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Chemistry of aminophenols. Part 1: Remarkable additive effect on Sonogashira cross-coupling of 2-carboxamidoaryl triflates and application to novel synthesis of indoles

Wei-Min Dai,* Dian-Shun Guo and Li-Ping Sun

Combinatorial Chemistry Laboratory, The Biotechnology Research Institute and Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

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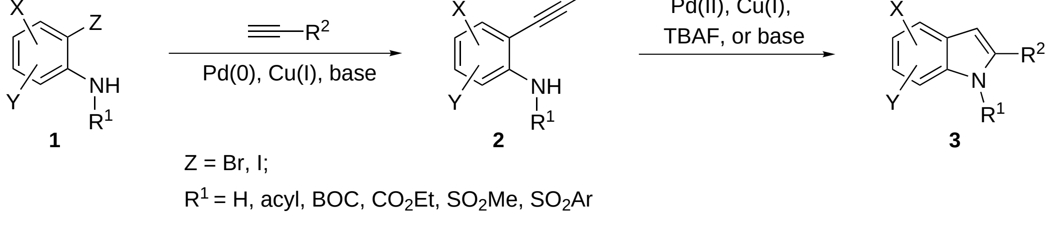
Abstract—A novel and general synthesis of indoles has been established by utilizing 2-aminophenols as the starting materials. The key step is a modified Pd(0)–Cu(I)-catalyzed cross-coupling of 1-alkynes with 2-carboxamidoaryl triflates in the presence of n-Bu_4NI as the additive. The 2-alkynylanilides obtained were subjected to an alkoxide-mediated cyclization to provide a number of indole containing compounds possessing substituents at the C2, C4, C5, and/or C6 position(s) in good overall yields. © 2001 Elsevier Science Ltd. All rights reserved.

Since the discovery and development of metal-catalyzed cross-coupling reactions in the 1970s, this powerful methodology has been widely used in synthetic organic chemistry over the last 30 years.[1] Among the active metals, Ni(0) and Pd(0)[2] complexes are the most popularly used catalysts for cross-coupling reactions. Numerous Pd(0) and Pd(II) complexes enjoy applications in the synthesis of heterocyclic compounds[3] that are biologically active and/or used as pharmaceutical compositions. For example, the Sonogashira cross-coupling reaction[4] of 2-haloanilides **1** with 1-alkynes in the presence of Pd(0)–Cu(I) gives 2-alkynylanilides **2** (Scheme 1). The latter cyclize under various metal-,[5] alkoxide-,[6] fluoride-,[7] or TMG (tetramethylguanidine)-[8] mediated conditions to furnish indoles **3**. On the other hand, 2-alkynylanilides **2** can react further with aryl or vinyl triflates[9] under Pd(0)–Cu(I) catalysis to produce 2,3-disubstituted indoles.[10] Moreover, 2,3-disubstituted indoles can be obtained directly from 2-iodoaniline derivatives **1** (Z = I) via the Pd(0)-catalyzed annulation with internal alkynes, a process referred to as the Larcok indole synthesis.[11] We report here on a novel synthesis of substituted indoles[12] using 2-aminophenols as the starting materials, and the remarkable effect of iodide anion on Sonogashira cross-coupling reactions of 2-carboxamidoaryl triflates with 1-alkynes.[13]

2-Alkynylanilides **2** are commonly synthesized from 2-iodoanilines which are prepared by iodination of anilines with bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4).[5p] Sometimes, 2-bromoanilines can be used in the cross-coupling reaction under rather harsh reaction conditions with low yields.[6b,f] The electron-deficient 2-nitroaryl chlorides and bromides are alternative sub-



Scheme 1.

