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Efficient Regioselective Synthesis of Indole *N*-Carboximidamides and *N*-Carboximidoates by a Sequential Aza-Wittig/Ag(I)-Catalyzed Cyclization

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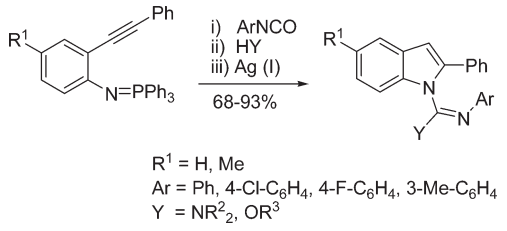

An efficient Ag(I)-catalyzed regioselective cyclization of (2-alkynylphenyl)guanidine or (2-alkynylphenyl)isourea to indole *N*-carboximidamides or *N*-carboximidoates has been developed. The approach has the advantages of high regioselectivity, mild reaction conditions, easily accessible starting materials, and good yields.

The chemistry of indoles has received particular attention because the indole moiety is a structural component of a vast number of bioactive natural and synthetic compounds.[1] Some *N*-aryl or *N*-acyl indoles exhibit wide pharmacological activity and could be used as selective hPPARγ receptor agonists,[2] high-affinity reagents for the 5-HT$_6$ receptor,[3] and cyclooxygenase (COX) inhibitors.[4] Indole-1-carboxamides could also be used as agrochemical fungicides,[5] anti-inflammatory drugs,[6] and perfume ingredients.[7] However, indole *N*-carboximidamides and *N*-carboximidoates are rarely investigated probably due to the fact that they are not easily accessible by routine synthetic methods.[8]

The synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous well-established classical methods for the preparation of indoles have been developed.[9] Recently, one of the most convenient methods for catalytic intramolecular cyclization of 2-alkynylaniline derivatives into polysubstituted indole derivatives has been paid particular attention.[10] The reaction could be catalyzed by a strong base, such as NaOEt,[11] KO*t*-Bu,[12] and KH,[13] or by Lewis acidic iodine complexes,[14] or by various late transition metal complexes involving Pd,[15] Cu,[16] In,[17] Au,[18] Fe,[19] Ag,[20] etc. However, to the best of our knowledge, analogous intramolecular cyclization of a (2-alkynylphenyl)guanidine (or isourea) has never been reported.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[21]

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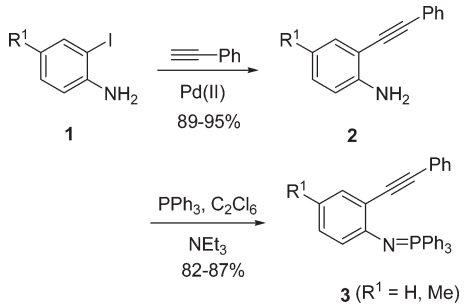
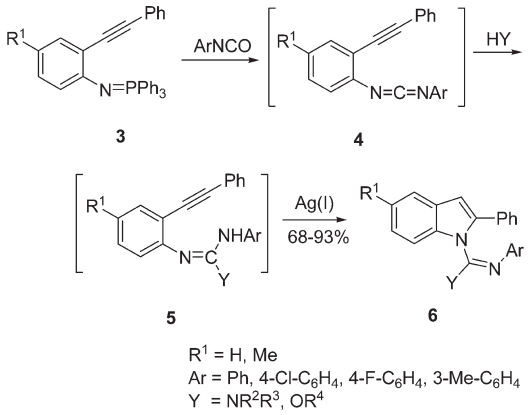
SCHEME 1



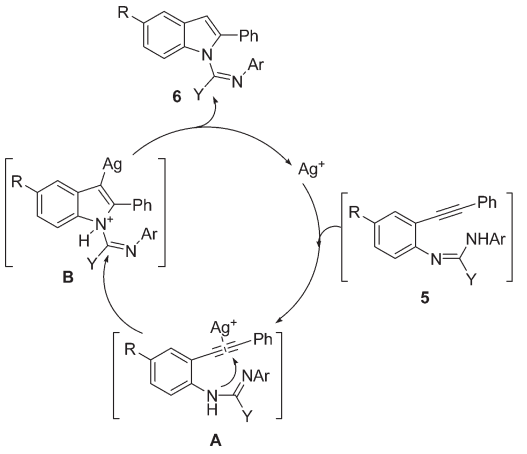
SCHEME 2



Recently we have been interested in the synthesis of thienopyrimidinones,[22] triazolopyrimidinones,[23] guanines,[24] quinazolinones,[25] and imidazolinones[26] via the aza-Wittig reaction, with the aim of evaluating their biological activities. In this study, we first report a mild and efficient synthesis of indole *N*-carboximidamides and *N*-carboximidoates by Ag(I)-catalyzed intramolecular cyclization of (2-alkynylphenyl)guanidines (or isoureas), which were obtained by aza-Wittig reaction and further reaction of the carbodiimides with amines or alcohols.

