Solid-state synthesis of Schiff bases

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A new preparative method for the synthesis of Schiff bases by the solid-state interaction of crystalline organic and organometallic aldehydes and amines is suggested. The possibility of direct synthesis of aldimines in the solid state from amine salts without isolation of the free amines is demonstrated.

Key words: Schiff bases, aldehydes, amines, amine salts, solid state.

Reactions of carbonyl compounds with amines and their derivatives are well studied and traditionally performed in various solvents, most often in benzene on heating with azeotropic distilling off of water or in absolute alcohol. We have shown recently that crystalline organic and organometallic aldehydes and secondary β -hydroxyamines (ephedrine and pseudo-ephedrine) react in the solid state at room temperature with the regio- and stereoselective formation of oxazolidines.^{1,2} This work is devoted to studying similar solid-state reactions of aldehydes with primary amines. We established that the solid-state reactions of mixtures of crystalline aldehydes **1a**—**f** with solid amines **2** and **3** result in the formation of Schiff bases (Scheme 1).

Scheme 1

$$R-C \stackrel{0}{\underset{H}{\leftarrow}} + H_2 N-R' \longrightarrow R-CH=N-R'$$
1a-f 2, 3 4a-f
5a-f

1, 4, 5: $R = 2 - NO_2 - C_6H_4$ (a); $4 - NO_2 - C_6H_4$ (b); $4 - HO - 3 - MeO - C_6H_3$ (c); $C_5H_5FeC_5H_4$ (d); $C_5H_5RuC_5H_4$ (e); $Mn(CO)_3C_5H_4$ (f) 2, 4: $R' = C_5H_5FeC_5H_4CH_2$; 3, 5: $R' = 4 - NO_2 - C_6H_4$

Reactions of aldehydes with amines without a solvent to form aldimines are known. However, in these cases, either one of the starting components is liquid,³ or the reactions occur at temperatures higher than the melting points of the starting solid compounds, *i.e.*, in melts.⁴

In all cases, mixing and periodical stirring of aminomethylferrocene (2) with equimolar quantities of aldehydes 1a-f at room temperature result in the fast formation of an oily reaction mass, from which products

differing noticeably from the starting compounds begin to crystallize. The ¹H NMR spectra of the reaction mass were obtained 1 day after mixing the reagents and showed that, in all cases, the corresponding Schiff bases were formed in high yields of 80-95%. The complete conversion of the reagents with the quantitative formation of aldimines is achieved in 48 h.

The authors of Ref. 5 have described the preparation of imines from amine 2 and benzaldehyde derivatives by the traditional method: heating in benzene with azeotropic distilling off of water. Under these conditions, the yield of Schiff bases does not exceed 40%, and the reactions are accompanied by the formation of benzene-insoluble decomposition products. In addition, the yield of imines depends strongly on the purity of starting amine 2. In fact, when freshly prepared amine 2 is kept in air even for a short time, a portion of it is transformed into a yellow substance, which is insoluble in organic solvents (ether, benzene, and others). Assuming that this compound is mainly carbonate of the amine (6), we carried out its reaction with an equimolar amount of ferrocenecarbaldehyde (1d) in the solid state at ~ 20 °C. The ¹H NMR spectrum of the reaction mixture 24 h after showed the formation of imine 4d in 80% yield. Therefore, Schiff bases in the solid state can be formed in reactions of aldehydes with both amines and their carbonates.



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In this connection, the solid-state interaction of aldehydes with other amine salts was studied, in particular, with accessible and abundant hydrochlorides.

The preparation of imines from glycine hydrochloride, without isolation of the free base, in a solution of methylene dichloride in the presence of triethylamine binding the acid is known.⁶ We established that the solid-state interaction of aldehydes 1d or 1e with the hydrochloride of (2S)-enantiomer of 2-amino-1methoxy-3-phenylpropane (7) in the presence of anhydrous K₂CO₃ at room temperature occurs for 3 days with the complete conversion of the reagents and quantitative formation of imines 8d and 8e (Scheme 2).

