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## Graphical Abstract

**2,2,2-Trifluoroethanol Activated One-Pot Mannich-Like Reaction of β-Nitroenamines, Secondary Amines and Aromatic Aldehydes**

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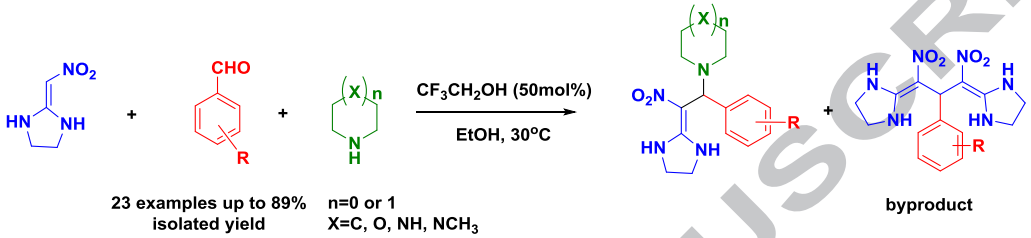

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# 2,2,2-Trifluoroethanol Activated One-Pot Mannich-Like Reaction of β-Nitroenamines, Secondary Amines and Aromatic Aldehydes

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ABSTRACT

A unique and efficient 2,2,2-trifluoroethanol-activated one-pot reaction of β-nitroenamines, secondary amines and aromatic aldehydes was developed under mild and convenient conditions. In the presence of 2,2,2-trifluoroethanol (TFEA), aromatic aldehydes were activated by hydrogen bonding with TFEA. The newly-developed reaction could afford the desired Mannich-like products in moderate to excellent yields with wide substrate scopes.



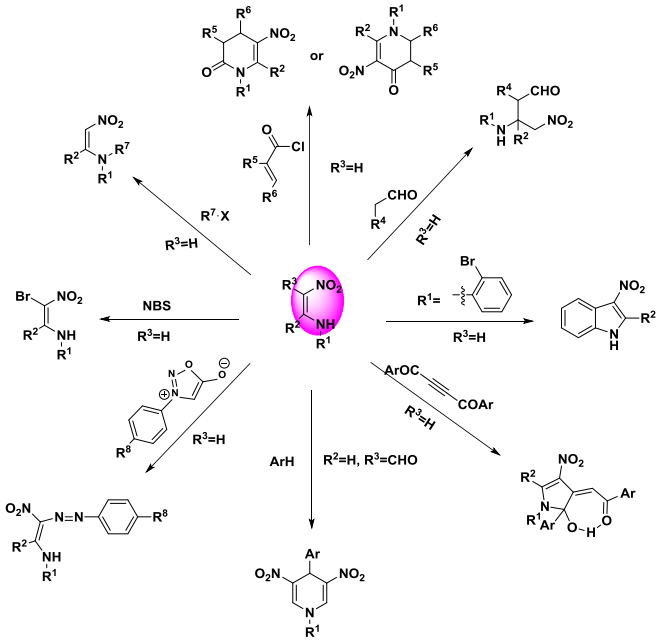
## 1. Introduction

β-Nitroenamines are push-pull alkenes[1] with the electron-donating amino groups and the electron-withdrawing group -$NO_2$.[2] They are important building blocks in organic chemistry for synthesizing heterocyclic or fused heterocyclic compounds[3] by virtue of their versatile reactivity as Michael acceptors, dipolarophiles, bis-nucleophiles and dienophiles. Significant progresses have been made towards the reaction diversities of β-nitroenamines (Scheme **1**), such as Michael reaction, [4] 1, 3-dipolar cycloaddition, [5] nucleophilic addition [6] or substitution, [7] coupling reaction [8] and Diels-Alder reaction. [9]

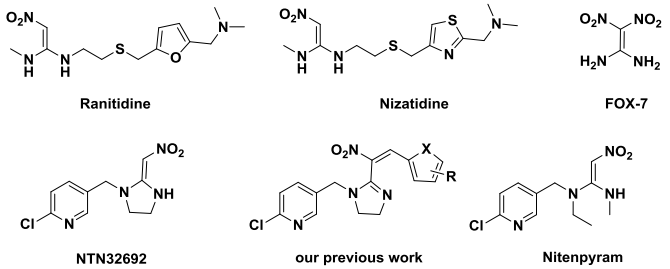
β-Nitroenamines are also useful building blocks in biologically active compounds. They exhibit pharmaceutical [10-11] or insecticidal activity [12-13]. In addition, β-nitroenamine FOX-7 is a new-type high-performance energetic and insensitive explosives (Scheme **2**). [14] In our previous study, we found series of novel compounds with excellent bioactivity through introduction of different heterocycles to the starting compound NTN32692. [15] There exist broad prospects for researchers to explore structural derivatives of β -nitroenamines.

