Parallel Synthesis of Trisubstituted Formamidines: A Facile and Versatile Procedure

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A focused library of formamidines having several diversity points has been prepared. The use of isocyanate resin as scavenger may offer several practical advantages over conventional procedures, such as the ease of workup and availability. The technique described herein was performed in a parallel synthesis format. The whole protocol has potential use in high throughput synthesis for the preparation and purification of libraries of unsymmetrical formamidines containing sets of different aliphatic substituents.

Formamidines are derivatives of the unstable imidic acid having a unique and fascinating spectrum of biological[1] and pharmacological activity;[2] therefore, they have been extensively studied in medicinal chemistry.[3] They have been used primarily as pesticides (e.g., amitraz, chlordimeform, formetanate),[4] histamine-receptor antagonists,[5] serine-protease inhibitors,[6] and nitric oxide synthase inhibitors.[7] Amidine derivatives acting as anti-inflammatory, analgesic,[8] antipyretic and antibacterial[9] compounds are also described in the literature. Their use as intermediates in organic synthesis is quite varied and extensive,[10] including roles as auxiliaries in asymmetric synthesis,[11] protecting groups for primary amines,[12] electrophiles,[13] nitrogen-based nucleophiles,[14] and bioisostere[15] for amides and linkers in solid-phase synthesis.[16]

In view of the versatility of this class of compounds both in organic synthesis and in medicinal chemistry, we were particularly interested in developing a facile and straightforward synthetic procedure for a solution-phase library of trisubstituted formamidines **1** (Figure 1). Furthermore, transformations that increase molecular diversity through a few synthetic steps are well suited for automated parallel solution-phase synthesis, as well as being of substantial interest.[17]

General routes to formamidines and related compounds are ruled by the reaction between primary amines **2** and *N*,*N*-dialkylformamide dimethylacetals **3** under neutral conditions (Scheme 1).[18] The subsequent exchange of the electron-donating dimethylamino fragment in *N*,*N*-dimethylformamidines (**4**) by a variety of amines **5** is one of the most popular method for the preparation of symmetrical and unsymmetrical formamidines **6** (Scheme 1).

Unfortunately, during our studies on the synthesis of formamidines, we have observed that this exchange is much less reliable than for analogous formamidines ureas.[19] In fact, formamidines are known[20] to be particularly unstable under many of the conditions encountered during their purification

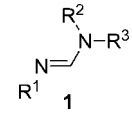

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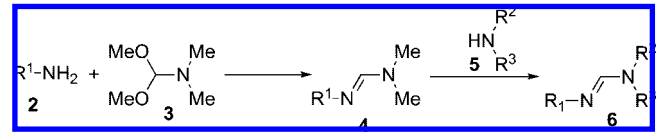
Figure 1. Trisubstituted formamidines.

Scheme 1. General Route to Prepare Trisubstituted Formamidines



steps. These factors make *trans-amidination* of *N*,*N*-dimethyl formamidines a very attractive synthetic route for the preparation of N^2,N^3-unsymmetrical formamidines but are not suitable for a combinatorial approach or for high-throughput synthesis. Therefore, new perspective is needed for the efficient workup. The use of solid-supported reagents opens an interesting perspective for efficient preparation of these compounds by greatly simplifying their isolation.

In an effort to make the above reaction more convenient, we decided to search for an alternative polymer-assisted solution-phase synthesis of trisubstituted formamidines **1** based on the widely used and high yielding trans-amidination of *N*,*N*-dimethyl formamidines **4**.

Our initial route to prepare formamidine libraries prompted us to explore scope and limitations of the coupling reaction between *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) and several primary amines (Scheme 2).

To optimize the procedure, we chose benzylamine **2a**, for a model reaction. Experiments were carried out varying combinations of equivalents of **2a** (from 1.0 to 3.0 equiv) and DMF-DMA (from 1.0 to 3.0 equiv), using solvent (MeOH or THF) and solvent-free conditions. We observed that the use of a base is not strictly necessary and does not produce any improvement in the process. Furthermore, a large excess of starting material has to be used to drive the reaction to completion. The yield of **4a** was maximized by the use of 3 equiv. of DMF-DMA, while the best results in terms of purity was obtained employing MeOH as solvent.