Scheme 2



Unlike the solid-state reactions of aldehydes with amine 2 considered above, aldehydes 1a-f studied by us react with 4-nitroaniline (3) in the solid state at room temperature fairly slowly (Table 1). The exception is the reaction with 2-nitrobenzaldehyde (1a). The ¹H NMR spectrum of an equimolar solid-state mixture of la with 3 recorded 1 day after the beginning of the reaction at ~20 °C testifies that imine 5a is formed in 90% yield. The reaction of amine 3 with 4-nitrobenzaldehyde (1b) at ~20 °C occurs substantially more slowly (24 h after, the yield of 5b is 30%), and under these conditions, no reaction with vanillin (1c) is observed. Nevertheless, heating of a solid mixture of 3 with 1b at 60 °C for 2 h results in the formation of spectrally pure imine 5b in a quantitative yield. Probably, the low reactivity of amine 3 is associated with its lower basicity and nucleophilicity in reactions with aldehydes.

Among organometallic aldehydes 1d-f, ferrocenecarbaldehyde reacts most readily with amine 3. Imine 5d is formed in 40% yield already at ~20 °C during 1 day. Heating of the reaction mixture accelerates substantially the reaction, the latter at 60 °C during 2 h results in the almost quantitative formation of 5d. The initial yelloworange color of the solid reaction mixture is transformed into dark-cherry-colored. It is noteworthy that the traditional method of preparation of 5d requires heating of the mixture of 1d and 3 in toluene with azeotropic distilling off of water during 48 h.⁷

The reaction of ruthenocenecarbaldehyde (1e) with amine 3 at 60 °C for 2 h results in the formation of imine 5e in 75% yield (10% of the product is formed at ~20 °C in a day), while cymantrenecarbaldehyde (1f) does not react with 3 in the solid state even on heating to 90 °C, which is much higher than the melting point of the aldehyde itself (70 °C). Therefore, 5f is not formed in the melt as well. Moreover, heating of the mixture in toluene with azeotropic distilling off of water during 2 h results in the formation of only an insignificant quantity of 5f and in the noticeable decomposition of 1f. In this case, the reaction is likely difficult because of both the low nucleophilicity of the amine and the strong electron-acceptor character of the cymantrenyl radical, which, on the one hand, prevents the elimination of water in the intermediate semi-aminal and, on the other hand, facilitates hydrolysis of azomethine. In fact, the solid-state interaction of a mixture of 1f with 3 in the presence of potash, which binds the water formed. at 90 °C for 24 h results in the formation of 5f in 10% yield. The yield was determined relatively to 4-nitroaniline by the signal of the aldiminic proton (δ 8.38, acetone-d₆).

Among all the above described reactions of crystalline aldehydes and amines in the absence of anhydrous K₂CO₃, the reactions of 2- and 4-nitrobenzaldehydes 1a,b with 4-nitroaniline 3 are true solid-state. In these cases, at all stages of the process, both at ~20 °C (in the case of 1a) and on heating (for 1b), the reaction mixtures remain solid friable powders. All other reactions give oily or glass-like masses, which crystallize as products are formed or after the reaction ceases. However, the aggregate state of the reaction mixture is not evidently the main reason determining the rate of interaction of reagents. For example, the completely solid-state reaction of 1a with 3 at ~20 °C for 24 h results in the formation of imine 5a in 90% yield, while the reaction of 1d with 3 under the same conditions, at the intermediate stage of which an oily mass is formed, gives imine 5d in 40% yield only. Moreover, stirring of powders of vanillin 1c and amine 3 results in a low-melting eutectic mixture; however, no interaction of the reagents occurs

Table 1. Yields of imines 5a-f under different reaction conditions

Compound	R	Yield (%)	
		~20 °C, 1 day	60 °C, 2 h
5a	2-NO2-C6H4	90	
5b	$4 - NO_2 - C_6 H_4$	30	100
5c	4-HO-3-MeOC ₆ H ₃	*	85**
5d	C ₅ H ₅ FeC ₅ H ₄	40	95
5e	C ₄ H ₅ RuC ₅ H ₄	10	75
5f	Mn(CO) ₃ C ₅ H ₄	*	*

* No reaction. ** Heating at 80 °C for 10 h.

at ~20 °C. The reaction of 1c with 3 occurs in the absence of a solvent and only in the melt on heating to 80 °C for 10 h, and the yield of 5c is 85%.

Thus, the solid-state reactions of crystalline aldehydes and amines proceed more efficiently and under milder conditions than similar reactions in solutions, which makes it possible to consider the solid-state process as a preparative method for obtaining aldimines. Amine salts, in particular, hydrochlorides, which are often more accessible and stable derivatives than free bases, also can be successfully used in the direct solidstate synthesis of azomethines.

