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A Synthesis of Acetamidines

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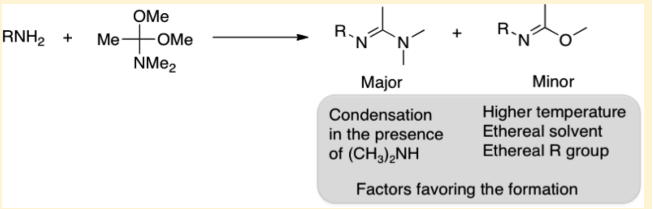
Supporting Information

ABSTRACT: The condensation of primary amine with *N*,*N*-dimethylacetamide dimethyl acetal yields a mixture of acetamidine and imidate ester. The product distribution in this reaction depends on the temperature, solvent, and structure of the primary amine. It is possible to suppress the formation of imidate ester by performing the reaction in the presence of excess dimethyl amine, yielding acetamidine as the exclusive product. For acetamidines that cannot be purified either by crystallization or distillation, this new method is necessary for the generation of pure acetamidines in good yields.



Amidines have applications in diverse areas such as catalyst design,[1] material science,[2] medicinal chemistry,[3] and superbase[4] promoted reactions. Our interest in this functional group stems from its application in materials that can change their properties depending on the concentration of carbon dioxide. Amidines readily form ionic amidinium bicarbonate salts in the presence of carbon dioxide and water. We have used amidines as switchable solvents,[5] switchable surfactants,[6a,b] and solutes.[6c] Other research groups are now using amidine switchable materials for a variety of applications.[7]

A review of synthetic methods indicates that nitriles and (thio)amides are the two most common building blocks for amidines.[8] The activation of the cyano group, by making it electron-deficient, with either protic acid, Lewis acid, or as nitrilium salts is warranted when nitriles are used for the synthesis of amidines (Scheme 1a).[8] (Thio)amides can be used for the synthesis of amidines (Scheme 1b), but like nitriles, they also require either Brønsted or Lewis acid to become sufficiently electrophilic. Alternatively, (thio)amides can be converted into (thio)imidate esters or imidoyl chlorides that offer good reactivity toward the nitrogen nucleophiles. Carboxylic acids can be used for the synthesis of amidines but often require harsher conditions than esters or ortho esters.[8] The activation of an amine as opposed to an amide is less frequently used. For the synthesis of acetamidines, the method developed by Raczyńska et al. (Scheme 1c) is particularly attractive because it appears to be a general method for the synthesis of both aryl and alkyl acetamidines in high yields. The method reacts the primary amine with modified ortho ester, *N*,*N*-dimethylacetamide dimethyl acetal.[9]

During our studies of long chain acetamidines as surfactants, we realized a need to create long-chain acetamidines with greater water solubility. Our original acetamidines had dodecyl or hexadecyl chains, which gave them very little water solubility. Poly(ethylene glycol) (PEG) is known to have good solubility in hexanes, ethers, and even water.[10] We envisioned that integrating a short PEG segment between the alkyl chain and the acetamidine headgroup might generate long-chain acetamidines with greater solubility in water.

The commercial availability of the PEG-based alcohols with assorted alkyl chain lengths and oxygen contents makes them good synthons for amidine syntheses. The proposed methodology depends on the conversion of the alcohol to a tosylate followed by substitution of the tosylate with the phthaloyl group from potassium phthalimide. Gabriel's dephthaloylation then would yield the primary amine,[11] which can be easily converted to amidine in one step, by *N*,*N*-dimethylacetamide dimethyl acetal using the method developed earlier by Raczyńska et al.[9] In addition to the desired amidine, unfortunately, the condensation of primary amines with *N*,*N*-dimethylacetamide dimethyl acetal yields an unwanted byproduct. While post-reaction purification is not difficult for very simple acetamidines, it is difficult for nonvolatile acetamidines, especially those that exhibit some surfactancy. The purification method some of us described some time ago for long-chain acetamidines[6b] (purification by precipitation of the bicarbonate salt) is, regrettably, not general. Therefore, it was necessary to identify a method that yields acetamidines with much greater selectivity. This article presents a study aimed at the characterization of the impurity and the development of a new method to improve the product selectivity of this reaction, evading the purification step. Some studies were carried out to uncover the factors that influence the extent of formation of the impurity.

RESULTS AND DISCUSSION

Amines from Poly(ethylene glycol)s. Each of a series of alcohols containing one or more ethylene glycol segments (compounds **1** in Scheme 2) was converted into the corresponding tosylate ester using a slight excess of the alcohol. The reaction was catalyzed by triethylamine and 4-(*N*,*N*-dimethylamino)-pyridine and was completed in 3 h, as indicated by the consumption of tosyl chloride by TLC and ^{1}H NMR spectroscopy.

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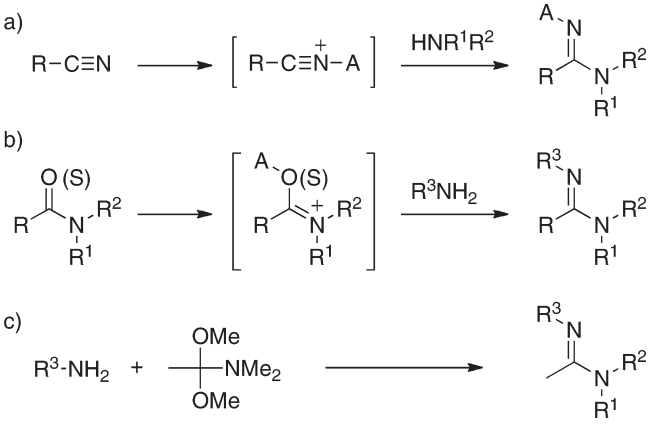
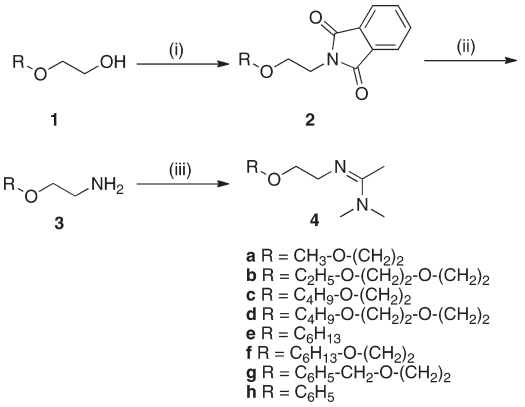
Scheme 1. General Methods for the Synthesis of Amidines



Scheme 2. Synthesis of Acetamidines with a Poly(ethylene glycol) Chain[a]

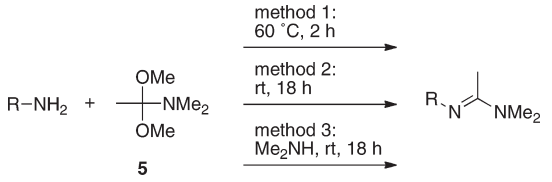


[a] Reagents and conditions: (i) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 3 h; then potassium phthalimide, DMF, 80 °C, 18 h; (ii) $N_2H_4.H_2O$, EtOH, 76 °C, 3 h; (iii) *N,N*-dimethylacetamide dimethyl acetal **5**, Me_2NH, rt, 18 h.

The conversion of the alcohol into the tosylate was quantitative or near quantitative. In certain cases, some alcohol remained unreacted with the tosylate ester after the aqueous workup; fortunately, the unreacted alcohol does not interfere with the subsequent phthaloylation and was easily removed after that step.