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* Corresponding author. Fax: +852 2358 1594; e-mail: chdai@ust.hk

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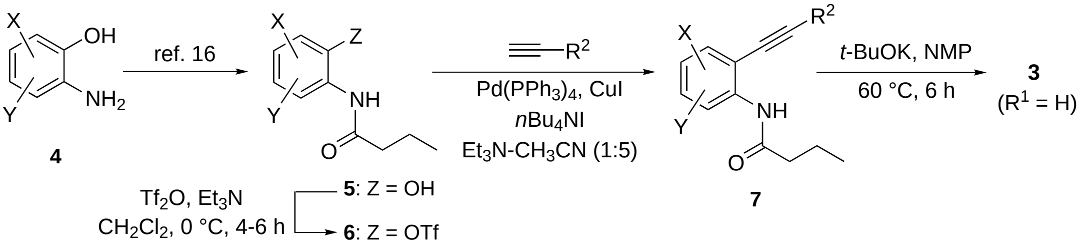
strates which exhibit reasonably good reactivity toward the Sonogashira cross-coupling reaction.[14] To the best of our knowledge, the commercially available 2-aminophenols **4** have not been used for the general synthesis of indoles. We took the advantage of the structural diversity of 2-aminophenols and used them as the starting materials for the design and synthesis of indole compound libraries. Therefore, we explored this synthetic approach, as illustrated in Scheme 2,[15] which consists of key cross-couplings of the triflates **6** with 1-alkynes. According to our previously reported procedures,[16] **4** can be selectively *N*-acylated to give the amides **5** in 89–98% yield by (i) heating with 3-butyryl-1,3-thiazoline-2-thione in refluxing THF (Method A); (ii) treating with NaH and butyryl chloride in THF at 20°C (Method B), and (iii) heating with butyryl chloride and pyridine in THF at 40–50°C (Method C).[17] Treatment of the amides **5** with 1.1 equiv. of Tf_2O and 1.3 equiv. of Et_3N in CH_2Cl_2 at 0°C gave the corresponding triflates **6** in 77–96% yield. Under these conditions, sulfonylation at the amide nitrogen atom could be avoided.

Aryl triflates have been reported to undergo the Sonogashira cross-coupling with 1-alkynes under the standard conditions of catalytic Pd(0) and Cu(I) plus an excess amine base.[13] A 2-alkoxycarbonyl group presented in the aryl and vinyl triflates did not show any inhibitory effect on the cross-coupling reaction.[13d,h] Selective stepwise cross-coupling of naphthalene 2,3-bistriflate with two different 1-alkynes was also achieved without difficulty.[13b,c] In 1996, Powell and Rychnovsky reported an iodide acceleration phenomenon in the Sonogashira cross-coupling of the substituted phenyl 1,2-bistriflates in the formation of 1,2-dialkynylbenzenes.[13f] Activation of Pd(0) catalyst by iodide anion before oxidative addition to the triflate was suggested. We observed a similar additive effect on the cross-coupling reactions of the triflates **6**. Some of the results are summarized in Table 1. In the absence of an additive (entry 1), reaction of **6a** with phenylacetylene initially proceeded in Et_3N–CH_3CN (1:5)[13g] at 20°C to form **7a**, but it stopped at about 30% conversion of **6a**. When 1.0–1.5 equiv. of n-Bu_4NBr was added, the isolated yield of **7a** increased from 29% to ca. 60% (entries 2–3). Sharp rate acceleration was observed when n-Bu_4NI was used (entries 4–7). Conversion of **6a** completed within 24 h in the presence of over 1.0 equiv. of n-Bu_4NI to provide **7a** in 84–91% yield (entries 5–7). These data indicated that iodide is a better additive than bromide. We also examined other palladium catalysts such as $Pd(PPh_3)_2Cl_2$ (entry 8), $Pd(PhCN)_2Cl_2$, and $Pd(OAc)_2$ and found that the cross-coupling reaction did not occur in the presence of iodide or bromide without PPh_3. A parallel experiment with the *meta* analog of the triflate **6** (X = Y = H), which underwent the cross-coupling reaction *without* n-Bu_4NI at 80°C, confirmed that the acyl group in **6** is the origin of the additive effect. It is highly possible that complexation of the acyl group with the Pd(II) species possessing a triflate anion ligand, which was formed in the oxidative addition step of the catalytic cycle, modifies the chemical and/or physical properties of the complex. Iodide anion may act by replacing the triflate anion in the square-planar Pd(II) complex or to form a new pentacoordinated anionic palladium species,[18] which makes the following transmetalation or reductive elimination occur easily. It is clear that the iodide anion *does not* activate the Pd(0) species for oxidative addition to the triflates **6** because the cross-coupling reaction proceeds without added iodide anion in the initial stage. The catalyst became poisoned by the triflate anion as the cross-coupling reaction progressed.

