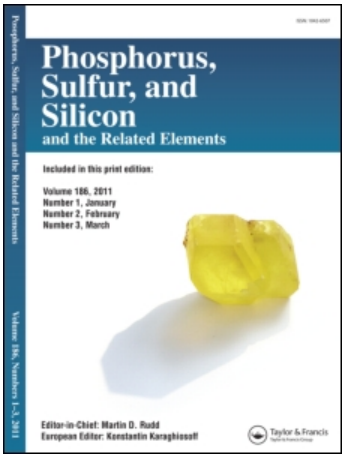

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A NEW PROTOCOL FOR THE PREPARATION OF AMINALS FROM AROMATIC ALDEHYDES AND THEIR FACILE CONVERSION TO PHOSPHONATES

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A NEW PROTOCOL FOR THE PREPARATION OF AMINALS FROM AROMATIC ALDEHYDES AND THEIR FACILE CONVERSION TO PHOSPHONATES

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A new and fast method for the preparation of aminals is reported from the reaction of aromatic aldehydes and secondary amines in the presence of potassium carbonate in high yields. The aminal can be converted to the corresponding iminum salt in reaction with acetyl chloride very easily and in very short time with high yield. Addition of trialkylphosphite, as one possible nucleophile, to the prepared iminium salt produces the α-amino phosphonate in very high yield.

Keywords: Aminal; iminium salt; phosphonate; trialkylphosphite

Preparation of Eschenmoser salts and other iminium salts are of great interest due to their increased and varied usage, and their functions in organic chemistry have been well documented.[1] However, due to the hygroscopicity of iminium salts and their susceptibility to hydrolysis (with the exception of Eschenmoser's salt), these salts have been prepared with different methods in situ.[2–4] The direct methods for the preparation of iminium ions were also reported which can be useful in some aspects.[5–7] Iminium salts were also prepared from aminals, derived from the aliphatic aldehydes.[8,9] According to the Mannich-Davidsen procedure,[10] aliphatic aminals can be easily prepared from aliphatic aldehyde and secondary amine in the presence of a dehydrating agent. Although aromatic aminals can be transferred to iminium salts, the procedure for the preparation of aromatic aminal is more difficult and is carried out under azeotropical removal of water with 83–98% yield or by dehydration with boric anhydride with 64–92% yield.[11] For example, according to one reported procedure, when benzaldehyde and piperidine were refluxed in benzene for 24 h with a Dean-Stark trap, the corresponding aminal was produced in 72% yield.[11b]

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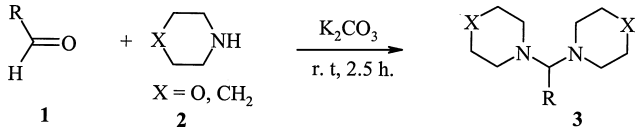
In this article, we describe a very simple, fast, and solvent-free method for the preparation of aromatic aminals. We also report the reaction of aromatic aminal with acetyl chloride, which produced the corresponding iminium salts in high yields.

α-Amino phosphonates are an important class of compounds since they are considered as structural analogues of the corresponding α-amino acids, and their utilities as enzyme inhibitors, antibiotics, pharmacological agents and many other applications are well documented.[12] The prepared iminium salt was reacted with trialkylphosphite, as one possible nucleophile for reaction with iminium salt, to give high yields of α-amino phosphonates at ambient temperature.

RESULTS AND DISCUSSION

Addition of benzaldehyde **1** to the mixture of secondary amine **2** and anhydrous potassium carbonate produced the aminal **3** after 2.5 h at room temperature. High yields are observed from the reaction of an aldehyde with a secondary cyclic amine by simply stirring at room temperature without using any solvent at the initial step. The reactions are run neat, there are no by-products, and the work-up procedure is easy. Recrystallization in the proper solvent (Table I) gave the pure aminal in high yield (Scheme 1). Other dehydrating agents such as anhydrous magnesium sulfate and zinc chloride also can be used. But in these cases, in the absence of a solvent, the mixture coagulates and the yield is low. Addition of a solvent at the initial step lowers the yield too. Our study shows that the best secondary amine for the preparation of aminal is morpholine. In this case the corresponding aminal can be crystallized very easily. Also, in contrast with the secondary cyclic amine the acyclic amines did not produce any aminal with this procedure.