The iminophosphoranes **3** (Scheme 1) were synthesized according to standard protocols.[27] Sonogashira coupling of 2-iodoaniline derivatives **1** with the phenyl acetylene led to 2-phenylethynylaniline derivatives **2** in excellent yields,[28] which were converted to the corresponding iminophosphoranes **3** via reaction with triphenylphosphine, hexachloroethane, and triethylamine.

SCHEME 3



Reaction of iminophosphorane **3** with aromatic isocyanates at room temperature furnished the required carbodiimides **4** (Scheme 2), which were allowed to react with nucleophiles (HY, such as secondary amines or alcohols) to provide the (2-alkynylphenyl)guanidine (or isourea) intermediates **5**. Even in the presence of a strong base, such as NaOEt, KO*t*-Bu, and NaH, under refluxing conditions, **5** did not cyclize. However, when a catalytic amount of $AgNO_3$ was added, **5** was converted easily to indole *N*-carboximidamides or *N*-carboximidoates **6** in moderate to excellent yields (68−93%) at room temperature. The results are listed in Table 1.

TABLE 1. Yields of Compounds 6a−w

compd	R	Ar	Y	yield (%)[a]
6a	H	Ph	NEt_2	84
6b	H	Ph	$N(Pr\text{-}n)_2$	74
6c	H	Ph	morpholin-4-yl	72
6d	H	Ph	pyrrolidin-1-yl	76
6e	H	4-F-Ph	NEt_2	85
6f	H	4-Cl-Ph	$N(Pr\text{-}n)_2$	74
6g	H	4-Cl-Ph	morpholin-4-yl	71
6h	H	4-Cl-Ph	piperidin-1-yl	70
6i	H	3-Me-Ph	$N(Pr\text{-}n)_2$	80
6j	H	3-Me-Ph	morpholin-4-yl	78
6k	H	3-Me-Ph	pyrrolidin-1-yl	71
6l	Me	Ph	morpholin-4-yl	72
6m	Me	Ph	piperidin-1-yl	81
6n	Me	Ph	pyrrolidin-1-yl	87
6o	Me	4-F-Ph	pyrrolidin-1-yl	83
6p	Me	4-Cl-Ph	morpholin-4-yl	72
6q	Me	4-Cl-Ph	piperidin-1-yl	88
6r	Me	3-Me-Ph	piperidin-1-yl	77
6s	H	Ph	OMe	78
6t	H	4-Cl-Ph	OMe	72
6u	H	4-Cl-Ph	OEt	88
6v	Me	Ph	OMe	93
6w	Me	4-Cl-Ph	OEt	68

[a]Isolated yield.

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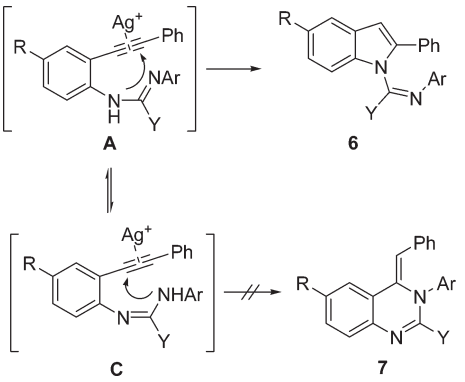
SCHEME 4



The intramolecular cyclization of 2-alkynylaniline derivatives to a triple bond has been extensively investigated by using various late transition metal reagents as effective catalysts; however, the cyclization often requires thermal conditions or needs a solvent with Lewis basicity or a general base. Considering the good nucleophilicity of the guanidine or isourea group in intermediate **5**, the cyclization of **5** to **6** was achieved at mild room temperature. We therefore compared the different catalytic abilities among Pd(II), Cu(I), and Ag(I) at room temperature. Cyclization of the (2-(phenylethynyl)phenyl)guanidine (**5a**) was examined first (Table 2). In the presence of 5 mol % of $AgNO_3$, the reaction of **5a** proceeded smoothly in a short time (0.5 h at 25 °C) in CH_3CN to give **6a** in 84% isolated yield (entry 1, Table 2). Through control experiments, we found $Pd(PPh_3)_2Cl_2$ was inactive (entry 2, Table 2); however, the reaction could be slowly catalyzed by $Pd(OAc)_2$ or CuI in DMF or CH_3CN for 24 h (entry 3−6, Table 2). The cyclization could also take place by a reaction with a catalyst such as $PdCl_2$ for 1−3 h in DMF or CH_3CN in low yields probably due to side reactions (entries 7 and 8, Table 2).

The crystal structure of indole **6c** has been determined by X-ray diffraction and is shown in Figure 1 in the Supporting Information. The X-ray crystal analysis confirmed the structure of the product and the (*Z*) geometry about the imine bond. On the basis of the results obtained and from the related literature,[29] a possible mechanism for the Ag(I)-catalyzed intramolecular cyclization can be proposed (Scheme 3). It presumably involves (i) the formation of complex **A** through the coordination of the alkynyl moiety of **5** with Ag(I), (ii) regioselective nucleophilic attack of the activated triple bond by NH of the guanidine or isourea to give the vinylsilver species **B**, and (iii) proton transfer with lose of Ag(I), which enters a new catalytic cycle, and formation of indole product **6**.

