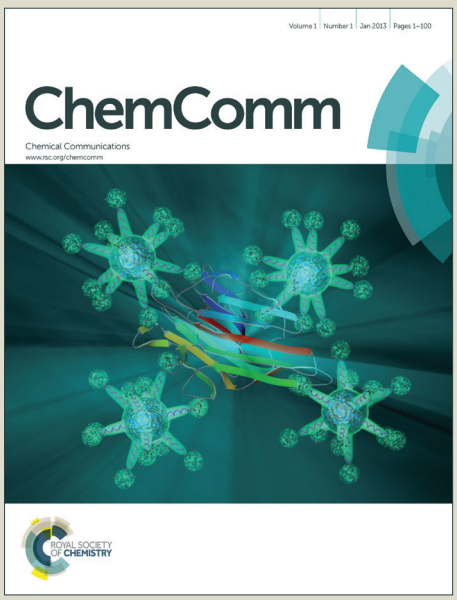
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chem Comm

RSCPublishing

COMMUNICATION

Direct Arylation of Pyridines without the Use of Transition Metal Catalyst

Cite this: DOI: 10.1039/x0xx00000x

Yahui Li, † Wei Liu, † and Chunxiang Kuang*†

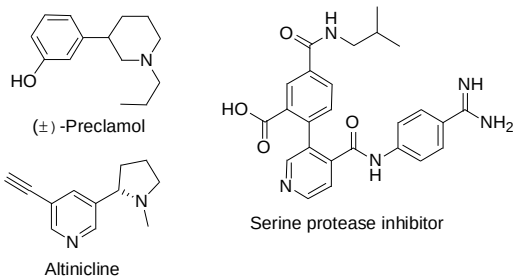
Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

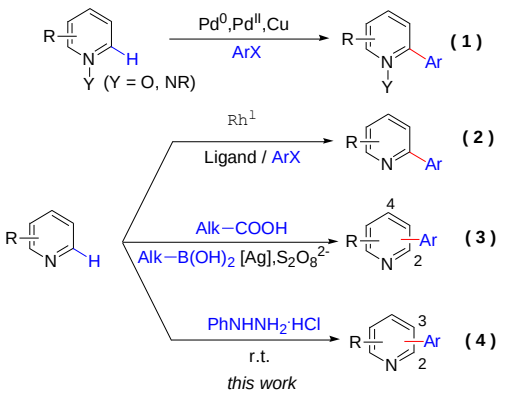
www.rsc.org/

A method for the direct arylation of pyridines with phenylhydrazine hydrochloride was developed in this study. This new reaction proceeds readily at room temperature without the use of any transition metal catalyst. This method allows rapid access to various arylated heterocycles that are more difficult to access through traditional methods.

Pyridine nuclei are among the most important heterocyclic structural motifs and are found in a large number of natural products and in many medicinally relevant compounds[1]. Examples of such compounds include preclamol[2a], which is used as antipsychotics, altinicline[2b,2c], which is used for the treatment of Parkinson's disease and (Scheme 1)[2]. However, despite the numerous applications of the arylation of pyridines, it remains a difficult challenge because pyridines are electron-poor and have a tendency to adopt a non-productive N-bound coordination mode



Scheme 1. Pharmaceutical drugs containing pyridine



Scheme 2. Transition Metal Catalyst direct arylation of Pyridine

with metal centers.[3, 4] Significant developments have been recently made in the direct arylation of pyridine (Scheme 2). Several C2-selective arylation reactions of pyridines (Eq. 1) via conversion to N-oxides and N-iminopyridinium ylides have been developed.[5] Significant work on the C2-selective arylation of unprotected 2-methylpyridine (Eq 2)[6] and the Ag-catalyzed arylation of pyridine have also been reported(Eq. 3)[7].

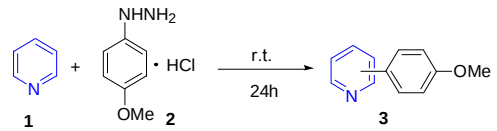
However, transition metal complexes, especially Pd, Rh, Ag, and Cu complexes, have key role in these reactions. To avoid the drawbacks of metal usage, such as toxicity and heavy transition metal impurities in final products, transition-metal-free cross-coupling reactions must be developed. Therefore new method that does not need noble metal catalyst, legend and any additive would be ideal in terms of both cost and simplicity.

