ORGANIC LETTERS

2013
Vol. 15, No. 24
6286–6289

6-Aroylated Phenanthridines via Base Promoted Homolytic Aromatic Substitution (BHAS)

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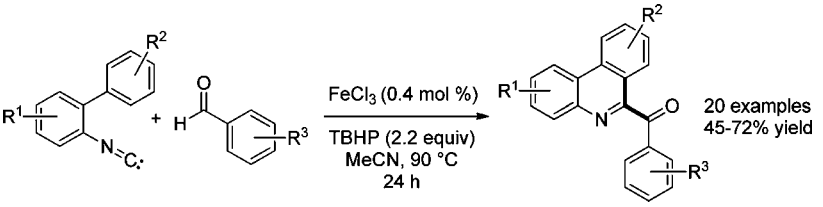
Received November 1, 2013

ABSTRACT



Readily accessible 2-isocyanobiphenyls react with aromatic aldehydes via base promoted homolytic aromatic substitution (BHAS) to give 6-aroylated phenanthridines. Reactions occur via addition of acyl radicals to the isonitrile functionality and subsequent intramolecular BHAS of the intermediate imidoyl radicals. Initiation of the radical chain reaction is best achieved with small amounts of $FeCl_3$ (0.4 mol %), and the commercially available and cheap *t*BuOOH is used as the oxidant.

Phenanthridines are biologically important compounds that occur in nature and are successfully used as drugs or drug candidates in medicinal chemistry. These heterocycles show antibacterial, antitumoral, cytotoxic, and antileukemic activity,[1] and therefore the development of novel methods for their preparation is important. Along with the traditional methods, phenanthridines have recently been successfully prepared by radical chemistry using cascades involving C-radical addition to 2-isocyanobiphenyls with subsequent homolytic aromatic substitution:[2,3] Tobisu and Chatani showed that aryl radicals derived from aryl boronic acids under oxidative conditions react with 2-isocyanobiphenyls to give the corresponding 6-arylated phenanthridines (Scheme 1, a).[2a,4] We[2b] and Zhou[2c] independently published work on the radical trifluoromethylation of biarylisonitriles for the preparation of 6-trifluoromethylated phenanthridines (Scheme 2, b). Guided by recent studies on base promoted homolytic aromatic substitution (BHAS) using aromatic aldehydes as C-radical

(1) (a) Simeon, S.; Rios, J. L.; Villar, A. *Pharmazie* **1989**, *44*, 593–597. (b) Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223–232. (c) Abdel-Halim, O. B.; Morikawa, T.; Ando, S.; Matsuda, H.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 1119–1124. (d) Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem.* **2008**, *6*, 263–265.

(2) Recent examples: (a) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363–11366. (b) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792–10795. (c) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846–4849.

(3) Early examples of radical chemistry with isonitriles: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863–5864. (b) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed.* **1996**, *34*, 2683–2684. (c) Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, T. *Tetrahedron* **1995**, *51*, 9045–9062. (d) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875–1878. Reviews: (e) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194. (f) Spagnolo, D.; Nanni, D. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; John Wiley & Sons: Chichester, 2012; Vol. 2, pp 1019−1057.

(4) For an early example of the synthesis of 6-phenyl-phenanthridine via phenyl radical addition to 2-isocyanobiphenyl, see ref 3c.

(5) (a) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928–931. See also: (b) Denney, D. B.; Klemchuk, P. P. *J. Am. Chem. Soc.* **1958**, *80*, 3289–3290. (c) Shi, Z.; Glorius, F. *Chem. Sci.* **2013**, *4*, 829–833. (d) Rao, H.; Ma, X.; Liu, Q.; Li, Z.; Cao, S.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 2191–2196.

