Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Improved synthesis of pyridyl–biaryl ring systems via benzidine rearrangements

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ARTICLE INFO

Article history:
Received 5 March 2014
Revised 11 April 2014
Accepted 30 April 2014
Available online xxxx

Keywords:
Benzidine rearrangement
Diazo compounds
[5,5] sigmatropic rearrangement
Hetero-biaryls
Pyridinium salt

ABSTRACT

The acid-catalyzed benzidine rearrangement of diazo compounds is known to involve several rearrangements with the major pathway being a [5,5] sigmatropic rearrangement to provide 4,4′-diaminobiaryls. A limitation of this rearrangement has been poor conversions with pyridyl systems. Herein, we address this long standing issue to furnish hetero-biaryls via a pyridinium salt in the presence of trimethylsilyl iodide.

There has been a long and controversial development of the benzidine reaction since the first discovery reported by Hoffman in 1863 on unsubstituted simple biaryl systems, and very lately by Cho and co-workers with substituent(s) at the *ortho* or *meta* positions.[1,2] Wildgrube and co-workers were the first to report on the pyridyl–aryl benzidine rearrangement which suffered from poor conversions due to tautomerization.[3] Thus, despite more than a century of attention by the synthetic community, only a few rather inefficient routes to heterobiaryls exist[4] and hence most mechanistic studies have been limited to the naphthyl or phenyl systems reviewed by Mamantov.[5a] There has been renewed interest in the benzidine rearrangement for the synthesis of chiral naphthyl ligands for catalysis and mechanistic investigations to determine the potential toxicity of azo dyes.[5b,c]

The hetero-biaryl moiety is a common functionality found in many pharmaceutical bioactive molecules[6] (Fig. 1). The current state of the art methods for their preparation is to employ transition metal catalyzed cross-coupling reactions as developed by Suzuki.[7] However, this method has several limitations such as, sourcing of an appropriate functionalized boronic acid or ester, chemoselectivity of the coupling in the presence of other halogen atoms and expensive Pd catalysts.[8] These requirements diminish optimal atom economy and generate waste, thus compromising some of the 12 principles of green chemistry.[9] In the context of an internal drug development effort, we were interested in the investigation of the benzidine rearrangement as a potential improvement to construct pyridyl–aryl linkages without using a boronic acid and particularly palladium that poses a potential regulatory hurdle.[10] Herein, we report our preliminary success on expanding the scope of this rearrangement to provide hetero-aryl systems in reasonable yields.

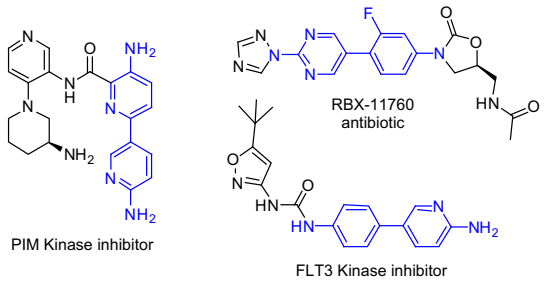

Figure 1. Bioactive molecules with hetero-biaryl systems.

A review of the literature indicated several unproductive pathways such as tautomerization and disproportionation, which prevent correct orientation for [5,5] sigmatropic rearrangement of the phenylhydrazinylpyridine to provide the benzidine rearrangement product **3**. We envisioned that protection of the nitrogen on the pyridine might shift the equilibrium from the

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http://dx.doi.org/10.1016/j.tetlet.2014.04.126
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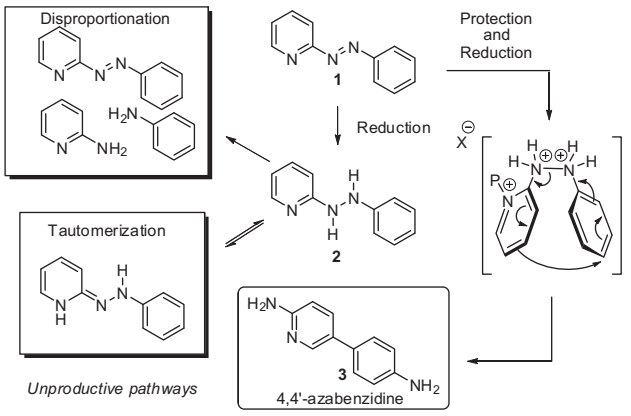
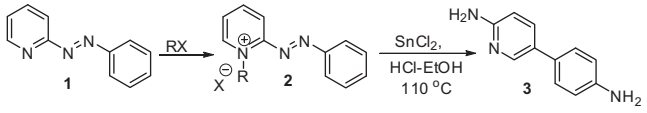


Scheme 1. Tautomerization of *N*-phenyl-*N*′-pyridin-2-ylhydrazine.