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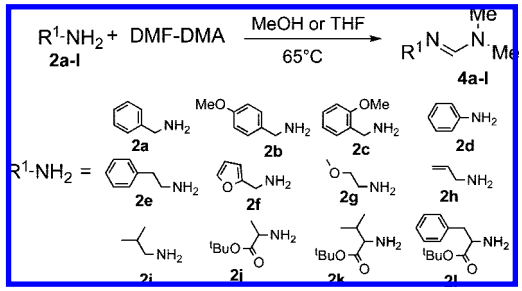
Scheme 2. Coupling Reaction Between *N*,*N*-Dimethylformamide Dimethylacetal (DMF-DMA) and Primary Amines



The reaction is easy to perform, and the excess of DMF-DMA could be removed by concentration in vacuo to leave formamidine **4a** pure and in quantitative yields. A combinatorial library (parallel format) of dimethyl formamidines was been smoothly prepared in almost quantitative yields using a series of commercially available primary amines (both aliphatic and aromatic) under these optimized conditions (Figure 2). The yields of the formamideacetals **4h** and **4i** were moderate (67% and 70% respectively) only when allyl and isobutyl amines were used, but this was attributed to the volatile character of the resulting final products.

Afterward, we focused our attention on the exchange of the dimethylamino fragment in *N*,*N*-dimethylformamidines **4a**−**l** with other commercially available amines. In particularly, we were interested in evaluating the introduction of other functional amines to increase molecular diversity.

First, the *N*,*N*-dimethylformamidine **4a**, prepared as previously described, was selected as a model and refluxed in dry acetonitrile with morpholine (Scheme 3).[21] The resulting solution was stirred at reflux until the secondary amine had completely disappeared as monitored by TLC.[22] Unfortunately, the dimethylamino group turned out to be a poor leaving group for our purposes and two moles of secondary amine per mole of **4a** were necessary to drive the reaction to completion.[23]

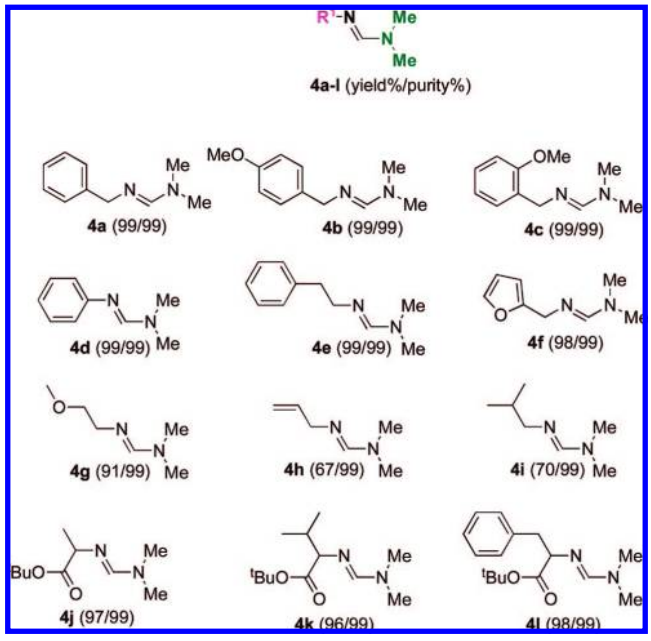
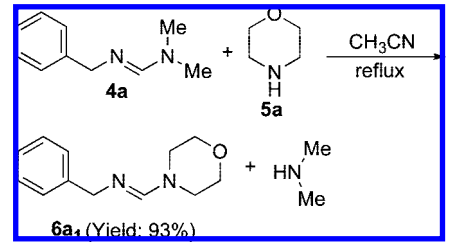
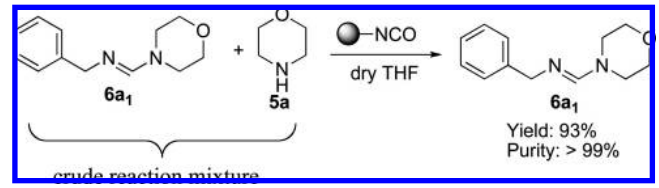


Figure 2. Structural diversity of the *N*,*N*-dimethylformamidine library.

Scheme 3. Trans-amidination Reaction of *N*′-benzyl-*N*,*N*-dimethylformimidamide with a Two-fold Excess of Morpholine



Scheme 4. Selective Sequestration of Morpholine Excess by PS-Isocyanate Scavenger Resin



To test the influence of the solvent in this protocol, a duplicate set of experiments with MeOH and CH_3CN were carried out. In general, the isolated yields for *N*,*N*-formamidine **6a$_1$** were comparable in both solvents. However, the purity of the final compounds was slightly better when CH_3CN was used.

