

FeCl₃·6H₂O catalyzed three components aza-Friedel-Crafts reaction
for the synthesis of *N*-Boc protected **α**-branched amines

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บทคัดย่อ

ในงานวิจัยนี้พบว่าสาร FeCl₃·6H₂O เป็นตัวเร่งปฏิกิริยาที่มีประสิทธิภาพในปฏิกิริยา aza-Friedel-Crafts ของสารตั้งต้นสามองค์ประกอบคือ arenes หรือ heteroarenes, *tert*-butyl carbamate และ aromatic aldehydes ภายใต้สภาวะที่ไม่รุนแรง โดยพบว่าเมื่อใช้ FeCl₃·6H₂O ปริมาณ 5 โมล% เร่งปฏิกิริยาของ 1,3,5-trimethoxybenzene 2-methyl furan หรือ 2-ethyl furan กับ *tert*-butyl carbamate และ aromatic aldehydes ในตัวทำละลายโทลูอีน ภายใต้สภาวะอุณหภูมิห้อง ได้สาร **α**-branched amines เป็นผลิตภัณฑ์ในร้อยละปานกลางถึงสูง ในขณะที่ปฏิกิริยาของ 2-methyl thiophene ซึ่งเป็นสารที่ไม่ว่องไวต่อการเกิดปฏิกิริยา พบว่าให้ผลิตภัณฑ์ **α**-branched amine ในร้อยละที่ต่ำ และปฏิกิริยาของ indole พบว่าได้ triarylmethane เป็นผลิตภัณฑ์หลัก ข้อดีของวิธีการในงานวิจัยนี้ คือ เป็นปฏิกิริยาการสังเคราะห์สารในขั้นตอนเดียว ภายใต้สภาวะที่ไม่รุนแรง ตัวเร่งที่ใช้ในการเกิดปฏิกิริยาราคาไม่แพง หาซื้อได้ง่าย และใช้เพียงปริมาณเล็กน้อย

คำสำคัญ : **α**-Branched amines / Aza-Friedel-Crafts Reaction / FeCl₃·6H₂O

Abstract

FeCl₃·6H₂O is shown to be an efficient catalyst for the three component aza-Friedel-Crafts reaction of arenes or heteroarenes, *tert*-butyl carbamate, and aromatic aldehydes under mild conditions. In the presence of 5 mol% of FeCl₃·6H₂O in toluene at room temperature, the reaction of 1,3,5-trimethoxybenzene, 2-methyl furan, and 2-ethyl furan gave the corresponding *N*-Boc protected **α**-branched amines, selectively, in moderate to excellent yields. However, the reaction of the less reactive 2-methyl thiophene afforded the **α**-branched amine adducts in low yield. On the other hand, the reaction of indole gave the triarylmethane as major product. The use of mild reaction condition, commercially available as well as inexpensive catalyst, low catalyst loading, and single step synthesis are the advantage of the presence procedure.

Keywords : **α**-Branched amines / Aza-Friedel-Crafts Reaction / FeCl₃·6H₂O

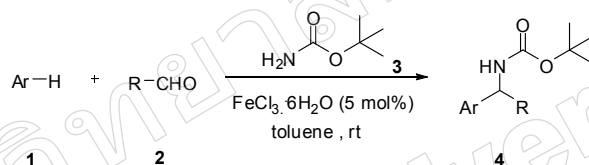
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1. Introduction

α -Branched amines are compounds of important therapeutic interest that can be used in a wide array of pharmaceutical applications (Kogen *et al.*, 2002; Shirakawa & Kobayashi, 2006; Gall *et al.*, 2009). Methodologies for the synthesis of α -branched amines have been developed which mainly centered around utilizing the Lewis acid catalyzed aza-Friedel-Crafts reaction (AFCR) between electron-rich aromatic compounds and imines (Wang *et al.*, 2006; Alonso *et al.*, 2008; Wang *et al.*, 2008; Thirupathi & Kim, 2010; Liu *et al.*, 2011; Jaratjaroonphong *et al.*, 2012; Fernández-Salas *et al.*, 2013). However, most of the methods are multi-step process and require the imine preparation and the electron-rich arenes appear to limit to 2-naphthol or indole derivatives.

