JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

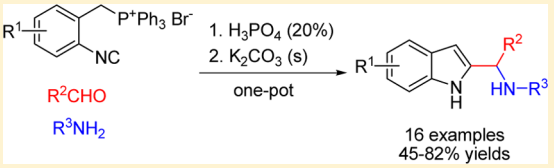
One-Pot Synthesis of Indoles by a Sequential Ugi-3CR/Wittig Reaction Starting from Odorless Isocyanide-Substituted Phosphonium Salts

Yan-Mei Yan, Yong Rao, and Ming-Wu Ding*

Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, People's Republic of China

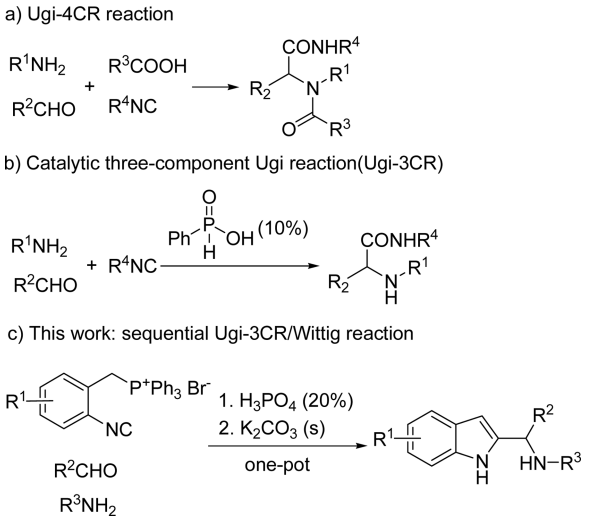
Supporting Information

ABSTRACT: A new one-pot preparation of indoles by a Ugi-3CR/Wittig sequence has been developed. The reaction of odorless isocyanide-substituted phosphonium salt **5**, aldehyde **6**, and amine **7** produced the indoles **9** in 45−82% yields via a sequential Ugi-3CR/Wittig reaction in the presence of H_3PO_4 and solid K_2CO_3, respectively.



Multicomponent reactions (MCRs) have attracted significant attention in organic chemistry because of their exceptional efficiency, high atom economy, and convenient one-pot operation.[1] MCRs usually are very useful for the construction of natural products and diverse heterocyclic scaffolds. The Ugi four-component (Ugi-4CR) reaction is an important MCR which generates an α-acylamino−carboxamide adduct efficiently by using the four components amine, aldehyde, acid, and isocyanide in a one-pot fashion (Scheme 1a).[2] The catalytic three-component Ugi reaction (Ugi-3CR), first reported by List, transforms an aldehyde, a primary amine, and an isocyanide to an α-amino amide in the presence of phenylphosphinic acid as catalyst (Scheme 1b).[3] Other acids were also successfully applied in the Ugi-3CR for preparation of 2-arylamino-2-phenylacetimidamides or isoindolin-1-ones.[4]

Scheme 1. Sequential Ugi-3CR/Wittig Reaction Approach to Indole Synthesis



Intramolecular Wittig reactions have received great attention in view of their utility in the synthesis of cyclic or heterocyclic compounds under mild reaction conditions.[5] The combination of the Ugi-4CR with a following intramolecular Wittig or Horner reaction has provided an efficient synthetic method for a series of heterocycles.[6] In our previous work, the Ugi-4CR/Wittig sequence was also utilized to prepare multisubstituted 1*H*-2-benzazepin-1-ones, 1,2-dihydroisoquinolines, and isoquinolin-1(2*H*)-ones starting from phosphonium precursors.[7] However, there has been no previous report on the sequential Ugi-3CR/Wittig reaction for the synthesis of heterocycles.[8]

The indole framework is one of the most valuable structures in many natural products and biologically active molecules.[9] Recently reported natural products include rhizovarins, melokhanines, vobatensines, and kopsiyunnanines, and some of them were found to show good cytotoxic activity.[10] The broad utility of indoles has prompted significant efforts toward their synthesis.[11] The traditional "Fischer indole synthesis" is an efficient method for the large-scale production of indoles starting from arylhydrazine and aldehyde or ketone.[12] A number of new methods based on transition-metal-catalyzed or other transformations have been reported in recent years.[13] For examples, some indole-2-carboxylate derivatives were prepared directly by palladium-catalyzed intramolecular aerobic amination of aryl C−H bonds.[13a] Rh-catalyzed C−H activation and alkyne annulations were successfully applied to the efficient synthesis of indoles by using hydrazone as a directing group.[13b] The 2,3-disubstituted indoles were synthesized by a base-promoted domino reaction starting from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes under mild conditions.[13c] Consequently, new and convenient synthetic methods to indoles are still desirable. Herein we wish to report a new, efficient synthesis of indoles by

