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Mild synthesis of *N*′-aryl-*N*,*N*-dimethylformamidinium chloride by Vilsmeier–Haack reagent

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Abstract

Formamidine derivatives could be used as the building blocks for substituted heterocyclic compounds with various biological activities. *N*′-Aryl-*N*,*N*-dimethylformamidinium chlorides have been synthesized in high yields by reaction of aromatic primary amines with Vilsmeier–Haack reagent at room temperature. The structures of all the new compounds were identified by ESI-MS, IR and NMR spectra. The steric structures of some of these compounds were clarified by X-ray single crystal analysis.

Keywords: Vilsmeier–Haack reagent; Formamidinium; X-ray single crystal

Vilsmeier–Haack reaction is a very useful method of synthesizing aromatic aldehydes [1]. In an effort to synthesize 4-methyl-5-formyl-1,3-thiazole (**2**), an intermediate for the preparation of cephalosporins used for treating bacteria infections, we found that no formylation reaction happened upon treatment of 4-methyl-1,3-thiazole (**1**) with Vilsmeier–Haack reagent. Considering that the higher π-electron density of thiazole ring may facilitate the Vilsmeier–Haack reaction, 2-amino-4-methyl-1,3-thiazole (**3**) was therefore chosen as an alternative starting material. Much to our surprise, a solid product was obtained and identified to be *N*′-(4-methylthiazol-2-yl)-*N*,*N*-dimethyl-formamidinium hydroxide salt (**4a**), instead of the expected formylation products **5** or **6** (Scheme 1).

N′-Aryl-*N*,*N*-dimethylformamidine has been widely used in the synthesis of heterocycles such as benzoimidazole [2], quinoline [3] and indole [4]. In recent years, the total synthesis of various quinazolines [5], as inhibitors of tyrosine kinase, has been a focus for medicinal chemists. Synthesis of *N*′-aryl-*N*,*N*-dimethylformamidine was the key step of heterocycle formation. The common method of the synthesis was through the condensation of aromatic amines and *N*,*N*-dimethylformamide dimethylacetal at relative high temperature. Therefore, development of a mild synthetic strategy is very important and will have broad application in the synthesis of heterocyclic compounds [6].

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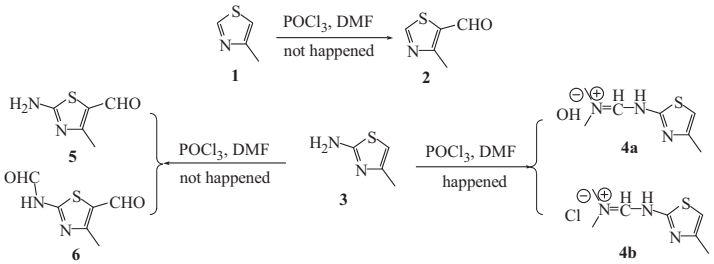


Scheme 1. Identified reactions of VH reagent.

1. Results and discussion

Upon further investigation of this reaction, we found that a white solid product precipitated from the solution gradually when the reaction was carried out at room temperature. After filtration and washing with solvents, the solid was characterized as *N*′-(4-methylthiazol-2-yl)-*N*,*N*-dimethylformamidinium chloride (**4b**). The ^{1}H NMR spectra of **4a** and **4b** were almost the same except some slightly differences in chemical shift values. However, their melting points were greatly different (Table 1). The structure was also confirmed by ESI-MS and IR spectra analyses.

Since few practical syntheses of *N*′-aryl-*N*,*N*-dimethylformamidinium have been reported so far [7], we decided to further investigate the versatility of such transformation. As shown in Table 2, a series of aromatic primary amines **7** were tested with this protocol. In all situations, solid products precipitated gradually from the solution after starting the materials were mixed at room temperature. All products were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ESI-MS and IR spectra, respectively, which revealed the formation of formamidinium salts (**8**). From ^{31}P NMR spectra of **8**, no phosphorus peak was observed. Qualitative analysis by silver nitrate demonstrated chloride is the counterpart anion. As shown in Table 2, most aromatic primary amines were compatible with this reaction protocol and the pure formamidinium products were obtained in over 50% yield upon simple reaction and filtration.

Furthermore, single crystals of *N*′-(2-methylphenyl)-*N*,*N*-dimethylformamidinium chloride **8b** and *N*′-(4-hydroxy carbonylphenyl)-*N*, *N*-dimethylformamidinium chloride **8p** were prepared. The X-ray analysis results were shown in Fig. 1 [8]. As expected, the two carbon atoms and nitrogen atom of dimethyl amino group were in one plane. The double bond existed between the groups of –N(CH$_3$)$_2$ and –CH, but the bond was very weak. Distinct hydrogen bonds existed between chloride anion and hydrogen on NH of anilines. In the crystal structure of **8p**, two water molecules were observed and formed other two hydrogen bonds with chloride anion.