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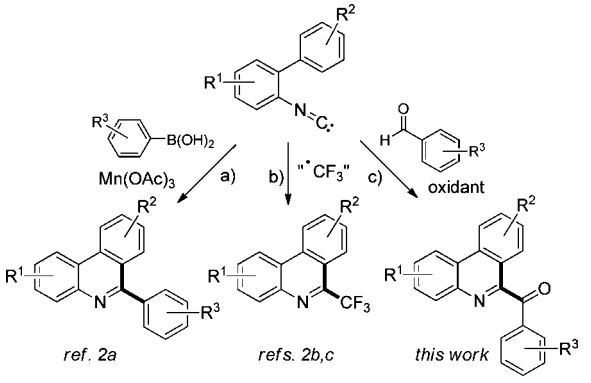
(7) Concept BHAS: Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018–5022.

10.1021/ol403147v
Published on Web 11/25/2013

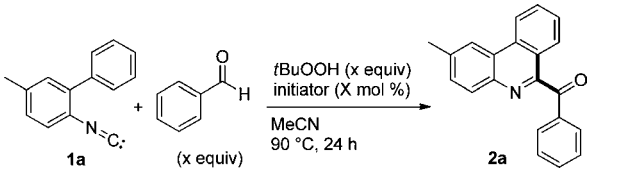
precursors,[5−7] we decided to investigate the modular synthesis of 6-aroylated phenanthridines by BHAS (Scheme 2, c). Since the biphenyl core in the starting 2-isocyanobiphenyls is readily constructed via cross-coupling chemistry, our method allows for preparation of the targeted 6-aroylated phenanthridines in a modular approach, which renders the method highly valuable for library synthesis.

Scheme 1. 6-Substituted Phenanthridines via C-Radical Addition to 2-Isocyanobiphenyls



The reaction was optimized using biarylisonitrile **1a** in combination with benzaldehyde as a C-radical precursor and *t*BuOOH as the oxidant using various radical initiators under different conditions to provide phenanthridine **2a** (Table 1). The initial reaction was conducted in benzene using a 4-fold excess of benzaldehyde and 2.2 equiv of *t*BuOOH in the presence of $FeCp_2$ as the initiator (1 mol %) at 90 °C (sealed tube) for 24 h. Pleasingly, **2a** was formed in 65% yield (entry 1). Since benzene is known to act as a radical acceptor we switched to MeCN as a solvent at 90 °C, and the yield was further improved to 71% (entry 2). Slightly lower yields were achieved upon lowering the amount of benzaldehyde to 3 and 2 equiv, respectively (68%, entries 3 and 4). However, the yield dramatically dropped to 7% if only 1.2 equiv of PhCHO were used under otherwise identical conditions (entry 5). Reaction did not work well in the presence of AcOH (entry 6). CuOAc, CuBr, and $CuCl_2$ were not efficient initiators for this radical cascade reaction (entries 7, 10, and 12), but CuI afforded a good yield (57%, entry 11). Likely, it is the iodide anion in CuI rather than the Cu-metal which is the initiator. Indeed, the nontransition metal based initiator Bu_4NI, which has recently been successfully used in radical chemistry,[8] afforded a good result (entry 8), but Bu_4NBr turned out to be an inefficient initiator (entry 9). The yield slightly improved to 76% by replacing $FeCp_2$ with $FeCl_3$ (entry 13). With the optimal initiator in hand we also varied the amount of initiator and found 0.4 mol % to be the ideal loading (entries 14−17). Lowering the concentration of the oxidant led to slightly lower yields (entries 18 and 19). Importantly, the amount of aldehyde could be lowered to 2 equiv without diminishing the yield to a large extent (entry 20). However, further lowering of the aldehyde amount to 1.5 and 1.2 equiv led to a significant reduction of the yield (entries 21, 22). Therefore, 2 equiv were regarded as optimal with respect to aldehyde economy and yield. The yield sharply dropped if reaction was conducted at 60 °C (entry 23).