Table 1
N-substitution effect on hetero-benzidine rearrangement



Entry	**2**[a]	**3** Yield (%)[b]
1[c]	N/A	15
2	R = Me; X = I	NA[d]
3	R = Ac; X = Cl	NA[d]
4	R = Ts; X = Cl	21
5	R = Ns; X = Cl	48
6	R = TBS; X = OTf	14
7	R = TMS; X = OTf	12
8	**R = TMS; X = I**	52

[a] Conditions: diazo compound (1 equiv), RX (1.1 equiv), rt, 8 h, isolated yield; for entries 2–5, CH_2Cl_2; entries 6–8, *n*-hexane as solvent.
[b] Conditions: $SnCl_2$ (1.3 equiv), concd HCl, EtOH, 110 °C, 2 h, isolated yield.
[c] Control with no protecting group.
[d] Unknown compounds at TLC baseline that could not be isolated.

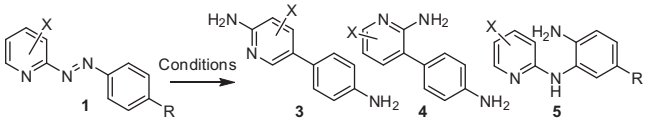
thermodynamically stable hydrazono tautomer of **2**, and also prevent disproportionation by-products (Scheme 1). The preliminary results of our investigation are summarized in Table 1.

Consistent with the reported literature, unsubstituted phenylazopyridine **1** (Table 1, entry 1) afforded the target compound **3** in only 15% yield without the use of a pyridinium salt. Interestingly, alkyl and acyl pyridinium salts led to unidentifiable mixtures of compounds with no desired benzidine **3** (Table 1, entries 2 and 3). Sulfonamide pyridinium salts were more successful with a notable three fold improvement in yield using the *para*-nosyl pyridinium salt. The two fold difference between tosyl and *para*-nosyl pyridinium salts has not been investigated (Table 1, entry 5). Silyl pyridinium salts derived from silyl triflates provided no improvement, however TMS-pyridinium salts derived from TMSI gave the best yield of 52% (Table 1, entry 8). At this point no further studies were undertaken to determine why TMSOTf was significantly worse than TMSI.[11]

At this point, no further optimization studies were conducted and the TMSI conditions were used to explore the substitution effect for the hetero-aryl benzidine rearrangement. In addition to [5,5] sigmatropic rearrangements to provide 4,4′-benzidine products, [3,5] and [1,3] sigmatropic rearrangements can provide diphenyline and *o*-semidine products. To explore if these rearrangements could be selective and to understand if substitution on the pyridyl versus phenyl ring had an effect on the product distribution, several substrates were synthesized.[12] The key diazo intermediates **1a–g** were prepared in moderate to good yields by reacting a substituted 2-aminopyridine with nitrosobenzene derivatives.[13] The rearrangement results are listed in Table 2.

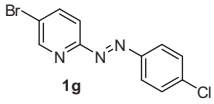
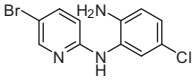
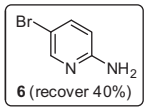
Consistent with unsubstituted **1**, 4-substituted aminopyridines **1a** and **1b** (Table 2, entry 1) furnished [5,5]-sigmatropic rearrangement products **3a** and **3b** in moderate yields. No other competing rearrangement products such as **4** or **5** were observed, thus indicating that the 4-position has relatively little impact on the reaction pathways. 5-Substituted aminopyridines **1c–e**, which block the benzidine rearrangement pathway provided only [3,5]-sigmatropic diphenyline products **4c–e**.[14] However, similar substitution to prevent the [5,5] rearrangement at the 4 position of the phenyl ring completely suppressed diphenyline formation. Only minor

Table 2
Substrate scope of the benzidine rearrangement[a]

