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Iodocyclisation and rearrangement reactions of *mono*-protected allyl substituted guanidines

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ABSTRACT

The iodocyclisation of a range *N*-allyl and *N*-homoallylguanidines using I_2/K_2CO_3 has been found to lead to a series of novel heterocycles which undergo selective rearrangements on variation of the reaction conditions, and predictable protecting group migration in the presence of trifluoroacetic acid in methanol.

We have previously reported[1,2] on the iodocyclisation[3] of bis-Boc- and bis-*Z*-protected allylguanidines **1a** and **1b** resulting in the formation of the corresponding five-membered heterocycles **2a** and **2b** in 85% and 79% yields, respectively, upon treatment with I_2 in acetonitrile (Scheme 1).

We wanted to study the effect of the protecting groups on the selectivity of the cyclisation, and to this end the three *mono*-protected guanidines **5a–c** were prepared by the reaction of *mono*-protected 1*H*-pyrazole carboxamidines **3a**,**b** with the corresponding amine or amine salt **4** in acetonitrile[4] (Scheme 2, Table 1).

Initial cyclisation of the *mono*-Boc-allylguanidine **5a** led to formation of product **6** in essentially quantitative yield as was evident from the ^{1}H NMR spectrum. Cyclisation occurred at the Boc-substituted nitrogen of the guanidine as was apparent from HMBC studies (Scheme 3).

Attempts at purifying the heterocycle by column chromatography were problematic as several new products were formed. Previous work[2] on the epoxidation of bis-protected guanidines had demonstrated that Boc and *Z*-protecting groups were prone to migration to hydroxy groups, and it was possible to mediate this by stirring with moist silica gel. An attempt to mimic this with **6** was found to give a complex mixture of products, and after purification, four compounds were isolated including **8** and **9** (3% and 4% yield) in which the Boc group had migrated to one of the other two guanidine nitrogens and a deprotected guanidine **10** (13% yield). Interestingly the urea **7** was also isolated in a low 2% yield which may have arisen via a sequence of Boc-transfer reactions and hydrolysis of the C=NBoc moiety by water[5] (Scheme 4).

On further analysis it was apparent that on standing at −20 °C, chloroform solutions of the crude product **6** underwent considerable decomposition/rearrangement, with NMR analysis indicating the presence of at least four different compounds. It was thought that trace moisture or acid might be mediating this and we thus took a solution of crude **6** and treated it with a threefold excess of trifluoroacetic acid (TFA) in dichloromethane for 16 h[6] (Scheme 5). On NMR analysis it was apparent that the initial compound **6** had been converted into a single major compound which had a ^{1}H NMR spectrum similar to that observed for structure **9** with diagnostic signals at δ_H 1.56 (9H, s), 3.35 (1H, dd, J = 10.7, 1.8 Hz), 3.47 (1H, dd, J = 10.5, 3.4 Hz), 3.53 (1H, dd, J = 10.5, 7.0 Hz), 3.87 (1H, app. t, J = 10.5 Hz) and 4.39 (1H, m) ppm. Final determination of the structure of **9** was obtained by HMBC. A strong correlation between the ring CH_2N signal and the Boc-carbonyl quaternary carbon was observed. Pure compound **9** could be obtained as its trifluoroacetate salt in 70% overall yield by recrystallisation from dichloromethane/petroleum ether (5:1).

We further investigated this process by utilising a Z-protected guanidine in the hope that this protecting group might be less likely to undergo rearrangement. Thus cyclisation of *mono*-Z allylguanidine **5b** was attempted. Again the expected 5-*exo*-product **11**

