Tetrahedron Letters 58 (2017) 3132–3135

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Hypervalent iodine mediated oxidative radical amination of heteroarenes under metal-free conditions

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ARTICLE INFO

Article history:
Received 27 April 2017
Revised 22 June 2017
Accepted 26 June 2017
Available online 27 June 2017

Keywords:
Heteroarenes
Amination
Radical
C—N bond
Metal-free conditions

ABSTRACT

A metal-free, $PhI(OCOCF_3)_2$-mediated C—N bond forming reaction was developed between quinolines and nitrogen source, affording a facile route for the construction of 2-aminoquinolines via a nitrogen-centered radical process. This reaction represents a significant addition to the limited number of existing transition metal-catalyzed processes for the C-2 amination of quinolines and will find practical application in the synthesis of nitrogen-functionalized quinolines.

Introduction

The development of new reactions for the amination of (hetero) arenes represents an important area of research because the resulting nitrogen-containing molecules are of considerable interest to the synthetic, biological, and medicinal sciences.[1] Compared with the well-established nucleophilic and electrophilic amination reactions, the synthetic potential of procedures based on nitrogen-centered radicals remains largely unexplored, despite the important roles played by nitrogen-centered radicals in many chemical and biological processes.[2] Considering the importance of quinolines and their derivatives in medicinal and materials chemistry,[3] the derivatization of quinolines has attracted considerable interest from synthetic chemistry in recent years, culminating in several transition metal-catalyzed reactions for the regioselective C—H amination of quinolines.[4] However, the application of these processes has been limited by their requirement for extensive purification processes to remove residual catalysts from the product stream, especially in the pharmaceutical industry. The development of alternative procedures for the organocatalyst-mediated amination of quinolines is therefore strongly desired to provide sustainable approaches for the introduction of nitrogen functional groups. Several organocatalyst-mediated, radical-type functionalization reactions involving quinolines have been reported to date, including azidation and hosphorylation reactions.[5] However, there have not been reports describing the highly regioselective radical-type amination of quinolines in this way, which could be attributed to the lack of relatively stable circumstantial factors and the availability of a convenient route for the generation of nitrogen-centered radicals.

Hypervalent iodine compounds are widely used in organic synthesis as selective oxidants and environmentally friendly reagents.[6] Hypervalent iodine reagent mediated C2-functionalization,[7] including the nitrogen radical-type amination of $C(sp^2)$—H bonds have also been exploited for several specific substrates. The functionalization of quinoline-type substrates with metal-based catalytic systems represents a challenging transformation because of the strong coordinating ability of these systems and their electron-deficient nature. It was therefore envisaged that hypervalent iodine regents could be ideal non-metallic promoters for the radical-type amination of quinolines because of their ability to avoid the issues associated with metal coordination and contamination. Indeed, heterocyclic compounds, such as quinolines, pyrroles, and even thiophenes, are ideal acceptors for nitrogen-centered radicals.[8] The addition of a nitrogen-centered radical to a heteroarene would generate a C—N bond and a carbon-centered radical, which would be oxidized to a carbocation followed by deprotonation to regenerate an aromatic ring. Zhang et al. recently

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http://dx.doi.org/10.1016/j.tetlet.2017.06.081
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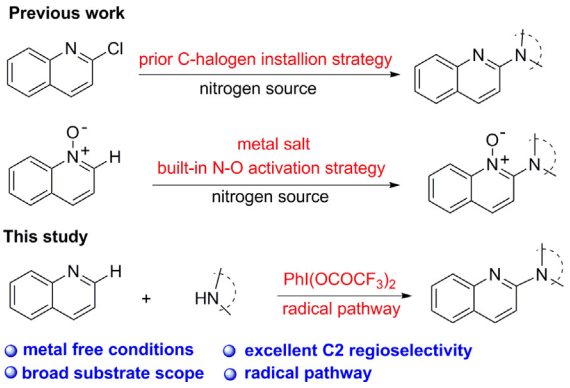


Scheme 1. C-2 amination of quinolines.

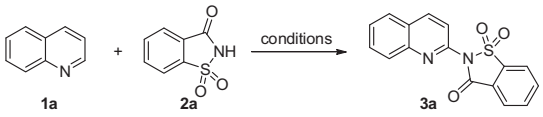
achieved the highly regioselective aminocyanation, diamination, and aminofluorination of alkenes via the addition of nitrogen-centered radicals to unsaturated bonds, as well as a radical-based cascade reaction between alkynes, sulfonamides, and alcohols.[9] As part of our ongoing interest in the development of new methods for the formation of C—N bonds,[10] we herein disclose our latest work on the hypervalent iodine regent-mediated regioselective C2 amination of various heterocyclic compounds using nitrogen-centered radicals (Scheme 1).

