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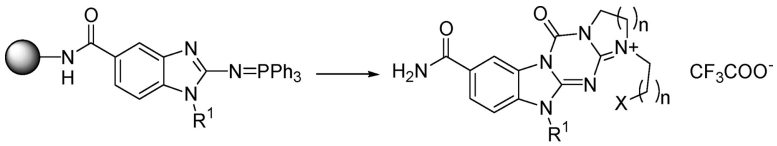

n = 1, 2
X = Cl, Br

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Halogenoalkyl Isocyanates as Bifunctional Reagents in an Aza-Wittig/Heterocyclization Reaction on the Solid Phase: Efficient Entry into New Tetracyclic Benzimidazole Systems

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An efficient one-pot procedure for the solid-phase synthesis of new tetracyclic 1,3,5-triazino[1,2-*a*]-benzimidazolium derivatives starting from resin-bound benzimidazoles is described. The synthetic strategy involves an unprecedented one-pot Aza-Wittig/heterocyclization/substitution reaction sequence using halogenoalkyl isocyanates. The structure of the tetracyclic ring system was determined by two-dimensional NMR experiments and X-ray analysis.

Introduction

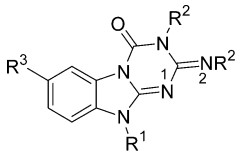
Aza-Wittig reactions using isocyanates provide a valuable method for the formation of functionalized carbodiimides as highly reactive intermediates able to perform a variety of heterocyclization reactions.[1] We envisioned that halogenoalkyl isocyanates could undergo an Aza-Wittig/heterocyclization reaction followed by an intramolecular nucleophilic substitution of the halogeno group. This reaction sequence could be an efficient strategy for the one-pot assembly of two heterocyclic rings. To our knowledge, there is no precedent for the use of halogenoalkyl isocyanates in Aza-Wittig/heterocyclization reactions, despite their great synthetic potential due to their bifunctional nature.

Recently, we reported a solid-phase tandem Aza-Wittig/annulation reaction starting from resin-bound benzimidazoles for the synthesis of 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]-benzimidazoles **1** (Scheme 1).[2] The reaction seemed to be suitable for exploration to determine whether halogenoalkyl isocyanates are able to undergo a Aza-Wittig/heterocyclization/substitution sequence. Both the imino nitrogen atom 2 and the triazino nitrogen 1 in compound **1** display nucleophilic properties and may substitute a halogeno functionality introduced by halogeno isocyanates ($R^2 = (CH_2)_nCH_2X$), thereby leading to new tetracyclic benzimidazolium derivatives **2** and **3** (Scheme 2). Benzimidazole derivatives have been extensively described in the literature as an important class of compounds with a wide variety of known biological properties, including anthelmintic, antiviral, antiallergic and antineoplastic activity.[3]

Results and Discussion

The preparation of all compounds described was carried out utilizing Houghten's "tea-bag" method.[4] This method permits the rapid synthesis of large numbers of compounds in a short time period. Four different amines were used to synthesize the solid-supported benzimidazoles **4**. Conversion

Scheme 1



1

to the resin-bound iminophosphoranes **5** was achieved using triphenylphosphine and diethyl azodicarboxylate or diisopropyl azodicarboxylate under typical Mitsunobu conditions (Scheme 2).[2]

Initial studies on the one-pot Aza-Wittig/heterocyclization/substitution procedure (Scheme 2) were carried out using 2-bromoethyl isocyanate. Following cleavage from the resin, the resulting product was analyzed by LC/MS. Subsequently to the Aza-Wittig/heterocyclization reaction, a nucleophilic displacement of one of the bromo atoms took place. However, purities and regioselectivities were found to be low (Table 1, entry 2a). It was known from previous results that, although aryl isocyanates undergo Aza-Wittig/heterocyclization at ambient temperatures, a high reaction temperature (100 °C) is required when employing alkyl isocyanates. Thus, potential optimization was limited. In view of this limitation, we decided to study the influence of the halogeno atom on regioselectivity and purity and conducted the reaction employing 2-chloroethyl isocyanate. The lower reactivity of the chloro atom was found to be advantageous. Good purities (>80%) and excellent yields (>94%) were achieved using 15 eqiv of chloroethyl isocyanate (0.2 M in toluene) at 100 °C. One regioisomer was predominantly formed in selectivities ranging between 90 and 96% (Table 1). To broaden the scope of the reaction, 3-chloropropyl isocyanate was used under the same reaction conditions, leading to tetrahydropyrimido-1,3,5-triazinobenzimidazolium salts. Good purities (>80%) and regioselectivities (93%) were obtained (Table 1).

