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Solid-phase synthesis of amidines by the reduction of amidoximes

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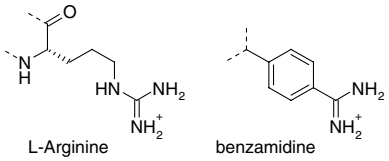
Abstract—Amidines can be prepared on a solid support by reducing polymer-bound amidoximes with $SnCl_2 \cdot 2H_2O$. The method has proved to be straightforward and highly efficient. Amidoximes attached to the solid support are readily available by treating resin-bound nitriles with hydroxylamine.

The amidine moiety is an important pharmacophore in medicinal chemistry. Aromatic amidines in particular have been shown to function as excellent arginine side-chain mimetics due to their favourable spatial and electrostatic properties.[1] This approach has been employed for preparing pharmacologically active compounds against numerous drug targets where arginine is involved as a part of their natural ligand binding sequence. These include serine proteases, for example, thrombin and factors Xa and VIIa and integrin receptors.[2]



L-Arginine benzamidine

Besides their role as a pharmacophore group in biologically active agents, amidines are also important building blocks in organic synthesis, especially for preparing various heterocyclic compounds.[3]

Numerous methods for the synthesis of amidines in solution are known, the most convenient being those utilizing nitriles as their chemical precursors.[4] The widely used Pinner synthesis comprises of first reacting a nitrile with an alcohol in the presence of excess gaseous HCl to give an alkyl imidate, then transforming this into the amidine by treatment with amines or salts thereof. A modified procedure involves forming a thioamide by introducing H_2S into a solution of the nitrile, its alkylation to a thioimidate and subsequent treatment with ammonia.

An alternative approach towards amidines is the reduction of amidoximes. Catalytic hydrogenation with palladium on charcoal proceeds well in the presence of acetic anhydride as an acylating agent.[5] Reduction with Zn in acetic acid has also been described.[6]

Synthesis of amidines from their chemical precursors on a solid support has not been reported. Roussel et al. attached preformed amidines to a solid support via a carbonate-type linker.[7] Several groups used such immobilized amidines for the further solid-phase synthesis of tissue factor/factor VIIa complex, factor Xa and thrombin inhibitors and GP IIb/IIIa integrin antagonists.[8]

Tin(II) chloride, usually in its dihydrate form ($SnCl_2 \cdot 2H_2O$), is a commonly employed reagent for reducing aromatic nitro compounds to amines on solid supports.[9] The reaction proceeds via hydroxylamines as intermediates, which can be trapped with electrophiles. We decided to investigate the potential of $SnCl_2$ to reduce amidoximes to amidines. Though conversions proceeded well in solution at elevated temperatures, the isolation of products was laborious due to the high polarity of the resulting amidines, which made them difficult to separate from tin salts.[10] We now report the reduction of amidoximes with $SnCl_2 \cdot 2H_2O$ on a solid support, which has proved to be a straightforward and highly efficient method for the solid-phase synthesis of amidines. Amidoximes attached to the solid support are readily

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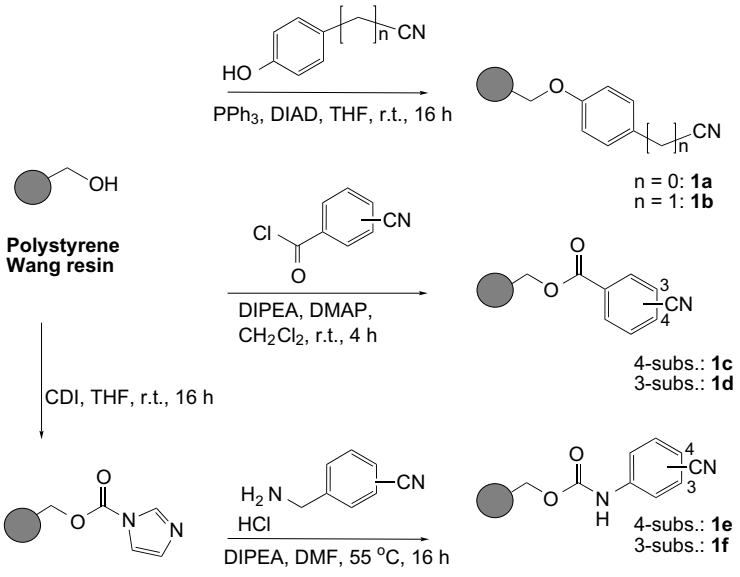
available by treating resin-bound nitriles with hydroxylamine.[11]

