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Efficient Regioselective Synthesis of 3-Iodoindole *N*-Carboximidamides and *N*-Carboximidoates by a Sequential Aza-Wittig/Iodine Induced Cyclization

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3-Iodoindole *N*-carboximidamides and *N*-carboximidoates **4** were prepared regioselectively via a sequential aza-Wittig/iodine induced cyclization, starting from easily accessible 2-alkynylphenyl iminophosphorane, isocyanates, various nucleophiles and iodine.

Keywords indole, aza-Wittig reaction, iodine, cyclization, iminophosphorane

Introduction

Among the electrophilic cyclization leading to heterocycles, iodine induced cyclization is a widely used process and has become an effective protocol in the preparation of a variety of heterocyclic and carbocyclic compounds.[1] For example, iodine induced cyclization of some alkynes has been proved to be an effective method for the synthesis of furans,[2] pyrroles,[3] thiophenes[4] and indoles[5,6] in recent years. Iodine induced cyclization has received considerable attention because the iodine is inexpensive, non-toxic and readily available.

Indole is one of the most ubiquitous heterocycle found in a large number of natural products and pharmacologically active compounds.[7] Due to the great structural diversity of biologically active indoles, the synthesis and functionalization of indoles has been a major focus in research. Several efficient methodologies have been developed for preparation of indoles. One of the synthetic method for polysubstituted indole derivatives is the intramolecular cyclization of 2-alkynylaniline derivatives, catalyzed by some expensive palladium, gold or silver complexes.[8] The reaction can also be carried out by iodine induced cyclization to give *N*-tosyl or *N*-Boc-protected 3-iodo-indoles.[6,9] However, 3-iodoindole *N*-carboximidamides and *N*-carboximidoates are not prepared by this method previously probably due to the fact that the starting material (2-alkynylphenyl)guanidines (or isoureas) are not easily accessible by routine synthetic methods.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[10] We have recently been interested in the synthesis of various heterocycles through aza-Wittig reactions, with the aim of evaluating their biological activities.[11] Herein we wish to report a mild and efficient synthesis of 3-iodoindole *N*-carboximidamides and *N*-carboximidoates by iodine induced cyclization of (2-alkynylphenyl)guanidines (or isoureas), which were obtained by aza-Wittig reaction and further reaction of the carbodiimides with amines or alcohols.

Experimental

General procedure

Melting points were determined using a Beijing Taike X-4 model apparatus and uncorrected. MS data were measured on a Finnigan Trace MS instrument. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 or 400 spectrometer using TMS as interal standard. Elemental analyses were taken on a Vario EL III elemental analysis instrument.

General procedure for the preparation of 4a—4k

To a solution of iminophosphorane **1**[12] (3.0 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (3.0 mmol) under nitrogen at room temperature. After the reaction mixture was left unstirred for 8—12 h at 0—5 ℃, enyne-carbodiimides **2** were obtained in high yield, which were used directly without further purification. To the solution of enyne-carbodiimides **2** prepared above was added secondary amines (HNR^2_2, 3.0 mmol). After the reaction mixture was stirred for 0.5—6 h, the guanidine-enyne interme-

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diate **3** was generated. The solvent was removed off under reduced pressure. To the solution of **3** prepared above in anhydrous acetonitrile (10 mL) was added I_2 (6.0 mmol, 1.5 g) and K_2CO_3 (9.0 mmol, 1.3 g). After the reaction mixture was stirred for 3 h, saturated aqueous $Na_2S_2O_3$ solution was added to remove the unreacted I_2. The mixture was extracted by methylene dichloride and the organic layer was evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/diethyl ether, V∶V=4∶1) to yield indole derivatives **4a**—**4k**.

4-Chloro-*N*-[(3-iodo-2-phenyl-1*H*-indol-1-yl)(morpholino)methylene]aniline (**4a**): White solid (yield 77%), m.p. 223—225 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.51—7.47 (m, 2H), 7.38—7.29 (m, 5H), 7.10—7.09 (m, 2H), 6.81—6.80 (m, 2H), 5.89 (d, J=8.4 Hz, 2H), 3.87—3.80 (m, 3H), 3.62—3.54 (m, 3H), 3.18—3.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.0, 143.9, 138.9, 136.1, 130.8, 130.3, 129.8, 128.7, 128.3, 127.9, 127.8,124.8, 123.0, 122.5, 122.3, 111.2, 66.5, 64.3, 46.5, 46.0; MS (EI, 70 eV) *m*/*z* (%): 541 (M^+, 4), 223 (100), 190 (6), 179 (12), 165 (3), 151 (6), 138 (4), 111 (10). Anal. calcd for $C_{25}H_{21}ClIN_3O$: C 55.42, H 3.91, N 7.76; found C 55.71, H 4.12, N 7.90.