To elucidate the structure of the major regioisomer obtained using 2-chloroethyl isocyanate and 3-chloropropyl

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Scheme 2

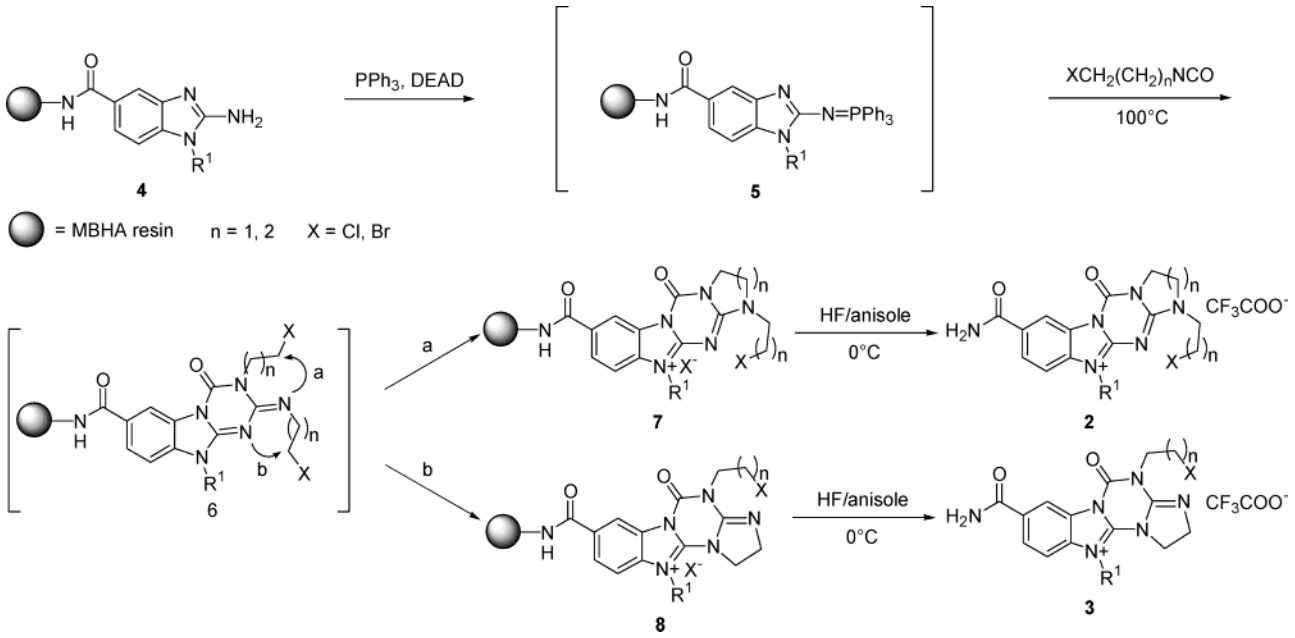


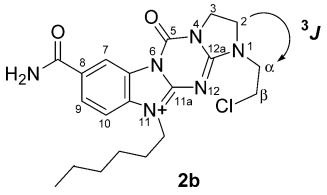
Table 1. Individual Tetracyclic Benzimidazolium Salts **2**

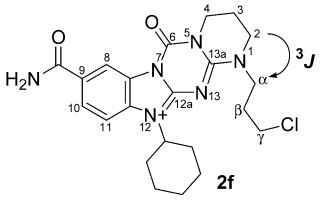
entry[a]	R^1	X	*n*	purity[b]	regioselectivity[b]
2a	hexyl	Br	1	50	30[c]
2b	hexyl	Cl	1	80	90
2c	butyl	Cl	1	83	92
2d	cyclohexyl	Cl	1	84	95
2e	3-methoxypropyl	Cl	1	82	96
2f	cyclohexyl	Cl	2	80	94
2g	hexyl	Cl	2	81	93
2h	3-methoxypropyl	Cl	2	85	96