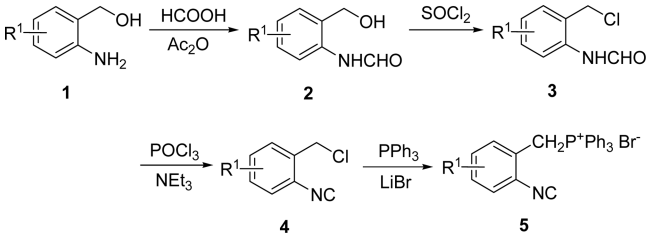
Received: January 3, 2017
Published: February 6, 2017

DOI: 10.1021/acs.joc.7b00004
J. Org. Chem. 2017, 82, 2772−2776

a sequential Ugi-3CR/Wittig reaction starting from odorless isocyanide-substituted phosphonium salts (Scheme 1c).

The isocyanide-substituted phosphonium salts **5** were prepared as illustrated in Scheme 2. Formylation of 2-aminobenzyl alcohols **1** with formic acid and acetic anhydride gave (2-hydroxymethylphenyl)formamides **2**, which were chlorinated with thionyl chloride to generate *N*-(2-chlorophenyl)formamides **3**. The formamides **3** were then converted into 2-(chloromethyl)phenyl isocyanides **4** upon treatment with phosphorus oxychloride in the presence of triethylamine. Final treatment of compounds **4** with PPh_3 and LiBr produced the isocyanide-substituted phosphonium salts **5**.[14] The phosphonium salts **5** were also reported as "neglected isocyanides" in a recent review on the use of the functionalized isocyanides.[15]

Scheme 2. Preparation of Isocyanide-Substituted Phosphonium Salts 5



Although many isocyanides were utilized in the Ugi reaction, the isocyanide-substituted phosphonium salts were not used previously.

We selected initially an Ugi reaction of (2-isocyanobenzyl)-triphenylphosphonium bromide (**5a**), 4-chlorobenzaldehyde (**6a**), and *m*-toluidine (**7a**) in the presence of an acid catalyst to optimize the reaction conditions (Scheme 3). As the above three compounds were stirred in methanol at room temperature for 24−48 h, the solvent was changed to toluene and the reaction mixture was heated to reflux for 1−2 h in the presence of solid K_2CO_3. The acid catalyst utilized had a notable effect on this sequential Ugi-3CR/Wittig reaction. When phenylphosphinic acid or $FeCl_3$ was used as the catalyst, no product **9a** was isolated (Table 1, entries 2 and 3). To our delight, when the catalyst was changed to phosphoric acid (20%), the product was obtained in 72% yield (entry 4). Reducing the amount of catalyst to 10% resulted in a rather lower yield (44%, entry 5). In cases where *p*-toluenesulfonic acid was utilized, the yields of **9a** decreased to 40−57% (entries 6 and 7).

Scheme 3. Preparation of Compound 9a

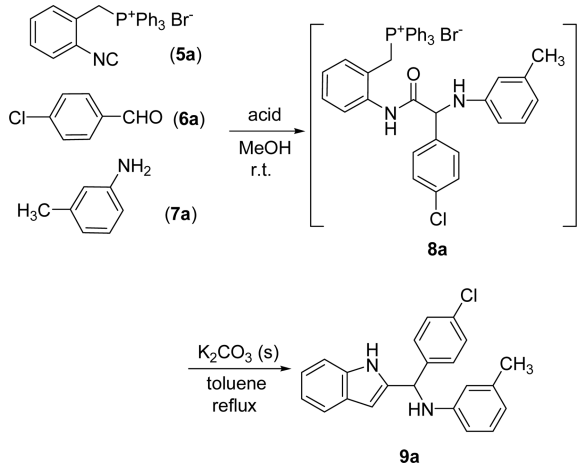
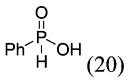
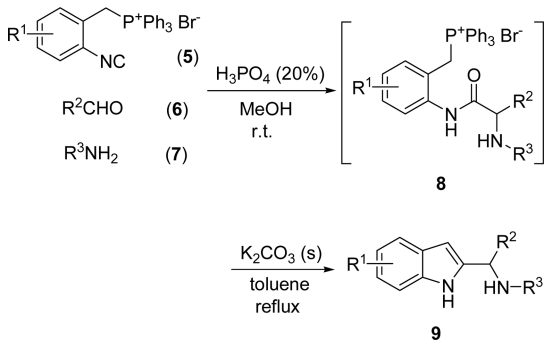