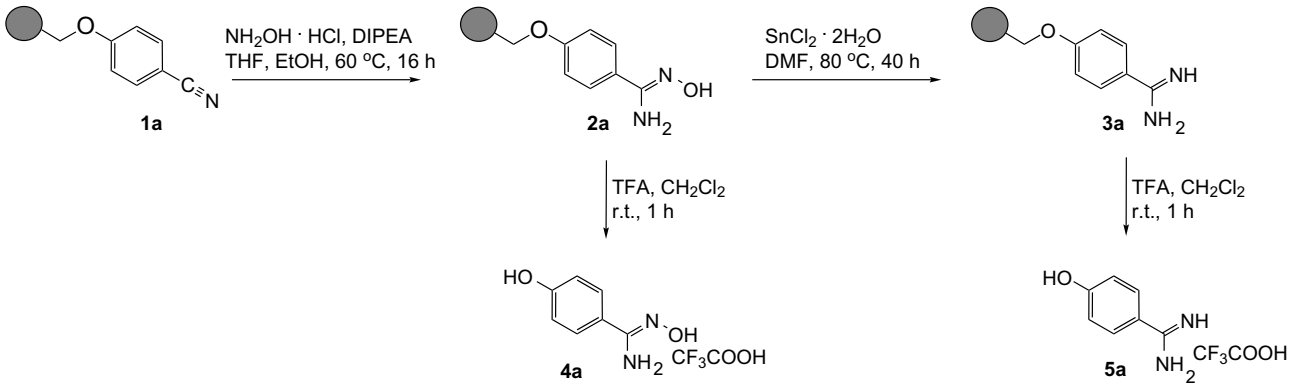
Nitriles were attached to the Wang resin under standard conditions, as shown in Scheme 1. 4-Hydroxybenzonitrile (for **1a**) and 4-hydroxybenzyl cyanide (for **1b**) were attached to the resin by Mitsunobu coupling using 5 equiv of the corresponding phenol, 5 equiv of PPh_3 and 5 equiv of diisopropyl azodicarboxylate (DIAD). 4-Cyanobenzoyl chloride (for **1c**) and 3-cyanobenzoyl chloride (for **1d**), 2 equiv each, were added to the resin in the presence of 2.5 equiv of diisopropylethylamine (DIPEA) and 0.1 equiv of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2. For attachment of amines via a carbamate bond, the resin was first activated with 1,1′-carbonyldiimidazole (CDI).[12] 4-(Aminomethyl)benzonitrile (for **1e**) and 3-(aminomethyl)benzonitrile (for **1f**) were then added to the imidazole carbamate resin.[13]

Resin-bound nitriles **1a**–**f** were split into approx. 0.5 mmol portions and further transformations were conducted in parallel using a Bohdan MiniBlock™ reactor. Transformations of 4-cyanophenoxy derivative **1a** are presented in Scheme 2.[14] Amidoximes **2a**–**f** were prepared by swelling resins **1a**–**f** in THF and adding 10 equiv of a 1 M solution of hydroxylamine hydrochloride and DIPEA in ethanol. The resulting amidoximes were then reduced using 15 equiv of $SnCl_2{\cdot}2H_2O$ (1 M solution in DMF) to yield resin-bound amidines **3a**–**f**. The reaction was allowed to proceed for 40 h to achieve complete conversion. Compounds were cleaved from the resins under standard conditions with 50% trifluoroacetic acid in CH_2Cl_2.