In recent years, iron salts as effective, alternative, and promising transition-metal catalysts have received much more attention because of their less expensive, readily available, and environmentally benign properties. These iron salts were found to have promising catalytic abilities in many organic transformations (Liu *et al.*, 2011). Iron(III) chloride hexahydrate (ferric chloride hexahydrate, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) is one type of the iron salts which can be used as effective catalyst for Friedel-Crafts reactions (Thirupathi & Kim, 2010)

In this research, we have interested to study a simple, mild and efficient method for the synthesis of α -branched amines *via* $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed one-pot, three component aza-Friedel-Crafts reaction of arenes with aldehydes and *tert*-butyl carbamate (Scheme 1).



Scheme 1 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed three component AFCR.

2. Materials and Methods

2.1 General methods

The high resolution 400 MHz ^1H NMR, together with 100 MHz ^{13}C NMR spectra were performed on Bruker DPX-400 spectrometers at chemistry department, faculty of science, Burapha university and all spectra were measured in CDCl_3 solvent. The IR spectra were recorded on a Perkin Elmer System 2000 FT-IR. High resolution mass spectra were recorded on Finnigan MAT 95. Radial chromatography on a chromatotron was performed using Merck silica gel 60 PF_{254} with $\text{CaSO}_4 \cdot 1/2 \text{H}_2\text{O}$ and was activated by heating in an oven at 80°C for 45 min. Thin layer chromatography (TLC) was performed with Merck silica gel 60 PF_{254} aluminium plate.

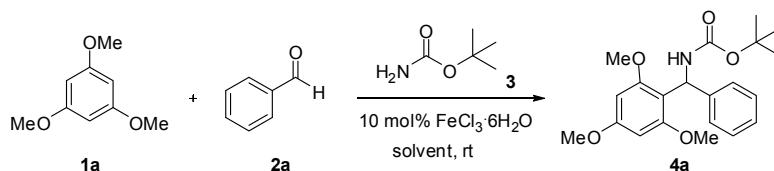
2.2 General procedure for synthesis α -branched amines

To a toluene solution (1 mL) of arene (1.0 mmol), aldehyde (1.1 mmol), and *tert*-butyl carbamate (1 mmol) in a test-tube open to air at room temperature was added $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%). After the reaction was stirred until completion (TLC analysis), the reaction mixture was quenched with aqueous NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , concentrated and purified by radial chromatography (hexanes/ EtOAc as eluent) to give *N*-Boc protected α -branched amines 4.

3. Results and Discussions

For initial optimization of the reaction condition, 1,3,5-trimethoxybenzene (**1a**), benzaldehyde (**2a**), and *tert*-butyl carbamate (**3**) were chosen as model substrates to be carried out under various solvents and the results are shown in Table 1.

Table 1 Model and optimization studies^a

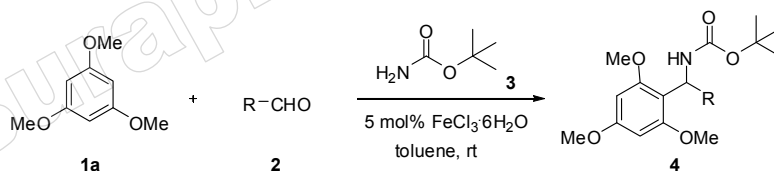


Entry	Catalyst (mol%)	Solvent	Time (h)	Product yield ^b (%)
1	10	ClCH ₂ CH ₂ Cl	24	86
2	10	THF	24	44
3	10	DMF	48	36
4	10	H ₂ O	24	35
5	10	toluene	24	88
6	10	toluene	12	89
7	20	toluene	2	80
8	10	toluene	2	91
9	5	toluene	2	86
10	2.5	toluene	2	59

^aReaction conditions : **1a**(1 mmol), **2a** (1.1 mmol), **3** (1 mmol), FeCl₃·6H₂O, solvent (1 mL), room temperature.