Significant progress has been recently made in the direct arylation of C−H bonds in the absence of transition metal catalyst.[8]Hayashi,[8a] Shi,[8b] and Lei et al.[8c] reported a base-mediated arylation of benzene with aryl halides in the presence of 1,10-phenanthroline or N,N′-dimethyl-ethylene diamine. Herein, we report the first direct arylation of pyridines using phenylhydrazine hydrochloride (a readily available and stable reagent) at room temperature and without any additive.

[a] *Department of Chemistry, Tongji University, Siping Road 1239, Shanghai 200092, China, E-mail: kuangcx@tongji.edu.cn*
Tel: (+)+86-21-6598319
[b] *Key Laboratory of Yangtze River Water Environment, Ministry of Education, Siping Road 1239, Shanghai 200092, China*

† Electronic Supplementary Information (ESI) available: characterization data, ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

Table 1. Influence of reaction conditions on the reaction of 1a with 2a



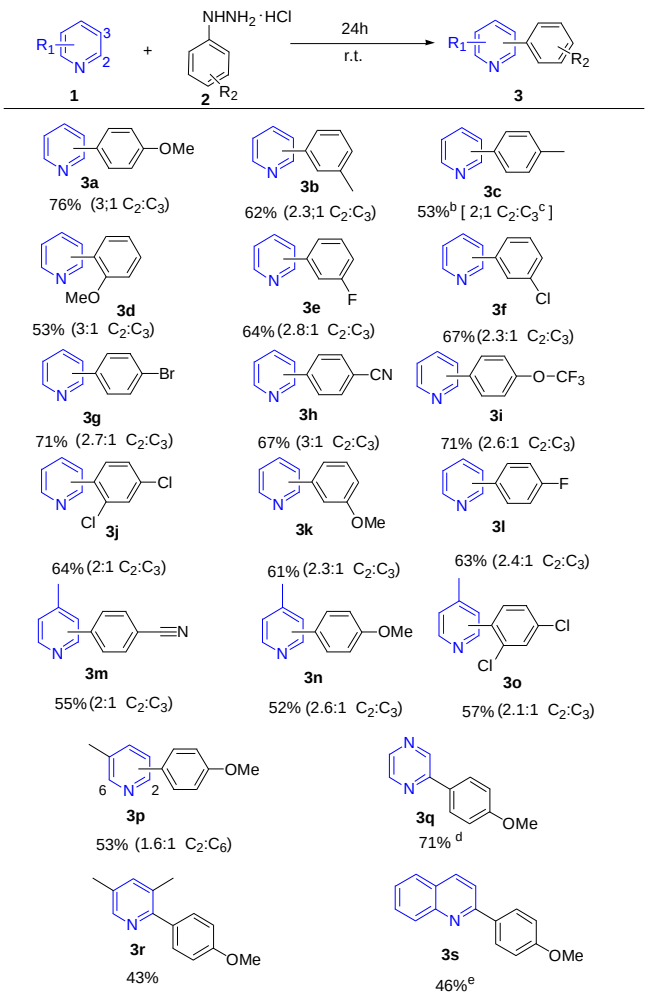
entry	catalyst	base	solvent	yields[b]
1	$Pd(AcO)_2$ (5 mol %)	K_2CO_3	–	14
2	$PdCl_2$ (5 mol %)	K_2CO_3	–	12
3	–	K_2CO_3	–	18
4	–	Na_2CO_3	–	22
5	–	Cs_2CO_3	–	14
6	–	NaOH	–	trace
7	–	–	–	76
8[c]	–	–	DCE	33
9[c]	–	–	Toulene	37
10[c]	–	–	DMF	46
11[d]	–	–	DMF	39

[a] Reaction conditions: pyridine (2 mL), 2a (0.2 mmol) in air, RT, 24 h,sealed tube. [b] Isolatedyields (Total yields of all isomers). [c] Pyridine (0.4 mL, 5.0 mmol) with solvent (1 mL) was used.[d] Pyridine (0.1mL, 1.25 mmol) with DMF (1 mL) was used, RT, 48 h, sealed tube.

