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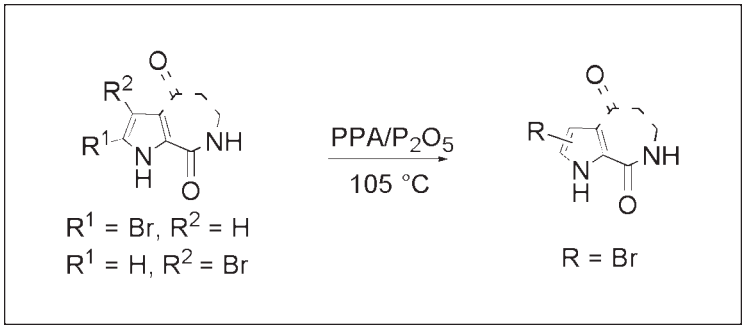

A study on the acid catalyzed halogen dance (ACHD) on deactivated bromopyrroles is reported. A different behavior is observed when considering singly deactivated pyrrole alkylcarboxamides, or doubly deactivated pyrroleketo-lactams (aldisines). Although less electron deficient pyrrole alkylcarboxamides suffer from ACHD, the double deactivation on keto-lactams disfavors pyrrole ring protonation thus preventing halogen scrambling. The mechanism involved in the rearrangement is hypothesized.

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INTRODUCTION

The first example of the well-known Halogen Dance (HD, also named halogen scrambling, halogen migration, halogen isomerization, halogen shift) reaction dates back to 1951, when Vaitiekunas isolated tetrabromothiophene instead of 2-ethynylthiophene by treating 2-bromothiophene with sodium acetylide in liquid ammonia [1]. The reaction was induced by the presence of the base and since then it has been largely investigated. Currently, the base catalyzed halogen dance (BCHD) is considered a useful tool for the introduction of halogen on aromatic and heteroaromatic substrates in positions that could be hardly reached with other methods. A recently published review thoroughly describes BCHD with elucidations of the mechanism and description of the factors that influence the reaction [2]. Among all the heteroaromatic substrates, no examples on pyrrole have been reported.

What is known in the literature referring to pyrroles solely deals with the effect of acids on substituents in the 2 position of the ring. In this context, acyl [3] and sulfinyl [4] moieties as well as halogens (bromine and chlorine) [5] have been considered. Rearrangement of 2-acylpyrroles aimed at the synthesis of 3-acyl isomers has been studied in the presence of strong acids (PPA, TFA). A [1,2]-acyl shift was hypothesized to rationalize the formation of the products [3(b)], as it was previously postulated for the isomerization of 2-acetylindoles [6]. Rearrangement as side-reaction, on the contrary, was observed in the sulfinylation of pyrroles with sulfinylchlorides: 2-sulfinylpyrroles were contaminated by 3-sulfinyl isomers, likely coming from an acid-catalyzed migration of the substituent in 2-position due to HCl released during the reaction [4]. Moreover, PPA-mediated cyclization of 3-(2-pyrrolyl)propionic acids afforded the expected products along with undesired regioisomers arising from both alkyl and acyl migration [3(a)]. Complex reaction mixtures were also obtained when pyrrole was treated with molecular bromine: beside the expected 2-bromopyrrole, products deriving from both isomerization and disproportionation of the brominated substrate were detected [5(a)]. The mechanism of bromine isomerization and disproportionation of *N*-benzyl-2-bromopyrrole in the presence of TFA has been recently investigated by Park *et al*., who suggested a 1,3-bromine shift to explain rearrangement on the corresponding *N*-benzyl-2-bromo-5-deuterio pyrrole [5(c)].

Thus, if on one hand halogen dance may be useful for the insertion of groups in specific positions of aromatic and heteroaromatic substrates, on the other hand it could represent a parasitic reaction when the shift of the halogen is unwanted. This is the case, for instance, of 2-bromoaldisine **1** (common name of 2-Bromo-6,7-

