Convenient Indole Synthesis from 2-Iodoanilines and Terminal Alkynes by the Sequential Sonogashira Reaction and the Cyclization Reaction Promoted by Tetrabutylammonium Fluoride (TBAF)

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The sequential Sonogashira reaction and the cyclization reaction of various 2-iodoanilines and terminal alkynes in the presence of a palladium catalyst and tetrabutylammonium fluoride (TBAF) gave the corresponding 2-substituted indoles in good yields.

Key words indole; sequential cyclization; palladium-catalyzed reaction; 2-ethynylaniline; tetrabutylammnonium fluoride; terminal alkyne

Indole derivatives occur widely in natural products and have unique biological activities,[1] and many synthetic methods for construction of the indole ring have been reported.[2] Several cyclization methods from 2-ethynylanilines to indoles have been reported[3] and the syntheses of some natural products were achieved by the cyclization.[4—7]

The indole syntheses *via* 2-ethynylanilines usually require two steps, introduction of the ethynyl group onto the benzene ring and the subsequent cyclization reaction. Concerning the indole cyclization, we have reported the synthesis of 2-substituted indoles from *N*-(2-iodophenyl)methanesulfonamides and terminal alkynes using palladium catalysts in 1988.[8] The indole synthesis was utilized for the resin-bounded system by Zhang, *et al*.[9] However, the indole synthesis has a limitation in that the reaction requires a methylsulfonyl group on the amino group of the anilines.

We have also reported that the cyclization reaction of 2-ethynylanilines with tetrabutylammonium fluoride (TBAF) proceeds at refluxing or room temperature in THF to give 2-substituted indoles in excellent yields without affecting the bromo, chloro, cyano, ethoxycarbonyl, and ethynyl groups.[10] The 2-ethynylanilines, which were the starting materials for indole synthesis by the reaction with TBAF, were prepared by the Sonogashira reaction of 2-iodoanilines and terminal alkynes.

Although the Sonogashira reaction, which is the cross-coupling reaction of an aryl halide and a terminal alkyne catalysed by a Pd/Cu system, is a useful method of introduction of an alkynyl moiety to an arene,[11,12] the Sonogashira reaction sometimes requires large amounts of amines as a solvent or co-solvent. Thus, several new conditions for the Sonogashira reaction have been reported in order to enhance the utility of the reaction.[13—17] Mori and his co-workers have recently reported that TBAF or tetrabutylammonium hydroxide instead of amines can be employed as a base in the Sonogashira reaction.[18,19]

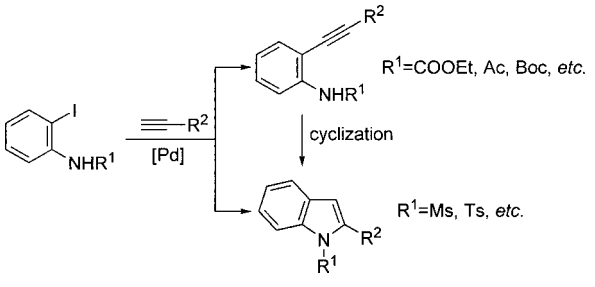

Chart 1

We here report a one-pot indole synthesis from 2-iodoanilines and terminal alkynes using a palladium catalyst in the presence of TBAF, combined with the above two applications of TBAF for cyclization reaction to indole and the Sonogashira reaction.

Results and Discussion

The reaction conditions for the indole synthesis from *N*-substituted 2-iodoanilines and 1-hexyne were examined as shown in Table 1. When a mixture of *N*-(2-iodophenyl)-methanesulfonamide (**1a**) and 1-hexyne with TBAF (3 eq), $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (10 mol%) in THF was refluxed for 2 h, 2-butyl-1-(methylsulfonyl)indole (**2a**) was afforded in 86% yield (entry 1). Under the previously reported conditions[8] using triethylamine, the Sonogashira reaction of **1a** and 1-hexyne at 80 °C for 24 h gave **2a** in 64% yield. Thus the reaction of 2-haloanilines having *N*-sulfonyl groups as a protection groups of amino group, and terminal alkynes using both TBAF and Et_3N gave the corresponding indoles.

