Methods for the Construction of New Highly Functionalised Guanidines

Eric Wellner, Helena Sandin,* Marie-Louise Swanstein

Active Biotech AB, Department of Drug Discovery, Box 724, 22007 Lund, Sweden
Fax +46(46)191246; E-mail: helena.sandin@activebiotech.com

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Abstract: In this study, we present a fast and chemoselective protocol to highly functionalised guanidines. Guanidines containing a hydroxy function were constructed in the microwave by regioselective ring opening of epoxides in the presence of ammonium hydroxide giving the primary amines, which then were reacted with isothiouronium salts. Direct coupling of an unsubstituted guanidine with an epoxide in the presence of *n*-BuLi gave the same product.

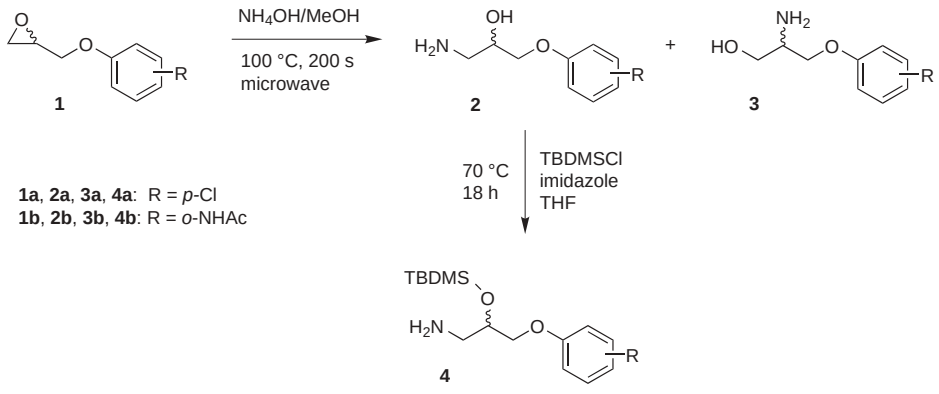
Key words: amino alcohols, epoxides, chemoselectivity, regioselectivity, ring opening

Guanidines are frequently used in medicinal chemistry[1] due to their interesting biological and pharmacological properties. While the access to acyclic guanidines is well studied and documented, the synthesis of cyclic guanidines is often difficult and time consuming.[1b,2] Usually, they can be obtained from isothiouronium salts and primary amines.[2] Recently, we reported a fast and easy route to substituted and unsubstituted cyclic guanidines, which substantially shortens the reaction time.[3] In continuation of our previous work in this field, we were particularly interested in expanding the scope of this methodology towards β-hydroxy-alkyl-guanidines. Another objective in this study was to investigate the alkylation of N,N′-disubstituted guanidines using epoxides as alkylating agent.[4] This would afford highly functionalised guanidines in one step starting from commercially available epoxides.

Initially, we were interested in the construction of hydroxylated primary amines. In the first step of the process, the amine derivatives **2** were prepared by regioselective ring opening of the racemic epoxides **1** in the presence of ammonium hydroxide at 100 °C for 200 seconds in a microwave.[5] Under these conditions, the formation of the secondary alcohols **2a** (93%) and **2b** (95%) was favoured, while the generation of the regioisomeric primary alcohols **3a** (3%) and **3b** (4%) played only a minor role (Scheme 1).

The amines were then reacted with the isothiouronium salts **5**[3] to yield the major products **6** (Scheme 2). In the ^{13}C NMR of **6c**, the signals at δ = 155.2 and 65.9 ppm could be assigned to C-2 and C-2′ (see Scheme 2) using DEPT, HMBC and HMQC. From this assignment it was however not possible to determine the absolute constitution.

Since it is known that both the amino group and the hydroxy group could function as nucleophiles,[3] we wanted to examine the chemoselectivity of the reaction to prove the formation of **6**. Therefore, the hydroxy group of **2** was protected with *tert*-butyldimethylsilyl chloride (Scheme 1) to give the silyl ethers **4** in excellent yields (**4a**: 95%, **4b**: 99%). The coupling of the amines **4** with the TFA salts **5** was performed in the microwave at 160 °C for 600 seconds. The excess amount of the amine was scavenged using methylisocyanate on resin.[6] To avoid the deacetylation of **6b** and **6d**, the desilylation was generally achieved under mild conditions using MeOH–5 M HOAc (aq) 1:2. The ^{1}H NMR and the ^{13}C NMR spectra of the isolated products **6** generated via path A and path B were identical proving the chemoselectivity of the reaction path A (Scheme 2, Table 1).[7]