Table 1. Reaction Optimization Using **1a** as a Substrate



entry	PhCHO (equiv)	*t*BuOOH (equiv)	initiator (mol %)	yield[a] (%)
1	4.0	2.2	$FeCp_2$ (1.0)	65[b]
2	4.0	2.2	$FeCp_2$ (1.0)	71
3	3.0	2.2	$FeCp_2$ (1.0)	68
4	2.0	2.2	$FeCp_2$ (1.0)	68
5	1.2	2.2	$FeCp_2$ (1.0)	7
6	4.0	2.2	$FeCp_2$ (1.0)	9[c]
7	4.0	2.2	CuOAc (1.0)	5
8	4.0	2.2	Bu_4NI (1.0)	60
9	4.0	2.2	Bu_4NBr (1.0)	4
10	4.0	2.2	CuBr (1.0)	5
11	4.0	2.2	CuI (1.0)	57
12	4.0	2.2	$CuCl_2$ (1.0)	6
13	4.0	2.2	$FeCl_3$ (1.0)	76
14	4.0	2.2	$FeCl_3$ (0.1)	33
15	4.0	2.2	$FeCl_3$ (0.4)	78
16	4.0	2.2	$FeCl_3$ (2.0)	76
17	4.0	2.2	$FeCl_3$ (4.0)	67
18	4.0	1.7	$FeCl_3$ (0.4)	75
19	4.0	1.1	$FeCl_3$ (0.4)	61
20	**2.0**	**2.2**	**$FeCl_3$ (0.4)**	**74**
21	1.2	2.2	$FeCl_3$ (0.4)	56
22	1.5	2.2	$FeCl_3$ (0.4)	62
23	2.0	2.2	$FeCl_3$ (0.4)	21[d]

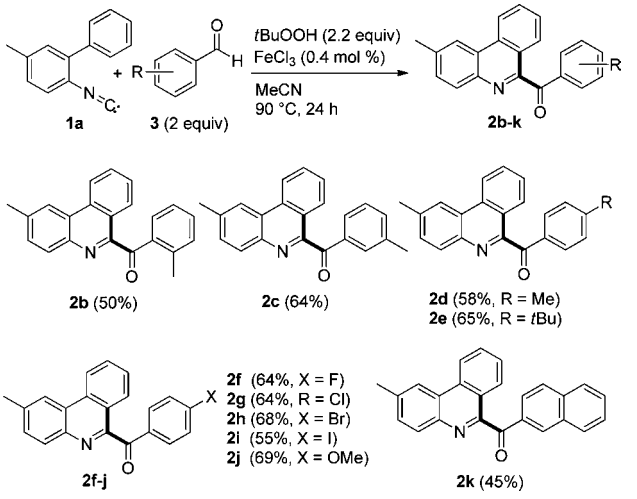
[a] Determined by ^1H NMR using an internal standard. [b] Reaction conducted in benzene. [c] Addition of AcOH (1 equiv). [d] At 60 °C.

With optimized conditions in hand (Table 1, entry 20) we next studied the scope and limitations of the phenanthridine synthesis by first varying the aldehyde component in the reaction with isonitrile **1a** (Scheme 2). *Ortho*-, *meta*-, and *para*-tolylaldehyde provided the corresponding products **2b**−**d** in 50−64% isolated yield, and as expected a similar yield was also obtained for the reaction with *para*-*tert*-butylbenzaldehyde (**2e**, 65%). Electronic effects in the aldehyde component turned out to be weak since similar yields were obtained with benzaldehyde derivatives bearing electron-donating and -accepting substituents at the *para* position (see **2f**−**j**). A slightly lower yield was noted in the reaction of **1a** with β-naphthaldehyde (see **2k**).

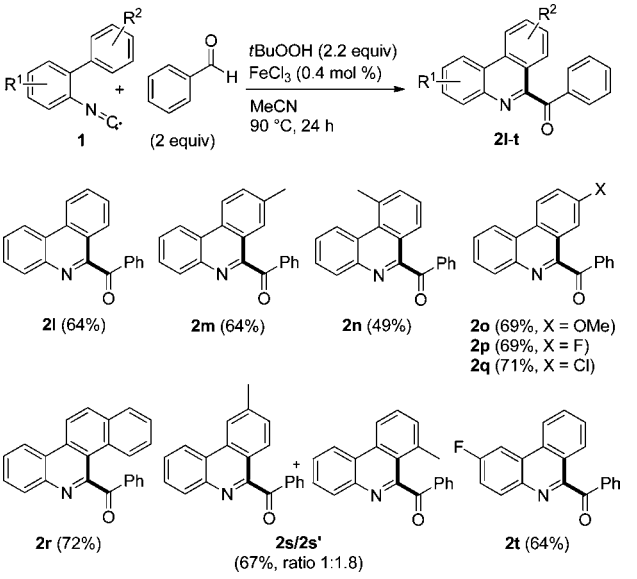
We continued the studies by varying the 2-isocyanobiphenyl component which is readily prepared by using literature protocols (see Supporting Information). Reactions were

(8) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, *45*, 979–999.