It is noteworthy that this reaction shows very high regioselectivity. Presumably the cyclization of (2-alkynylphenyl)guanidine (or isourea) intermediate **5** could produce two products (Scheme 4). The indole derivatives **6** should be obtained from the complex **A**, while the complex **C** could cyclize into quinazoline derivatives **7**. However, only one exclusive product **6** was observed and isolated in satisfactory yields, and their structure was confirmed by spectral and X-ray crystallographic analysis. The reasons for the above regioselectivity are not yet very clear.

TABLE 2. Different Catalytic Abilities among Pd(II), Cu(I), and Ag(I)[a]

entry	catalyst	solvent	time (h)	yield (%)[b]
1	$AgNO_3$	CH_3CN	0.5	84
2	$Pd(PPh_3)_2Cl_2$	CH_3CN	24	0
3	$Pd(OAc)_2$	DMF	24	30
4	$Pd(OAc)_2$	CH_3CN	24	35
5	CuI	DMF	24	27
6	CuI	CH_3CN	24	34
7	$PdCl_2$	DMF	3	30
8	$PdCl_2$	CH_3CN	1	35

[a]Reactions were carried out with 0.4 mmol of **5a** and 5 mL of solvent in the presence of 5 mol % of catalyst at 25 °C. [b]Isolated yield.

In summary, a highly efficient cyclization of (2-alkynylphenyl)guanidine (or isourea) intermediates to indole *N*-carboximidamides or *N*-carboximidoates was developed by using Ag(I) as a catalyst under mild reaction conditions. The versatile one-pot approach has the advantages of high regioselectivity, mild reaction conditions, easily accessible starting materials, and good yields.

Experimental Section

Representative Procedure for the Preparation of Indole Derivatives (6). To a solution of iminophosphorane (**3**) (3.0 mmol) in dry methylene chloride (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 °C, the solvent was removed under reduced pressure and Et_2O/petroleum ether (1:2, 12 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides (**4**), which were used directly without further purification. To a solution of carbodiimides (**4**) prepared above in anhydrous acetonitrile (10 mL) was added secondary amines (HNR^2_2, 3.0 mmol) or anhydrous alcohol (ROH, 5 mL) with several drops of sodium alkoxide (RONa) in the corresponding ROH. After the reaction mixture was stirred for 0.5−6 h, the guanidine or isourea intermediate (**5**) was generated. Without further purification, the reaction mixture was treated with $AgNO_3$ (0.15 mmol, 25 mg) and stirred for 0.5 h at room temperature until the color of the reaction mixture turned dark. The mixture was filtered to remove the solid catalyst and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1, petroleum ether:diethyl ether) to yield indole derivatives (**6**).

(*Z*)-*N*,*N*-Diethyl-*N*′,2-diphenyl-1*H*-indole-1-carboxamidine (6a): light yellow oil (yield 84%); IR (KBr, cm^{-1}) 3058, 2947, 2933, 1625, 1589, 1455, 1421, 1343, 761, 748, 693; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.54 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.34−7.29 (m, 5H), 7.22−7.19 (m, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.75 (t, J = 7.8 Hz, 2H), 6.66 (t, J = 7.2 Hz, 1H), 6.57 (s, 1H), 6.07 (d, J = 7.8 Hz, 2H), 3.79−3.74 (m, 2H), 3.15−3.07 (m, 2H), 1.37 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 147.6, 144.2, 139.4, 137.3, 131.8, 128.1, 127.8, 127.6, 127.2, 122.8, 121.7, 121.6, 121.0, 120.5, 111.2, 103.6, 41.9, 41.4, 14.0, 11.7; MS (EI, 70 eV) m/z (%) 367 (M^+, 42), 295 (3), 193 (19), 175 (100), 165 (15), 147 (11), 119 (37), 92 (3), 77 (14). Anal. Calcd for $C_{25}H_{25}N_3$: C, 81.71; H, 6.86; N, 11.43. Found: C, 81.89; H, 6.93; N, 11.69.

(*E*)-Methyl 2-phenyl-*N*-phenyl-1*H*-indole-1-carbimidate (6s): white solid (yield 78%); mp 100−101 °C; IR (KBr, cm^{-1}) 3079,

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3062, 3001, 2949, 1685, 1595, 1454, 1440, 1370, 1320, 1271, 1214, 1127, 760, 741, 692; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.55 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.25−7.07 (m, 7H), 6.81−6.79 (m, 3H), 6.47 (s, 1H), 5.99−5.97 (m, 2H), 4.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 147.1, 144.3, 139.3, 137.1, 131.8, 128.3, 128.1, 127.5, 127.0, 123.3, 123.2, 121.6, 121.4, 120.6, 111.5, 105.0, 55.5; MS (EI, 70 eV) m/z (%) 326 (M^+, 97), 234 (5), 206 (100), 193 (19), 165 (28), 119 (67), 91 (16), 77 (9). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.17; H, 5.62; N, 8.73.

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Supporting Information Available: Full spectral details, X-ray diffraction of **6c**, and copies of the ^{1}H and ^{13}C NMR spectra of compounds **6a**−**w**. This material is available free of charge via the Internet at http://pubs.acs.org.