4-Fluoro-*N*-[(3-iodo-2-phenyl-1*H*-indol-1-yl)(morpholino)methylene]aniline (**4b**): White solid (yield 80%), m.p. 196—198 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.51—7.47 (m, 2H), 7.38—7.29 (m, 5H), 7.10—7.09 (m, 2H), 6.56—6.53 (m, 2H), 5.91—5.89 (m, 2H), 3.85—3.79 (m, 3H), 3.62—3.54 (m, 3H), 3.18—3.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 159.7, 158.1, 143.8, 142.5, 138.9, 136.2, 130.8, 130.4, 129.7, 128.7, 127.9, 124.7,122.8, 122.4, 122.2, 114.9, 114.8, 111.3, 66.3, 64.2, 46.5, 46.0; MS (EI, 70 eV) *m*/*z* (%): 525 (M^+, 3), 311 (1), 207 (100). Anal. calcd for $C_{25}H_{21}FIN_3O$: C 57.15, H 4.03, N 8.00; found C 57.12, H 4.21, N 8.26.

N-[(3-Iodo-2-phenyl-1*H*-indol-1-yl)(morpholino)-methylene]aniline (**4c**): White solid (yield 85%), m.p. 191—193 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.49—7.47 (m, 2H), 7.37—7.23 (m, 5H), 7.09—7.07 (m, 2H), 6.85—6.76 (m, 3H), 6.00 (d, J=7.8 Hz, 2H), 3.84—3.74 (m, 3H), 3.58—3.48 (m, 3H), 3.14—3.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.3, 143.5, 139.0, 136.2, 130.8, 130.4, 129.8, 128.6, 128.2, 127.8, 124.5, 122.8, 122.3, 122.0, 121.6, 111.4, 66.3, 64.1, 46.4, 46.0; MS (EI, 70 eV) *m*/*z* (%): 507 (M^+, 3), 293 (1), 191 (5), 189 (100). Anal. calcd for $C_{25}H_{22}IN_3O$: C 59.18, H 4.37, N 8.28; found C 59.36, H 4.51, N 8.22.

N-[(3-Iodo-2-phenyl-1H-indol-1-yl)(morpholino)-methylene]-4-methylaniline (**4d**): White solid (yield 84%), m.p. 214—216 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.50—7.44 (m, 2H), 7.36—7.24 (m, 5H), 7.14—7.12 (m, 2H), 6.69—6.66 (m, 2H), 5.97 (d, J=7.8 Hz, 2H), 3.79—3.42 (m, 6H), 3.08—3.02 (m, 2H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.7, 143.2, 139.0, 136.1, 132.2, 130.7, 130.5, 129.8, 128.9, 128.6, 127.8, 124.5, 122.2, 122.0, 121.5, 111.5, 66.4, 63.9, 46.3, 46.1, 20.7; MS (EI, 70 eV) *m*/*z* (%): 521 (M^+, 2), 203 (100), 197 (1), 191 (4). Anal. calcd for $C_{26}H_{24}IN_3O$: C 59.89, H 4.64, N 8.06; found C 59.56, H 4.79, N 8.30.

N-[(3-Iodo-2-phenyl-1*H*-indol-1-yl)(morpholino)-methylene]-3-methylaniline (**4e**): White solid (yield 81%), m.p. 170—172 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.52—7.48 (m, 2H), 7.36—7.24 (m, 5H), 7.06—7.04 (m, 2H), 6.70—6.59 (m, 2H), 5.75—5.73 (m, 2H), 3.88—3.80 (m, 3H), 3.62—3.56 (m, 3H), 3.20—3.15 (m, 2H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.2, 143.6, 139.2, 137.7, 136.5, 130.8, 130.5, 129.8, 128.5, 128.0, 127.7, 124.5, 123.5, 123.2, 122.3, 122.1, 122.0, 117.8, 111.4, 66.5, 63.9, 46.6, 46.5, 21.1; MS (EI, 70 eV) *m*/*z* (%): 521 (M^+, 3), 203 (100), 197 (1), 191 (4), 175 (1). Anal. calcd for $C_{26}H_{24}IN_3O$: C 59.89, H 4.64, N 8.06; found C 60.12, H 4.66, N 8.19.

