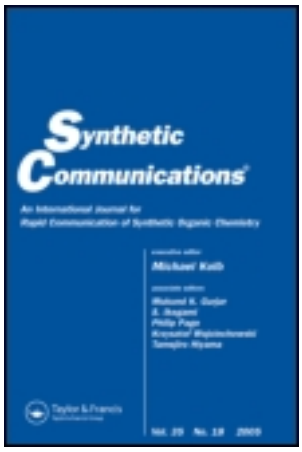

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Synthesis of Monoimidazole/Polyamine Amides

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ABSTRACT

A facile and efficient route has been reported to selectively prepare a series of unsymmetrical monoimidazole/polyamine amides without protection process of the polyamines. These amides are versatile building blocks for the synthesis of DNA sequence recognition ligands and other biologically functional molecules.

Key Words: Polyamine; Monoimidazole; Spermine; Amides.

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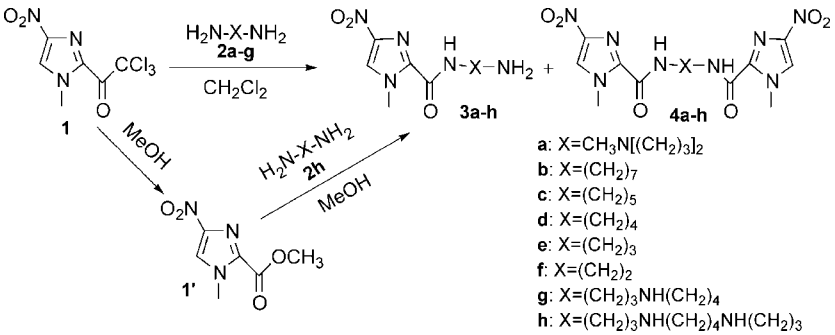
INTRODUCTION

A number of studies have shown that natural polyamines and polyamine amides play a profound role in cellular processes.[1–4] Under physiological conditions, polycations of these structures bind tightly to anionic cellular components, such as DNA, and strongly modulate their functions.[5,6] Thus, the synthesis and exploration of the biological activities of such amides and their analogs has attracted much attention.[7–11]

In the present study, a facile and efficient method was developed for the synthesis of a series of unsymmetrical polyamine amides **3a–h**. These amides are all new compounds and potential analogs for channel blocking toxins.[12,13] They are also important building blocks or intermediates for the design and synthesis of diverse netropsin and distamycin analogs or related conjugates having DNA-binding activity or multiple functions.[14–18]

Typically, the synthesis of **3a** was initiated with 3,3′-diamino-*N*-methyldipropylamine **2a** (Sch. 1), which has been frequently used for the design and synthesis of sequence-specific DNA binding molecules.[14,19–24] The employed imidazole acyl donor, 4-nitro-1-methyl-2-trichloroacetylimidazole **1**, was prepared from *N*-methyl-imidazole as described previously.[25]

Because **1** is very reactive with amines,[25,26] it was expected to react with triamine **2a** to readily produce the undesired bisimidazole amide **4a**. However, we found that the desired monoimidazole *N*-acylated polyamine conjugate (monoimidazole amide) **3a** could be selectively obtained. This selectivity exhibited a remarkable solvent-dependence but was insensitive to temperature. Thus, although low yields (<60%) were obtained in tetrahydrofuran, dioxane, or chloroform, impressive yields were obtained in dichloromethane. Therefore, we decided to apply this method for the preparation of a series of the targeted molecules **2a–h** as described below and in Sch. 1.



Scheme 1.

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Reaction of imidazole **1** with **2a** (2 equiv.) in CH_2Cl_2 gave a crude resulting mixture, which was separated by column chromatography over silica gel to afford monoimidazole amide **3a** and the bisimidazole amide by-product **4a** in 80% and 3% yields, respectively. By the same method, amides **3b–g** were also obtained in good selectivity and yields as summarized in Table 1. For the triamine of spermidine **2g**, there is a secondary amino group situated between the two primary terminal amino groups. Owing to the higher nucleophilicity of the secondary amino group than the primary amino groups, its preferential *N*-acylation by **1** was expected. However, this was not observed, presumably because the nucleophilicity of the secondary amine is masked by the greater steric hindrance of spermidine **2g**.[7,27] Additionally, since spermidine **2g** is unsymmetrical, its reaction with **1** was expected to give two kinds of monoimidazole amides. However, on the basis of identification[28] of the products by electrospray ionization tandem mass spectrometry (ESI-MS/MS), it was found that only one monoimidazole amide, **3g**, was produced (72%) together with some bisimidazole amide **4g** (12%), suggesting the regio-selective *N*-acylation of spermidine by imidazole **1**.

