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Cyclisation reactions of bis-protected guanidines

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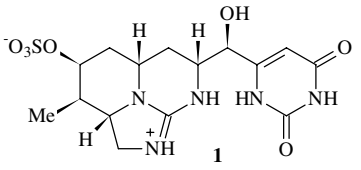
Abstract—The cyclisation of *N*-allyl- and *N*-homoallylguanidines using DMDO or I_2/K_2CO_2 leading to novel heterocycles is reported.

As part of a project directed towards the synthesis of the marine hepatotoxin cylindrospermopsin **1**[1] we wished to investigate further[2] the electrocyclic reactions of *N*-allyl and *N*-homoallyl guanidines **4**. The substrates were prepared in high yields by reaction of the corresponding *N*,*N*′-bis-*Z*- or -bis-Boc-1*H*-pyrazole carboxamidine **2**[3] with amines **3** (Table 1, Scheme 1).

We have previously reported[2] that the Boc-protected guanidine **4a** underwent cyclisation on treatment with DMDO under neutral conditions to give the 5-membered guanidine **5** in good yield after 16 h. On reinvestigation of this reaction we found that the formation of **5** was observed, but on column chromatography, a second product was always isolated in variable yield which corresponded to the rearranged product **6** as shown by X-ray crystallography (Fig. 1).[4] The complete conversion of **5** into **6** could be effected if a solution of the crude reaction mixture in dichloromethane was stirred with silica gel overnight giving **6** in 63% yield after purification. A similar result was observed with the *Z*-protected guanidine **4b** which was again treated with an excess of DMDO in acetone at −20 °C and the reaction monitored by proton NMR. Epoxidation of **4b** was found to occur rapidly as evidenced by signals at δ 2.62 (1H), 2.80 (1H) and 3.20 (1H) ppm, but on continued stirring, signals at δ 3.45 (1H), 3.50 (1H), 3.85 (1H), 3.92 (1H) and 4.09 (1H) appeared which are evidence for



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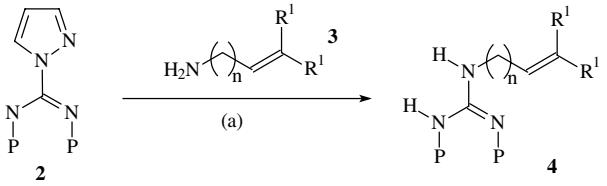

2 **3** **4**

(a)

Table 1

4	P	n	R^1	Method	Yield	Mpt
4a	Boc	1	H	A	79%	87-89 °C
4b	Z	1	H	A	92%	46-48 °C
4c	Boc	1	Me	B	93%	129-132 °C
4d	Z	1	Me	B	95%	73-76 °C
4e	Boc	2	H	B	85%	82-83 °C

Scheme 1. Reagents and conditions: (Method A) amine **3**, CH_3CN, 16–24 h; (Method B) **3**·HCl, NEt_3, CH_3CN, 16–24 h.

Keywords: Guanidines; DMDO epoxidation; Iodocyclisation.
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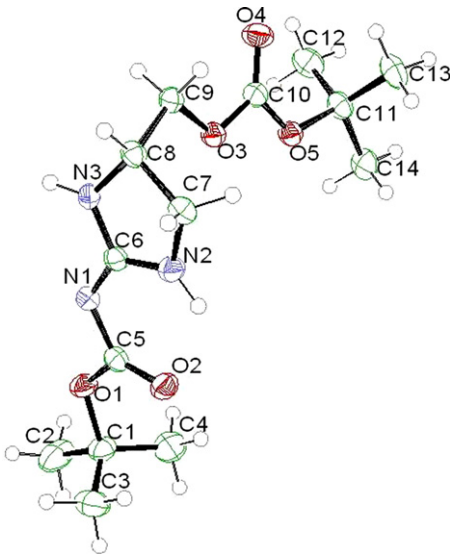


Figure 1.