Initially, pyridine and 4-methoxyphenylhydrazine hydrochloride were chosen as the substrates for the model reaction in the presence of 5 mol% of $Pd(OAc)_2$ and 2 equiv. of K_2CO_3 in air. The target product was obtained with a yield of 14%. As such, various conditions were screened, and the results are summarized in Table 1. First, some catalysts, such as $Pd(OAc)_2$ and $PdCl_2$, were screened (Table1, entries1 and 2). Further investigation demonstrated that higher yield was obtained in the absence of a base or catalyst (Table 1, entry 1-6). Under the best conditions, excess pyridine substrate was needed to obtain practical yields. Moreover, the yield decreased significantly from 76% to 22% when pyridine was reduced to 6 equiv in 1 mL of N,N-dimethylformamide (DMF) (entry 9). The use of 25 equiv of pyridine in 1 mL of DMF, however, afforded the arylated product a 46% yield (entry 10). The compatibility of this catalytic reaction with DMF solvent is important for further development in reducing the amount of the pyridine substrate to 1 equiv. It is of note that this reaction can occur at room temperature. These results indicate that this transformation is facile and practical, as it did not require the use of an expensive catalyst, any additive and rigorous exclusion of air. Thus, this feature is expected to have numerous important applications in medicine and materials chemistry.

With this optimized reaction condition, the general application of this novel process was investigated using various arylhydrazines, and the results are summarized in Table 2. Regioselectivity of the heterocycle that was predominantly for the 2-, 3-, and 4- positions was proven to be minimal. The

Table 2 . The reaction of arylhydrazines with pyridine

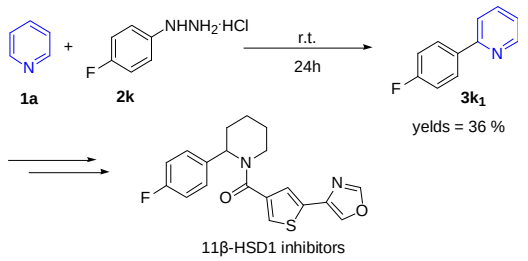


[a] Reaction conditions: pyridine (2 ml), 2a (0.2 mmol), in air, RT, 24 h, sealed tube. [b]Isolated yields(Total yields of all isomers) [c].$3x_1$ represent the product of C_2 and $3x_2$ represent the product of C_3, [d] Pyridine (320mg, 4 mmol) with DMF (1 mL) was used, [e] Trace of C_3 product was obtained

generality of this novel process was explored using various phenylhydrazines hydrochloride, and the results are summarized in Table 2. As outlined, a wide range of phenylhydrazine hydrochloride compounds that incorporate electron-donating and electron-withdrawing groups into the *ortho*-, *meta*-, and *para*-positions gave the desired products in good yields (3a–3l ,Table 2). The ortho-substituted phenylhydrazine hydrochloride also readily reacted to give the desired product in good yields (3d and 3j, Table 2). Functional group, such as cyano, was noted to be compatible in this reaction (3h and 3m, Table 2). High chemoselectivities were observed when 2, 4-dichlorophenyl-hydrazine hydrochloride (3j, Table 2) and 4-bromophenyl-hydrazine hydrochloride (3g, Table 2) were used in this coupling reaction. Aryl halides were tolerated, providing handles for further functionalization (e.g., with a Suzuki reaction). We note that this reaction will substantially reduce the cost of these

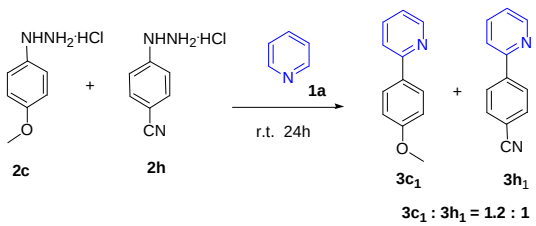
compounds compared to known methods. To further illustrate the efficacy of this coupling reaction, the scope of pyridine substrates was also briefly surveyed. For example, 4-methoxyphenyl-hydrazine hydrochloride reacted with 3-methylpyridine to produce the product with a yield of 53% (3p, Table 2), and the reaction between 4-methoxyphenylhydrazine hydrochloride and 4-methylpyridine resulted in a yield of 52%.The reaction proved to be fairly general for other electron-poor heterocycles, such as, pyrazine (3q, Table 2), also proved to be viable substrates, as well as pyridine derivatives.

To demonstrate the applicability of this method in the synthesis of these types of molecules, we prepared 2-(4-fluoro-phenyl)-pyridine on a gram scale using the optimized conditions (Scheme 3). Compared with previous approaches requiring expensive air-sensitive organometallic reagents, harsh reaction conditions, and have toxic and heavy transition metal impurities in final products, this new method is expected to have numerous important applications in medicine and materials chemistry