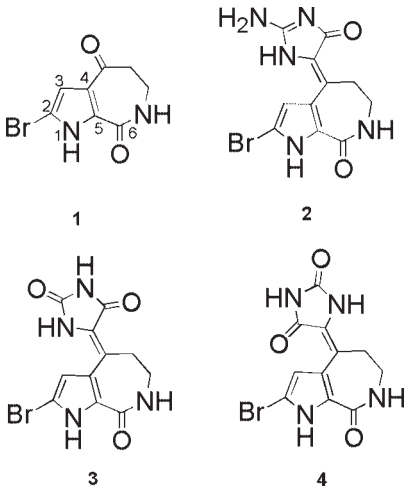


Figure 1. Bromopyrrole alkaloids derived from 2-bromoaldisine **1**.

dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione), envisaged as the key-intermediate for the synthesis of some bromopyrrole alkaloids, such as (*Z*)-hymenialdisine **2** [7], (*Z*)-axinohydantoin **3,** and (*E*)-axinohydantoin **4** [8] (Fig. 1).

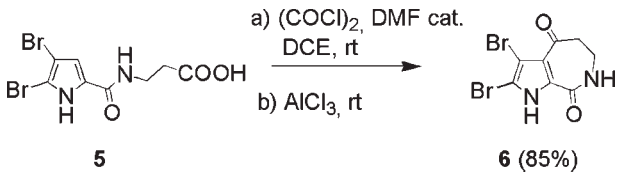
The synthesis of **1** was reported for the first time by Annoura by means of a PPA/P_2O_5-mediated cyclization of the corresponding 2-bromopyrrole propionic acid [7(a)]. The reaction suffered from bromine scrambling, delivering a 1:1 mixture of hardly separable bromoaldisine regioisomers. Interestingly, this was the first example of acid catalyzed halogen dance (ACHD) on deactivated pyrroles.

This side-reaction was later efficiently avoided by exploiting a Friedel-Craft-type cyclization on the acyl chloride intermediate in the presence of $AlCl_3$, affording **1** as the sole product in 69% optimized yield [8]. The same synthetic protocol allowed the preparation of 2,3-dibromoaldisine **6** [9] from the corresponding dibromoacid **5** [10] in 85% yield without any bromine rearrangement, differently from what previously reported in the presence of PPA/P_2O_5 [10] (Scheme 1).

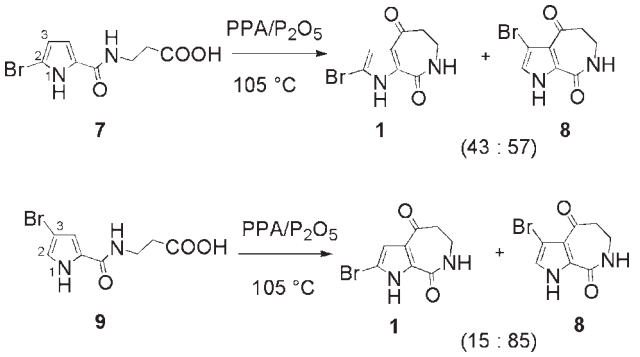
RESULTS AND DISCUSSION

The different reaction outcomes that a protic acid (PPA/P_2O_5) *versus* a Lewis acid ($AlCl_3$) displayed while performing the synthesis of bromoaldisines **1** and **6**, prompted us to study in more detail the ACHD on variously deactivated bromopyrroles in a strong acidic environment.

Scheme 1. Lewis acid-mediated synthesis of **6.**



Scheme 2. ACHD on bromopyrrolecarboxamides **7** and **9.**



To this purpose we decided, at first, to confirm the observations previously published for the synthesis of 2-bromo (**1**) and 3-bromoaldisine (**8**), by using the same reaction conditions (reagents, temperature, and reaction time) in the cyclization of **7** and **9** [11] (Scheme 2). As described, treatment of **7** with PPA/P_2O_5 at 105°C for 1 h produced a mixture of **1** and **8** in a 43:57 ratio (measured by ^1H NMR). On the contrary, in our hands regioisomer **9** [12] gave rise to a 15:85 mixture of **1** and **8** under the same conditions, in contrast with the literature (1:1 ratio as for **7**) [7(a)].

