Journal of Physical Organic Chemistry

Received: 17 July 2015, Revised: 8 October 2015, Accepted: 24 November 2015,

(wileyonlinelibrary.com) DOI: 10.1002/poc.3529

An experimental and theoretical study on the preparation of 4,4′-methylene-bis (*N,N*-dimethylaniline) in ionic liquid

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The reaction of *N,N*-dimethylaniline with tetrachloromethane in ionic liquid was found to give 4,4′-methylene-bis (*N,N*-dimethylaniline) in considerable yield. The ionic liquid was prepared from *N,N*-dimethylaniline which is also the one of raw materials for the preparation of 4,4′-methylene-bis (*N,N*-dimethylaniline), and acts as both solvent and catalyst in the reaction. Mild reaction conditions, enhanced rates, improved yields, and reagents' reactivity which is different from that in conventional organic solvents are the remarkable features observed in ionic liquids. In addition, the results of calculations are in good accordance with the experimental outcomes. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: 4,4′-methylene-bis (*N,N*-dimethylaniline); Gaussian 98; ionic liquid; PCM; solvent effects

INTRODUCTION

4,4′-Methylene-bis (*N,N*-dimethylaniline) (Michler's base) is promising key intermediate because of its easy transformation to many chemicals such as fine-chemicals, pharmaceuticals, and polymers.[1] The preparation method of Michler's base has been documented in previous papers.[1–6] Thus, this preparation method is of much interest and a variety of reaction conditions which have been developed. Many of these conditions are inevitably associated with certain disadvantages, including the complicated operation, excessive acid catalysts consumption, and a large number of by-products,[2–6] which have become the barriers and restrict the application in industry.

Recently, Yoshio Matsubara *et al.* found a convenient method for synthesis 4,4′-methylene-bis (*N,N*-dimethylaniline) with good yields (84%) by the reaction of *N,N*-dimethylaniline with tetrabromomethane in acetonitrile.[3] Accordingly, the disadvantages mentioned above can be avoided and the product acquired. However, when tetrachloromethane was used in the reaction instead of tetrabromomethane, the yield of product was only 8%. And when *N,N*-dimethyl-aniline reacted with tetrahalomethane such as tetrabromomethane and tetrachloromethane in dichloromethane or in solvent-free, no product could be detected. The experimental results indicated that solvents play an important role in the reaction. Tetrachloromethane solvent toxicity is a large and serious pollution, so it is of significance to develop a preparation method of Michler's base with tetrachloromethane as the one of raw materials, which is helpful to reduce the pollution of tetrachloromethane on environment and make waste profitable.

Ionic liquids (ILs) as a kind of very attractive and green solvent have been widely used in synthesis and separations owing to their low vapor pressure and high stability in a wide temperature range.[7,8] Examples of their application in both reactions[9] and separations[10] have been demonstrated. Recently ILs are attracting more attention because they could be used as efficient catalyst for showing significant role in controlling the reaction.[11] A variety of ILs are successfully applied in many types of reactions such as Friedel–Crafts acylations[12] and alkylations.[13]

In our previous work, an effective and green preparation method of Michler's base that ILs as both solvent and catalyst for the reaction along with *N,N*-dimethylaniline and tetrachloromethane as raw materials was established for the first time (Fig. 1).[14] As part of the ongoing studies, further investigation on the effect of temperature and solvent on the reaction, and the reaction mechanism was carried out. Furthermore, study on the experimental results with calculations by the Gaussian 98 suite of program was developed.

EXPERIMENTAL

Instrumental analysis and measurements

Melting points were determined on digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a BRUKER-500 MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. GC-MS spectra were recorded on HP6890 Gas Chromatograph with a HP5973 Mass Spectrometric Detector.

General experimental procedure for the preparation of Michler's base

To 0.26 mol of *N,N*-dimethylaniline, hydrogen chloride gas was introduced. The reaction mixture was stirred at 0 °C and the

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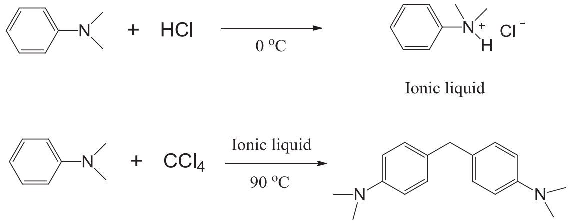


Figure 1. The preparation method of Michler's base

white solid quickly generated. This white solid is the IL which would be used in the second step reaction.