Petasis reaction had some common features with Mannich reaction. [16] They were three-component reaction containing amines and aldehydes except for one substrate replaced by boronic acids. It was also been named as Mannich-like reaction. Many Mannich-like reactions have been reported, using reagents such as phenylacetylene, organozinc reagents, indoles and 2-naphthols in the presence of amines and aldehydes. [17]

Herein, we developed a new kind of Mannich-like reaction of β-nitroenamine secondary amines and aromatic aldehydes. Normally, Mannich reactions are catalyzed by the conventional Lewis/Brønsted acids for electrophilic activation of the aldehyde carbonyl. Here, we found that 2,2,2-trifluoroethanol (TFEA) as an additive could raise the yield of Mannich-like reaction by activating aromatic aldehydes through hydrogen bonding interaction with TFEA..




**Scheme 1** Reactions of β-nitroenamines..



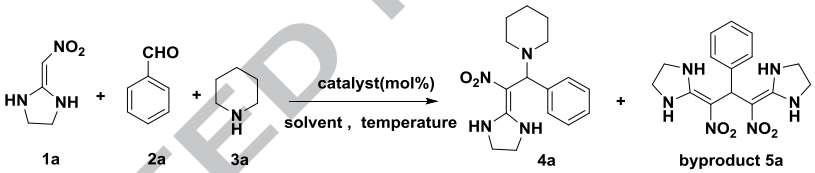

**Scheme 2** Biological active compounds containing β-nitroenamine.

## 2. Results and discussion

2-(Nitromethylene)imidazolidine (**1a**), benzaldehyde (**2a**) and piperidine (**3a**) were selected as the model substrates to optimize the reaction conditions. The results were summarized in Table 1. Initially, the reaction was carried out in ethanol at 30°C and the product was obtained in 70% yield after 7 days (Table 1, entry 1). Inspired by this result, different Brønsted acids including HCOOH, $CH_3COOH$, $CF_3COOH$, $TsOH•H_2O$ were employed as catalysts but with no improvement in yields due to the formation of byproduct **5a** (Table 1, entries 2-5). Then several Lewis acids and inorganic acids were examined (Table 1, entries 6-8), and desired product **4a** was obtained in 72% yield in the presence of $BF_3•Et_2O$. Surprisingly, when fluorinated alcohols such as 2,2,2-Trifluoroethanol (TFEA) , 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) were used, the reaction afforded target product **4a** in 89% and 85% yield, respectively (Table **1**, entries 9-10). TFEA and HFIP as important members of fluorinated alcohols, possess a wide range of physicochemical properties such as high hydrogen bonding donor strength, acidic character, high polarity, low nucleophilicity and high ionizing power. [18] Owing to these unique properties, they are employed as solvents, cosolvents, additives and weak nucleophilic reagents, leading to a variety of reactions with excellent yields and regionselectivity, for instance, etherification, [19] esterification, [20] formation of O-heteroatom bonds, [21] reductive reaction, [22] oxidation, [23] Michael addition, [24] Mannich reaction, [25] cycloaddition[26] and so on.

The effect of different solvents such as ethyl acetate, toluene, dichloromethane, chloroform, acetonitrile, methanol, isopropanol, tert-butyl alcohol, dimethyl formamide and water was proved to be inferior to ethanol (Table **1**, entries 13-22). As a matter of course, the amount of TFEA was taken into consideration. However, no improvement in yield was observed (Table **1**, entries 23-25). Increasing the temperature was detrimental to the reaction although the reaction rate was accelerated (Table **1**, entries 26-28). These results were consistent with the fact that more byproduct **5a** appeared with the increasing temperature; on the other hand, hydrogen bond donating ability of TFEA decreased continuously with increasing temperature. No product was traced when the reaction was performed in refluxing EtOH (Table **1**, entry 29). Therefore, the optimized reaction conditions was the treatment of starting materials **1a**, **2a** and **3a** in the presence of 0.5 equivalent of TFEA as additive in EtOH at 30°C for 7 days (Table **1**, entry 9).

