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Authors: Hitesh Jalani, Jyotirling Mali, Hyejun Park, Jae Kyun Lee, Kiho Lee, Kyeong Lee, and Yongseok Choi

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Iodine-Promoted One-pot Synthesis of Highly Substituted 4-Aminopyrroles and Bis-4-aminopyrrole from Aryl Methyl Ketones, Arylamines, and Enamines

Hitesh B. Jalani[a,§], Jyotirling R. Mali[b,§], Hyejun Park[a], Jae Kyun Lee[c], Kiho Lee[d], Kyeong Lee[b]*, Yongseok Choi[a]*

[a] School of Life Sciences and Biotechnology, Korea University, Seoul 02841, Republic of Korea. E-mail: ychoi@korea.ac.kr
[b] College of Pharmacy, Dongguk University-Seoul, Goyang 10326, Republic of Korea. E-mail: kaylee@dongguk.edu
[c] Center for Neuromedicine, Korea Institute of Science and Technology, Seoul 02792, Republic of Korea.
[d] College of Pharmacy, Korea University, Sejong-ro 2511, Republic of Korea.
[§]These authors contributed equally to this work.
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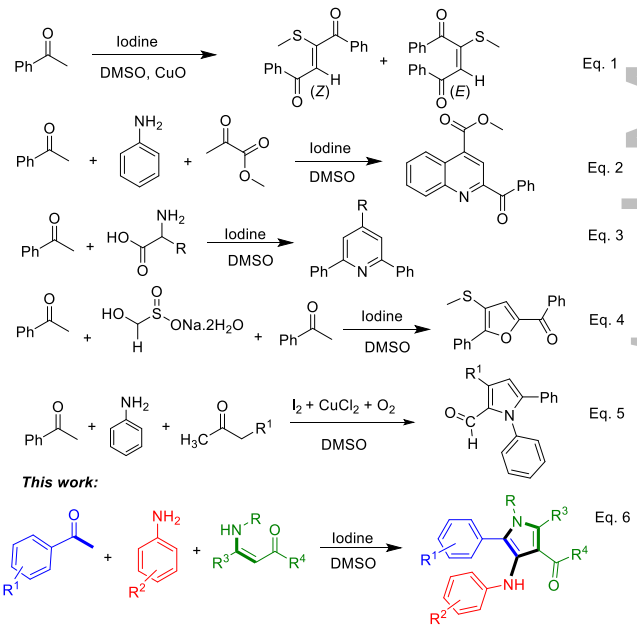
Abstract. An iodine-promoted one-pot synthesis of functionally diverse and highly substituted 4-aminopyrroles directly from aryl methyl ketones, arylamines, and enamines was developed. The reaction involves in-situ oxidation of aryl methyl ketone to glyoxal, subsequent imine formation by aniline, followed by nucleophilic addition of enamine, and cyclization to afford highly substituted 4-aminopyrroles. This reaction involved the formation of two C-N bonds and one C-C bond by a formal [1+1+3] annulation approach. The present method provides an interesting framework of two 4-aminopyrrole units directly attached to a biphenyl core by the reaction of 4,4'-diacyl biphenyl, amine, and enamine groups. This Hantzsch-type one-pot reaction provides diverse 4-aminopyrroles, which could be useful in medicinal/material chemistry.

Keywords: 4-Aminopyrroles; Kornblum oxidation; Enamines; Hantzsch-type one-pot approach.

Pyrrole is one of the simplest and biologically important heterocycles present in a variety of natural products and medicines such as heme, chlorophyll, porphyrins, marine-derived Marino pyrrole-A, pseudilin, lamellarin-G, Atorvastatin, and Sunitinib.[1-3] In view of the importance of pyrroles in diverse fields, various synthetic methods have been developed for the synthesis of substituted pyrroles.[4] One of the most common and classical approach to access this scaffold is the Hantzsch pyrrole synthesis, which involves the reaction of chloroacetone, acetoacetic ester, and aqueous ammonia.[5] Despite the availability of numerous methods,[6] the access to suitably functionalized pyrroles is essential for progress in the field of biology[7] and material science.[8] This has motivated chemists to develop newer synthetic routes, particularly concise, efficient, and straightforward approaches. Over the past few years, novel methodologies using iodine-mediated transformations of methyl ketones have attracted attention as these methods provide a powerful and straightforward method for the conversion of substituted methyl ketones towards diverse oriented heterocyclic systems.[9-11]



Scheme 1. Application of methyl ketones towards diverse scaffolds and strategy for highly substituted 4-aminopyrroles.