2. Experimental

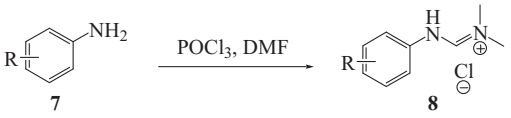
Melting points were taken on a WRS-1 digital melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in CDCl$_3$ on a JEOL JNM-ECA300 spectrometer operating at 300 and 75 MHz,

Table 1
Contrast of ^{1}H NMR and ^{13}C NMR data of **4a** and **4b.**

	4a[a] δ (ppm)		**4b**[b] δ (ppm)	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
N═CH-*N*	8.17	155.1	9.24	159.4
N-Me-1	3.05	34.6	3.09	41.9
N-Me-2	3.09	40.4	3.27	35.6
4-Me	2.30	17.4	2.37	14.2
5-H	6.33		6.30	
2-C		173.9		175.4
4-C		149.0		139.5
5-C		106.4		105.3

[a] mp 62–64 °C.
[b] mp 198–199 °C.

Table 2
Condensation between aromatic amine and VH reagent.



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7	8	mp (°C)	Yield[a] (%)
Aniline	**8a**	255–260	83.8
2-Methylanaline	**8b**	237–240	52.0
3-Methylanaline	**8c**	233–235	73.9
4-Methylanaline	**8d**	250–255	83.6
2,6-Dimethylaniline	**8e**	218–220	26.7
2-Fluroaniline	**8f**	248–252	36.5
3-Fluroaniline	**8g**	190–192	24.9
4-Fluroaniline	**8h**	247–249	45.6
2,4-Difluroaniline	**8i**	270–275	58.4
2,5-Difluroaniline	**8j**	225–227	58.4
2-Chloroaniline	**8k**	226–228	38.5
3-Chloroaniline	**8l**	225–228	65.4
4-Chloroaniline	**8m**	248–252	75.0
2-Aminobenzoic acid	**8n**	165–168	35.3
3-Aminobenzoic acid	**8o**	230–233	60.8
4-Aminobenzoic acid	**8p**	240 dec	100
4-Aminophenol	**8q**	198–202	100
4-Aminosulfonic acid	**8r**	275–280	91.4

[a] Isolated yield.

respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as an internal standard, and coupling constants (J) are given in hertz (Hz). IR spectra were recorded on Nicolet AVATAR 360 FT-IR E.S.P. All reagents were purchased and used without further purification.

2.1. General protocol for the synthesis of **8**

A normal Vilsmeier–Haack reagent (15.6 mL) was cooled down with an ice-water bath, to this yellow solution was added a solution of primary aromatic amine (2.4–4.5 g, 26 mmol) in DMF (15 mL). Since the reaction was exothermic, the reaction mixture was cooled with an ice-bath to keep bellow room temperature (r.t.). After addition, the solution was allowed to warm up and was kept stirring at r.t. until the product fully precipitated. The product was collected by filtration and washed with DMF, acetone, Et_2O respectively. Evaporation of the solvent

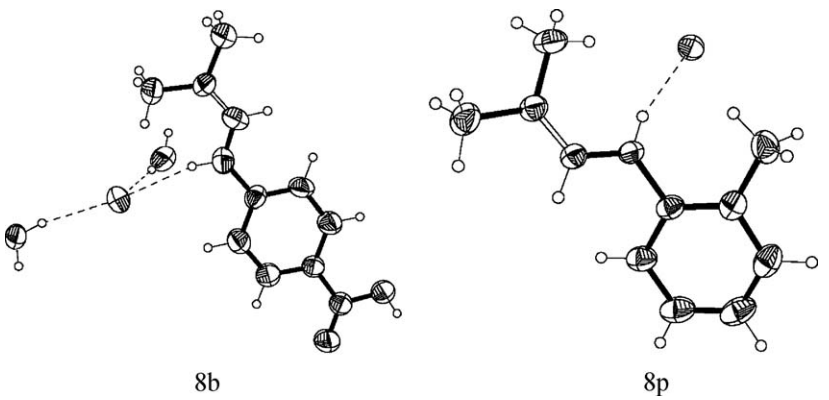

Fig. 1. ORTEP view of crystal structures of **8b** and **8p** with 35% probability ellipsoids.

under *vacuo* could provide another part of product as white or slightly yellow powder. IR (cm^{-1}) 3009 (m), 2854 (st, w), 1693 (s), 1595 (s), 1339 (s), ^1H NMR (300 MHz, D_2O): δ 8.26 (s, 1H, N=C*H*N), 7.39–7.19 (m, 5H, Ph*H*), 3.29 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), ^{13}C NMR (300 MHz, D_2O): δ 153.30 (1 C, N=*C*HN), 136.65 (1C, 1-Ph*C*NMe_2), 129.96 (2C, 3,5-Ph*C*), 126.85 (1C, 4-Ph*C*), 119.57 (2C, 2,6-Ph*C*), 43.60 (1C, N*C*H_3), 36.68 (1C, N*C*H_3), EI-MS (*m*/*z*), (M−Cl) 149.

3. Conclusions

Although Vilsmeier–Haack reaction has been used for the direct synthesis of foramidines, most reported methods have drawbacks such as harsh reaction conditions and difficulties in work up. Our method offers a very easy, mild and efficient way for the preparation of *N*′-aryl-*N*,*N*-dimethylformamidinium salts for the synthesis of various heterocyclic compounds, which might have various biological activities. The structures of the final products were verified by X-ray single crystal determination.

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