Results and discussion

We commenced our study by examining the reaction of quinoline **1a** with saccharin **2a** under various catalytic conditions (Table 1). We found that $PhI(OAc)_2$ failed to mediate the desired C—N bond forming reaction in acetonitrile at 90 °C, with **1a** being recovered unchanged after 8 h (Table 1, entry 1). Pleasingly, saccharin **2a** was incorporated at the C2 position of quinoline to give the desired product **3a**, albeit in a low yield, in the presence of $PhI(OCOCF_3)_2$ (Table 1, entry 2). Several other hypervalent iodine reagents, including 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **I** (Togni reagent-**I**) and 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one **II** (Togni reagent-**II**) were also tested, but failed to afford any of the desired product **3a** (Table 1, entries 3 and 4). A variety of different solvents were also screened against the reaction, and the results revealed that polar solvents appeared to facilitate the coupling procedure (Table 1, entries 5–10). Among the solvents examined (CH_3CN, THF, CH_3NO_2, EtOAc, chlorobenzene, DCE, and cyclohexane), EtOAc gave the best results, affording **3a** in 73% yield (Table 1, entry 7). THF also performed well in this reaction (Table 1, entry 5). Gratifyingly, the yield was increased to 79% when the temperature was decreased to 60 °C (Table 1, entries 11–13). The amount of $PhI(OCOCF_3)_2$ was also found to be important for improving the reaction efficiency (Table 1, entry 14). After surveying a variety of oxidants, solvents, and temperatures, we found that the combination of 2 eq. of $PhI(OCOCF_3)_2$ in EtOAc at 60 °C gave the optimal conditions for this transformation. These results highlight the attractive features of this facile transformation, in that it does not require pre-activated substrates, the addition of a metal catalyst or ligand, or high-temperature conditions.

With the optimized conditions in hand, we proceeded to investigate the scope of this reaction using a variety of different quinolines **1** and saccharin **2a** (Table 2). Notably, the positioning of the substituent on the quinoline ring had no discernible impact on the reaction efficiency. For example, quinoline substrates bearing a 3-methyl, 4-methyl, 5-bromo, 6-methoxy, or 8-methyl substituent all reacted smoothly with saccharin **2a** to give the corresponding addition products in good yields (**3b**–**3i**, Table 2). Various other functional groups that are commonly used in synthetic chemistry were also found to be compatible with the optimized reaction conditions, including halogen (**1g**, **1h**, **1k**), thereby significantly expanding the synthetic utility of this newly developed C—N bond forming protocol. Isoquinoline **1m**, quinoxaline **1n** and quinazoline **1o** also reacted efficiently under the optimized reaction conditions to give the corresponding addition products in high yields (**3m**–**3o**, Table 2). 1*H*-benzotriazoles can be found in a wide range of compounds exhibiting interesting

Table 1
Optimization of the reaction conditions.[a]



Entry	Oxidant	Additive	Temp (°C)	Yield (%)[b]
1	$PhI(OAc)_2$	CH_3CN	90	0
2	$PhI(OCOCF_3)_2$	CH_3CN	90	34
3	Togni reagent-**I**	CH_3CN	90	0
4	Togni reagent-**II**	CH_3CN	90	0
5	$PhI(OCOCF_3)_2$	THF	90	51
6	$PhI(OCOCF_3)_2$	CH_3NO_2	90	27
7	$PhI(OCOCF_3)_2$	EtOAc	90	73
8	$PhI(OCOCF_3)_2$	Chlorobenzene	90	<10
9	$PhI(OCOCF_3)_2$	DCE	90	<10
10	$PhI(OCOCF_3)_2$	Cyclohexane	90	<10
11	$PhI(OCOCF_3)_2$	EtOAc	60	79
12	$PhI(OCOCF_3)_2$	EtOAc	40	71
13	$PhI(OCOCF_3)_2$	EtOAc	20	60
14	$PhI(OCOCF_3)_2$	EtOAc	60	48[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol) and oxidant (1.0 mmol) in solvent (3 mL) under air for 8 h.
[b] Yield of isolated product.
[c] 1 eq. $PhI(OCOCF_3)_2$ was added.