It is worth noting that the reaction of imidazole **1** with spermine **2h** always produced the bisimidazole amide **4h** predominantly, together with only a little amount of the desired monoimidazole amide **3h** as checked by TLC. To solve this problem, imidazole **1** was converted to its methyl ester **1′** followed by aminolysis by spermine **2h** (Sch. 1) to achieve the mono *N*-acylation, affording **3h** in 66% yield.

By the same method, monopyrrole *N*-acylated polyamine conjugates (monopyrrole amides), which are potential compounds for the design of

Table 1. Production yields of the reactions of **1** with polyamine **2a–h**.[a]

Polyamine **2** (equiv.)	Solvent	Monoimidazole amide **3**[b] (%)	Bisimidazole amide **4**[b] (%)
a (2)	CH_2Cl_2	**a** (83)	**a** (1)
b (2)	CH_2Cl_2	**b** (80)	**b** (8)
c (2)	CH_2Cl_2	**c** (88)	**c** (2)
d (4)	CH_2Cl_2	**d** (84)	**d** (3)
e (2)	CH_2Cl_2	**e** (87)	**e** (4)
f (4)	CH_2Cl_2	**f** (93)	**f** (nd[c])
g (2)	CH_2Cl_2	**g** (73)	**g** (12)
h (2)	MeOH	**h** (66)	**h** (10)

[a]The reactions were conducted at rt.
[b]Based on isolated product.
[c]Not detected.

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DNA binding molecules,[14,16] can also be easily synthesized from 4-nitro-1-methyl-2-trichloroacetylpyrrole.

EXPERIMENTAL

***N*-[3′-*N*,*N*-(3″-Aminopropylmethyl)-aminopropyl]-4-nitro-1-methyl-imidazole-2-carboxamide 3a.** To a solution of **2a** (103 mg, 0.79 mmol) in CH_2Cl_2 (4 mL) with stirring was added 4 mL CH_2Cl_2 solution of **1** (114 mg, 0.42 mmol) dropwise during 2 hr at rt. The reaction mixture was stirred at the same temperature overnight, concentrated under reduced pressure, and chromatographied by column over silica gel ($CHCl_3$/MeOH = 10 : 3) to give **3a** as white powder in 83%. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.84 (br, 1H), 7.78 (s, 1H), 4.15 (s, 3H), 3.48 (s, 2H), 2.79 (t, J = 6.9 Hz, 2H), 2.50 (dd, J = 11.9, 5.9 Hz, 2H), 2.44 (dd, J = 7.9, 6.8 Hz, 2H), 1.71–1.78 (m, 6H); ESI MS (rel. int.): m/z 321 (3), 299 (100), 282 (16), 254 (4), 242 (4), 211 (7), 172 (3); Hi-resolution (HR)-FABMS: m/z calcd for $C_{12}H_{23}N_6O_3$ (M + 1) 299.1826, found 299.1822.

Using the same procedure, **3b–g** were also synthesized.

***N*-(7′-Aminoheptyl)-4-nitro-1-methyl-imidazole-2-carboxamide 3b.** ^{1}H NMR ($CDCl_3$, 500 MHz): 7.84 (s, 1H), 7.40 (br, 1H), 4.15 (s, 3H), 3.39 (dd, J = 13.8, 6.9 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H), 1.57–1.63 (m, 2H), 1.42–1.47 (m, 4H), 1.35–1.37 (m, 6H); ESI MS (rel. int.): m/z 284 (100), 267 (3), 183 (4).

***N*-(5′-Aminopentyl)-4-nitro-1-methyl-imidazole-2-carboxamide 3c.** ^{1}H NMR ($CDCl_3$, 500 MHz): 7.80 (s, 1H), 7.43 (br, 1H), 4.16 (s, 3H), 3.40 (dd, J = 13.8, 6.9 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H), 1.62–1.66 (m, 2H), 1.46–1.50 (m, 2H), 1.39–1.44 (m, 2H), 1.31 (br, 2H); ESI MS (rel. int.): m/z 256 (100), 239 (8), 183 (2).