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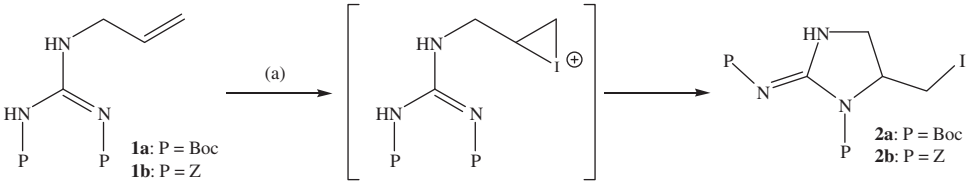
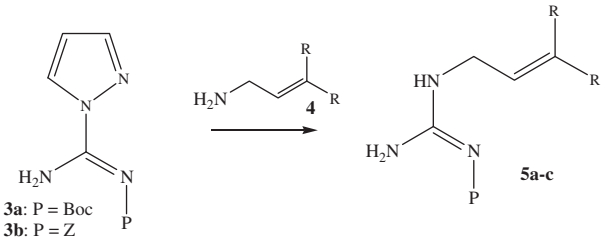


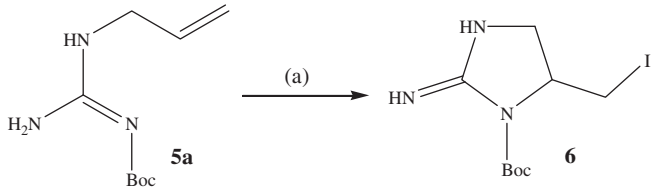
Scheme 1. Reagents and conditions: (a) I_2, CH_3CN, K_2CO_3, 0 °C to rt, 16–24 h.



Scheme 2. Method A: amine **4**, Δ, 2.5 h. Method B: **4**·HCl, NEt_3, CH_3CN, 16 h, rt then 50 °C 6 h.

Table 1

Product	P	R	Method	Yield (%)	Mp (°C)
5a	Boc	H	A	80	75–78
5b	Z	H	A	61	119–121
5c	Z	Me	B	74	81–83

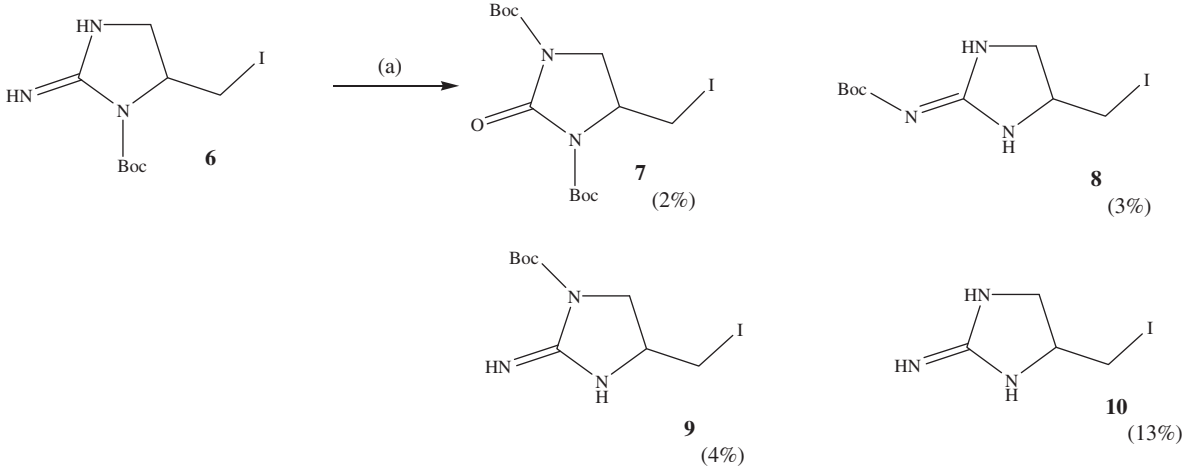


Scheme 3. Reagents and conditions: (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C to rt, 16 h.

