Tetrahedron 66 (2010) 7142–7148

Contents lists available at ScienceDirect

Tetrahedron

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

A facile protocol for the synthesis of mono-*N*-methyl anilines via formimidate intermediates

Nan Sun [a], Shuai Wang [a], Weimin Mo [a,*], Baoxiang Hu [a], Zhenlu Shen [a], Xinquan Hu [a,b,*]

[a] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, PR China
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 12 April 2010
Received in revised form 9 June 2010
Accepted 30 June 2010
Available online 23 July 2010

Keywords:
Mono-*N*-methyl anilines
Formimidate
MCM-41-SO_3H mesoporous zeolite
$NaBH_3(OAc)$ reduction

ABSTRACT

A general procedure for the preparation of mono-*N*-methyl anilines has been developed with excellent yields. This protocol relies on a $NaBH_3(OAc)$ reduction of formimidate intermediates that are quantitatively generated by treatment of primary substituted anilines with triethyl orthoformate under the catalysis of MCM-41-SO_3H mesoporous zeolite. The newly developed procedure was facile, efficient, and environmentally benign.

1. Introduction

Mono-*N*-alkyl anilines and their derivatives have been versatile in the applications as the building blocks for the construction of important organic chemicals, which are widely used in pharmaceutical, agrochemical, and dyes industries.[1] Traditionally, these mono-*N*-alkyl anilines were prepared by direct N-alkylation of primary anilines with alkyl halides or sulfates in the presence of bases[2] or under the catalysis of alkali cation exchanges X- and Y-zeolites.[3] Recently, in the environmental point of view, non-toxic alcohols and dialkyl carbonates were also used as alkylating reagents for the direct mono-N-alkylation of primary anilines with various heterogeneous catalysts under the gas conditions.[4] Another important alternative of the direct mono-N-alkylation of primary anilines was reductive amination with aldehydes or ketones as alkylating reagents.[5] Although these reported methods were widely applied in the mono-N-alkylation of primary anilines, most of them are not in high selectivity and often some amount of *N*,*N*-dialkylated by products are generated. Especially, *N*,*N*-dimethyl anilines were always obtained as the major products in the cases of mono-N-methylation of anilines due to the less steric hindrance of the methyl group. In order to improve the selectivity of mono-N-methylation, some reagents, such as, $CH(OCH_3)_3/H_2SO_4$,[6] $Bi(CH_3)_3/Cu(OAc)_2$,[7] supercritical methanol,[8] methanol/tetraphosphonate cavitand,[9] $CH_3OH/Ph_3P/DDQ$,[10] $CH_3B(OH)_2/Cu(OAc)_2$,[11] have been developed to use as methylating reagents for the direct mono-N-methylation of primary anilines. Besides these special reagents, ionic liquids were also reported as the efficient reaction media for this transformation.[12] However, the chemical selectivity and the yields of these methods are far from ideal. The difficulty of over methylation inherent in the direct mono-N-methylation has led to the development of the indirect mono-N-methylation methods to improve the selectivity. Of the indirect mono-N-methylation methods, the most common procedure contains a multi-step approach, including amine protection, followed by methylation and deprotection.[13] However, the additional protection and deprotection operations led to the tedious labor work, loss of yield and also significantly cost increasing. Alternatively, reductive methylation has been developed as an efficient method for the indirect mono-N-methylation of primary anilines. The method was based on the initial introduction of formacyl, methylene or their equivalents to the primary anilines, then reduction to form methyl group. Following these reductive methylation strategies, a number of aniline derivatives were prepared from primary anilines including *N*-(arylaminomethyl)phthalimides,[14] *N*-(arylaminomethyl)succinimides,[15] *N*-alkoxymethylarylamines,[16] *N*-(arylaminomethyl)benzotriazoles,[17] 3-methylbenzothiazol-2-(3*H*)-imines,[18] 1,3,5-triarylhexahydro-1,3,5-triazines,[19] *N*-arylformimidates,[20] *N*-arylformamidines,[21] *N*-arylformamides,[22] and *N*-arylcarbamates,[23] which were successively reduced to obtain mono-*N*-methyl anilines in high

* Corresponding authors. E-mail addresses: mowm@zjut.edu.cn (W. Mo), xinquan@zjut.edu.cn (X. Hu).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.091

selectivity. Indeed, these modified reductive methylation provided high selectivity during the preparation of desired mono-*N*-methyl anilines for the synthetic chemists. However, some of these reductive methylation methods required powerful reducing reagents, such as LAH, or catalytic hydrogenation under high pressure and/or high temperature. Among them, the reduction of *N*-arylformimidates, which was proposed by Blanton and Crochet,[20] was one of the most efficient and convenient mono-N-methylation methods, because the intermediate *N*-arylformimidate could be readily prepared from primary anilines and triethyl orthoformate, followed by the reduction with $NaBH_4$ under mild conditions. No dimethylated byproduct would occur in this procedure. Moreover, the reagents were commercially available and less expensive. It seemed that this is an ideal procedure for the preparation of mono-*N*-methyl anilines. But in their report, only limited substrates, which mainly focused on the electron-rich anilines, were described with moderate to good yields. Due to our interests in this transformation, we decided to scrutinize this procedure for the preparation of mono-*N*-methyl anilines. As a result of our current investigation, we herein reported a highly efficient procedure for preparation of mono-*N*-methyl anilines in two convenient steps, MCM-41-SO_3H mediated the quantitative formation of the *N*-arylformimidate intermediates from primary anilines and triethyl orthoformate, followed by the reduction with $NaBH_3(OAc)$ under mild conditions in good to excellent yields.