***N*-(4′-Aminobutyl)-4-nitro-1-methyl-imidazole-2-carboxamide 3d.** ^{1}H NMR ($CDCl_3$, 500 MHz): 7.81 (s, 1H), 7.71 (br, 1H), 4.17 (s, 3H), 3.42 (dd, J = 12.8, 6.9 Hz, 2H), 2.75 (t, J = 6.9 Hz, 2H), 1.63–1.69 (m, 2H), 1.51–1.56 (m, 2H), 1.28 (br, 2H); ESI MS (rel. int.): m/z 242 (100), 225 (36), 183 (3).

***N*-(3′-Aminopropyl)-4-nitro-1-methyl-imidazole-2-carboxamide 3e.** ^{1}H NMR ($CDCl_3$, 500 MHz): 7.87 (br, 1H), 7.79 (s, 1H), 4.16 (s, 3H), 3.51 (dd, J = 12.8, 5.9 Hz, 2H), 2.83 (t, J = 6.9, 5.9 Hz, 2H), 1.75 (dd, J = 12.8, 6.9 Hz, 2H), 1.47 (br, 2H); ESI MS (rel. int.): m/z 228 (100), 211 (98), 183 (10).

***N*-(2′-Aminoethyl)-4-nitro-1-methyl-imidazole-2-carboxamide 3f.** ^{1}H NMR ($CDCl_3$, 500 MHz): 7.80 (s, 1H), 7.65 (br, 1H), 4.18 (s, 3H), 3.46 (dd, J = 11.8, 5.9 Hz, 2H), 2.93 (t, J = 5.9 Hz, 2H), 1.32 (br, 2H); ESI MS (rel. int.): m/z 236 (16), 214 (100), 197 (96).

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***N*-[3′-*N*-(4″-Aminobutyl)- aminopropyl]-4-nitro-1-methyl-imidazole-2-carboxamide 3g.** ^{1}H NMR ($CDCl_3$, 500 MHz): 8.58 (br, 1H), 7.80 (s, 1H), 4.15 (s, 3H), 3.49 (dd, $J = 7.8$, 5.8 Hz, 2H), 2.80 (t, $J = 6.8$ Hz, 2H), 2.72 (dd, $J = 9.8$, 13.8 Hz, 2H), 2.65 (dd, $J = 7.9$, 13.8 Hz, 2H), 1.67–1.81 (m, 4H), 1.55–1.66 (m, 2H), 1.49–1.53 (m, 2H); ESI MS (rel. int.): m/z 321 (7), 299 (100), 282 (49), 211 (3), 155 (3); MS/MS: m/z 299 (5), 282 (100), 228 (6), 211 (4), 155 (3); HR-FABMS: m/z calcd for $C_{12}H_{23}N_6O_3$ (M + 1) 299.1826, found 299.1824.

***N*^{1}-(4′-Nitro-1′-methyl-imidazole-2′-carboxyl)-1,12-diamino-4,9-diazadodecane 3h.** A solution of **1** (102 mg, 0.37 mmol) in MeOH (4 mL) was stirred for 1 hr to give methyl 4-nitro-1-methyl-imidazole-2-carboxylate (**1′**), which was checked by ESI MS and MS/MS. The resulting solution was added dropwise to a solution of spermine **2h** (168 mg, 0.83 mmol) in 4 mL MeOH. The reaction mixture was stirred overnight and concentrated under reduced pressure to give a residue, which was dissolved in a mixed solvent (MeOH/3% aq.HCl = 10 : 1) and separated by column chromatography over ODS gel (H_2O/MeOH = 7 : 3) to produce **3h** in 66% yield. RP-HPLC analysis: 3.2 min (96%) and 6.7 min (4%). ^{1}H NMR (D_2O, 500 MHz): 8.14 (s, 1H), 3.93 (s, 3H), 3.40 (t, $J = 13.8$, 6.9 Hz, 2H), 3.02–3.06 (m, 10H), 1.98–2.00 (m, 2H), 1.91–1.96 (m, 2H), 1.69 (m, 4H); ESI MS (rel. int.): m/z 378 (2), 356 (100), 282 (60), 211 (8), 156 (13), 129 (17); HR-FABMS: m/z calcd for $C_{15}H_{30}N_7O_3$ (M + 1) 356.2404, found 356.2404.

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