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Regioselective C−H Azidation of Anilines and Application to Synthesis of Key Intermediate for Pharmaceutical

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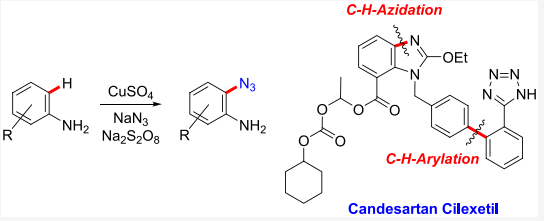
ABSTRACT: A catalytic system for regioselective C−H azidation of inactive anilines was developed. In the presence of $CuSO_4·5H_2O$, simultaneous addition of NaN_3 and $Na_2S_2O_8$ to aq. CH_3CN solution of free anilines under weakly acidic conditions (pH 4.5) smoothly underwent C−H azidation to provide corresponding α-azidated products in high yields. Methyl α-azidoanthranilate obtained by this method was readily transformed via simple reduction followed by cyclization to methyl 2-ethoxybenzimidazol-7-carboxylate, a key intermediate for antihypertensive Candesartan Cilexetil.



Candesartan Cilexetil (**1**, CAN) has received considerable attention as an antihypertensive drug due to high efficacy and safety.[1a−c] An efficient synthesis of **1** has been reported by our research group through C−H arylation using tetrazole as a directing group (Scheme 1).[2] Nonetheless, preparation of an intermediate, methyl 2-ethoxybenzimidazol-7-carboxylate (**2**, BIM), required relatively longer steps (6 steps) due to the need for classical reactions such as nitration and Curtius rearrangement to install the required nitrogen functionality.[1] In view of establishing a more practical synthetic method of **1**, we sought to explore an efficient synthesis of **2** by means of C−H activation.

As a strategy to shorten the access to **2**, we devised the idea to synthesize **2** by means of C−H azidation as shown in Scheme 2. If methyl anthranilate **3a** is to be azidated α to the amino group, subsequent reduction and cyclization might give **2** in a highly straightforward manner.

Regarding C−H azidation of anilines, a limited number of literature precedents[3] were available in comparison with aliphatic couterparts[4] (Scheme 3). Jiao et al. reported a pioneering work on copper-catalyzed C−H azidation employing CuBr and TBHP.[5] However, reported substrates were only reactive anilines carrying electron-donating groups. Hao et al. published use of a hypervalent azide which could eliminate addition of oxidant to regenerate active copper species.[6] However, inactive anilines with electron-withdrawing groups were not tested. More recently, Zhu disclosed use of inexpensive combination of NaN_3, $Cu(OAc)_2$, and H_2O_2 in aq. CH_3CN to effect the C−H azidation though inactive anilines were not tested as the substrate as well.[7]

In our initial study, we tested Jiao's procedure[5] for C−H azidation of methyl anthranilate (Table 1, entry 1). However, it did not give any desired product. In contrast, use of Zhu procedure[7] furnished the α-azidated aniline though in very poor yield (1%, Table 1, entry 2). Nonetheless, encouraged by the latter result where the desired product was really obtained, we decided to explore a more efficient method for the C−H azidation.

To improve the yield, we considered use of a more powerful oxidant than those employed in the previous procedure (TBHP, H_2O_2) because this type of reaction was reported to proceed through a radical cation generated by oxidation of the benzene ring.[8] Expectedly, when $Na_2S_2O_8$ was employed,[9] a remarkable increase of the yield was observed in the presence of a stoichiometric amount of $Cu(OAc)_2$ (66%, Table 1, entry 3 vs entry 2). However, the yield decreased when a lower amount (25 mol %) of catalyst was employed (28%, Table 1, entry 4). Use of iron catalysts was totally inactive for the azidation reaction (Table 1, entries 5−7).

The copper-catalyzed azidation reaction was further optimized with regard to pH, temperature, and addition mode (Table 2). To our delight, the yield was doubled when the pH was adjusted to 7.0 by sequential addition of NaOH during the reaction and with elevation of temperature from 20 to 40 °C (50%, Table 2, entry 2 vs entry 1). The yield was further improved to 58% and 65% when the pH was adjusted to slightly acidic 6.0 and 4.5, respectively (Table 2, entries 3 and 4). Finally, use of $CuSO_4·5H_2O$ in place of $Cu(OAc)_2$ and portionwise addition of both $Na_2S_2O_8$ and NaN_3 simultaneously resulted in a much higher yield of the desired product (84%, Table 2, entry 5).

