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PII: S0040-4039(14)01112-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.06.099
Reference: TETL 44824

To appear in: *Tetrahedron Letters*

Received Date: 25 March 2014
Revised Date: 12 June 2014
Accepted Date: 26 June 2014

Please cite this article as: Jiang, T., Chen, S-Y., Zhuang, H., Zeng, R-S., Zou, J-P., Air-promoted direct radical arylation of anilines with arylhydrazines, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.06.099

Graphical Abstract

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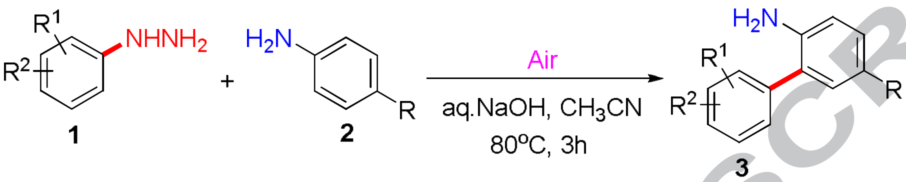

Tetrahedron Letters
journal homepage: www.elsevier.com

Air-promoted direct radical arylation of anilines with arylhydrazines

Tao Jiang,[a] Sheng-Yan Chen, [a] Huan Zhuang, [a] Run-Sheng Zeng, *[a] Jian-Ping Zou*[a, b]

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

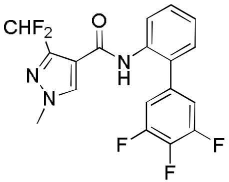
Keywords
radical reaction
arylhydrazine
2-aminobiaryl
air oxidation

ABSTRACT

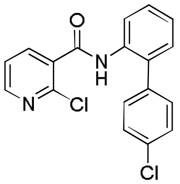
Air-promoted coupling reaction of arylhydrazines and arylamines is developed for the selective synthesis of 2-aminobiaryls. This protocol provides a green, cost-effective and scale-up method for preparation of 2-aminobiaryls.

Biaryl is core structure of many fuctional compounds, medicines and materials, [1] so they have attracted considerable attention. Gomberg–Bachmann reaction is a well-known method for synthesis of biaryls, it was first reported in 1924, [2] so far, the reaction conditions had been much improved. During the past decades, a lot of new cross-coupling reactions catalyzed or promoted by transition-metal were discovered, which provided the powerful tools for synthesis of biaryls. [3] Along with the rapid development of the transition-metal catalyzed reaction, controllable radical reactions have gained increasing interests since 1980's, many novel radical process were disclosed, [4] the radical reactions play more important role in current organic synthesis. [5]

Arylhydrazines are easily oxidized by various oxidants to yield aryldiazene (aryldiimide), then aryl radicals, which react with arenes to afford biaryls. Although the properties, reactions and mechanisms of aryl radicals derived from arylhydrazines had been much investigated, however, arylhydrazine did not become a good substrate for synthesis of biaryls because of diverse products and lower yield until early 1980's. [6] Afterwards, several transition-metal promoted or catalyzed reactions of arylhydrazines and alkenes, arenes, heteroarenes and C60 were reported,[7] however, metal-free reaction is less explored. [8]



Xemium



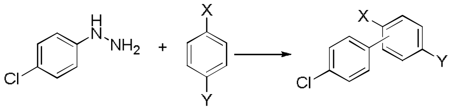
Boscalid

2-Aminobiaryls are key intermediates for synthesis of best-selling fugicides such as **Xemium**, **Boscalid** and other funtional compounds, [9] so developing metal-free, cost-effective and scale-up method for synthesis of 2-aminobiaryls are significant both in academia and industry. In connection to our research on selective radical reactions, [10] herein, we report an air-promoted direct radical arylation of anilines with arylhydrazines to afford 2-aminobiaryls, this reaction proceeds in aqueous sodium hydroxide solution, with no need of oxidants.

In our previous paper, [10c] the copper-catalyzed coupling reaction of arylhydrazines and trialkylphosphites was described, in which CuO and base are crucial for C-P bond formation. We consider whether C-C bond can be formed in the absence of a metal catalyst. In the initial experiment, the reaction of 4-chlorophenylhydrazine and benzene was selected as model, which gave the expected 4-chlorobiphenyl in 11% yield (Table 1, entry 1). Then, phenol, anisole, aniline and 4-chloroaniline were employed for the reaction, 4-chloroaniline gave the selective 2-amino-4'-chlorobiphenyl in 73% yield (Table 1, entries 2-5). It is worthy to note that 10 equivalent of 4-chloroaniline is necessary to trap 4-chlorophenyl radical intermediate completely. After base, solvent and time screening (Table 1, entries 6-19), the optimal reaction conditions were determined to be: the reaction of 4-chlorophenylhydrazine and 4-chloroaniline carried out in the presence of 6 equivalent of NaOH in CH_3CN/H_2O(3:2) at 80 °C for 3h in air (Table 1, entry 18).