All the three-necked flasks were loaded with *N,N*-dimethylaniline (0.26 mol), tetrachloromethane (0.26 mol), and IL (0.26 mol) which was achieved in the first step reaction. The reaction mixture was stirred at 90 °C for an appropriate time. The reactions were monitored by thin layer chromatography (TLC, ethyl acetate/petroleum ether = 2:8). After the reaction, the mixture was cooled to room temperature, neutralized with sodium hydroxide and extracted with methylene chloride (3 × 20 mL). The organic phase was dried with sodium sulfate, filtered, and evaporated to dryness *in vacuo* to give the crude product. The pure product was obtained by column chromatography (ethyl acetate/petroleum ether = 1:10) on silica gel of the crude product. All the products are properly characterized by their ^{1}H NMR and GC-MS. Furthermore, the reaction conducted in H_2O, CH_3CH_2OH, CH_2Cl_2, and CCl_4 respectively, was compared with that in the IL.

Table 1. The reaction of *N,N*-dimethylaniline with tetrachloromethane in ionic liquid

Entry	A: B: C[a]	Time (h)	Temperature (°C)	Yield (%)
1	1:1:0	48	90	0
2	1:1:1	24	35	10
3	1:1:1	24	60	17
4	1:1:1	24	80	32
5	1:1:1	24	90	40
6	1:1:1	24	100	38
7	1:1:1	32	90	47
8	1:1:1	35	90	47
9	1:2:1	24	90	50
10	1:2:1	32	90	61
11	1:2:1	35	90	61
12	1:4:1	24	90	20
13	1:4:1	32	90	26

[a] A is *N,N*-dimethylaniline, B is tetrachloromethane, C is the IL.

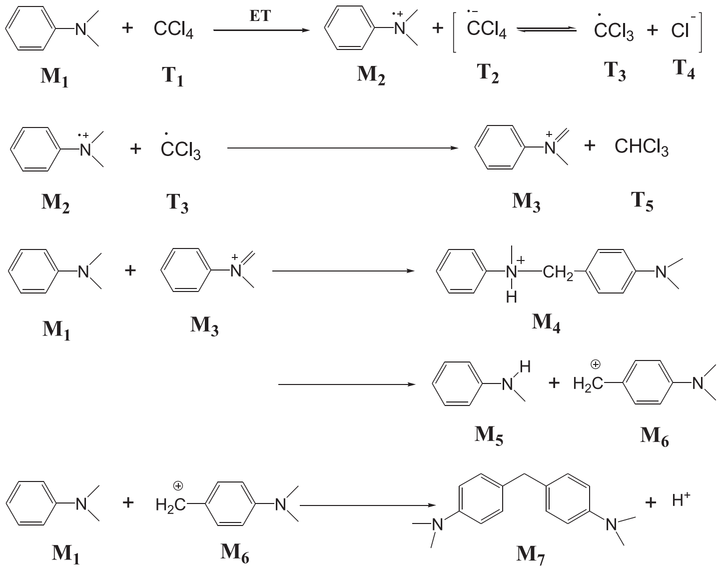
4,4′-Methylene-bis(N,N-dimethylaniline): Mp 89.0–91.0 C. ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 3.4 (s, 12H), 3.7 (s, 2H), 6.4–6.8 (m, 8H). GC-MS (m/z): 254 (M^+), 237, 210, 165, 134, 91.

CALCULATION METHODS

All calculations were performed with the GAUSSIAN 98 program package.[15] The geometries of all the stationary points were fully optimized at the B3LYP/6-31 + G*[16] level of theory. The B3LYP functional is composed of Becke's three-parameter hybrid exchange functional (B3),[17,18] as implemented in GAUSSIAN 98,[19] and the correlation functional of Lee, Yang, and Parr (LYP).[20] The solvation energies for products and intermediates were computed using solvation model PCM with the permittivities of 78.39, 24.55, 8.93, and 2.228, for H_2O, CH_3CH_2OH, CH_2Cl_2, and CCl_4, respectively.

RESULTS AND DISCUSSION

The desirable results of experiments made it certain that the reaction in ILs is substantially faster than the corresponding reaction in traditional organic solvents. The reaction of *N,N*-dimethylaniline with tetrachloromethane was initially tested at 35 °C for 24 h in the presence of IL; the yield of product was only 10% when the molar ratio of *N,N*-dimethylaniline, tetrachloromethane and IL is 1:1:1 (Table 1, Entry 2). The yield of product would increase with the reaction time extending or the amount of tetrachloromethane increasing. The subsequent condition optimization experiments revealed that the yield of product