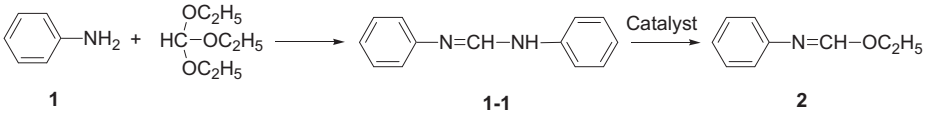
2. Results and discussion

First, the mono-N-methylation of aniline via ethyl *N*-phenylformimidate was chosen as a model reaction in our study.[24] The process of synthesizing ethyl *N*-phenylformimidate from aniline and triethyl orthoformate under the acidic catalysis was already well described in literature.[25] Aniline first reacted with triethyl orthoformate to form intermediate *N*,*N*′-diphenylformamidine (**1-1**), which was further reacted with excess triethyl orthoformate to afford ethyl *N*-phenylformimidate (**2**, Scheme 1). Some conventional homogeneous acids catalysts, such as, H_2SO_4, HCl, HOAc, CF_3COOH, and *p*-toluenesulfonic acid (TsOH), were already employed in this reaction. But with either of these acids, the intermediate **1-1** was not able to transform completely to ethyl *N*-phenylformimidate (**2**), which resulted in the unsatisfied yields. Moreover, using of these conventional homogeneous acids brought tedious separation procedures and some other serious drawbacks, such as the corrosive problem, hazard handling, and treatment of toxic waste. In the recent decade, it has become a trend that using easy recoverable and reusable solid acids replaces the conventional homogeneous acids as the catalysts in the synthetic chemistry.[26] Based on this, we turned our interests to investigate this transformation with the application of some solid acids under the heterogeneous conditions. Initially, unsubstituted aniline was selected as model substrate to react with triethyl orthoformate for the preparation of *N*-methyl aniline via ethyl *N*-phenylformimidate. Various heterogeneous solid acids, such as, Amberlyst-15 (sulfonic resin), H-ZSM-5 (aluminosilicate zeolite, Si/Al=50), MCM-41 (mesoporous zeolite), and MCM-41-SO_3H (propylsulfonic acid-functionalized mesoporous zeolite),[27] were chosen to serve as the heterogeneous solid acid catalysts in the reaction of aniline and triethyl orthoformate to form ethyl *N*-phenylformimidate. Meanwhile, CF_3COOH was also employed as the homogeneous liquid acid catalyst for comparison. The reaction was also carried out in the absence of catalyst as for the blank test. The results were summarized in Table 1. Complete conversion of aniline was observed in 20 min under the reaction conditions either in the absence or in the presence of all tested catalysts by GC analysis. But the rate of conversion of intermediate *N*,*N*′-diphenylformamidine (**1-1**) to the product ethyl *N*-phenylformimidate (**2**) was strongly depended on the catalysts. Without catalysts, 77% of ethyl *N*-phenylformimidate (**2**) and 23% of intermediate *N*,*N*′-diphenylformamidine (**1-1**) were observed after 24 h under the reaction conditions (entry 1, Table 1), and the ratio of **2** and **1-1** showed almost no change even prolonging the reaction time. The reaction could be accelerated by liquid acid CF_3COOH but without significant improvement on the selectivity (entry 2, Table 1), which was consistent with the results obtained using other liquid acids in the literature.[25] The results by solid acids, H-ZSM-5 and MCM-41, showed no obvious difference compared to the blank test (entries 3 and 4 vs entry 1, Table 1). Amberlyst-15 and MCM-41-SO_3H, which are sulfonic acid-functionalized solid acids with strong protic acidity, exhibited excellent catalytic ability (entries 5 and 6, Table 1). Using either Amberlyst-15 or MCM-41-SO_3H as the catalyst, no intermediate **1-1** was detected within a much shorter reaction time, and nearly quantitative yield of ethyl *N*-phenylimidate was obtained.[28] Comparing the results obtained by Amberlyst-15 and MCM-41-SO_3H in Table 1, it seemed that the catalytic behavior of Amberlyst-15 and MCM-41-SO_3H showed no obvious difference except the reaction rate. Even though possessing the advantages, such as commercial availability and less expensive, the fatal limitations of Amberlyst-15, that is, its bad temperature endurance ability (up to 120 °C during the transformation of **1-1** to **2**) and also its weak mechanical strength (partly smashed during the stirring), drove us to put attention on the potential recycling of MCM-41-SO_3H. It is pleased that it could be reused for up to five times without obvious loss of the catalytic activity (entries 6–11, Table 1). Therefore, MCM-41-SO_3H was chosen as catalyst in the transformation of anilines to formimidates for our further researches.

Table 1
Reaction of aniline with triethyl orthoformate in the presence of different catalysts[a]

Entry	Catalyst	Time (h)	Product (%, by GC)		Yield[b] (%)
			1-1	**2**	
1	None	24	23	77	
2	CF_3COOH	6	19	76	
3	H-ZSM-5	24	16	84	
4	MCM-41	24	23	77	
5	Amberlyst-15	6	ND	97	95
6	MCM-41-SO_3H	3 (Fresh)	ND	100	97
7	MCM-41-SO_3H	3 (Recycle 1)	ND	100	95
8	MCM-41-SO_3H	3 (Recycle 2)	ND	100	95
9	MCM-41-SO_3H	4 (Recycle 3)	ND	100	96
10	MCM-41-SO_3H	4 (Recycle 4)	ND	100	95
11	MCM-41-SO_3H	6 (Recycle 5)	ND	100	96

[a] All the reactions were carried out with 20 mmol of aniline, 0.10 g of catalyst, and 10 mL of triethyl orthoformate at 120 °C, and ethanol generated in the reaction was distilled off via a 10-cm Vigreux distillation column during the reaction.
[b] GC yield by internal standard method and ethyl benzoate used as internal standard.



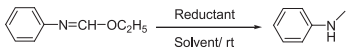
Scheme 1.

