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**Title:** Iodine-promoted Semmler-Wolff reactions: step economic access to meta-substituted primary anilines via aromatization

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# Iodine-promoted Semmler−Wolff reactions: step economic access to *meta*-substituted primary anilines via aromatization

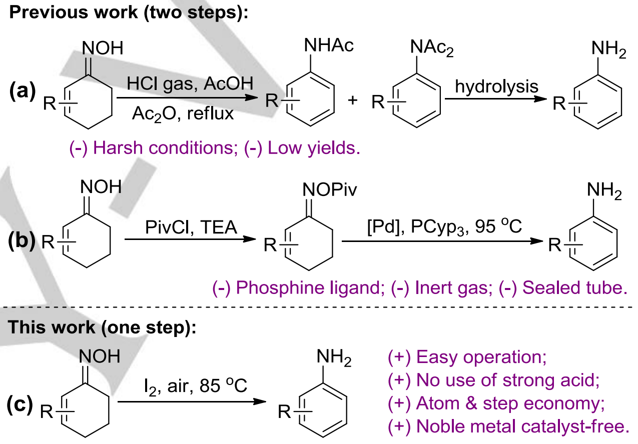
Shi-Ke Wang,[a] Xia You,[a] Da-Yuan Zhao,[a] Neng-Jie Mou[a] and Qun-Li Luo*[a]

**Abstract:** An atom and step economic access to an array of unprotected *meta*-substituted primary anilines was disclosed via the Semmler−Wolff reaction promoted by molecular iodine, in which noble metal catalysts and inert atmosphere are unnecessary while the forcing reaction conditions and the lengthy synthesis can be avoided. The synthetic utility of this approach is evident in the *de novo* syntheses of three bioactive molecules with good total yields.

Aromatic amines are prevalent in our society at scales ranging from the laboratory bench to the industrial manufacture of fine and bulk chemicals. They are widely used in various fields as intermediates for the manufacture of numerous chemical products such as pharmaceuticals, agrochemicals, dyes, surfactants, polymers and flame retardants.[1] Metal-catalyzed C−N cross-coupling with aryl halides, arylboronic acid derivatives, or other substituted arenes provides reliable methods for the synthesis of secondary and tertiary aryl amines.[2] Primary aryl amines play a key role as intermediates in chemical synthesis. However, direct introduction of the unprotected amino functionality is recognized as a key challenge through the strategies of C−N cross-coupling.[3] The general approach to prepare *ortho*- and *para*-substituted primary anilines normally relies on the reduction of nitro arenes,[4] but regiospecific synthesis of *meta*-substituted counterparts through such approach frequently suffered from tedious multistep synthesis due to the regioselectivity in aromatic substitution chemistry.[5] Accordingly, amination/aromatization of cyclohex-2-enones has been appropriate for an alternative choice, enabling good yields of variously substituted secondary and tertiary aryl amines in concise routes.[6] Nevertheless, the advances on the related methods to directly afford the primary amines are frustrating.[7] The condensation of ketones with ammonia is not as favored as that with a primary or secondary amine.[6b] The oxidative aromatization of the imines derived from cyclohex-2-enones with ammonia is expected to form the mixtures of phenol and aniline products. It is unlikely that primary anilines could be prepared by a similar approach.

The Semmler−Wolff reaction is a classic method for the synthesis of protected primary aryl amines in which hydroxylamine is conveniently used as the ammonia surrogate, but it is rarely utilized, particularly in relation to the harsh reaction conditions and low yields (Scheme 1a).[8] In order to avoid the use of strong Brønsted acids, the variant methods underwent the indirect protocols by the conversion of oximes to *O*-acyl oximes in advance, but trialkyl phosphine-coordinated Pd catalysts and inert atmosphere were necessary for the aromatization step (Scheme 1b).[9]

To date, almost all of the Semmler−Wolff reactions required either strong Brønsted acids or transition metal as promoters, and were conducted in two steps.[8, 9] In continuation of our work on the iodine-mediated methodologies for organic synthesis,[10] we unprecedentedly realized a dehydrative aromatization of cyclohex-2-enone oximes through a metal-free one-step protocol (Scheme 1c). This protocol provided a practical route from inexpensive commercial chemicals to the unprotected *meta*-substituted primary anilines.