The palladium-catalyzed reaction of ethyl *N*-(2-iodophenyl)carbamate (**1b**) and 1-hexyne with TBAF gave 2-butyl-1-(ethoxycarbonyl)indole (**2b**) in 81% yield (entry 2). However, the Sonogashira reaction of **1b** and 1-hexyne using triethylamine instead of TBAF as a base for 24 h also gave the coupling product (**4b**) in 90% yield, and **2b** or 2-butylindole could not be detected (entry 3).

Concerning the substituents on the amino group of 2-iodoanilines, the reaction of *N*-*tert*-butoxycarbonyl- (**1c**) and *N*-benzoyl-2-iodoaniline (**1e**) also gave the corresponding *N*-substituted indoles (**2c**, **e**) in 79 and 96% yields, respectively. However, for the efficient Sonogashira reaction and the subsequent indole cyclization of *N*-benzoyl-2-iodoaniline, 5 eq of TBAF was necessary, because the reactivity of *N*-acyl-2-iodoanilines was lower than that of *N*-phenylcarbamates. Although the reaction of *N*-acetyl-2-iodoaniline (**1d**) with 3 eq of TBAF gave a mixture of 2-butylindole (**3**) and *N*-acetyl-2-(1-hexynyl)aniline (**4d**), the reaction of **1d** with 5 eq of TBAF gave **3** as a sole product in 78% yield.

These results show that TBAF effectively functioned as a base in the Sonogashira reaction and also as a cyclization

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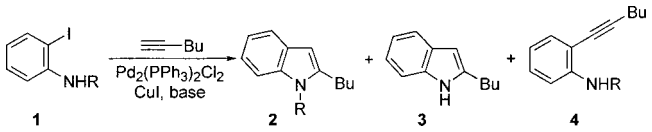
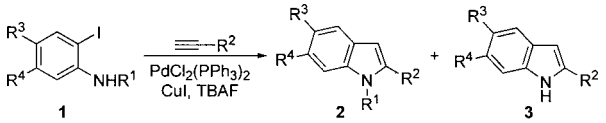
Table 1. Palladium-Catalyzed Reaction of 2-Iodoanilines and 1-Hexyne in the Presence of TBAF



Entry	1	R	Base (eq)	Time (h)	Yield (%)		
					2	3	4
1	**a**	SO_2Me	TBAF (3)	2	86 (64)[a]	0	0
2	**b**	COOEt	TBAF (3)	2	81	0	0
3	**b**	COOEt	Et_3N	24	0	0	90
4[b]	**c**	Boc	TBAF (3)	16	79	0	0
5	**d**	Ac	TBAF (3)	24	0	48	44
6	**d**	Ac	TBAF (5)	24	0	78	0
7	**e**	COPh	TBAF (5)	24	96	0	0

a) Figure in parentheses is a yield using Et_3N instead of TBAF (ref. 5). *b*) $Pd(PPh_3)_2Cl_2$ (10 mol%) and CuI (20 mol%) were used.

Table 2. The Palladium-Catalyzed Indole Synthesis from 2-Iodoanilines Having Various Substituents in the Presence of TBAF



Entry	1	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	
							2	3
1	**f**	COOEt	Ph	CN	H	4	0	90
2	**g**	COOEt	Bu	H	OMe	4	75	0
3[a]	**h**	Ac	Ph	H	Cl	16	0	94
4	**i**	Ac	Bu	H	Cl	21	0	84
5[a]	**j**	Ac	Bu	H	Cl	4	0	91

a) TBAF (5 eq) was used.

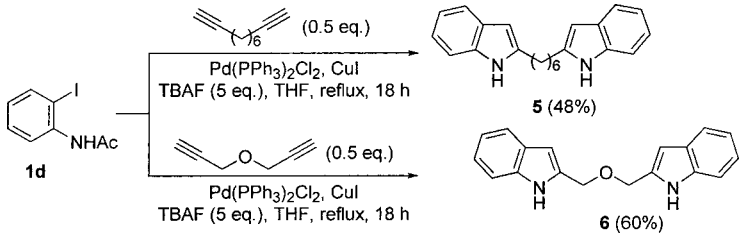


Chart 2

reagent from 2-ethynylanilines to the corresponding indoles.