Scheme 2. Variation of the Aldehyde Component



Scheme 3. Variation of the Isonitrile Component



studied with benzaldehyde as a second component under the above-described optimized conditions (Scheme 3).

2-Isocyanobiphenyl and the its *para*-methyl derivative provided the same isolated yield (**2l**,**m**: 64%). The *ortho*-methylbiphenylisonitrile afforded a slightly lower yield (**2n**, 49%). Interestingly, we found 8% of the demethylated phenanthridine **2l** as an inseparable side product resulting from a radical *ipso* attack with subsequent methyl radical fragmentation in this transformation. Electronic effects exerted by a *para* substituent at the arene of the biphenyl moiety lacking the isonitrile functionality are weak, and similar yields were achieved with halo and methoxy substituted 2-isocyanobiphenyl derivatives (see **2o**–**q**). We also investigated the regioselectivity of the BHAS process and found that the naphthyl derivative cyclized with very high selectivity: phenanthridine **2r** was formed in 72% yield containing traces of its regioisomer (analytically pure **2r** was isolated after crystallization).[9] As expected, the *meta*-methyl derivative provided the targeted products **2s** and **2s′** with moderate regioselectivity. The structure of the major isomer **2s′** was unambiguously confirmed by X-ray analysis (Figure 1). The arene ring in the biphenyl bearing the isocyano substituent can be further substituted as shown by the successful transformation of the *meta* fluoro derivative to **2t** (64%).

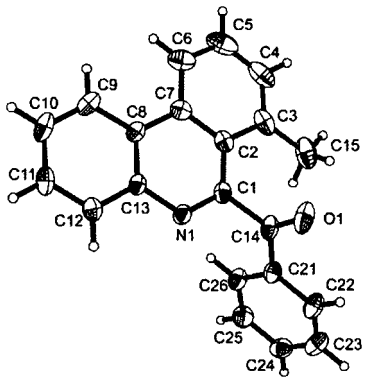
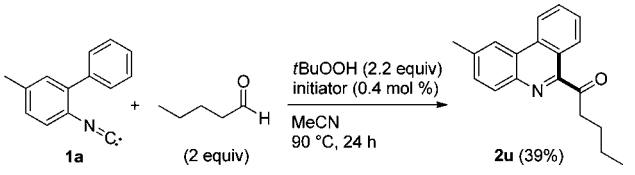


Figure 1. X-ray structure of phenanthridine **2s′**.

Finally, we also tested whether aliphatic aldehydes work as substrates and reacted pentanal under the optimized conditions with isonitrile **1a** (Scheme 4). Phenanthridine **2u** was isolated in 39% yield.[10]

Scheme 4. Reaction with Pentanal



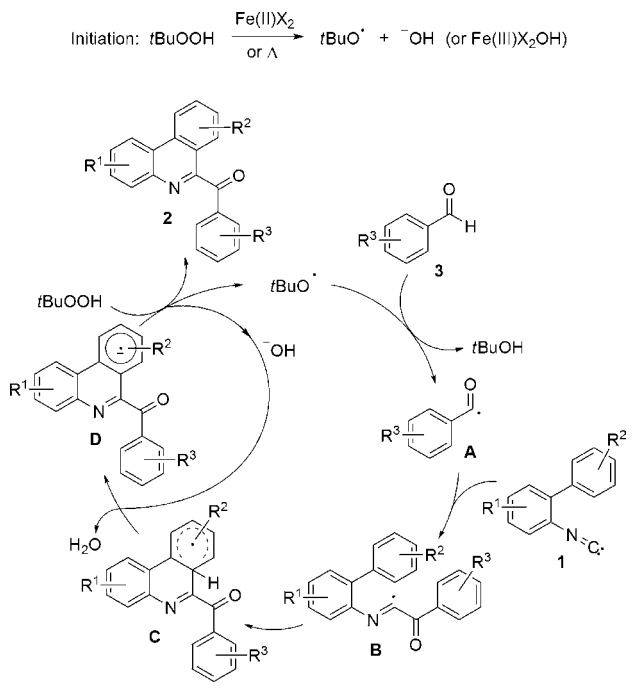
In Scheme 5 the suggested mechanism for the phenanthridine synthesis is presented. Initiation likely occurs by reducing *t*BuOOH with FeX_2 to give the *tert*-butoxyl radical along with an Fe(III) complex.[11] The *tert*-butoxyl radical then abstracts the H-atom from the aldehyde to

