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Tetrahedron Letters 45 (2004) 8815–8818
Tetrahedron Letters

Efficient guanylation of N^{α},N^{ω}-difunctionalized polyamines at the secondary amino functions

Constantinos M. Athanassopoulos,* Thomas Garnelis, Evangelia Pantazaka and Dionissios Papaioannou

Department of Chemistry, University of Patras, GR-265 00 Patras, Greece

Received 29 July 2004; revised 23 September 2004; accepted 1 October 2004

Abstract—Treatment of N^{α},N^{ω}-ditritylated linear and aromatic polyamines and of polyamine conjugates of the alkaloid kukoamine A (KukA) type with *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea in the presence of Mukaiyama's reagent produced high yields of derivatives guanylated at the secondary amino functions.

The guanidine group is a common structural key element in a variety of natural and synthetic compounds, which show interesting biological properties or chemical behavior and have therefore found important applications in medicinal,[1–4] bioorganic,[5] and supramolecular[1] chemistry, and most recently in asymmetric synthesis.[6] Replacement of an amino group in a biologically active compound by the strongly basic guanidinium group results in a significant increase of its potency and/or selectivity.[3,7,8] The guanidinium function is also found in a variety of biologically interesting natural and synthetic polyamine (PA) analogs and conjugates (PAC).[7–15] The most popular synthetic protocol for the preparation of guanidinium compounds in liquid[2,3] or on solid phase[1] is by reacting the corresponding amino compound with a suitable guanylating reagent. Frequently used reagents for this purpose are either of the 1*H*-pyrazole-1-carboxamidine type (e.g., **1**) or of the *N*,*N*′-disubstituted thiourea (**2**) or *S*-methylisothiourea (**3**) type or recently, *N*,*N*′-disubstituted-*N*″-triflylguanidines (**4**). A comparative study of the guanylating potencies of various guanylating reagents has been published.[16] Primary amines react smoothly and efficiently with these reagents whereas sterically more demanding secondary or electronically deactivated aromatic amines present various problems. In these cases, the reagents of choice seem to be **1c**,[17] **2** activated by either $HgCl_2$[18] or Mukaiyama's reagent (MR, **5**)[19] or carbodiimides,[1,20] **3** also activated by $HgCl_2$[3] and **4**.[5d,16,21] Although several examples of guanylation of the primary amino functions of selectively protected polyamines and conjugates have been reported, guanylation at their secondary amino functions is rare.[7,22] We now wish to report our preliminary results on the efficient guanylation of the secondary amino functions of (a) linear and aromatic PAs, selectively protected at their primary amino functions with the bulky, mild-acid sensitive, and hydrogenolytically labile triphenylmethyl (trityl, Trt) group, and (b) PACs of the alkaloid KukA type.

In order to establish the most efficient reagent for this transformation, we used the readily available N^{α},N^{ω}-ditritylated spermidine (SPD) and spermine (SPM) derivatives, **6a**[23] and **7a**[24a,b] (Scheme 1) as model compounds. As the reagent **1a**, employed by Golding and co-workers to obtain polyamines guanylated at their primary amino functions,[10] failed to produce but trace quantities of mono- and di-nitroguanylated products from **6a**, we turned our attention to the reagents **3**, also commercially available. However, treatment of **6a** with **3a** produced the byproduct **8a** in 90% yield and with **3b** the byproducts **6b** (34% yield) and **8b** in small quantities, all arising from nucleophilic attack at the carbonyl carbon of the protecting groups. On the other hand, reaction of **6a** with the powerful guanylating reagent **4a**[5d,16,21] produced the Boc-protected derivative **6c** in 93% yield. This side reaction has also been observed during the synthesis of the polyamine alkaloid smirnovine by Baker and Goodman.[22] We finally examined

Keywords: Polyamines; Kukoamine A analogs; Guanylation; Thiourea derivatives; Mukaiyama's reagent; Protecting groups.
* Corresponding author. E-mail: kath@chemistry.upatras.gr