**Table 1.** Reaction Optimization.

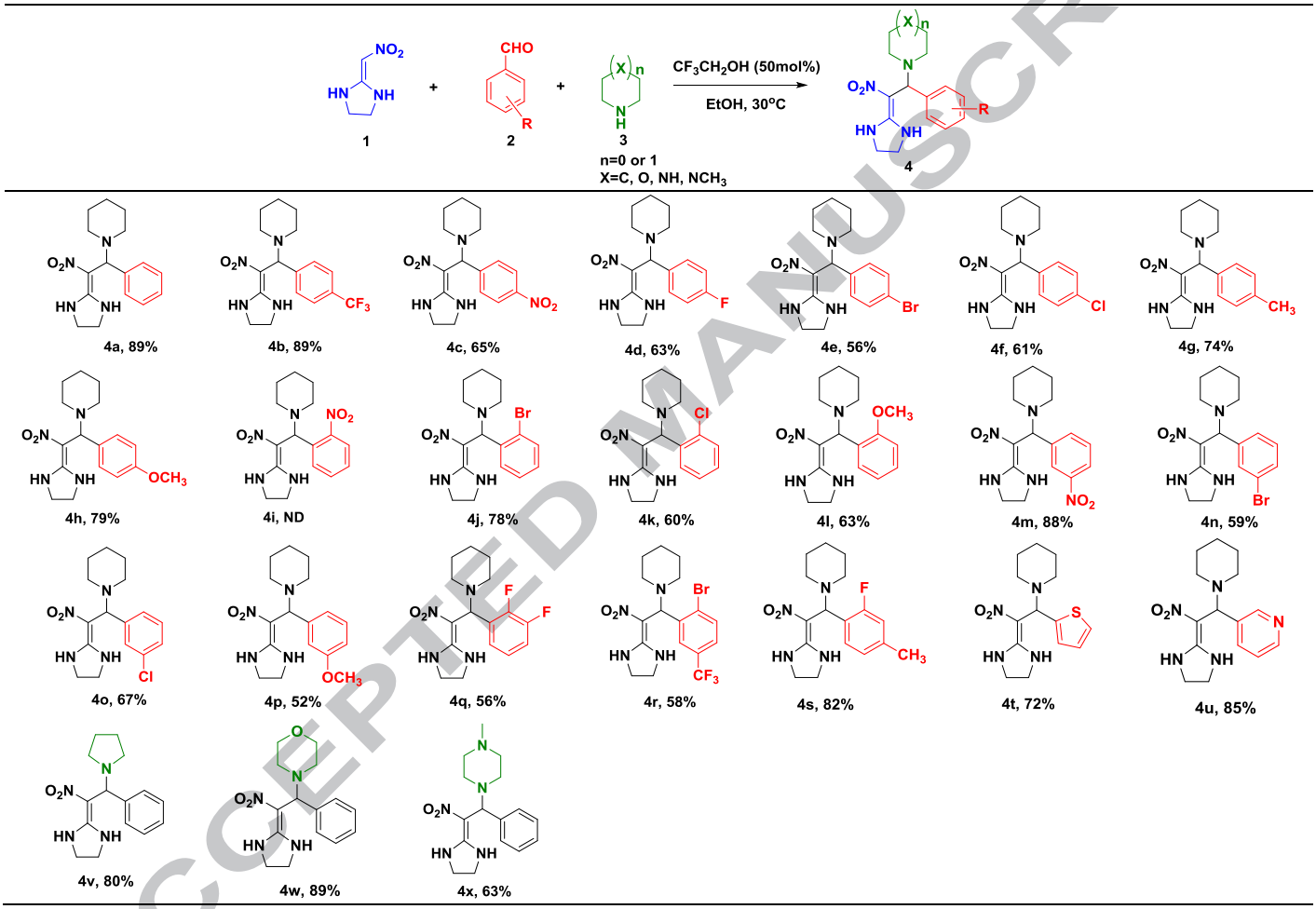



| Entry | Catalyst or Additive (equiv.) | Solvent | *T* (°C) | Yield[a] | pKa (Catalyst or Additive) |
|---|---|---|---|---|---|
| 1 | none | EtOH | 30 | 70% | - |
| 2 | HCOOH（0.5） | EtOH | 30 | 67% | 3.74 |
| 3 | $CH_3COOH$（0.5） | EtOH | 30 | 61% | 4.74 |
| 4 | $CF_3COOH$（0.5） | EtOH | 30 | 62% | 0.23 |
| 5 | $TsOH•H_2O$（0.5） | EtOH | 30 | 66% | -2.80 |
| 6 | $AlCl_3$（0.5） | EtOH | 30 | 61% | - |
| 7 | $BF_3•Et_2O$（0.5） | EtOH | 30 | 72% | - |
| 8 | HCl（0.5） | EtOH | 30 | 43% | -8.00 |
| 9 | TFEA（0.5） | EtOH | 30 | 89% | 12.40 |
| 10 | HFIP（0.5） | EtOH | 30 | 85% | 9.30 |
| 11 | pentafluorophenol | EtOH | 30 | 68% | 5.11 |
| 12 | phenol | EtOH | 30 | 61% | 9.96 |
| 13 | TFEA（0.5） | Ethyl acetate | 30 | 76% | 12.40 |
| 14 | TFEA（0.5） | Toluene | 30 | 85% | 12.40 |
| 15 | TFEA（0.5） | $CH_2Cl_2$ | 30 | 69% | 12.40 |
| 16 | TFEA（0.5） | $CHCl_3$ | 30 | 86% | 12.40 |
| 17 | TFEA（0.5） | $CH_3CN$ | 30 | 67% | 12.40 |
| 18 | TFEA（0.5） | MeOH | 30 | 66% | 12.40 |
| 19 | TFEA（0.5） | i-PrOH | 30 | 78% | 12.40 |
| 20 | TFEA（0.5） | t-BuOH | 30 | 81% | 12.40 |
| 21 | TFEA（0.5） | DMF | 30 | 75% | 12.40 |
| 22 | TFEA（0.5） | $H_2O$ | 30 | 25%[c] | 12.40 |
| 23 | TFEA（0.2） | EtOH | 30 | 73% | 12.40 |
| 24 | TFEA（0.8） | EtOH | 30 | 83% | 12.40 |
| 25 | TFEA（1.0） | EtOH | 30 | 82% | 12.40 |
| 26[b] | TFEA（0.5） | EtOH | 20 | 74% | 12.40 |
| 27 | TFEA（0.5） | EtOH | 40 | 41%[d] | 12.40 |
| 28 | TFEA（0.5） | EtOH | 50 | 39%[e] | 12.40 |