(9) Due to signal overlap it was not possible to unambiguously determine the regioisomer ratio. The major isomer was assigned based in literature precedence; see ref 2a.

(10) 6-Butylphenanthridine derived from decarbonylation of the intermediate pentoyl radical was not observed. However, if **1a** was reacted with cyclohexanecarbaldehyde, the targeted 6-acylated product was observed along with the decarbonylated 6-cyclohexylphenanthridine (ratio 43:57, 44% combined yield).

(11) The $FeCl_3$ salt is first reduced by *t*BuOOH to $FeCl_2$ via ligand exchange to form $FeCl_2OOtBu$ followed by Fe–O homolysis to give $FeCl_2$ and the *tert*-butyl hydroperoxyl radical which can also initiate a chain by aldehyde H-abstraction. See: Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756–10759 and references cited therein.

Scheme 5. Suggested Mechanism



give acyl radical **A** which attacks the isonitrile functionality in substrate **1** to give the imidoyl radical **B**. This radical then cyclizes to the arene to generate the cyclohexadienyl radical **C**. Radical **C** can be deprotonated with the basic hydroxide anion to give biaryl radical anion **D**.

We have previously calculated that similar cyclohexadienyl radicals show surprisingly high acidity.[2b] Moreover, the reaction did not work well in the presence of acetic acid (see Table 1, entry 6) indicating the importance of the hydroxide anion in this chain reaction. Therefore, we currently disfavor the alternative mechanism where the cyclohexadienyl radical **C** gets oxidized by *t*BuOOH. Biaryl radical anion **D** reduces *t*BuOOH by SET to eventually provide phenanthridine **2** and the chain propagating *tert*-butoxyl radical along with the basic hydroxide anion. We believe that the radical anion **D** and the cyclohexadienyl radical **C** can reduce the Fe(III) complex generated in the initiation step thereby regenerating the active Fe(II)-initiator.[12]

In conclusion, we disclosed a novel method for the synthesis of 6-aroylated phenanthridines starting with readily prepared 2-isocyanobiphenyls and commercially available aromatic aldehydes. The phenanthridine core, which can be found in many natural products and in drugs or drug candidates, is constructed during the radical cascade process. Reactions which comprise two C−C bond forming steps occur via acyl radical addition to the isonitrile functionality of the 2-isocyanobiphenyls and subsequent base promoted homolytic aromatic substitution of the intermediately generated imidoyl radical. The aroyl substituent is introduced into the phenanthridine core with complete regioselectivity at the 6-position. As oxidant for this cross dehydrogenative coupling reaction, cheap and commercially available *t*BuOOH was used. The radical chains are long because only a small amount of initiator is necessary to run these cascades. As the initiator, commercially available and cheap $FeCl_3$ can be used. Due to the modularity of the presented synthesis, the method should be useful for preparation of phenanthridine libraries.

Acknowledgment. This work was supported by the program "Sustainable Chemical Synthesis (SusChemSys)" which is cofinanced by the European Regional Development Fund (ERDF) and the state of North Rhine-Westphalia, Germany, under the Operational Program "Regional Competitiveness and Employment" 2007−2013.

Supporting Information Available. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) These processes can only be side reactions since only a very small amount of initiator is necessary to run these cascades.

The authors declare no competing financial interest.