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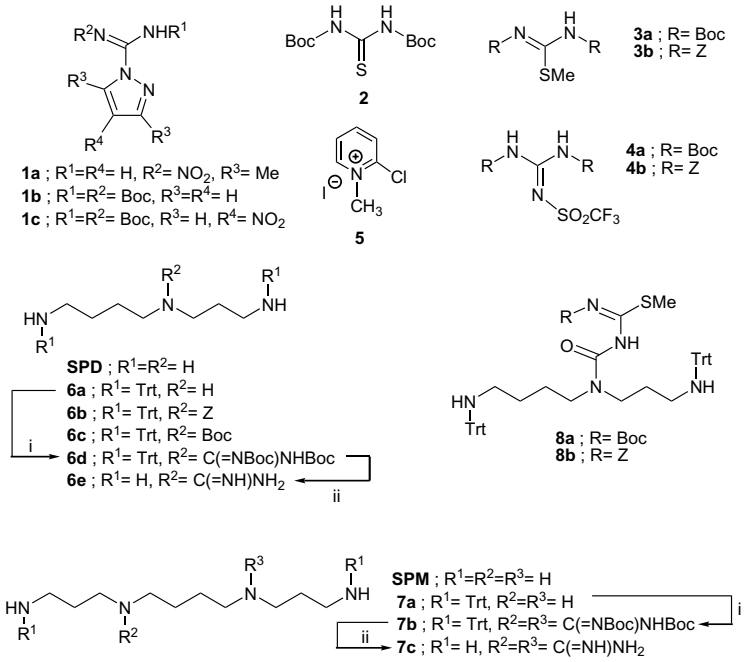
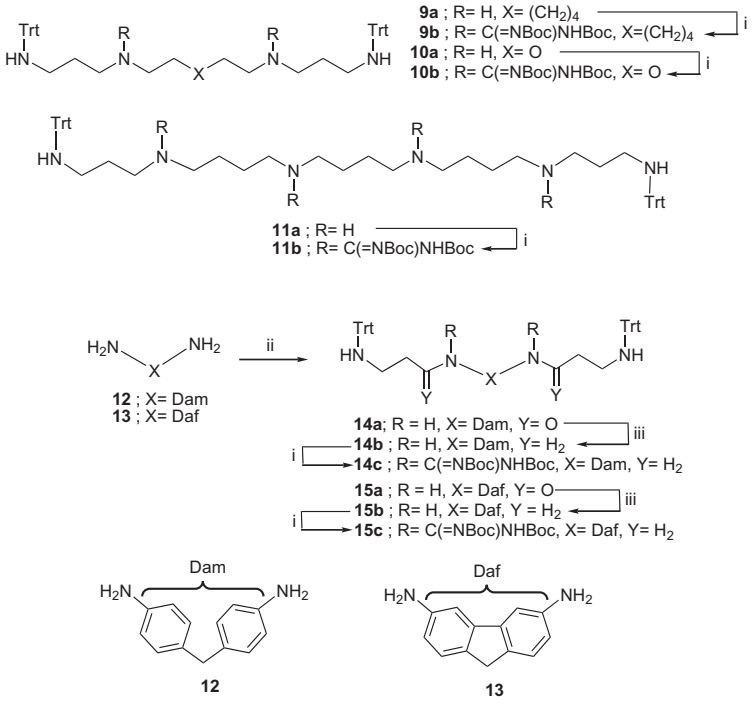
doi:10.1016/j.tetlet.2004.10.012



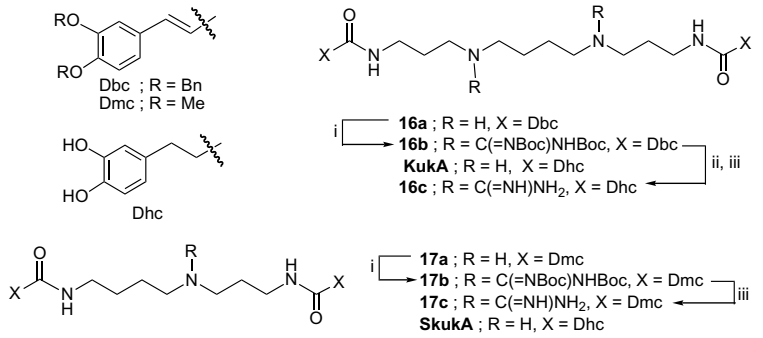
Scheme 1. Guanylation of N^{α},N^{ω}-ditritylated SPD and SPM with various reagents. Reagents and conditions: (i) DBTU/MR/Et_3N, CH_2Cl_2; (ii) TFA/CH_2Cl_2 (1:1).

the combinations of reagent **2** (DBTU), also commercially available and readily prepared through a reported procedure,[25] with MR (**5**) or *N*,*N*′-dicyclohexylcarbodiimide (DCC). Under identical reaction conditions, the former combination reacted with **6a** much faster (15 min at 25 °C) and more efficiently (96% isolated yield) to give the expected guanylated product **6d**,[26] whereas the latter did not effect completion of guanylation even after 2 h in refluxing CH_2Cl_2. Under identical reaction conditions, **7a** was converted to the diguanylated derivative **7b** in 92% yield.

Further application of this combination of reagents to a variety of other polyamine derivatives, such as the linear tetra-amine **9a**,[24b] the oxa-tetra-amine **10a**,[24b] and the hexa-amine **11a** (Scheme 2),[24b] and the aromatic PAs



Scheme 2. Guanylation of N^{α},N^{ω}-ditritylated linear and aromatic polyamine analogs with DBTU in the presence of MR. Reagents: (i) DBTU/MR/Et_3N, CH_2Cl_2; (ii) Trt-βAla-OSu/Et_3N, DMF; (iii) $LiAlH_4$, THF.