Experimental

¹H NMR spectra were obtained on a Bruker-AMX-400 instrument. Optical rotation was measured on a Perkin-Elmer 141 polarimeter.

Ferrocenecarbaldehyde,⁸ ruthenocenecarbaldehyde,⁹ cymantrenecarbaldehyde,¹⁰ and (ferrocenylmethyl)amine¹¹ were synthesized according to previously published procedures.

Solid-state reactions of aldehydes 1a—e with amines 2 and 3 (general procedure). Crystalline amine (1 mmol) was mixed with aldehyde (1 mmol), and the mixture was let to stand in an open flask in the dark. The mixture was stirred from time to time or heated. The reaction run was monitored by ¹H NMR spectra. When the reaction ceased, the products were crystallized. The yields of imines 4a—f are quantitative, and the yields of imines 5a—e are presented in Table 1. The temperature in the room, in which the work with low-melting (m.p. 30-35 °C) amine 2 was carried out, was not higher than 17 °C.

Solid-state reactions of aldehydes 1d,e with salts 6 and 7 (general procedure). Amine salt (1 mmol) was mixed with aldehyde (1 mmol) and K_2CO_3 (2 mmol), and the resulting mixture was let to stand in the dark in an open flask and stirred from time to time. When the reaction ceased, hexane and K_2CO_3 were added to the reaction mixture, which was then filtered off, and the solution was concentrated *in vacuo*. The yields of imines 8d,e are quantitative. To obtain analytically pure samples, the products were crystallized.

N-(2-Nitrobenzylidene)ferrocenylmethylamine (4a) is darkorange crystals with m.p. 90–92 °C (EtOH). ¹H NMR (acetone-d₆), δ : 4.13 (m, 2 H, C₅H₄); 4.17 (s, 5 H, C₅H₅); 4.25 (m, 2 H, C₅H₄); 4.61 (s, 2 H, CH₂); 7.73 (m, 1 H, C₆H₄); 7.81 (m, 1 H, C₆H₄); 8.04 (m, 1 H, C₆H₄); 8.15 (m, 1 H, C₆H₄); 8.71 (s, 1 H, HC=N). Found (%): C, 62.48; H, 4.66; N, 7.94. C₁₈H₁₆FeN₂O₂. Calculation (%): C, 62.09; H, 4.63; N, 8.05.

N-(4-Nitrobenzylidene)ferrocenylmethylamine (4b) is darkred crystals with m.p. 154–155 °C (EtOH, Ref. 12: 151–153 °C). ¹H NMR (acetone-d₆), &: 4.13 (m, 2 H, C₅H₄); 4.16 (s, 5 H, C₅H₅); 4.24 (m, 2 H, C₅H₄); 4.62 (s, 2 H, CH₂); 8.09 (m, 2 H, C₆H₄); 8.33 (m, 2 H, C₆H₄); 8.56 (s, 1 H, HC=N). Found (%): C, 62.24; H, 4.48; N, 7.62. C₁₈H₁₆FeN₂O₂ · 1/6 EtOH. Calculated (%): C, 61.88; H, 4.82; N, 7.87.

N-(4-Hydroxy-3-methoxybenzylidene)ferrocenylmethylamine (4c) is yellow crystals with m.p. 132–133 °C (benzene—hexane). ¹H NMR (acetone-d₆), δ : 3.88 (s, 3 H, CH₃O); 4.10 (m, 2 H, C₅H₄); 4.15 (s, 5 H, C₅H₅); 4.21 (m, 2 H, C₅H₄); 4.46 (s, 2 H, CH₂); 6.88 (m, 1 H, C₆H₃); 7.19 (m, 1 H, C₆H₃); 7.48 (m, 1 H, C₆H₃); 8.05 (br.s, 1 H, OH); 8.25 (s, 1 H, HC=N). Found (%): C, 65.41; H, 5.71; N, 3.89. C₁₉H₁₉FeNO₂. Calculated (%): C, 65.35; H, 5.48; N, 4.01.

N-(Ferrocenylmethylene)ferrocenylmethylamine (4d) is dark-yellow crystals with m.p. 166–167 °C (EtOH). ¹H NMR (C₆D₆), δ : 4.08 (s, 5 H, C₅H₅); 4.09 (m, 2 H, C₅H₄); 4.13 (m, 2 H, C₅H₄); 4.18 (s, 5 H, C₅H₅); 4.24 (m, 2 H, C₅H₄); 4.40 (m, 2 H, C₅H₄); 4.70 (s, 2 H, CH₂); 8.05 (s, 1 H, HC=N). Found (%): C, 64.35; H, 5.38; N, 3.26. C₂₂H₂₁Fe₂N. Calculated (%): C, 64.28; H, 5.15; N, 3.41.