Table 1. Optimization of the Reaction Conditions

Entry	Catalyst (%)	Yield (%)
1	-	0
2	$FeCl_3$ (20)	0
3	 (20)	0
4	H_3PO_4 (20)	72
5	H_3PO_4 (10)	44
6	TsOH (20)	57
7	TsOH (10)	40

With the optimized conditions (Table 1, entry 4), various (2-isocyanobenzyl)triphenylphosphonium bromides **5**, aldehydes **6**, and amines **7** were employed for the one-pot reaction (Scheme 4). The reactions were carried out smoothly to give the corresponding indoles **9**, and moderate to good yields were often obtained with different substituents of the reactants (Table 2). When an aromatic aldehyde or amine (R^2 or R^3 = aryl) was used, good yields of the products (compounds **9a−j**, 70−82%) were generally reached; however, moderate yields (45−64%) were obtained in cases where an aromatic aldehyde or amine substituted by an ortho or strongly electron donating (OCH_3) group (compounds **9k−n**) was utilized, probably due to the diminished reactivity of the imine intermediates. Using an aliphatic aldehyde as one of the reaction components gave good yields of the indoles (compounds **9o,p**, 77−81%). However, no product was obtained when an aliphatic primary or secondary amine was applied (compounds **9q,r**). List and co-workers have reported that aliphatic primary and secondary amines reacted, albeit with lower yields (36−42%), under their Ugi-3CR conditions.[3] However, the isocyanides they used were all aliphatic isocyanides, which are generally more reactive than aromatic isocyanides in the Ugi reaction. The isocyanides we used were all substituted with aromatic groups, which have lower reactivity, and resulted in no product formation when aliphatic amines were used. Finally, when the R^1 substituent on phosphonium salts **5** was an electron-withdrawing group (R^1 = 5-Cl, 4-F; **9s,t**), no product was obtained, probably due to the lower reactivity of the isocyanide-substituted phosphonium salt **5**.

Scheme 4. Preparation of Indoles 9



DOI: 10.1021/acs.joc.7b00004
J. Org. Chem. 2017, 82, 2772−2776

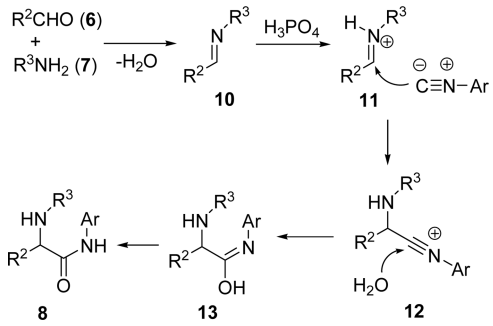
Table 2. Preparation of Indoles 9[a]

entry		R^1	R^2	R^3	yield[b] (%)
1	**9a**	H	4-ClC_6H_4	3-$CH_3C_6H_4$	72
2	**9b**	5-CH_3	4-ClC_6H_4	3-$CH_3C_6H_4$	73
3	**9c**	H	4-ClC_6H_4	4-$CH_3C_6H_4$	74
4	**9d**	H	4-ClC_6H_4	4-ClC_6H_4	76
5	**9e**	H	4-$CF_3C_6H_4$	Ph	82
6	**9f**	5-CH_3	3-BrC_6H_4	Ph	75
7	**9g**	H	4-$CH_3C_6H_4$	4-ClC_6H_4	71
8	**9h**	5-CH_3	Ph	Ph	74
9	**9i**	H	Ph	4-$CH_3C_6H_4$	70
10	**9j**	H	Ph	3-ClC_6H_4	73
11	**9k**	H	4-ClC_6H_4	2-$CH_3C_6H_4$	64
12	**9l**	H	2-$CH_3C_6H_4$	2-EtC_6H_4	46
13	**9m**	H	4-$CH_3OC_6H_4$	4-ClC_6H_4	57
14	**9n**	H	4-ClC_6H_4	4-$CH_3OC_6H_4$	45
15	**9o**	H	Et	4-ClC_6H_4	77
16	**9p**	H	*n*-Pr	4-ClC_6H_4	81
17	**9q**	H	4-$CF_3C_6H_4$	*n*-Bu	0
18	**9r**	H	4-ClC_6H_4	Et_2[c]	0
19	**9s**	5-Cl	4-ClC_6H_4	4-ClC_6H_4	0
20	**9t**	4-F	4-$CF_3C_6H_4$	Ph	0

[a]Reaction conditions: (i) MeOH, room temperature, 24−48 h; (ii) toluene, K_2CO_3 (s), 110 °C, 1−2 h. [b]Yields based on phosphonium **5**. [c]Diethylamine was used.