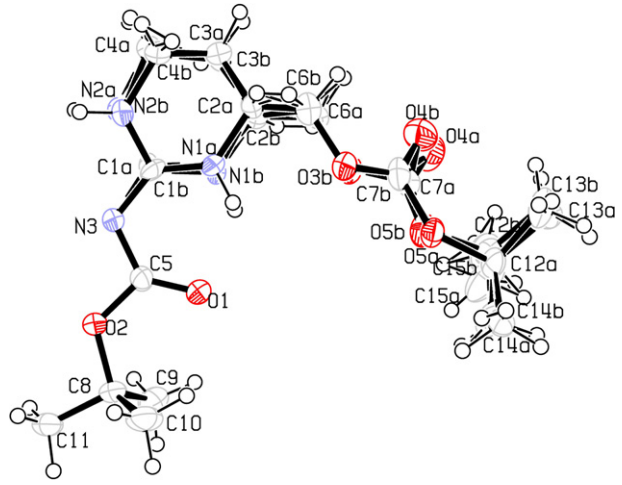
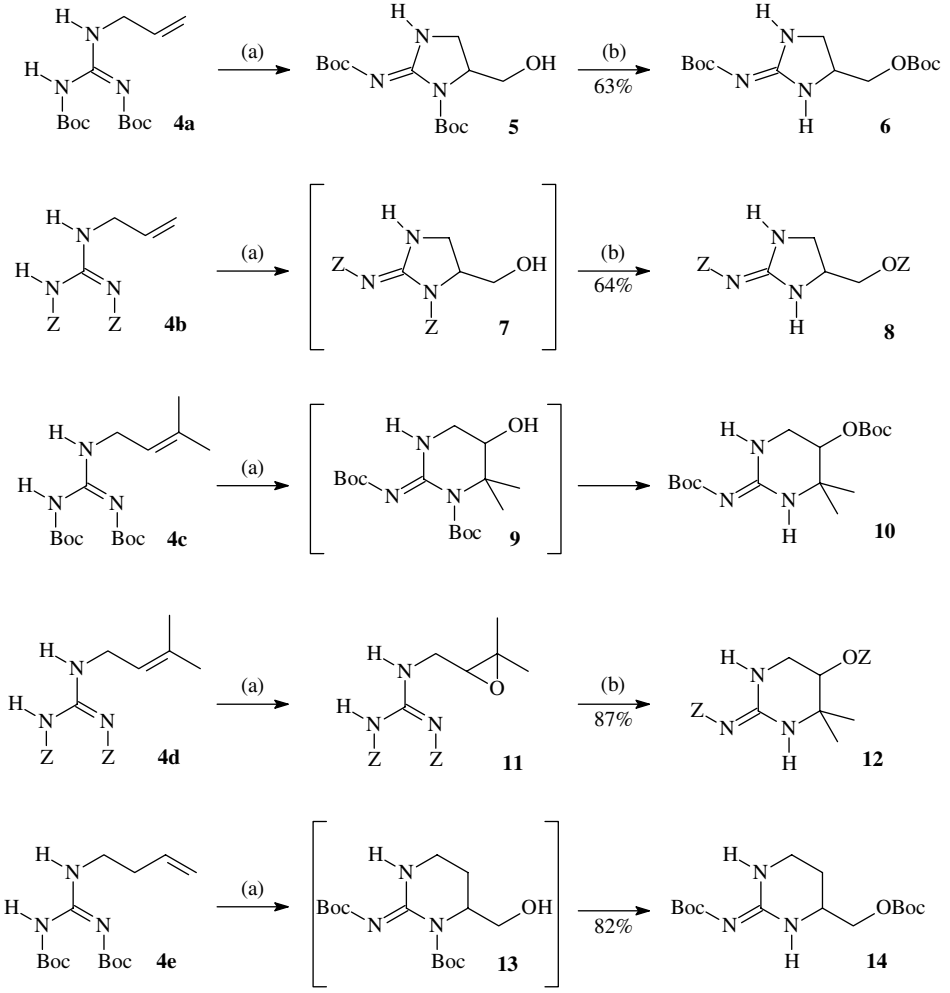
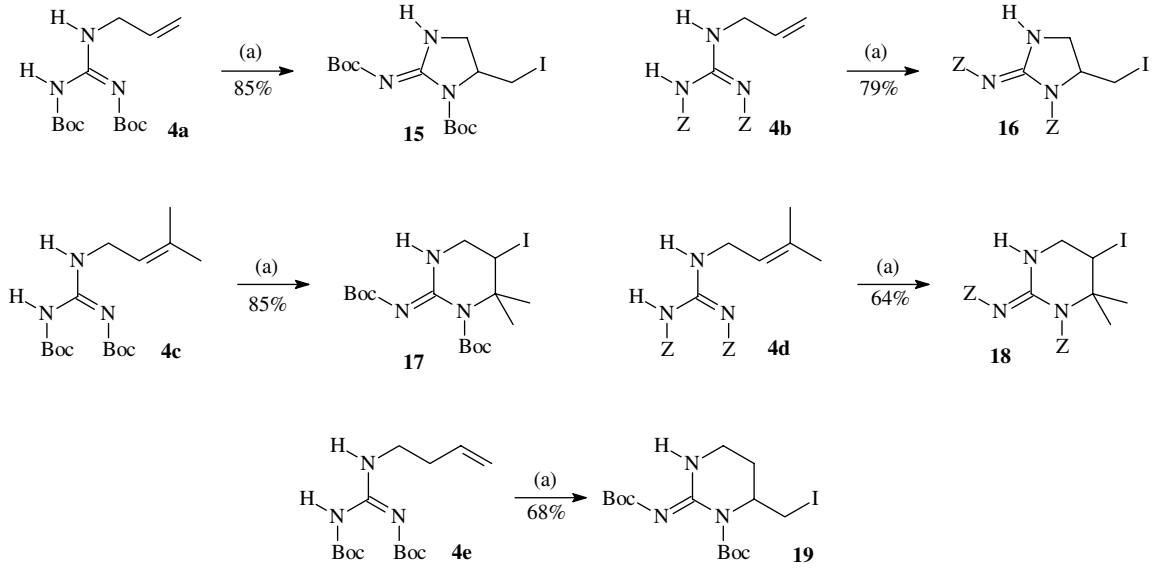