Wu and co-workers employed a versatile self-sorting tandem reaction of methyl ketone, iodine, and dimethyl sulfoxide (DMSO) in the presence of copper oxide to synthesize a cis-trans mixture of 2-(methylthio)-1,4-diphenylbut-2-ene-1,4-diones (Scheme 1, eq. 1).[11a] They designed an elegant synthesis pathway of an iodine-catalyzed Povarov-type reaction of arylamine with two different methyl ketones (Scheme 1, eq. 2), wherein the

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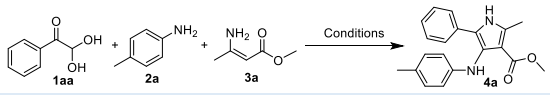
catalytic amount of the HI co-product serves as a promoter to accelerate quinoline synthesis.[12] Following this, in 2016, the same research group reported the iodine promoted synthesis of pyridines using α-amino acids and two molecules of methyl ketone (Scheme 1, eq. 3).[13] Subsequently, they reported the iodine-promoted synthesis of furan-3-methanethiol from methyl ketones and hydroxy methyl sulfonates (Scheme 1, eq. 4).[14] During the preparation of this manuscript, Wu and co-workers reported the synthesis of trisubstituted pyrrole-2-carbaldehydes from methyl ketones, anilines, and alkyl aryl ketones (Scheme 1, eq. 5).[15] In addition to Wu and co-workers, the Li and Tu groups contributed towards the synthesis of interesting heterocycles directly from aryl glyoxals as starting materials.[16]

Considering the significance of iodine-mediated oxidation of methyl ketones, we were interested in a recent report by Wu and coworkers[12] that detailed the one-pot synthesis of substituted quinolines under the influence of a co-product promoted Povarov reaction of acetophenones, arylamines, and α-keto esters (Scheme 1, eq. 2). During the synthesis of quinolines, the transient formation of a highly active C-acyl imine ion in the postulated mechanism particularly attracted our initial attention. Upon examination of Wu's proposed mechanism, we envisioned that replacing activated α-keto esters with an enamine such as methyl-3-aminobut-2-enoate would permit the nucleophilic addition of enamine onto the C-acylimine ion, which could then be followed by intra-molecular cyclization to yield 4-aminopyrroles (Scheme 1, eq. 6). Therefore, we considered the possibility of preparing 4-aminopyrroles (**4a**) via a byproduct catalyzed approach, wherein the reaction of aromatic ketones with iodine generates HI as a byproduct during iodination and Kornblum oxidation. HI, in turn, could promote cyclization after the addition of enamine to the C-acylimine ion.

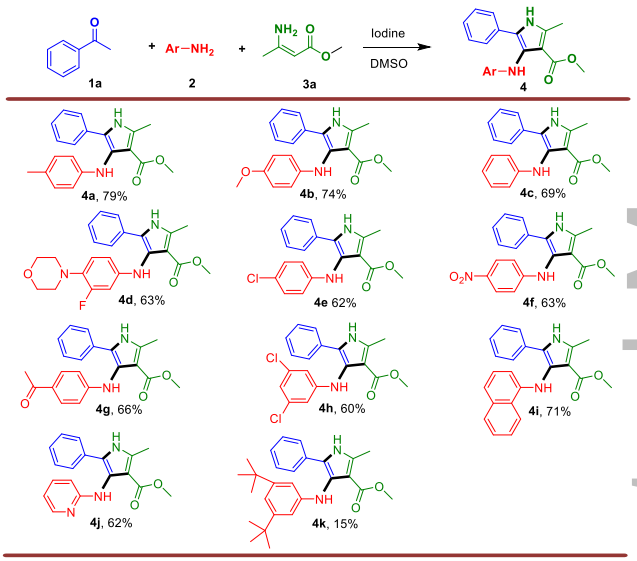


Entry	Catalyst (mol%)	Temp (°C)	Solvent	Yield[b] (%)
1	No Catalyst	80	Ethanol	21
2	PTS (50)	80	Ethanol	59
3	I_2 (20)	100	DMSO	59
4	I_2 (30)	100	DMSO	62
5	I_2 (40)	100	DMSO	65
6	I_2 (50)	100	DMSO	70
7	I_2 (50)	110	DMSO	72
8	I_2 (50)	120	DMSO	75
9	**I_2 (50)**	**130**	**DMSO**	**79**
10	HI (5)	110	DMSO	68
11	HI (10)	110	DMSO	64
12	HI (15)	110	DMSO	60

[a]Reaction conditions: **1aa** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), DMSO (2 mL).
[b]Isolated yield.