N,*N*-Dibutyl-3-iodo-*N*′,2-diphenyl-1*H*-indole-1-carboximidamide (**4f**): White solid (yield 84%), m.p. 95—97 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.46—7.45 (m, 1H), 7.37—7.30 (m, 4H), 7.27—7.22 (m, 4H), 6.86—6.83 (m, 2H), 6.75—6.74 (m, 1H), 6.13 (d, J=7.2 Hz, 2H), 3.63—3.62 (m, 1H), 3.48—3.46 (m, 1H), 2.87—2.84 (m, 2H), 1.59—1.56 (m, 2H), 1.44—1.41 (m, 2H), 1.27—1.26 (m, 2H), 1.04—1.00 (m, 2H), 0.92 (t, J=7.2 Hz, 3H), 0.68 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.2, 143.2, 139.0, 136.4, 130.7, 130.5, 130.0, 128.5, 128.2, 127.8, 124.1, 122.1, 121,8, 121.7, 111.8, 63.3, 47.5, 47.1, 30.6, 28.6, 20.4, 20.0, 14.0, 13.6; MS (EI, 70 eV) *m*/*z* (%): 549 (M^+, 2), 319 (2), 293 (3), 231 (100). Anal. calcd for $C_{29}H_{32}IN_3$: C 63.39, H 5.87, N 7.65; found C 63.56, H 6.08, N 7.83.

3-Iodo-*N*,*N*-diisopropyl-*N*′,2-diphenyl-1*H*-indole-1-carboximidamide (**4g**): White solid (yield 79%), m.p. 128—130 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.47—7.45 (m, 1H), 7.37—7.34 (m, 6H), 7.25—7.22 (m, 2H), 6.87—6.85 (m, 2H), 6.74—6.72 (m, 1H), 6.20 (d, J=7.8 Hz, 2H), 3.59—3.58 (m, 1H), 3.32—3.30 (m, 1H), 1.67 (d, J=6.0 Hz, 3H), 1.49 (d, J=6.0 Hz, 3H), 1.00 (d, J=6.0 Hz, 3H), 0.88 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.1, 139.9, 138.7, 136.6, 130.5, 130.4, 130.2, 128.7, 128.2, 127.7, 123.9, 122.0, 121.8, 111.6, 62.3, 49.1, 49.0, 46.6, 21.6, 21.2, 20.4, 19.7; MS (EI, 70 eV) *m*/*z* (%): 521 (M^+, 2), 293 (2), 203 (100). Anal. calcd for $C_{27}H_{28}IN_3$: C 62.19, H 5.41, N 8.06; found C 62.34, H 5.53, N 8.28.

3-Iodo-*N*′,2-diphenyl-*N*,*N*-dipropyl-1*H*-indole-1-carboximidamide (**4h**): White solid (yield 84%), m.p. 111—113 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.47—7.46 (m, 1H), 7.37—7.31 (m, 4H), 7.28—7.20 (m, 4H), 6.85—6.83 (m, 2H), 6.75—6.73 (m, 1H), 6.09 (d, J=7.8 Hz, 2H), 3.57—3.45 (m, 2H), 2.88 (t, J=7.8 Hz, 2H), 1.66—1.63 (m, 2H), 1.52—1.49 (m, 2H), 0.88 (t, J=7.2 Hz, 3H), 0.68 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.2, 143.2, 139.0, 136.5, 130.8, 130.5, 130.0, 128.6, 128.2, 127.7, 124.1, 122.1, 121.8, 121.7, 121.6, 111.7, 63.4, 49.6, 21.8, 19.7, 11.7, 11.4; MS (EI, 70 eV) *m*/*z* (%): 521 (M^+, 2), 293 (2), 203 (100). Anal. calcd for $C_{27}H_{28}IN_3$: C 62.19, H 5.41, N 8.06; found C 62.28, H 5.57, N 8.24.

N-[(3-Iodo-5-methyl-2-phenyl-1*H*-indol-1-yl)(piperidin-1-yl)methylene]aniline (**4i**): White solid (yield 75%), m.p. 154—156 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.39—7.25 (m, 5H), 7.15—7.13 (m, 1H), 7.05—7.04 (m, 2H), 6.82—6.80 (m, 2H), 6.76—6.73 (m, 1H), 5.93 (d, J=7.8 Hz, 2H), 3.97—3.95 (m, 1H), 3.45—3.39 (m, 1H), 3.25—3.24 (m, 1H), 3.00—2.99 (m, 1H), 2.50 (s, 3H), 1.75—1.69 (m, 3H), 1.55—1.44 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.0, 144.0, 139.2, 134.9, 131.6, 130.8, 130.7, 129.8, 128.3, 128.1, 127.6, 125.8, 122.2, 121.7, 121.6, 121.5, 111.5, 111.4, 63.1, 47.2, 46.6, 25.9, 25.3, 24.4, 21.4, 21.3; MS (EI, 70 eV) *m*/*z* (%): 519 (M^+, 2), 205 (3), 196 (2), 187(100). Anal. calcd for $C_{27}H_{26}IN_3$: C 62.43, H 5.05, N 8.09; found C 62.38, H 5.25, N 8.26.

