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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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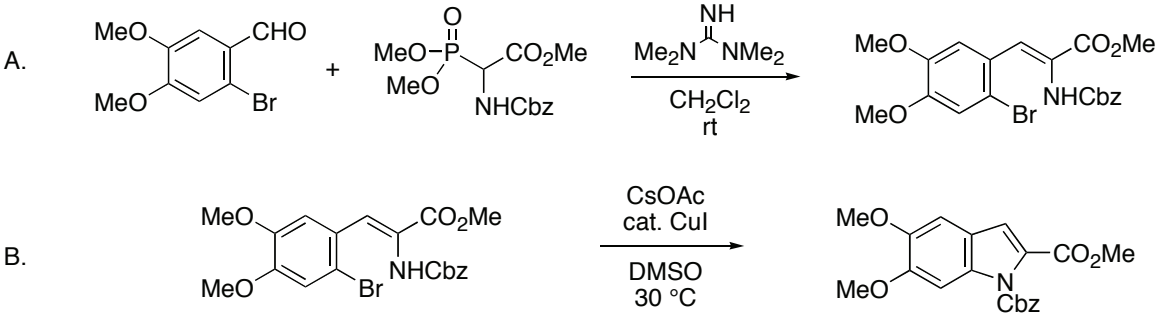
AN INTRAMOLECULAR AMINATION OF ARYL HALIDES WITH A COMBINATION OF COPPER (I) IODIDE AND CESIUM ACETATE: PREPARATION OF 5,6-DIMETHOXYINDOLE-1,2-DICARBOXYLIC ACID 1-BENZYL ESTER 2-METHYL ESTER



Submitted by Toshiharu Noji[1], Kentaro Okano[1], Tohru Fukuyama[2], and Hidetoshi Tokuyama.[1]
Checked by Mark Lautens and Lei Zhang.

1. Procedure

A. *(Z)-2-Benzyloxycarbonylamino-3-(2-bromo-4,5-dimethoxyphenyl) acrylic acid methyl ester.* A 300-mL three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.0 cm), a rubber septum, a glass stopper, and an argon gas inlet is charged with 6-bromoveratraldehyde (7.35 g, 30.0 mmol) (Note 1) and methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (10.43 g, 31.5 mmol, 1.05 equiv). The flask is evacuated and backfilled with argon and is charged with dry dichloromethane (30 mL) (Note 2). The resulting mixture is cooled to 0 °C with stirring at 300 rpm, and to the suspension is added 1,1,3,3-tetramethylguanidine (4.14 mL, 33.0 mmol, 1.1 equiv) (Note 3) dropwise over 10 min (Note 4). The cooling bath is then removed, and the mixture is stirred at room temperature for 5 h (Note 5). The reaction is quenched with 1 M aq. HCl (30 mL). The reaction mixture is transferred into a 500-mL separatory funnel with the aid of dichloromethane (100 mL) and water (60 mL). After partitioning, the aqueous layer is extracted with

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dichloromethane (2 x 100 mL). The combined organic extracts are washed with sat. aq. $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4 (40 g), and filtered. The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 30 mmHg), and the residue is dried *in vacuo* to afford 15.2 g of the crude product as a pale yellow solid, which is purified by recrystallization to provide 2-benzyloxycarbonylamino-3-(2-bromo-4,5-dimethoxyphenyl)acrylic acid methyl ester as colorless needles (11.2 g, 83%) (Notes 6 and 7).

B. *5,6-Dimethoxyindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester*. A 200-mL three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.0 cm), a rubber septum, a glass stopper, and an argon gas inlet is charged with cesium acetate (9.60 g, 50.0 mmol, 2.5 equiv) (Notes 8 and 9), 2-benzyloxycarbonylamino-3-(2-bromo-4,5-dimethoxyphenyl)acrylic acid methyl ester (9.01 g, 20.0 mmol), and copper(I) iodide (761 mg, 4.00 mmol, 0.2 equiv) (Note 10). The flask is evacuated and backfilled with argon and is charged with dry dimethyl sulfoxide (67 mL) (Note 11). After stirring at 300 rpm for 24 h at 30 °C in an oil bath (Note 12), the reaction is quenched by slow addition of 7% NaCl in 10% aq. NH_3 (100 mL) with cooling of the reaction mixture in an ice bath (Note 13). The resulting mixture is transferred into a 500-mL separatory funnel with the aid of EtOAc (100 mL) and water (60 mL). After partitioning, the aqueous layer is extracted with EtOAc (2 x 100 mL). The combined organic extracts are washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4 (40 g), and filtered. The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 30 mmHg), and the residue is dried *in vacuo* to afford 8.03 g of the crude product as a pale yellow solid, which is purified by recrystallization to provide 5,6-dimethoxy-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester as colorless needles (5.58 g, 76%) (Notes 14 and 15).