To convert the tosylate into alkyl phthalimide, the tosylate was allowed to react with a slight excess of potassium phthalimide in DMF at 80 °C. The reaction was allowed to run for 18 h at 80 °C. From the ^{1}H NMR spectra, it was apparent that approximately 10% detosylation to the alcohol occurred as a side reaction during the phthaloylation reaction of the tosylate obtained from **1e**. The isolation of phthalimide was modified to maximize its recovery, and column chromatography (ethyl acetate in hexanes) was used to obtain the final product in high purity. The purification step was crucial to get rid of phthalimide, DMF, and any of the original alcohol (either remaining from the tosylation or produced by detosylation during the phthaloylation step). This is the only step of the synthesis where column chromatography is required. Isolation of the pure product in the subsequent steps of the syntheses was easily accomplished by simple procedures such as precipitation, extraction, and/or evaporation under reduced pressure.

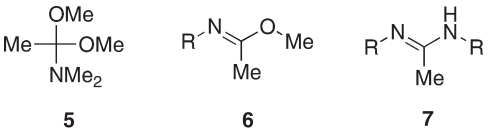
Scheme 3. Syntheses of Acetamidines by Condensation of Primary Amines with 5



The synthesis of amine from the *N*-alkylphthalimide was accomplished by Gabriel's amine synthesis.[11] The amine was isolated in good yield from the reaction mixture by ensuring the complete removal of ethanol, followed by the separation of the amine from the phthalhydrazide using cold diethyl ether.

We made an attempt to bypass column chromatography of the phthalimide and postpone the purification to the workup after the amine synthesis, assuming that the distillation of the amine might be a good way to purify it. Thus for series **f**, a continuous tosylation, phthaloylation, and hydrazinolysis was attempted to yield a crude amine that was subjected to vacuum distillation. From the ^{1}H NMR analysis of the crude product at different steps, it appears that significant detosylation occurs during phthaloylation that results in the formation of alcohol, which was distilled with the amine. Although a careful fractional distillation might be possible in some cases, we preferred to purify the phthalimide instead.

Condensation of Poly(ethylene glycol) Based Amines with *N,N*-Dimethylacetamide Dimethyl Acetal. The synthesis of amidines from primary amines and **5** (last step of Scheme 2, method 1 in Scheme 3) has only moderate selectivity for the amidine. For example, NMR spectroscopy showed that the product of condensation of **3g** with **5** at 60 °C and 2 h reaction time also contained a significant impurity. Similar impurities were observed in other acetamidines prepared by this method. An NMR study including ^{1}H, ^{13}C{^{1}H}, DEPT-135, and HSQC NMR spectroscopy showed that the impurity contains two new methyl groups at δ_C 14.50/δ_H 1.58 and δ_C 52.06/δ_H 3.55, a new CH_2 group at δ_C 49.69/δ_H 3.28 and at least three CH_2 peaks at 70.05, 70.96, and 72.41 that are visible beside the peaks of **4g** in the ^{13}C NMR spectrum.[12] All of those CH_2 peaks of the impurity are very closely matched to the CH_2 peaks for **4g**, suggesting that the impurity had the same tail group as the desired amidine **4g** but a different headgroup. On the basis of the NMR evidence, the most probable structure for the impurity seems to be the imidate ester **6a**. However, the ESI mass spectrum of the reaction mixture indicated the presence of amidine **7a**.



a R = Ph-CH_2-O-$(CH_2)_2$-O-$(CH_2)_2$
b R = C_8H_{17}

To resolve this apparent disagreement between the NMR and MS evidence, a pure sample of an imidate ester was prepared by a literature method. Because the purification of imidate ester **6b** is

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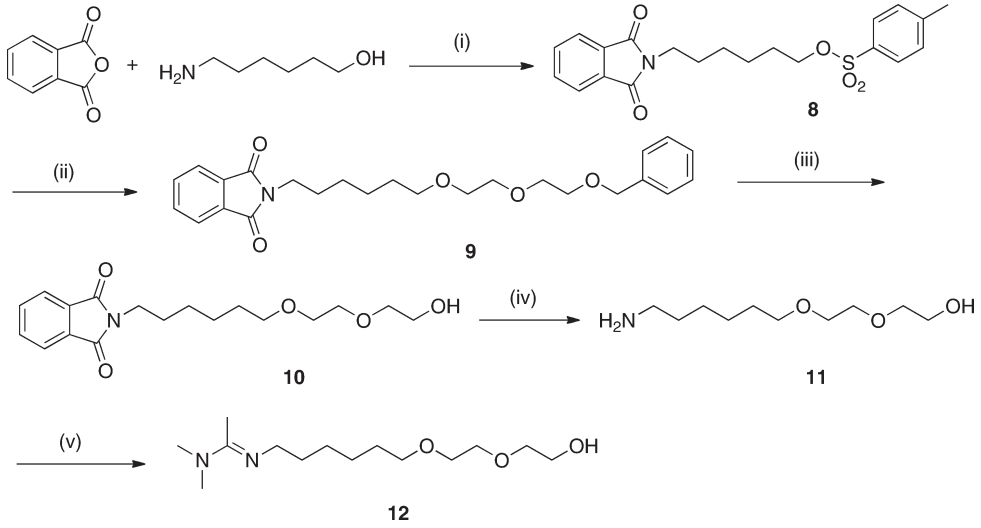
Scheme 4. Synthesis of Amidines with Terminal Di(ethylene glycol) Chain[a]



[a] Reagents and conditions: (i) 120 °C, 3 h; TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 18 h; (ii) C_6H_5-CH_2-O-$(CH_2)_2$-O-$(CH_2)_2$-OH, NaH, THF, 65 °C, 18 h; (iii) Pd−C (10%), EtOH, rt, 6 h; (iv) $N_2H_4 \cdot H_2O$, EtOH, 76 °C, 3 h; then HCl, 76 °C, 3 h; (v) *N*,*N*-dimethylacetamide dimethyl acetal **5**, Me_2NH, rt, 18 h.

easier than **6a**, **6b** was derived from *N*-acetyl octylamine by the procedure reported earlier by Pilotti et al.,[13] replacing distillation by column chromatography (50% ethyl acetate, 1% triethylamine in hexanes) for the final purification. By ^1H and $^{13}C\{^1H\}$ NMR, it is clear that **6b** was pure; no additional peaks were detected and the integration of the methyl groups relative to the octyl chain was correct for structure **6b** and not for **7b**. Nevertheless, the ESI-MS of the imidate ester **6b** showed equally prominent peaks at *m*/*z* 186.16 and 283.34 amu corresponding to imidate **6b** $[M + H]^+$ and amidine **7b** $[M + H]^+$, respectively. Amidine **7** appears to be formed in the mass spectrometer. Similarly, ESI-MS of imidate ester **6a** present in the product obtained from the reaction of **3g** with **5** using method 1 includes a peak at *m*/*z* 415.25, corresponding to **7a** $[M + H]^+$. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **6b** prepared by the literature method match those of the impurity obtained from the reaction of **3g** with **5**.

The PEG chain in the targeted amidines imparts desirable properties (liquids at room temperature, optimal viscosity, low mp, good hydrophilicity) but results in an increase in their boiling points (when compared to the corresponding nonoxygenated counterparts). This can become disadvantageous because a liquid with a very high boiling point cannot be separated by common distillation procedures. The higher oxygen content and the presence of a basic amidine headgroup increases the polarity of the PEG-based amidines, making the purification by column chromatography quite tedious. Therefore, a method that generates these amidines in a pure form was desirable, so that post-reaction purification would be unnecessary.