The results are summarized in Table 1 and exemplified in Figure 1. Reduction of amidoximes with $SnCl_2{\cdot}2H_2O$ on solid support gives amidines in high yield and purity. As shown, the method can be applied for aromatic as well as aliphatic amidines. It also allows attachment of the parent compound through various functional groups. We believe the method can readily be applied for the generation of amidine-containing combinatorial libraries, which will undoubtedly have an important role in the near future as an increasing number of new drug

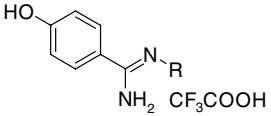
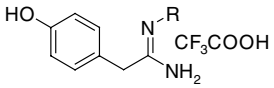
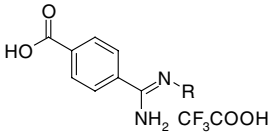
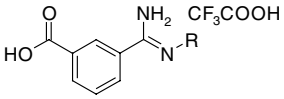
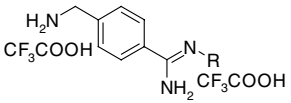
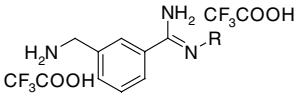


Scheme 1. Attachment of nitriles to the Wang resin.



Scheme 2. Representative solid-phase synthesis of amidines by the reduction of amidoximes, which are readily available from resin-bound nitriles.

Table 1. Yields and spectroscopic data

Compd		R	Yield[a] (%)	Purity[b] (%)	^{1}H NMR (DMSO, 300 MHz) δ (ppm), J (Hz)	MS
	**4a**	OH	90	87	6.94 (d, 2H, J = 8.7, Ar), 7.58 (d, 2H, J = 8.7, Ar), 8.91 (s, 2H, NH_2), 10.55 (s, 1H, ArOH), 11.08 (s, 1H, NOH)	152.0586 (EI)
	5a	H	89	74	6.95 (d, 2H, J = 9.0, Ar), 7.72 (d, 2H, J = 9.0, Ar), 8.84 (s, 2H, NH_2), 9.03 (s, 2H, NH_2^+), 10.68 (s, 1H, OH)	136.0636 (EI)
	**4b**	OH	87	82	3.53 (s, 2H, CH_2), 6.75 (d, 2H, J = 8.3, Ar), 7.16 (d, 2H, J = 8.3, Ar), 8.77 (s, 2H, NH_2), 9.50 (s, 1H, ArOH), 10.94 (s, 1H, NOH)	166.0746 (EI)
	5b	H	87	71	3.55 (s, 2H, CH_2), 6.75 (d, 2H, J = 8.3, Ar), 7.19 (d, 2H, J = 8.7, Ar), 8.70 (s, 2H, NH_2), 8.98 (s, 2H, NH_2^+), 9.50 (s, 1H, OH)	151 (FAB, MH^+)
	**4c**	OH	85	76	7.82 (d, 2H, J = 8.3, Ar), 8.06 (d, 2H, J = 8.3, Ar), 8.20 (s, 2H, NH_2), 11.00 (s, 1H, NOH)	180.0536 (EI)
	5c	H	94	72	7.91 (d, 2H, J = 8.3, Ar), 8.13 (d, 2H, J = 8.7, Ar), 9.24 (s, 2H, NH_2), 9.44 (s, 2H, NH_2^+)	165 (FAB)
	**4d**	OH	88	81	7.71 (m, 1H, Ar), 7.96 (m, 1H, Ar), 8.19 (m, 1H, Ar), 8.26 (m, 1H, Ar), 8.59 (s, 2H, NH_2), 11.06 (s, 1H, NOH)	180.0535 (EI)
	5d	H	96	82	7.76 (m, 1H, Ar), 8.04 (m, 1H, Ar), 8.26 (m, 1H, Ar), 8.35 (m, 1H, Ar), 9.25 (s, 2H, NH_2), 9.45 (s, 2H, NH_2^+)	165 (FAB, MH^+)
	**4e**	OH	85	78	4.13 (s, 2H, CH_2), 7.60 (d, 2H, J = 8.3, Ar), 7.75 (d, 2H, J = 8.3, Ar), 8.36 (s, 3H, NH_3^+), 11.04 (s, 1H, NOH)	165.0905 (EI)
	5e	H	86	72	4.17 (s, 2H, CH_2), 7.67 (d, 2H, J = 8.7, Ar), 7.87 (d, 2H, J = 8.3, Ar), 8.41 (s, 3H, NH_3^+), 9.32 (s, 2H, NH_2), 9.37 (s, 2H, NH_2^+)	150 (FAB, MH^+)
	**4f**	OH	83	86	4.09 (d, 2H, J = 5.3, CH_2), 7.57 (m, 1H, Ar), 7.68 (m, 2H, Ar), 7.81 (s, 1H, Ar), 8.28 (s, 3H, NH_3^+), 10.72 (s, 1H, NOH)	165.0906 (EI)
	5f	H	91	71	4.14 (s, 2H, CH_2), 7.69 (m, 2H, Ar), 7.81 (d, 1H, J = 7.2, Ar), 7.92 (s, 1H, Ar), 8.37 (s, 3H, NH_3^+), 9.37 (s, 3H, $C(NH)NH_2$)	150 (FAB, MH^+)