2. Notes

1. 6-Bromoveratraldehyde (98%) was purchased from Aldrich and used as received without further purification.

2. Dichloromethane (>99.8%, water content: <0.0001%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

3. 1,1,3,3-Tetramethylguanidine (99.0%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

4. The submitters observed that the internal temperature rose to 9 °C after addition of 1,1,3,3-tetramethylguanidine.

5. The reaction typically requires 5 h to consume 6-bromoveratraldehyde and is monitored by TLC analysis on Merck silica gel 60F-254 plate eluting with hexanes-EtOAc (1:1). The R_f values of the starting aldehyde and the product are 0.58 and 0.31, respectively (visualized with 254 nm UV lamp and stained with an ethanol solution of 2,4-dinitrophenylhydrazine (DNP). After dipping the TLC plate in the DNP solution, the chromatogram is developed by heating on a hot plate).

6. To crystallize the product, the residue is dissolved in hot EtOAc-hexanes, 7:5 (240 mL) using an oil bath (bath temperature: 80 °C) with the flask under a nitrogen atmosphere. The solution is then cooled to room temperature over 5 h. The colorless fine needles are collected by filtration (9.94 g). The second crop of crystals (1.18 g) is provided by dissolving the solid, which was obtained by concentration of the mother liquor, in hot EtOAc (20 mL) using an oil bath (bath temperature: 80 °C), followed by cooling to room temperature over 5 h.

7. The compound exhibits the following physicochemical properties: R_f = 0.31 (hexanes-EtOAc = 1:1); Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with an ethanol solution of 2,4-dinitrophenylhydrazine (DNP). After dipping the TLC plate in the DNP solution, the chromatogram is developed by heating on a hot plate); mp = 134–136 °C; IR (NaCl, $CDCl_3$): 3328, 2952, 1716, 1597, 1387, 1261, 1210, 1169, 1053, 819, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.55 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 5.07 (s, 2 H), 6.50 (s, 1 H), 6.99 (s, 1 H), 7.08 (s, 1 H), 7.17 – 7.38 (m, 5 H), 7.44 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.86, 55.76, 56.14, 67.56, 111.48, 115.28, 116.39, 124.48, 126.11, 128.45, 128.47, 128.58, 129.55, 135.84, 148.01, 150.12, 153.69, 165.57. Anal. calcd. for $C_{20}H_{20}BrNO_6$: C, 53.35; H, 4.48; N, 3.11. Found: C, 53.49; H, 4.62; N,

3.07.

8. Cesium acetate (>99.99%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

9. Cesium acetate is extremely hygroscopic. The submitters transferred this reagent in a plastic bag filled with argon to prevent rapid absorption of moisture. The checkers transferred the reagent to a sealed vial in a glovebox under nitrogen atmosphere and stored the vial in a desiccator.

10. Copper (I) iodide (99.5%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

11. Anhydrous dimethyl sulfoxide (≥99.9%, water content: <0.005%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

12. The reaction typically requires 24 h to consume almost all of the 2-benzyloxycarbonylamino-3-(2-bromo-4,5-dimethoxyphenyl)acrylic acid methyl ester. The ^{1}H NMR spectrum of the crude material shows that the relative ratio of the signal for the starting enamide (δ 5.08, 2 H) to that for the indole (δ 5.40, 2 H) is less than 0.08. The reaction is also monitored by TLC analysis on Merck silica gel 60F-254 plate eluting with hexanes-EtOAc-toluene (2:1:1). The R_f values of the intermediate and the product are 0.37 and 0.27, respectively (visualized with 254 nm UV lamp and an ethanol solution of 2,4-dinitrophenylhydrazine (DNP). After dipping the TLC plate in the DNP solution, the chromatogram is developed by heating on a hot plate).

13. The solution is prepared by dissolving 35 g of NaCl in 465 g of 10% aq. NH_3. The addition of this solution is exothermic.