Figure 2.

structure **7**. However, on purification on silica gel a new product was formed in 64% yield, which had a considerably simpler spectrum with signals at δ 3.34 (1H), 3.67 (1H) and 4.07 (3H) ppm and the two guanidine protons at δ 7.87 (1H) and δ 8.03 (1H) ppm assigned the structure as **8**. Again it was possible to effect this rearrangement by stirring the crude reaction product with silica gel in dichloromethane.



Scheme 2. Reagents and conditions: (a) DMDO, acetone, −20 °C–rt, 1–7 days; (b) silica gel, CH_2Cl_2, 16–24 h.[5]



Scheme 3. Reagents and conditions: (a) I_2, CH_3CN, K_2CO_3, 0 °C–rt, 16–24 h.[5]

We next investigated the epoxidation of the dimethylallyl guanidine **4c** and found that on treatment with DMDO an epoxide (CH at δ 2.97, dd, J 4.4, 7.6 Hz) was formed which slowly underwent ring opening to give initially the 6-membered guanidine **9** after 2–3 days but ultimately (7 days) gave the rearranged 6-membered product **10**, as evidenced by the methine signal at δ 4.15 (1H, dd, J 2.5, 8.5 Hz) giving an axial coupling constant of 8.5 Hz. Attempted purification of this material was difficult as the product obtained was a gum which could not be recrystallised and was also prone to decomposition on silica gel which was presumably occurring via the loss of a Boc protecting group. A similar reaction of bis-*Z* protected **4d** gave epoxide **11** as a stable product, which on attempted recrystallisation from dichloromethane/petrol (10:1) deposited a precipitate of the cyclised and rearranged guanidine **12**. Again the methine signal at δ 4.10 ppm (1H, dd, J 10.5, 6.1 Hz) and the guanidine protons at δ 8.17 ppm (1H, br s, NH) and δ 8.93 ppm (1H, br s, NH) were indicative of the 6-membered product. The slow rearrangement could be accelerated if a solution of the crude reaction mixture in dichloromethane was stirred with silica gel overnight, to give an 87% yield of **12**. Finally, we investigated the DMDO cyclisation of the homoallyl guanidine **4e** and found that it smoothly cyclised and rearranged to give the 6-membered guanidine **14** in 82% yield; the structure being determined by X-ray crystallography (Fig. 2)[4] (Scheme 2).