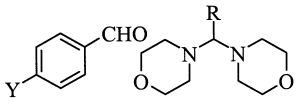
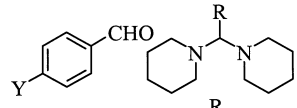
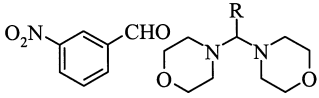
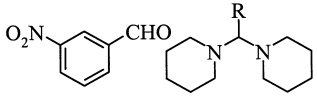
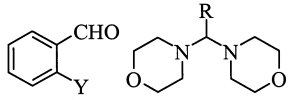
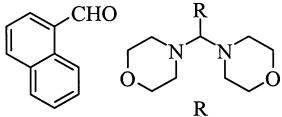
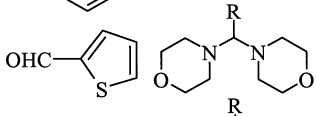
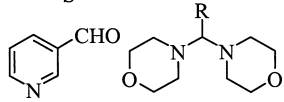


1 2 3

SCHEME 1

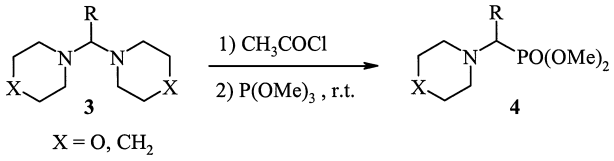
In the past few years we have shown that iminium ions can be prepared from aldehydes and secondary amines in situ in the concentrated ethereal solution of lithium perchlorate, and they can be trapped by different nucleophiles.[2] In the present work we report that the reaction

TABLE I Synthesis of Aminals Using K_2CO_3 as Dehydrating Agent

Aldehyde	Product	Solvent used for crystallization		Conv. yield (%)	Isolated yield (%)
		**3a**, Y= H,	pet. ether	96	85
		3b Y= NO_2,	CH_2Cl_2, pet. ether	96	82
		3c, Y= Cl,	ethyl acetate	100	80
		3d, Y= Br,	ethyl acetate	100	90
		3e, Y= OMe,	ethyl acetate	90	76
		**3f**, Y= H,	pet. ether	94	80
		3g, Y= NO_2,	pet. ether	97	86
		**3h**	acetone	100	87
		**3i**	pet. ether	94	80
		**3j**, Y=Me	pet. ether	96	75
		3k, Y=OMe	pet. ether	100	90
		**3l**	ethyl acetate	84	70
		**3m**	pet. ether	96	82
		**3n**	pet. ether	100	92

of the aminals with acetyl chloride in THF produced the iminium salt in less than 1 min. The iminium salt, which is detected by ^{13}C-NMR spectroscopy in the solution,[13] can be used for addition reaction.

The reported procedures for the preparation of α-amino phosphonates are a three-component reaction between an aldehyde, a secondary amine, and dialkylphosphite,[12] or trialkylphosphite,[14] or addition of triethylphosphite to preformed vinylogous iminium salt.[12h] In the present work, addition of nucleophiles such as trimethylphosphite to the prepared iminium salt gave a high yield of α-amino phosphonate **4** at ambient temperature and in a very short time (Scheme 2). The results are summarized in Table II.

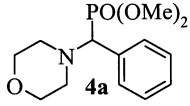
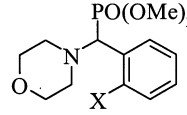
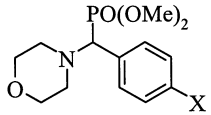
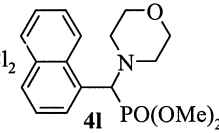
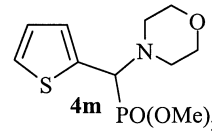
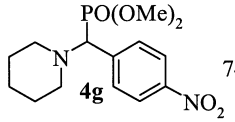
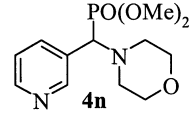
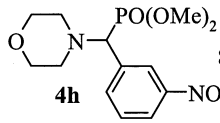
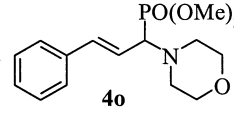
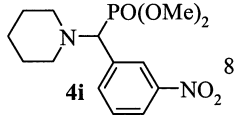


SCHEME 2

Solvent Effect

As mentioned above, an aldehyde and a cyclic secondary amine were mixed without using any solvent at the initial step. Using dichloromethane or acetonitrile at the initial step, lowers the reaction

TABLE II Synthesis of α Amino Phosphonate from Aminal

Aminal	Solvent	Product	Isolated yield (%)	Aminal	Solvent	Product	Isolated yield (%)
3a	CH_2Cl_2	 **4a**	90	**3j**	CH_2Cl_2	 **4j**, X = Me	88
3b	CH_2Cl_2	 **4b**, X = NO_2	78	**3k**,	THF	**4k**, X = OMe	84
3c	CH_2Cl_2	**4c**, X = Cl	82	**3l**	THF/CH_2Cl_2	 **4l**	70
3d	CH_2Cl_2	**4d**, X = Br	87				
3e	THF	**4e**, X = OMe	88	**3m**	THF	 **4m**	84
3g	THF	 **4g**	74	**3n**	THF	 **4n**	84
3h	CH_2Cl_2	 **4h**	80	**3o**	THF	 **4o**	80
3i	THF	 **4i**	85				

yield. After stirring the reaction mixture for 1 h, dichloromethane was added.