On the basis of the above observations and literature reports,[3,4] a plausible mechanism for an H_3PO_4-catalyzed Ugi-3CR is depicted in Scheme 5. The reaction of aldehyde **6** and amine **7** produced imine **10** with loss of water. Protonation of **10** gave the intermediate **11**, which favored the nucleophilic attack of aryl isocyanide **5** to provide the intermediate **12**. Subsequently, water attacked the intermediate **12** to give **13**, which underwent a further 1,3-hydrogen shift to generate the product **8**.

Scheme 5. Plausible Mechanism for H_3PO_4-Catalyzed Ugi-3CR



Attempts to prepare indoles by an Ugi four-component reaction (Ugi-4CR) of (2-isocyanobenzyl)triphenylphosphonium bromides **5**, aldehyde **6** (R^2 = 4-ClC_6H_4, 4-$MeOC_6H_4$), amine **7** (R^3 = 4-ClC_6H_4, 4-MeC_6H_4, *n*-Bu), and acid R^4COOH (R^4 = 4-ClC_6H_4, 4-MeC_6H_4, CH_3) failed. This is probably due to the low reactivity of (2-isocyanobenzyl)-triphenylphosphonium bromides **5** under the normal Ugi reaction conditions.

In summary, we have developed a new method utilizing a sequential Ugi-3CR/Wittig reaction to synthesize indoles in a one-pot fashion, starting from odorless isocyanide-substituted phosphonium salts. The amines, aldehydes, and isocyanides used can be varied broadly, producing products with three potential points of diversity. The method was adapted to the synthesis of various indoles in a one-pot fashion under mild reaction conditions, which will make it useful in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

One-Pot Synthesis of Indoles 9 via Sequential Ugi-3CR/Wittig Reaction. A mixture of isocyanide-substituted phosphonium salt **5** (1 mmol), aldehyde **6** (1 mmol), amine **7** (1 mmol), and H_3PO_4 (0.02 g, 0.2 mmol) was stirred in methanol (5 mL) at room temperature for 24−48 h, and then the solvent was evaporated under reduced pressure. Toluene (5 mL) and K_2CO_3 (0.41 g, 3 mmol) were added to the reaction system, and the reaction mixture was heated to 110 °C for 1−2 h to form indoles **9**. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 100/1−80/1 v/v) to give **9**.

N-((4-Chlorophenyl)(1H-indol-2-yl)methyl)-3-methylaniline (***9a***). White solid (yield 0.25 g, 72%). Mp: 165−166 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.21 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.33−7.24 (m, 5H), 7.17−7.01 (m, 3H), 6.59 (d, J = 7.8 Hz, 1H), 6.45−6.41 (m, 2H), 6.29 (s, 1H), 5.69 (d, J = 3.0 Hz, 1H), 4.20 (d, J = 2.4 Hz, 1H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 146.7, 139.6, 139.2, 135.8, 133.7, 129.2, 129.0, 128.7, 128.4, 122.0, 120.5, 120.1, 119.7, 114.6, 111.0, 110.7, 101.1, 56.8, 21.6. MS (EI, 70 eV): m/z (%) 346 (M^+, 5), 240 (100), 204 (39), 107 (14). Anal. Calcd for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08. Found: C, 76.40; H, 5.56; N, 8.15.

N-((4-Chlorophenyl)(5-methyl-1H-indol-2-yl)methyl)-3-methylaniline (***9b***). White solid (yield 0.26 g, 73%). Mp: 95−96 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.13 (s, 1H), 7.34−7.29 (m, 5H), 7.19 (d, J = 8.4 Hz, 1H), 7.04−6.98 (m, 2H), 6.58 (d, J = 7.2 Hz, 1H), 6.45−6.41 (m, 2H), 6.22 (s, 1H), 5.68 (s, 1H), 4.19 (s, 1H), 2.42 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 146.8, 139.7, 139.2, 139.1, 134.1, 133.6, 129.3, 129.2, 129.0, 128.7, 123.6, 120.1, 119.6, 114.5, 110.7, 110.6, 100.6, 56.8, 21.6, 21.4. MS (EI, 70 eV): m/z (%) 360 (M^+, 4), 254 (100), 218 (51). Anal. Calcd for $C_{23}H_{21}ClN_2$: C, 76.55; H, 5.87; N, 7.76. Found: C, 76.50; H, 5.66; N, 7.65.