[a] Yields are relative to the resin-bound nitriles.[15]

[b] HPLC purity, determined with a UV detector at 254 nm. Results are in accordance with ^{1}H NMR data.

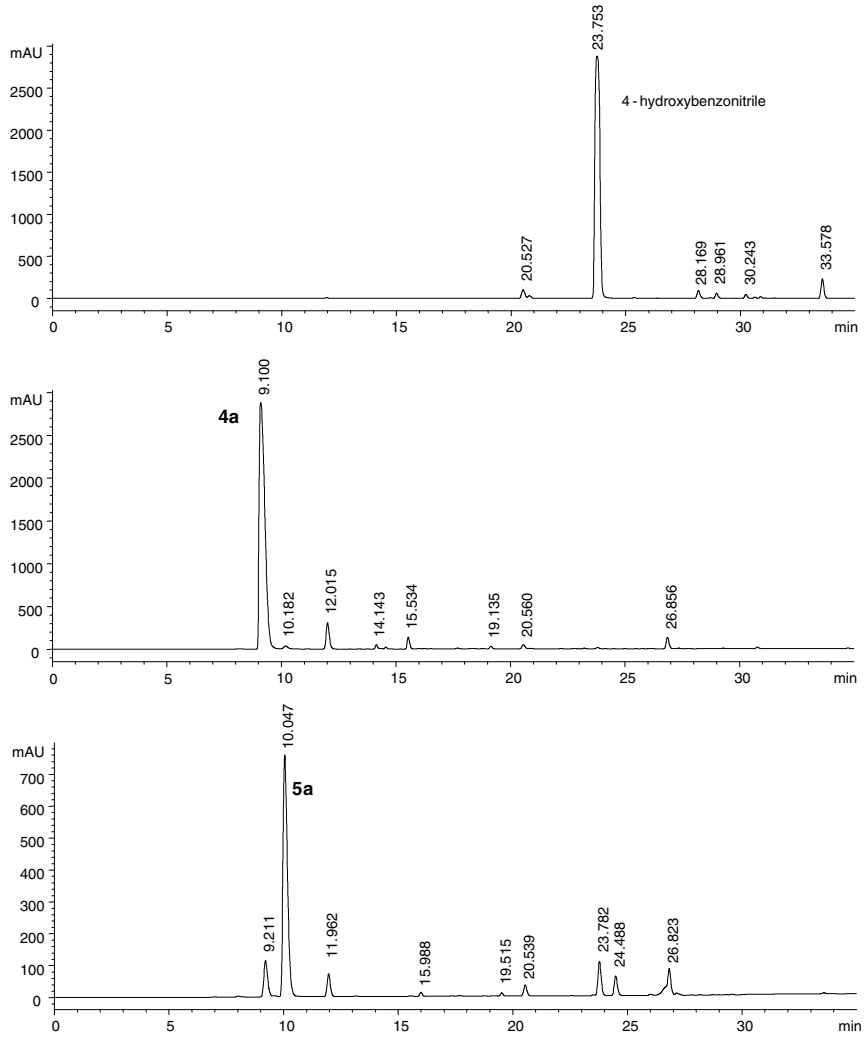


Figure 1. HPLC chromatograms of 4-hydroxybenzonitrile (top), 4-hydroxybenzamidoxime **4a** (middle) and 4-hydroxybenzamidine **5a** (bottom) after cleavage from resins.[15] HPLC was performed using a Eurospher C_{18} 250 × 4.6 mm column at 0.7 mL/min flow rate. Phase A: 0.1% TFA in H_2O. Phase B: 0.1% TFA in MeCN. Gradient 5% to 70% B over 25 min, then 70% B for 5 min and then back from 70% to 5% B over 5 min. Monitored at 254 nm.

targets and peptide leads arise from the genomic and proteomic developments. In addition, support-bound amidines can serve as useful building blocks for the further solid-phase synthesis of heterocycles.

Acknowledgements

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14. Representative procedure: To a solution of 4-cyanophenol (1.28 g, 11 mmol) in freshly distilled THF (30 mL), Wang resin (2.00 g, 0.9–1.1 mmol/g, 100–200 mesh; Acros Organics) was added. After swelling for 10 min, PPh_3 (2.91 g, 11 mmol) was added. The mixture was flushed with argon and cooled to 0 °C. A precooled solution of DIAD (2.27 mL, 11 mmol) in THF (10 mL) was added and the mixture shaken for 16 h at room temperature. The mixture was then filtered and the resin washed with THF (3×20 mL), DMF (3×20 mL), MeOH (3×20 mL) and CH_2Cl_2 (2×20 mL). 4-Cyanophenyl-substituted resin **1a** was dried in vacuo at 45 °C to a constant weight of 2.238 g. Resin **1a** (560 mg, ~0.5 mmol) was suspended in THF (3 mL) and allowed to swell for 10 min. A 1 M solution of hydroxylamine in ethanol (6 mL) was then added (prepared by adding hydroxylamine hydrochloride (3.51 g, 50 mmol) and DIPEA (9.17 mL, 52.5 mmol) to a 50 mL measuring flask, making up to 50 mL with absolute ethanol