**Scheme 1.** Semmler−Wolff reactions for the syntheses of *meta*-substituted primary anilines.

At the start of the investigation, the model reaction of cyclohex-2-enone oxime **1a** was explored to optimize the reaction conditions (Table S1).[11] The reaction in DMSO at 60 °C led to the decomposition of substrate, accompanied by the 3,5-diaryl phenol in low yield. No intended product in toluene was obtained albeit the decomposition became slow. When increasing the reaction temperature to 100 °C, the desired aniline (**2a**) was isolated in low yield. The reaction became complicated when the temperature was elevated to reflux in toluene or to 120 °C in DMF. We then screened some polar solvents of boiling point ranging from 60 to 110 °C (Table 1, entries 1–4). The results were better in ether solvents than that in others at the temperature higher than 80 °C, and the best solvent was DME. The outcome under acidic conditions was slightly inferior to that under neutral conditions, whereas the reaction did not occur in the presence of base. By the use of 1.5 equivalents of iodine, the reaction became more efficient as demonstrated by thin-layer chromatography (TLC) and the yield slightly increased (entry 5). The experiments on halogen source screening showed that NIS was less efficient than molecular iodine, whereas NCS, NBS and iodides were unworkable. Based on an overall consideration of the investigated parameters, we established optimized conditions. The aromatization was accomplished under refluxing for 24 h in DME using 1.5 equivalents of molecular iodine.

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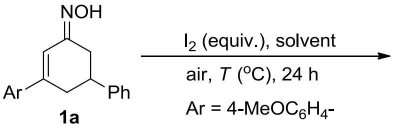
**Table 1.** Optimization of the reaction conditions [a]



**1a** **2a**

| entry | I$_2$ (equiv.) | solvent | $T$ (°C)[b] | Yield (%) |
|---|---|---|---|---|
| 1 | 1.2 | MeCN | 82 | 55 |
| 2 | 1.2 | DME | 85 | 60 |
| 3 | 1.2 | THF | 66 | 0 |
| 4 | 1.2 | 1,4-dioxane | 101 | 53 |
| 5 | 1.5 | DME | 85 | 65 |

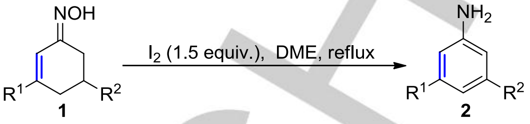
[a] Reaction conditions: **1a** (0.2 mmol), solvent (1 mL) under ambient air. Isolated yields are given. [b] The boiling point of the corresponding solvent.

We then applied the optimized conditions to a series of oximes (**1**) and were pleased to successfully achieve a diverse array of *meta*-substituted primary anilines (Table 2). In general, 3,5-diaryl-substituted cyclohex-2-enone oximes performed effectively in the transformation (entries 1–13). For the 3,5-diaryl-substituted substrates, the electronic (entries 2 vs 1, 3–4) and steric (entries 5 vs 6) effects of R$^1$ had few influences on the reactions, whereas an electron-withdrawing R$^2$ was slightly superior to an electron-donating one (entries 10 vs 7–9). An alkyl substituent at the 2- or 6-position of substrates hardly impacted the yields of aromatization (entries 12 vs 1, entries 13 vs 2, respectively).

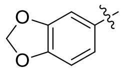
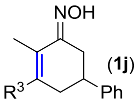
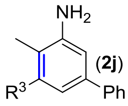
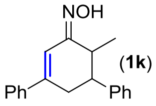
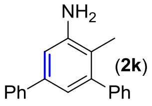
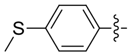
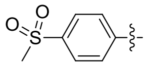
Following the protocol, two bioactive *m*-terphenyl amines with sulfur-containing substituents were straightforward obtained (entries 14–15). Compounds **2l** and **2m** were identified as selective inhibitors of COX-1.[12] The previous syntheses of **2l** and **2m** included steps of the deprotection of amino and the remove of cyano that were carried out at the temperature as high as 220 °C under high pressure in strong alkaline solutions.[5a] Luckily, we *de novo* synthesized the two compounds with widely available and inexpensive reagents in concise routes. In each step, the reaction conditions were relatively mild, heavy metal reagents were not used, and it was unnecessary to protect any functional groups.

Pleasingly, a 5-aryl substituted 3-aminobenzoic acid and its derivatives were prepared successfully (entries 16–19). Esters could tolerate the reaction conditions (entry 17) despite of the fact that a compound containing ester functionality is labile to aminolysis under the conditions of heating.[10c] 3-Amino-5-arylbenzoic acids and their derivatives are prevalent as structural motifs and intermediates in drug discovery. Their preparations were mainly available in the patent literature in which frequent transformations of functional group were involved.[13] A straightforward access to them has not been reported. The present protocol provides a facile route to *meta*-substituted 3-aminobenzoic acids and their derivatives.