We then turned our attention to the preparation of the desired mono-*N*-methyl aniline via reduction of ethyl *N*-phenylformimidate.[29] Following the literature procedure, the reduction of ethyl *N*-phenylformimidate by $NaBH_4$ was carried out in ethanol under ambient temperature.[20] The reduction results were listed in Table 2. When ethyl *N*-phenylformimidate was treated with 3 equiv of $NaBH_4$ in ethanol after 3 h at room temperature, only 21% of ethyl *N*-phenylformimidate was converted and the selectivity of *N*-methyl aniline was only 43% (entry 1, Table 2). However, an increased conversion (84%) and selectivity (96%) was achieved after refluxing the ethanol mixture for 24 h (entry 2, Table 2). The reduction of ethyl *N*-phenylformimidate with $NaBH_4$ was also carried out in other solvents, such as THF, 1,2-dichloromethane (DCM), and DMF, but unfortunately failed (entries 3–5, Table 2). Considering that the reduction activity of $NaBH_4$ could be modified by addition of acetic acid to form acetoxyborohydride, which was widely used in the $NaBH_4$ reduction reactions,[30] $NaBH_3(OAc)$ was prepared by addition of equal equivalent of acetic acid to the $NaBH_4$/ethanol suspension at room temperature, then the in situ prepared $NaBH_3(OAc)$/ethanol was tested in the reduction of ethyl *N*-phenylformimidate. It was pleased to find that a complete conversion of ethyl *N*-phenylformimidate was observed in 3 h under room temperature, but the selectivity of the desired product was only 56% (entry 6, Table 2). This result greatly inspired us to optimize the reaction conditions. Again, we screened the above-mentioned solvents for $NaBH_4$ reduction. To our delight, an excellent result of nearly quantitative conversion and selectivity was achieved when THF was used as the reaction solvent (entry 9, Table 2). Then the amount of $NaBH_3(OAc)$ was also optimized, and the results showed that 2 equiv of $NaBH_3(OAc)$ was enough to complete the reduction (entries 9–11, Table 2).

The optimized procedure was then applied to the mono-*N*-methylation of substituted anilines by reaction of substituted anilines and triethyl orthoformate and the consequent reduction. The results were summarized in Table 3. Various primary substituted anilines were quantitatively converted to their corresponding formimidate intermediates using MCM-41-SO_3H as the catalyst under the optimal reaction conditions. As can be seen from Table 3, the reaction rate was remarkably affected by the property and the position of substituents bearing to the phenyl ring. Except 4-methoxy aniline, all other substituted anilines required longer reaction time to complete the reaction. Moreover, those substituents at *ortho*- or *meta*-position required relatively longer reaction time compared to the *para*-analogues. This could be attributed to the shape selectivity of the ordered mesoporous material MCM-41-SO_3H. The unsubstituted aniline with the minimum molecular size moved faster in the pores of the MCM-41-SO_3H zeolite than the substituted anilines, and thus required shorter time to reach the catalytic reactive centers, therefore, the fastest reaction rate was observed when aniline was the substrate (entry 1, Table 3). Furthermore, the anilines with substituted group at *para* position has higher molecular symmetry than those with substituents at *ortho* or *meta* positions. It was obvious that faster reaction rates were obtained for *para*-substituted anilines (entries 2 and 5 vs entries 3 and 4 and entries 6 and 7, Table 3). Moreover, anilines with the electron-withdrawing substituted group required longer reaction times to complete the reaction than those with electron-donating substituted groups. Probably, this was ascribed to the weaker nucleophilicity of their electron-deficient property for the substituted anilines with electron-withdrawing groups.

The obtained formimidate intermediates were then treated with $NaBH_3(OAc)$ in THF at room temperature, the results were also listed in Table 3. All formimidates can be smoothly converted to the corresponding mono-*N*-methyl anilines in a period of 3 h. The isolated products were all in good to excellent yields. The results in Table 3 showed that the structural and electronic properties of the substituted groups attached to the phenyl ring don't have obvious effect during the reduction reaction. Interestingly, the reducible functional groups, such as, COOEt, CN, and NO_2, can endure the reduction conditions (entries 11–13, Table 3). However, substrate with carbonyl group was partially reduced to hydroxyl group.[32] Under the optimal reaction condition, the developed process also suited for the preparative scale with high isolated yield (0.2 mol scale for aniline, datum in parentheses of entry 1,

Table 2
Reduction of ethyl *N*-phenylformimidate under different conditions[a,b]