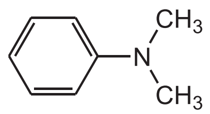
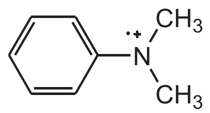
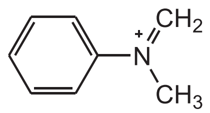
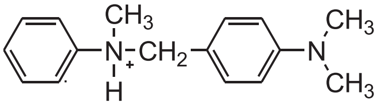
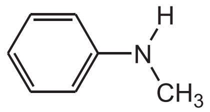
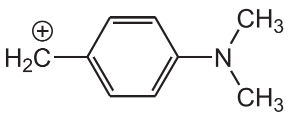
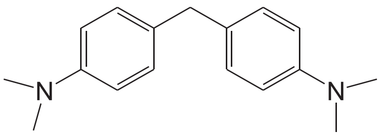


Scheme 1. The mechanism of the reaction

could reach 61% when the reaction was carried out at 90 °C for 32 h in IL with the molar ratio of *N,N*-dimethylaniline, tetrachloromethane and IL of 1:2:1 (Table 1, Entry 10). The yield of product would decrease when the amount of tetrachloromethane continued to increase (Table 1, Entry 13). In addition, the IL in the reaction was prepared from *N,N*-dimethylaniline which is also one of the raw materials for the preparation of Michler's base, so the use of IL not only will not give rise to by-products to pollute reaction, but also will increase the amount of *N,N*-dimethylaniline to enhance the reaction rate. Some blank experiments were also carried out to demonstrate the catalysis of the IL. As shown in Table 1, when the reaction was performed without the IL, the yield was 0% after 2 days (**Entry 1**).

The mechanism of the reaction, as depicted in Scheme 1, is widely accepted. It is the electron transfer (ET) mechanism proposed by Yoshio Matsubara *et al.*.[3] Many kinds of intermediates which possess partial charges generate in the mechanism. The ET is one of the most important elementary processes in the

Table 2. The calculated energies (Hatree) of the reactants, intermediates, and products *in vacuo* and in four distinct solvents

		Vacuo	H_2O	CH_3CH_2OH	CH_2Cl_2	CCl_4
1		−366.228829	−366.2369073	−366.2364248	−366.2384564	−366.2312070
2	CCl_4	−1878.8598643	−1878.8547223	−1878.856341	−1878.8604801	−1878.8565105
3		−365.9720014	−366.0473541	−366.045482	−366.0365442	−366.0082192
4	CCl_3	−1418.6284291	−1418.6241456	−1418.6254564	−1418.6289487	−1418.6255791
5	Cl^-	−460.2747259	−460.395153	−460.3917252	−460.3727993	−460.3346964
6	**$\Delta H_f(5+4+3-2-1)$**	0.2135369	0.0249769	0.0301022	0.0606443	0.1192228
7		−365.3724368	−365.4516294	−365.4497357	−365.4386548	−365.4094156
8	$CHCl_3$	−1419.2843136	−1419.284705	−1419.2856733	−1419.2872764	−1419.2828159
9	**$\Delta H_f(7+8-3-4)$**	−0.0563199	−0.0648347	−0.0644706	−0.0604383	−0.0584332
10		−731.6440958	−731.7201289	−731.7141766	−731.7078572	−731.6810177
11		−326.9236611	−326.9322369	−326.931906	−326.9327772	−326.9258403
12		−404.6890112	−404.7566695	−404.7555317	−404.7486014	−404.7214129
13	**$\Delta H_f(12+11-7-1)$**	−0.0114065	−0.0003697	−0.0012772	−0.0042674	−0.0066306
14		−770.5726074	−770.5845599	−770.5844952	−770.5877638	−770.5741629
15	H^+	0	0	0	0	0
16	**$\Delta H_f(15+14-1-12)$**	−0.3452328	−0.4090169	−0.4074613	−0.399294	−0.378457
17	**$\Delta H_f(15+14+11+5+8-3\times1-2)$**	0.4910433	0.3687894	0.3718157	0.3891378	0.432616

chemical and biochemical reactions.[21] Although many reactions via CT complexes as the ET process have been reported,[22] to our knowledge, useful ones as the synthetic reactions are very few. Very recently, Yoshio Matsubara *et al.* reported a versatile, single-step synthesis of cyanocinnolines from aromatic hydrazones (p-donor) and TCNE (p-acceptor) via radical ion pair dyad.[23] Selective radical bromination of adamantane using OH– (s-donor)/CBr4 (s-acceptor) is also reported.[24] In the reaction, it is considered that Michler's base is produced using *N*,*N*-dimethylaniline (p-donor) and tetrabromomethane (s-acceptor) (Scheme 1).

According the reaction mechanism (Scheme 1), the total energies and solvation energies of reactants, intermediates and products in four distinct solvents are collected respectively in Tables 2 and 3. In Table 2, entries 6, 9, 13, and 16 present ΔH_{298} of the four steps in the reaction, respectively. Entries 17 present ΔH_{298} of the whole reaction. Because ILs are formed from cations and anions, it is difficult to conduct calculation with the Gaussian 98 suite of program on the interaction of ILs with chemical compounds. Therefore, the theoretical explains for ILs' effect on the reactions can only be done basing on the tendency obtained from the calculation for some selected solvents other than shown directly with calculations.