Variations on the method were compared. Imidate ester is also formed when a PEG-amine and **5** are heated for only a short time (20 min at 60 °C). For example, 12% of the imidate ester was detected by ^1H NMR spectroscopy after the reaction of **5** with **3f**. Performing the reaction of **3g** with **5** at room temperature instead of 60 °C (method 2 in Scheme 3) did not greatly increase the purity of the product. Because imidate ester formation was a result of loss of dimethylamine from the reaction mixture, the reaction was attempted in the presence of 2 equiv of dimethylamine, Me_2NH (2 M) in THF (method 3 in Scheme 3). These reaction conditions indeed favored the formation of the desired amidine over the imidate ester. For example, the amount of imidate ester (calculated from the relative integration of the triplet at 3.28 δ_H with respect to the triplet at 3.73 δ_H) decreased only from 14% to 11% when the reaction was attempted at room temperature; the imidate ester was practically undetectable by ^1H NMR spectroscopy when the reaction was attempted in the presence of 2 equiv of Me_2NH. The protocol thus seems to have eliminated the need for a purification step.

Synthesis of Amidines Starting with Protected Di(ethylene glycol) Chain. An alternative design of a PEG-containing acetamidine would be **12** (Scheme 4), where the amidine and ethylene glycol units are separated by long alkyl chain. The synthesis of **12** involved connecting monoprotected di(ethylene glycol) with *N*-protected 6-amino-1-hexanol via a Williamson's ether synthesis. This was followed by Pd/C catalyzed hydrogenolysis to deprotect the blocked -OH and hydrazinolysis to release the -NH_2 group. Unlike **2(a−h)**, generation of the amine from phthalimide **10** involved its reaction with hydrazine hydrate followed by acid-catalyzed hydrolysis to yield the amino alcohol **11**. We observed a remarkable regioselectivity of **5** toward the amino group in the presence of the alcoholic -OH group. This may be a cumulative effect of the higher nucleophilicity of the -NH_2 group and favorable formation of the nitrogen−carbon double bond. The condensation of amine **11** with **5** was carried out in the presence of 2 equiv of Me_2NH to avoid the possibility of the formation of any imidate ester during the reaction.

Improved Preparation of a Range of Acetamidines. The three methods for the preparation of acetamidines (Scheme 3) were compared for a series of amines (Table 1). For the solid amines, THF was used as a solvent. Generally, the recovery of the product from the reactions was very good in all cases.

For the conversion of short-chain amines and benzyl amines to acetamidines, there is no benefit to the addition of Me_2NH. Butyl amine produced the desired product with good purity by methods 1, 2, and 3. Benzyl amines seem to produce only

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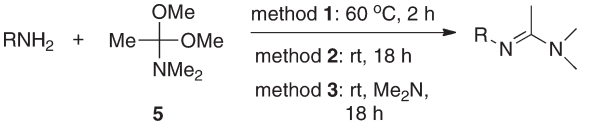
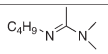
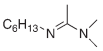
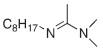
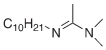
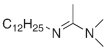
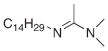
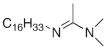
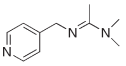
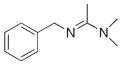
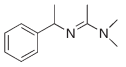
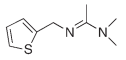
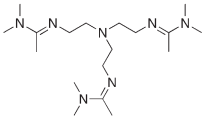
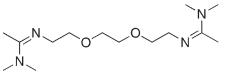
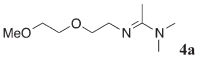
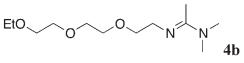
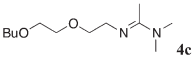
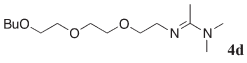
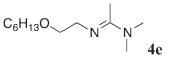
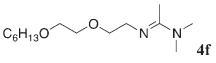
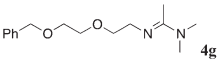
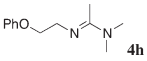
Table 1. Synthesis of Acetamidines from Primary Amines



Entry	Amidine	Optimal method	Isolated Yield (%)[a]
1		1/2	92/95
2		3	99
3		3	97
4		3	Quantitative
5		3	Quantitative
6		3	Quantitative
7		3	99
8		3	Quantitative
9		1/2	Quantitative/ Quantitative
10		1/2	94/98
11		1/2	Quantitative/ Quantitative
12		3	Quantitative
13		3	99
14	 **4a**	3	92 (46)
15	 **4b**	3	94 (78)
16	 **4c**	3	92 (66)
17	 **4d**	3	96 (75)
18	 **4e**	3	91 (70)
19	 **4f**	3	Quantitative (75)
20	 **4g**	3	97 (67)
21	 **4h**	3	94 (64)

[a] The yield from the amine. Values shown in parentheses are the overall yields from the original alcohol.

negligible quantities of imidate ester when reacted with **5** at room temperature in the absence of Me_2NH, although another unidentified impurity was apparent; distillation might prove useful for improving the purity and appearance of the product particularly in entries 9 and 11.

Longer-chain acetamidines, in contrast, must be prepared by method 3. Some imidate ester was detected by NMR spectroscopy in the product obtained from the reaction of hexyl or octylamine with **5** by method 1 (Table 1). When method 1 was used for the synthesis of amidines, the extent of the formation of the imidate ester was higher for amines with longer alkyl chains (Table 2). For example, 18% of the imidate ester was detected in the product from hexadecyl amine using method 1. Method 3 offers product of good purity without need for post-reaction purification. Although the separation/purification of this particular amidine is fairly easy,[6b] increased formation of the imidate ester means a reduction in the yield of the desired amidine. The δ values of the signals in ^1H and ^{13}C NMR spectra of methyl *N*-octylacetimidate **6b** perfectly matched the new signals of the impurity in the sample obtained from the reaction of higher amines such as tetradecyl and hexadecyl amine by method 1. The chemical shifts of the α -CH_2- of the imidate ester derived from the simple aliphatic amines (Table 2, entries 1−7) are downfield (by approximately 0.2 δ) compared to the peaks obtained for the

Table 2. Imidate Ester Formation As a Function of Alkyl Chain Length for the Syntheses Carried out by Method 1

entry	primary amine	yield (%)[a]	imidate ester (%)
1	$C_4H_9NH_2$	92	0
2	$C_6H_{13}NH_2$	91	4
3	$C_8H_{17}NH_2$	98	4
4	$C_{10}H_{21}NH_2$	quantitative	9
5	$C_{12}H_{25}NH_2$	98	9
6	$C_{14}H_{29}NH_2$	quantitative	13
7	$C_{16}H_{33}NH_2$	quantitative	18

[a] Yield of impure amidine.

imidate ester from the amine with the PEG chain because of the ethereal O-atom on the β-carbon atom.

An increase in the percentage of the imidate ester with an increase in the alkyl chain length may also be a result of a solvent effect caused by THF, because higher amines are solids and were dissolved in THF to achieve the synthesis. When tetradecyl- and hexadecylamine were heated with **5** at 60 °C for 2 h in the absence of any solvent, the products contained 6% and 7% of imidate ester, respectively. However, the use of THF as a solvent had no effect on

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the formation of imidate ester during the similar conversion of octylamine (4% imidate ester with and without THF).

Reacting a mixture of acetamidine and imidate ester with Me_2NH does not convert the imidate ester into an amidine. Thus the product obtained from the reaction of hexadecyl amine (Table 2, entry 7) with **5**, containing 18% of the imidate ester, when stirred with a solution of Me_2NH in THF for 18 h, did not show any reduction in the percentage of the imidate ester. Considering this reaction might require higher temperatures, we diverted our attention to the reaction of imidate ester with a secondary amine such as Pr_2NH, having a boiling point much higher than Me_2NH. When the same hexadecyl acetamidine (contaminated with 18% imidate ester) was reacted with Pr_2NH at 60 °C for 2 h, 12% imidate ester was detected in the product by ^{1}H NMR analysis. Therefore, high temperatures might favor the formation of amidines from the imidate esters.