On the basis of the above results, we next examined the indole synthesis from 2-iodoanilines having various substituents on the benzene ring with terminal acetylenes under the same reaction conditions. As shown in Table 2, the synthesis of the 2-phenyl- (**3f**, **h**) and 2-butylindoles (**2g**, **3i**) with a functional group such as a cyano, chloro, or methoxy group on the benzene moiety could also be achieved in 75—94% yields using the corresponding terminal acetylenes. In these cyclizations, except for the reaction of ethyl *N*-(2-iodo-5-methoxyphenyl)carbamate (**1g**), the removal of the substituents on the amino group occurs, and *N*-unsubstituted indoles (**3f**, **h**, **i**) were obtained.

As an application of this method, synthesis of 1,ω-di(2-indolyl)alkanes from 2-iodoanilines and terminal ω-alkadiynes was examined. The reaction of *N*-acetyl-2-iodoaniline with deca-1,9-diyne or dipropargyl ether under the same conditions, the Sonogashira reaction, the cyclization reaction with TBAF and the removal of the acetyl group doubly proceeded to give the corresponding 1,ω-di(2-indolyl) derivatives (**5**, **6**) in 48 and 60% yields, respectively, as shown in Chart 2.

We have also reported the selective monodesulfonylation of *N*,*N*-disulfonylarylamines with TBAF, because the synthesis of *N*-sulfonylarylamines by the reaction of some arylamines with sulfonyl chlorides yields a mixture of *N*-sulfonyl- and *N*,*N*-disulfonylarylamines.[20] On the basis of the selective monodesulfonylation of *N*,*N*-disulfonylarylamines, we tried a one-pot indole synthesis from *N*,*N*-bis(methylsul-

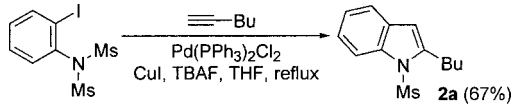


Chart 3

fonyl)-2-iodoaniline and 1-hexyne. As shown in Chart 3, the selective monodesulfonylation, the Sonogashira reaction, and the indole cyclization reaction with TBAF proceeded to give 2-butyl-1-(methylsulfonyl)indole (**2a**) in 67% yield.

Conclusion

The one-pot indole synthesis from 2-iodoanilines and terminal alkynes is achieved without the effect of functional groups under Sonogashira reaction conditions with TBAF as a base without dry conditions and complicated operations. Considering the easy availability of haloanilines, the good reactivity of the Sonogashira reaction, and the efficient cyclization reaction of 2-ethynylanilines with TBAF, the sequential indole synthesis with functional groups seems to be an easily and widely usable method.

Experimental

General Procedure for the Indole Synthesis from 2-Iodoanilines and Terminal Alkynes Using TBAF Promoted Palladium-Catalyzed Reaction A mixture of a 2-iodoaniline (1 mmol), an alkyne (1.5 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), THF (10 ml) and TBAF (1 M solution in THF, 3 or 5 mmol) was refluxed for the time shown in Tables 1 and 2. After removal of the THF, the residue was diluted with H_2O and extracted with AcOEt. The AcOEt extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography and recrystallization or distillation.

2-Butyl-1-(methylsulfonyl)indole (**2a**): Colorless needles from hexane. mp 79—80 °C (lit.[8] 81—82 °C). IR (KBr) cm^{-1}: 1454. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.45 (2H, sextet, J=7.3 Hz), 1.75 (2H, quintet, J=7.3 Hz), 2.95 (2H, t, J=7.3 Hz), 6.45 (1H, s), 7.23—7.29 (2H, m), 7.49 (1H, d, J=8.4 Hz), 7.99 (1H, d, J=8.5 Hz). MS m/z (%): 251 (M^+, 37), 209 (41), 130 (100).