N-((4-Chlorophenyl)(1H-indol-2-yl)methyl)-4-methylaniline (***9c***). White solid (yield 0.26 g, 74%). Mp: 185−186 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.25 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.34−7.24 (m, 5H), 7.16−7.07 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 6.28 (s, 1H), 5.66 (s, 1H), 4.14 (s, 1H), 2.22 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 144.3, 139.6, 139.3, 135.8, 133.6, 129.8, 129.0, 128.6, 128.3, 128.0, 122.0, 120.5, 120.0, 113.8, 110.9, 101.0, 57.0, 20.4. MS (EI, 70 eV): m/z (%) 346 (M^+, 7), 240 (100), 204 (30), 106 (32). Anal. Calcd for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08. Found: C, 76.35, H, 5.34; N, 8.20.

4-Chloro-N-((4-chlorophenyl)(1H-indol-2-yl)methyl)aniline (***9d***). White solid (yield 0.28 g, 76%). Mp: 189−190 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.16 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.35−7.25 (m, 5H), 7.18−7.08 (m, 4H), 6.53 (d, J = 9 Hz, 2H), 6.31 (s, 1H), 5.66 (d, J = 4.2 Hz, 1H), 4.29 (d, J = 4.2 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 145.1, 138.9, 138.5, 135.9, 133.9, 129.1, 128.6, 128.2, 123.3, 122.2, 120.6, 120.1, 114.8, 110.9, 101.4, 56.8. MS (EI, 70 eV): m/z (%) 367 (M^+, 6), 240 (100), 204 (32). Anal. Calcd for $C_{21}H_{16}Cl_2N_2$: C, 68.68; H, 4.39; N, 7.63. Found: C, 68.40, H, 4.25; N, 7.74.

N-((1H-Indol-2-yl)(4-(trifluoromethyl)phenyl)methyl)aniline (***9e***). White solid (yield 0.30 g, 82%). Mp: 116−117 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.24 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.56−7.54 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.18−7.09 (m, 4H), 6.77 (t, J = 7.2 Hz, 1H), 6.62 (d, J = 7.8 Hz, 2H), 6.29 (s, 1H), 5.79 (s, 1H), 4.31 (s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz): δ (ppm) 147.6, 147.0, 140.3, 136.4, 128.9, 128.3, 128.0, 127.8, 127.6, 127.1, 125.4, 123.5, 121.0, 119.9, 119.0, 116.7, 113.3, 111.3, 99.9, 55.1. MS (EI, 70 eV): m/z (%) 366 (M^+, 5), 274 (100), 204 (17). Anal. Calcd

DOI: 10.1021/acs.joc.7b00004
J. Org. Chem. 2017, 82, 2772−2776

for $C_{22}H_{17}F_3N_2$: C, 72.12; H, 4.68; N, 7.65. Found: C, 72.10, H, 4.64; N, 7.79.

*N-((3-Bromophenyl)(5-methyl-1H-indol-2-yl)methyl)aniline (**9f**).* White solid (yield 0.29 g, 75%). Mp: 130−131 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.12 (s, 1H), 7.56−6.98 (m, 9H), 6.76 (t, J = 6.9 Hz, 1H), 6.60 (d, J = 7.8 Hz, 2H), 6.24 (s, 1H), 5.64 (s, 1H), 4.24 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 146.6, 143.4, 138.8, 134.1, 131.0, 130.4, 130.2, 129.3, 128.6, 125.9, 123.6, 122.9, 120.2, 118.6, 113.7, 110.6, 100.7, 56.9, 21.4. MS (EI, 70 eV): m/z (%) 392 (M^+, 3), 298 (100), 218 (40), 204 (22). Anal. Calcd for $C_{22}H_{19}BrN_2$: C, 67.53; H, 4.89; N, 7.16. Found: C, 67.36, H, 4.80; N, 7.15.

*N-((1H-Indol-2-yl)(p-tolyl)methyl)-4-chloroaniline (**9g**).* White solid (yield 0.25 g, 71%). Mp: 172−173 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.16 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.29−7.06 (m, 9H), 6.54 (d, J = 9.0 Hz, 2H), 6.35 (s, 1H), 5.63 (d, J = 3.0 Hz, 1H), 4.28 (d, J = 2.4 Hz, 1H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 145.4, 139.4, 137.8, 137.5, 135.8, 129.6, 129.0, 128.3, 127.1, 122.8, 121.8, 120.4, 119.9, 116.2, 114.7, 110.9, 100.9, 57.1, 21.1. MS (EI, 70 eV): m/z (%) 346 (M^+, 7), 240 (100), 204 (30), 106 (32). Anal. Calcd for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08. Found: C, 76.13, H, 5.76; N, 8.21.