CONCLUSION

In our quest to achieve the synthesis of a range of long-chain acetamidines, we have found that the post-synthesis purification of certain acetamidines is difficult or impossible. The last step of the synthesis, a condensation reaction of primary amines with *N*,*N*-dimethylacetamide dimethyl acetal **5**, was modified to increase the selectivity for acetamidine so that a subsequent purification would be unnecessary. Imidate ester is the primary byproduct formed in these condensations. The identity of the imidate ester byproduct has been established by ^{1}H, ^{13}C, ^{13}C DEPT-135, and HSQC NMR spectroscopy. Pure acetamidine, without imidate ester, can be generated by performing the condensation reaction in the presence of Me_2NH. The method is compatible with the presence of ether and alcohol functional groups in the amine.

EXPERIMENTAL SECTION

The signal frequency of the ^{1}H NMR experiment was 400 MHz, and for ^{13}C NMR experiments was 100 MHz. Unless stated otherwise, NMR samples of phthalimides and amines were prepared in $CDCl_3$ (δ_H 7.26 (s) and δ_C 77.23 (t)), and those of amidines were prepared in C_6D_6 (δ_H 7.15 (s) and δ_C 128.00 (t)). Commercial $CDCl_3$ contains too much acid to be used as an inert solvent for NMR spectroscopy of amidines. Silia*Flash* F60 (40−63 μm) obtained from SiliCycle was used for flash column chromatography. The yields of phthalimides are based on alcohols. Alcohols (compounds **1a**−**h**) and the amines required to make entries 1−13 in Table 1 were all purchased and used as received. *N*,*N*-Dimethylacetamide dimethyl acetal (stabilized with 5−10% methanol) was used as received from TCI America.

The synthesis of tosylate was performed starting with 20.0 g of alcohol. In all of the syntheses of phthalimide derivatives, 12.0 g of tosylate was used. For the synthesis of amine, 2.00 g of phthalimide was deprotected by hydrazinolysis to yield the corresponding amine. A typical procedure for each synthetic transformation for series **f** has been outlined below.

Synthesis of Tosylate Esters from 1. In a typical synthesis, alcohol **1f**, (20.0 g, 105 mmol) was mixed with dichloromethane (250 mL) in a round-bottom flask, and *p*-toluenesulfonyl chloride (19.7 g, 103 mmol) and 4-(*N*,*N* dimethylamino)pyridine (100 mg) were added to this solution. A reflux condenser was attached to the round-bottom flask, and the mixture was stirred for 10 min. Triethylamine (11.7 g, 116 mmol) was added to the reaction mixture dropwise over 15 min, and as the stirring was continued, a white solid (triethylammonium chloride) precipitated out of the reaction mixture. This was accompanied by the liberation of heat that caused visible evaporation and condensation of dichloromethane from the reaction mixture. After 1 h, the reflux condenser was removed from the mouth of the round-bottom flask and replaced by a stopper. The reaction mixture was stirred for 2 h, after which it was treated with 1 M hydrochloric acid solution (200 mL). The dichloromethane layer was separated from the aqueous layer, washed with water (200 mL), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield the tosylate ester in near-quantitative yields. This product was carried through to the phthaloylation step without purification except for **1h**, which was crystallized using dichloromethane (50 mL) and hexanes (400 mL).

Synthesis of 2. A mixture of tosylate ester from **1f** (12.0 g, 34.8 mmol), finely powdered potassium phthalimide (7.73 g, 41.8 mmol), and *N*,*N*-dimethylformamide (30 mL) were combined in a round-bottom flask. The reaction mixture was stirred at 80 °C under an air condenser for 18 h. Diethyl ether (250 mL) was added to the reaction mixture, which was then filtered to remove precipitated potassium tosylate. The salt was washed with diethyl ether and the washings were combined with the filtrate. To remove the solvents, diethyl ether was first evaporated under reduced pressure on a rotary evaporator. This was followed by vacuum distillation of *N*,*N*-dimethylformamide until approximately 25−27 mL was collected in the receiving flask. The residue was purified by column chromatography using 15−40% ethyl acetate in hexanes. The optimal polarity of the solvent system used for the separation of the phthalimide depends on its polarity. The only exception was **2h**, where the ether washing was not attempted. Instead, *N*,*N*-dimethylformamide was first removed at reduced pressure and then the product was purified by crystallization using dichloromethane (100 mL) and hexanes (400 mL).

2-(2-(2-Methoxyethoxy)ethyl)isoindoline-1,3-dione (2a). Yield: 76%. Eluent: 40% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 3.26 (s, 3H), 3.43−3.46 (t, J = 4.6 Hz, 2H), 3.59−3.61 (t, J = 4.6 Hz, 2H), 3.69−3.72 (t, J = 6.0 Hz, 2H), 3.84−3.87 (t, J = 6.0 Hz, 2H), 7.65−7.67 (m, 2H), 7.76−7.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 37.21, 59.03, 67.98, 69.95, 71.94, 123.25, 132.20, 133.96, 168.28.

2-(2-(2-(2-Ethoxyethoxy)ethoxy)ethyl)isoindoline-1,3-dione (2b). Yield: 83%. Eluent: 40% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 1.08−1.11 (t, J = 7.0 Hz, 3H), 3.38−3.45 (m, 4H,), 3.49−3.59 (m, 6H), 3.65−3.68 (t, 2H, J = 5.8 Hz), 3.80−3.83 (t, 2H, J = 6.0 Hz), 7.63−7.66 (m, 2H), 7.73−7.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.13, 37.24, 66.52, 67.85, 69.75, 70.10, 70.53, 70.65, 123.15, 132.11, 133.89, 168.15.

2-(2-(2-Butoxyethoxy)ethyl)isoindoline-1,3-dione (2c). Yield: 78%. Eluent: 20% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 0.84−0.88 (t, 3H, J = 7.2 Hz), 1.24−1.33 (m, 2H), 1.44−1.51 (m, 2H), 3.36−3.40 (t, J = 6.6 Hz, 2H), 3.51−3.53 (t, J = 4.4 Hz, 2H), 3.61−3.64 (t, J = 4.6 Hz, 2H), 3.72−3.75 (t, J = 5.8 Hz, 2H), 3.88−3.91 (t, J = 5.8 Hz, 2H), 7.69−7.71 (m, 2H), 7.82−7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.06, 19.38, 31.84, 37.40, 68.04, 70.20, 70.26, 71.36, 123.37, 132.33, 134.04, 168.41.

2-(2-(2-(2-Butoxyethoxy)ethoxy)ethyl)isoindoline-1,3-dione (2d). Yield: 83%. Eluent: 25% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 0.88−0.92 (t, J = 7.4 Hz, 3H), 1.31−1.37 (m, 2H), 1.51−1.56 (m, 2H), 3.41−3.44 (t, J = 6.6 Hz, 2H), 3.50−3.52 (m, 2H), 3.57−3.67 (m, 6H), 3.73−3.76 (t, J = 5.8 Hz, 2H), 3.89−3.92 (t, J = 5.8 Hz, 2H), 7.71−7.73 (m, 2H), 7.84−7.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.98, 19.30, 31.72, 37.31, 67.94, 70.06, 70.17, 70.60, 70.68, 71.19, 123.25, 132.18, 133.97, 168.27.

2-(2-(Hexyloxy)ethyl)isoindoline-1,3-dione (2e). Yield: 83%. Eluent: 15% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 0.81−0.84 (t, J = 6.8 Hz, 3H), 1.22−1.29 (m, 6H), 1.47−1.54 (m, 2H), 3.43−3.46 (t, J = 6.6 Hz, 2H), 3.66−3.69 (t, J = 6.0 Hz, 2H), 3.88−3.91 (t, J = 6.0 Hz, 2H), 7.70−7.77 (m, 2H), 7.83−7.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.14, 22.72, 25.83, 29.66, 31.74, 37.60, 67.49, 71.12, 123.36, 132.30, 134.03, 168.42.