Scheme 1

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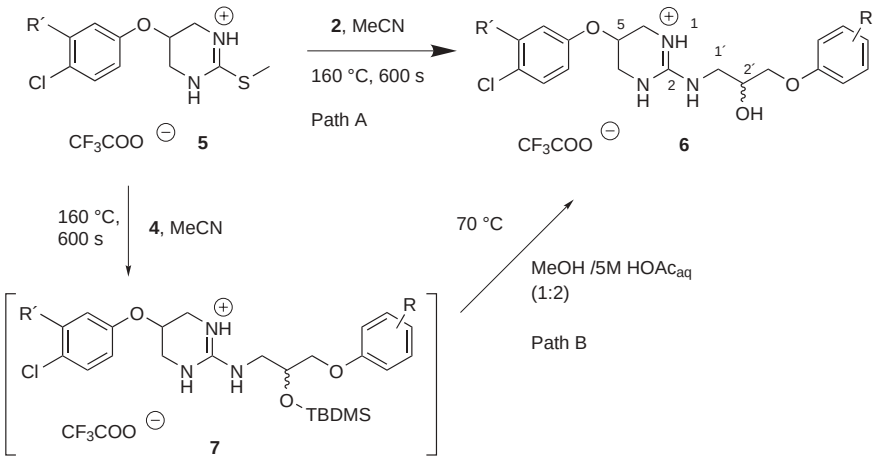


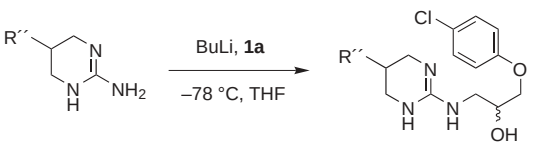
Scheme 2

Table 1 Reaction of Isothiuronium Salts **5** with Primary Amines **2** and **4** and Yield of **6** (%)

TFA salt	**2a** (R = *p*-Cl)	**2b** (R = *o*-NHAc)	**4a** (R = *p*-Cl)	**4b** (R = *o*-NHAc)
5a (R′ = H)	**6a** (56)	**6b** (31)	**6a** (70)[a]	**6b** (65)[a]
5b (R′ = Cl)	**6c** (43)	**6d** (39)	**6c** (54)[a]	**6d** (63)[a]

[a] Over two steps with **7** as intermediate.

Next, we focused our efforts on the direct coupling[8] of the unsubstituted guanidine **8**[3] and the epoxide **1a** avoiding the construction of the primary amines **2**. Heating the mixture of compound **8** and **1a** with EtOH as solvent in the microwave at 120 °C for 300 seconds failed to produce the alcohol **9** in an epoxide opening reaction. At higher temperatures (160 °C) decomposition of the building blocks occurred. These results demonstrated the low reactivity of guanidines towards electrophilic reagents. To increase the nucleophilicity, *n*-BuLi was added to a solution of compound **8** in THF at –78 °C (Scheme 3). A stabilisation of the guanidine moiety with electron withdrawing groups to support the delocalisation of the negative charge was not necessary.[9] The crude product of this reaction revealed a complex mixture of starting materials, compound **9** and by-products.[10] After flash column chromatography the guanidine **9** could be isolated in 19% yield. The poor yield of this reaction makes this method less efficient than the guanylation of the isothiouronium salts.



Scheme 3

In conclusion, we have developed two fast pathways for the preparation of highly functionalised guanidines. While the chemoselective pathway A using amino-alcohols is more straightforward, the yields substantially increased applying silyl ethers as staring material (path B). Both approaches are expected to be readily adaptable to the synthesis of other β-hydroxy-alkyl-guanidines. Further, we have presented a fast and regioselective ring opening of epoxides using microwave-assisted chemistry.

Compound **5** was synthesised[3] in 3 steps from 2-hydroxy-1,3-diamino-propane and the appropriate fluorobenzene with an overall yield of 40%.

General Procedure for the Preparation of 2: A solution of epoxide **1** (1 mmol) in MeOH (3 mL) and NH_4OH (1 mL) was heated in the microwave at 100 °C for 200 s. The solvent was removed in vacuo and the residue was submitted to flash column chromatography (CH_2Cl_2:MeOH:NH_4OH, 9:1:0.1) to give the pure isolated product **2**.

Selected Data for Compound 2a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 6.81 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 3.93–3.88 (3 H, m, C*H*-OH, CH_2-O), 2.93–2.77 (2 H, m, CH_2N). ESI-MS: *m/z* (%) = 202 (100) [M + H$^+$].

General Procedure for the Preparation of 4: To a solution of amine **2** (0.32 mmol) in THF (3 mL) *tert*-butyldimethylsilylchloride (57 mg, 0.38 mmol) and imidazole (31 mg, 0.45 mmol) were added and the reaction mixture was stirred overnight at r.t. The solvent was removed in vacuo, $CHCl_3$ was added and washed with 1 M aq NaOH. The solvent was removed under reduced pressure and the residue submitted to flash column chromatography (CH_2Cl_2: MeOH:Et_3N, 10:1:0.1%) to give the pure isolated product **4**.