We synthesized a number of 2-alkynylanilides **7a**–**i** in 71–98% yield from triflates **6a**–**g** via the Pd(0)–Cu(I)-catalyzed cross-coupling reaction in the presence of 1.5 equiv. of n-Bu_4NI (Scheme 2 and Table 2). Electron-rich substituents deactivated the triflates and the reac-



Scheme 2.

Table 1. Effects of additives on the cross-coupling of triflate **6a** (X = Y = H) with phenylacetylene[a]

Entry	Additive (mol%)	t (h)	**7a** (R^2 = Ph, %)	Entry	Additive (mol%)	t (h)	**7a** (R^2 = Ph, %)
1	None[b]	17	29	5	n-Bu_4NI (100)	24	84
2	n-Bu_4NBr (100)[b]	24	58	6	n-Bu_4NI (150)	24	91
3	n-Bu_4NBr (150)	24	62	7	n-Bu_4NI (300)[b]	15	91
4	n-Bu_4NI (50)	24	56	8	n-Bu_4NI (300)[c]	36	82

[a] Carried out with 10 mol% $Pd(PPh_3)_4$ and 30 mol% CuI in Et_3N–CH_3CN (1:5) at 20°C under N_2.

[b] 20% CuI was used.

[c] $Pd(PPh_3)_2Cl_2$ was used to replace $Pd(PPh_3)_4$.

Table 2. Synthesis of 2-alkynylanilides **7**[a] and indoles **3** ($R^1=H$)

Entry	X and Y;[b] R^2	*t* (h), **7** (%)	**3** (%)	Entry	X and Y;[b] R^2	*t* (h), **7** (%)	**3** (%)
1	**a**: H, H; Ph	24, 91	81	6	**f**: H, 6-Cl; Ph	6, 94	81
2	**b**: H, 5-Me; Ph	22, 96	81	7	**g**: H, 6-SO_2Et; Ph	3, 92	76
3	**c**: H, 6-Me; Ph	2, 97[c]	84	8	**h**: H, H; $SiMe_3$	3, 94	93 ($R^2=H$)
4	**d**: 4,6-Me_2; Ph	24, 71[c]	78	9	**i**: H, H; *n*-Pr	3, 98	86
5	**e**: 5,6-$(CH_2)_4$; Ph	10, 95	81				

[a] Carried out with 10 mol% $Pd(PPh_3)_4$, 30 mol% CuI, and 150 mol% *n*-Bu_4NI in Et_3N–CH_3CN (1:5) at 20°C under N_2.

[b] Indole skeleton numbering was used here.

[c] The cross-coupling reactions were carried out at refluxing temperature. **7c** was obtained in 67% yield at 20°C for 24 h.

tions proceeded on heating (entries 3 and 4). In contrast, electron-deficient substituents activated the triflates so that the reaction times decreased from 24 h for **6a** to 3–6 h for **6f,g** at 20°C (entries 6 and 7). Cyclization of **7** occurred upon exposure to *t*-BuOK (1.2 equiv.)[6e–g] in 1-methyl-2-pyrrolidinone (NMP) at 60°C to provide indoles **3** where the 1-acyl group was removed presumably after the indole ring formation.[6b,d,e] We found that both *N*-benzoyl[6b] and benzyloxyacetyl analogs of **7a** gave the same indole **3a** under the basic conditions. The $SiMe_3$ group in **7h** was lost during the indole ring closure to give **3h**.[6b,e,f] Moreover, TMG could be used to replace *t*-BuOK for indole ring closure.[8]

In summary, we have successfully developed a novel and general synthesis of substituted indoles from 2-aminophenols. This approach enables indole compound library synthesis by taking advantage of the structural diversity of commercially available 2-aminophenols. A remarkable rate enhancement was observed for the Sonogashira cross-coupling reactions of 2-carboxamidoaryl triflates **6** in the presence of iodide anion. This finding is useful for understanding the reaction mechanisms of the related cross-coupling reactions of significance in contemporary organic synthesis. Transfer of our indole synthesis from solution to solid supports is underway in our laboratory.

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