Addition of acetyl chloride to the aminal in a solvent gives the iminium salt. Using THF as a solvent for all aminals gave the iminium salt in less than one min. Although aminals derived from morpholine gave the corresponding iminium salt in dichloromethane or acetonitrile in 10 min, aminals derived from piperidine gave no product after stirring for 24 h at room temperature. The best solvent for the reaction of each iminium ion with trialkylphosphite is indicated in Table II.

Table I shows the prepared aminals and the best solvent system for their recrystallization. The conversion yields for the prepared aminals are between 84%–100%. The structures of the known and the new compounds have been unambiguously characterized on the basis of their IR, NMR (^{1}H, ^{13}C), MS spectra and by comparison with those reported in the literature.[11] The ^{1}H and ^{13}C NMR spectra display the characteristic signals of protons and carbons of all the constituents.

CONCLUSION

In summary, aromatic aminals have been prepared with secondary cyclic amine in good yields and in short time. The aminals can be converted to the iminium salts almost immediately by reaction with acetyl chloride. The iminium ions were reacted with trimethylphosphite as one possible nucleophile to produce the corresponding α-amino phosphonates.

EXPERIMENTAL

Preparation of (Dimorpholinomethyl)benzene 3a. Typical Procedure

Benzaldehyde (10 mmol, 1.06 g) was added drop wise to the mixture of morpholine (30 mmol, 2.6 g) and anhydrous potassium carbonate (1.3 g) during 1 h. Then dichloromethane (1.5 mL) was added and the mixture was stirred at room temperature for 1.5 h. Dichloromethane (20 mL) was added and the potassium carbonate filtered off. The solvent was removed to give the crude product. Recrystallization in petroleum ether gave the pure aminal **3a**. Proper recrystallization solvent for each aminal is given in Table I.

General Procedure for the Preparation of α-Amino Phosphonates 4

The aminal (2.7 mmol) was dissolved in THF or CH_2Cl_2 (5 mL) and acetyl chloride (2.8 mmol) was added. The iminium salt was precipitated immediately. Then trimethylphosphite (3.5 mmol) was added and the mixture was stirred at room temperature until all the iminium salt was used. Dichloromethane (10 mL) and 2 M aqueous HCl (10 mL) were added. The aqueous phase was separated, neutralized with 5 M NaOH solution, extracted with dichloromethane, dried over $MgSO_4$, and the solvent was removed. Almost pure crude product was obtained. The structures of the products were determined by comparison of the spectroscopic data with those reported in the literature.[12]

(Dimorpholinomethyl)benzene (3a)

Known,[11a,11c] m.p. 104–105.5°C (pet. ether, lit. 105°C), 85% (isolated yield); IR (KBr), 1113.7 (s, CH—N) cm^{-1}; ^{1}HNMR ($CDCl_3$), δ, 2.44 (m, 8H), 3.66 (s.1H), 3.70 (t, $J = 10.53$ Hz, 8H), 7.20–7.38 (m, 5H); ^{13}CNMR ($CDCl_3$), 49.9 (CH_2—N), 68.2 (CH_2—O), 89.5 (N—CH—N), 128.2 (CH), 129.2 (CH), 129.3 (CH), 134.45 (C).

1-Bromo-4-(dimorpholinomethyl)benzene (3d)

M.p. 138.6–140°C (ethyl acetate), 90% (isolated yield); IR (KBr), 1111.9 (s, CH—N) cm^{-1}; ^{1}HNMR ($CDCl_3$), δ, 2.39–2.45 (m, 8H), 3.64 (s, 1H), 3.68 (t, $J = 4.65$ Hz, 8H), 7.11 (d, $J = 8.55$ Hz, 2H), 7.5 (d, $J = 8.25$ Hz, 2H); ^{13}CNMR ($CDCl_3$), 49.9 (CH_2—N), 67.5 (CH_2—O), 88.8 (N—CH—N), 122.1 (C), 130.7 (CH), 131.4 (CH), 133.5 (C).