*N-((5-Methyl-1H-indol-2-yl)(phenyl)methyl)aniline (**9h**).* White solid (yield 0.23 g, 74%). Mp: 108−109 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.19 (s, 1H), 7.40−7.31 (m, 5H), 7.26−7.12 (m, 4H), 6.97 (d, J = 7.8 Hz, 1H), 6.75−6.63 (m, 3H), 6.28 (s, 1H), 5.70 (s, 1H), 4.28 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 147.1, 141.3, 139.7, 134.1, 129.3, 129.2, 128.9, 128.0, 127.3, 123.3, 120.1, 118.4, 113.7, 110.6, 100.2, 57.7, 21.4. MS (EI, 70 eV): m/z (%) 312 (M^+, 6), 206 (100), 178 (5), 106 (13) Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.77, H, 6.29; N, 8.70.

*N-((1H-Indol-2-yl)(phenyl)methyl)-4-methylaniline (**9i**).* White solid (yield 0.22 g, 70%). Mp: 145−146 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 11.08 (d, J = 6.0 Hz, 1H), 7.50−7.23 (m, 7H), 7.02−6.61 (m, 6H), 6.23 (d, J = 7.2 Hz, 1H), 6.11 (s, 1H), 5.75 (d, J = 6.6 Hz, 1H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 144.8, 141.4, 139.9, 135.8, 129.8, 129.7, 128.9, 128.6, 128.0, 127.9, 127.7, 127.4, 121.8, 120.4, 119.9, 113.9, 110.9, 100.8, 57.8, 20.5. MS (EI, 70 eV): m/z (%) 312 (M^+, 6), 206 (100), 178 (7), 106 (13). Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.72, H, 6.28; N, 8.76.

*N-((1H-Indol-2-yl)(phenyl)methyl)-3-chloroaniline (**9j**).* White solid (yield 0.24 g, 73%). Mp: 144−145 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.13 (s, 1H), 7.54 (s, 1H), 7.37−7.03 (m, 9H), 6.70−6.62 (m, 2H), 6.49 (s, 1H), 6.36 (s, 1H), 5.70 (s, 1H), 4.37 (s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz): δ (ppm) 149.2, 141.5, 140.5, 136.2, 133.3, 130.1, 128.3, 127.6, 127.3, 127.2, 120.7, 119.6, 118.7, 115.7, 112.4, 111.6, 111.1, 99.6, 55.3. MS (EI, 70 eV): m/z (%) 332 (M^+, 5), 206 (100), 178 (10), 127 (16). Anal. Calcd for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42. Found: C, 75.72, H, 5.13; N, 8.66.

*N-((4-Chlorophenyl)(1H-indol-2-yl)methyl)-2-methylaniline (**9k**).* White solid (yield 0.22 g, 64%). Mp: 116−117 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.22 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.37−7.25 (m, 5H), 7.18−7.09 (m, 3H), 7.00 (t, J = 7.8 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 6.32 (s, 1H), 5.76 (d, J = 3.6 Hz, 1H), 4.12 (d, J = 3.0 Hz, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 144.6, 139.5, 139.2, 135.8, 133.6, 130.2, 129.1, 128.6, 128.3, 127.2, 122.4, 122.0, 120.5, 120.0, 118.3, 111.3, 111.0, 101.2, 56.6, 17.7. MS (EI, 70 eV): m/z (%) 346 (M^+, 7), 240 (100), 204 (45), 106 (36). Anal. Calcd for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08. Found: C, 76.29, H, 5.59; N, 8.11.

*N-((1H-Indol-2-yl)(o-tolyl)methyl)-2-ethylaniline (**9l**).* White solid (yield 0.16 g, 46%). Mp: 90−91 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.18 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.33−6.98 (m, 9H), 6.73 (t, J = 6.6 Hz, 1H), 6.47 (d, J = 7.2 Hz, 1H), 6.34 (s, 1H), 5.91 (s, 1H), 4.18 (s, 1H), 2.54−2.37 (m, 5H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 144.4, 139.1, 136.0, 135.8, 130.9, 128.6, 127.9, 127.7, 127.1, 126.7, 121.8, 120.5, 120.0, 118.1, 111.2, 111.0, 101.2, 54.2, 24.0, 19.1, 13.0. MS (EI, 70 eV): m/z (%) 340 (M^+, 4), 220 (100), 204 (15). Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23. Found: C, 84.50, H, 7.26; N, 8.49.