N-(Ruthenocenylmethylene)ferrocenylmethylamine (4e) is pale-yellow crystals, m.p. 148–149 °C (benzene-hexane). ¹H NMR (C_6D_6): 4.07 (m, 2 H, C_5H_4); 4.17 (s, 5 H, C_5H_5); 4.19 (m, 2 H, C_5H_4); 4.33 (m, 2 H, C_5H_4); 4.52 (s, 5 H, C_5H_5); 4.54 (m, 2 H, C_5H_4); 5.13 (s, 2 H, CH₂); 7.93 (s, 1 H, HC=N). Found (%): C, 58.49; H, 4.57; N, 3.10. $C_{22}H_{21}$ FeNRu · 1/6 C_6H_6 . Calculated (%): C, 58.86; H, 4.72; N, 2.98.

N-(Cymantrenylmethylene)ferrocenylmethylamine (4f) is yellow crystals with m.p. 100–102 °C (hexane). ¹H NMR (C₆D₆), δ : 3.91 (m, 2 H, C₅H₄); 4.05 (m, 2 H, C₅H₄); 4.13 (s, 5 H, C₅H₅); 4.14 (m, 2 H, C₅H₄); 4.27 (m, 2 H, C₅H₄); 4.77 (s, 2 H, CH₂); 7.44 (s, 1 H, HC=N). Found (%): C, 55.77; H, 3.61; N, 3.20. C₂₀H₁₆FeMnNO₃. Calculated (%): C, 55.98; H, 3.76; N, 3.26.

N-(2-Nitrobenzylidene)-4-nitroaniline (5a) is orange crystals with m.p. 141-143 °C (benzene-hexane, Ref. 14: 141 °C). ¹H NMR (acetone-d₆), δ : 7.49 (m, 2 H, C₆H₄); 7.86 (m, 1 H, C₆H₄); 7.94 (m, 1 H, C₆H₄); 8.17 (m, 1 H, C₆H₄); 8.31 (m, 1 H, C₆H₄); 8.35 (m, 2 H, C₆H₄); 9.01 (s, 1 H, HC=N). Found (%): C, 57.51; H, 3.42; N, 15.39. C₁₃H₉N₃O₄. Calculated (%): C, 57.57; H, 3.35; N,15.49.

N-(4-Nitrobenzylidene)-4-nitroaniline (5b) is yellow crystals with m.p. 201-203 °C (benzene-hexane. Ref. 15: 198-200 °C). ¹H NMR (acetone-d₆), δ : 7.53 (m, 2 H, C₆H₄); 8.30 (m, 2 H, C₆H₄); 8.34 (m, 2 H, C₆H₄); 8.43 (m, 2 H, C₆H₄); 8.87 (s, 1 H, HC=N). Found (%): C, 57.64; H, 3.17; N, 15.52. C₁₃H₉N₃O₄. Calculated (%): C, 57.57; H, 3.35; N, 15.49.

N-(4-Hydroxy-3-methoxybenzylidene)-4-nitroaniline (5c) is yellow crystals with m.p. 158–159 °C (benzene-hexane). ¹H NMR (acetone-d₆), &: 3.93 (s, 3 H, CH₃O); 6.98 (m, 1 H, C₆H₃); 7.39 (m, 2 H, C₆H₄); 7.45 (m, 1 H, C₆H₃); 7.65 (m, 1 H, C₆H₃); 8.29 (m, 2 H, C₆H₄); 8.49 (s, 1 H, OH); 8.51 (s, 1 H, HC=N). Found (%): C,61.87; H, 4,41; N, 10.29. C₁₄H₁₂N₂O₄. Calculated (%): C, 61.76; H, 4.44; N, 10.29.

N-(Ruthenocenylmethylene)-4-nitroaniline (5e) is yellow crystals with m.p. 159--160 °C (benzene--hexane). ¹H NMR (acetone-d₆), δ : 4.68 (s, 5 H, C₅H₅); 4.87 (m, 2 H, C₅H₄); 5.19 (m, 2 H, C₅H₄); 7.24 (m, 2 H, C₆H₄); 8.23 (m, 2 H, C₆H₄); 8.33 (s, 1 H, HC=N). Found (%): C, 54.01; H, 3.92; N, 7.60. C₁₇H₁₄N₂O₂Ru. Calculated (%): C, 53.82; H, 3.72; N, 7.38.

