Tetrahedron Letters 54 (2013) 2849–2852

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Catalyst-free diastereoselective synthesis of 2-methyl-4-amino-1,2,3,4-tetrahydro-quinoline derivatives in water

Lin Wu [a], Ran Jiang [b], Jin-Ming Yang [a], Shun-Yi Wang [b,*], Shun-Jun Ji [b,*]

[a] Key Laboratory of Coastal Wetland Bioresources and Environmental Protection of Jiangsu Province, College of Chemistry and Chemical Engineering, Yancheng Teachers University, Yancheng 224002, China
[b] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

ARTICLE INFO

Article history:
Received 18 December 2012
Revised 15 March 2013
Accepted 22 March 2013
Available online 3 April 2013

Keywords:
Catalyst free
Tetrahydroquinoline
Water
Diastereoselective
tert-Enamides

ABSTRACT

A diastereoselective synthesis of 2-methyl-4-amino-1,2,3,4-tetrahydro-quinoline derivatives was achieved through the reaction of aromatic amines and *tert*-enamides in water under reflux conditions. The desired products could be obtained in moderate to excellent yields utilizing water as solvent without any catalyst or additive.

The quinoline fragment widely exists in a wide variety of pharmacologically and biologically active compounds.[1] And the introduction of different functional groups in quinoline may further alter the properties of quinoline derivatives for pharmacological and biological purposes. 2-Alkyl-4-amino-quinolines or its hydrogenated products are widely featured in commercial drugs and other useful materials.[2] For example, Tacrine **Ia** (Fig. 1), is a prototypical cholinesterase inhibitor for the treatment of Alzheimer's disease;[2a] Torcetrapib **Ib** (Fig. 1), is a drug capable of treating hypercholesterolemia and preventing cardiovascular disease;[2b] and 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one **Ic** (Fig. 1), is a gummy material.[2c] Therefore, synthesis of C2 and/or C4 substituted quinoline has attracted considerable attention from the synthetic community.[3] However, the reaction was usually conducted under strongly acidic condition at high temperature to construct these compounds.[4] Recently, several transition metals, such as Ru,[5] Pd,[6] In,[3a] and Cu[3d] species have been shown to be efficient catalysts for the synthesis of quinoline derivatives from amines with compounds bearing unsaturated bonds. Despite the superiority of these transition metal-catalyzed protocols, there are several drawbacks such as toxic solvent, expensive catalyst as well as harsh conditions, which limited their applications in organic synthesis.

In recent decades, water has emerged as an attractive alternative to conventional organic solvents in organic synthesis due to its inherent advantages, such as non-toxicity, non-flammability, wide abundance, and cheap cost. The use of water as reaction solvent is also in accordance with the principle of 'Green Chemistry' and meets the requirement of sustainable development of modern society.[7] Since a pioneer work reported by Rideout and Breslow[8] about Diels–Alder reactions in water, considerable progress has been made by Chan, Li, Kobayashi, Loh, Cozzi et. al. in developing organic reactions in water.[9] To the best of our knowledge, there was no report about the synthesis of compound **Ic** and its derivatives in water. As a continuation of our works on enamide-based synthesis of functionalized molecules,[10] herein, we disclose a practical and green approach for the synthesis of compound **Ic** and its analogs[11] via aza-Diels–Alder-type reaction[12] in water. The

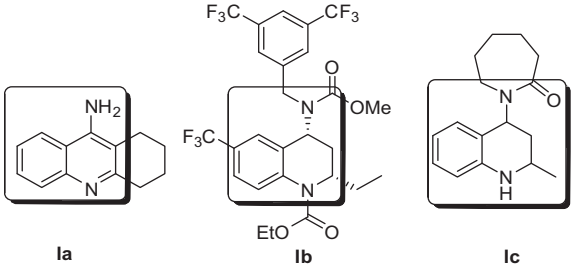
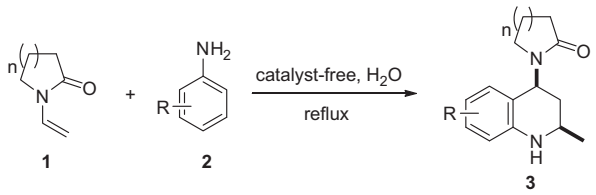


Figure 1. Pharmaceuticals and materials containing 2-alkyl-4-aminoquinoline fragment.

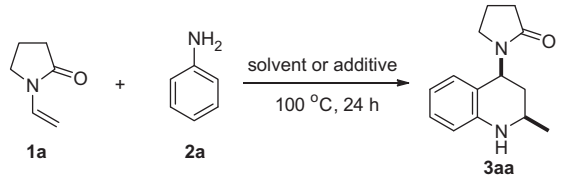
* Corresponding authors.
E-mail addresses: shunyi@suda.edu.cn (S.-Y. Wang), shunjun@suda.edu.cn (S.-J. Ji).

0040-4039/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2013.03.091



Scheme 1. The reaction of **1** with **2** in water.