| 29 | TFEA（0.5） | EtOH | reflux | Trace[f] | 12.40 |

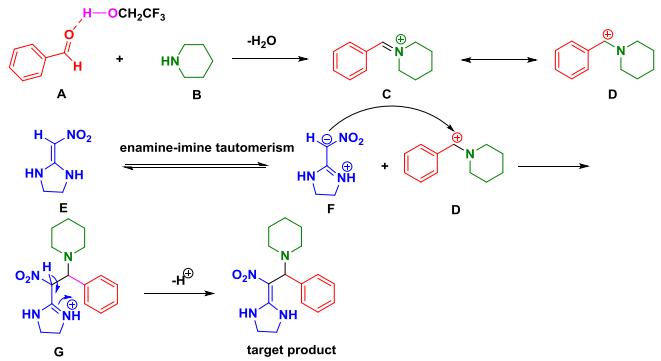
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), **3a** (1.5mmol), catalyst or additive, solvent (5.0 mL), temperature, 7 days. [b] Isolated yield. [c] Poor solubility. [d] Reaction time: 4 days. [e] Reaction time: 3 days. [f] Reaction time: 2 days.

With the optimized conditions in hand, we explored the substrate scopes, and the results were shown in Table **2**. No matter aromatic aldehydes containing electron-withdrawing groups or electron-donating groups in the para-position, the corresponding products were obtained in moderate to excellent yields (**4a-4h**). Aromatic aldehydes bearing electron-deficient groups, such as -$NO_2$ in meta-position (**4m**) and -Br in o-position (**4j**), proceeded with high yields, while those bearing electron-rich groups such as -$OCH_3$ in para-position (**4h**) gave acceptable yields. Electron-withdrawing group -Cl in different position didn't show notable difference (**4f, 4k, 4o**). Disubstituted aromatic aldehydes and heteroaromatic aldehydes turned out to undergo smooth reaction in moderate to good yields (**4q-4u**). Notably, pyrrolidine and morpholine worked well in 80% and 89% yields, while *N*-methyl piperazine afforded in 63% yields (**4v-4x**). Nevertheless, the modification of β-nitroenamines was not successful. It turned to be unsuccessful when replacing -$NO_2$ with electron-withdrawing group -COOEt or changing the ring size.