In these examples, PPA/P_2O_5 mediates both cyclization and scrambling of bromine atom. With the aim of trying to understand whether halogen dance (HD) took place before or after cyclization, the same acidic treatment was performed directly on brominated aldisines **1** and **8**. 2-Bromoaldisine **1** was synthesized as already described [8], while 3-bromoaldisine **8** was successfully isolated from the enriched mixture (15:85) deriving from **9** (see Scheme 2) by means of preparative HPLC. The two substrates have then been subjected to PPA/P_2O_5 treatment. The results highlighted minor differences, namely 2-bromoaldisine **1** was not prone at all to

Scheme 3. ACHD on aldisines **1** and **8.**

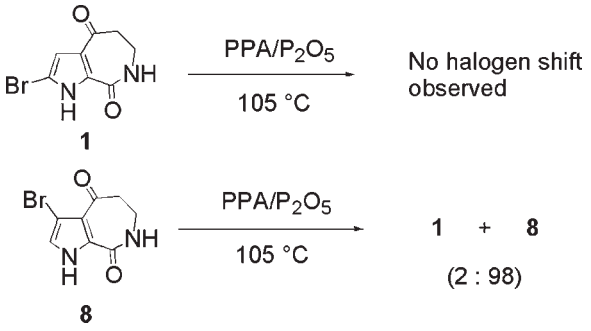


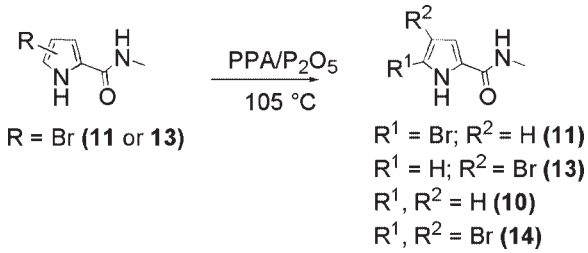
Table 1

Results of ACHD on **1**, **8**, **7**, and **9** (105°C, 1 h).

Entry	Substrate	**1** (%)[a]	**8** (%)[a]
1	**1**	100	–
2	**8**	2	98
3	**7**	43	57
4	**9**	15	85

[a] Measured by integrating pyrrole CH signal in ^{1}H NMR spectrum.

Scheme 5. ACHD on **11** and **13.**



rearrangement, while 3-bromoaldisine **8** produced a small percentage (2%) of 2-bromoisomer **1** (Scheme 3). This means that these keto-lactams hardly undergo halogen scrambling and HD occurs before cyclization.

The observations of ACHD on these substrates are summarized in Table 1.

Intrigued by these outcomes, we decided to evaluate the effect of PPA/P_2O_5 on bromopyrroles that: (a) were singly deactivated, like pyrrole alkylcarboxamides **7** and **9**, and (b) could not undergo cyclization, differently from **7** and **9**. Bromopyrrole methylcarboxamides **11** and **13** [11] have been chosen as the suitable substrates to the purpose, having the same EWG as **7** and **9**. Their synthesis is reported in Scheme 4: treatment of 2-trichloroacetylpyrrole with methylamine and subsequent bromination of **10** with NBS in THF/MeOH (2:1) afforded **11** (60% yield over two steps). The direct bromination of the same starting material with Br_2 in $CHCl_3$ and subsequent reaction of intermediate **12** with methylamine yielded **13** [13] (70% yield over two steps).

Both bromopyrroles **11** and **13** underwent rearrangement in different ratios, along with disproportionation that generated des-bromo derivative **10** and 4,5-di-bromomethylamide **14** (Scheme 5, Table 2).

As previously mentioned, the amount of the products has been determined by integrating isolated pyrrole CH signals in the ^{1}H NMR spectra of the reaction mixtures [Fig. 2(a,b)].

These results allowed us to make some considerations about the kinetics/thermodynamics of the ACHD on deactivated pyrroles compared to cyclization and to hypothesize a possible mechanism. First, it is evident that pyrrole alkylcarboxamides (*i.e.*, **7**, **9**, **11**, and **13**) are more prone to halogen rearrangement (Table 1, Entries 3 and 4; Table 2) than aldisines (Table 1, Entries 1 and 2). Second, scrambling of the halogen is faster when involving a shift from 2- to 3-position at the pyrrole ring (Table 1, Entry 3; Table 2, Entry 1) than vice versa (Table 1, Entry 4; Table 2, Entry 2). The ratio of 2-bromo and 3-bromoaldisine generated from **7** and the distribution of 2- and 3-regioisomers deriving from **11** (Table 1, Entry 3; Table 2, Entry 1) are the same. This means that the two mixtures reach the equilibrium during the reaction (thermodynamic conditions). Moreover, considering that aldisines are insensitive to ACHD, it is fair to assert that, for **7**, $V_{2S} > V_{2C}$, where V_{2S} represents the velocity of scrambling, and V_{2C} the velocity of cyclization (Scheme 6).