As shown in Table 2, the first step of the reaction is endothermic, as the reaction is endothermic as, but other step of the reaction is exothermic. It indicates that the first step of the reaction is the rate-limiting step. In stronger polar H_2O solvent, the free energy of reaction (ΔG_{298}) of the reaction is lower than that *in vacuo* and in other solvents (**Entry 17**). It indicates that

Table 3. The solvation energies(kcal/mol) of the reactants, intermediates and products in four distinct solvents

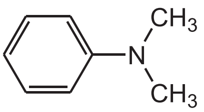
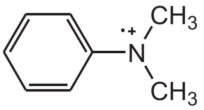
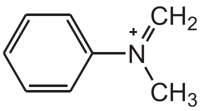
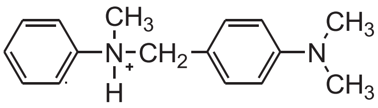
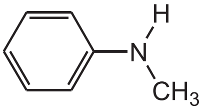
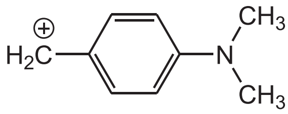
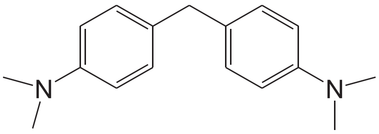
		H_2O	CH_3CH_2OH	CH_2Cl_2	CCl_4
1		−6.14	−5.73	−2.19	−1.01
2	CCl_4	−0.50	−0.47	−0.18	−0.09
3		−49.14	−47.59	−37.47	−22.98
4	CCl_3	−0.34	−0.32	−0.10	−0.05
5	Cl^-	−77.06	−74.85	−61.03	−37.80
6		−52.69	−50.94	−39.20	−23.85
7	$CHCl_3$	−3.47	−3.24	−1.38	−0.61
8		−50.61	−46.04	−41.55	−23.49
9		−6.83	−6.40	−2.61	−1.20
10		−45.25	−43.85	−34.98	−21.48
11		−12.31	−11.57	−4.29	−1.87

Table 4. The preparation of Michler's base in five solvents at 90 °C

Entry	Solvent	Time (h)	Yield (%)
1	IL	24	40
2	IL	32	47
3	H_2O	24	17
4	H_2O	32	22
5	CH_3CH_2OH	24	5
6	CH_3CH_2OH	32	11
7	CH_2Cl_2	32	0
8	CCl_4	32	0

[a] The reactions were carried out with the molar ratio of *N,N*-dimethylaniline, tetrachloromethane, and solvent of 1:1:1.

the reaction proceeds more easily in stronger polar solvents. The calculations present that the reaction is endothermic, which indicates a higher temperature can promote the reaction, but the temperature should not exceed a certain range (Table 1). It must be noted that the value of free energy (ΔG_{298}) is approximately represented by the value of enthalpy (ΔH_{298}) for explaining the reaction equation, because the term of TS is commonly little, which determines the value of enthalpy (ΔH_{298}) is close to the value of free energy (ΔG_{298}).

As shown in Table 3, the solvation energy (negative value) decreases with the increasing polarity of the solvent. This clearly indicates that reactants, intermediates, and products become more stable when polarity of solvent increases. Thus, the reactants, intermediates, and products in ILs are more stable compared with those in other organic solvents. This can be rationalized that the polarity of IL is the highest among all solvents considered and ILs are formed from large organic cations and inorganic anions, which can promote the stability of intermediates which possess partial charges. Solvents play a crucial role in the reaction by stabilizing ionic charges and providing an alternative lower energy pathway by which the reaction may proceed. Hence, The reaction of *N,N*-dimethylaniline with tetrachloromethane in ILs can be definitely promoted. Furthermore, calculated results were verified by experiments on solvent effect (Table 4).

CONCLUSION

In summary, the ILs have been proved to be an effective catalyst and solvent for the preparation of Michler's base. In the presence of IL, tetrachloromethane can be used as the one of the raw materials for the preparation of Michler's base. The present method has many obvious advantages compared to previous methods, such as environmentally more benign, the ease of product isolation, the simplicity of methodology, the high yield, the generality, and the convenience of preparing the ILs using *N,N*-dimethylaniline which is also one of the raw materials for the preparation of Michler's base. Moreover, enhanced rate resulting from IL-based activation was speculated and proved by calculations with the Gaussian 98 suite of program, as well as reagents' reactivity which is different from that in traditional organic solvents. Further studies aiming at exploring the scope of organocatalytic reactions in ILs are in progress.

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