The above optimal conditions were applied for the reaction of phenylhydrazine and aniline derivatives. The results in Table 2 showed that phenyl radical facilitated the attack of

Table 1. Optimization of the reaction conditions [a]



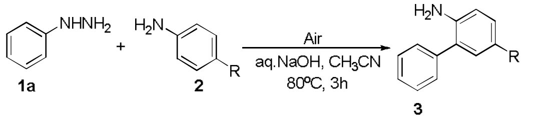
Entry	Base	Substrate	H_2O (mL)	Time (h)	Solvent (3mL)	Yield[b] (%)
1	NaOH	Benzene	2	5	CH_3CN	11
2	NaOH	Phenol	2	5	CH_3CN	Trace
3	NaOH	Anisole	2	5	CH_3CN	Trace
4	NaOH	Aniline	2	5	CH_3CN	41
5	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	CH_3CN	73
6	KOH	$4\text{-}ClC_6H_4NH_2$	2	5	CH_3CN	53
7	*t*-BuOK	$4\text{-}ClC_6H_4NH_2$	2	5	CH_3CN	45
8	Cs_2CO_3	$4\text{-}ClC_6H_4NH_2$	2	5	CH_3CN	61
9	*n*-Bu_4NOH	$4\text{-}ClC_6H_4NH_2$	2	5	CH_3CN	39
10	NaOH	$4\text{-}ClC_6H_4NH_2$	3	5	CH_3CN	42
11	NaOH	$4\text{-}ClC_6H_4NH_2$	1	5	CH_3CN	64
12	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	Toluene	23
13	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	EtOH	32
14	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	THF	43
15	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	DMSO	17
16	NaOH	$4\text{-}ClC_6H_4NH_2$	2	5	DMF	25
17	NaOH	$4\text{-}ClC_6H_4NH_2$	2	1	CH_3CN	21
18	NaOH	$4\text{-}ClC_6H_4NH_2$	2	3	CH_3CN	72
19	NaOH	$4\text{-}ClC_6H_4NH_2$	2	10	CH_3CN	73

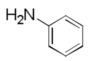
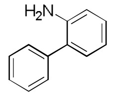
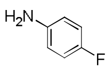
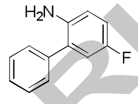
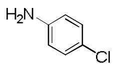
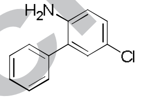
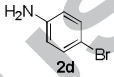
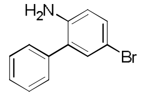
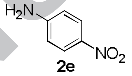
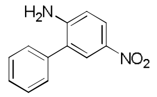
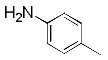
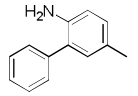
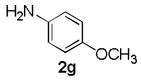
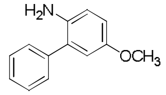
[a] Reaction conditions: 4-chlorophenylhydrazine (1.0 mmol), substrate (10.0 mmol), base (6.0 mmol) and H_2O (2 mL) in CH_3CN (3.0 mL) at 80 °C for 3h in air. [b] Isolated yield.

the site with high electron density, so aniline gave the 2-aminobiaryl as major product in 45% yield and minor 4-aminobiaryl was observed but not isolated. Therefore, anilines bearing *para*-substituted electron-withdrawing groups such as F, Cl and Br afforded the 2-aminobiaryls in high yields (Table 2, entries 2-4) except 4-nitroaniline (Table 2, entry 5), but anilines bearing *para*-substituted electron-donating groups such as CH_3, OCH_3 lowered the yield slightly (Table 2, entries 6-7).

Subsequently, the scope of arylhydrazines was investigated. As seen in the Table 3, arylhydrazines with electron-withdrawing groups such as F, Cl and Br favored the reaction and afforded the expected product, 2-aminobiaryls in good yields (Table 3, entries 1-3), but 4-nitrophenylhydrazine gave a trace amount of product (Table 3, entry 4) and no reaction was observed for the 3-chloro-5-trifluoromethylphenylhydrazine (Table 3, entry 5). On the contrary, arylhydrazines with electron-donating groups such as CH_3, isopropyl, *t*-butyl and OCH_3 reduced the yield (Table 3, entries 6-11). The reactions of *p*-methyl- and *m,m*-dimethylphenylhydrazines with 4-chloroaniline afforded the corresponding aminobiaryls in 51% and 48% yields, respectively (Table 3, entries 6 and 7), compared to the *o*-methyl- and *o*-ethylphenylhydrazines which afforded the corresponding products in 35% and 31% yields, respectively (Table 3, entries 12 and 13). It is worthy to note the steric effect of *ortho*-substituent on arylhydrazine. To know the scope and limitations of this methodology, the reaction was extended to the *t*-butylhydrazine, phenylsulfonyl hydrazine and benzoylhydrazine, disappointedly, no reaction was observed.