On the contrary, the same treatment on **9** and **13** did not spring out analogous results. The ratios of the two aldisines (products of **9**) and of 2- and 3-regioisomers arising from **13** measured in the experiments are different, meaning that these reaction mixtures are under kinetic conditions. It is possible to postulate that, for **9**, $V_{3C} \geq V_{3S}$, meaning that the velocity of cyclization and of scrambling are competitive (see Table 1, Entry 4). Furthermore, rearrangement from 2-position of **7** and **11** is faster than from carbon 3 of **9** and **13**, that explains the higher velocity with which **11** and **7** reach the equilibrium ($V_{2S} > V_{3S}$, see Table 1, Entries 3 and 4, and Table 2). Finally, disproportionation on **7** and **9** and on aldisines **1** and **6** has never been observed, while for **11** and **13** only to a less extent, meaning that this side-reaction is the slowest ($V_D << V_S$ and V_C, being V_D = velocity of disproportionation).

Scheme 4. Synthesis of pyrrolecarboxamides **11** and **13.**

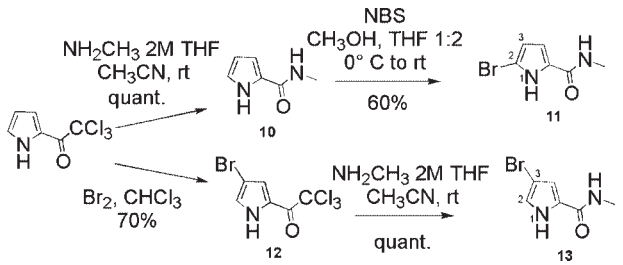


Table 2

Results of ACHD on **11** and **13** (105°C, 1 h).

Entry	Substrate	**11** (%)[a]	**13** (%)[a]	**10** (%)[a]	**14** (%)[a]
1	**11**	32 (46)[b]	38 (54)[b]	15	15
2	**13**	25 (34)[b]	49 (66)[b]	13	13

[a] Measured by integrating isolated pyrrole CH signals in ^{1}H NMR spectrum.
[b] In brackets the relative percentage of **11** and **13** is reported.