2-(2-(2-(Hexyloxy)ethoxy)ethyl)isoindoline-1,3-dione (2f). Yield: 83%. Eluent: 25% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 0.83−0.87 (t, 3H, J = 6.8 Hz), 1.19−1.29 (m, 6H), 1.45−1.50 (m, 2H), 3.35−3.39 (t, J = 6.8 Hz, 2H), 3.50−3.53 (m, 2H), 3.61−3.64 (m, 2H), 3.72−3.75 (t, J = 5.8 Hz, 2H), 3.88−3.90 (t, J = 5.8 Hz, 2H), 7.68−7.72 (m, 2H), 7.80−7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.11, 22.65, 25.77, 29.64, 31.73, 37.30, 67.93, 70.10, 70.16, 71.58, 123.25, 132.22, 133.94, 168.28.

2-(2-(2-(Benzyloxy)ethoxy)ethyl)isoindoline-1,3-dione (2g). Yield: 75%. Eluent: 25% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): 3.59−3.61 (m, 2H), 3.67−3.70 (m, 2H), 3.76−3.79 (t, J = 5.8 Hz, 2H), 3.91−3.94 (t, J = 5.8 Hz, 2H), 4.51 (s, 2H), 7.23−7.33 (m, 5H), 7.68−7.72 (m, 2H), 7.81−7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 37.44, 68.06, 69.53, 70.32, 73.29, 123.32, 127.60, 127.72, 128.42, 132.25, 133.99, 138.37, 168.36.

2-(2-Phenoxyethyl)isoindoline-1,3-dione (2h). Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): 4.03−4.06 (t, J = 5.8 Hz, 2H), 4.14−4.17 (t, J = 5.8 Hz, 2H), 6.80−6.87 (m, 3H), 7.15−7.19 (m, 2H), 7.63−7.67 (m, 2H), 7.77−7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 37.55, 64.79, 114.80, 121.30, 123.55, 129.64, 132.24, 134.23, 158.48, 168.37.

Synthesis of 3. The phthalimide **2f** (2.00 g, 6.27 mmol), hydrazine hydrate (0.63 mL of 64 wt.% solution, 12.5 mmol), and ethanol (30 mL) were combined in a round-bottom flask. The reaction mixture was stirred while being refluxed at 76 °C for 3 h, during which a white solid (phthalhydrazide) was formed in the reaction mixture. Ethanol was removed from the reaction mixture by rotary evaporation until the precipitate was nearly dry. Cold diethyl ether (75 mL) was added in to the round-bottom flask, and the amine was extracted from the fluffy phthalhydrazide by stirring the mixture over a magnetic stir plate. The solution was filtered and the residual phthalhydrazide was washed using cold diethyl ether (2 × 10 mL). The combined filtrate and washings were evaporated under reduced pressure to obtain **3f** in good yield.

2-(2-Methoxyethoxy)ethanamine (3a). Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (bs, 2H), 2.86−2.89 (t, J = 5.4 Hz, 2H), 3.39 (s, 3H), 3.50−3.52 (t, J = 5.2 Hz, 2H), 3.54−3.56 (m, 2H), 3.61−3.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 41.79, 59.06, 70.26, 71.94, 73.56.

2-(2-(2-Ethoxyethoxy)ethoxy)ethanamine (3b). Yield: quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): 1.16−1.20 (t, J = 7.0 Hz, 3H), 1.64 (bs, 2H), 2.82−2.85 (t, J = 5.2 Hz, 2H), 3.47−3.64 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.28, 41.93, 66.76, 69.96, 70.42, 70.72, 70.82, 73.58.

2-(2-Butoxyethoxy)ethanamine (3c). Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.90−0.94 (t, J = 7.4 Hz, 3H), 1.32−1.42 (m, 2H), 1.54−1.61 (m, 2H), 1.73 (bs, 2H), 2.86−2.89 (t, J = 5.2 Hz, 2H), 3.45−3.49 (t, J = 6.8 Hz, 2H), 3.51−3.53 (t, J = 5.2 Hz, 2H), 3.58−3.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.86, 19.23, 31.67, 41.62, 69.99, 70.32, 71.14, 73.11.

2-(2-(2-Butoxyethoxy)ethoxy)ethanamine (3d). Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.85−0.89 (t, J = 7.4 Hz, 3H), 1.27−1.36 (m, 2H), 1.49−1.56 (m, 4H), 2.81−2.84 (t, J = 4.6 Hz, 2H), 3.40−3.43 (t, J = 6.8 Hz, 2H), 3.46−3.48 (t, J = 5.2 Hz, 2H), 3.53−3.64 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.03, 19.37, 31.81, 41.90, 70.18, 70.41, 70.70, 70.77, 71.31, 73.53.

2-(Hexyloxy)ethanamine (3e). Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.88−0.91 (t, J = 6.8 Hz, 3H), 1.31−1.39 (m, 6H), 1.55−1.62 (m, 2H), 1.86 (bs, 2H), 2.87−2.89 (t, J = 5.2 Hz, 2H), 3.43−3.48 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.16, 22.74, 25.96, 29.81, 31.82, 42.04, 71.35, 73.01.

2-(2-(Hexyloxy)ethoxy)ethanamine (3f). Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.87−0.91 (t, J = 6.8 Hz, 3H), 1.30−1.37 (m, 6H), 1.55−1.63 (m, 2H), 1.84 (bs, 2H), 2.87−2.90 (t, J = 5.2 Hz, 2H), 3.45−3.48 (t, J = 6.8 Hz, 2H), 3.52−3.54 (t, J = 5.2 Hz, 2H), 3.58−3.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.03, 22.62, 25.78, 29.61, 31.69, 41.79, 70.03, 70.36, 71.54, 73.41.

2-(2-(Benzyloxy)ethoxy)ethanamine (3g). Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.51 (bs, 2H), 2.88−2.90 (t, J = 5.2 Hz, 2H), 3.52−3.55 (t, J = 5.2 Hz, 2H), 3.64−3.68 (m, 4H), 4.60 (s, 2H), 7.28−7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 41.84, 69.41, 70.37, 73.23, 73.50, 127.60, 127.71, 128.36, 138.26.

2-(Phenyloxy)ethanamine (3h). Yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.51 (bs, 2H), 3.10−3.12 (t, J = 5.2 Hz, 2H), 4.00−4.02 (t, J = 5.2 Hz, 2H), 6.93−6.99 (m, 3H), 7.28−7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 41.70, 70.12, 114.59, 120.90, 129.57, 158.98.

Synthesis of 4. Amine **3f** (1.00 g, 5.29 mmol) was condensed with **5** (0.845 g, 6.35 mmol) in the presence of Me_2NH (5.3 mL of 2 M solution in THF, 10.6 mmol) following the procedure described in method 3 below.

***N′*-(2-(2-Methoxyethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4a).** Yield: 92%. ^{1}H NMR (400 MHz, C_6D_6): 1.46 (s, 3H), 2.59 (s, 6H), 3.14 (s, 3H), 3.39−3.41 (t, J = 5.0 Hz, 2H), 3.52−3.55 (t, J = 6.6 Hz, 2H), 3.58−3.60 (t, J = 5.0 Hz, 2H), 3.79−3.83 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.23, 37.75, 50.72, 58.64, 70.88, 72.42, 73.65, 158.43. HRMS (ES^+) calcd ($C_9H_{20}N_2O_2$ + H) 189.1603, obsd 189.1605.

***N′*-(2-(2-(2-Ethoxyethoxy)ethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4b).** Yield: 94%. ^{1}H NMR (400 MHz, C_6D_6): 1.06−1.09 (t, J = 6.8 Hz, 3H), 1.47 (s, 3H), 2.59 (s, 6H), 3.27−3.32 (q, J = 6.9 Hz, 2H), 3.42−3.45 (t, J = 4.8 Hz, 2H), 3.50−3.55 (m, 6H), 3.58−3.61 (t, J = 4.8 Hz, 2H), 3.77−3.80 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.30, 15.44, 37.80, 50.60, 66.53, 70.36, 71.02, 71.05, 71.09, 73.53, 158.61. HRMS (ES^+) calcd ($C_{12}H_{26}N_2O_3$ + H) 247.2022, obsd 247.2012.