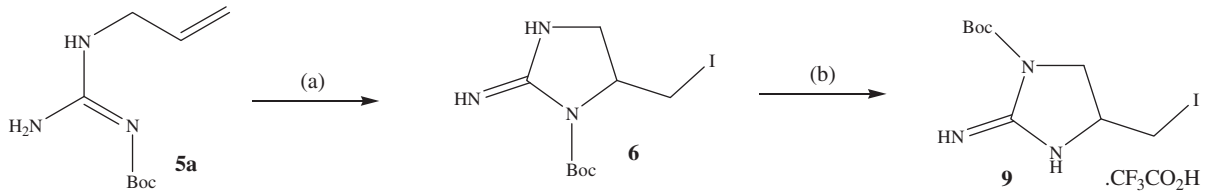
was observed which was identified by ^{1}H NMR signals at δ_H 3.28 (1H, dd, J = 6.5, 9.8 Hz), 3.38 (1H, dd, J = 4.7, 9.8 Hz), 3.70 (1H, dd, J = 5.7, 10.7 Hz), 4.05 (1H, dd, J = 9.1, 10.5 Hz) 4.16 (1H, dddd, J = 6.5, 4.7, 5.7, 9.1 Hz), 5.35 (2H, d, J = 12.3 Hz) and 7.5 (5H, m). However, as was observed with the Boc-protected analogue **6**, attempted purification led to decomposition and only two compounds were obtained, the previously originally identified product **10** in 22% yield and the rearranged compound **12** in 10% yield. In order to ascertain if the Z-protecting group was migrating in a similar manner to that observed in Boc-protected **5a**, the reaction was repeated and the resulting crude compound **11** treated with TFA in methanol overnight. This resulted in the formation of **12**, identical to the product isolated previously, as the major product. Compound **12** gave ^{1}H NMR signals at δ_H 3.32 (1H, br d, J = 10.4 Hz), 3.45 (1H, m), 3.54 (1H, dd, J = 10.8, 4.1 Hz), 3.88 (1H, dd, J = 10.8, 9.8 Hz), 4.47 (1H, m), 5.31 (1H, d, J = 11.7 Hz), 5.40 (1H, d, J = 11.7 Hz) and 7.38–7.45 (5H, m) ppm which correlate very closely to **9**, and as before, the position of the Z group was confirmed by HMBC correlation studies. Pure compound **12** could be obtained in 47% overall yield by crystallisation from dichloromethane/diethyl ether/petroleum ether (5:2:2) (Scheme 6).

We next investigated the cyclisation of the *Z*-dimethylallyl guanidine **5c**. In related work,[2] it had been reported that the bis-*Z*-dimethylallyl guanidine **13** underwent cyclisation to give the six-membered product **14** in 64% yield and we wanted to see if a similar reaction was possible with **5c** (Scheme 7).

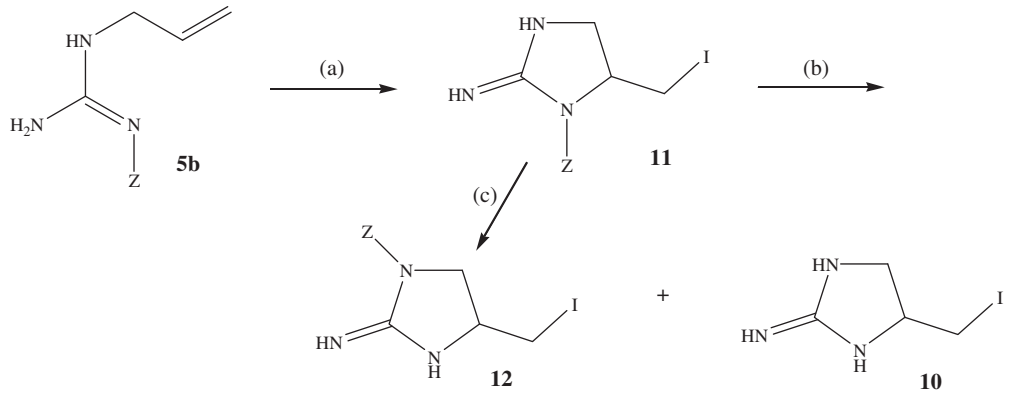
We thus treated **5c** under the previously employed conditions, and on work-up, obtained a crude product which appeared to be composed of two compounds in a 63:37 ratio by ^{1}H NMR. Further analysis of the proton NMR spectrum indicated that the minor compound had an ABX coupling pattern at δ_H 3.49 (1H, dd, J = 9.5, 13.6 Hz), 3.60 (1H, dd, J = 4.9, 13.6 Hz) and 4.00 (1H, dd, J = 4.9, 9.5 Hz) ppm whilst the major product had a similar pattern at δ_H 3.43 (1H, dd, J = 9.2, 13.6 Hz), 3.55 (1H, dd, J = 4.6, 13.6 Hz) and 3.97 (1H, dd, J = 4.6, 9.2 Hz) ppm. Analysis of the ^{13}C NMR spectrum indicated that the CH_2 signals were at 46.4 and 5.8 ppm for the two species. The first of these was as expected for a CH_2N group and the structure was determined to be the