[a] Crude yields ranged from 94 to 99% and were calculated on the basis of the initial loading of the resin (1.1 meqiv/g). [b] Purities and regioselectivities were determined from the relative peak areas (%) of HPLC chromatograms using a gradient of 5−95% acetonitrile in water (0.05% TFA) over 10 min at $\lambda = 214$ nm. [c] Regioselectivity was determined by ^{1}H NMR due to insufficient separation by HPLC.

isocyanate, we performed a two-dimensional NMR study on purified compounds **2b** and **2f**. For compound **2b**, the crucial protons of the dihydroimidazo ring and the chloroethyl chain appear in the ^{1}H NMR spectrum between 3.98 and 4.36 ppm (20 °C, DMSO-d_6). It is noteworthy that all four protons of the ring formed by the nucleophilic displacement of the chloro atom appear as a singlet at 3.98 ppm. The ^{13}C and ^{1}H assignments were made using $^1J_{CH}$ HMQC and ^{1}H,^{1}H COSY. Analysis of a ^{13}C HMBC spectrum, which allows detection of a correlation between a proton and the carbon atoms two and three bonds away, led to the unambiguous identification of the predominant regioisomer. The correlation between the α-carbon atom of the chloroethyl chain and the ring hydrogen atom H-2 revealed that dihydroimidazo-1,3,5-triazino[1,2-*a*]benzimidazole **2b** was formed as the major regioisomer (route a, Scheme 2). Only in structure **2** are H-2 and the α-CH_2 expected to show an easily observable long-range correlation (^3J), whereas in structure **3**, the distance between the α-CH_2 and the imidazo ring hydrogens is much longer (^5J), and detection of a correlation is unlikely. In addition, a correlation between C-11a and a dihydroimidazo proton expected for structure **3** was not observed. The crucial correlations are summarized in Table 2. To corroborate the 2D NMR study, an X-ray structure was obtained for **2b**

Table 2. Crucial 2D NMR Correlations for the Structure Elucidation of **2b** and **2f**





position	δ (^{1}H)	^{1}H, ^{1}H COSY	HMBC	δ (^{13}C)[a]	position	δ (^{1}H)	^{1}H, ^{1}H COSY	HMBC	δ (^{13}C)[a]
2,3	3.99		C-2, C-3, C-12a, α-CH_2 (^3J)	40.6, 46.2	2	3.95	H-3	C-3, C-4, C-13a, α-CH_2 (^3J)	48.5
α-CH_2	4.13	β-CH_2	βCH_2, C-12a	46.1	3	2.19	H-2, H-4	C-4, C-2	29.3
β-CH_2	4.31	α-CH_2	α-CH_2	41.3	4	3.79	H-3	C-2, C-3	42.8
12a				157.2	α-CH_2	3.71	β-CH_2	β-CH_2, γ-CH_2	46.3
					β-CH_2	2.11	α-CH_2, γ-CH_2		18.4
					γ-CH_2	4.06	β-CH_2	β-CH_2, α-CH_2	41.3

[a] The ^{13}C assignment was made using $^1J_{CH}$ HMQC.

Table 3. Nucleophilic Substitution to Di- and Trisubstituted Benzimidazolium Derivatives (**10**)[a]

entry	R_1	R_2	R_3	*n*	mass (M^+)	yield[b]	purity[c]
10a	hexyl	butyl	H	1	454.3	97	80
10b	hexyl	3-methoxypropyl	H	1	470.4	99	80
10c	2-ethylpropyl	3-fluorophenethyl	H	1	506.2	94	77
10d	cyclohexyl	3-phenylpropyl	H	1	514.3	90	82
10e	butyl	butyl	$NH_2COCHPh$	1	573.5	94	78

[a] $n = 1$. [b] Crude yields were calculated on the basis of the initial loading of the resin (1.1 meqiv/g). [c] Purities were determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) over 10 min at $\lambda = 214$ nm.