**Table 2.** Substrate scope for the synthesis of nitroenamine Mannich bases [a,b]



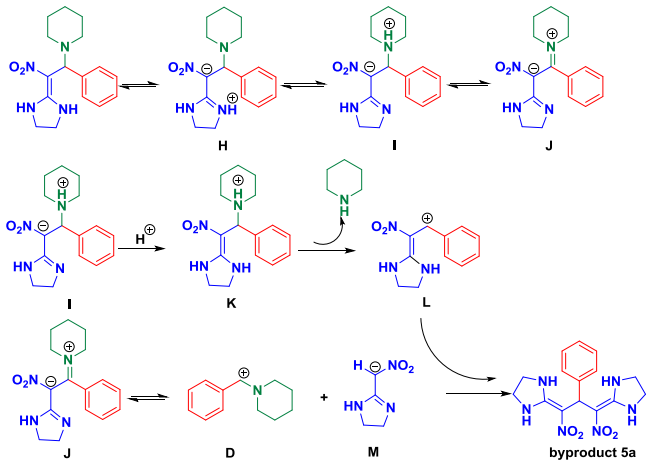

[a] Reaction conditions: 50% equiv. TFEA was added to a stirred 5 mL EtOH of **1a** (1.0 mmol), **2a** (1.2 mmol) and **3a** (1.5 mmol) at 30 °C, the solution was completed as indicated by TLC, the mixture was purified by flash chromatography on silica gel eluting with dichloromethane/acetone. [b] Isolated yield.




**Scheme 3** Plausible mechanism of Mannich-like reaction

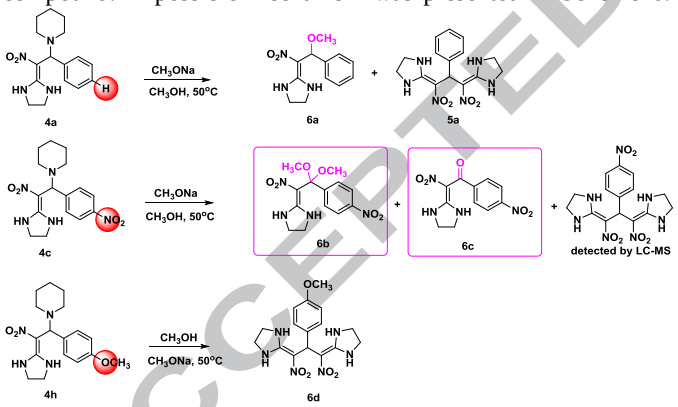
A plausible mechanism of the reaction is proposed in Scheme **3**. In this process, we proposed that 2,2,2-trifluoroethanol (TFEA) would act as an activator to increase the electrophilic ability of benzaldehyde **A** owing to its of acidic character[27] and high hydrogen bonding donor ability.[28] Initially, benzaldehyde **A** activated by TFEA reacted with piperidine **B** to generate cationic intermediate **C** or **D** with elimination of $H_2O$, which was detected by MS (ESI+) with m/z=174. Subsequently, β-nitroenamine **E** underwent a rapid process of enamine-imine tautomerism to form intermediate **F**. Finally, intermediate **F** reacted with cationic intermediate **D** to afford intermediate **G**, which could be converted to the target product by deprotonation.

Target compound **4a** could form three tautomeric intermediate **H, I** and **J** through enamine-imine tautomerism. If target product was put in protonated condition or under high temperature, intermediate **K** will form, and then eliminate a molecule of piperidine to provide cationic intermediate **L**. Meanwhile intermediate **J** split into intermediate **D** and **M**. Then the reaction of Intermediate **M** and intermediate **L** supported the formation of the byproduct **5a**.