Table 1
Optimization of the reaction conditions by using different solvents[a]



Entry	Solvent	Yield[b] (%)
1	Glycerol	24
2	Glycol	31
3	EtOH	7
4	PEG-400	<5
5	H_2O	66
6	DMF	<5
7	Toluene	11
8	THF	30
9	H_2O/AcOH = 1:1	31
10	H_2O	64[c]
11	H_2O	20[d]
12	H_2O	93[e]

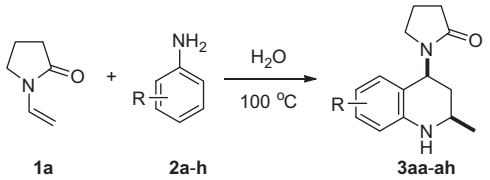
[a] Unless otherwise noted, the reactions were carried out at 100 °C for 24 h by using **1a** (2.5 mmol), **2a** (1.0 mmol), and solvent (2.0 mL).
[b] Isolated yield.
[c] At 80 °C.
[d] 5 mol % tetrabutyl ammonium bromide (TBAB) was used.
[e] 3.5 mmol **1a** was used.

reactions involving aromatic amines and *tert*-enamides proceeded efficiently in water under catalyst-free conditions, leading to the desired products 2-methyl-4-amino-1,2,3,4-tetrahydro-quinolines in moderate to good yields (Scheme 1).

We initiated our study by the reaction of 1-vinylpyrrolidin-2-one **1a** (2.5 mmol) and aniline **2a** (1.0 mmol) in glycerol at 100 °C. 1-(2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)pyrrolidin-2-one **3aa** was isolated in 24% yield with high diastereoselectivities after 24 h (Table 1, entry 1). Subsequently, other solvents such as glycol, EtOH, PEG-400, and water were surveyed as well (Table 1, entries 2–5). To our delight, the yield of **3aa** was increased to 66% when water was used as solvent (Table 1, entry 5). The AcOH and H_2O (1:1) solvent system decreased the yield to 31% under reflux conditions (Table 1, entry 9). Then, we focused on the optimization of reaction conditions by employing water as solvent under different conditions. A little lower yield was observed when the reaction was performed at 80 °C (Table 1, entry 10). We were delighted to find that product **3aa** could be produced in an excellent yield of 93% with high diastereoselectivities when the amount of **2a** was increased from 2.5 to 3.5 equiv (Table 1, entry 12).

With the optimal conditions in hand, we explored the substrate scopes. As illustrated in Table 2, a series of substituted 2-methyl-1,2,3,4-tetrahydroquinolines **3aa–ah** were facilely synthesized with high diastereoselectivities via the reactions of **1a** with different anilines **2** in water under reflux conditions. It was found that aniline with either an electron-donating or an electron-withdrawing group could perform well under the standard conditions. For

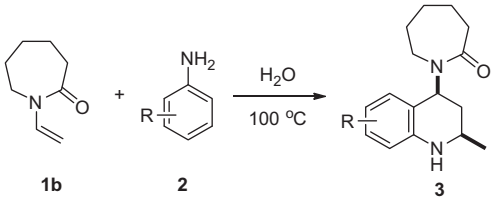
Table 2
The reaction of 1-vinylpyrrolidin-2-one **1a** and anilines **2** in water under reflux conditions[a]



Entry	R	Product	Yield[b] (%)
1	H (**2a**)	R = H (**3aa**)	93
2	4-Me (**2b**)	R = 4-Me (**3ab**)	53
3	4-MeO (**2c**)	R = 4-MeO (**3ac**)	63
4	4-CN (**2d**)	R = 4-CN (**3ad**)	46
5	4-COOEt (**2e**)	R = 4-COOEt (**3ae**)	48
6	4-Cl (**2f**)	R = 4-Cl (**3af**)	81
7	2-Cl (**2g**)	R = 6-Cl (**3ag**)	48
8	4-Br (**2h**)	R = 4-Br (**3ah**)	74

[a] The reactions were carried out at 100 °C for 24 h by using **1a** (3.5 mmol), **2** (1.0 mmol), H_2O (2.0 mL).
[b] Isolated yield and only *trans* products were isolated in all cases.

Table 3
The reaction of **1b** with **2** in water[a]



Entry	R	Product	Yield[b] (%)
1	**2a**	R = H (**3ba**)	76
2	**2b**	R = 4-Me (**3bb**)	68
3	**2c**	R = 4-MO (**3bc**)	79
4	**2h**	R = 4-Br (**3bh**)	82

[a] The reactions were carried out at 100 °C for 24 h by using **1b** (3.5 mmol), **2** (1.0 mmol), H_2O (2.0 mL).
[b] Isolated yield and only *cis* products were isolated in all cases.

example, both 4-methylaniline **2b** and 4-methoxylaniline **2c** could undergo reaction smoothly with 1-vinylpyrrolidin-2-one **1a** to furnish the desired products **3ab** and **3ac** in 53% and 63% yields, respectively (Table 2, entries 2 and 3). Additionally, both 4-aminobenzonitrile **2d** and ethyl 4-aminobenzoate **2e** were also demonstrated to be suitable candidates for the reaction, though moderate yields of the desired products were obtained, respectively (Table 2, entries 4 and 5). When 4-chloroaniline **2f** was applied to the reaction with **1a**, the corresponding substituted 2-methyl-1,2,3,4-tetrahydroquinoline **3af** was performed in 81% yield. When more steric hindered 2-chloroaniline **2g** was subjected to the reaction, the corresponding product **3ag** could also be obtained in 48% yield (Table 2, entries 6 and 7).[13]

We further investigated the reaction of 1-vinylazepan-2-one **1b** with anilines **2** under identical conditions. The results were summarized in Table 3. All the reactions proceeded smoothly in water to give the *cis* products. The reaction of **1b** with aniline **2a** in water under the optimized conditions, furnished the desired *trans* product **3ba** in 76% yield (Table 3, entry 1). When **1b** and 4-bromoaniline **2h** were applied to the reaction under identical conditions, the desired *cis* product **3bh** could be obtained in 82% yield (Table 3, entry 4).