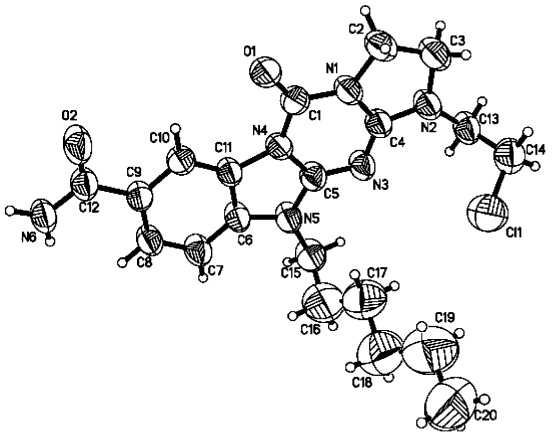
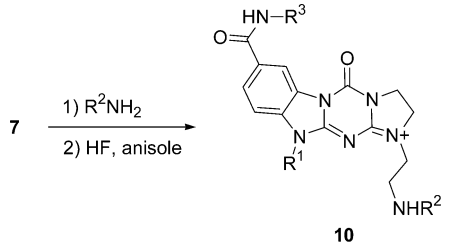


Figure 1. X-ray structure of **2b**.

Scheme 3



(Figure 1). To prove the structural assignment of the tetrahydropyrimido derivatives **2** ($n = 2$), a similar NMR study was performed. Again, correlation between α-CH_2 and the ring proton H-2 allows unambiguous identification of compound **2** as the major regioisomer (Table 2).

To increase the diversity around the tetracyclic benzimidazolium template, we substituted the chloro atom in selected compounds **7** with primary amines (Scheme 3). Treatment of the selected compounds **7** with 10 eqiv of amine (0.04 M in DMF) at 25 °C for 4 h and cleavage from the resin led to the respective 1-(2-alkylaminoethyl)benzimidazolium salts **10** (Table 3). A third diversity (R^3) was introduced using a resin preloaded with an amino acid. (Table 3).[2]

Summary

In summary, we have developed an unprecedented consecutive Aza-Wittig/heterocyclization/substitution synthesis on the solid phase starting from resin-bound benzimidazoles. The synthetic approach provides convenient access to new structurally complex, pharmacologically interesting tetracyclic benzimidazolium derivates in high yields and good purities. Further investigation to assess the applicability of the synthetic strategy for the construction of various heterocycles is under way.

Experimental Section

General Methods. *p*-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.15 mequiv/g substitution), HF, and argon were purchased from Air Products (San Marcos, CA). All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. Analytical RP-HPLC was performed on a Beckman System Gold Instrument (Fullerton, CA). HPLC chromatograms were run with a gradient of 5−95% acetonitrile in water (0.05% TFA) over 10 min at 214 nm. Purification of the samples was made using a Vydac 218TP54 C18 column (0.46 × 25 cm). LC/MS (ESI) data were recorded on Finnigan Mat LCQ (ThermoQuest Corporation, CA) using a Betasil C18 column (3 μm, 100A, 3 × 50 mm) at 214 nm. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions at 400 and 500 MHz (^1H) and 125 MHz (^{13}C), respectively.

Typical Procedure for the Solid-Phase Aza-Wittig/Heterocyclization/Substitution Reaction. Methylbenzhydrylamine (MBHA) resin (50 mg, 1.15 meqiv/g, 100−200 mesh) was sealed inside a polypropylene mesh packet. Resin-bound compounds **4** were synthesized according to the literature.[2] The reaction was performed in 50-mL Kimax tubes under argon. A 1.080-g portion of PPh_3 (4.11 mmol, 25 eqiv) and 638 mL (4.05 mmol, 25 eqiv) of DEAD were added to 150 mg of the resin-bound benzimidazole derivative **4** in 15 mL of anhydrous THF. The reaction mixture was shaken for 48 h at room temperature. The solution was removed via cannula. The resulting resin-bound iminophosphorane intermediate **5** was washed with anhydrous toluene (1×) under argon. The resin was treated under argon with the respective halogenoalkyl isocyanate (15 eqiv, 0.2 M) in 11 mL of anhydrous toluene for 24 h at 100 °C. The resin was vigorously washed with toluene (11×, 15 min each) and DCM (3×). The final compounds **2** or **3** were obtained after cleavage from the resin by anhydrous HF in the presence of anisole for 1.5 h at 0 °C, extracted with 95% acetic acid in H_2O, and lyophilized.