2-Butyl-1-ethoxycarbonylindole (**2b**): White solid. bp 180 °C/3 mmHg (lit.[10] 180—190 °C/3 mmHg). IR (KBr) cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.4 Hz), 1.49—1.51 (5H, m), 1.64—1.74 (2H, m), 3.01 (2H, t, J=6.8 Hz), 4.52 (2H, q, J=7.4 Hz), 6.37 (1H, s), 7.17—7.24 (2H, m), 7.44 (1H, d, J=5.9 Hz), 8.11 (1H, d, J=8.2 Hz). MS m/z (%): 245 (M^+, 80), 203 (100), 174 (22), 130 (61).

Ethyl 2-(1-Hexynyl)phenylcarbamate (**4b**): Colorless liquid. bp 170 °C/3 mmHg (lit.[10] 170—175 °C/3 mmHg). IR (KBr) cm^{-1}: 3394, 2224, 1742. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.33 (3H, t, J=7.1 Hz), 1.36—1.66 (4H, m), 2.50 (2H, t, J=7.0 Hz), 4.24 (2H, q, J=7.1 Hz), 6.95 (1H, dt, J=7.9, 1.3 Hz), 7.26—7.30 (1H, m), 7.33 (1H, dd, J=7.9, 1.6 Hz), 7.41 (1H, m), 8.12 (1H, d, J=7.9 Hz). MS m/z (%): 245 (M^+, 71), 216 (21), 130 (100).

1-*tert*-Butoxycarbonyl-2-butylindole (**2c**): Colorless liquid. IR (KBr) cm^{-1}: 1732. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4 Hz), 1.44 (2H, sextet, J=7.4 Hz), 1.63—1.73 (11H, m), 3.00 (3H, t, J=7.9 Hz), 6.33 (1H, s), 7.14—7.24 (2H, m), 7.24 (1H, d, J=8.0 Hz), 8.10 (1H, d, J=8.0 Hz). MS m/z (%): 273 (M^+, 27), 217 (56), 175 (42), 130 (53), 57 (100). HR-MS m/z: 273.1719 (Calcd for $C_{17}H_{23}NO_2$: 273.1729).

2-Butylindole (**3**): Colorless liquid. bp 160 °C/3 mmHg (lit.[10] 155—160 °C/4 mmHg). IR (KBr) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.42 (2H, sextet, J=7.3 Hz), 1.71 (2H, quintet, J=7.3 Hz), 2.76 (2H, t, J=7.3 Hz), 6.23 (1H, s), 7.06 (1H, t, J=7.2 Hz), 7.13 (1H, t, J=7.2 Hz), 7.31 (1H, d, J=7.2 Hz), 7.53 (1H, d, J=7.2 Hz), 7.80—7.92 (1H, br). MS m/z (%): 173 (M^+, 57), 130 (100).

N-Acetyl-2-(1-hexynyl)aniline (**4d**): Colorless scales form hexane. mp 45 °C. IR (KBr) cm^{-1}: 3245, 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (2H, t, J=7.1), 1.54 (2H, sextet, J=7.1 Hz), 1.64 (2H, quintet, J=7.1 Hz), 2.2 (3H, s), 2.52 (2H, t, J=7.1 Hz), 7.00 (1H, t, J=7.6 Hz), 7.27 (1H, t, J=7.6 Hz), 7.34 (1H, d, J=7.6 Hz), 7.94 (1H, br), 8.35 (1H, d. J=7.6 Hz). MS m/z (%): 215 (M^+, 82), 173 (79), 158 (31), 144 (62), 130 (100). *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51%. Found: C, 78.08; H, 7.93; N, 6.54.

1-Benzoyl-2-butylindole (**2e**): Colorless liquid. IR (KBr) cm^{-1}: 3404, 1666. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 1.34 (2H, sextet, J=7.3 Hz), 1.63 (2H, quintet, J=7.3 Hz), 2.84 (2H, t, J=7.4 Hz), 6.47 (1H, s), 6.85 (1H, d, J=8.3 Hz), 6.97 (1H, t, J=8.3 Hz), 7.12 (1H, t, J=7.5 Hz), 7.49 (3H, t, J=7.8 Hz), 7.63 (1H, t, J=7.5 Hz), 7.73 (2H, d, J=7.8 Hz). MS m/z (%): 277 (M^+, 41), 248 (10), 235 (21), 105 (100). HR-MS m/z: 277.1479 (Calcd for $C_{19}H_{19}NO$: 277.1466).

