[13] with a slight modification) (40.1 g, 93%, HPLC, 0.0775 mol) was dissolved in xylene (120 mL); tri-*n*-butyltin azide (51.4 g, 0.154 mol) was then added. The resultant solution was heated to reflux for ∼24−30 h, and the progress was monitored by TLC using chloroform−methanol (8:1) as eluent. After that, the solvent was evaporated under reduced pressure to give the tetrazole−Sn complex (**3**) as a yellowish viscous oil which was used for the next step without further purification.

2.3. New Procedure for the Synthesis of Benzyl Ester of Valsartan (2). The above tetrazole−Sn complex (**3**) was dissolved in methanol (600 mL), and then concentrated hydrochloric acid (23.2 mL) was added. The solution was heated to reflux in an oil bath for ∼2−3 h, and the progress was monitored by TLC using chloroform−methanol (8:1) as eluent. After being cooled to room temperature, the volatile solvent was removed under reduced pressure to afford a yellow viscous oil. The residue, ethyl acetate (230 mL), and an aqueous solution of sodium fluoride (8.0 g in 200 mL water) were mixed and heated to 40−50 °C for 2 h, accompanied by formation of white precipitates. The resultant precipitate was collected by suction filtration, washed with ethyl acetate, and dried in air to give tri-*n*-butyltin fluoride (49.3 g) which can be recycled with the further procedures. MS: 235.1, 291.1, 309.1. IR (KBr) ν_{max}/cm^{-1}: 2956(s), 2930(s), 2871(m), 2854(m),1636(w), 1463(m), 1418(w), 1376(m), 1340(w), 1292(w), 1182(w), 1155(w), 1077(m), 1022(w), 962(w), 877(m), 698(m), 672(w), 615(w).

The organic phase was separated out from the above filtrate, washed with water (40 mL) and brine (30 mL), respectively, and then dried with sodium sulphate for 10 h. After filtration, active carbon (5 g) was added to the solution and then heated to reflux for 45 min. The resulting solution was filtered while it was still hot. The solvent was removed from the filtrate under reduced pressure to furnish benzyl ester of valsartan (**2**) as a colorless hemisolid (HPLC, 92.9%) with a yield of 97.5% based on tetrazole−Sn complex. ESI-MS (-p): 524.1, 1049.0.

2.4. New Procedure for the Synthesis of Valsartan (1). Valsartan benzyl ester (**2**) (10.0 g), water (80 mL), and sodium

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hydroxide (5.0 g) were mixed and stirred until completely dissolved. Then the resultant solution was heated to 65 °C for 2.5 h. After cooling to room temperature, the solution was washed with *n*-heptane (60 mL). The pH value of the separated aqueous layer was adjusted to 2.0 by adding dilute hydrochloric acid at ambient temperature. After that, the aqueous layer was extracted with methylene dichloride (100 mL). The organic layer was washed with water (150 mL) and then with 10% sodium chloride solution (30 mL). The organic phase was dried with sodium sulfate and then distilled under vacuum at 60 °C to give 9.0 g of residue. The residue was added to a mixture of ethyl acetate (20 mL) and diisopropyl ether (20 mL) and heated to reflux. Then the reaction mass was treated with activated charcoal, filtered, and washed with the mixture of diisopropyl ether (7 mL) and ethyl acetate (7 mL). The clear filtrate was heated to reflux, and then a further quantity of diisopropyl ether (60 mL) was added. After being cooled to room temperature, it was put into a refrigerator for 2 h; the contents were then filtered; the recovered solid was washed with chilled diisopropyl ether (10 mL) and dried to give pure valsartan (**1**) (6.5 g, HPLC, 99.7%) as a white crystalline powder with a yield of 72.5% calculated on valstartan benzyl ester (**2**), mp 113−117 °C (lit.:[14] mp 105−115 °C, from ethyl acetate). ESI-MS (-p): 434.32. HPLC purity 99.62%, ee =100% (OD-H, mobile phase: *n*-hexane and isopropyl alcohol in the ratio of 850:150). $[\alpha]^{20}_{D} = (-)$ 67.2 (1% w/v in methanol). ^{1}H NMR (DMSO-d_6) δ: 0.69−0.94 (m, 9H), 1.10−1.20 (m, 1H), 1.28−1.58 (m, 3H), 1.98−2.10 (m, 1H), 2.17−2.50 (m, 2H), 4.07−4.63 (m, 3H), 6.96−7.21(m, 4H), 7.51−7.71 (m, 4H), 12.69 (br, 1H), 16.29 (br, 1H). IR (KBr) ν_{max}/cm^{-1}: 3446(br, w), 3060(w), 2963(s), 2932(m), 2873(m), 2744(w), 2612(w), 1732(s), 1604(s), 1471(s), 1410(m), 1390(w), 1354(w), 1273(w), 1204(m), 1166(m), 1129(w), 1105(w), 1065(w), 1052(w), 1025(w), 996(w), 939(w), 901(w), 852(w), 822(w), 777(w), 760(m), 682(w), 670(w), 624(w), 559(w).