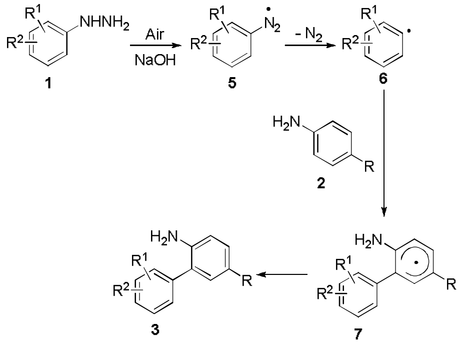
Table 2. Coupling reactions of phenylhydrazine (**1a**) with *para*-substituted anilines (**2**) [a]



Entry	Aniline **2**	Product **3**	Yield (%)[b]
1	 **2a**		**3aa** (45)
2	 **2b**		**3ab** (62)
3	 **2c**		**3ac** (60)
4	 **2d**		**3ad** (61)
5	 **2e**		**3ae** (trace)
6	 **2f**		**3af** (48)
7	 **2g**		**3ag** (52)

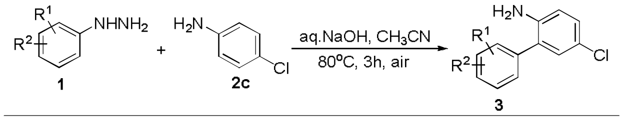
[a] Reaction conditions: **1a** (1.0 mmol), **2** (10.0 mmol), NaOH (6.0 mmol) and H_2O (2 mL) in CH_3CN (3.0 mL) at 80 °C for 3h in air. [b] Isolated yield.

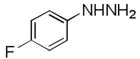
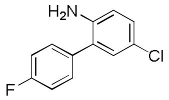
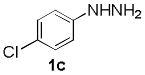
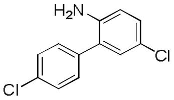
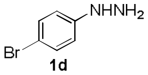
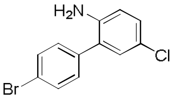
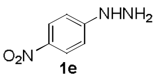
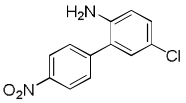
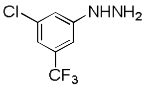
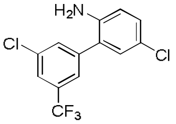
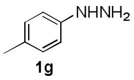
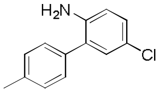
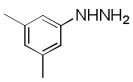
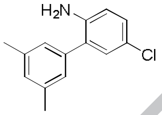
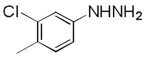
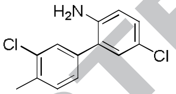
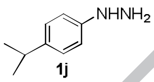
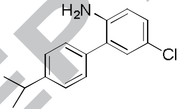
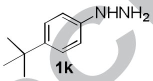
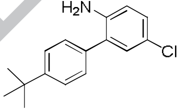
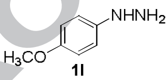
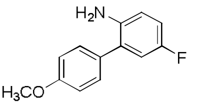
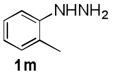
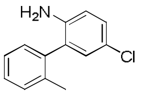
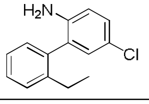
A plausible mechanism for the air-promoted selective coupling reaction of arylhydrazines and arylamines is proposed in Scheme 1. Arylhydrazines (**1**) are oxidized by air (O_2) to form arylhydrazyl radicals (**5**), followed by release of N_2 to yield aryl radicals (**6**), which are selectively added to the *ortho*-position of anilines (**2**) to produce radical (**7**), 2-aminobiaryls (**3**) are formed by rearomatization of **7**.



Scheme 1 Mechanism for the reaction of arylhydrazines and arylamines

Table 3. Coupling reactions of arylhydrazines (**1**) with 4-chloroaniline (**2c**) [a]



Entry	Hydrzine **1**	Product **3**	Yield (%)[b]
1	 **1b**		**3bc** (73)
2	 **1c**		**3cc** (71)
3	 **1d**		**3dc** (69)
4	 **1e**		**3ec** (trace)
5	 **1f**		**3fc** (N. R.)
6	 **1g**		**3gc** (51)
7	 **1h**		**3hc** (48)
8	 **1i**		**3ic** (51)
9	 **1j**		**3jc** (60)
10	 **1k**		**3kc** (43)
11	 **1l**		**3lc** (54)
12	 **1m**		**3mc** (35)
13	 **1n**		**3nc** (31)

[a] Reaction conditions: hydrazine (1.0 mmol), **2c** (10.0 mmol), NaOH (6.0 mmol) and H_2O (2 mL) in CH_3CN (3.0 mL) at 80 °C for 3h in air. [b] Isolated yield.

In conclusion, a novel air-promoted method for selective synthesis of 2-aminobiaryls was developed from the coupling reaction of arylhydrazines and arylamines. The reaction proceeded under mild conditions in aqueous sodium hydroxide solution to afford 2-aminobiaryls in moderate to good yields. 2-Aminobiaryls are key intermediates for the synthesis of fungicides such as **Xemium** and **Boscalid**, also they are used as building blocks for dyes, liquid crystals, organic devices and conductors, ligands for metal catalysts and medicines. This protocol provides a green, cost-effective and scale-up method for preparation of 2-aminobiaryls.

Acknowledgments

JPZ thanks the National Natural Science Foundation of China for financial support (No. 20772088, 21172163) and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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