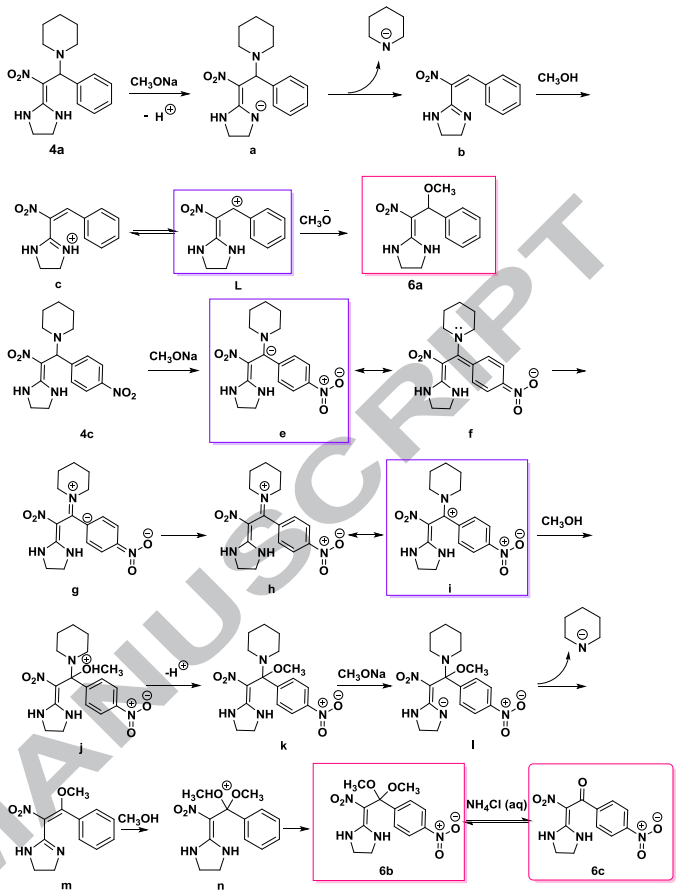
**Scheme 4** A possible formation mechanism of byproduct **5a**

To verify the processes in the above-mentioned mechanism, three controlled experiments were next carried out to explore the formation mechanism of byproduct **5a** and new application of the target compound. Basic situation ($CH_3OH/CH_3ONa$) and elevated temperature (50°C) were chosen due to the fact that acid condition and high temperature could afford byproduct. Compound **4a** was successfully converted to ether derivative **6a** under basic condition, while compound **4c** was converted to ketal compound **6b** and carbonyl compound **6c**. However, compound **4h** only afforded the byproduct **6d** (Scheme **5**) under the same condition. Target compounds with different substituent group had significant effect on the products. For example, when substituent group was electron-withdrawing group such as $NO_2$, it afforded ketal compound and carbonyl compound instead of ether compound. A possible mechanism was presented in Scheme **6**.



**Scheme 5** Derivatives of target compounds

In presence of alkali $CH_3ONa$, the N-H on imidazole ring was seized to form intermediate **a**. Intermediate **a** then took off a molecular piperidine to provide cationic intermediate **L** through tautomerism. Initially, $CH_3O^-$ will combine with intermediate **L** to give ether derivative **6a** which supported the mechanism above. But when the phenyl ring was substituted with electron-withdrawing group **(4c)**, hydrogen atom on tertiary hydrocarbon will easily get away to form anion **e** and then transferred to intermediate **i.** Subsequently, reaction between cation intermediate **i** and menthol could gave access to intermediate **l** after deprotonation. Then the formation of **6b** performed similar mechanism as **6a**. Finally, product **6b** was hydrolyzed to **6c** under acidic conditions. We predict the electron-donating group such as $–OCH_3$ **(4h)** could reduce the electrophilic ability of cation intermediate **L** so that we need a stronger nucleophile to perform similar reaction.



**Scheme 6** A possible mechanism of compound **6a, 6b** and **6c**

In summary, we developed a mild, convenient one-pot three-component Mannich-like reaction in EtOH at 30 °C by using β-nitroenamines, secondary amines and aromatic aldehydes. Notably, TFEA as an additive formed hydrogen bond with aromatic aldehydes to activate its electrophilicity, and also increased the acidity of the reaction to activate the reaction in moderate to excellent yields.

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**Highlights**

- A unique and efficient one-pot reaction of β-nitroenamines, secondary amines and aromatic aldehydes.
- 2,2,2-trifluoroethanol (TFEA) was used to activate this reaction.
- Afford the desired Mannich-like products in moderate to excellent yields with wide substrate scopes.