14. The submitters observed that the crude material became yellow upon standing at room temperature. Thus, it was immediately purified by recrystallization. To crystallize the product, the residue is dissolved in hot hexanes-EtOAc, 5:2 (140 mL) using an oil bath (bath temperature: 60 °C). The solution is then cooled at 0 °C in an ice bath for 5 h. The colorless needles are collected by filtration (5.26 g). The second crop of crystals (0.92 g) is provided by dissolving the solid, which was obtained by concentration of the mother liquor, in hot hexanes-EtOAc, 3:1 (40 mL) using an oil bath (bath temperature: 60 °C), followed by cooling at 0 °C in an ice bath for 5 h.

The checkers observed that the concentrated mother liquor from the first crop was an oil that was contaminated with ~20% starting material. During the half scale run, the concentrated mother liquor was treated with 20 mL of diethyl ether to form a suspension. The suspension was filtered, and the solids were washed with 20 mL of diethyl ether. The filtrate was concentrated, and the resulting residue was recrystallized by dissolving in hexanes-diethyl ether-EtOAc, 2:1:1 (20 mL) in an oil bath at 35 °C, followed by cooling at 0 °C in an ice bath for 5 h. An additional 0.295 g of the product was isolated.

15. The compound exhibits the following physicochemical properties: R_f = 0.27 (hexanes-EtOAc-toluene = 2:1:1); Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with an ethanol solution of 2,4-dinitrophenylhydrazine (DNP). After dipping the TLC plate in the DNP solution, the chromatogram is developed by heating on a hot plate); mp = 98–100 °C. IR (NaCl, $CDCl_3$): 2951, 1721, 1538, 1488, 1470, 1436, 1393, 1331, 1301, 1227, 1160, 1126, 1065, 1016, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.73 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 5.40 (s, 2 H), 6.98 (s, 1 H), 7.08 (s, 1 H), 7.33 – 7.43 (m, 3 H), 7.47 (dd, *J* = 7.8, 1.6 Hz, 2 H), 7.57 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.07, 55.93, 56.02, 69.58, 97.83, 102.75, 116.64, 119.99, 128.49, 128.66, 128.78 (2), 132.82, 134.49, 147.15, 150.15, 150.79, 161.84. Anal. calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.03; H, 5.38; N, 3.75.

Safety and Waste Disposal Information

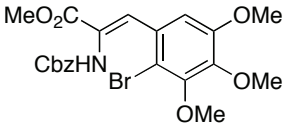
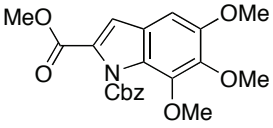
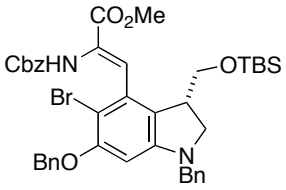
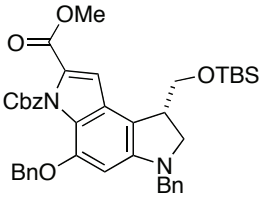
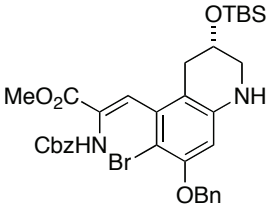
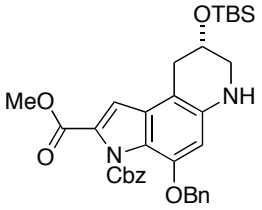
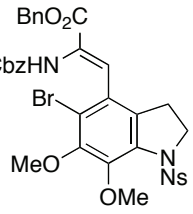
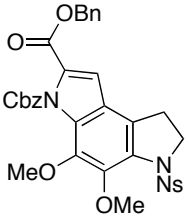
All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

Since the indole skeleton is found in a variety of biologically important natural products and therapeutic agents, the development of methods for indole synthesis has been one of the main topics in organic synthesis. We

have recently developed a copper-mediated aryl amination[3] using the combination of CuI and CsOAc,[4] which was applied to the formation of *N*-Cbz-2-alkoxycarbonylindoles. The aryl amination proceeds smoothly even at the congested position at room temperature without the addition of any special ligand (Table 1). The procedure provides a facile synthetic method for preparation of a Cbz-protected indole carboxylic acid ester from

Table 1. Synthesis of indole-2-carboxylic acid ester.