(2.5)-1-Methoxy-3-phenyl-*N*-(ferrocenylmethylidene)propylamine (8d) is yellow crystals with m.p. 66-68 °C (pentane), α_D^{21} -20° (c 0.4, hexane). ¹H NMR (CDCl₃), 8: 2.92 (m, 2 H, CH₂Ph); 3.37 (s, 3 H, CH₃O); 3.51 (m, 3 H, NCH and CH₂O); 4.01 (s, 5 H, C₅H₅); 4.30 (m, 2 H, C₅H₄); 4.57 (m, 1 H, C₅H₄); 4.59 (m, 1 H, C₅H₄); 7.16-7.32 (m, 5 H, C₆H₅); 7.92 (s, 1 H, HC=N). Found (%): C, 69.98; H, 6.65; N, 3.74. C₂₁H₂₃FeNO. Calculated (%): C, 69.82; H, 6.42: N, 3.88.

(2.5)-1-Methoxy-*N*-(ruthenoc enylmethylidene)-3-phenylpropylamine (8e) is colorless crystals with m.p. 80-82 °C (pentane), α_D^{21} +26.5° (*c* 0.36, hexane). ¹H NMR (CDCl₃), δ : 2.87 (m, 2 H, CH₂Ph); 3.35 (s, 3 H, CH₃O); 3.49 (m, 3 H, NCN and CH₂O); 4.42 (s, 5 H, C₅H₅); 4.64 (m, 2 H, C₅H₄); 4.90 (m, 1 H, C_5H_4); 4.97 (m, 1 H, C_5H_4); 7.17–7.29 (m, 5 H, C_6H_5); 7.76 (s, 1 H, HC=N). Found (%): C, 62.04; H, 5.66; N, 3.48. $C_{21}H_{23}NORu$. Calculated (%): C, 62.05; H, 5.70; N, 3.45.

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References

- N. S. Khrushcheva, N. M. Loim, E. V. Vorontsov, and V. I. Sokolov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 2250 [*Russ. Chem. Bull.*, 1994, 43, 2130 (Engl. Transl.)].
- N. S. Khrushcheva, N. M. Loim, V. I. Sokolov, and V. D. Makhaev, J. Chem. Soc. Perkin. Trans. 1, 1997, 2425.
- 3. I. K. Barben, J. Chem. Soc., 1961, 1827.
- 4. M. Kobayashi, M. Yoshida, and H. Minato, J. Org. Chem., 1976, 41, 3322.
- 5. R. Bosque, C. Lopez, and J. Sales, J. Organometal. Chem., 1995, 498, 147.

- G. Stork, A. Y. W. Leong, and A. M. Touzin, J. Org. Chem., 1976, 41, 3493.
- A. Houlton, N. Jasim, R. M. G. Roberts, J. Silver, D. Cunningham, P. McArdle, and T. Higgins, J. Chem. Soc. Dalton Trans., 1992, 2235.
- M. Sato, H. Kono, M. Shiga, I. Motoyama, and K. Hata, Bull. Chem. Soc. Jpn., 1968, 41, 252.
- 9. O. Hofer and K. Schlogl, J. Organomet. Chem., 1968, 13, 443.
- V. A. Tsyryapkin, I. E. Zel'tser, N. M. Loim, Yu. N. Belokon', V. M. Belikov, Z. N. Parnes, and D. N. Kursanov, *Izv. Akad. Nauk, Ser. Khim.*, No. 4, 872 1979 [Bull. Acad. Sci. USSR, Div. Chem. Sci., 1979, 28, 817 (Engl. Transl.)].
- 11. D. E. Bublitz, J. Organometal. Chem., 1970, 23, 225.
- V. I. Boev, Zh. Obshch. Khim., 1987, 48, 1594 [J. Gen. Chem. USSR, 1987, 48 (Engl. Transl.)].
- 13. W. Reid and M. Wilk, J. Liebigs Ann. Chem., 1954, 590, 91.
- 14. B. A. Porai-Koshits, E. M. Poznanskaya, V. S. Shevchenko, and L. A. Pavlova, Zh. Obshch. Khim. [J. Gen. Chem. USSR], 1947, 17, 1774 (in Russian).

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