We next investigated the iodocyclisation[2,6] of the allylated guanidines and found that both the Boc- and *Z*-protected allyl guanidines **4a** and **4b** gave the corresponding 5-membered heterocycles **15** and **16** in high yields on treatment with I_2 in acetonitrile. Reaction of the Boc-protected dimethylallyl guanidine **4c** was more problematic in that a high yield (ca. 85%) of the 6-membered product **17** was obtained as evidenced by the CH at δ_H 4.27 (1H, dd, J 9.1, 5.5 Hz) and δ_C 30.1 ppm, however, the material decomposed on attempted silica gel chromatography, presumably due to the loss of the Boc group adjacent to the two methyl groups. Guanidine **17** was also freely soluble in petroleum ether and gave only an amorphous solid on slow evaporation. The reaction of *Z*-protected **4d** was more successful in that the cyclised product was easily purified by recrystallisation from dichloromethane/petroleum ether and was obtained in 64% yield with signals at δ_H 4.27 (1H, dd, J 8.8 and 5.5 Hz) and δ_C 29.2 ppm corresponding to the methine proton. Finally, the homoallyl guanidine **4e** was cyclised under standard conditions and gave the 6-membered guanidine **19** in 68% yield after chromatography with signals for the CH_2I group being observed at δ_H 3.08 (1H, dd, J 10.4, 9.9 Hz) and δ_H 3.50 (1H, dd, J 3.8, 9.9 Hz) and δ_C 6.1 ppm (Scheme 3).

In conclusion, we have demonstrated that guanidines **4a**–**e** undergo cyclisation to give 5- and 6-membered cyclic guanidines and in the epoxide cyclisation both the *N*-Boc and *N*-*Z* protecting group are prone to migration to the alcohol function in a predictable manner. We are currently investigating this process in more detail and applying this methodology to a synthesis of cylindrospermopsin.