As discussed above, the real limiting of this two-step procedure were the cumbersome manipulations required for the purification and isolation of the final products. Moreover, traditional distillation and chromatographic methods are unsuitable for chemical library synthesis, and thus polymer-scavenging reagents were used for a selective removal of unreacted secondary amine.[24] In literature,[25] several scavenger resins have been employed to remove excess amines from crude reaction products. One of the most popular is polystyrene methyl isocyanate (PS-isocyanate),[26] which is commonly used for the selective sequestration of secondary amines. Polystyrene-based scavengers are the most widely available form of solid-supported scavengers because low cost of manufacturing. As a rule, a 2−3-fold excess of the resin is used for 1−18 h to remove unreacted amines.

At first, we thought to add the scavenger resin directly to the crude reaction mixture, but the removal of excess amines was not completed (about 35%) because acetonitrile is a poor solvent for swelling 1% cross-linked polystyrene.[27] The PS backbone deeply influences the behavior of the scavenger in terms of solvent compatibility and reaction rate. PS-based scavenger must be allowed to swell in highly compatible solvents such as THF to work effectively. Therefore, upon completion of the reaction, the crude reaction mixture was evaporated to dryness,[28] and the residue was dissolved in anhydrous THF, and treated with PS-isocyanate.[29] As all the byproduct remained polymer-bound through the formation of urea, filtration, washing of beads, and concentration afforded **6a$_1$** (93%) as the sole product (Scheme 4).

The resin was also tested for the removal of amines in a series of model solution-phase reactions. Under optimal conditions, an array of *N*,*N*-dimethylformamidines (**4a**−**l**) was also smoothly converted to the corresponding forma-