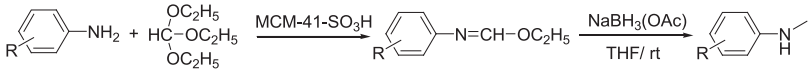
2 3

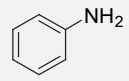
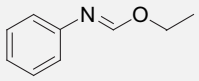
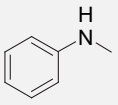
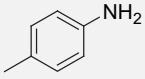
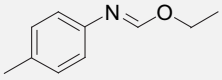
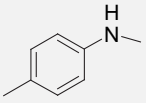
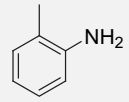
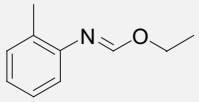
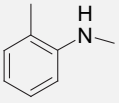
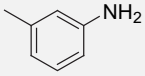
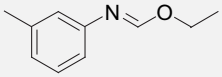
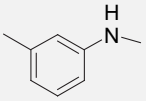
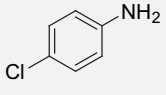
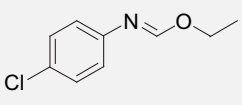
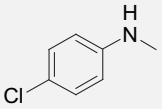
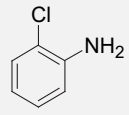
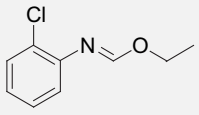
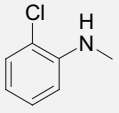
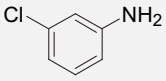
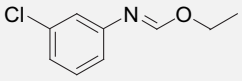
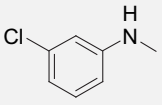
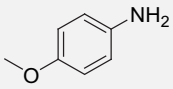
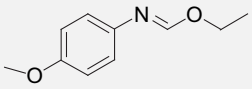
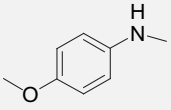
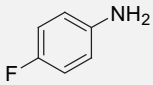
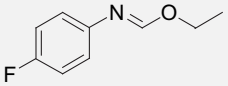
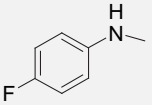
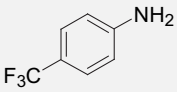
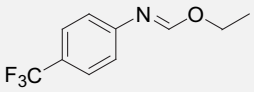
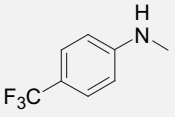
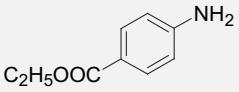
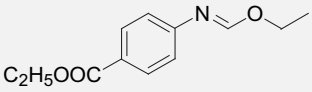
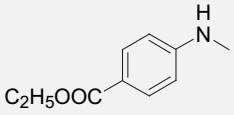
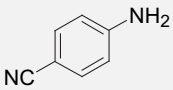
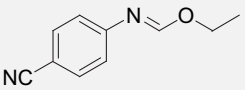
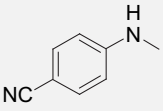
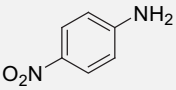
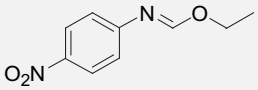
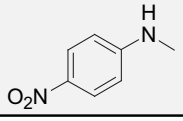
Entry	Reductant	*X* equiv reductant	Solvent	Time (h)	Conversion[c] (%)	Selectivity[c] (%)
1	$NaBH_4$	3.0	EtOH	3	21	43
2[d]	$NaBH_4$	3.0	EtOH	24	84	96
3	$NaBH_4$	3.0	THF	3	1.5	0
4	$NaBH_4$	3.0	DCM	3	0	0
5	$NaBH_4$	3.0	DMF	3	1.8	0
6	$NaBH_3(OAc)$	3.0	EtOH	3	100	56
7	$NaBH_3(OAc)$	3.0	DCM	3	99	64
8	$NaBH_3(OAc)$	3.0	DMF	3	99	94
9	$NaBH_3(OAc)$	3.0	THF	3	100(96)[e]	100
10	$NaBH_3(OAc)$	2.0	THF	3	100(96)[e]	100
11	$NaBH_3(OAc)$	1.5	THF	3	97	97

[a] All the reactions were carried out by dropping 20 mmol of ethyl *N*-phenylformimidate in 10 mL of solvent to the reductant in 40 mL of solvent at room temperature.
[b] $NaBH_3(OAc)$ was in situ prepared by addition of equal equivalent of CH_3COOH to $NaBH_4$ in reaction solvent.
[c] Determined by GC.
[d] The reaction was carried out under reflux conditions.
[e] Data in parentheses were the isolated yields.

Consideration that the intermediate ethyl *N*-phenylformimidate could partially decompose during the stage of column chromatographic purification to form *N*-phenylformamide, we tried to explore the possibility of direct reduction of crude ethyl *N*-phenylformimidate with $NaBH_3(OAc)$ in THF. After the reaction of aniline and triethyl orthoformate catalyzed by MCM-41-SO_3H was complete, the heterogeneous catalyst was filtered off and washed with THF. Then the filtrate was concentrated in vacuo to recover the excess triethyl orthoformate. The resulting residual[31] was directly reduced with $NaBH_3(OAc)$ in THF under ambient temperature. With this simplified reduction procedure, the isolated *N*-methyl aniline showed no obvious decrease of yield (entry 1, Table 3).

Table 3
Synthesis of mono-*N*-methyl anilines via formimidate intermediates[a,b]



Entry	Substrate	Time[c] (h)	Formimidate	Product	Yield[d] (%)
1		3			93(94[e])
2		5			91
3		8			94
4		12			91
5		8			92
6		12			87
7		12			94
8		3			83
9		10			87
10		12			93
11		18			86
12		24			93
13		24			76

[a] Anilines (20 mmol), 0.10 g of MCM-41-SO_3H, and 10 mL of triethyl orthoformate were used for the preparation of intermediate formimidates.
[b] The formimidates did not isolate and was reduced at room temperature for 3 h with $NaBH_3(OAc)$ in 40 mL of THF, which was in situ generated by reaction of 40 mmol of CH_3COOH with 40 mmol of $NaBH_4$ in THF.
[c] Complete conversion of anilines to formimidates.
[d] Overall yield based on anilines.
[e] The reaction was carried out in 0.2 mol scale of aniline, product was separated via vacuum distillation.

Table 3). It is noteworthy that this process is also suitable for the preparation of *N*-propyl and *N*-phenyl aniline.[33] We also attempted to extend the screened catalyst MCM-41-SO_3H in the reaction of triethyl orthoformate and other type of amine substrates, for examples, the primary alkyl amine (benzyl amine) and heterocyclic amine (4-aminopyridine), however, the reactions were much complicated compared to the anilines. As for benzyl amine, the relatively lower conversion and selectivity of desired imidate were observed, a sequential reduction only afforded a 45% of isolated yield of desired *N*-methyl benzyl amine, while for 4-aminopyridine, the selectivity of formation of imidate intermediate was rather good, unfortunately, the $NaBH_3(OAc)$ failed to afford the desired product.