Elevating the temperature under these conditions resulted in a decrease of yield (61%, Table 2, entry 6). Finally, other oxidants were tested. Use of Oxone gave a much lower yield

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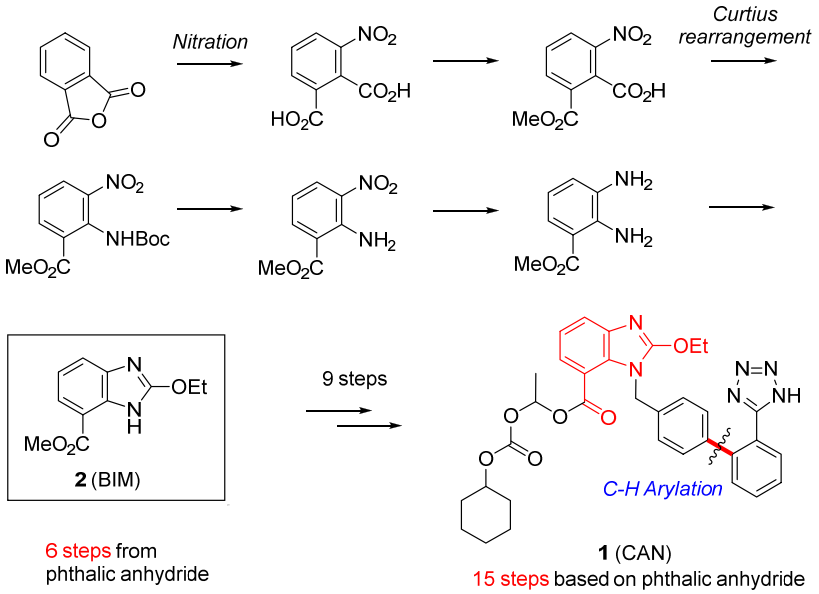
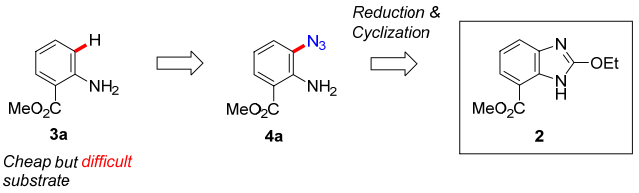
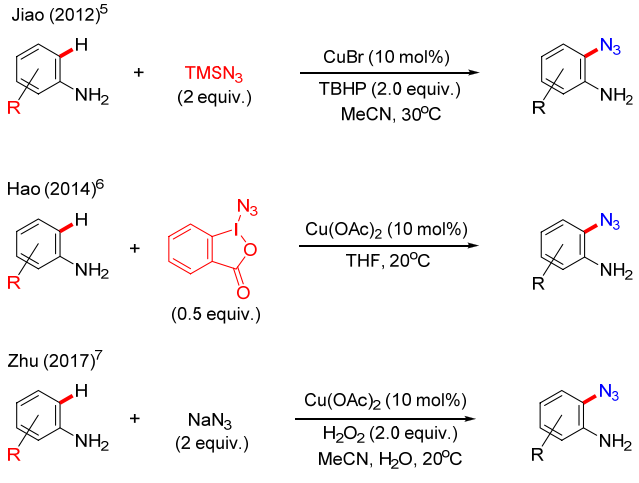
Scheme 1. Previous Synthesis of Candesartan Cilexetil (CAN)



Scheme 2. Strategy for New Synthesis of BIM, a Key Intermediate for CAN



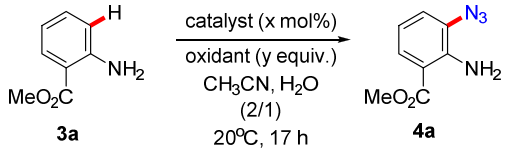
Scheme 3. Literature Precedents for C−H Azidation of Anilines



(29%, Table 2, entry 7). Different salts of peroxysulfate such as $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were tested to provide inferior yields (63%, 56%, respectively, Table 2, entries 8, 9). The scale up of the optimized conditions employing 3.0 g of **3a** was conducted to furnish a similar yield of **4a** without any difficulty (80%, Table 2, entry 10).