Table 1. Optimization of reaction conditions. [a, b]

Kornblum oxidation of acetophenone in the presence of iodine and DMSO resulted in phenylglyoxal, and hence, we initially optimized the procedure for the preparation of 4-aminopyrroles using phenylglyoxal (**1ab**) with *p*-toluidine (**2a**) and methyl 3-aminobut-2-enoate (**3a**). When the reaction was carried out at 80 °C in ethanol without a catalyst, surprisingly, the reaction proceeded within 6 h to afford (**4a**) in 21% yield (Table 1, entry 1). This result encouraged us to test various catalysts to find the suitable conditions to prepare 4-aminopyrroles. It is well known that protic acids can catalyze various reactions, therefore, using 50 mol% of *p*-toluenesulfonic acid (PTS) at 80 °C in ethanol afforded (**4a**) with 59% yield (Table 1, entry 2). Considering the role of iodine in the reaction, it is possible that trace amounts of HI, generated during the reaction, might be enough as a catalyst for this process. Therefore, some control experiments were performed using different amounts of HI (Table 1, entries 10-12). It can be seen that 5 mol% HI is sufficient to catalyze the reaction, resulting in (**4a**) with a good yield at 110 °C after 1 h. After several screenings, we found that heating phenylglyoxal (**1aa)** in the presence of iodine (50 mol%) at 130 °C for 1 h, followed by the addition of *p*-toluidine (**2a**) and methyl 3-aminobut-2-enoate (**3a**) at 130 °C, and heating again for another 1 h provided the desired product (**4a**) in good yield (79%). These reaction conditions were then applied to acetophenone.



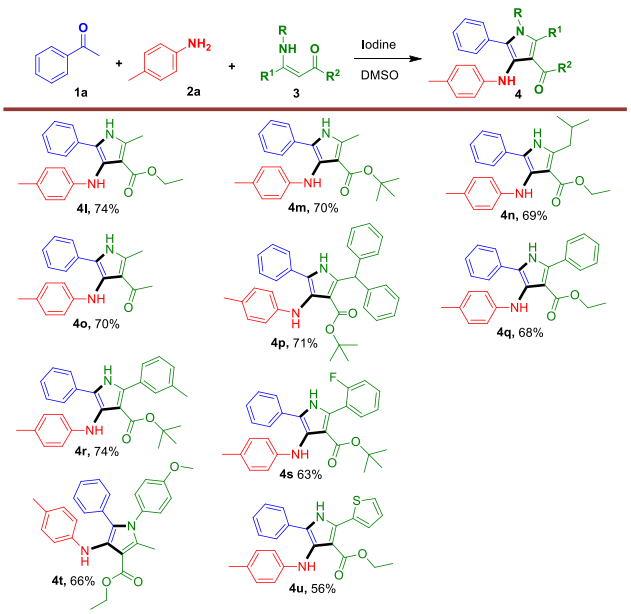
[a]Reaction conditions: **1a** (0.5 mmol), I_2 (0.25 mmol), **2** (0.5 mmol) and **3a** (0.75 mmol) in DMSO (2 mL).
[b]Isolated yield.

Scheme 2. Substrate scope for arylamines. [a, b]

With established reaction conditions in hand, we focused on exploring the substrate scope with respect to various amines for the one-pot synthesis of 4-aminopyrroles. We explored various aromatic amines and the desired products were obtained in satisfactory yields (Scheme 2). Interestingly, both electron-rich and electron-deficient anilines could be smoothly converted to the desired products (79-15%, **4a-k**). In general, aromatic amines containing electron-rich substituents, such as methyl, methoxy, phenyl, and 4-morpholinophenyl groups, showed better activities with good yields (97-63%, **4a-d**). Amines bearing electron-withdrawing substituents like 4-chloro, 4-nitro, 4-acetyl, and 3,5-dichloro resulted in comparatively lower yields (62-60%, **4e-h**). 1-

Naphthylamine was suitable for this protocol and resulted in (**4i**) with a 71% yield. Substrates bearing heterocyclic scaffolds, such as 2-aminopyridine also functioned well and resulted in the corresponding pyridine containing 4-aminopyrrole (**4j**) with reasonably good yield (62%). However, bulky 3,5-ditertbutylaniline gave poor (15%) yield of (**4k**), but from the diversity point of view, such compounds are worth exploring even though they resulted in low yields.

