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Three-component one-pot synthesis of 1,2,3,4-tetrahydroquinoline derivatives in hexafluoroisopropanol

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Abstract

The one-pot aza-Diels-Alder reaction of substituted aromatic amines, ethyl glyoxylate and benzyl vinylcarbamate or *N*-benzyloxycarbonyl 2-pyrroline was conducted in hexafluoroisopropanol, providing the desired 1,2,3,4-tetrahydroquinline derivatives in moderate yields.

Keywords: Aza-Diels-Alder reaction; Tetrahydroquinoline; Hexafluoroisopropanol (HFIP); Fluorinated solvent

The biologically active alkaloids, which target on G-protein coupled receptor [1], dopamine D_2 receptor [2], NMDA receptor [3] and CETP [4], often incorporate a tetrahydroquinoline subunit in their frame structures. Up to date, many methodologies have been developed for the synthesis of tetrahydroquinoline derivatives [5]. The Diels-Alder reaction of *N*-arylimines and structurally divergent diennophiles is very powerful for the construction of pyridine and quinoline derivatives [6,7]. The aza-Diels-Alder reaction could be accelerated by an array of catalysts such as $BF_3{\cdot}OEt_2$ [8], trifluoroacetic acid [9], indium trichloride [10], lanthanide triflates [11], Ti (IV) complex [12] and squaric acid [13].

Trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) have been used for the synthesis of sulfoxide [14], 2-aminoalcohol [15] and quinazolinone [16] owing to their unique physical chemical properties, such as low nucleophilicity, high polarity and strong hydrogen bond donating ability (TFE $\alpha = 1.51$, HFIP $\alpha = 1.96$). To the best of our knowledge, few Diels-Alder reactions have been reported in the fluorinated solvents [17–19].

Not many derivatives of 2-carbethoxy-4-amino-1,2,3,4-tetrahydroquinoline and 4-carbethoxy-2,3,3a,4,5, 9b-hexahydro-1H-pyrrolo[3,2-*c*]quinoline, which are useful scaffolds for our lead generation, have been reported. Generally, those compounds were synthesized in the presence of $BF_3{\cdot}OEt_2$ [20] and $InCl_3$ [21] in low or moderate yields, respectively. Herein, we reported that a range of 2-carbethoxy-4-amino-1,2,3,4-tetrahydro-quinoline and 4-carbethoxy-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-*c*]quinoline derivatives could be achieved via a three-component reaction in moderate yields when HFIP was taken as the reaction medium.

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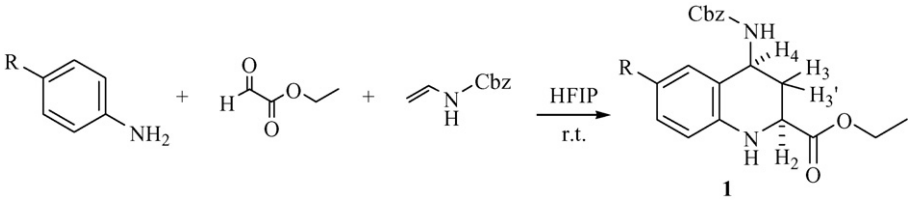
Table 1
Synthesis of 2-carbethoxy-4-amino-1,2,3,4-tetrahydroquinoline derivatives in HFIP



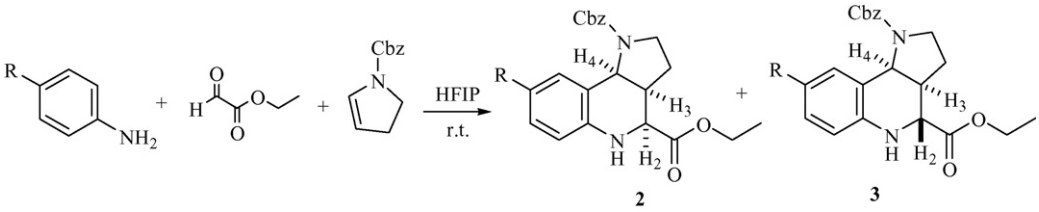
1

Entry	Product	R	Time (h)	Yield[a] (%)	M.p. (°C)
1	1a	Cl	1.0	64	123–124
2	1b	CF_3	1.5	53	133–135
3	1c	NO_2	1.5	23	160–162
4	1d	OCH_3	1.0	59	123–124

[a] Isolated yield.

The typical procedure is described as follows: treatment of 1 equiv. of aniline with 1 equiv. of ethyl glyoxylate in HFIP gave rise to the intermediate *N*-arylimine within 0.5–1 h as TLC indicated. Then 1 equiv. of benzyl vinylcarbamate or *N*-benzyloxycarbonyl 2-pyrroline was added to the resulted solution and the cycloaddition reaction completed within 0.5 h [22]. As shown in Table 1, when benzyl vinylcarbamate as dienophile was subjected to structurally diverse *N*-arylimine, only the *cis*-isomer of 2-carbethoxy-4-amino-1,2,3,4-tetrahydroquinolines (**1a**–**1d**) was isolated in 22–64% yield (Table 1, entries 1–4), no *trans*-isomer was detected in this reaction. While *N*-benzyloxycarbonyl 2-pyrroline was used as a dienophile to perform the same cycloaddition reaction, both *cis*- and *trans*-4-carbethoxy-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-*c*] quinolines (**2** and **3**) were isolated in a total yield of 23–52% (Table 2, entries 1–3). In general, under kinetic control the *endo*-transition state was highly preferred due to the secondary orbital interaction and *endo*-cycloaddition stereoisomer would predominate and sometimes formed exclusively. This is the case with benzyl vinylcarbamate as dienophile. However, when some destabilization occurs to the *endo*-transition state mostly caused by steric interaction and electrostatic repulsion, the Diels-Alder reaction will proceed through *endo*- and *exo*-transition state in a competitive way, both *endo*- and *exo*-stereoisomer will be generated. With *N*-benzyloxycarbonyl 2-pyrroline as dienophile, due to the possible steric interaction of pyrroline ring with the *N*-arylimine, the desired product was obtained as mixture of two diastereomers with varying diastereoselectivity as shown in Table 2. While the nitro group is introduced at *para* position on aniline, it is assumed that both steric interaction and electrostatic repulsion largely contribute to the destabilization to the *endo*-transition state, which would overrule the stabilizing effect of secondary orbital interaction. Therefore, the preferred *exo*-transition state resulted in the major *trans*-diastereomer **3c**. The electronic complementarity of the diene and dienophile are crucial to the successful aza-Diels-Alder cycloaddition. In both case of benzyl vinylcarbamate and

Table 2
Synthesis of 4-carbethoxy-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-*c*]quinoline derivatives in HFIP



2 3

Entry	Product	R	Time (h)	Ratio (**2**:**3**)	Yield[a] (%)	M.p. (°C) (**2**)	M.p. (°C) (**3**)
1	2a + 3a	Cl	1.0	3.3:1	52	46–48	135–136
2	2b + 3b	CF_3	1.5	3:1	23	33–34	61–62
3	2c + 3c	NO_2	1.5	1:3.6	38	133–135	96–98

[a] Isolated yield.