Selected Data for Compound 4a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 6.83 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 4.02 (1 H, m$_c$, C*H*OH), 3.90 (2H, m$_c$, CH_2O), 2.94–2.81 (2 H, m, CH_2N), 0.92 [9 H, s, C(CH_3)$_3$], 0.14 (3 H, s, CH_3), 0.11 (3 H, s, CH_3). ESI-MS: *m/z* (%) = 317 (100) [M + H$^+$].

General Preparation for the Compounds 6 and 7: To a solution of the amine **2** (or **4**) (0.12 mmol) in MeCN (600 μL) **5** (0.1 mmol) was added and the mixture was heated at 160 °C for 600 s in the microwave. THF–MeCN (3:1, 2 mL) and Wang resin[11] (2.5 equiv) were added and the mixture was heated for additional 1000 s at 150 °C in the microwave. To remove the excess amine methylisocyanate on resin (3 equiv) were added and the mixture was agitated

for 3 h at r.t. The resins were filtered off, washed with MeOH and CH_2Cl_2 and the filtrate was concentrated in vacuo to give **6** and **7**. The silyl ether **7** was deprotected in a mixture of MeOH (1 mL) and 5 M aq HOAc (2 mL) at 70 °C overnight. The solvent was removed and the residue triturated in Et_2O to give the desilylated product **6**.

Selected Data for Compound 6a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.27 (1 H, br s, N*H*), 7.26–7.21 (4 H, m), 6.83–6.81 (4 H, m), 4.63 (1 H, br s, *H*-5), 4.19 (1 H, br s, *H*-2′), 3.94 (2 H, d, *J* = 5.5 Hz, *H*-3′), 3.55–3.36 (6 H, m, *H*-4,6, *H*-1′). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.1, 154.4, 129.9, 129.5, 126.6, 118.2, 117.9, 115.8, 70.2, 69.3, 65.9, 44.7, 42.0. ESI-MS: *m/z* (%) = 411 (100) [M + H$^+$].

Selected Data for Compound 6b: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.74 (1 H, d, *J* = 6.7 Hz, *H*-Arom.), 7.30 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 7.10–6.94 (3 H, m, *H*-Arom.), 6.98 (2 H, d, *J* = 9.0 Hz, *H*-Arom.), 4.90 (1 H, m$_c$, *H*-5), 4.14 (1 H, m$_c$, *H*-2′), 4.05 (2 H, m$_c$, *H*-3′), 3.53–3.43 (6 H, m, *H*-4,6, *H*-1′), 2.17 (3 H, s, C*H*$_3$). ESI-MS: *m/z* (%) = 434 (100) [M + H$^+$].

Selected Data for Compound 6c: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (1 H, d, *J* = 8.8 Hz, *H*-Arom.), 7.23 (2 H, d, *J* = 8.9 Hz, *H*-Arom.), 7.00 (1 H, d, *J* = 2.8 Hz, *H*-Arom.), 6.82 (2 H, d, *J* = 8.9 Hz, *H*-Arom.), 6.75 (1 H, dd, *J* = 8.8, 2.8 Hz, *H*-Arom.), 4.66 (1 H, m$_c$, *H*-5), 4.20 (1 H, br s, *H*-2′), 3.94 (2 H, m$_c$, *H*-3′), 3.57–3.47 (5 H, m, *H*-4,6, *H*-1′), 3.39–3.34 (1 H, m, *H*-1′). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.2, 154.8, 133.5, 131.2, 129.6, 126.7, 118.4, 116.1, 115.8, 70.4, 69.3, 65.9, 44.6, 42.0. ESI-MS: *m/z* (%) = 446 (100) [M + H$^+$].

Procedure for the Preparation of 9: To a solution of **8**[3] (0.2 mmol, 45 mg) in THF (dry, 3 mL) *n*-BuLi (100 μL, 2 M in hexane) was added at –78 °C. After 30 min, the epoxide **1a** (0.2 mmol, 37 mg) was added and the mixture was allowed to attain r.t. overnight. After concentration in vacuo and flash column chromatography (CH_2Cl_2: MeOH:NH_4OH, 90:10:1) the guanidine **9** was obtained in 19% yield. Protonation of **9** in CH_2Cl_2–THF (1:1) gave the TFA salt. ^{1}H NMR, ^{13}C NMR spectra as well as the mol peak in mass spectrometry are identical to **6a**.

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(10) NMR spectroscopy indicates also the formation of a by-product with unsymmetrical ring substitution. Attempts to isolate this compound failed.

(11) The addition of Wang resin ensures the removal of the unreacted isothiouronium salt. This underlines the ambivalent reactivity of the starting material **5** towards alcohols[3] and amines under microwave conditions.