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FeCl₃-Mediated synthesis of polysubstituted tetrahydroquinolines *via* domino Mannich/Friedel–Crafts reactions of aldehydes and amines[†]

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A useful method to construct highly substituted tetrahydroquinolines has been developed through an iron(III) chloridemediated domino Mannich and intramolecular Friedel– Crafts alkylation followed by intermolecular Friedel–Crafts alkylation reactions of aliphatic aldehydes with aromatic amines.

Tetrahydroquinoline derivatives are an important class of biologically active compounds, which are widely used in organic synthesis and pharmaceutical chemistry.1 Currently, much effort in this area is focused on constructing polysubstituted tetrahydroquinolines, for instance the aza Diels-Alder reactions,² hydrogenations of quinolines,³ benzotriazole-mediated indirect electrophilic substitution,⁴ electrophilic cyclization,⁵ ring expansion reactions,⁶ palladium-catalyzed cross-coupling reactions,7 organocatalytic hydroarylations of enals,8 hydroaminations of aniline alkynes,9 and intramolecular redox reactions.10 However, to the best of our knowledge, intermolecular Friedel-Crafts (FC) alkylation to construct polysubstituted tetrahydroquinolines has been rarely reported. Crabb et al. reported a protonic acid-catalyzed condensation of anilines with two molecules of an aldehyde affording a mixture of the cis- and trans- isomers of 2,6-dimethyl-4hydroxy-1,2,3,4-tetrahydroquinoline in an approximate ratio of 1:2 [Scheme 1, eqn (1)].¹¹ In recent years, significant efforts have been focused on benzylic arylation chemistry utilising Friedel-Crafts alkylations.12 Friedel-Crafts reactions of benzylic alcohols have been studied with traditional Lewis and Brønsted acids.13 Beller et al. demonstrated that late transition metal salts such as HAuCl₄, IrCl₃, [MesW(CO)₃], RhCl₃, H₂PdCl₄, H₂PtCl₆ and FeCl₃ effectively catalyze the addition of benzyl acetates and benzyl alcohol to arenes.¹⁴ We envisioned that FeCl₃ is an attractive alternative to rare-earth triflates since it is non-toxic, cheap and readily available.¹⁵ With these thoughts in mind, we decided to test a new domino reaction involving a cascade Mannich/intramolecular Protonic acid-catalyzed condensations of aniline with two molecules of an aldehyde.



Scheme 1 Proposed domino Mannich/intramoleculer FC alkylation/intermolecular FC alkylation reactions.

Friedel-Crafts alkylation/intermolecular Friedel-Crafts alkylation sequence.

Domino reactions are attractive to industrial and laboratory chemists because of their potential to save solvents, reagents, time and energy.¹⁶ Our group is persistently interested in domino reactions to synthesize various functionalized heterocyclic compounds.¹⁷ Herein, we report our results of the cascade reactions of aliphatic aldehydes with aromatic amines in the presence of FeCl₃. This strategy provides a pathway in one-pot manner to the synthetically useful tetrahydroquinolines.

We conducted many trials to approach our goal by treating a threefold excess of N-methylaniline 1a (1.2 mmol) with phenylacetaldehyde 2a (0.4 mmol) in the presence of 0.3 equivalents of iron catalyst and 50 mg of 4 Å molecular sieves (MS) in CH_3NO_2 (3 mL) under argon. Gratifyingly, the desired product 3a was formed in 33% and 38% yield by using of FeCl₃ and FeBr₂ respectively, after 8 h at 60 °C (Table 1, entries 1 and 4). No reaction was observed in anisole when FeBr₂ was used as catalyst, whereas FeCl₃ gave a 78% yield (entries 5 and 6). Using anisole as solvent, the yield was improved greatly. The reaction performed in other solvents afforded inferior yields (entries 7-10). Lewis acid such as Sc(OTf)₃ and InCl₃ showed comparable catalytic activity to give **3a** in 61% and 71% yield, respectively (entries 13 and 14). Brønsted acids were also examined, and only HSbF6.6H2O worked and gave 62% yield (entry 16), whereas TFA and TsOH did not catalyze this reaction. 10 mol% and 20 mol% of FeCl₃ gave lower yields (entries 19 and 20). When the reaction was conducted at ambient temperature, it proceeded with a lower reaction yield (entry 21, 45%). Surprisingly, a higher reaction temperature did not increase the yield (entry 22, 51%). As the reaction proceeds with loss of two equivalents of

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[†] Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra for compounds **3a–3k**, **4a–4f**. CCDC reference number 807037. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05646h