**Table 2.** Substrate scope of iodine-promoted Semmler−Wolff reaction[a]



**1** **2**

| entry | R$^1$ | R$^2$ | **1/2** | Yield (%) |
|---|---|---|---|---|
| 1 | 4-CH$_3$OC$_6$H$_4$- | Ph- | **1a/2a** | 65 |
| 2 | Ph- | Ph- | **1b/2b** | 67 |
| 3 | 4-CH$_3$C$_6$H$_4$- | Ph- | **1c/2c** | 63 |
| 4 | 4-ClC$_6$H$_4$- | Ph- | **1d/2d** | 64 |
| 5 | 2-naphthalenyl | Ph- | **1e/2e** | 61[b] |
| 6 | 2-furanyl | Ph- | **1f/2f** | 60[b] |
| 7 | Ph- | 4-CH$_3$OC$_6$H$_4$- | **1a'/2a** | 58 |
| 8 | Ph- | 4-CH$_3$C$_6$H$_4$- | **1c'/2c** | 60 |
| 9 | Ph- |  | **1g/2g** | 57 |
| 10 | Ph- | 4-nitrophenyl | **1h/2h** | 69[c] |
| 11 | 2-thiopheneyl | 4-ClC$_6$H$_4$- | **1i/2i** | 70[b] |
| 12 |  NOH R$^3$ Ph (**1j**) |  NH$_2$ R$^3$ Ph (**2j**) | **1j/2j** | 66[c] |
| 13 |  NOH Ph Ph (**1k**) |  NH$_2$ Ph Ph (**2k**) | **1k/2k** | 67[b] |
| 14 |  | Ph- | **1l/2l** | 52[b] |
| 15 |  | Ph- | **1m/2m** | 54[b] |
| 16 | Ph- | -CO$_2$H | **1n/2n** | 63 |
| 17 | Ph- | -CO$_2$Et | **1o/2o** | 65 |
| 18 | Ph- | -CONHPh | **1p/2p** | 57 |
| 19 | Ph- | -CONHBn | **1q/2q** | 53 |
| 20 | Me- | Ph- | **1r/2r** | 35[b] |
| 21 | Me- | 4-BrC$_6$H$_4$- | **1s/2s** | 35[b] |
| 22 | Me- | 4-CH$_3$OC$_6$H$_4$- | **1t/2t** | 34[b] |
| 23 | H- | Ph- | **1u/2u** | 41[b] |
| 24 | 4-CH$_3$OC$_6$H$_4$- | H- | **1v/2v** | 48[b] |

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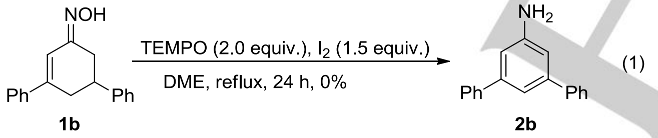
[a] Reaction conditions: **1** (0.2 mmol), $I_2$ (0.3 mmol), DME (1 mL), under ambient air for 24 h unless otherwise stated. $R^3$ = 4-MeOC$_6$H$_4$-. Isolated yields are given. [b] For 36 h. [c] For 48 h.

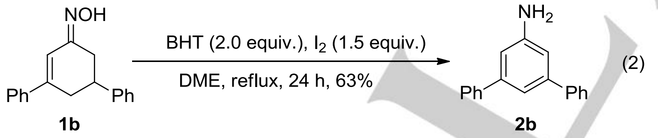
Remarkably, the conjugated effect of substituents at the 3- and 5-positions of the cyclohexene ring highly impacted on the reactions. The yields significantly decreased when either $R^1$ or $R^2$ was a nonconjugated substituent, *i.e.*, a hydrogen atom or an alkyl (entries 20–24 vs 1–19). Improving the yields of **2r**–**2v** was unsuccessful despite several attempts under various reaction conditions.

Compared with the traditional Semmler−Wolff reaction, our method required neither the harsh conditions of strong Brønsted acids in the aromatization step, nor the extra step of acid/base hydrolysis for the cleavage of acyl protected group(s). Unlike Stahl's variant, the present transformations did not require strict atmospheric controls, extra derivations of substrates, and Pd catalyst systems sensitive to air. The reaction installation was as simple as in a common reaction tube with a condenser. After oximes **1** were completely consumed as monitored by TLC, the mixtures were quenched with aqueous sodium thiosulfate and subjected to the conventional aqueous work-up and purification with column chromatography on silica gel. Such procedure represents an example in which the experiment process is facile to operate and the reaction results are well repeatable. Overall, our protocol ranks among the most benign method suggested for the Semmler−Wolff reaction.