In summary, we have successfully developed a facile method for the synthesizing of mono-*N*-methyl anilines. In this newly method, the substituted anilines reacted with triethyl orthoformate in quantitative conversion catalyzed by heterogeneous catalyst, MCM-41-SO_3H. A simple filtration recovered the heterogeneous catalyst and stripping the excess triethyl orthoformate afforded the crude formimidate intermediates, which were directly reduced with in situ prepared $NaBH_3(OAc)$ in THF at room temperature to the corresponding mono-*N*-methyl anilines in good to excellent yields. Moreover, the recovered heterogeneous catalyst MCM-41-SO_3H after simple washing can be directly reused and kept for its catalytic activity even after five recycling runs.

3. Experimental section

3.1. General

Heterogeneous catalyst H-ZSM-5 (Si/Al=25) and MCM-41 (r_{av}=3.8 nm, S_{BET}=1000 m^2/g) were purchased from Nankai University Catalyst Co., Ltd, Tianjin, China, Amberlyst-15 was purchased from Alfa Aesar Company. MCM-41-SO_3H was prepared from MCM-41 by grafting method according to the literature procedure. The sulfonic acid loading of the MCM-41-SO_3H (mmol/g) was determined by thermogravimetric analysis on a Seiko Pyris Diamond TG/DTA instrument and was calculated based on the weight loss between 260 and 550 °C. The specific surface area and pore-size distribution of the MCM-41-SO_3H were measured by recording nitrogen adsorption/desportion isotherms at liquid N_2 temperature on a Thermo Micromeritics ASAP 2021C apparatus. The pore-size distribution was determined from desorption branch of the isotherm by the BJH (Barrett–Joyner–Halenda) method using the Halsey equation and the pore volume (V_p) was taken at P/P_o=0.97 single point. The ordered mesoporous structure of the MCM-41-SO_3H was confirmed by XRD analysis on a PANalytical X'Pert PRO diffractometer using Cu Kα radiation and TEM analysis on a Philips Tecnai G2 F30 microscope. All proton NMR spectra were recorded on Bruker AVANCE III 500 MHz spectrometer in deuterium solvents with tetramethylsilane (TMS) as internal standard. GC–MS analyses were performed in EI mode on Thermo Finnigan Trance DSQ mass spectrometer with a 2000 series gas chromatography (HP-5 column, 30 m×0.25 mm (i.d.), 0.25 μ). GC analyses were performed on Agilent 6890 instrument with FID detector using an HP-5 capillary column (30 m×0.25 mm (i.d.), 0.25 μ). Flash column chromatography was performed with basic Al_2O_3 (200–300 mesh) with ethyl acetate/petroleum as eluent. Melting points (uncorrected) were determined on BUCHI B-545 apparatus. All solvents and reagents were directly used without further purification.

3.2. Procedure for the preparation of the catalyst MCM-41-SO_3H

MCM-41 (7.0 g) was dried at 120 °C for 3 h under N_2 atmosphere and then cooled down to room temperature. A solution of 3-mercaptopropyltrimethyloxysilane (14.8 g) in 400 mL of dry toluene was introduced, and the mixture was refluxed for 24 h. After the slurry was cooled down to room temperature, the solid was collected by suction and washed thoroughly with toluene and dried at 70 °C for 4 h. The obtained white solid (14.6 g) was treated with a mixture of 60 mL of 35% H_2O_2 and 40 mL methanol at room temperature for 24 h. Again, the solid was collected by suction and consecutively washed with de-ionized water and ethanol. In order to confirm that all the sulfonic acid groups are protonated, the solid material was further suspended in 0.1 M H_2SO_4 (200 mL) for 4 h. The solid was then filtered and washed with de-ionized water till neutral. After dried at 60 °C overnight, 9.2 g of corresponding SO_3H-MCM-41 was obtained. The sulfonic acid loading of the prepared catalyst MCM-41-SO_3H was about 1.7 mmol/g. The specific surface area and pore volume of the catalyst was 560 m^2/g and 0.27 cm^3/g, respectively. Both XRD and TEM patterns showed that the hexagonal structure of MCM-41 did not undergo major changes after functionalizing with propylsulfonic acid group.

3.3. General procedure for the synthesis of mono-*N*-methyl anilines

A mixture of anilines (20 mmol), 0.10 g of MCM-41-SO_3H, and 10 mL of triethyl orthoformate was heated at 120 °C and the co-product ethanol was distilled off through a 10 cm Vigreux distillation column as it was produced. The progress of the reaction was monitored by GC or TLC. After the reaction was finished, the mixture was cooled to room temperature. Then the catalyst MCM-41-SO_3H was filtered off, and washed with THF (5 mL×3). The combined filtrate was concentrated in vacuo to recover the excess triethyl orthoformate. The resulting residual was dissolved in 15 mL of THF and directly performed the reduction at room temperature by dropwise addition in a period of ca. 1 h to a suspension of 40 mmol of $NaBH_3(OAc)$ (2 equiv), which was pre-prepared by addition of 2.40 g of CH_3COOH (40 mmol) to a suspension of 1.51 g of $NaBH_4$ (40 mmol) in 40 mL of THF. Then the mixture was stirred for another 2 h to complete the reduction. After the reduction completed, the reaction was carefully quenched by slowly adding 0.1 N NaOH (20 mL) until no gas emission. The resulting mixture was extracted with CH_2Cl_2 (50 mL×3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered off, and the solvent was removed under reduced pressure. The residual was purified by flash column chromatography on basic Al_2O_3 (petroleum ether/ethyl acetate) to afford the desired mono-*N*-methyl anilines.