With the optimized conditions in hand, the substrate scope of the reaction was examined (Scheme 4). Methyl and chloro substituted anilines (**3b**, **3c**) were compatible with this

Table 1. Screen of Catalytic System for C−H Azidation of Methyl Anthranilate[a]



entry	Azide (2 equiv)	catalyst (x mol %)	oxidant (y equiv)	yield (%)
1[b]	$TMSN_3$	CuBr (10)	TBHP (2.0)	0
2[c]	NaN_3	$Cu(OAc)_2$ (10)	H_2O_2 (2.0)	1
3	NaN_3	$Cu(OAc)_2$ (100)	$Na_2S_2O_8$ (1.5)	66
4	NaN_3	$Cu(OAc)_2$ (25)	$Na_2S_2O_8$ (1.5)	28
5	NaN_3	$FeCl_3$ (25)	$Na_2S_2O_8$ (1.5)	3
6	NaN_3	$FeCl_2$ (25)	$Na_2S_2O_8$ (1.5)	0
7	NaN_3	$Fe(OAc)_2$ (25)	$Na_2S_2O_8$ (1.5)	0

[a]The reaction was conducted using methyl anthranilate (1.0 g, 6.62 mmol), azide (2.0 equiv), catalyst (x mol %), and oxidant (y equiv) in a mixture of CH_3CN (10 mL) and H_2O (5 mL) at 20 °C for 17 h. [b]The reaction was conducted in CH_3CN at 30 °C. [c]NaN_3 (2.0 equiv) and H_2O (as a solvent) were employed.

reaction to afford α-azidated products (**4b**, **4c**). Inactive substrates carrying ketone (**3d**, **3e**, **3f**, **3g**, **3h**) as well as an ester moiety (**3a**, **3i**) underwent expected α-azidation as well. It should be noted that substrates with an electron-withdrawing group such as nitrile (**3j**) and even a nitro group (**3k**) were effective in this protocol, which demonstrates wide applicability of the present reaction to the synthesis of invaluable α-azidated aniline derivatives.[10]

A possible mechanism for the C−H azidation is shown in Scheme 5. First, the amino group of aniline **3a** coordinates to $Cu^{II}SO_4$ to produce **5**. Then, an azide radical ($\cdot N_3$), generated through interaction of HN_3 with sulfate radical ($SO_4^{\bullet-}$),[11] combines with **5** to give Cu^{III} species **6**. Radical cation **7** is then produced by single electron transfer (SET)[12] from the benzene ring to the adjacent Cu^{III} atom. Azide transfer follows to give azide aryl radical **8** which should be oxidized by $SO_4^{\bullet-}$ to generate azide aryl cation **9**. Then, amino anion **10** abstracts

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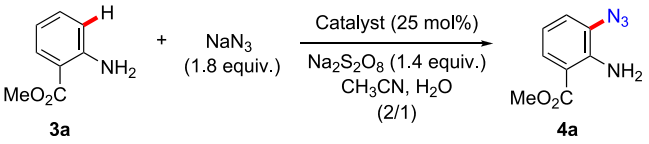
Table 2. Optimization of Cu-Catalyzed C−H Azidation of Methyl Anthranilate[a]



entry	catalyst (25 mol %)	temp (°C)	pH	time (h)	yield (%)
1	$Cu(OAc)_2$	20	–[b]	17	28
2[c]	$Cu(OAc)_2$	40	7	3	50
3[c]	$Cu(OAc)_2$	40	6	3	58
4[c]	$Cu(OAc)_2$	40	4.5	3	65
5[c,d]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	84
6[c,d]	$CuSO_4{\cdot}5H_2O$	50	4.5	3	61
7[c,d,e]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	29
8[c,d,f]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	63
9[c,d,g]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	56
10[c,d,h]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	80
11[c,d,i]	$CuSO_4{\cdot}5H_2O$	40	4.5	3	0

[a]The reaction was conducted using methyl anthranilate (1.0 g, 6.62 mmol), NaN_3 (0.77 g, 11.8 mmol, 1.8 equiv), catalyst (25 mol %), and $Na_2S_2O_8$ (2.2 g, 1.4 equiv) in a mixture of CH_3CN (10 mL) and H_2O (5 mL). [b]pH was not adjusted. [c]pH was adjusted by adding aq. NaOH. [d]Both $Na_2S_2O_8$ and NaN_3 were portionwise added. [e]Oxone (3 equiv) was used in place of $Na_2S_2O_8$. [f]$K_2S_2O_8$ was used in place of $Na_2S_2O_8$. [g]$(NH_4)_2S_2O_8$ was used in place of $Na_2S_2O_8$. [h]Use of methyl anthranilate (3.0 g). [i]TEMPO (1 equiv) was added.

the neighboring H atom[12] and goes through the aromatization to form the final azide product **4a** with concomitant regeneration of $Cu^{II}SO_4$. The sulfate radical ($SO_4^{\bullet-}$) thus plays a crucial role in the current transformation which is generated by heating of $Na_2S_2O_8$.[13] To confirm the hypothesis mentioned above, the reaction was conducted in the presence of TEMPO (1 equiv) and no reaction occurred which verifies intervention of the radical species in the reaction (Table 2, entry 11).