			HN		
2	N ⁺ H + 2	P H Ph Catalyst, Solvent,	4Å MS 60°C, Ar	H Ph MH H Ph	
	Id	2a	3a		
Entry	Catalyst	Loading (mol%)	Solvent	Yield (%) ^b	
1	FeC1.	30	CH-NO.	33	
2	$Fe(NO_2)_2$	30	CH ₃ NO ₂	NR	
3	Fe(acac)	30	CH ₂ NO ₂	NR	
4	FeBr ₂	30	CH ₂ NO ₂	38	
5	FeBr ₂	30	Anisole	NR	
6	FeCl	30	Anisole	78	
7	FeCl ₃	30	CH ₃ CN	48	
8	FeCl ₃	30	DCE	39	
9	FeCl ₃	30	Toluene	38	
10	FeCl ₃	30	Chlorobenzene	22	
11	AlCl ₃	30	Anisole	NR	
12	$Cu(OTf)_2$	30	Anisole	32	
13	$Sc(OTf)_3$	30	Anisole	61	
14	InCl ₃	30	Anisole	71	
15	BF3·Et ₂ O	30	Anisole	47	
16	HSbF ₆ ·6H ₂ O	30	Anisole	62	
17	TFA	30	Anisole	NR	
18	TsOH	30	Anisole	NR	
19	FeCl ₃	10	Anisole	15	
20	FeCl ₃	20	Anisole	31	
21 ^c	FeCl ₃	30	Anisole	45	
22 ^d	FeCl ₃	30	Anisole	51	

^{*a*} Conditions: 1.2 mmol **1a**, 0.4 mmol **2a** and 50 mg of 4 Å MS with 0.3 equivalents of catalyst in solvent (3.0 mL) at 60 °C under Ar after 8 h. ^{*b*} Isolated yield. ^{*c*} Performed at room temperature after 24 h. ^{*d*} Performed at 80 °C.

Table 2 FeCl₃-Mediated synthesis of tetrahydroquinolines with aromatic amines^a

	R ²	R^2		R ¹ H Ph	
	1	2a	R [∠] 3		
	1				
Entry	\mathbf{R}^1	\mathbb{R}^2	Time (h)	Yield (%) ^b	Ratio of isomers ^e
1	Н	Me	8	78 (3a)	88:12
2	3-Me	Me	10	72 (3b)	72:28
3	3-OMe	Me	12	42 (3c)	75:25
4	3-F	Me	10	69 (3d)	90:10
5	3-Cl	Me	10	65 (3e)	86:14
6	3-Br	Me	14	56 (3f)	89:11
7	3-CO ₂ Me	Me	12	47 (3 g)	87:13
8	3,5-Dimethyl	Me	10	NR	
9	Ĥ	Ph	10	58 (3h)	86:14
10	Н	3-Me-Ph	10	47 (3i)	79:21
11	1,2,3,4-Tetra-hydroquinoline		12	38 (3 j)	51:49
12	N-Methyl-1-naphthylamine		12	10 (3k)	67:33

2 Ph Ph 0.3 equiv FeCl₃, 4Å MS

^{*a*} Reactions were conducted with 1 (1.2 mmol), **2a** (0.4 mmol) and 50 mg of 4 Å MS with 0.3 equivalents of FeCl₃ in anisole (3 mL) at 60 °C under Ar. ^{*b*} Isolated yield. ^{*c*} The ratio of (2,3-*trans*-2,4-*trans*) isomer to (2,3-*trans*-2,4-*cis*) isomer was determined by ¹H NMR analysis.

water, the addition of 4 Å MS was essential. After the systematic screening, the use of 0.3 equivalents of FeCl₃ with 4 Å MS in dry anisole at 60 $^{\circ}$ C under argon was considered to be the optimum and selected as the standard conditions.

With the optimized conditions in hand, we first explored the scope of amines for this reaction, as summarized in Table 2. The reaction proceed well with substituents on the meta positions of N-methylanilines. Aromatic amines with electron-donating groups on the benzene rings gave higher yields than those with electronwithdrawing groups except the 3-methoxy group (entries 2-7). This shows that steric effects had a strong influence on the reaction. With a 3,5-dimethyl group on the aniline, however, no desired product was obtained (entry 8). The methodology also tolerated well the R^2 position being occupied by a phenyl group, affording the desired product **3h** in 58% yield (entry 9). To investigate the steric effects, we found that 3-methyldiphenylamine 1i reacted with 2a to produce the major product 3i in 47% yield, showing little steric hindrance (entry 10). Interestingly, the use of a highly hindered secondary amine 1j was also allowed, which gave an approximate 1:1 mixture of two isomers of 5,6,7trisubstituted julolidine 3j (entry 11).18 Furthermore, N-methyl-1naphthylamine gave the by-product 5-methyl-1-naphthylamine in 50% yield, but the desired product 3k was obtained in 10% yield (entry 12). Finally, it is worthwhile to note that N-methylanilines with ortho and para substituents didn't work at all. According to the ¹H NMR and X-ray diffraction analysis of 3e (Fig. 1), the 2,3-trans-2,4-trans isomers were proved to be the major products; in most cases, the minor isomers exhibited the 2,3-trans-2,4-cis configuration.