3.3.1. N-Methyl aniline. Yield 93%, colorless oil. GC–MS (EI): *m*/*z* 107 [M^+, 100%]. ^1H NMR ($CDCl_3$) δ 2.84 (s, 3H, N–CH_3), 6.61–6.63 (m, 2H, Ar–H), 6.70–6.73 (m, 1H, Ar–H), 7.18–7.21 (m, 2H, Ar–H).

3.3.2. N-Methyl-p-toluidine. Yield 91%, colorless oil. GC–MS (EI): *m*/*z* 121 [M^+, 100%]. ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.82 (s, 3H, N–CH_3), 6.56–6.58 (m, 2H, Ar–H), 7.00–7.02 (m, 2H, Ar–H).

3.3.3. N-Methyl-o-toluidine. Yield 94%, colorless oil; GC–MS (EI): *m*/*z* 121 [M^+, 100%]. ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 2.90 (s, 3H, N–CH_3), 3.78 (br s, 1H, N–H), 6.62–6.64 (m, 1H, Ar–H), 6.66–6.69 (m, 1H, Ar–H), 7.05–7.06 (m, 1H, Ar–H), 7.14–7.17 (m, 1H, Ar–H).

3.3.4. N-Methyl-m-toluidine. Yield 91%, colorless oil; GC–MS (EI): *m*/*z* 121 [M^+, 74%], 120 (100). ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.83 (s, 3H, N–CH_3), 6.45–6.47 (m, 2H, Ar–H), 6.55–6.56 (m, 1H, Ar–H), 7.07–7.10 (m, 1H, Ar–H).

3.3.5. 4-Chloro-N-methylbenzenamine. Yield 92%, colorless oil; GC–MS (EI): *m*/*z* 141 [M^+, 93%], 143 (M+2, 31), 139 (100). ^1H NMR ($CDCl_3$)

δ 2.82 (s, 3H, N–CH_3), 6.56–6.68 (m, 2H, Ar–H), 7.13–7.16 (m, 2H, Ar–H).

3.3.6. 2-Chloro-N-methylbenzenamine. Yield 87%, colorless oil; GC–MS (EI): *m/z* 141 [M^+, 78%], 143 (M+2, 26), 139 (100). ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3H, N–CH_3), 4.41 (br s, 1H, N–H), 6.62–6.66 (m, 2H, Ar–H), 7.15–7.18 (m, 1H, Ar–H), 7.24–7.26 (m, 1H, Ar–H).

3.3.7. 3-Chloro-N-methylbenzenamine. Yield 94%, colorless oil; GC–MS (EI): *m/z* 141 [M^+, 92%], 143 (M+2, 29), 139 (100). ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H, N–CH_3), 3.94 (br s, 1H, N–H), 6.47–6.49 (m, 1H, Ar–H), 6.58–6.59 (m, 1H, Ar–H), 6.66–6.68 (m, 1H, Ar–H), 7.06–7.09 (m, 1H, Ar–H).

3.3.8. 4-Methoxy-N-methylbenzenamine. Yield 83%, yellowish oil; GC–MS (EI): *m/z* 137 [M^+, 54%], 122 (100). ^{1}H NMR ($CDCl_3$) δ 2.81 (s, 3H, N–CH_3), 3.75 (s, 3H, O–CH_3), 6.61–6.63 (m, 2H, Ar–H), 6.80–6.81 (m, 2H, Ar–H).

3.3.9. 4-Fluoro-N-methylbenzenamine. Yield 87%, colorless oil; GC–MS (EI): *m/z* 125 [M^+, 89%], 124 (100). ^{1}H NMR ($CDCl_3$) δ 2.81 (s, 3H, N–CH_3), 3.66 (br s, 1H, N–H), 6.54–6.57 (m, 2H, Ar–H), 6.88–6.92 (m, 2H, Ar–H).

3.3.10. N-Methyl-4-(trifluoromethyl)benzenamine. Yield 93%, colorless oil; GC–MS (EI): *m/z* 175 [M^+, 70%], 174 (100). ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3H, N–CH_3), 4.36 (br s, 1H, N–H), 6.12–6.63 (m, 2H, Ar–H), 7.41–7.43 (m, 2H, Ar–H).

3.3.11. Ethyl 4-(methylamino)benzoate. Yield 86%, white solid, mp 63–65 °C (lit.[14] mp 65–67 °C); GC–MS (EI): *m/z* 179 [M^+, 70%], 134 (100). ^{1}H NMR ($CDCl_3$) δ 1.37 (t, *J*=7.0 Hz, 3H, –CH_2CH_3), 2.88 (s, 3H, N–CH_3), 4.19 (br s, 1H, N–H), 4.32 (q, *J*=7.0 Hz, 2H, –CH_2CH_3), 6.54–6.56 (m, 2H, Ar–H), 7.87–7.90 (m, 2H, Ar–H).

3.3.12. 4-(Methylamino)benzonitrile. Yield 93%, white solid, mp 90–92 °C (lit.[13j] mp 86 °C); GC–MS (EI): *m/z* 132 [M^+, 76%], 131 (100). ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H, N–CH_3), 4.46 (br s, 1H, N–H), 6.56–6.58 (m, 2H, Ar–H), 7.43–7.45 (m, 2H, Ar–H).

3.3.13. N-Methyl-4-nitrobenzenamine. Yield 76%, yellow solid, mp 150–152 °C (lit.[13b] mp 149–151 °C); GC–MS (EI): *m/z* 152 [M^+, 100%]. ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3H, N–CH_3), 6.60–6.61 (m, 2H, Ar–H), 7.30 (br s, 1H, N–H), 8.00–8.02 (m, 2H, Ar–H).

3.4. Procedure for recovering the catalyst MCM-41-SO_3H

After the reaction of aniline and triethyl orthoformate was complete, the reaction mixture was cooled to room temperature. The catalyst was filtered off and successively washed with THF (5 mL×3) and ethanol (5 mL×3), then dried at 100 °C for 2 h. The recovered MCM-41-SO_3H catalyst was then reused directly in the next reaction.