Scheme 3. Guanylation of KukA analogs with DBTU in the presence of MR. Reagents: (i) DBTU/MR/Et_3N, CH_2Cl_2; (ii) H_2/Pd–C, MeOH/AcOH/H_2O (5:1:0.1); (iii) TFA/CH_2Cl_2 (1:1).

Table 1. Guanylation of secondary amino functions of PAs and PACs with the combination of reagents DBTU and MR[a]

Entry	PA/PAC	Reaction time	Product	Yield (%)[b]
Guanylations				
1	**6a**	15 min	**6d**	96
2	**7a**	15 min	**7b**	92
3	**9a**	1 h[c]	**9b**	83
4	**10a**	2 h	**10b**	80
5	**11a**[d]	10 h	**11b**	30[e]
6	**14b**	30 h[f]	**14c**	83
7	**15b**	45 min	**15c**	85
8	**16a**	45 min	**16b**	70
9	**17a**	15 min	**17b**	72
Selected deprotections				
10	**6d**		**6e**.3TFA	75
11	**7b**		**7c**.4TFA	70
12	**16b**		**16c**.2TFA	73[g]
13	**17b**		**17c**.TFA	84

[a] The structures of new compounds described in this communication were determined by a combination of spectroscopic techniques (IR, ESI-MS, NMR) and MALDI-TOF/TOF HR-MS. For selected data see Ref. 29.
[b] Isolated yield after FCC and using as eluents PhMe/EtOAc (various combinations from 7:3 to 9:1) for compounds **6d**, **7b**, **9b**–**11b**, **14c**, and **15c**, EtOAc for compound **16b** and $CHCl_3$/MeOH (95:5) for compound **17b**.
[c] Addition of 0.2 mmol each of DBTU, MR, and Et_3N after 15 min at 25 °C.
[d] Obtained crude from $LiAlH_4$ reduction of the corresponding tetra-amide (see Ref. 24b).
[e] Total yield for two steps, namely $LiAlH_4$ reduction, followed by guanylation.
[f] Addition of 0.2 mmol each of DBTU, MR and Et_3N after 10 h and then another 0.6 mmol of DBTU, MR and Et_3N after 15 h at 25 °C.
[g] Total yield in two steps, namely catalytic hydrogenation/hydrogenolysis, followed by TFA-mediated acidolysis.

14b and **15b**[27] as well as the PACs **16a** and **17a**[28] (Scheme 3) of the alkaloid KukA type was unexceptional and gave the corresponding guanylated products **9**–**11b** and **14c**, **15c**, **16b** and **17b** in very good yields (Table 1). Simultaneous removal of both acid-labile groups, namely Trt and Boc, can be effected by routine treatment with 50% CF_3CO_2H (TFA) in CH_2Cl_2 for 10 min at 0 °C and then for 45 min at 25 °C. In the case of the conjugate **16a**, simultaneous *O*-deprotection and double bond saturation were effected by catalytic hydrogenolysis in MeOH/AcOH/H_2O (5:1:0.1) in the presence of 10% Pd–C (0.2 g per gram of **16a**) for 3 h at 25 °C. Subsequent TFA-mediated acidolysis of the Boc groups gave the novel KukA analog **16c**. The spermidine KukA (SkukA) analog **17c** was also readily obtained from **17b** through TFA-mediated acidolysis.

In conclusion, the present study shows that DBTU with MR is a powerful and reliable combination of reagents for the fast and efficient guanylation of secondary amino functions of PAs and PACs under very mild reaction conditions. Tests to determine the biological activities of these novel compounds are currently in progress.