The control experiments indicated that 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) totally inhibited the transformation (Equation 1), but butylated hydroxytoluene (BHT) hardly affected the yield of the reaction (Equation 2).

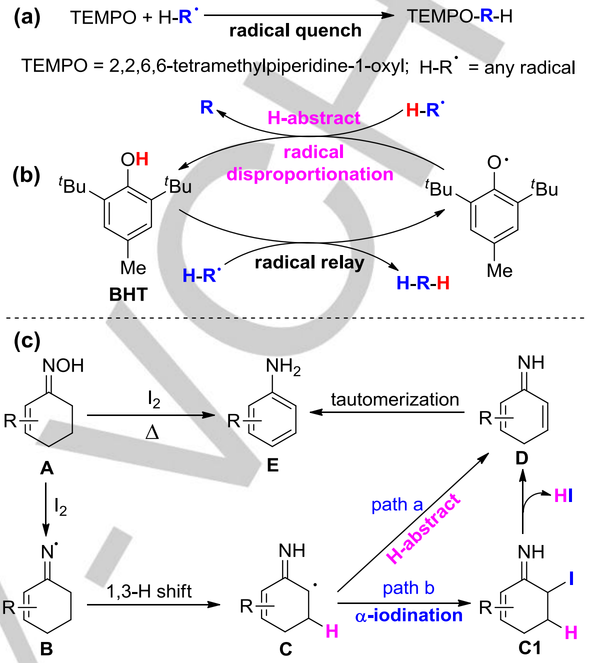


(1)

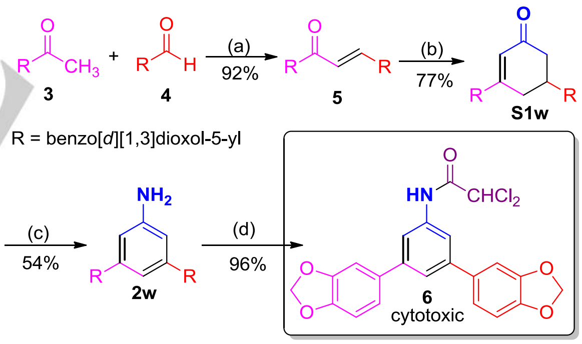


(2)

Lei and co-workers proved that the conjugated radical intermediates were possibly produced from ketone oxime derivatives under heating.[14] The trap of a radical by TEMPO will lead to the quench of radicals (Scheme 2a).[15] However, the reaction of BHT with a radical will form BHT radical that is able to abstract a hydrogen atom from a certain radical (via radical disproportionation) or molecule (via radical relay), as shown in Scheme 2b.[16] Therefore, our observations are preliminarily in agreement with a radical mechanism (Scheme 2c). The $I_2$-mediated homolysis of N-O bond in oxime **A** gives imine radical **B**,[17] which may quickly isomerize to α-carbon radical **C** via 1,3-H shift.[14, 17] Radical **C** undergoes two possible paths. In path a, the abstract of one hydrogen atom on **C** by a radical (e.g., iodine radical) leads to imine **D** that tautomerizes to the final product **E**. Such path is similar to the disproportionation of free radicals in Scheme 2b.[16] In path b, the α-iodination of radical **C** by iodine radical or other iodine species causes iodo imine **C1**,[10d, 14] which subsequently generates imine **D** via the elimination of HI. The two paths can not be ruled out at the current stage.[18, 19]



**Scheme 2.** Proposed mechanism.



**Scheme 3** *De novo* synthesis of anticancer agent **6**. Reaction conditions: (a) NaOH, EtOH, r.t., 6 h. (b) acetone, NaOMe, Ar, 50 °C, 4 h. (c) (i) $NH_2OH{\cdot}HCl$, AcONa, MeOH, reflux, 4 h; (ii) $I_2$ (150 mol%), DME, reflux, 24 h. (d) $CHCl_2CO_2H$, $I_2$, $P(OMe)_3$, $NEt_3$, DCM, 0 °C to r.t., 3 h.