*N-((1H-Indol-2-yl)(4-methoxyphenyl)methyl)-4-chloroaniline (**9m**).* White solid (yield 0.20 g, 57%). Mp: 172−173 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.18 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.29−7.25 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H), 7.10−7.06 (m, 3H), 6.88 (d, J = 9 Hz, 2H), 6.54 (d, J = 8.4 Hz, 2H), 6.35 (s, 1H), 5.62 (d, J = 4.2 Hz, 1H), 4.26 (d, J = 4.2 Hz, 1H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 159.3, 145.5, 139.5, 136.7, 135.8, 132.7, 130.5, 129.0, 128.4, 122.9, 121.9, 120.4, 119.9, 114.8, 114.3, 110.9, 100.8, 56.9, 55.3. MS (EI, 70 eV): m/z (%) 362 (M^+, 1), 244 (23), 236 (100). Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.58, H, 5.06; N, 7.89.

*N-((4-Chlorophenyl)(1H-indol-2-yl)methyl)-4-methoxyaniline (**9n**).* White solid (yield 0.16 g, 45%). Mp: 115−116 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 11.2 (s, 1H), 7.53−7.32 (m, 6H), 7.01−6.66 (m, 6H), 6.18 (s, 1H), 6.07 (s, 1H), 5.75 (s, 1H), 3.59 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz): δ (ppm) 151.2, 141.7, 141.5, 141.0, 136.3, 131.6, 129.4, 128.3, 127.6, 120.8, 119.7, 118.8, 114.5, 114.3, 111.2, 99.6, 55.6, 55.2. MS (EI, 70 eV): m/z (%) 362 (M^+, 6), 240 (100), 204 (44), 123 (38). Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.96, H, 5.40; N, 7.69.

*N-(1-(1H-Indol-2-yl)propyl)-4-chloroaniline (**9o**).* Orange oil (yield 0.22 g, 77%). ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.90 (s, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.02−6.91 (m, 4H), 6.62 (d, J = 8.4 Hz, 2H), 6.25 (s, 1H), 6.09 (d, J = 6.0 Hz, 1H), 4.40 (t, J = 6.6 Hz, 1H), 1.89−1.86 (m, 2H), 0.92 (t, J = 8.4 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz): δ (ppm) 147.2, 141.7, 135.9, 128.3, 127.8, 120.2, 119.4, 119.0, 118.6, 114.0, 111.0, 98.3, 52.9, 28.8, 10.8. MS (EI, 70 eV): m/z (%) 284 (M^+, 13), 253 (4), 158 (100). Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.77; H, 5.88; N, 9.94.

*N-(1-(1H-Indol-2-yl)butyl)-4-chloroaniline (**9p**).* Orange oil (yield 0.24 g, 81%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.27 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.14−7.04 (m, 4H), 6.54 (d, J = 8.4 Hz, 2H), 6.40 (s, 1H), 4.49 (t, J = 6.6 Hz, 1H), 3.94 (s, 1H), 1.91−1.85 (m, 2H), 1.48−1.43 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ (ppm) 146.0, 140.6, 135.4, 129.1, 128.7, 122.8, 121.4, 120.1, 119.8, 114.6, 110.8, 99.1, 53.1, 38.9, 19.2, 13.8. MS (EI, 70 eV): m/z (%) 298 (M^+, 16), 255 (10), 172 (100), 130 (80), 127 (72). Anal. Calcd for $C_{18}H_{19}ClN_2$: C, 72.35; H, 6.41; N, 9.37. Found: C, 72.30, H, 6.56; N, 9.54.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00004.

^{1}H and ^{13}C NMR spectra of compounds **9a**−**p** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for M.-W.D.: mwding@mail.ccnu.edu.cn.

ORCID

Ming-Wu Ding: 0000-0002-3464-4774

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (Nos. 21572075 and 21172085).

■ REFERENCES

(1) (a) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323−8359. (b) Dömling, A.; Wang, W.; Wang, K. *Chem.*