***N′*-(2-(2-Butoxyethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4c).** Yield: 92%. ^{1}H NMR (400 MHz, C_6D_6): 0.82−0.86 (t, J = 7.2 Hz, 3H), 1.32−1.38 (m, 2H), 1.46−1.53 (m, 5H), 2.59 (s, 6H), 3.31−3.34 (t, J = 6.4 Hz, 2H,), 3.49−3.56 (m, 4H), 3.63−3.64 (t, J = 5.0 Hz, 2H), 3.81−3.84 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.36, 14.08, 19.69, 32.33, 37.86, 50.47, 70.69, 71.06, 71.09, 73.53, 158.65. HRMS (ES^+) calcd 231.2073 ($C_{12}H_{26}N_2O_2$ + H), obsd 231.2079.

***N′*-(2-(2-(2-Butoxyethoxy)ethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4d).** Yield: 96%. ^{1}H NMR (400 MHz, C_6D_6): 0.83−0.87 (t, J = 7.4 Hz, 3H), 1.32−1.37 (m, 2H), 1.48−1.53 (m, 5H), 2.60 (s, 6H), 3.30−3.33 (t, J = 6.4 Hz, 2H), 3.45−3.61 (m, 10H), 3.78−3.81 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.25, 14.08, 19.68, 32.30, 37.77, 50.68, 70.66, 71.06, 71.10, 71.12, 73.61, 158.41. HRMS (ES^+) calcd ($C_{14}H_{30}N_2O_3$ + H) 275.2335, obsd 275.2341.

***N′*-(2-(Hexyloxy)ethyl)-*N*,*N*-dimethylacetimidamide (4e).** Yield: 91%. ^{1}H NMR (400 MHz, C_6D_6): 0.83−0.86 (t, J = 7.0 Hz, 3H), 1.20−1.25 (m, 4H), 1.33−1.37 (m, 2H), 1.50 (s, 3H), 1.56−1.60 (m, 2H), 2.61 (s, 6H), 3.41−3.45 (t, J = 6.6 Hz, 2H), 3.53−3.56 (t, J = 6.8 Hz, 2H), 3.76−3.79 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.26, 14.24, 23.03, 26.36, 30.39, 32.10, 37.78, 50.74, 71.41, 73.27, 158.36. HRMS (ES^+) calcd ($C_{12}H_{26}N_2O$ + H) 215.2123, obsd 215.2124.

***N′*-(2-(2-(Hexyloxy)ethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4f).** Yield: quantitative. ^{1}H NMR (400 MHz, C_6D_6): 0.84−0.87 (t, J = 6.6 Hz, 3H), 1.19−1.28 (m, 4H), 1.30−1.37 (m, 2H), 1.47 (s, 3H), 1.53−1.57 (m, 2H), 2.60 (s, 6H), 3.33−3.36 (t, J = 6.4 Hz, 2H), 3.51−3.56 (m, 4H), 3.64−3.66 (t, J = 5.2 Hz, 2H), 3.82−3.85 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.24, 14.24, 23.00, 26.29, 30.28, 32.06, 37.76, 50.75, 70.74, 71.09, 71.48, 73.68, 158.36. HRMS (ES^+) calcd ($C_{14}H_{30}N_2O_2$ + H) 259.2386, obsd 259.2372.

***N′*-(2-(2-(Benzyloxy)ethoxy)ethyl)-*N*,*N*-dimethylacetimidamide (4g).** Yield: 97%. ^{1}H NMR: (400 MHz, C_6D_6): 1.46 (s, 3H), 2.59 (s, 6H), 3.50−3.56 (m, 4H), 3.61−3.64 (t, J = 5.0 Hz, 2H),

3.81−3.84 (t, J = 6.6 Hz, 2H), 4.39 (s, 2H), 7.08−7.10 (m, 1H), 7.14−7.19 (m, 2H), 7.28−7.30 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.28, 37.77, 50.66, 70.13, 71.00, 73.15, 73.60, 127.46, 127.71, 128.43, 139.39, 158.52. HRMS (ES^+) calcd ($C_{15}H_{24}N_2O_2$ + H) 265.1916, obsd 265.1900.

***N,N*-Dimethyl-*N′*-(2-phenoxyethyl)acetimidamide (4h).** Yield: 94%. ^{1}H NMR (400 MHz, THF-d_8): 1.84 (s, 3H), 2.83 (s, 6H), 3.49−3.52 (t, J = 6.8 Hz, 2H), 4.03−4.07 (t, J = 6.8 Hz, 2H), 6.81−6.90 (m, 3H), 7.17−7.22 (m, 2H). ^{13}C NMR(100 MHz, THF-d_8): 12.57, 38.08, 50.21, 70.26, 115.21, 120.81, 129.93, 159.63, 160.46. HRMS (ES^+) calcd ($C_{12}H_{18}N_2O$ + H) 207.1497, obsd 207.1494.

Methyl *N*-octylimidate (6b). The imidate was derived from *N*-acetyl octylamine by the procedure reported earlier by Torssell et al., replacing distillation by column chromatography (50% ethyl acetate, 1% triethylamine in hexanes) for the final purification.[13] Yield: 36%. ^{1}H NMR (400 MHz, C_6D_6): 0.88−0.92 (t, J = 6.8 Hz, 3H), 1.27−1.31 (m, 8H), 1.39−1.43 (m, 2H), 1.58 (s, 3H), 1.63−1.67 (m, 2H), 3.09−3.12 (t, J = 6.8 Hz, 2H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): 14.17, 14.33, 23.07, 27.88, 29.81, 30.00, 32.11, 32.28, 49.39, 51.96, 160.29. HRMS (ES^+) calcd ($C_{11}H_{23}NO$ + H) 186.1858, obsd 186.1853.

6-(1,3-Dioxoisoindolin-2-yl)hexyl 4-methylbenzenesulfonate (8). The mixture of finely powdered phthalic anhydride (29.6 g, 200 mmol) and 6-amino-1-hexanol (23.4 g, 200 mmol) are combined in a 500 mL round-bottom flask and the mixture was heated at 120 °C for 3 h, while being stirred. The condensation was marked by liberation of water, which was very vigorous during the initial stages of the reaction. The fused mass was dissolved in dichloromethane (250 mL). *para*-Toluenesulfonyl chloride (42.0 g, 220 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (200 mg) were added to this solution and the mixture was stirred to obtain a clear solution. A reflux condenser was attached to the round-bottom flask and triethylamine (40.4 g, 400 mmol) was added dropwise to the reaction mixture while being stirred. The stirring was continued for 18 h after the addition of triethylamine. Hydrochloric acid (20.9 mL of 35 wt.% HCl mixed with 200 mL of water, 200 mmol) was added to the reaction and the mixture was stirred vigorously for 15 min. Dichloromethane was separated from the aqueous layer, dried over anhydrous magnesium sulfate (10 g) and evaporated under reduced pressure. Ethanol (300 mL) was added to the residue and the mixture was heated at 76 °C with stirring for 1 h. This solution was allowed to slowly cool down to 0 °C (while been stirred) to obtain a crystalline white solid (seeding with crystals obtained from earlier batches was very helpful). The solution was allowed to remain at 0 °C for 3 h and then filtered while cold. This was followed by washing (2 × 20 mL) with cold ethanol. The crystallization process was repeated to obtain **8**. Yield: 43.36 g, 54%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26−1.38 (m, 4H), 1.61−1.67 (m, 4H), 2.46 (s, 3H), 3.63−3.66 (t, J = 7.2 Hz, 2H), 4.00−4.04 (t, J = 6.4 Hz, 2H), 7.34−7.36 (d, J = 8.0 Hz, 2H) 7.71−7.73 (m, 2H), 7.78−7.80 (d, J = 8.0 Hz, 2H), 7.84−7.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.80, 25.13, 26.35, 28.53, 28.85, 37.92, 70.58, 123.36, 128.05, 130.01, 132.29, 133.36, 134.09, 144.86, 168.58.