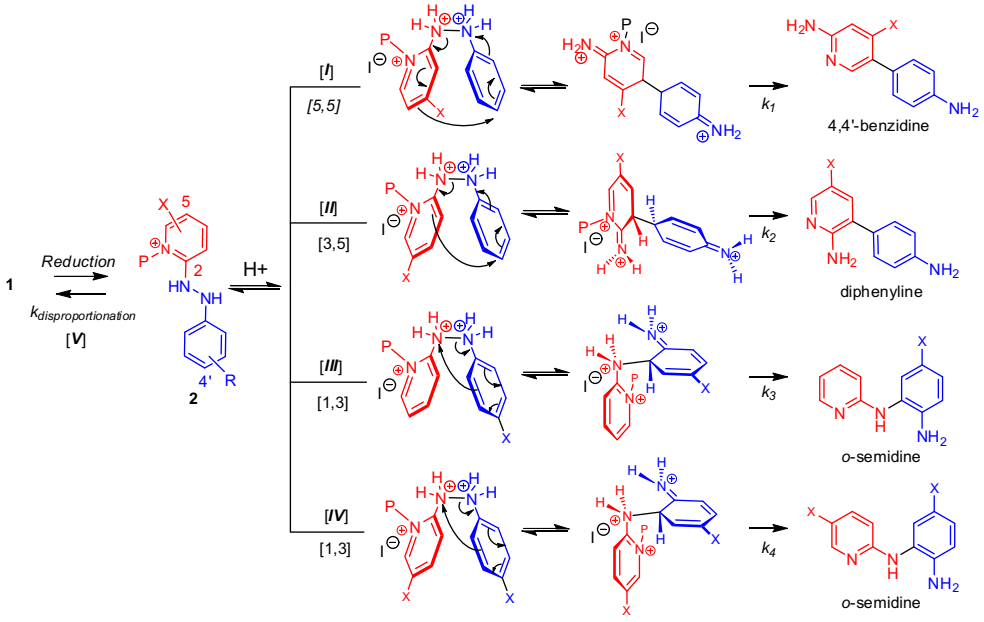


Entry	Substrate	Product	Yield (%)[b]	
1	**1a** X = Br **1b** X = I		**3a** X = Br **3b** X = I	54 46
2	**1c** X = Cl **1d** X = Br **1e** X = I	4,4′-benzidine diphenyline	**4c** X = Cl **4d** X = Br **4e** X = I	52 48 40
3	**1f**	*o*-semidine	**5f** (**1f** recovery 90%)	5

Table 2 (*continued*)

Entry	Substrate	Product	Yield (%)[b]
4	 **1g**	 *o*-semidine	**5g** 37  **6** (recover 40%)

[a] Conditions: (1) diazo compound (1 equiv), TMSI (1.1 equiv), rt, 8 h; (2) $SnCl_2$, EtOH–HCl, 110 °C.
[b] Isolated yield.



Scheme 2. Simplified mechanistic proposal for the formation of **4** and **5**.

amounts of *o*-semidene **5f** were observed, and 90% of **1f** was recovered indicating that disproportionation pathways were also shut down.[15] 5-Bromo-2-(4-chlorophenyl)diazenylpyridine (**1g**), which blocks both positions required for the benzidine rearrangement, provided *o*-semidine **5g** in 37% yield along with 40% of the disproportionation fragment, 5-bromo-2-aminopyridine (**6**) (Table 2, entry 4). Interestingly this suggests that the 5 position of the aminopyridine ring overrides the influence of the substitution at the 4 position on the phenyl ring.

It is apparent that while the [5,5] sigmatropic rearrangement proposed in Scheme 2 is the major pathway when the 5 and 4′ positions are unsubstituted, there are competing and alternate processes depending on the location of the substituents on the phenylhydrazinylpyridine **2**. Based on the previous mechanistic studies proposed by Shine[16] on the bis-aryl system, we hypothesize the following plausible mechanistic considerations depicted in Scheme 2 for the effect of substitution on the pyridyl and aryl rings. There are as few as five competing pathways (***I***–***V***) for the intermediate bis-substituted phenylhydrazinylpyridine **2**. When the pyridyl is unsubstituted or substituted at the 4 position the reaction occurs predominately through pathways ***I*** and ***V*** ($k_1 > k_{dis} >> k_2, k_3, k_4$). When the substitution is such that benzidine rearrangement is blocked on the pyridyl ring, pathway ***II*** [3,5] predominates ($k_2 > k_{dis} >> k_3, k_4 >> k_1$). However the same substitution on the phenyl ring either shuts down pathway ***III*** [1,3] or disproportionation ***V*** occurs ($k_{dis} > k_3 > k_4, k_2 >> k_1$). When both rings are substituted to prevent [5,5] rearrangement pathway ***IV*** [1,3] is now preferred along with disproportionation ($k_4 = k_{dis} > k_2, k_3 >> k_1$). These preliminary results that there are subtle effects from the substitution that may affect the mechanism for these pyridyl–aryl rearrangements. Further substrate scope studies and more extensive experiments will need to be conducted in order to determine the underpinning mechanistic rationale. In addition, the roles of the counterion (OTf vs I) and the difference between nosyl and tosyl versus silyl will need to be studied in more depth.

In conclusion, we have developed a method using pyridinium salts to provide a threefold improvement in yield to construct various substituted phenylpyridines. Importantly, this method circumvents the use of expensive boronic acids and palladium catalysts. Work in this area as well as detailed mechanistic studies will be reported in due course.

Acknowledgments

We thank Ms. Doris Tan (ICES) for high-resolution mass spectrometric (HRMS) assistance. Financial support for this work was provided by the Agency for Science, Technology and Research (A*STAR).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.126.

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