Rev. **2012**, *112*, 3083−3135. (c) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707−2752.
(2) (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89.
(3) Pan, C. S.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622−3625.
(4) (a) Kumar, A.; Saxena, D.; Gupta, M. K. *Green Chem.* **2013**, *15*, 2699−2703. (b) Khan, A. T.; Basha, R. S.; Lal, M.; Mir, M. H. *RSC Adv.* **2012**, *2*, 5506−5509. (c) Yuan, D.; Duan, Z.; Rao, Y.; Ding, M. W. *Tetrahedron* **2016**, *72*, 338−346.
(5) For recent applications of intramolecular Wittig reactions in cyclic or heterocyclic synthesis, see: (a) Zhang, K.; Cai, L.; Jiang, X.; Garcia-Garibay, M. A.; Kwon, O. *J. Am. Chem. Soc.* **2015**, *137*, 11258−11261. (b) Lee, C.-J.; Chang, T.-H.; Yu, J.-K.; Reddy, G. M.; Hsiao, M.-Y.; Lin, W. *Org. Lett.* **2016**, *18*, 3758−3761. (c) Wang, J.; Yao, J.; Wang, H.; Chen, H.; Dong, J.; Zhou, H. *J. Org. Chem.* **2016**, *81*, 5250−5255. (d) Saleh, N.; Voituriez, A. *J. Org. Chem.* **2016**, *81*, 4371−4377. (e) Zhao, G.; Zhang, Q.; Zhou, H. *J. Org. Chem.* **2014**, *79*, 10867−10872. (f) Fan, Y.-S.; Das, U.; Hsiao, M.-Y.; Liu, M.-H.; Lin, W. *J. Org. Chem.* **2014**, *79*, 11567−11582. (g) Zhou, R.; Wang, J.; Yu, J.; He, Z. *J. Org. Chem.* **2013**, *78*, 10596−10604. (h) Tsai, Y.-L.; Fan, Y.-S.; Lee, C.-J.; Huang, C.-H.; Das, U.; Lin, W. *Chem. Commun.* **2013**, *49*, 10266−10268. (i) Lee, Y.-T.; Lee, Y.-T.; Lee, C.-J.; Sheu, C.-N.; Lin, B.-Y.; Wang, J.-H.; Lin, W. *Org. Biomol. Chem.* **2013**, *11*, 5156−5161.
(6) (a) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875−2878. (b) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39−42.
(7) (a) Wang, L.; Ren, Z. L.; Ding, M. W. *J. Org. Chem.* **2015**, *80*, 641−646. (b) Wang, L.; Guan, Z. R.; Ding, M. W. *Org. Biomol. Chem.* **2016**, *14*, 2413−2420. (c) Duan, Z.; Gao, Y.; Yuan, D.; Ding, M. W. *Synlett* **2015**, *26*, 2598−2600.
(8) Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12*, 2852−2855.
(9) Kochanowska-Karamyan, A. J.; Harmann, M. T. *Chem. Rev.* **2010**, *110*, 4489−4497.
(10) (a) Gao, S.-S.; Li, X.-M.; Williams, K.; Proksch, P.; Ji, N.-Y.; Wang, B.-G. *J. Nat. Prod.* **2016**, *79*, 2066−2074. (b) Cheng, G.-G.; Li, D.; Hou, B.; Li, X.-N.; Liu, L.; Chen, Y.-Y.; Lunga, P.-K.; Khan, A.; Liu, Y.-P.; Zuo, Z.-L.; Luo, X.-D. *J. Nat. Prod.* **2016**, *79*, 2158−2166. (c) Sim, D. S.-Y.; Teoh, W.-Y.; Sim, K.-S.; Lim, S.-H.; Thomas, N. F.; Low, Y.-Y.; Kam, T.-S. *J. Nat. Prod.* **2016**, *79*, 1048−1055. (d) Kitajima, M.; Nakazawa, M.; Wu, Y.; Kogure, N.; Zhang, R.-P.; Takayama, H. *Tetrahedron* **2016**, *72*, 6692−6696.
(11) (a) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108−7149. (b) Platon, M.; Amardeil, R.; Djako-vitch, L.; Hierso, J. C. *Chem. Soc. Rev.* **2012**, *41*, 3929−3968. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215−PR283. (d) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195−7210. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920.
(12) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911.
(13) (a) Clagg, K.; Hou, H.; Weinstein, A. B.; Russell, D.; Stahl, S. S.; Koenig, S. G. *Org. Lett.* **2016**, *18*, 3586−3589. (b) Zheng, L.; Hua, R. *Chem. - Eur. J.* **2014**, *20*, 2352−2356. (c) Wu, Y.-D.; Ma, J.-R.; Shu, W.-M.; Zheng, K.-L.; Wu, A.-X. *Tetrahedron* **2016**, *72*, 4821−4826 and references cited therein. (d) Morimoto, Y.; Shimizu, S.; Mokuya, A.; Ototake, N.; Saito, A.; Kitagawa, O. *Tetrahedron* **2016**, *72*, 5221−5229. (e) Park, J.; Kim, D.-H.; Das, T.; Cho, C.-G. *Org. Lett.* **2016**, *18*, 5098−5101.
(14) (a) Kobayashi, K.; Iitsuka, D.; Fukamachi, S.; Konishi, H. *Tetrahedron* **2009**, *65*, 7523−7526. (b) Michelin, R. A.; Facchin, G.; Braga, D.; Sabatino, P. *Organometallics* **1986**, *5*, 2265−2274.
(15) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, DOI: 10.1039/C6CS00444J.

DOI: 10.1021/acs.joc.7b00004
J. Org. Chem. 2017, 82, 2772−2776