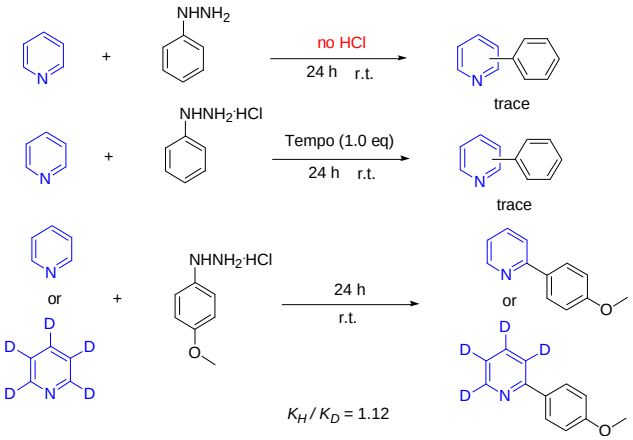
Scheme 3. Prepared arylation of pyridines on a gram scale

The effect of the arylhydrazines hydrochloride on the reaction was investigated through a competition experiment (Scheme 4). Under the reaction conditions, pyridine was treated with both 4-methoxyphenylhydrazine hydrochloride and 4-cyanophenyl-hydrazine hydrochloride. The yields from the competition experiment indicates that no significant difference in the yield between phenylhydrazine hydrochloride bearing electron-donating groups and phenylhydrazine hydrochloride bearing electron-withdrawing groups in this system.

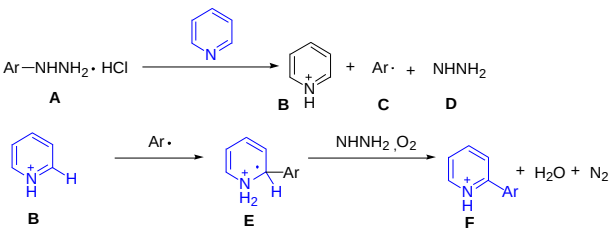


Scheme 4. Competition experiment.

To obtain some insights into the mechanism of this novel method, the following experiments were conducted Scheme 5. Trace amounts of the desired product was observed when we used phenylhydrazine instead of phenylhydrazine hydrochloride. The result demonstrated that hydrochloride has an important role in the reaction. And trace of the desired product was observed when we used Tempo (1.0 eq.). Subsequently, kinetic isotope effects (KIE) was investigated with regard to the C–H/D bonds for pyridine. No significant KIE value (k_H/k_D= 1.12) was obtained. Basing on the results of the reaction in the experiment and previous literature[9], we outlined a plausible reaction mechanism as shown in Scheme 6. The results have shown that the presence of pyridines, phenylhydrazine hydrochloride disproportionates into aryl radicals. This aryl radical **C** reacts with protonated heterocycle **B** to form radical cation **E,** which in turn is re-oxidized by O_2, producing the desired product **F.**



Scheme 5. Hydrochloride ,Tempo and Isotope Effect



Scheme 6. Plausible Mechanism

Despite the generality and practicality of the reaction, there are several apparent limitations. First, the regioselectivity is not governed by the reagents but by the inherent reactivity of the substrates. Second, the yields are mediocre in some cases. In addition to a detailed investigation of the mechanism of this reaction, future studies should aim to overcome these limitations.

In summary, a reaction to achieve the direct coupling of phenylhydrazine hydrochloride (ca. 3 cent/g) to electron-deficient heterocycles without any catalyst and co-oxidant has been developed. The reaction proceeds under mild conditions (room temperature) and does not require pre-functionalization of the heterocycle. The reaction did not require excessive time, harsh reaction conditions, catalyst, and exclusion of air. This cost-effective methodology will be very attractive for both the academia and industry because commercially available arylhydrazines are used as coupling partner. Lastly, this work sets a precedent for the mild generation of highly reactive species

(tentatively assumed to be radicals) from phenylhydrazine hydrochloride, a platform that may find use in other areas of reaction design.

We thank the Natural Science Foundation of China (No. 21272174), the Key Projects of Shanghai in Biomedicine (No. 08431902700), and the Scientific Research Foundation of the State Education Ministry for Returned Overseas Chinese Scholars for the support of this research.