N-[(3-Iodo-5-methyl-2-phenyl-1*H*-indol-1-yl)(pyrrolidin-1-yl)methylene]aniline (**4j**): White solid (yield 79%), m.p. 175—177 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.34—7.28 (m, 4H), 7.26—7.24 (m, 1H), 7.16—7.15 (m, 1H), 7.05—7.04 (m, 2H), 6.81—6.79 (m, 2H), 6.75—6.74 (m, 1H), 5.94 (d, J=7.8 Hz, 2H), 3.72—3.69 (m, 2H), 3.28—3.24 (m, 2H), 2.51 (s, 3H), 2.02—2.00 (m, 2H), 1.92—1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.1, 142.3, 138.4, 134.5, 131.4, 130.9, 130.8, 129.6, 128.3, 128.1, 127.7, 126.0, 122.0, 121.9, 121.8, 121.7, 111.0, 62.4, 47.9, 25.7, 25.0, 21.4; MS (EI, 70 eV) *m*/*z* (%): 505 (M^+, 3), 204 (3), 189 (11), 173(100). Anal. calcd for $C_{26}H_{24}IN_3$: C 61.79, H 4.79, N 8.31; found C 61.92, H 4.87, N 8.09.

N-[(3-Iodo-5-methyl-2-phenyl-1*H*-indol-1-yl)(morpholino)methylene]aniline (**4k**): White solid (yield 80%), m.p. 187—189 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.39—7.31 (m, 4H), 7.26—7.25 (m, 1H), 7.15—7.14 (m, 1H), 7.07—7.06 (m, 2H), 6.86—6.84 (m, 2H), 6.80—6.79 (m, 1H), 6.01 (d, J=6.6 Hz, 2H), 3.84—3.76 (m, 3H), 3.60—3.51 (m, 3H), 3.16—3.10 (m, 2H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.3, 143.7, 139.0, 134.5, 131.8, 130.9, 130.5, 129.7, 128.4, 128.2, 127.7, 126.1, 122.7, 121.7, 111.1, 66.5, 63.7, 46.4, 46.0, 21.3; MS (EI, 70 eV) *m*/*z* (%): 521 (M^+, 3), 205 (4), 189 (100). Anal. calcd for $C_{26}H_{24}IN_3O$: C 59.89, H 4.64, N 8.06; found C 59.67, H 4.72, N 8.25.

N-((2-((Benzyloxy)methyl)-3-iodo-1*H*-indol-1-yl)-(morpholino)methylene)aniline (**4l**): White solid (yield 82%), m.p. 116—118 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.76—7.24 (m, 9H), 6.96—6.79 (m, 3H), 6.47—6.43 (m, 2H), 4.58—4.56 (m, 2H), 4.46—4.26 (m, 2H), 3.92—3.40 (m, 6H), 2.78—2.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.7, 144.3, 137.4, 136.9, 135.7, 129.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 124.9, 122.0, 121.9, 121.7, 121.4, 111.2, 111.1, 85.6, 73.3, 73.1, 66.5, 65.4, 64.5, 64.4, 46.5, 46.4; MS (EI, 70 eV) *m*/*z* (%): 551 (M^+, 1), 189 (100), 145 (9), 119 (7), 91 (14), 77 (21). Anal. calcd for $C_{27}H_{26}IN_3O_2$: C 58.81, H 4.75, N 7.62; found C 58.97, H 4.88, N 7.83.

N-((2-((Benzyloxy)methyl)-3-iodo-1*H*-indol-1-yl)-(morpholino)methylene)-4-chloroaniline (**4m**): White solid (yield 78%), m.p. 121—123 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.77—7.16 (m, 9H), 6.92—6.88 (m, 2H), 6.38—6.34 (m, 2H), 4.59—4.54 (m, 2H), 4.49—4.22 (m, 2H), 3.89—3.79 (m, 3H), 3.58—3.38 (m, 3H), 2.76—2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.7, 145.4, 137.3, 136.6, 136.4, 135.9, 133.4, 130.9, 128.8, 128.7, 128.5, 128.4, 128.2, 124.9, 122.8, 122.7, 122.1, 112.8, 110.9, 85.7, 73.1, 66.0, 65.6, 64.4, 64.3, 46.4, 46.2; MS (EI, 70 eV) *m*/*z* (%): 585 (M^+, 3), 494 (4), 479 (5), 223 (100), 179 (10), 138 (4), 111 (4), 91 (7). Anal. calcd for $C_{27}H_{25}ClIN_3O_2$: C 55.35, H 4.30, N 7.17; found C 55.42, H 4.34, N 7.32.