Encouraged by the good tolerance and generality of amines in the one-pot synthesis of 4-aminopyrroles, we concentrated on exploring various enamines, as described in Scheme 3. The reactions were mild enough to be compatible with a broad range of enamines, such as ethyl 3-aminobut-2-enoate, tert-butyl 3-aminobut-2-enoate, and ethyl 3-amino-5-methylhex-2-enoate (74-69%; **4l-n**). Interestingly, methyl 3-aminobut-2-one (**4o**) also underwent the reaction with 72% yield and this compound can be further functionalized due to the presence of methyl ketone. Bulky diphenylmethane enamine also provided the expected product (**4p**) with 71% yield. Furthermore, the optimized conditions could be applied to various enamines bearing aromatic substituents, such as phenyl, 3-tolyl, and 2-fluorophenyl groups, which satisfactorily reacted to give very good yields (74-68%, **4q-s**). X-ray single crystal analysis of compound (**4s**)[17] provided information about the substituent pattern in the pyrrole scaffold (Figure 1). N-substituted enamines, such as ethyl 3-(4-methoxyphenylamino)but-2-enoate, provided a typical fully substituted 4-aminopyrrole (**4t**) with 66% yield. Furthermore, heteroaryl enamines, such as ethyl 3-amino-3-(thiophen-2-yl)acrylate gave the corresponding product (**4u**) with a reasonable yield of 56%. Thus, the present one-pot protocol is useful for the exploration of various enamines[18] in synthesizing the corresponding 4-aminopyrroles.



[a]Reaction conditions: **1a** (0.5 mmol), I_2 (0.25 mmol), **2a** (0.5 mmol) and **3** (0.75 mmol) in DMSO (2 mL).
[b]Isolated yield.

Scheme 3. Substrate scope for enamines. [a, b]

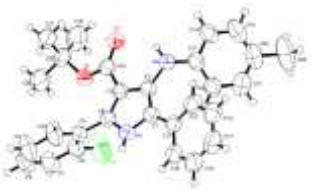
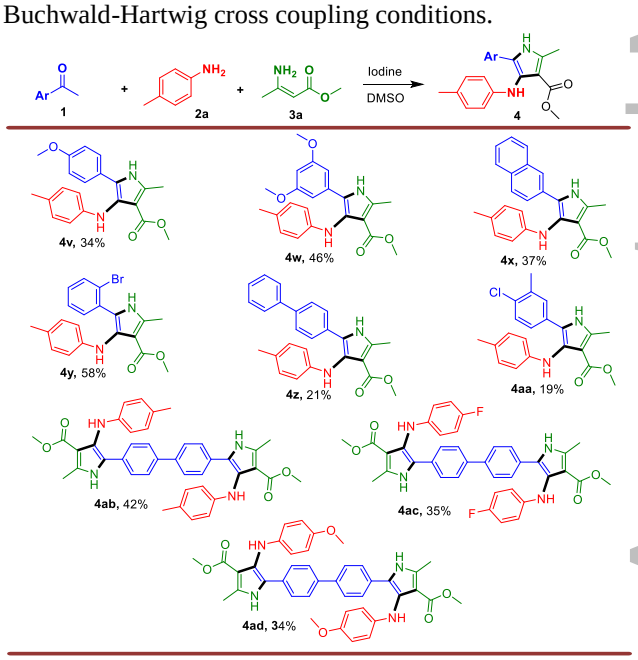


Figure 1. X-ray single crystal structure of **4s**.

Next, we explored various methyl ketones for the one-pot synthesis of 4-aminopyrroles as described in Scheme 4. The reactions were mild enough to be compatible with a broad range of acetophenone bearing electron-donating and electron-withdrawing groups (**4v-4aa**). These reactions somewhat gave lower yields compared to the parent acetophenone. Surprisingly, acetophenone substrates bearing diverse substitutions are being used to construct various heterocycles, however, to the best of our knowledge, the reactions of 4,4'-diacyl biphenyl have not been explored for the synthesis of bis-pyrroles. An interesting framework of two symmetrical 4-aminopyrrole units directly attached to a biphenyl core was developed by the treatment of 4,4'-diacyl biphenyl with *p*-toluidine and enamine under slightly modified reaction conditions (Supporting Information), provided with (**4ab**), (42% yield). Similarly, 4-fluoroaniline (**4ac,** 35%), and *p*-anisidine (**4ad,** 34%) have furnished bis-pyrroles with moderate yields. We expect that use of 4,4'-diacyl biphenyl to construct bis-pyrroles will certainly attract the attention of synthetic and medicinal chemists. In addition to this, pyrroles such as (**4y**) could be transformed to dihydropyrrolo[3,2-*b*]indoles[19] using intra-molecular Buchwald-Hartwig cross coupling conditions.