(Dipiperidinomethyl)benzene (3f)

Known,[11a] m.p. 82.5–84.0°C (pet. ether), 80% (isolated yield); IR (KBr), 1111.8 (s, CH—N) cm^{-1}; ^{1}HNMR ($CDCl_3$), δ, 1.38 (m, 4H), 1.55 (m, 8H), 3.58 (s, 1H), 7.21–7.90 (m, 5H).

3-(Dimorpholinomethyl)-1-nitrobenzene (3h)

Known,[11c] m.p. 143–144.5°C (pet. ether, lit. 140–142°C), 87% (isolated yield); IR (KBr), 1110.1 (s, CH—N) cm^{-1}; ^{1}HNMR ($CDCl_3$), δ, 2.40-2.47 (m, 8H), 3.70–3.75 (m, 8H), 3.81 (s, 1H), 7.58–8.20 (m, 4H).

1-(Dipiperidinomethyl)-3-nitro benzene (3i)

M.p. 89–90.3°C (pet. ether), 80% (isolated yield); IR (KBr), 1104.0 (s, CH—N), 1344, 1525 (s, NO_2) cm^{-1}; ^{1}HNMR ($CDCl_3$), δ, 1.40 (m, 4H), 1.52–1.57 (m, 8H), 2.30–2.35 (m, 8H), 3.75 (s, 1H), 7.51-7.57 (m, 2H), 8.07 (s, 1H), 8.15 (m, 1H); ^{13}C-NMR ($CDCl_3$), δ, 25.4 (CH_2) , 26.5 (CH_2),

50.5 (CH_2—N) , 89.2 (N—CH—N), 122.6 (CH), 123.3 (CH), 128.7 (CH), 134.8 (CH), 139.0 (CH), 148.3 (C).

2-(Dimorpholinomethyl)-1-methoxybenzene (3k)

Known,[11c] m.p. 75.5–77°C (pet. ether, lit. 70–74°C), 90% (isolated yield); ^{1}HNMR ($CDCl_3$), δ, 2.40–2.44 (m, 8H), 3.65–3.70 (m, 8H), 3.80 (s, 3H), 4.41(s, 1H), 6.92–6.98 (m, 2H), 7.25–7.36 (m, 2H); ^{13}C-NMR ($CDCl_3$), 50.0 (CH_2—N), 55.7 (OCH_3), 67.7 (CH_2—O), 79.5 (N—CH—N), 111.2 (CH), 120.1 (CH), 123.1 (CH), 128.8 (CH), 129.8 (C), 158.8 (C).

2-(Dimorpholinomethyl) Pyridine (3n)

M.p. 102.2–103.7°C (pet. ether), 92% (isolated yield); IR (KBr), 1114.3 (s, CH—N) cm^{-1}; ^{1}HNMR (acetone-d_6), δ, 2.39–2.42 (m, 8H), 3.58–3.64 (m, 8H), 3.88 (s, 1H), 7.31 (m, 1H), 7.39 (m, 1H), 7.8 (d, $J = 1.8$ Hz, 1H), 8.6 (m, 1H); ^{13}C-NMR (acetone-d_6) 49.9 (CH_2—N), 67.5 (CH_2—O), 90.0 (N—CH—N) , 123.0 (CH), 123.2 (CH), 135.86 (CH), 149.4 (C), 155.5 (C).

α-Morpholino Phosphonates (4a)

Known,[12] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (t, $J = 6.3$ Hz, 2H), 2.79 (t, $J = 6.1$ Hz, 2H), 3.51 (m, 3H), 3.67–3.74 (m, 4H), 3.81–3.88 (m, 4H), 7.187–7.43 (m, 5H), ^{13}C NMR: 125 MHz, $CDCl_3$): δ 24.3 (CH_2), 26.5 (CH_2), 52.3 (CH_2), 54.8 (d, $J = 6.8$ Hz, CH_3), 54.9 (d, $J = 7.8$ Hz, CH_3), 63.9 (d, $J = 161.3$ Hz, CH), 128.1 (CH), 128.8 (CH), 131.2 (d, $J = 5.6$ Hz, CH), 134.8 (d, $J = 3.4$ Hz, C).

α-Piperidino Phosphonates (4g)

Known,[12] ^{1}H NMR (500 MHz, $CDCl_3$): 1.34 (t, $J = 6.2$ Hz, 2H), 1.56–1.64 (m, 4H), 2.41 (m, 2H), 2.78 (m, 2H), 3.54 (d, $J = 8.6$ Hz, 3H), 3.92 (d, $J = 8.7$ Hz, 3H), 4.01 (d, $J = 22.8$ Hz, 1H), 7.67 (d, $J = 8.0$, 2H), 8.22 (d, $J = 8.4$, 2H).

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