N-((2-((Benzyloxy)methyl)-3-iodo-1*H*-indol-1-yl)-(pyrrolidin-1-yl)methylene)-4-chloroaniline (**4n**): White solid (yield 72%), m.p. 108—110 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77—6.86 (m, 11H), 6.38—6.34 (m, 2H), 4.58—4.22 (m, 4H), 3.69—3.66 (m, 2H), 2.95—2.78 (m, 2H), 1.89—1.66 (m, 2H), 1.46—0.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.5, 146.2, 142.5, 135.8, 135.6, 133.3, 130.9, 129.5, 128.7, 128.4, 128.1, 128.0, 127.5, 124.9, 123.1, 123.0, 122.0, 121.7, 112.6, 110.7, 85.2, 73.2, 64.6, 48.1, 46.8, 25.0; MS (EI, 70 eV) *m*/*z* (%): 569 (M^+, 1), 463 (3), 272 (1), 207 (100), 165 (14). Anal. calcd for $C_{27}H_{25}ClIN_3O$: C 56.91, H 4.42, N 7.37; found C 57.02, H 4.49, N 7.13.

N-((2-((Benzyloxy)methyl)-3-iodo-1*H*-indol-1-yl)-(piperidin-1-yl)methylene)-4-chloroaniline (**4o**): Light yellow oil (yield 74%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75—6.85 (m, 11H), 6.40—6.36 (m, 2H), 4.57—4.26 (m, 4H), 3.94—3.44 (m, 2H), 2.70—2.64 (m, 2H), 1.73—0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.4, 137.6, 136.0, 135.6, 133.0, 130.7, 129.5, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 124.7, 122.9, 122.8, 121.9, 113.2, 111.3, 85.5, 73.0, 64.5, 63.6, 47.2, 25.8, 25.0, 24.3; MS (EI, 70 eV) *m*/*z* (%): 583 (M^+, 1), 492 (1), 221 (100), 165 (8), 91 (5), 69 (4). Anal. calcd for $C_{28}H_{27}ClIN_3O$: C 57.60, H 4.66, N 7.20; found C 57.87, H 4.73, N 7.26.

General procedure for the preparation of 4p—4w

To the solution of enyne-carbodiimides **2** prepared above was added anhydrous alcohol (ROH, 10 mL) with several drops of sodium alkyloxide (RONa) in corresponding ROH. After the reaction mixture was stirred for 0.5—6 h, the solvent was removed off under reduced pressure. Then anhydrous acetonitrile (10 mL), I_2 (6.0 mmol, 1.5 g) and K_2CO_3 (9.0 mmol, 1.3 g) were added. After the reaction mixture was stirred for 3 h, saturated aqueous $Na_2S_2O_3$ solution was added to remove the unreacted I_2. The mixture was extracted by methylene dichloride and the organic layer was evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/diethyl ether, V∶V=4∶1) to yield indole derivatives **4p**—**4w**.

Ethyl *N*-(4-chlorophenyl)-3-iodo-2-phenyl-1*H*-indole-1-carbimidate (**4p**): White solid (yield 68%), m.p. 187—189 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.49—7.48 (m, 1H), 7.42—7.41 (m, 1H), 7.33—7.22 (m, 5H),

7.12—7.11 (m, 2H), 6.85—6.84 (m, 2H), 6.80—6.79 (m, 2H), 5.91 (d, J=7.2 Hz, 2H), 4.81—4.75 (m, 2H), 1.45—1.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.6, 142.8, 138.3, 136.0, 130.9, 130.6, 129.4, 128.9, 128.4, 127.9, 124.7, 122.8, 122.5, 122.0, 111.6, 64.9, 14.0; MS (EI, 70 eV) *m*/*z* (%): 500 (M^+, 21), 347 (39), 205 (25), 191 (56), 165 (35), 154 (100). Anal. calcd for $C_{23}H_{18}ClIN_2O$: C 55.17, H 3.62, N 5.59; found C 55.35, H 3.57, N 5.32.