Acknowledgements

The authors gratefully acknowledge the financial support of the National Natural Science Foundation of China (No. 20772111) and the Natural Science Foundation of Zhejiang Province (Y407193).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.06.091.

References and notes

1. (a) Kirk, R. E.; Othmer, D. F.; *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley-Interscience: New York, NY, 1978; Vol. 2, pp 309–321; (b) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.
2. (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, NY, 2001, pp 499–501; (b) Verma, M.; Singh, K. N.; Clercq, E. D. *Heterocycles* **2006**, *68*, 11–22; (c) Li, X.; Mintz, E. A.; Bu, X. R.; Zehnder, O.; Bosshard, C.; Gunter, P. *Tetrahedron* **2000**, *56*, 5785–5791; (d) Willson, F. G.; Wheeler, T. S. *Organic Syntheses*; John Wiley & Sons: New York, NY, 1941; Collect. Vol. 1; p 102.
3. (a) Onaka, M.; Ishikawa, K.; Izumi, Y. *Chem. Lett.* **1982**, *11*, 1783–1786; (b) Onaka, M.; Umezono, A.; Kawai, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1202–1203.
4. For selected literature, see: (a) Niphadkar, P. S.; Joshi, P. N.; Gurav, H. R.; Deshpande, S. S.; Bokade, V. V. *Catal. Lett.* **2009**, *133*, 175–184; (b) Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, *48*, 3367–3370; (c) Ebenezer, W. J.; Hutchings, M. G.; Jones, K.; Lamberta, D. A.; Watt, I. *Tetrahedron Lett.* **2007**, *48*, 1641–1643; (d) Vijayaraj, M.; Gopinath, C. S. *Appl. Catal. A: General* **2007**, *320*, 64–68; (e) Nishamol, K.; Rahna, K. S.; Sugunan, S. *J. Mol. Catal. A: Chem.* **2004**, *209*, 89–96; (f) Nagaraju, N.; Kuriakose, G. *New J. Chem.* **2003**, *27*, 765–768; (g) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687–2690; (h) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677–680; (i) Sreekumar, K.; Mathew, T.; Mirajkar, S. P.; Sugunan, S.; Rao, B. S. *Appl. Catal. A: General* **2000**, *201*, L1–L8.
5. (a) Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. *J. Org. Chem.* **2007**, *72*, 9815–9817; (b) Reddy, P. S.; Kanjilal, S.; Sunitha, S.; Prasad, R. B. N. *Tetrahedron Lett.* **2007**, *48*, 8807–8810; (c) Da Silva, R. A.; Estevam, I. H. S.; Bieber, L. W. *Tetrahedron Lett.* **2007**, *48*, 7680–7682; (d) Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, *48*, 1273–1276; (e) Nagaiah, K.; Kumar, V. N.; Rao, R. S.; Reddy, B. V. S.; Narsaiah, A. V.; Yadav, J. S. *Synth. Commun.* **2006**, *36*, 3345–3352; (f) Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, *61*, 5725–5734 and references cited therein.
6. (a) Padmanabhan, S.; Reddy, N. L.; Durant, G. J. *Synth. Commun.* **1997**, *27*, 691–699; (b) Roberts, R. M.; Vogt, P. J. *Organic Syntheses*; John Wiley & Sons: New York, NY, 1963; Collect. Vol. 4; p 420.
7. Barton, D. H. R.; Ozbalik, N.; Ramesh, M. *Tetrahedron Lett.* **1988**, *29*, 857–860.
8. Takebayashi, Y.; Morita, Y.; Sakai, H.; Abe, M.; Yoda, S.; Furuya, T.; Sugeta, T.; Otake, K. *Chem. Commun.* **2005**, 3965–3967.
9. Yebeutchou, R. M.; Dalcanale, E. *J. Am. Chem. Soc.* **2009**, *131*, 2452–2453.
10. Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N.; Khalili, D. *Tetrahedron* **2009**, *65*, 3893–3899.
11. Gonzalez, I.; Mosquera, J.; Guerrero, C.; Rodriguez, R.; Cruces, J. *Org. Lett.* **2009**, *11*, 1677–1680.
12. Chiappe, C.; Piccioli, P.; Pieraccini, D. *Green Chem.* **2006**, *8*, 277–281.
13. For examples of protection and deprotection with sulfonyl groups (tosyl, nosyl), see: (a) Cardullo, F.; Donati, D.; Fusillo, V.; Merlo, G.; Paio, A.; Salaris, M.; Solinas, A.; Taddei, M. *J. Comb. Chem.* **2006**, *8*, 834–840; (b) Pera, A. L.; Leggio, A.; Liguori, A. *Tetrahedron* **2006**, *62*, 6100–6106; (c) Li, B. F.; Yuan, K.; Dai, L. X.; Hou, X. L. *Synlett* **2005**, 535–537; (d) Sabitha, G.; Reddy, B. V. S.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569–1570; For examples of protection and deprotection with alkoxycarbonyl groups (Boc, CBz), see: (e) Suarez-Castillo, O. R.; Montiel-Ortega, L. A.; Melendez-Rodriguez, M.; Sanchez-Zavala, M. *Tetrahedron Lett.* **2007**, *48*, 17–20; (f) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319–9324; (g) Strazzolini, P.; Misuri, N.; Polese, P. *Tetrahedron Lett.* **2005**, *46*, 2075–2078; For examples of protection and deprotection with acyl groups, see: (h) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2006**, *2*, 309–314; (i) Luh, T.-Y.; Fung, S. H. *Synth. Commun.* **1979**, *9*, 757–763; (j) Kakimoto, S.; Tone, I. *J. Med. Chem.* **1965**, *8*, 867–868; For examples of protection and deprotection with formyl group, see: (k) Ge, Y.; Hu, L. *Tetrahedron Lett.* **2007**, *48*, 4585–4588; (l) Blankenship, C.; Cremer, S. E. *J. Organomet. Chem.* **1989**, *371*, 19–30.
14. Sekiya, M.; Ito, K. *Chem. Pharm. Bull.* **1966**, *14*, 1007–1009.
15. (a) Kadin, S. B. *J. Org. Chem.* **1973**, *38*, 1348–1350; (b) Sekiya, M.; Ito, K. *Chem. Pharm. Bull.* **1967**, *15*, 1339–1342.
16. (a) Barluenga, J.; Bayon, A. M.; Campos, P.; Asensio, G.; Gonzalez-Nunez, E.; Molina, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1631–1636; (b) Barluenga, J.; Baybn, A. M.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1109–1110.
17. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805–809.
18. Katritzky, A. R.; Drewniak, M.; Aurrecoechea, J. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2539–2541.
19. Ha, H.-J.; Ahn, Y.-G. *Synth. Commun.* **1997**, *27*, 1543–1546.
20. Crochet, R. A., Jr.; Blanton, C. D., Jr. *Synthesis* **1974**, 55–56.
21. Zhang, J.; Chang, H.-M.; Kane, R. R. *Synlett* **2001**, 643–645.
22. (a) Zakyzewska, A.; Kolehmainen, E.; Osmialowski, B.; Gawinecki, R. *J. Fluorine Chem.* **2001**, *111*, 1–10; (b) Coppola, G. M.; Schuster, H. F. *J. Heterocycl. Chem.* **1989**, *26*, 957–964; (c) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315–3318.
23. Blackburn, C.; LaMarche, M. J.; Brown, J.; Che, J. L.; Cullis, C. A.; Lai, S.; Maguire, M.; Marsilje, T.; Geddes, B.; Govek, E.; Kadambi, V.; Doherty, C.; Dayton, B.; Brodjian, S.; Marsh, K. C.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2621–2627.
24. The preparation of *N*-methyl aniline via ethyl *N*-phenylformimidate starting from unsubstituted aniline was not described in Blanton and co-workers' research in the Ref. 20.
25. The reaction between aniline and triethyl orthoformate under the catalysis of acids have been investigated by Roberts and co-workers, and the preparation version of ethyl *N*-phenylformimdate have been reported in*Organic Syntheses*; John Wiley & Sons: New York, NY, 1963; Collect. Vol. 4; p 464; See also: (a) Roberts, R. M. *J. Am. Chem. Soc.* **1949**, *71*, 3848–3849; (b) Roberts, R. M. *J. Am.*