2-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)hexyl)isoindoline-1,3-dione (9). In a 250 mL round-bottom flask, **8** (32.8 g, 81.6 mmol) was heated at 100 °C under high vacuum for 1 h to remove any bound water or water of crystallization. The flask was slowly brought down to rt and then purged with argon. Dry THF (150 mL) was added to this tosylate. A solution of sodium salt of diethyleneglycol monobenzyl ether was prepared by adding the diethyleneglycol monobenzyl ether (18.4 g, 93.8 mmol) dropwise in to a suspension of NaH (3.75 g of 60 wt.% suspension in mineral oil, 93.8 mmol) in dry THF (150 mL) under inert atmosphere. The solution of **8** was gradually transferred in to the solution of the alkoxide at rt while continuing to maintain the inert atmosphere. The reaction mixture was heated at 65 °C under a reflux condenser for 18 h and then allowed to cool down to rt. THF was evaporated under reduced pressure and diethyl ether (300 mL) was added to the resulting mass causing the white solid to separate from the sticky mass. This solution was filtered and the residue was washed with diethyl ether (3 × 50 mL) to separate the crude product from the salt. The filtrate and washings were evaporated under reduced pressure to yield a crude product, which was purified further by column chromatography using 30% ethyl acetate in hexanes to yield **9**. Yield: 24.64 g, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.37−1.38 (m, 4H), 1.55−1.64 (m, 2H), 1.64−1.70 (m, 2H), 3.44−3.47 (t, J = 6.6 Hz, 2H), 3.57−3.70 (m, 10H), 4.58 (s, 2H), 7.26−7.35 (m, 5H), 7.70−7.73 (m, 2H), 7.82−7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 25.77, 26.76, 28.61, 29.54, 38.01, 69.54, 70.17, 70.74, 71.32, 73.27, 123.19, 127.60, 127.77, 128.39, 132.23, 133.90, 138.40, 168.44.

2-(6-(2-(2-Hydroxyethoxy)ethoxy)hexyl)isoindoline-1,3-dione (10). To the solution of **9** (19.2 g, 45.2 mmol) in ethanol (200 mL) in a two neck round-bottom flask, a 10% Pd−C (0.950 g) was added. The solution was allowed to stir at rt for 6 h, while hydrogen atmosphere was maintained with a continuous and gentle flow of gaseous hydrogen. The reaction mixture was filtered and washed with ethanol (3 × 20 mL). The filtrate and washings were combined and evaporated first under reduced pressure on a rotary evaporator and finally under high vacuum to yield **10**. Yield: 15.15 g, quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): 1.38−1.40 (m, 4H), 1.56−1.63 (m, 2H), 1.65−1.72 (m, 2H), 1.97 (s, 1H), 3.45−3.48 (t, J = 6.6 Hz, 2H), 3.57−3.75 (m, 10H), 7.70−7.73 (m, 2H), 7.84−7.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 25.77, 26.75, 28.64, 29.51, 38.05, 61.93, 70.28, 70.58, 71.43, 72.67, 123.29, 132.28, 133.99, 168.58.

2-(2-((6-Aminohexyl)oxy)ethoxy)ethanol (11). To the solution of **10** (15.0 g, 44.8 mmol) in ethanol (250 mL), hydrazine hydrate (4.48 mL of 64 wt.% solution, 89.6 mmol) was added and the reaction mixture was refluxed at 76 °C for 3 h. Hydrochloric acid (9.3 mL of 35 wt.% solution in 80 mL of water, 89.6 mmol) was added to the reaction mixture and the heating/stirring was further continued under the reflux condenser at 76 °C for 3 h. A solution of potassium hydroxide (7.64 g, 134 mmol) in ethanol (20 mL) was added to the reaction mixture and the mixture was allowed to stir for 5 min at rt. Ethanol was evaporated first under reduced pressure on a rotary evaporator and finally under high vacuum to yield a sticky white solid. Dichloromethane (3 × 100 mL) was used for separation/extraction of amino alcohol from the hydrazinolysis byproduct. Dichloromethane extracts were combined and evaporated first under reduced pressure on a rotary evaporator and finally under high vacuum to yield **11**. Yield: 7.53 g, 82%, ^{1}H NMR (400 MHz, $CDCl_3$): 1.36−1.38 (m, 4H), 1.41−1.49 (m, 2H), 1.58−1.65 (m, 2H), 2.49 (s, 3H), 2.68−2.72 (t, J = 6.8 Hz, 2H), 3.47−3.50 (t, J = 6.6 Hz, 2H), 3.58−3.74 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): 25.89, 26.52, 29.53, 33.23, 41.91, 61.79, 70.33, 70.64, 71.43, 72.89.

***N′*-(6-(2-(2-Hydroxyethoxy)ethoxy)hexyl)-*N*,*N*-dimethylacetimidamide (12).** The aminoalcohol **11** (5.73 g, 27.9 mmol) and Me_2NH (27.9 mL of 2 M solution in THF, 55.8 mmol) were combined in a round-bottom flask and allowed to stir at rt. *N*, *N*-Dimethylacetamide dimethyl acetal **5** (4.46 g, 33.5 mmol) was added to this combination dropwise over 5 min. The reaction mixture was stirred for 10 min and then left standing for 18 h in the dark. Most of the THF and Me_2NH were removed from the reaction mixture by rotary evaporation. This was followed by heating the contents at 55 °C with stirring on high vacuum for 8 h. Yield: 7.66 g, 99%. ^{1}H NMR (400 MHz, C_6D_6): 1.45−1.51 (m, 7H), 1.56−1.66 (m, 2H), 1.73−1.78 (m, 2H), 2.62 (s, 6H), 3.24−3.42 (m, 10H), 3.56−3.59 (t, J = 4.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.16, 26.56, 27.79, 30.21, 32.74, 37.93, 50.13, 61.63, 70.54, 70.75, 71.48, 73.26, 158.08. HRMS (EI^+) calcd ($C_{14}H_{30}N_2O_3$) 274.2256, obsd 274.2263.

Synthesis of Amidines from Primary Amines (Table 1). For each amine the reactions were performed using methods **1**, **2** and **3**. The reactions were typically performed on 0.500 g scale with respect to the amine. The three procedures are described below.

Method 1. The mixture of decylamine (0.500 g, 3.18 mmol) and **5** (0.508 g, 3.82 mmol) were heated at 60 °C for 2 h. The reaction mixture was evaporated at rt on a rotary evaporator. The contents were further heated at 55 °C on high vacuum for 8 h to yield the product. For solid amines, THF (5 mL) was used as a solvent.

Method 2. Decylamine (0.500 g, 3.18 mmol) was added dropwise in to **5** (0.508 g, 3.82 mmol) over 5 min, while it was stirred for 10 min at rt. The reaction mixture was allowed to stand for 18 h at rt. The work up involved evaporation on a rotary evaporator at rt followed by evaporation at 55 °C under high vacuum for 8 h to yield the product. For solid amines, THF (5 mL) was used as a solvent and **5** was added dropwise in to the solution of amine in THF.