Ethyl 3-iodo-5-methyl-*N*,2-diphenyl-1*H*-indole-1-carbimidate (**4q**): White solid (yield 85%), m.p. 116—118 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.31—7.28 (m, 5H), 7.13—7.10 (m, 3H), 6.89—6.86 (m, 3H), 6.03—6.02 (m, 2H), 4.48—4.45 (m, 2H), 2.50 (s, 3H), 1.42—1.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.3, 144.2, 138.6, 134.5, 131.9, 130.9, 129.4, 128.4, 128.2, 127.8, 126.0, 123.6, 121.5, 111.5, 64.6, 21.4, 14.0; MS (EI, 70 eV) *m*/*z* (%): 480 (M^+, 29), 333 (17), 219 (17), 205 (32), 190 (17), 178 (11), 148 (11), 120 (100). Anal. calcd for $C_{24}H_{21}IN_2O$: C 60.01, H 4.41, N 5.83; found C 60.26, H 4.68, N 6.04.

Ethyl *N*-(4-chlorophenyl)-3-iodo-5-methyl-2-phenyl-1*H*-indole-1-carbimidate (**4r**): White solid (yield 76%), m.p. 159—161 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.32—7.29 (m, 4H), 7.25—7.10 (m, 4H), 6.86—6.84 (m, 2H), 5.91 (d, J=7.2 Hz, 2H), 4.49—4.45 (m, 2H), 2.50 (s, 3H), 1.42 (t, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.8, 142.9, 138.3, 134.4, 132.1, 131.0, 130.8, 129.3, 128.8, 128.4, 128.3, 127.9, 126.2, 122.8, 121.7, 111.4, 64.8, 21.4, 14.0; MS (EI, 70 eV) *m*/*z* (%): 514 (M^+, 17), 361 (42), 333 (30), 234 (13), 219 (24), 205 (56), 190 (28), 178 (17), 154 (100). Anal. calcd for $C_{24}H_{20}ClIN_2O$: C 56.00, H 3.92, N 5.44; found C 55.73, H 4.09, N 5.48.

Ethyl 3-iodo-5-methyl-2-phenyl-*N*-(*p*-tolyl)-1*H*-indole-1-carbimidate (**4s**): White solid (yield 81%), m.p. 100—102 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.33—7.24 (m, 5H), 7.13—7.10 (m, 3H), 6.71—6.70 (m, 2H), 5.98 (d, J=7.2 Hz, 2H), 4.43—4.42 (m, 2H), 2.50 (s, 3H), 2.18 (s, 3H), 1.36—1.34 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.0, 141.7, 138.7, 134.4, 133.0, 131.8, 131.0, 130.9, 129.4, 129.0, 128.2, 127.8, 126.0, 121.5, 121.3, 111.5, 64.5, 21.4, 20.8, 14.0; MS (EI, 70 eV) *m*/*z* (%): 494 (M^+, 9), 361 (17), 205 (20), 190 (10), 178 (6), 162 (11), 134 (100). Anal. calcd for $C_{25}H_{23}IN_2O$: C 60.74, H 4.69, N 5.67; found C 60.98, H 4.52, N 5.83.

Methyl 3-iodo-5-methyl-*N*,2-diphenyl-1*H*-indole-1-carbimidate (**4t**): White solid (yield 84%), m.p. 147—150 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.32—7.25 (m, 5H), 7.15—7.14 (m, 1H), 7.06—6.87 (m, 5H), 5.99—5.93 (m, 2H), 4.06 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.1, 144.0, 138.4, 134.6, 131.9, 130.9, 130.7, 129.2, 128.4, 128.2, 127.8, 126.1, 123.6, 121.6, 121.4, 111.5, 64.4, 55.6, 21.4; MS (EI, 70 eV) *m*/*z* (%): 466 (M^+, 17), 347 (37), 205 (21), 190 (11), 178 (6), 134 (100). Anal. calcd for $C_{23}H_{19}IN_2O$: C 59.24, H 4.11, N 6.01; found C 59.15, H 4.06, N 6.24.

Methyl *N*-(4-chlorophenyl)-3-iodo-5-methyl-2-phenyl-1*H*-indole-1-carbimidate (**4u**): White solid (yield 74%), m.p. 189—191 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.32—7.27 (m, 5H), 7.17—7.16 (m, 1H), 7.08—7.06 (m, 2H), 6.85—6.84 (m, 2H), 5.86 (d, J=6.6 Hz, 2H), 4.07 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.5, 142.7, 138.1, 134.4, 132.1, 131.0, 130.5, 129.2, 128.9, 128.3, 127.9, 126.2, 122.7, 121.7, 121.6, 111.4, 64.8, 55.8, 21.4; MS (EI, 70 eV) *m*/*z* (%): 500 (M^+, 21), 347 (70), 205 (35), 190 (19), 178 (10), 168 (84), 153 (100). Anal. calcd for $C_{23}H_{18}ClIN_2O$: C 55.17, H 3.62, N 5.59; found C 55.35, H 3.86, N 5.38.