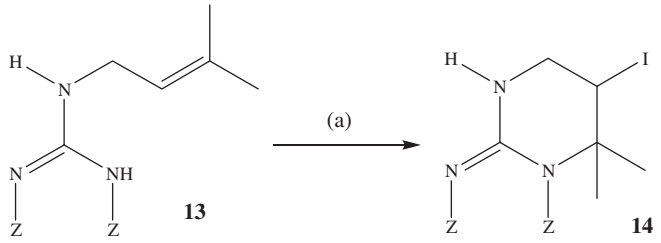
Scheme 4. Reagents and conditions: (a) SiO_2, CH_2Cl_2, stir, 5 d.



Scheme 5. Reagents and conditions: (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C to rt; (b) TFA, MeOH, 16 h, 70%.



Scheme 6. Reagents and conditions: (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C to rt, 16 h; (b) SiO_2, CH_2Cl_2, stir, 5 d; (c) TFA, MeOH, 16 h, 47%.



Scheme 7. Reagents and conditions: (a) CH_3CN, 4.5 equiv K_2CO_3, 4 equiv I_2, −15 °C to rt, 16 h, 64%.

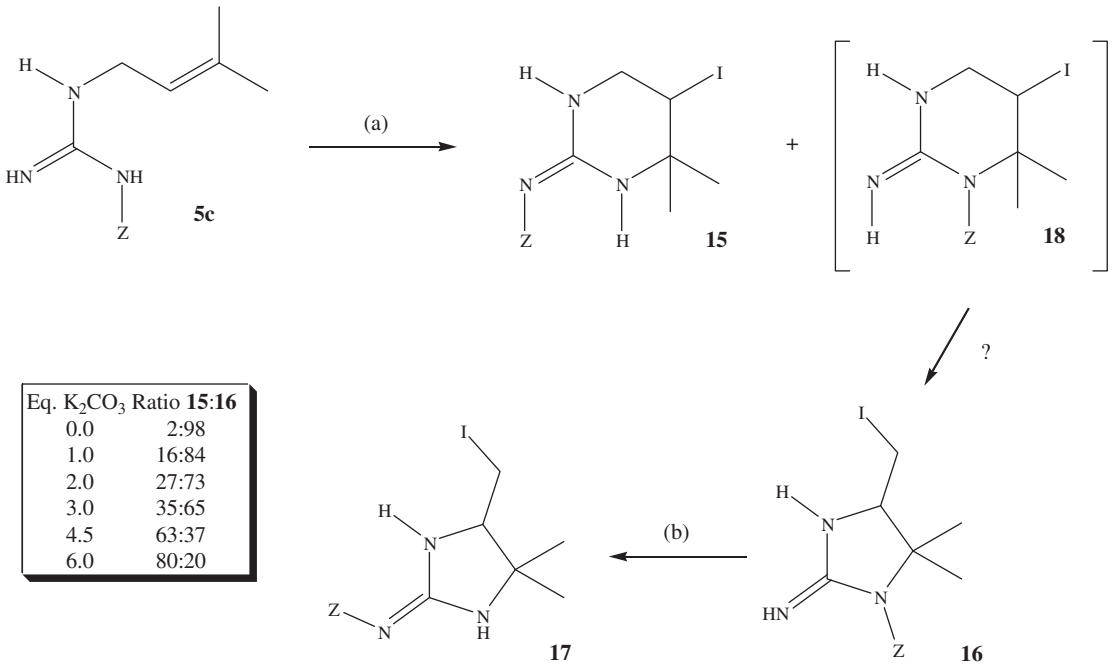
six-membered product **15**, however, the signal at 5.8 ppm suggests that structure **16** containing a CH_2I moiety had formed. As with previous examples, both **15** and **16** decomposed when in contact with silica gel and they were thus treated with methanolic TFA to give a crude mixture containing two rearranged products. NMR analysis of the crude mixture indicated that the signals for the major product **15** remained unchanged whilst the minor compound had a rearranged structure, guanidine **17**, in which the Z-group had migrated to the exocyclic nitrogen. This compound displayed an ABX pattern at δ_H 3.39 (1H, dd, J = 7.6, 11.0 Hz), 3.56 (1H, dd, J = 4.4, 11.0 Hz) and 3.94 (1H, dd, J = 4.4, 7.6 Hz) ppm. Compound **15** could be separated from the mixtures in 75–85% yield at either stage of this process by dissolution in MeOH, followed by cooling (−15 °C), which resulted in its precipitation. The precise structures of compound **15** and the rearranged products **16** and **17** were confirmed by HMBC correlation studies which demonstrated that **16** and **17** were two isomeric five-membered compounds differing only in the position of the Z-protecting group (Scheme 8).