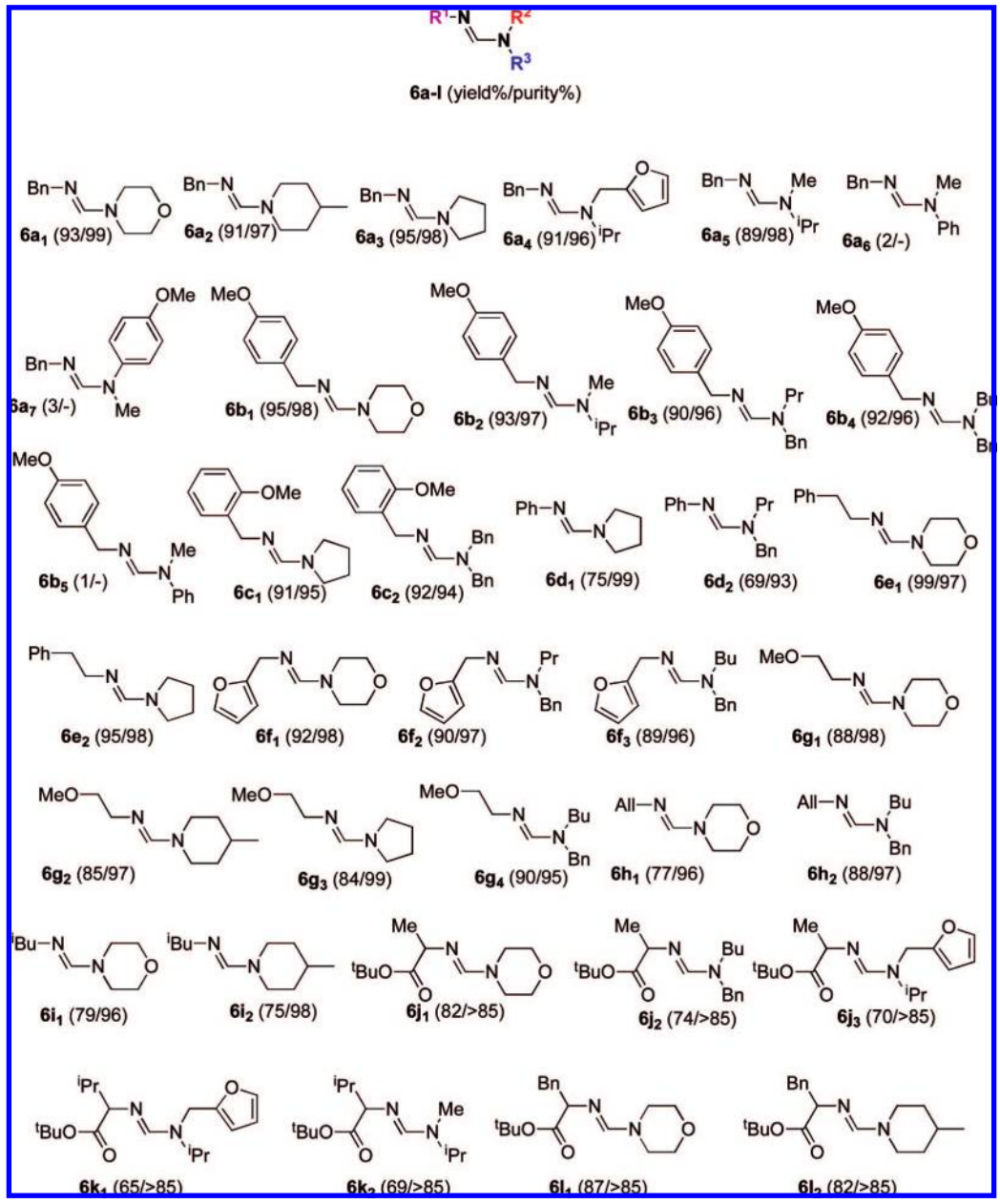


Figure 3. Structural diversity of the formamidine library.

midine derivatives by replacement of the NMe_2 group with a range of secondary amines. The unreacted excess amines[30] were then scavenged using resin-bound isocyanate, every time affording the desired compounds in high purity and good yields. Typically, the complete removal of cyclic secondary amines required a 2-fold excess of resin over a 6-h reaction period. In contrast, scavenging of hindered secondary amines was effected with longer reaction times (usually 12 h) at reflux (by sonification of THF solution). By application of this scavenging protocol, all the purification problems were significantly reduced because the excess amines used to drive the reaction to completion could be selectively removed. Final formamidines were pure enough for full characterization, which is crucial because formamidines do not withstand chromatographic purification on silica gel.[31]

The outcome of the NMe_2 substitution depends on the type of secondary amine employed, and the results are summarized in Figure 3. We have observed that the substitution reaction with cyclic secondary amines affords the desired products in excellent yields and high purities (entry **6a$_1$**−**6a$_3$**, **6b$_1$**, **6c$_1$**−**6c$_2$**, **6f$_1$**, **6g$_1$**−**6g$_3$**, **6h$_1$**, **6i$_1$**−**6i$_2$**, etc). Under the current conditions, pyrrolidine and *N*-benzylpropylamine reacted with **4d** to give the corresponding formamidines **6d$_1$** and **6d$_2$** with >95% purity and yields in the 69−75% range. In general, both aromatic and aliphatic *N*,*N*-dimethyl formamidines proceed with good effectiveness to give aromatic or aliphatic *N*,*N*′-disubstituted formamidines **6**, although the yields are somewhat less satisfactory with the aromatic substrates (R^1 = aromatic residue).

It is known from the literature that the stability of the formamidines having an aliphatic residue R^1, in comparison with N^1-aryl-N^2,N^3-alkylformamidine (entry **6d$_1$** and **6d$_2$**, Figure 3) is much reduced, and they are quickly decomposed to the corresponding amines when exposed to silica gel. On the contrary, our approach is well suited to prepare a library

of aliphatic *N*,*N*′-disubstituted formamidines in a high throughput manner and in high purity, without additional purification steps.[32]

Out of 36 compounds, obtained on the basis of Scheme 1, special attention was given to 17 ($R^2 \neq R^3$) of them (entry **6a$_4$**−**6a$_7$**, **6b$_2$**−**6b$_5$**, **6d$_2$**, **6f$_2$**−**6f$_3$**, etc). The process allows the introduction of a further point of molecular diversity employing a set of secondary amines having a residue R^2 different from R^3 (nonsymmetrical amines). The library was designed to contain both alkyl and aryl substituents on the final formamidine **1** affording two interesting diversity elements.

Long chain *N*-alkylated secondary amines gave good yields (entry **6b$_4$**, **6f$_3$**, **6g$_4$**, **6h$_2$**, etc., Figure 3) in the analogous exchange reaction, although they required longer reaction times (overnight). Interestingly, under these reaction conditions, hindered formamidines such as compounds **6a$_4$** and **6a$_5$** could also be synthesized. Any attempt to perform a similar substitution in *N*,*N*-dimethyl-*N*′-phenylformimidamide **4a** with *N*-alkyl substituted anilines as a nucleophile was unsuccessful; only a small amount of the desired formamidine **6a$_6$** and **6a$_7$** was recovered. In most cases, the major contaminants were the unreacted formamidine acetals. Increase of either the reaction time or temperature (sealed vial) was not successful to improve the yield of these expected derivatives. Temperatures above 100 °C resulted in increasing side reactions or degradation of the starting *N*,*N*-dimethylformamidines.[33] Further studies and efforts to extend the scope of this last transformation are currently underway.