Substrate	Product	CuI (equiv)	CsOAc (equiv)	Yield (%)
		1.5	7	98
		2	18	quant
		1	2.5	quant
		1	5	77

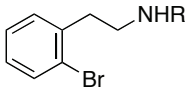
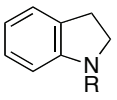
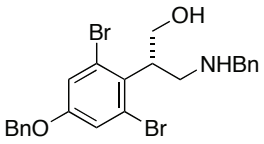
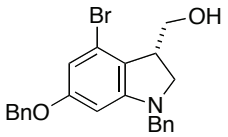
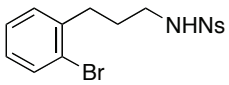
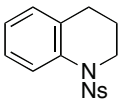
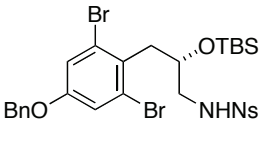
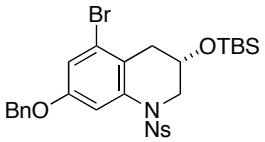
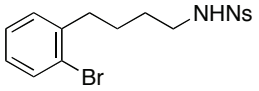
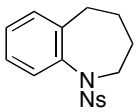
Reaction Conditions: CuI (1–2 equiv), CsOAc (2.5–18 equiv), DMSO, rt.

the corresponding *o*-bromobenzaldehyde derivative and readily available Horner-Wadsworth-Emmons reagent in a two-step sequence. Compared to the representative method for thermolysis of an α-azidecinnamic acid ester,[5]

this method is able to circumvent regiochemical problems and potential explosion hazards.

The aryl amination was also applicable to the synthesis of indoline bearing a variety of protecting groups on the nitrogen (Table 2). It is notable that *o*-Ns amides have been found to be a particularly suitable substrate. By utilizing *o*-Ns amides, tetrahydroquinoline and tetrahydrobenzoazepine were

Table 2. Scope of the intramolecular aryl amination.

Substrate	Product	CuI (mol%)	CsOAc (equiv)	Temp. (°C)	Yield (%)
	 R = Boc Alloc Bn Ns	200 200 10 1	10 10 5 2	90 90 90 90	82 75 83 97
		10	1.4	rt	67
		10	5	90	96
		50	5	60	83
		100	5	90	74

Reaction Conditions: CuI (1–200 mol%), CsOAc (1.4–10 equiv), DMSO, rt – 90 °C.

also constructed by this methodology. The reaction conditions are compatible with a wide range of functional groups, including both acid and base labile protective groups. One of the advantages over palladium catalyzed processes[6] is that the bromo group remained unreacted after the reaction, allowing for further functionalization to take place. The aryl amination was applied to the total syntheses of duocarmycins,[7] (+)-yatakemycin,[8] and PDE-II.[9]

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2. Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: fukuyama@mol.f.u-tokyo.ac.jp This work was supported by The Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6-Bromoveratraldehyde: Benzaldehyde, 2-bromo-4,5-dimethoxy-; (5392-10-9)

Acetic acid, 2-(dimethoxyphosphinyl)-2-[[(phenylmethoxy)carbonyl]-amino]-, methyl ester: Benzyloxycarbonylamino(dimethoxy-phosphoryl)acetic acid methyl ester; (88568-95-0)

1,1,3,3-Tetramethylguanidine: Guanidine, *N,N,N',N'*-tetramethyl-; (80-70-6)
Dichloromethane: Methane, dichloro-; (75-09-2)
Cesium acetate: Acetic acid, cesium salt (1:1); (3396-11-0)
Copper(I) iodide: Copper iodide (CuI); (7681-65-4)
Dimethyl sulfoxide: Methane, 1,1'-sulfinylbis-; (67-68-5)

Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a postdoctoral fellow with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed Associate Professor in 2003. In 2006, he moved to Tohoku University, where he is currently Professor of Pharmaceutical Sciences. His research interest is on the development of synthetic methodologies and total synthesis of natural products.

Toshiharu Noji was born in Fukushima in 1986. He received his B.S. in 2009 from Faculty of Pharmaceutical Sciences, Tohoku University, where he carried out undergraduate research in the laboratories of Professor Hidetoshi Tokuyama. In the same year, he then began his doctoral studies at Graduate School of Pharmaceutical Sciences, Tohoku University under the supervision of Professor Hidetoshi Tokuyama. His graduate research has focused on benzyne chemistry and its application to total synthesis of natural products containing multisubstituted heteroaromatic rings.

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