As evident in Table 2, under weaky acidic conditions, the reaction did go well. It produces HN_3 from NaN_3 to accelarate formation of the azide radical ($\cdot N_3$).[11] When the reaction proceeds, the mixture becomes acidic by generation of H^+ at the final stage of the reaction. This is periodically neutralized by sequential addition of aq. NaOH to adjust the pH to weakly acidic pH 4.5. Maintaining mildly acidic conditions should be significant to push the reaction and to simultaneously prevent decomposition of the reagents and product.

Having obtained the required α-azidated aniline **4a** in hand, we then moved to the synthesis of **2** from **4a** (Scheme 6). Reduction of **4a** to diamine **11** smoothly proceeded by treatment with zinc dust in the presence of NH_4Cl. The diamine **11** obtained was converted to **2** by simple treatment with $(EtO)_4C$ in acetic acid.[1d]

CONCLUSIONS

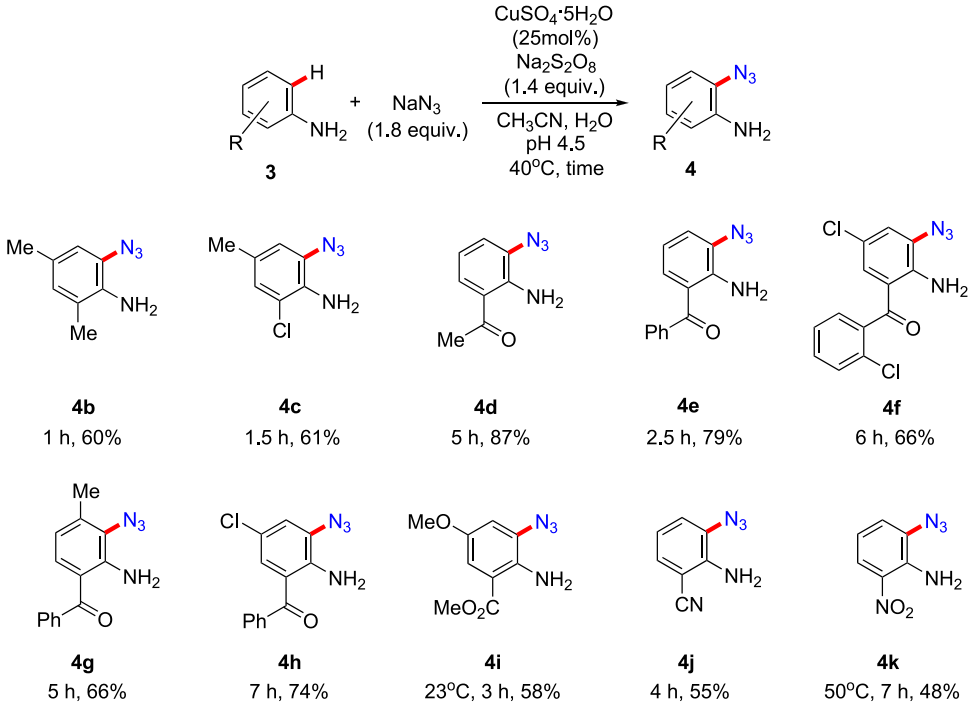
A highly effective and practical synthetic method for regioselective C−H azidation of anilines has been determined whereby even inactive substrates carrying an electron-withdrawing group can be α-azidated rapidly, specifically, and inexpensively. It should be particularly notified that the new protocol employs a readily accessible catalyst ($CuSO_4{\cdot}5H_2O$), an azide source (NaN_3), and an oxidant ($Na_2S_2O_8$).

By applying the methodology, methyl anthranilate **3a** was successfully α-azidated to **4a** which was converted in two steps to **2** (BIM), a key intermediate for antihypertensive drug **1** (CAN).

EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded with

Scheme 4. Substrate Scope of the Cu-Catalyzed C−H Azidation



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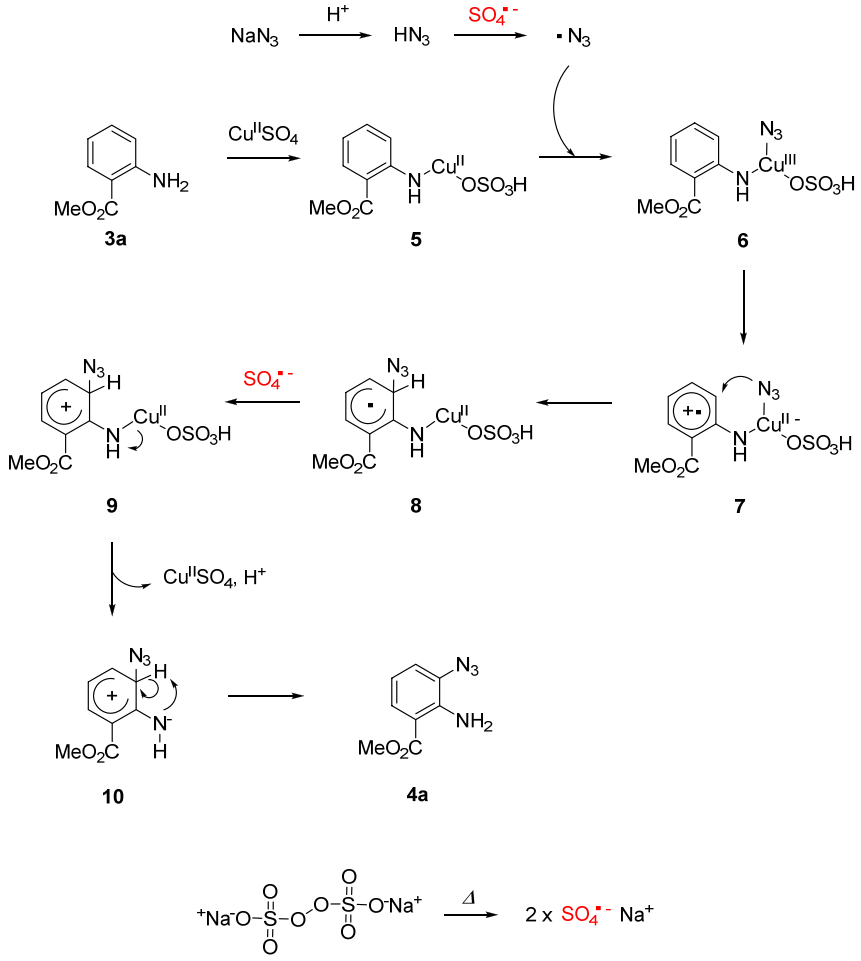
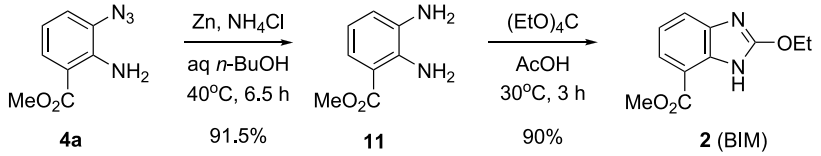
Scheme 5. Possible Mechanism of Cu-Catalyzed C−H Azidation of Anilines

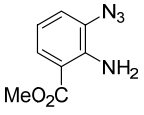


Scheme 6. Synthesis of BIM (2) from Azide (4a)



tetramethylsilane used as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol−heat or visualized by UV light where feasible. All solvents and reagents were used as received. ***Note***: for every reaction, the handling of hazardous reagents (NaN_3, $Na_2S_2O_8$) and/or product (azides) should be conducted in a well ventilated hood with an appropriate protector being set in front of the reactor. Before the procedure is to be applied to a large scale reaction, sufficient safety assessment must be undertaken.

*A Typical Procedure for C−H Azidation of Aniline Derivatives. Syntheis of Methyl 3-Azideanthranilate (**4a**).* To a solution of