We wanted to investigate this process further and envisaged that we might be able to influence the ratios of the two products by varying the amount of potassium carbonate used in the reaction, as it was postulated that the rearrangement might be due to the presence of HI in the reaction medium. The results of a series of experiments are shown in Scheme 8.

Interestingly, it was observed that in the reaction of **5c** in the absence of potassium carbonate the rearranged product **16** was formed almost exclusively and only a trace amount of **15** was observed. As the amount of base was increased a steady switch to the formation of **15** was observed. This suggests that under acidic conditions the cyclisation proceeds via the ZNH function, leading to intermediate **18**, possibly because of protonation of one of the other nitrogens.

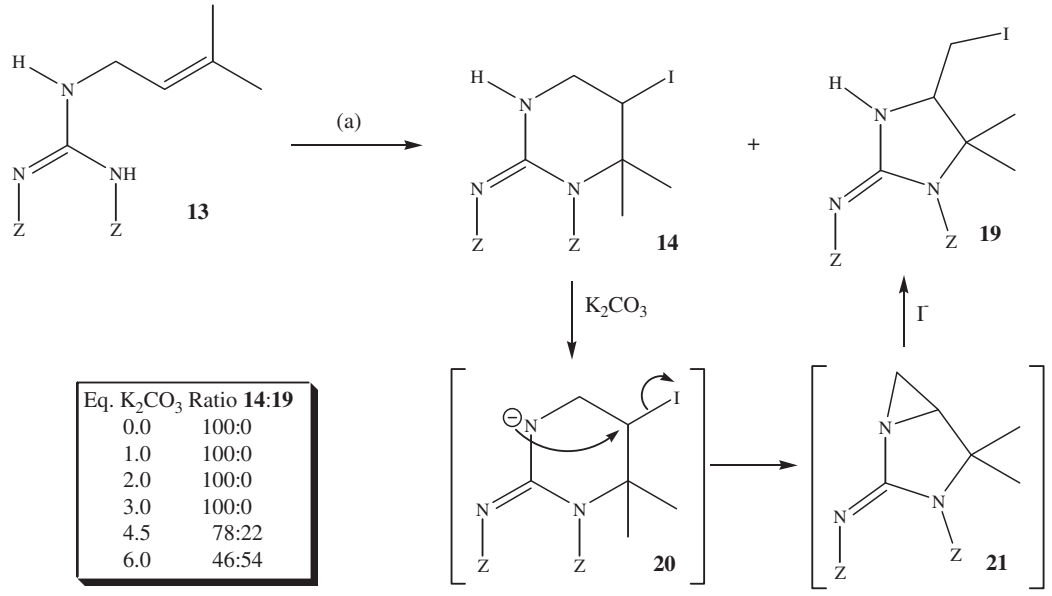
In order to elucidate further information regarding this reaction we reinvestigated the cyclisation of the bis-*Z*-dimethylallylguanidine **13** using varying amounts of potassium carbonate in the reaction mixture. The results of a series of experiments are shown in Scheme 9. It was found that in the absence of potassium carbonate only the six-membered product **14** was observed in the crude reaction mixture. However, when more than 4 equiv of base were utilised a second product was observed, which was on isolation, and was shown to be the five-membered product **19**. It is possible that this compound **19** arose through a base-mediated ring contraction via the anion **20** and the aziridine **21**. In order to test this proposal we took a purified sample of **14** and treated it with 5 equiv of finely powdered potassium carbonate in acetonitrile for 16 h at room temperature and found that it rearranged to give the heterocycle **19** as the only product (Scheme 9).