2-Phenylindole-5-carbonitrile (**3f**): Colorless needles from hexane. mp 193—195 °C (lit.[10] 195 °C). IR (KBr) cm^{-1}: 3320, 2220. ^{1}H-NMR ($CDCl_3$) δ: 6.88 (1H, s), 7.37—7.51 (5H, m), 7.68 (2H, d, J=8.1 Hz), 7.85 (1H, s), 8.60—8.72 (1H, br). MS m/z (%): 218 (M^+, 100).

2-Butyl-1-ethoxycarbonyl-6-methoxyindole (**2g**): Colorless liquid. IR (KBr) cm^{-1}: 1738. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4 Hz), 1.40—1.54 (5H, m), 1.66 (2H, quintet, J=7.4 Hz), 3.00 (2H, t, J=7.4 Hz), 3.86 (3H, s), 4.49 (2H, q, J=7.4 Hz), 6.28 (1H, s), 6.84 (1H, dd, J=8.4, 2.4 Hz), 7.31 (1H, d, J=8.5 Hz), 7.74 (1H, d, J=2.4 Hz). MS m/z (%): 275 (M^+, 99), 232 (100), 204 (36), 160 (64). HR-MS m/z: 275.1519 (Calcd for $C_{16}H_{21}NO_3$: 275.1521).

2-Phenyl-6-chloroindole (**3h**): Colorless scales from hexane. mp 180—181 °C. IR (KBr) cm^{-1}: 3431. ^{1}H-NMR ($CDCl_3$) δ: 6.75 (1H, s), 7.08 (1H, dd, J=8.3, 2.0 Hz), 7.33 (1H, t, J=7.4 Hz), 7.38 (1H, s), 7.45 (2H, t, J=7.8 Hz), 7.51 (1H, d, J=8.5 Hz), 7.63 (2H, d, J=7.5 Hz), 8.34 (1H, br). MS m/z (%): 229 (M^++2, 37), 227 (M^+, 100), 192 (13). *Anal.* Calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15%. Found: C, 74.09; H, 4.52; N, 6.10.

2-Butyl-6-chloroindole (**3i**): Colorless scales from hexane. mp 88—90 °C. IR (KBr) cm^{-1}: 3402. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz), 1.43 (2H, sextet, J=7.3 Hz), 1.71 (2H, quintet, J=7.3 Hz), 2.73 (2H, t, J=7.3 Hz), 6.22 (1H, s), 7.05 (1H, dd, J=8.5, 2.0 Hz), 7.23 (1H, d, J=2.0 Hz) 7.42 (1H, d, J=8.5 Hz), 7.82 (1H, br). MS m/z (%): 209 (M^++2, 10), 207 (M^+, 31), 164 (100). *Anal.* Calcd for $C_{12}H_{14}ClN$: C, 69.39; H, 6.79; N, 6.74%. Found: C, 69.62; H, 6.75; N, 6.71.

1,6-Di(2-indolyl)hexane (**5**): Colorless scales from hexane–acetone. mp 164—165 °C IR (KBr) cm^{-1}: 3379. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.46 (4H, m), 1.71—1.73 (4H, m), 2.74 (4H, t, J=7.6 Hz), 6.22 (2H, s), 7.06 (2H, t, J=7.1 Hz), 7.11 (2H, t, J=7.5 Hz), 7.28 (2H, d, J=7.7 Hz), 7.52 (2H, d, J=7.5 Hz), 7.82 (2H, br). MS m/z (%): 316 (M^+, 83), 130 (100). *Anal.* Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.43; H, 7.67; N, 8.73.

Di(2-indolylmethyl)ether (**6**): Colorless needles from hexane–acetone. mp 140—141 °C. IR (KBr) cm^{-1}: 3388. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (4H, s), 6.44 (2H, s), 7.10 (2H, t, J=7.6 Hz), 7.17 (2H, t, J=7.7 Hz), 7.27 (2H, d, J=7.8 Hz), 7.58 (2H, d, J=7.8 Hz), 8.21 (2H, br). MS m/z (%): 276 (M^+, 14), 147 (12), 130 (100).

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