The utility of our methodology was further exemplified in the synthesis of terphenyl-derived bioactive molecules (Scheme 3). 2,2-Dichloroacetanilides that the phenyl was substituted at both the 3- and 5-positions, especially compound **6**, showed efficient anticancer activity.[20] The previous route involved the Pd-catalyzed Suzuki coupling of substituted phenylboronic acids with *N*-haloaryl amides. However, the coupling was very inefficient due to the low activity of the haloarenes. The isolated yield of the coupling step for **6** was as low as 36% even by the use of an iodoarene.[20] Meanwhile, the haloarenes required to be synthesized in multiple steps due to their commercial unavailability. By contrast, the *de novo* synthesis of **6** was accomplished for the first time in 4 steps from common commercial chemicals in 36.7% of total yield via the sequence of dehydrative condensation, cyclization, dehydrative aromatization and amide formation (Scheme 3).[10a] By the use of this route, heavy metal reagents and protective groups were not utilized, and the requirements of rigorous reaction conditions and special or expensive reagents were totally avoided in each step. The avoidance of the use of heavy metal reagents are beneficial to the pharmaceutical manufacturers, since the concentrations of residual metals may be required at the ppm level by government regulations in the active pharmaceutical ingredients (API) while the process to remove residual metals is costly.[21]

In conclusion, an iodine-promoted protocol for the Semmler−Wolff reaction is developed, which is particularly efficient for the concise preparation of unprotected *meta*-substituted primary anilines under mild conditions. As a consequence, several bio-interesting molecules or intermediates were *de novo* synthesized in good total yields. The high atom and step economy, benign reaction conditions, wide availability of reagents, low cost of chemicals, structural diversity of products, and no requirements of heavy metal catalysts make the method a green[22] and favorable alternative to prepare primary aryl amines that contain functionalities or substituents at the *meta*-positions of amino.

## Acknowledgements

The authors thank the financial support from the National Natural Science Foundation of China (20971105), the Science Foundation of Chongqing Science & Technology Commission (cstc2017jcyjAX0423), and the Experimental Technology Foundation of Southwest University (SYJ2016019)

**Keywords:** amines • aromatization • enones • iodine • synthetic methods

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[17] Imine radical **B** could be formed in the presence of molecular iodine, see: H. Huang, J. Cai, L. Tang, Z. Wang, F. Li, G.-J. Deng, *J. Org. Chem.* **2016**, *81*, 1499–1505.

[18] a) The experiments on halogen source screening showed that molecular iodine was much more efficient than NBS and NCS (Table S1, entries 12–16). These results could be explained with the persistent radical effect. Compared with bromine and chlorine radicals, iodine radical is relatively stable (persistent radical), and can be reversibly produced from molecular iodine via heating. The abstract of one hydrogen atom on radical **C** (transient radical)[14] by iodine radical may result in imine **D** (path a). Such transformation is similar to the radical disproportionation.[16] On the other hand, path b that the coupling of radical **C** (transient radical) with iodine radical (persistent radical) lead to iodo imine **C1** is also possible, which is similar to the radical/radical cross-coupling pathway reported by Lei et al.[14 b) For reviews of persistent radical effect, see: H. Fischer, *Chem. Rev.* **2001**, *101*, 3581–3610.

[19] The mechanism provides explanations for the observations that the conjugated substituents at the 3- and 5-positions of the cyclohex-2-ene ring were significantly more favourable to the aromatization than H-atoms and alkyls (Table 2, entries 1–19 vs 20–24). A pi-delocalized substituent at the 3-position (e.g., $R^1$ = Ar) is capable of accelerating the formation of imine radical **B** via the delocalization stabilization of the conjugated system while one at the 5-position (e.g., $R^2$ = Ar, acyl) can facilitate the hydrogen abstract of **C** or the HI elimination of **C1** via the delocalization stabilization of **D** (Scheme 2).

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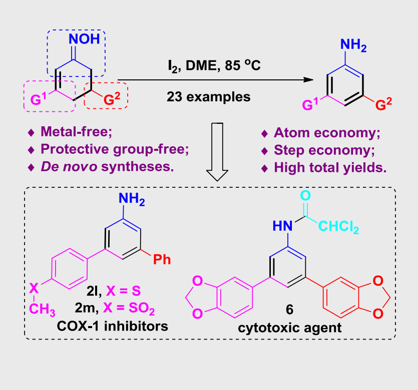
## Entry for the Table of Contents

## COMMUNICATION

**$I_2$ worked**: An atom and step economic access to an array of unprotected *meta*-substituted primary anilines was developed via the iodine-promoted Semmler−Wolff reaction. The synthetic utility of this approach is evident in the *de novo* syntheses of three bioactive molecules with good total yields.



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