The reason for the different conditions required to effect these two ring contraction reactions might lie in the nature of the guanidine substituents. In compound **14** the delocalization of electron density by the two Z-protecting groups reduces the nucleophilicity of the remaining ring nitrogen, but leads to increased NH acidity enabling the reaction to proceed under basic conditions. In the case of compound **18** it is possible that the single Z-protecting group does not have such a profound effect and it can be postulated that sufficient nucleophilicity is present to enable a similar rearrangement (Scheme 10).



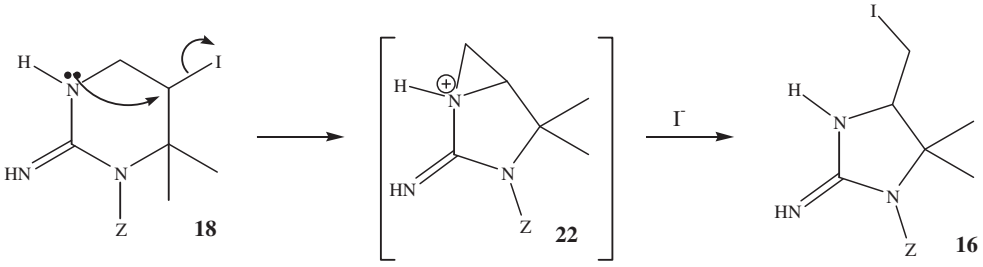
Eq. K_2CO_3	Ratio **15**:**16**
0.0	2:98
1.0	16:84
2.0	27:73
3.0	35:65
4.5	63:37
6.0	80:20

Scheme 8. Reagents and conditions: (a) CH_3CN, K_2CO_3, 4 equiv I_2, −15 °C to rt, 16 h; (b) TFA, MeOH, 16 h, 49% (for **17**, two steps).



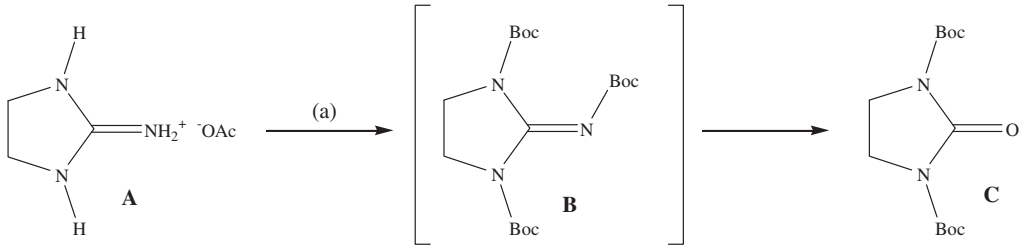
Eq. K_2CO_3	Ratio **14**:**19**
0.0	100:0
1.0	100:0
2.0	100:0
3.0	100:0
4.5	78:22
6.0	46:54

Scheme 9. Reagents and conditions: (a) CH_3CN, K_2CO_3, 4 equiv I_2, −15 °C to rt, 16 h.



Scheme 10. Rearrangement of intermediate **18**.

In conclusion, we have demonstrated that the cyclisation of *mono*-protected guanidines is a considerably more complex process than for the bis-protected analogues and the products of these reactions proved to be very sensitive to silica gel chromatography and acid. However, the reactions of simple allyl-substituted guanidines do proceed in high yield and in a predictable manner. Both the *mono*-Z-protected and the bis-Z-protected guanidines **5c** and **13** undergo predictable ring contraction rearrangements which can be controlled by carefully selecting the conditions and these processes should be of synthetic interest in preparing highly substituted cyclic guanidines.