Notes and references

1 (a) M. G. P. Buffat, Tetrahedron2004, 60, 1701. (b) F.-X. Felpin;J. M Lebreton, Eur. J. Org. Chem.2003, 3693. (c) P. M. Weintraub,J. S S abol; J. M. Kane, D. R. Borcherding, Tetrahedron2003, 59,2953

2 (a) M-C Ye, G-L Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris,and J-Q Yu, J. Am. Chem. Soc. 2011,133,19090.(b) N.D.P. Cosford et al. Pharmaceutica Acta Helvetiae.2000(74) 125.(c) F. F. Wagner and D. L. Comins, J. Org. Chem. 2006, 71, 8673-8675.(d) W. Masayuki, T.W.Brady and J-Q Yu Angew. Chem. Int. Ed.2010, 49, 1275 ;

3 (a) I. B. Seiple, S.Su,; R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, J. Am. Chem. Soc.2010, 132, 13194. (b) M. Li, R. Hua, Tetrahedron Lett.2009, 50, 1478. (c) O.Kobayashi,;D. Uraguchi,T. Yamakawa, Org. Lett.2009, 11, 2679. (d) S. Yanagisawa, K.Ueda, T. Taniguchi, K. Itami, Org. Lett.2008,10, 4673. (e) S. Mukhopadhyay, G. Rothenberg, D. Gitis,; M. Baidossi,;D. E. Ponde, Y.J. Sasson, Chem. Soc., Perkin Trans. 22000,1809.

4 For a recent review of CH functionalization of pyridines, see: Y. Nakao, Synthesis. 2011, 3209

5 (a) L.C. Campeau, S. Rousseaux, K.J. Fagnou, J. Am. Chem. Soc. 2005, 127,18020.(b) K.S. Kanyiva,; Y. Nakao, T. Hiyama, Angew. Chem. Int. Ed. 2007, 46, 8872. (c) S. H. Cho, S. J. wang, S. Chang, J. Am. Chem. Soc.2008, 130, 9254. (d) J. Wu, X. Cui, L.Chen, G. Jiang, Y.J. Wu, J. Am. Chem. Soc.2009,131,13888.(e) P. Xi, F. Yang, S.Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J.S. You, J. Am. Chem. Soc. 2010, 132, 1822. (f) A. Lariv, J. J. Mousseau, A. B. Charette, J. Am. Chem. Soc. 2008, 130,52

6 (a) A. M. Berman,; J. C. Lewis, R. G. Bergman, J. A. Ellman, J. Am. Chem. Soc.2008, 130,14926. (b) T. Kawashima, T. Takao, H.J. Suzu ki, J. Am. Chem. Soc.2007,129, 11006.(c) M. Tobisu, I. Hyodo, N. C hatani, J. Am. Chem. Soc.2009, 131, 12070 a

7 (a) F. Minisci, E. Vismara, F. Fontana, Heterocycles1989, 28, 489. (b) F. Minisci, F. Fontana, E.J. Vismara, Heterocycl. Chem.1990, 27, 79. (c) D. C. Harrowven, B. J. Prog. Sutton, Heterocycl. Chem.2004, 16, 27 (d) B. Seiple, S Su, R A. Rodriguez, R Gianatassio, Y Fujiwara, A L. Sobel, and P. S. Baran. J. Am. Chem. Soc. 2010, 132, 13194–13196

8 (a) E. Shirakawa, K.-I. Itoh,; T. Higashino, T. Hayashi, J. Am.Chem. Soc.2010, 132, 15537. (b) C.-L.Sun, H. Li,;D.-G.Yu, M. Yu,X. Zhou, X.-Y. Lu,; K. Huang, S.-F. Zheng,;B.-J. Li,;Z.-J. Shi, Nat.Chem.2010, 2, 1044. (c) W. Liu,;H. Cao,;H. Zhang, K. H. Chung, C. He, H. Wang,;Kwong, F. Y. A. Lei, J. Am. Chem.Soc.2010, 132, 16737. (d) O. Vakuliuk, B. Koszarna,; D. T. Gryko, Adv. Synth. Catal. 2011, 353, 925. (e) S. Yanagisawa, K. Ueda, T.Taniguchi, K. Itami, Org. Lett.2008, 10, 4673. (f) S. Yanagisawa,K. Itami, ChemCatChem. 2011, 3, 827. (g) N. E. Leadbeater, Nat.Chem.2010, 2, 1007. (h) D. S. Roman, Y. Takahashi, A. B. Charette, Org. Lett.2011, 13, 3242. (i) Y. Qiu, Y. Liu, K. Yang, W. Hong, Z. Li,Z. Wang, Z. Yao, S. Jiang, Org. Lett.2011, 13, 3556. (j) T. Truong,O. Daugulis, J. Am. Chem. Soc. 2011, 133, 4243.

9 (a) A. G. Myers; M. Movassaghi; B.Zheng, Tetrahedron Lett. 1997, 38, 6569 (b) E. M. Kosower; P.-K. C.Huang; T. Tsuji, J. Am. Chem. Soc. 1969, 91, 2325. (c) J. Hofmann; H. Jasch; M. R..Heinrich, J. Org. Chem. 2014, 79, 2314