$CuSO_4·5H_2O$ (0.41 g, 1.64 mmol, 25 mol %) in a mixed solvent of CH_3CN (10 mL) and H_2O (5 mL) was added methyl anthranilate **3a** (1.0 g, 6.62 mmol), and the mixture was stirred at 40 °C in a water bath for 15 min. After the pH of the mixture was adjusted to 4.5 by adding 24% aq. NaOH, NaN_3 (0.77 g, 11.8 mmol, 1.8 equiv) and $Na_2S_2O_8$ (2.20 g, 9.24 mmol, 1.4 equiv) were simultaneously added in 10 portions at 40 °C in a water bath over 1.5 h during which time the pH of the mixture was maintained at 4.5 by adding 24% aq. NaOH. The mixture was further stirred at the same temperature for 3 h while remaining at pH 4.5 by adding 24% aq. NaOH. When the reaction completed, the mixture was cooled down to 25 °C and $Na_2S_2O_3$ was added until iodo-starch detection becomes negative. Then, after the pH of the mixture was adjusted to 0.9 by adding c-HCl, the organic phase was subjected to HPLC analysis (X Bridge, 30 °C, 50−100% CH_3CN, 0−20 min, 1.0 mL/min, 254 nm) to obtain an assay yield of **4a** (1.07 g, 84%). A part of the extract was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/AcOEt = 8:1) to give an analytically pure sample of **4a**. Brown crystalline solid. Mp: 65−66 °C; IR (neat): ν_{max} = 3484, 3352, 2116, 1687, 1245, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65 (1H, dd, J = 8.2, 1.2 Hz), 7.12−7.11 (1H, m), 6.66−6.62 (1H, m), 5.97 (2H, brs), 3.86 (3H, s); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 168.2, 142.6, 127.6, 125.9, 122.0, 115.5, 111.4, 51.8; HRMS (FAB): $[M - N_2 + H]^+$ calcd for $C_8H_9O_2N_2$ 165.0664, found 165.0658

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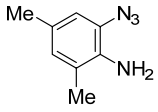
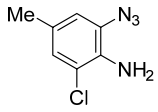
*Scale up of the Synthesis of **4a** from **3a** (3.0 g).* To a solution of $CuSO_4 \cdot 5H_2O$ (1.23 g, 4.92 mmol, 25 mol %) in a mixed solvent of CH_3CN (30 mL) and H_2O (15 mL) was added methyl anthranilate **3a** (3.0 g, 19.9 mmol), and the mixture was stirred at 40 °C in a water bath for 15 min. After the pH of the mixture was adjusted to 4.5 by adding 24% aq. NaOH, NaN_3 (2.31 g, 35.4 mmol, 1.8 equiv) and $Na_2S_2O_8$ (6.60 g, 27.7 mmol, 1.4 equiv) were simultaneously added at 40 °C over 1.5 h in a water bath during which time the pH of the mixture was maintained at 4.5 by adding 24% aq. NaOH. The mixture was further stirred at the same temperature for 4 h while maintaining the pH at 4.5 by adding 24% aq. NaOH. When the reaction completed, the mixture was cooled down to 25 °C and $Na_2S_2O_3$ was added until iodo-strach detection becomes negative. Then, after the pH of the mixture was adjusted to 0.9 by adding c-HCl, the organic phase was subjected to HPLC analysis to give the assay yield of **4a** (3.06 g, 80%).

*2-Azido-4, 6-dimethylaniline (**4b**).* The compound was prepared according the typical procedure for the synthesis of **4a** except for the



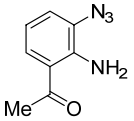
reaction time (1 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 644 mg (60%). Brown crystalline solid. Mp: 36−37 °C. IR (neat): ν_{max} = 3419, 3396, 3327, 2913, 2855, 2101, 1626, 1583, 1496, 1316 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.72 (1H, s), 6.68 (1H, s), 3.61 (2H, brs), 2.24 (3H, s), 2.12 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 133.8, 128.0, 127.6, 124.7, 123.6, 116.3, 20.5, 17.3. HRMS (FAB): $[M - N_2 + H]^+$ calcd for $C_8H_{11}N_2$ 135.0922, found 135.0917.

*2-Azido-6-chloro-4-methylaniline (**4c**).* The compound was prepared according the typical procedure for the synthesis of **4a**



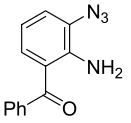
except for the reaction time (1.5 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. 737 mg (61%). Brown crystalline solid. Mp: 41−42 °C. IR (neat): ν_{max} = 3438, 3328, 2103, 1497, 1271, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.87 (1H, s), 6.75 (1H, s), 4.02 (2H, brs), 2.43 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 132.8, 128.2, 125.9, 119.6, 117.2, 20.4; HRMS (FAB): $[M + H]^+$ calcd for $C_7H_8N_4Cl$ 183.0437, found 183.0419.

*2-Azido-6-acetylaniline (**4d**).* The compound was prepared according the typical procedure for the synthesis of **4a** except for



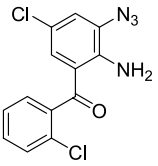
the reaction time (5 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 1015 mg (87%). Brown crystalline solid. Mp: 89−90 °C. IR (neat): ν_{max} = 3449, 3326, 2100, 1645, 1542, 1288 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.53 (1H, dd, J = 8.0, 1.2 Hz), 7.14 (1H, dd, J = 8.0, 1.2 Hz), 6.67 (1H, dd, J = 8.0, 8.0 Hz), 6.55 (2H, brs), 2.57 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 200.4, 142.4, 128.2, 126.2, 122.0, 118.5, 114.9, 28.1. HRMS (FAB): $[M]^+$ calcd for $C_8H_8ON_4$ 176.0698, found 176.0716.