^bIsolated yield.

Table 2 FeCl₃·6H₂O catalyzed reaction of arene **1a**, *tert*-butyl carbamate, and various aldehydes^a



Entry	R	Product yield ^b (%)
1	C ₆ H ₅	4a (86)
2	4-MeO-C ₆ H ₄	4b (83)
3	4-Cl-C ₆ H ₄	4c (68)
4	4-Br-C ₆ H ₄	4d (64)
5	4-F-C ₆ H ₄	4e (83)
6	2-F-C ₆ H ₄	4f (85)
7	4-O ₂ N-C ₆ H ₄	4g (66)
8	4-MeO ₂ C-C ₆ H ₄	4h (81)

^aReaction conditions : **1a**(1 mmol), **2a** (1.1 mmol), **3** (1 mmol), FeCl₃·6H₂O, solvent (1 mL), room temperature.

^bIsolated yield.

From the solvent effect studied (entry 1-5), it was found that toluene was the solvent of choice. We also investigated the influence of catalyst loading and reaction time on the model reaction in toluene (entry 5-10). The results showed that the reaction in the presence of 5 mol% of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and stirring the reaction in 2 h (entry 9) gave the desired product **4a** in moderate yield and these condition was chosen as standard condition for the further study.

Table 3 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed reaction of various arenes with aromatic aldehyde and *tert*-butyl carbamate^a

Entry	Ar-H	Time (h)	Products yield (%)	
			4	5
1		2		
2		24		
3		2		
4		2		
5		3		
6		2		

^aReaction conditions : **1a**(1 mmol), **2a** (1.1 mmol), **3** (1 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, solvent (1 mL), room temperature.

^bIsolated yield. ^cThe reaction was carried out using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) in toluene at 0 °C.

The scope of the reaction under the optimized condition (Table 1, entry 9) was then investigated by varying the aldehyde substrate and the results are summarized in Table 2. In the presence of 5 mol% of FeCl₃·6H₂O, 1,3,5-trimethoxybenzene and *tert*-butyl carbamate reacted with a number of aromatic aldehyde possessing either electron-withdrawing (F, Cl, Br, NO₂) or electron-donating (OMe) substituents to afford the corresponding *N*-Boc protected diarylmethylamines **4a-h** in good to excellent yields.

Encouraged by these results, we next investigated the three-component AFCR with an array of arenes as well as heteroarenes, aldehyde, and *tert*-butyl carbamate. The results presented in Table 3 showed that the reaction led to selective formation of α -branched amines **4a-v** in good yields. In the case of entry 2 and 3, the triarylmethane derivatives **5b** and **c** were also obtained as a minor product. On the other hand, the reaction of the less reactive 2-methyl thiophene gave only low yield of the product. In contrast, the aza-Friedel-Crafts reaction of more electron-rich arene substrate, such as indole gave the desired product **4v** only in 5% yield and triarylmethane **5f** was obtained as major product in high yield. This type of side product **5f** is the result of a facile further Friedel-Crafts alkylation of the *tert*-butyl (indol-3-yl)phenyl methyl carbamate intermediate *via* a highly stabilized (indol-2-yl)phenyl methyl carbocation (Alonso *et al.*, 2008). The results in Table 3 indicated that the nucleophilicity of arene or heteroarene have effect on the product yields and the formation of the side product which undergo *via* double Friedel-Crafts reaction.

4. Conclusions

In conclusion, we have demonstrated an efficient FeCl₃·6H₂O catalyzed, one pot, three components aza-Friedel-Crafts reaction of arenes/heteroarenes, *tert*-butyl carbamate and a wide variety of aldehydes in toluene under mild conditions. The reaction of *N*-Boc protected α -branched amines were obtained in moderate to excellent yields. The use of mild reaction conditions, commercially available as well as inexpensive catalyst, low catalytic loading, and single step synthesis are the advantages of the present procedure. The reactions employing aliphatic aldehydes are in progress.

5. Acknowledgments

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