Methyl 3-iodo-5-methyl-2-phenyl-*N*-(*p*-tolyl)-1*H*-indole-1-carbimidate (**4v**): White solid (yield 79%), m.p. 152—154 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.29—7.20 (m, 5H), 7.12—7.07 (m, 3H), 6.69—6.68 (m, 2H), 5.90 (d, J=7.2 Hz, 2H), 4.00 (s, 3H), 2.48 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.8, 141.4, 138.5, 134.5, 133.1, 131.8, 130.9, 130.8, 129.3, 129.0, 128.2, 127.8, 126.0, 121.5, 121.3, 111.5, 64.2, 55.5, 21.4, 20.8; MS (EI, 70 eV) *m*/*z* (%): 480 (M^+, 14), 347 (35), 205 (18), 190 (10), 178 (5), 148 (74), 133 (100). Anal. calcd for $C_{24}H_{21}IN_2O$: C 60.01, H 4.41, N 5.83; found C 60.34, H 4.37, N 6.04.

Methyl *N*-(4-chlorophenyl)-3-iodo-2-phenyl-1*H*-indole-1-carbimidate (**4w**): White solid (yield 74%), m.p. 159—161 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.52—7.49 (m, 1H), 7.45—7.42 (m, 1H), 7.38—7.30 (m, 5H), 7.10—7.09 (m, 2H), 6.86—6.85 (m, 2H), 5.90—5.84 (m, 2H), 4.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.4, 142.6, 138.2, 136.1, 130.9, 130.4, 129.2, 129.0, 128.4, 128.0, 124.8, 122.7, 122.6, 122.0, 111.7, 64.2, 55.5, 21.4, 20.8; MS (EI, 70 eV) *m*/*z* (%): 486 (M^+, 18), 333 (58), 204 (10), 190 (35), 170 (28), 168 (84), 153 (100). Anal. calcd for $C_{22}H_{16}ClIN_2O$: C 54.29, H 3.31, N 5.76; found C 54.46, H 3.09, N 5.82.

Results and Discussion

The easily accessible iminophosphoranes **1** were treated with aromatic isocyanate in dry CH_2Cl_2 to give carbodiimides **2**. Further reaction of **2** with various nucleophiles (HY, such as secondary amines or alcohols) provided the (2-alkynylphenyl)guanidine (or isourea) intermediates **3**. In the presence of 3 equiv. of anhydrous potassium carbonate and 2 equiv. of molecular iodine, the (2-alkynylphenyl)guanidines (or isoureas) **3** were converted easily to 3-iodoindole *N*-carboximidamides and *N*-carboximidoates **4** in satisfactory yields at room temperature (Scheme 1). The results are listed in Table 1. The structure of indoles **4** was confirmed by their spectrum data. For example, the ^{1}H NMR spectrum of **4a** shows multiplets at δ 3.87—3.54 and 3.18—3.14 due to the OCH_2 and NCH_2 respectively. The signals attributable to the ArH are found at δ 7.51—5.88 as mutiplet (the relative high field absorption at δ 5.89 can be due to the aryl-2-H of the ArN= group, showing its existence as *N*-carboximidamide). The ^{13}C NMR spec-

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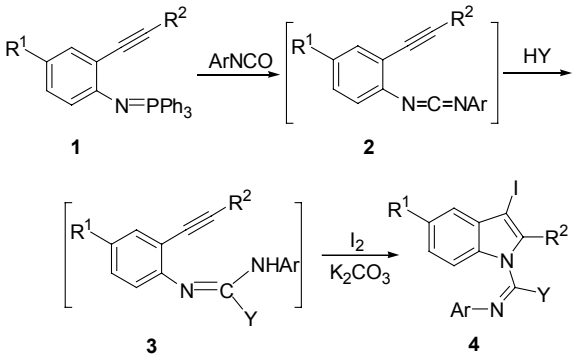
trum data in **4a** showed the signals of the two OCH_2 at δ 66.5 and 64.3, and the two NCH_2 at δ 46.5 and 46.0. The MS spectrum of **4a** shows molecular ion peak at *m*/*z* 541 with 4% abundance.