Mixture of 8-(Aminocarbonyl)-1-(2-bromoethyl)-11-hexyl-5-oxo-2,3-dihydro-1*H*-imidazo [2′,1′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-11-ium Trifluoroacetate (2a) and 8-(Aminocarbonyl)-4-(2-bromoethyl)-11-hexyl-5-oxo-2,4,5,11-tetrahydro-1*H*-imidazo[1′,2′:1,6][1,3,5]triazino-[3,2-*a*]benzimidazol-12-ium Trifluoroacetate (3a). t_R = 2.96 min. ^1H NMR (DMSO-d_6) δ 0.85 (t, $J = 8.9$ Hz, 3H), 1.23−1.33 (m, 6H), 1.80−1.83 (m, 2H), 3.84 (t, $J = 6.0$ Hz, 1.4H), 3.99 (s, 1.2H), 4.07 (t, $J = 6.0$ Hz, 1.4 H), 4.13 (dd, $J = 8.4$, 9.7 Hz, 2H), 4.30−4.37 (m, 4H), 7.60 (br, 1H), 7.99 (d, $J = 8.9$ Hz, 1H), 8.13 (dd, $J = 1.4$, 8.9 Hz, 1H),

8.29 (br, 1H), 8.62 (s, 1H). **2a**/**3a** = 30/70. ^{13}C NMR (DMSO-d_6) δ 13.9, 21.9, 25.3, 27.3, 28.7, 30.6, 40.0, 40.6, 41.4, 43.1, 45.9, 46.1, 111.6, 113.7, 124.6, 126.1, 131.5, 132.5, 142.7, 152.4, 157.1, 166.5. MS (ESI) *m*/*z* calcd [M$^+$] 461.1, found 461.3.

8-(Aminocarbonyl)-1-(2-chloroethyl)-11-hexyl-5-oxo-2,3-dihydro-1*H*-imidazo[2′,1′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-11-ium Trifluoroacetate (2b). t_R = 2.89 min. ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 6.9 Hz, 3H), 1.23−1.33 (m, 6H), 1.78−1.85 (m, 2H), 3.99 (s, 4H), 4.13 (dd, J = 8.2, 9.8 Hz, 2H), 4.30−4.37 (m, 4H), 7.60 (br, 1H), 7.99 (d, J = 8.7 Hz, 1H), 8.15 (dd, J = 1.5, 8.7 Hz, 1H), 8.29 (br, 1H), 8.62 (d, J = 1.5 Hz). ^{13}C NMR (DMSO-d_6) δ 13.9., 21.9, 25.3, 27.3, 30.7, 40.1, 40.6, 41.3, 46.1, 46.2, 111.7, 113.7, 124.6, 126.1, 131.5, 132.5, 142.7, 152.4, 157.2, 166.5. MS (ESI) *m*/*z* calcd [M$^+$] 417.2, found 417.4.

8-(Aminocarbonyl)-11-butyl-1-(2-chloroethyl)-5-oxo-2,3-dihydro-1*H*-imidazo[2′,1′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-11-ium Trifluoroacetate (2c). t_R = 2.46 min. ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.3 Hz, 3H), 1.29−1.36 (m, 2H), 1.78−1.83 (m, 2H), 3.99 (s, 4H), 4.13 (dd, J = 8.1, 9.9 Hz, 2H), 4.33 (dd, J = 8.1, 10.5 Hz, 2H), 4.37 (t, J = 6.7 Hz, 2H), 7.60 (br, 1H), 7.99 (d, J = 8.6 Hz, 1H), 8.15 (dd, J = 1.6, 8.6 Hz), 8.28 (br, 1H), 8.62 (s, 1H). MS (ESI) *m*/*z* calcd [M$^+$] 389.2, found 389.4.

8-(Aminocarbonyl)-1-(2-chloroethyl)-11-cyclohexyl-5-oxo-2,3-dihydro-1*H*-imidazo[2′,1′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-11-ium Trifluoroacetate (2d). t_R = 2.67 min. ^{1}H NMR (DMSO-d_6) δ 1.33−1.40 (m, 1H), 1.46−1.54 (m, 2H), 1.71−1.74 (m, 1H), 1.88−1.91 (m, 4H), 2.28−2.36 (m, 2H), 4.01 (s, 4H), 4.13 (dd, J = 8.2, 9.7 Hz, 2H), 4.31 (dd, J = 8.2, 9.7 Hz, 2H), 4.71−4.76 (m, 1H), 7.60 (br, 1H), 8.12−8.13 (m, 2H), 8.31 (br, 1H), 8.65 (s, 1H). MS (ESI) *m*/*z* calcd [M$^+$] 415.2, found 415.3.