[a]Reaction conditions: **1a** (0.5 mmol), I_2 (0.25 mmol), **2a** (0.5 mmol) and **3** (0.75 mmol) in DMSO (2 mL).
[b]Isolated yield.

Scheme 4. Substrate scope for aryl methyl ketones and arylamines. [a, b]

After establishing the scope of all three components in the present method, the reaction mechanism was

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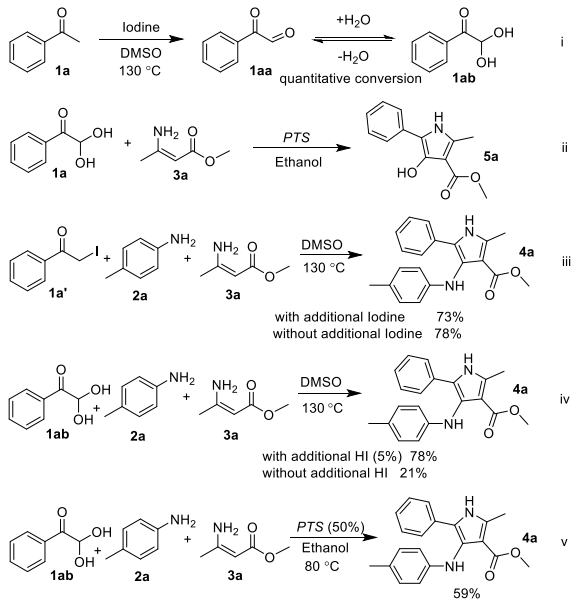
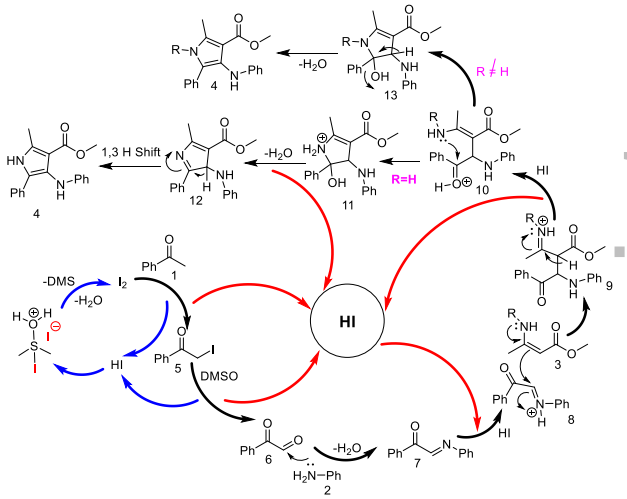
considered. Acetophenone (**1a**) was reacted with iodine in DMSO at 130 °C to obtain phenylglyoxal (**1aa**), and the corresponding hydrated form (**1ab**) in quantitative yield (Scheme 5, i). The reaction of (**1a**) with enamine (**3a**) in the presence of *p*-toluenesulfonic acid using ethanol at reflux temperature (without aniline), resulted in 4-hydroxypyrrole (**5a**) (Scheme 5, ii), suggesting the formation of phenylglyoxal followed by its reaction with enamine to give 4-hydroxylpyrrole. Replacing acetophenone with α-iodoacetophenone (**1a'**), which was identified as a probable precursor of α-keto aldehyde (**1aa**), the desired product (**4a**) was obtained in good yield, both with iodine (50 mol%) and without additional iodine (Scheme 5, iii). When C-acylimine (from glyoxals and amine) was tested in the presence of HI, the desired product (**4a**) was formed with an excellent yield.

However, the adduct was isolated in poor yields when the reaction was conducted in the absence of HI (Scheme 5, iv), indicating that the catalytic amount of HI generated as a co-product during upstream iodination and Kornblum oxidation may be responsible for the process. Interestingly, employing *p*-toluenesulfonic acid (50 mol%) as a catalyst, the desired product (**4a**) was obtained with 59% yield (Scheme 5, v), suggesting that the reaction can also proceed in presence of an acid catalyst.