Method 3. *N*,*N*-Dimethylacetamide dimethyl acetal **5** (0.508 g, 3.82 mmol) and Me_2NH (3.8 mL of 2 M solution in THF, 7.64 mmol) are combined in a round-bottom flask and allowed to stir at rt. Decylamine (0.500 g, 3.18 mmol) was added to this combination dropwise over 5 min at rt. The reaction mixture was allowed to stir for 10 min and then left standing for 18 h in the dark. Most of the THF and Me_2NH were removed from the reaction mixture by rotary evaporation. This was followed by stirring the contents at 55 °C under high vacuum for 8 h. For solid amines, THF was used as a solvent and **5** was added dropwise to the solution of amine and Me_2NH in THF.

***N′*-Butyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.92−0.95 (t, J = 7.6 Hz, 3H), 1.44−1.52 (m, 5H), 1.66−1.67 (m, 2H), 2.62 (s, 6H), 3.15−3.18 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.0, 14.4, 21.1, 35.3, 37.8, 50.0, 157.2. HRMS (ES^+) calcd ($C_8H_{18}N_2$ + H) 143.1548, obsd 143.1545.

***N′*-Hexyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.86−0.89 (t, J = 7.2 Hz, 3H), 1.30−1.33 (m, 4H), 1.44−1.47 (m, 2H), 1.53 (s, 3H), 1.63−1.71 (m, 2H), 2.63 (s, 6H), 3.16−3.20 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 11.98, 14.35, 23.23, 27.82, 32.45, 33.07, 37.83, 50.39, 157.07. HRMS (EI^+) calcd ($C_{10}H_{22}N_2$) 170.1783, obsd 170.1788.

***N′*-Octyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.86−0.89 (t, J = 6.8 Hz, 3H), 1.26−1.39 (m, 8H), 1.52 (bs, 5H), 1.73−1.77 (m, 2H), 2.64 (s, 6H), 3.23−3.26 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 11.99, 14.33, 23.10, 28.18, 29.94, 30.21, 32.36, 33.14, 37.83, 50.44, 157.11. HRMS (EI^+) calcd ($C_{12}H_{26}N_2$) 198.2096, obsd 198.2097.

***N′*-Decyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.86−0.90 (t, J = 6.8 Hz, 3H), 1.25−1.41 (m, 12H), 1.49−1.54 (m, 5H), 1.73−1.77 (m, 2H), 2.64 (s, 6H), 3.22−3.26 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.01, 14.35, 23.11, 28.20, 29.84, 30.15, 30.28, 30.31, 32.35, 33.15, 37.84, 50.44, 157.11. HRMS (EI^+) calcd ($C_{14}H_{30}N_2$) 226.2409, obsd 226.2407.

***N′*-Dodecyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.87−0.91 (t, J = 6.8 Hz, 3H), 1.26−1.40 (m, 16H), 1.52−1.55 (m, 5H), 1.74−1.77 (m, 2H), 2.64 (s, 6H), 3.23−3.26 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.01, 14.35, 23.12, 28.21, 29.84, 30.14, 30.20, 30.22, 30.30, 30.33, 32.35, 33.16, 37.85, 50.44, 157.09. HRMS (EI^+) calcd ($C_{16}H_{34}N_2$) 254.2722, obsd 254.2732.

***N′*-Tetradecyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.88−0.91 (t, J = 6.8 Hz, 3H), 1.28−1.40 (m, 20H), 1.52 (bs, 5H), 1.74−1.78 (m, 2H), 2.64 (s, 6H), 3.23−3.26 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.02, 14.36, 23.12, 28.21, 29.84, 30.14, 30.20, 30.21, 30.22, 30.31, 30.34, 32.36, 33.16, 37.85, 50.44, 157.09. HRMS (EI^+) calcd ($C_{18}H_{38}N_2$) 282.3035, obsd 282.3040.

***N′*-Hexadecyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 0.89−0.92 (t, J = 6.8 Hz, 3H), 1.31−1.43 (m, 24H), 1.51−1.59 (m, 5H), 1.80−1.83 (m, 2H), 2.64 (s, 6H), 3.27−3.31 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.02, 14.35, 23.10, 28.22, 29.82, 30.12, 30.17, 30.18, 30.19, 30.21, 30.22, 30.30, 30.33, 32.33, 33.17, 37.84, 50.45, 157.18. HRMS (EI^+) calcd ($C_{20}H_{42}N_2$) 310.3348, obsd 310.3347.

***N*,*N*-Dimethyl-*N′*-(pyridin-4-ylmethyl)acetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 1.41 (s, 3H), 2.62 (s, 6H), 4.19 (s, 2H), 7.24−7.25 (m, 2H), 8.58−8.60 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.5, 37.7, 52.5, 122.8, 149.9, 152.4, 159.0. HRMS (EI^+) calcd ($C_{10}H_{15}N_3$) 177.1266, obsd 177.1272.

***N′*-Benzyl-*N*,*N*-dimethylacetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 1.58 (s, 3H), 2.76 (s, 6H), 4.54 (s, 2H), 7.21−7.25 (m, 1H), 7.35−7.39 (m, 2H), 7.60−7.62 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.4, 37.8, 53.7, 126.1, 127.7, 128.3, 143.8, 158.5. HRMS (EI^+) calcd ($C_{11}H_{16}N_2$) 176.1313, obsd 176.1326.

***N*,*N*-Dimethyl-*N′*-(1-phenylethyl)acetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 1.44 (s, 3H), 1.53−1.55 (m, 3H), 2.62 (s, 6H), 4.42−4.48 (q, J = 6.4 Hz, 1H), 7.08−7.12 (m, 1H), 7.23−7.27 (m, 2H), 7.53−7.55 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): 12.3, 27.7, 37.7, 58.4, 126.2, 127.0, 128.5, 149.5, 156.6. HRMS (EI^+) calcd ($C_{12}H_{18}N_2$) 190.1470, obsd 190.1472.

***N*,*N*-Dimethyl-*N′*-(thiophen-2-ylmethyl)acetimidamide.** ^{1}H NMR (400 MHz, C_6D_6): 1.40 (s, 3H), 2.61 (s, 6H), 4.51 (s, 2H), 6.85−6.87 (m, 2H), 6.96−6.98 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6): 12.3, 37.7, 49.3, 122.0, 123.3, 126.6, 149.0, 158.6. HRMS (EI^+) calcd ($C_9H_{14}N_2S$) 182.0878, obsd 182.0883.

***N′*,*N″*,*N‴*-(Nitrilotris(ethane-2,1-diyl))tris(*N*,*N*-dimethylacetimidamide).** ^{1}H NMR (400 MHz, C_6D_6): 1.53 (s, 9H), 2.61 (s, 18H), 2.92−2.96 (t, J = 7.6 Hz, 6H), 3.38−3.42 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, C_6D_6): 12.2, 37.9, 49.9, 58.6, 157.7. HRMS (ES^+) calcd ($C_{18}H_{39}N_7$ + H) 354.3345, obsd 354.3347.

***N′*,*N″*-((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(*N*,*N*-dimethylacetimidamide).** ^{1}H NMR (400 MHz, C_6D_6): 1.50 (s, 6H), 2.59 (s, 12H), 3.41−3.44 (t, J = 6.8 Hz, 4H), 3.57 (bs, 4H), 3.68−3.72 (t, J = 6.8 Hz, 4H). ^{13}C NMR (100 MHz, C_6D_6): 12.2, 37.8, 50.7, 71.1, 73.6, 158.4. HRMS (ES^+) calcd ($C_{14}H_{30}N_4O_2$ + H) 287.2447, obsd 287.2443.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Comparison of ^{1}H and ^{13}C NMR spectra of product obtained by condensation of **3g** with **5** by methods 1, 2, and 3, ^{13}C DEPT-135 and HSQC NMR spectra of the product obtained by condensation of **3g** with **5** by method 1, ^{1}H and ^{13}C spectra of compounds **2**−**4**(**a**−**h**), **6b**, and **8**−**12** and for all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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