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4. X-ray data crystal structure analyses: Suitable crystals were selected and data collected on a Bruker Nonius KappaCCD Area Detector equipped with a Bruker Nonius FR591 rotating anode ($\lambda_{\text{Mo-K}\alpha} = 0.71073$ Å) at 120 K driven by COLLECT,[7] and processed by DENZO[8] software and corrected for absorption by using SADABS.[9] The structures were determined in SHELXS-97 and refined using SHELXL-97.[10] All non-hydrogen atoms were refined anisotropically with hydrogen atoms included in idealised positions with thermal parameters riding on those of the parent atom. Crystal Data for **6**: $C_{14}H_{25}N_3O_5$, $M = 329.40$, triclinic, $a = 9.0231(6)$ Å, $b = 9.1863(6)$ Å, $c = 12.5757(9)$ Å, $\alpha = 106.174(4)°$, $\beta = 97.221(4)°$, $\gamma = 110.245(4)°$, $U = 910.30(11)$ Å^3, $T = 120(2)$ K, space group $P\bar{1}$, $Z = 2$, $\mu(\text{Mo-K}_\alpha) = 1.239$ mm^{-1}, 17,747 reflections measured, 4139 unique ($R_{\text{int}} = 0.0682$) which were used in all calculations. Final $R_1 = 0.0883$, $wR_2 = 0.1374$ [$F^2 > 2\sigma(F^2)$], $R_1 = 0.1405$, $wR_2 = 0.1583$ (all data). Full crystallographic details in the form of a CIF have been deposited with the Cambridge Crystallographic Data Centre with deposition number 654570. Crystal Data for **14**: $C_{15}H_{27}N_3O_5$, $M = 329.40$, monoclinic, $a = 15.2537(9)$ Å, $b = 10.4010(5)$ Å, $c = 11.1871(6)$ Å, $\beta = 95.981(2)°$, $U = 1765.21(16)$ Å^3, $T = 120(2)$ K, space group $P2_1/c$, $Z = 4$, $\mu(\text{Mo K}_\alpha) = 1.239$ mm^{-1}, 26,343 reflections measured, 4036 unique ($R_{\text{int}} = 0.0855$) which were used in all calculations. Final $R_1 = 0.1158$, $wR_2 = 0.2434$ [$F^2 > 2\sigma(F^2)$], $R_1 = 0.1597$, $wR_2 = 0.2649$ (all data). Full crystallographic details in the form of a CIF have been deposited with the Cambridge Crystallographic Data Centre with deposition number 654569.
5. Typical experimental procedures: Benzyl-((2*Z*)-2-{[(benzyloxy)carbonyl]imino}imidazolidin-4-yl)-methyl carbonate **8**: Finely powdered *N*-allyl-*N*′,*N*″-bis-*Z*-guanidine **4b** (0.309 g, 0.84 mmol) was cooled in an ice/salt bath for 20 min prior to the addition of pre-cooled (−78 °C), dried DMDO (excess) solution in acetone. The solution was stirred to rt slowly (overnight) and then for a further 5 days. After evaporation of the acetone the crude product was dissolved in dichloromethane (5 mL) and silica gel (1 g) was added and the slurry stirred overnight. Evaporation of the dichloromethane and column chromatography of the residue (0–100% EtOAc in petrol) gave **8** (0.208 g, 0.54 mmol, 64%) as a white solid. Mp 155–157 °C; R_f 0.46 (EtOAc); δ_H (500 MHz, $CDCl_3$) 3.34 (1H, dd, *J* 10, 4 Hz) 3.67 (1H, m), 4.07 (3H, m), 5.06 (2H, s), 5.16 (2H, s), 7.4 (10H, m), 8.1–9.4 (2H, br s); δ_H (500 MHz, DMSO-d_6) 3.31 (2H, m) 3.61 (1H, t, *J* 10 Hz), 4.1–4.2 (2H, m), 5.0 (2H, s), 5.15 (2H, s), 7.2–7.4 (10H, m), 7.87 (1H, br s), 8.03 (1H, br s); δ_C (125 MHz, $CDCl_3$) 44.5 (CH_2), 52.3 (CH), 66.4 (CH_2), 68.1 (CH_2), 69.9 (CH_2), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 134.9 (C), 137.2 (C), 154.6 (C), 163.1 (C), 165.1 (C); $\nu_{\max}$ cm^{-1} 3398, 3100–2900 (br), 3065, 3035, 2956, 1748, 1654, 1623, 1264; MS (CI, NH_3) *m*/*z* 384 (M+H, 33%); HRMS (ES+) $C_{20}H_{22}N_3O_5$ [M+H$^+$] requires 384.1554, found 384.1558. 2-*tert*-Butoxycarbonylimino-6-iodomethyl-tetrahydro-pyrimidine-1-carboxylic acid *tert*-butyl ester **19**: *N*-homoallyl-*N*′*N*′-bis-(*tert*-butoxycarbonyl)-guanidine **4e** (0.37 g, 1.18 mmol), iodine (1.19 g, 4.72 mmol, 4 equiv) and potassium carbonate (0.65 g, 4.72 mmol, 4 equiv) were dissolved in dry acetonitrile (10 mL) and left to stir overnight under an argon atmosphere. The solution was then treated dropwise with sodium thiosulfate solution (saturated) until the excess iodine was consumed, then diluted with chloroform (20 mL) and water (50 mL). After separation, the organic phase was washed with water (3 × 20 mL), dried ($MgSO_4$) and evaporated in vacuo. Silica gel column chromatography (gradient elution 15–60% EtOAc) gave **19** (0.35 g, 0.68 mmol, 68%) as a white crystalline solid. R_f 0.34 (30% EtOAc in petrol). Mp 107–108 °C; δ_H (500 MHz, CD_3OD, NH exchanged) 1.47 (9H, s, 3 × Me) 1.51 (9H, s, 3 × Me), 1.82 (1H, m, CH), 2.04 (1H, m, CH), 3.37 (1H, m, CH), 3.44 (1H, m, CH), 3.77 (1H, m, CH), 4.08 (1H, dd, *J* 11.0, 6.6 Hz, *C*H), 4.23 (1H, dd, *J* 11.0, 4.9 Hz, *C*H); δ_C (125 MHz, $CDCl_3$) 6.4(CH_2), 25.6 (CH_2), 27.8 (CH_3), 28.0 (CH_3), 36.0 (CH_2), 54.0 (CH), 79.2 (C), 83.2 (C), 151.6 (C), 158.0 (C), 162.7 (C); $\nu_{\max}$ cm^{-1}(Nujol Mull) 3153, 2920, 2725, 1735, 1714, 1650, 1549, 1457, 1376, 1296, 1154. MS (EI) *m*/*z* 439.0 (M$^+$, 3%); HRMS (EI) $C_{15}H_{26}N_3O_4I$ [M$^+$] requires 439.0968, found 439.0967.
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