and stirring for 1 h to yield a clear solution). The reaction mixture was shaken (480 rpm) for 16 h at 60 °C. The resulting resin-bound amidoxime **2a** was filtered off and washed with MeOH (3×6 mL), THF (3×6 mL) and DMF (3×6 mL). In cases where we wished to remove amidoxime from the support in the next step, the resin was additionally washed with CH_2Cl_2 (3×6 mL).
Compound **2a** was reduced by adding a 1 M solution of $SnCl_2 \cdot 2H_2O$ in DMF (7.5 ml). The reaction mixture was flushed with argon and shaken for 40 h at 80 °C. After filtration, the resin-bound amidine **3a** was washed with DMF (10×6 mL), 5% DIPEA in MeOH (1×6 mL), MeOH (3×6 mL) and CH_2Cl_2 (3×6 mL). In some cases, formation of tin salt precipitates was observed; therefore, extensive washing with DMF was needed.
Cleavage of 4-cyanophenol, 4-hydroxybenzamidoxime **4a** and 4-hydroxybenzamidine **5a** from the support was achieved by adding a 50:50 (v/v) mixture of TFA and CH_2Cl_2 (6 mL) to resins **1a**, **2a** and **3a**, respectively. After shaking for 1 h at room temperature the reaction mixtures were filtered and residual solids washed with TFA (2 mL) and MeOH (3 mL). Solvents were evaporated and the products dried in vacuo in the presence of solid NaOH at 45 °C to constant weight.
15. Analytical data suggested that the amidoximes are in the trifluoroacetate forms: the NMR signal for NH_2 shifts from around 6 ppm (unprotonated form, sharp) to 8–9 ppm (broad), while the integral value remains around 2. When a TFA buffered mobile phase is used for HPLC, amidoximes show shorter retention times than the corresponding amidines. On the other hand, when phosphate buffer (pH = 4.4) and methanol are used, amidoximes exhibit much longer retention times than amidines, but peaks become broader. Poor definition of the trifluoroacetate salts may result in lower yields for amidoximes than for amidines.