*2-Azido-6-benzoylaniline (**4e**).* The compound was prepared according the typical procedure for the synthesis of **4a** except for the reaction time (2.5 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 1246 mg (79%). Brown crystalline solid. Mp: 68−69 °C. IR (neat): ν_{max} = 3473, 3359, 2107, 1611, 1290, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63−7.61 (2H, m), 7.53−7.47 (1H, m), 7.47−7.45 (2H,



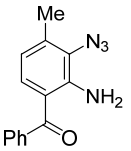
m), 7.27−7.25 (1H, m), 7.16−7.14 (1H, m), 6.63−6.61 (1H, m), 6.32 (2H, brs). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 198.6, 142.9, 139.8, 131.3, 130.8, 129.2, 128.1, 126.2, 121.9, 118.6, 114.8. HRMS (FAB): $[M]^+$ calcd for $C_{13}H_{10}ON_4$ 238.0855, found 238.0854.

*2-Azido-4-chloro-6-(2-chlorobenzoyl)aniline (**4f**).* The compound was prepared according the typical procedure for the synthesis of **4a**



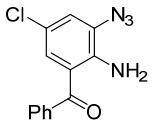
except for the reaction time (6 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 1342 mg (66%). Brown crystalline solid. Mp: 64−65 °C. IR (neat): ν_{max} = 3488, 3364, 2105, 1539, 1227 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.45−7.26 (4H, m), 7,116−7.122 (1H, m), 6.944−6.938 (1H, m), 6.70 (2H, brs). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 196.1, 142.1, 138.8, 130.9, 130.7, 130.1, 129.3, 128.4, 127.6, 126.8, 122.7, 119.3, 118.0. HRMS (FAB): $[M]^+$ calcd for $C_{13}H_8ON_4Cl_2$ 306.0075, found 306.0055.

*2-Azido-6-benzoyl-2-methylaniline (**4g**).* The compound was prepared according the typical procedure for the synthesis of **4a**



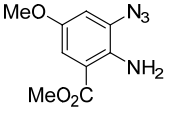
except for the reaction time (5 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 1102 mg (66%). Brown oil. IR (neat): ν_{max} = 3478, 3340, 2098, 1606, 1242, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.61−7.59 (2H, m), 7.54−7.50 (1H, m), 7.46−7.42 (2H, m), 7.23 (1H, d, J = 8.4 Hz), 6.52 (2H, brs), 6.41 (1H, d, J = 8.4 Hz), 2.43 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 198.3, 145.0, 139.9, 138.2, 131.9, 131.1, 129.0, 128.1, 124.4, 117.4, 116.9, 18.2. HRMS (FAB): $[M]^+$ calcd for $C_{14}H_{12}ON_4$ 252.1011, found 252.1007.

*2-Azido-6-benzoyl-4-chloroaniline (**4h**).* The compound was prepared according the typical procedure for the synthesis of **4a**



except for the reaction time (7 h) and solvent for silica gel column chromatography: hexane/AcOEt = 50:1. Assay yield 1336 mg (74%). Brown crystalline solid. Mp: 104−105 °C. IR (neat): ν_{max} = 3486, 3371, 2122, 1689, 1635, 1545, 1445, 1290, 1229 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.64−7.61 (2H, m), 7.58−7.54 (1H, m), 7.50−7.47 (2H, m), 7.23 (1H, d, J = 2.4 Hz), 7.13 (1H, d, J = 2.4 Hz), 6.29 (2H, brs). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 197.6, 141.6, 139.1, 131.8, 129.5, 129.2, 128.4, 127.6, 121.9, 119.3, 119.0. HRMS (FAB): $[M]^+$ calcd for $C_{13}H_9ON_4Cl$ 272.0465, found 272.0465.