To expand further the scope of the reaction, we also investigated other aldehydes. Aldehydes unbranched at the α -position react similarly producing 1,2,3,4-tetrahydroquinoline derivatives. Table 3 demonstrates the generality and scope of the reaction







^{*a*} Reactions were conducted with **1a** (1.2 mmol), 0.4 mmol of **2**, 50 mg of 4 Å MS and 0.3 equivalents of FeCl₃ in anisole (3 mL) at 60 °C under Ar after 10 h. ^{*b*} Isolated yield. ^{*c*} Determined by the ¹H NMR analysis. ^{*d*} dr = 3 : 1.

of N-methylaniline 1a with aliphatic aldehydes 2 to form the corresponding products under optimized conditions. However, acetaldehyde was less efficient in this transformation (entry 1). The increase in the length of the aldehyde chain caused a decrease in yield of the reaction (entries 2-4). When octanal was added to the reaction system, no desired product was observed. Enolization of the aldehyde becomes difficult with the increase in chain length. In addition, reactions of 3-phenylpropanal with N-methylaniline can also be carried out, affording a mixture of 1:1 isomers, which was determined from the ¹H NMR spectrum, in 70% combined yield (entry 5). When enantiomerically pure methyl-(S)-2-N,Ndi-tert-butoxycarbonyl-5-oxopentanoate 2f, which can be readily synthesized in four conventional steps from L-glutamic acid,¹⁹ was subjected to the standard reaction conditions, the product 4f was obtained as a mixture of 3:1 diastereoisomers (entry 6). The enantiomeric excess of each isomer was determined to be higher than 99% by chiral HPLC analysis. It appears that 2f did not racemize during this process. The relative configurations of the major isomers 4a, 4b, and 4f were assigned by Nuclear Overhauser Effect (NOE) spectroscopy (cf. ESI[†]) and additionally confirmed by an X-ray crystal structure analysis of 3e (Fig. 1).

The mechanism for this transformation is proposed to be as depicted in Scheme 2.20 Iminium ion A is formed by the condensation of aniline 1 with aldehyde 2, which adds to a molecule of iron(III) enolate²¹ 2' to produce aldehyde B by a Mannich reaction.²² Then, aldehyde B undergoes an FeCl3-catalyzed intramolecular Friedel-Crafts type ring closure to furnish a benzyl alcohol intermediate C, which in the presence of a proton loses water and releases FeCl₃ to produce carbocation intermediate D. Finally, excess N-protected aniline²³ as the aromatic nucleophile attacks the carbocation intermediate D via an intermolecular Friedel-Crafts reaction, which loses a proton to afford tetrahydroquinoline skeleton 3 or 4. In this transformation, carbocation intermediate D is the key intermediate leading to compound 3 or 4. If we decrease the temperature or reduce the catalyst loading, there will be some iminium ion A left unreacted. Thus, the $S_N 1$ step to generate carbocation intermediate **D** is the rate determining step.

In summary, we have developed a simple method for a one-pot domino Mannich/intramolecular Friedel–Crafts alkylation/intermolecular Friedel–Crafts alkylation reactions by using iron(III) chloride as catalyst, which leads to the synthesis of 1,2,3,4tetrahydroquinoline derivatives. The advantages of this method



Fig. 1 X-Ray structure of compound 3e.



Scheme 2 Plausible reaction mechanism.

include good substrate generality, mild conditions, environmentfriendly catalyst and easy availability of starting materials. Further exploration of Lewis acid-catalyzed reactions to construct useful structures is the future goal of our research group.

Typical experimental procedure for FeCl₃-mediated synthesis of 3a–3k, 4a–4f

To a solution of 1 (1.2 mmol), 2 (0.4 mmol) and 4 Å MS 50 mg in dry anisole (3 mL) was added FeCl₃ (19.5 mg, 0.12 mmol). The mixture was stirred under argon at 60 °C. On completion of the reaction as shown by TLC analysis, the reaction mixture was filtered and partitioned between sat. aq. NaHCO₃ and ethyl acetate. The aqueous layer was further extracted with ethyl acetate (3 × 20 mL). The combined organic extracts was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography using petroleum ether/ethyl acetate as eluent on alkalescent silica gel to give the desired product.

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