Chem. Soc. **1950**, *72*, 3603–3608; (c) Roberts, R. M.; DeWolfe, R. H.; Ross, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 2277–2281; (d) DeWolfe, R. H.; Roberts, R. M. *J. Am. Chem. Soc.* **1953**, *75*, 2942–2947; (e) Roberts, R. M.; DeWolfe, R. H. *J. Am. Chem. Soc.* **1954**, *76*, 2411–2414; (f) DeWolfe, R. H.; Roberts, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 4379–4381; (g) Roberts, R. M.; Higgins, H., Jr.; Noyes, P. *J. Am. Chem. Soc.* **1955**, *77*, 3801–3805; (h) Roberts, R. M.; Vogt, P. J. *J. Am. Chem. Soc.* **1956**, *78*, 4778–4782; (i) Roberts, R. M.; Hussein, F. A. *J. Am. Chem. Soc.* **1959**, *82*, 1950–1953; (j) DeWolfe, R. H. *J. Org. Chem.* **1962**, *26*, 490–493.

26. (a) Okuhara, T. *Chem. Rev.* **2002**, *102*, 3641–3666; (b) Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791–797.
27. MCM-41-SO_3H was prepared from MCM-41 according to the references: (a) Bossaert, W. D.; De Vos, D. E.; Van Rhijn, W. M.; Bullen, J.; Grobet, P. J.; Jacobs, P. A. *J. Catal.* **1999**, *182*, 156–164; (b) Das, D.; Lee, J.-F.; Cheng, S. *J. Catal.* **2004**, *223*, 152–160.
28. The results of proton NMR and GC showed that only ethyl *N*-phenylformimidate and excess triethyl orthoformate were detected in the reaction mixture.
29. Initially we tried to purify ethyl *N*-phenylformimidate intermediate by flash column chromatography, but it was found that ethyl *N*-phenylformimidate was partially decomposed to form *N*-phenylformamide. We then scaled up the reaction to 0.2 mol scale, and then purified ethyl *N*-phenylformimidate via vacuum distillation and used for further research.
30. For reviews, see: (a) Burkhardt, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617–2650; (b) Gribble, G. W. *Org. Process Res. Dev.* **2006**, *10*, 1062–1075; (c) De Souza, M. V. N.; Vasconcelos, T. R. A. *Appl. Organomet. Chem.* **2006**, *20*, 798–810; (d) Periasamy, M.; Thirumalaikumar, M. *J. Organomet. Chem.* **2000**, *609*, 137–151.
31. The results of proton NMR and GC showed that there was still some triethyl orthoformate remaining in the residual.
32. Carbonyl group was partially reduced by $NaBH_3(OAc)$, and the ratio of reduction was not repeated between batches.
33. With triethyl orthopropionate or triethyl orthobenzoate as the alkylation reagent, the anilines could quantitatively convert into their corresponding imidate intermediates using MCM-41-SO_3H as catalyst. However, the second reduction should performed with $NaBH_3(OCOCF_3)$. The isolated yields are ranged from 85 to 95%.