2.5. New Procedure for the Recovery of Tri-*n*-butyltin Chloride. The tri-*n*-butyltin fluoride (25 g), ethyl acetate (150 mL), and hydrochloric acid aqueous solution (20 mL, 1:1, v/v) were mixed in a PTFE flask and stirred with a magnetic stirrer for 10 h at room temperature accompanying the disappearance of the solid. The organic phase was separated out, washed with water (30 mL) and brine (30 mL), respectively, and then dried with sodium sulphate and kept for 10 h. After removing the solvent, the residue was distilled to collect the fraction of 115−120 °C/1 mm to afford tri-*n*-butyltin chloride (26.2 g, GC purity = 95.3%) as a colorless oil in 99.6% yield. MS: 235.1,291.1. IR (KBr) ν_{max}/cm^{-1}: 2957(s), 2930(s), 2871(s), 2854(s), 1625(w), 1462(s), 1415(w), 1377(m), 1341(w), 1292(w), 1250(w), 1180(w), 1152(w), 1075(m), 1023(w), 960(w), 876(m), 697(m), 672(m), 602(w), 512(w).

3. CONCLUSION

The tetrazole−Sn complex, reacted by trialkyltin chloride and carbonitrile in a solvent of hydrocarbons with higher boiling points, such as toluene or xylene, was synthesized in excellent yield. Then it was decomposed by hydrochloric acid in methanol to afford free tetrazole compound and trialkyltin chloride, which can be separated by adding an aqueous solution of sodium fluoride in the formation of precipitated trialkyltin fluoride. The fluoride can be converted to the corresponding chloride quantitatively with the decomposed procedure by hydrochloric acid. As a result, trialkyltin halide can be reused in the formation of the tetrazole group. In conclusion, the synthetic route adopted in this article offers an opportunity for manufacturing valsartan with the second synthetic route efficiently in industrial scale.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Cody, R. J. The Clinical Potential of Renin Inhibitors and Angiotensin Antagonists. *Drugs* **1994**, *47*, 586–598.
(2) Demko, Z. P.; Sharpless, K. B. Preparation of 5-Substituted 1*H*-Tetrazoles from Nitriles in Water. *J. Org. Chem.* **2001**, *66*, 7945–7950.
(3) Galante R. J.; Somerville N. J. Method of Synthesizing Sterically Hindered 5-Substituted 1*H*-Tetrazoles from Nitriles Using a Lewis Acid and an Azide. U.S. Patent 5,502,191, 1996.
(4) Chao, S. J.; Hui, X. P.; Li, S.; Qiu, Z. Z.; Xu, P. F.; Zhang, Z. Y.; Wang, Q.; Guan, Z. W. Synthesis and Antibacterial Activities of Novel Biphenyltetrazole Derivatives Bearing 1,3,4-Oxadiazole. *J. Chin. Chem. Soc. (Taipei, Taiwan)* **2005**, *52*, 539–544.
(5) Silvo Z.; Anica P.; Rok Z. A Process for the Synthesis of Valsartan. EP 1661891, 2006.
(6) Duncia, J. V.; Pierce, M. E.; Santella, J. B. Three Synthetic Routes to a Sterically Hindered Tetrazole: A New One-Step Mild Conversion of an Amide into a Tetrazole. *J. Org. Chem.* **1991**, *56*, 2395–2400.
(7) Aldrich P. E.; Pierce M. E.; Duncia J. J. V. Preparation of 5-(2-Biphenylyl)-tetrazole Derivatives as Intermediates for Antihypertensives. EP 291969, 1988.
(8) Wang, G. X.; Sun, B. P.; Ru, Z. L. Synthesis and Characterization of 4′-Bromomethyl-2-(*N*- trityl-1*H*-tetrazol-5-yl)biphenyl. *Synth. Commun.* **2008**, *38*, 3577–3581.
(9) Senthil, K. N.; Reddy, S. B.; Sinha, B. K.; Mukkanti, K.; Dandala, R. New and Improved Manufacturing Process for Valsartan. *Org. Process Res. Dev.* **2009**, *13*, 1185–1189.
(10) Mitchell, T. N.; Kwetkat, K.; Godry, B. Simple Procedure for Conversion of a Trialkyltin Fluoride into the Corresponding Chloride or Bromide. *Organometallics* **1991**, *10*, 1633–1634.
(11) Wiss, J.; Zilian, A. Online Spectroscopic Investigations (FTIR/Raman) of Industrial Reactions: Synthesis of Tributyltin Azide and Hydrogenation of Chloronitrobenzene. *Org. Process Res. Dev.* **2003**, *7*, 1059–1066.
(12) Barker A. C.; Pearce R. J.; Roberts D. A.; Russell S. T. Preparation of Tetrazolyl Quinoline Derivatives as Antagonists of Angiotensin II. GB 2,252,557, 1992 .
(13) Beutler, U.; Boehm, M.; Fuenfschilling, P. C.; Heinz, T.; Mutz, J. P.; Onken, U.; Mueller, M.; Zaugg, W. A High-Throughput Process for Valsartan. *Org. Process Res. Dev.* **2007**, *11*, 892–898.
(14) Arlesheim B. P.; Riehen F. O.; Basel T. S. Acyl Compounds. U.S. Patent 5,399,578, 1995.