(a) NaH (excess), $(Boc)_2O$ (excess), THF, 0 ºC, 16 h.

Acknowledgements

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4. *Typical experimental procedure*: *N*-Boc-1*H*-pyrazole-1-carboxamide (**3a**) (2.0 g, 9.51 mmol) was dissolved in excess allylamine (10 ml) and the mixture refluxed for 2.5 h. The solvent was removed under reduced pressure and the residue crystallised from CH_2Cl_2/petroleum ether to give **5a** (1.51 g, 80%) as a white solid. Mp 75–78 °C; δ_H (500 MHz, $CDCl_3$) 1.46 (9H, s, 3 × CH_3), 3.83 (2H, d, J = 4.9 Hz, CH_2), 5.24 (1H, br d, J = 10.4 Hz, CH) 5.33 (1H, br d, J = 17.1 Hz, CH), 5.83 (1H, ddt, J = 17.1, 10.4, 4.9 Hz, CH), 6.34 (1H, br s, NH), 7.60 (2H, br s, 2 × NH); δ_c (125 MHz, $CDCl_3$) 28.4 (CH_3), 43.9 (CH_2), 78.1 (C), 117.3 (CH_2), 133.5 (CH), 162.1 (C), 163.6 (C); HRMS (ES+) m/z: $C_9H_{18}O_2N_3$ ([M+H]$^+$); requires 200.1394; found 200.1391.
5. We previously observed that attempts to protect the cyclic guanidine **A** using excess NaH and $(Boc)_2O$ led to the formation of urea **C** as the main product in 30% yield. It is thought that this occurs via hydrolysis of intermediate **B** on aqueous work-up or chromatography.[7]
6. *Typical experimental procedure*: *N*-Boc-allylguanidine **5a** (0.30 g, 1.5 mmol) was dissolved in acetonitrile (20 ml) and cooled (−15 °C) using an ice/salt bath. K_2CO_3 (0.83 g, 6 mmol, 4 equiv) was added, followed by I_2 (1.53 g, 6 mmol, 4 equiv). The mixture was stirred at rt for 16 h before being diluted with H_2O (50 ml). $Na_2S_2O_3$ solution (saturated) was then added until the I_2 colour had dispersed and the mixture was extracted with EtOAc (3 × 50 ml), dried ($MgSO_4$) and evaporated to dryness to give crude **6** (0.498 g). This product was dissolved in MeOH (5 ml), TFA (0.38 ml, 4.9 mmol) was added and the mixture stirred for 16 h. On evaporation, a solid (0.65 g) was obtained which was dissolved in a minimum volume of CH_2Cl_2 (ca. 5–10 ml), diluted with petroleum ether (1–2 ml) and placed in a freezer overnight to give a pale yellow solid. The supernatant liquid was decanted and the solid washed with petroleum ether to give **9**·HCO_2CF_3 (0.34 g, 70%) as a pale yellow solid. Mp 90–92 °C; R_f: 0.29 (10% MeOH/$CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.56 (9H, s, ^{t}Bu), 3.35 (1H, dd, J = 10.7, 1.8 Hz, CH), 3.47 (1H, dd, J = 10.5, 3.4 Hz, CH), 3.53 (1H, dd, J = 10.5, 7.0 Hz, CH), 3.87 (1H, app. t, J = 10.5 Hz, CH), 4.39 (1H, m, CH), 7.75 (1H, br s, NH), 11.07 (1H, br s, NH), 11.88 (1H, br s, NH); δ_C (125 MHz, $CDCl_3$) 7.0 (CH_2), 27.8 (3 × CH_3), 46.9 (CH_2), 56.8 (CH), 87.4 (C), 116.5 (q, $^1J_{C-F}$ = 292 Hz, C), 149.9 (C), 156.9 (C), 163.2 (q, $^2J_{C-C-F}$ = 35 Hz, C); IR ν_{max} 3306, 1752, 1679 cm^{-1}; MS m/z: 326 (45%, [M+H]$^+$), 270 (100%); HRMS (ES+) m/z: $C_9H_{17}N_3IO_2$ [(M+H)$^+$]; requires; 326.0360; found 326.0363.
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