*Methyl 3-Azido-5-methoxyanthranilate (**4i**).* The compound was prepared according the typical procedure for the synthesis of **4a**



https://doi.org/10.1021/acs.joc.1c00734
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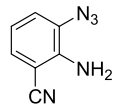
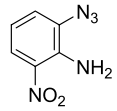
except for the reaction temperature and time (23 °C, 3 h). Assay yield 868 mg (58%). Brown crystalline solid. Mp: 65−66 °C; IR (neat): ν_{max} = 3501, 3378, 2951, 2124, 1689, 1552, 1431, 1219 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.18 (1H, d, J = 2.4 Hz), 6.83 (1H, d, J = 2.8 Hz), 5.64 (2H, brs), 3.88 (3H, s), 3.78 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 167.9, 149.9, 137.5, 111.6, 111.2, 109.7, 56.0, 51.8. HRMS (FAB): $[M]^+$ calcd for $C_9H_{10}O_3N_4$ 222.0753, found 222.0752.

2-Azido-6-cyanoaniline (4j). The compound was prepared according the typical procedure for the synthesis of **4a** except for



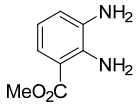
the reaction time (4 h). Assay yield 579 mg (55%). Brown crystalline solid. Mp: 128−129 °C. IR (neat): ν_{max} = 3441, 3346, 2218, 2114, 1622, 1477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.20−7.16 (2H, m), 6.76 (1H, dd, J = 8.0, 7.6 Hz), 4.60 (2H, brs). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 141.7, 128.3, 125.9, 122.1, 117.9, 116.8, 96.7. HRMS FAB): $[M - N_2 + H]^+$ calcd for $C_7H_6N_3$ 132.0562, found 132.0556

2-Azido-6-nitroaniline (4k). The compound was prepared according the typical procedure for the synthesis of **4a** except for



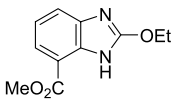
the raection temperature and time (50 °C, 7 h). Assay yield 569 mg (48%). Brown crystalline solid. Mp: 95−96 °C. IR (neat): ν_{max} = 3494, 3378, 2122, 1615, 1509, 1245 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.94 (1H, dd, J = 8.8, 1.2 Hz), 7.24−7.22 (1H, m), 6.72 (1H, dd, J = 8.8, 8.0 Hz), 6.32 (2H, brs); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 137.4, 128.1, 122.9, 122.3, 115.5. HRMS (FAB): $[M]^+$ calcd for $C_6H_5O_2N_5$ 179.0443, found 179.0447.

Methyl 3-Aminoanthranilate (11).[1d] Zinc dust (1.30 g, 19.9 mmol) was added to a solution of NH_4Cl (1.06 g, 19.8 mmol) in a



mixed solvent of H_2O (3 mL) and *n*-butanol (6 mL) at 25 °C, and the mixture was heated up to 40 °C in a water bath. To the suspension was added dropwise crude methyl 3-azideanthranilate (**4a**) CH_3CN solution obtained above (containing 1.07 g of **4a**, 5.57 mmol) at the same temperature over 30 min. Then the mixture was stirred at 40 °C in a water bath for 6 h. Aftter completion of the reaction, the mixture was diluted with AcOEt (20 mL) and filtered through Celite. The filtrate was subjected to HPLC analysis (X Bridge, 30 °C, 50−100% CH_3CN, 0−20 min, 1.0 mL/min, 254 nm) to obtain the assay yield of **11** (847 mg, 91.5%). A part of the extract was evaporated *in vacuo*, and the residue was purified by silic gel column chromatography (hexane/AcOEt = 2:1) to give an analytically pure sample of **11**. Dark brown crystalline solid. Mp: 66−67 °C. IR (neat): ν_{max} = 3365, 3314, 1701, 1619, 1610, 1433, 1281, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.47 (1H, dd, J = 8.0, 1.6 Hz), 6.84 (1H, dd, J = 7.2, 1.6 Hz), 6.60−6.57 (1H, m), 3.87 (3H, s). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 169.1, 141.3, 134.3, 122.8, 120.8, 116.8, 112.1, 51.7.

Methyl 3-Ethoxybenzimidazol-7-carboxylate (2).[1d] According to a literature procedure,[1d] compound **2** was prepared from **11** in 90% yield. White crystalline solid. Mp: 132−133 °C. IR (neat): ν_{max} = 3339, 1695, 1551, 1437, 1264 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.60 (1H, brs), 7.74−7.69 (2H, m), 7.18 (1H, dd, J = 8.0, 8.0 Hz), 4.61 (2H, q, J = 6.8 Hz), 3.97 (3H, s), 1.48 (3H, t, J = 6.8 Hz). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 167.1, 158.7, 142.0, 133.3, 122.6, 122.5, 121.1, 112.1, 66.3, 52.1, 14.7.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00734.

^1H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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