Scheme 5. Control experiments.

On the basis of our findings and previous reports,[12] a possible mechanism can be proposed using acetophenone (**1**), aniline (**2**), and methyl 3-aminobut-2-enoate (**3**) as the model substrates (Scheme 6). The initial iodination of acetophenone generates α-iodo ketone (**5**) in situ, which is then converted to phenyl glyoxals (**6**) due to Kornblum oxidation under the employed reaction conditions and releases HI as a co-product. The reaction of aniline (**2**) with the formyl group of phenylglyoxal results in C-acylimine (**7**). Subsequent nucleophilic attack by methyl 3-aminobut-2-enoate [18] on iminocarbon (**8**) affords the enamino-β-ketoamine adduct (**9**). The carbonyl group of this adduct is protonated by HI to allow **10**, which becomes susceptible to nucleophilic attack by the amino group of enamine and allows intra-molecular cyclization in a 5-exo-trig manner to give **11**. Finally, it undergoes sequential dehydration to give **12** followed by 1,3-hydrogen shift to afford the desired pyrroles (**4**). In the case of substituted enamine, it is directly cyclized to **13**, which undergoes dehydration to yield highly substituted 4-aminopyrrole (**4**). This pathway is regioselective and leads to 4-aminopyrroles which is supported by the X-ray single crystal structure analysis of **4s** as shown in Figure 1.



Scheme 6. Plausible reaction mechanism.

In conclusion, a Hantzsch-type one-pot synthesis of biologically interesting 4-aminopyrroles was developed by iodine-mediated reactions of readily available building blocks, such as aryl methyl ketones, arylamines, and enamines. This protocol provides regioselective access to functionally diverse 4-aminopyrroles. In addition, the bis-pyrroles synthesized by the present protocol could be useful in the generation of compound libraries of bis-4-aminopyrroles. Due to the potential biological activity of these scaffolds and the applicability of this protocol in synthesizing bis-pyrrole molecules, we hope this methodology will gain attention from the chemistry community. Further work on bis-pyrroles is currently undergoing in our laboratory.

Experimental Section

General procedure for the synthesis of substituted 4-aminopyrroles and bis-4-aminopyrroles

Procedure A

A sealed tube was charged with acetophenone (0.5 mmol) and iodine (50 mol %) at room temperature, and then dried solvent DMSO (2 mL) was added. The resulting mixture was stirred at 130 ℃. After the disappearance of the reactants (approx. 1-2 hours, monitored by TLC), *p*-toluidine (0.5 mmol) and enamine (0.75 mmol) were added at 130 ℃ and allowed to react for another 1 h. After the reaction was completed, 50 mL of water was added to the mixture, followed by extraction with ethyl acetate. The extract was washed with $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and evaporated. The crude mixture was

purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford **4**.

Procedure B
A sealed tube was charged with substituted acetophenone (1 eq.) and iodine (50 mol %) at room temperature, and then dried solvent DMSO (2 mL) was added. The resulting mixture was stirred at 130 ℃ after disappearance of the reactants (approx. 1-2 hours, monitored by TLC), *p*-toluidine (1.5 eq.) and enamine (2 eq.) were added at 130 ℃ and allowed to react for another 1 h. After the reaction was completed, 50 mL of water was added to the mixture, followed by extraction with ethyl acetate. The extract was washed with a $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford **4**.

Control Experiment:
Phenylglyoxal **1a** (0.5 mmol) was dissolved in dry ethanol (3 mL), *p*-toluene sulfonic acid (50 mol%) and enamine **3a** (0.75 mmol) were added and heated at 80 ℃. Up on completion of the reaction, the solvent was removed and the crude mixture was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford **5a**.

Acknowledgements

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[17] CCDC 1844338 (**4s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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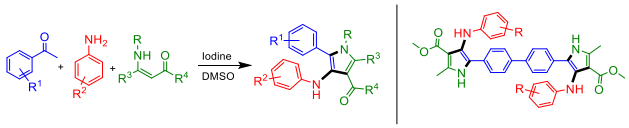
Iodine-Promoted One-pot Synthesis of Highly Substituted 4-Aminopyrroles and bis-4-Aminopyrrole from Aryl Methyl Ketones, Arylamines, and Enamines



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Hitesh B. Jalani, Jyotirling R. Mali, Hyejun Park, Jae Kyun Lee, Kiho Lee, Kyeong Lee, Yongseok Choi