8-(Aminocarbonyl)-1-(2-chloroethyl)-11-(3-methoxypropyl)-5-oxo-2,3-dihydro-1*H*-imida-zo[2′,1′:4,5][1,3,5]triazino-[1,2-*a*]benzimidazol-12-ium Trifluoroacetate (2e). t_R = 1.97 min. ^{1}H NMR (DMSO-d_6) δ 2.05−2.07 (m, 2H), 3.18 (s, 3H), 3.36 (t, J = 6.3 Hz, 2H), 4.00 (s, 4H), 4.14 (dd, J = 8.2, 9.7 Hz, 2H), 4.33 (dd, J = 8.2, 10.0 Hz, 2H), 4.41 (t, J = 6.3 Hz, 2H), 7.60 (br, 1H), 7.93 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.30 (br, 1H), 8.62 (s, 1H). MS (ESI) *m*/*z* calcd [M+] 405.1, found 405.3.

9-(Aminocarbonyl)-1-(3-chloropropyl)-12-cyclohexyl-6-oxo-1,2,3,4-tetrahydropyrimi-do[2′,1′:4,5][1,3,5]triazino-[1,2-*a*]benzimidazol-12-ium Trifluoroacetate (2f). t_R = 2.80 min. ^{1}H NMR (DMSO-d_6) δ 1.36−1.40 (m, 1H), 1.46−1.51 (m, 2H), 1.70−1.73 (m, 1H), 1.88−1.91 (m, 4H), 2.11−2.16 (m, 2H), 2.16−2.22 (m, 2H), 2.28−2.35 (m, 2H), 3.71 (t, J = 5.7 Hz, 2H), 3.79 (t, J = 6.3 Hz, 2H), 3.95 (t, J = 7.0 Hz, 2H), 4.06 (t, J = 5.7 Hz, 2H), 4.71−4.75 (m, 1H), 7.58 (br, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.13 (dd, J = 1.6, 8.8 Hz, 1 H), 8.29 (br, 1H), 8.66 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 18.4, 24.4, 25.1, 29.1, 29.3, 41.3, 42.8, 46.3, 48.5, 55.5, 112.0, 113.7, 124.5, 126.0, 130.8, 131.9, 144.3, 148.6, 152.3, 166.5. MS (ESI) *m*/*z* calcd [M$^+$] 461.1, found 443.2.

Typical Procedure for the Nucleophilic Substitution by Amines. Following the Aza-Wittig/heterocyclization/substitution reaction, the resin-bound compounds sealed in polypropylene mesh packets were treated with 10 eqiv of the respective amine (0.04 M in DMF) at 25 °C for 4 h. The resin was washed with DMF (3×) and DCM (3×). The final compounds **10** were obtained after cleavage from the resin by anhydrous HF in the presence of anisole for 1.5 h at 0 °C, extracted with 95% acetic acid in H_2O, and lyophilized.

8-(Aminocarbonyl)-1-[2-(butylamino)ethyl]-11-hexyl-5-oxo-2,3-dihydro-1*H*-imidazo[2′,1′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-11-ium Trifluoroacetate (10a). t_R = 2.97 min. ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 6.8 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H), 1.25−1.36 (m, 8H), 1.49−1.53 (m, 2H), 1.73−1.77 (m, 2H), 3.25−3.29 (m, 2H), 3.84 (dd, J = 8.6, 9.8 Hz, 2H), 3.94−4.01 (m, 4H), 4.22 (dd, 8.6, 9.8 Hz, 2H), 4.61 (dd, J = 2.9, 5.9 Hz, 2H), 7.52 (br, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.98 (dd, J = 1.4, 8.7 Hz, 1H), 8.08 (br, 1H), 8.24 (s, 1H), 8.43 (t, J = 5.8 Hz, 1H). MS (ESI) *m*/*z* calcd [M$^+$] 454.3, found 454.3.

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Supporting Information Available. Representative spectroscopic data for **2a**, **3a**, **2b**, **2f** and **10a**, and X-ray data for **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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