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26. Typical guanylation: To an ice-cold solution of PA/PAC (1 mmol), DBTU [1.2 mmol per secondary amino group (p.sag)] and Et_3N (1.2 mmol p.sag) in anhydrous CH_2Cl_2 (10 mL) was added MR (1.2 mmol p.sag) and the resulting mixture was stirred at 0 °C for 10 min and at 25 °C for the time indicated in Table 1. The solvent was evaporated and the residue was taken up in EtOAc. Washing twice with water, followed by drying (Na_2SO_4) and evaporation left an oily residue, from which the guanylated compounds were obtained pure by routine flash column chromatography (FCC) on Merck (230–400 mesh) silica gel. For eluents see Table 1.
27. These aromatic polyamines were obtained as follows: To a solution of 5 mmol of aromatic diamine (**12** or **13**) in dry DMF (5 mL) was added Et_3N (15 mmol) and Trt-βAla-OSu[24b] (10.5 mmol) and the resulting mixture was heated to 60 °C for 15–20 h and then triturated with 40 mL $CHCl_3$. A first crop of the product was collected by filtration, following washing with ice-cold $CHCl_3$ (60 mL) and Et_2O (30 mL). Concentration of the $CHCl_3$ filtrates to one third of the volume, overnight refrigeration and filtration gave a second crop of pure bisamide **14a** or **15a** (yields: 63–65%). Treatment of 2 mmol of bisamide **14a** or **15a** with $LiAlH_4$ (10 mmol) in refluxing anhydrous THF (20 mL) for 36 h (**14a**) or 3 days (**15a**), followed by routine work-up[24b] and FCC purification with EtOAc/PhMe (95:5) as eluent, gave pure PAs **14b** (68%) and **15b** (57%).
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29. Characterization of representative products: **6d**: foam; R_f (PhMe/EtOAc = 7:3) 0.76; FT-IR: 3430, 1746, 1630, and 1604 cm^{-1}; ESI-MS (*m/z*): 872.13 ($M + H^+$), 630.09 ($M + H^+$–Trt), 242.94 (Trt^+); HR-MS (*m/z*): Found 872.5118 ($M^+ + 1$), $C_{56}H_{66}N_5O_4$ requires $M^+ + 1 = 872.5109$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.85 (1H, br s, BocN*H*), 7.45, 7.25, and 7.15 (30H, three m, Ph–*H*), 3.54 and 3.30 (4H, two unresolved m, CH_2–C(=NBoc)NHBoc), 2.10 (4H, unresolved t, TrtNHCH_2), 1.74 (4H, unresolved quint., CH_2–CH_2–CH_2), 1.41 (18H, s, C–CH_3) ppm; ^{13}C NMR (100 MHz $CDCl_3$): δ 155.6, 146.1, 128.6, 127.8, 125.3, 71.2, 48.2, 46.0, 43.4, 40.7, 31.2, 28.6, and 25.4 ppm.
14b: foam; R_f (PhMe/EtOAc = 7:3) 0.68; FT-IR: 3398, 3303, and 1612 cm^{-1}; ESI-MS (*m/z*): 797.19 ($M+H^+$), 243.14 (Trt^+); HR-MS (*m/z*): Found 797.4570 ($M^+ + 1$), $C_{57}H_{57}N_4$ requires $M^+ + 1 = 797.4583$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45, 7.24, and 7.15 (30H, three m, Ph–*H*), 6.97 (4H, d, *J* 8.3 Hz, Ar–*H*), 6.51 (4H, d, *J* 8.4 Hz, Ar–*H*), 3.76 (2H, s, Ar–CH_2-Ar), 3.18 (4H, t, *J* 6.6 Hz, ArN-CH_2), 2.34 (4H, s, N*H*), 2.25 (4H, t, *J* 6.5 Hz, TrtNHCH_2), 1.74 (4H, quint., *J* 6.5 Hz, CH_2–CH_2–CH_2) ppm; ^{13}C NMR (100 MHz $CDCl_3$): δ 146.0, 128.2, 127.8, 126.3, 146.5, 130. 9, 129.6, 113.0, 71.1, 42.8, 41.8, 40.1, and 30.4 ppm.
14c: foam; R_f (PhMe/EtOAc = 7:3) 0.61; FT-IR: 3270, 1765, 1634, and 1591 cm^{-1}; ESI-MS (*m/z*): 1282.53 ($M + H^+$), 1040.06 ($M + H^+$–Trt), 243.13 (Trt^+); HR-MS (*m/z*): Found 1281.7124 ($M^+ + 1$), $C_{79}H_{93}N_8O_8$ requires $M^+ + 1 = 1281.7116$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.51 (2H, br s, BocN*H*), 7.44, 7.23 and 7.13 (30H, three m, Ph–*H*), 7.00 (4H, d, *J* 8.4 Hz, Ar–*H*), 6.90 (4H, d, *J* 8.4 Hz, Ar–*H*), 4.07 (4H, t, *J* 6.8 Hz, ArN–CH_2), 3.82 (2H, s, Ar–CH_2–Ar), 2.35 (2H, s, TrtN*H*), 2.10 (4H, t, *J* 6.0 Hz, TrtNHCH_2), 1.70 (4H, quint., *J* 6. 4 Hz, CH_2–CH_2–CH_2), 1.36 and 1.14 (36H, br s, C–CH_3) ppm; ^{13}C NMR (100 MHz $CDCl_3$): δ 154.7, 146.3, 140.5, 138.5, 129.2, 128.7, 127.7, 126.2, 126.0, 71.1, 40.7, 40.1, 29.7, 28.2, and 27.9 ppm.