Interestingly, we have observed that formamidine acetals **4j**−**l** containing α-aminoacids residue at R^1 undergo clean transformation into α-formamidino esters **6j**−**l** (Figure 3). Unfortunately, these compounds were unstable and slowly decomposed forming complex mixtures.[34]

In summary, we have demonstrated the utility and versatility of using a scavenging resin for the generation of a focused library of formamidines having several diversity points. In particular, this strategy enables the preparation and purification of a library of unsymmetrical formamidines containing a set of different aliphatic substituents ($R^1 \neq R^2 \neq R^3$). The use of isocyanate resins as scavengers may offer several practical advantages over conventional procedures, such as the ease of workup and availability. The technique described could be easily used in a parallel synthesis format. The whole protocol has potential use in high throughput synthesis for this class of compounds.

Experimental Section

General Routes to *N*,*N*-Dimethylformamidine Libraries. A solution of the benzylamine **2a** (0.107 g, 1.0 mmol, 1 equiv) and DMF dimethyl acetal (0.36 g, 3 mmol, 3 equiv) in methanol (3.0 mL) was heated to 70 °C with stirring under nitrogen for 3 h or until completion as indicated by TLC. The reaction was cooled to room temperature, and the product was isolated via evaporated to dryness to give **4a** as colorless oil in quantitative yield (0.162 g). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.33 (s, 1H), 7.25 (m, 5H), 4.44 (s, 2H), 2.83 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 155.4, 142.0, 127.8, 127.0, 125.9, 59.2, 36.8. HRMS Calcd for $C_{10}H_{15}N_2$ $[M + H]^+$: 163.1235. Found: 163.1229.

Typical Procedure for Trans-amidination of *N*,*N*-Dimethyl Formamidines. To a solution of dimethyl formamide **4c** (0.192 g, 1 mmol) in dry CH_3CN (5 mL), under nitrogen, was dropwise added dibenzylamine (0.591 g, 3 mmol) at rt. The reaction mixture was heated at reflux for 20 h and cooled at rt., and the solvent was evaporated under vacuum. The crude product was then redissolved in dry THF (5 mL), and the excess benzylamine was scavenged by adding PS-Isocyanate resin (2 equiv relative to excess amine). The beads allowed to react at reflux by sonification for about 12 h were removed by filtration and washed with THF (2 × 5 mL), and the combined filtrate was concentrated under vacuum to afford the **6c$_2$** as the sole product in 92% yield (0.317 g). Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 7.37−7.16 (m, 12H), 6.94−6.81 (m, 2H), 4.44 (s, 4H), 3.81 (s, 3H), 2.88 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 156.6, 156.0, 135.8, 130.5, 128.4, 127.1, 124.1, 120.3, 109.7, 55.1, 53.5, 52.8. HRMS (ESI) *m*/*z* Calcd for $C_{23}H_{25}N_2O$ $[M + H]^+$: 345.1961. Found: 345.1968.

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Supporting Information Available. General experimental conditions, details of experimental procedures, and spectroscopic data for synthesized compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(27) To overcome these swelling problems, we have used without success macroporous polystyrene-bound isocyanate (Biotage, MP-Isocyanate, lot no. 03498, P/N 801409, loading 0.88 mmol/g).
(28) GC analysis showed that only 15% of the starting excess morpholine was removed during evaporation to dryness step and any further attempt to purify the reaction mixture only by rotary evaporation (increasing the evaporation time or decreasing vacuum pressure) reduces the yields of the final compound.
(29) The polymer-bound reagent Ps-isocyanate was obtained from Biotage, part no. 800261, lot no. 03668, loading 1.89 mmol/g.
(30) At all times, we have observed (GC analysis) an uncompleted removal of amine excess by rotary evaporation.
(31) The purities and identities of all the library members were assessed by the direct analysis of the final products using LC/MS and GC/MS. The presence of all the desired compounds was unambiguously confirmed by the molecular mass with an excellent purity range.
(32) As in literature there are a few reports to prepare aliphatic *N*,*N*′-disubstituted formamidines, we have focused our attention on these last substrates.
(33) In this transamination reaction, we have observed no beneficial effect by a acid-mediated exchange.
(34) α-Formamidino esters **6j**−**l** were isolated in 70−75% yields with a good level of purity (>85% at ^{1}H NMR). Confirmation of the structures was obtained from both proton and ^{13}C NMR of the purified materials. All the spectroscopy analysis were carried out on fresh prepared compounds. Any further attempt to purify **6i**−**l** increase only the number of side products.

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