Scheme 1 Preparation of 3-iodoindoles **4** by a sequential aza-Wittig/iodine induced cyclization



R^1 = H, Me; R^2 = Ph, CH_2OCH_2Ph
Ar = Ph, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 3-Me-C_6H_4
Y = NR^3R^4, OR^5

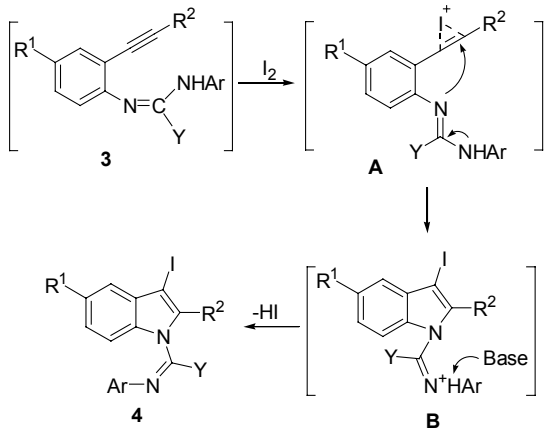
Table 1 Preparation of compounds **4a**—**4s**

	R^1	R^2	Ar	Y	Yield[a]/%
4a	H	Ph	4-Cl-C_6H_4	Morpholin-4-yl	77
4b	H	Ph	4-F-C_6H_4	Morpholin-4-yl	80
4c	H	Ph	Ph	Morpholin-4-yl	85
4d	H	Ph	4-Me-C_6H_4	Morpholin-4-yl	84
4e	H	Ph	3-Me-C_6H_4	Morpholin-4-yl	81
4f	H	Ph	Ph	N(*n*-Bu)$_2$	84
4g	H	Ph	Ph	N(*i*-Pr)$_2$	79
4h	H	Ph	Ph	N(*n*-Pr)$_2$	84
4i	Me	Ph	Ph	Piperidin-1-yl	75
4j	Me	Ph	Ph	Pyrrolidin-1-yl	79
4k	Me	Ph	Ph	Morpholin-4-yl	80
4l	H	CH_2OCH_2Ph	Ph	Morpholin-4-yl	82
4m	H	CH_2OCH_2Ph	4-Cl-C_6H_4	Morpholin-4-yl	78
4n	H	CH_2OCH_2Ph	4-Cl-C_6H_4	Pyrrolidin-1-yl	72
4o	H	CH_2OCH_2Ph	4-Cl-C_6H_4	Piperidin-1-yl	74
4p	H	Ph	4-Cl-C_6H_4	OEt	68
4q	Me	Ph	Ph	OEt	85
4r	Me	Ph	4-Cl-C_6H_4	OEt	76
4s	Me	Ph	4-Me-C_6H_4	OEt	81
4t	Me	Ph	Ph	OMe	84
4u	Me	Ph	4-Cl-C_6H_4	OMe	74
4v	Me	Ph	4-Me-C_6H_4	OMe	79
4w	H	Ph	4-Cl-C_6H_4	OMe	74

[a] Isolated yield.

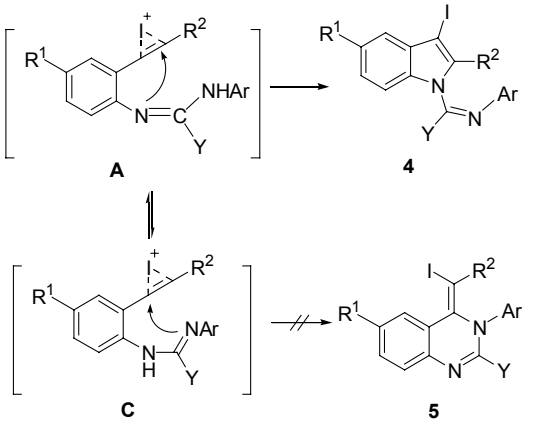
A plausible mechanism for the transformations described above was suggested in Scheme 2. It presumably involves (i) the formation of complex **A** through the coordination of the alkynyl moiety of **3** with the electrophile iodide, (ii) regioselective nucleophilic anti-attack of the nitrogen of the guanidine or isourea on the activated triple bond to produce the salt **B**, and (iii) dehydroiodination of the presumed intermediate **B** by the base K_2CO_3 and formation of indole product **4**.

Scheme 2 Proposed mechanism for the synthesis of **4**



It is noteworthy that this reaction shows very high regioselectivity. Presumably the cyclization of (2-alkynylphenyl)guanidine (or isourea) intermediate **3** could produce two products (Scheme 3). The indole derivatives **4** should be obtained from the complex **A**, while the complex **C** could cyclize into quinazoline derivatives **5**. However, only one exclusive product **4** was observed and isolated in satisfactory yields.

Scheme 3 Regioselective formation of 3-iodoindoles **4**



Conclusions

We have developed an efficient regioselective synthesis of 3-iodoindole *N*-carboximidamides and *N*-carboximidoates via aza-Wittig/iodine induced cyclizations. The mild reaction conditions and the easy commercial availability of starting material make this method a valuable tool for generating 3-iodoindole *N*-carboximid-

amides and *N*-carboximidoates, which may serve as versatile intermediates for further transformation in combinatory or medicinal chemistry.

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