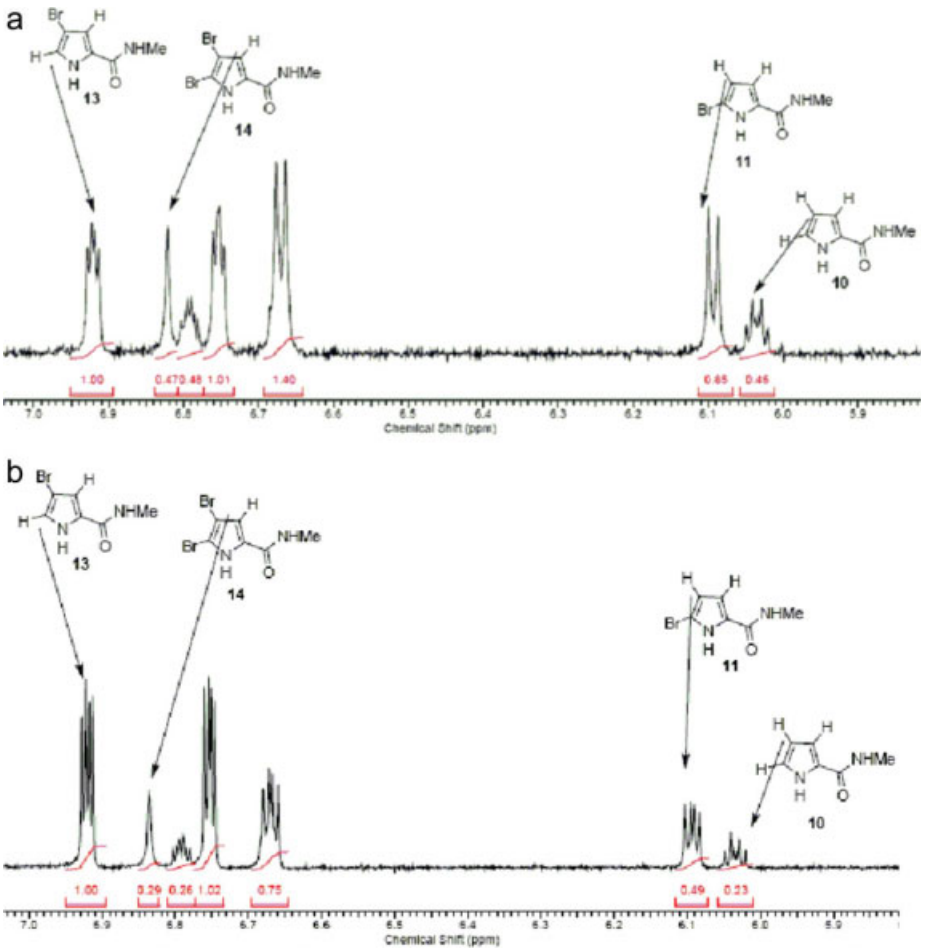


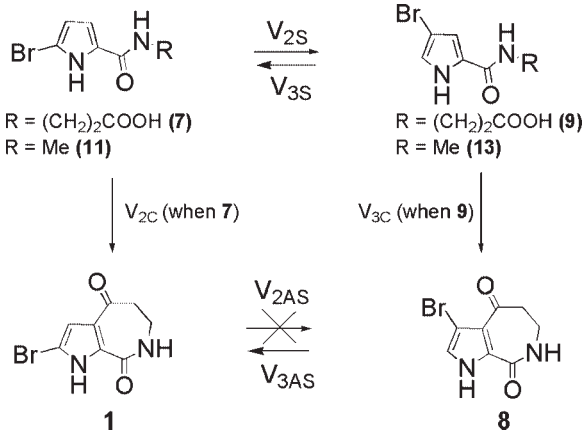
Figure 2. ^{1}H NMR analysis of ACHD on **11** (**2a**: top) and **13** (**2b**: bottom). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

A rearrangement mechanism was postulated to explain ACHD (Scheme 7). In strong acid media, **7** and **11** are subjected to protonation at the 2-position of the pyrrole affording **7a** and **11a**, respectively, which undergo a 1,2-bromine shift toward **9a** and **13a**, passing through transient cyclic bromonium intermediate **15**. The same mechanism can be invoked for **9** and **13**, that are protonated at 3-position generating **9a** and **13a**, respectively. A cyclic bromonium intermediate has been hypothesized instead of free Br^{+} cation because statistically this would have generated a higher amount of dibrominated pyrrole from **11** and **13** (see Table 2) and the presence of dibromo/desbromo aldisines from **7** and **9** (see Table 1).

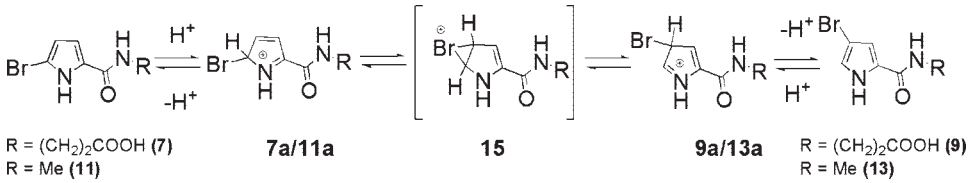
EXPERIMENTAL

General. Melting points were determined in open glass capillaries with a Buchi 535 melting point apparatus, and are uncorrected. NMR spectra (1D ^{1}H and 2D H-C hetero correlated) were recorded at 25°C in DMSO-d_6 on a Varian Inova 500 spectrometer equipped with a 5 mm ^{1}H{^{13}C,^{15}N} z-axis-PFG indirect detection cold probe or at 28°C on a Varian Mercury 300 spectrometer equipped with a 5 mm switchable probe ^{15}N-^{31}P{^{1}H,^{19}F}. Residual solvent signal was used as

Scheme 6. Velocity of cyclization *versus* scrambling.



Scheme 7. ACHD mechanism hypothesized.



reference; chemical shifts and coupling constants are reported, respectively, in δ (ppm) and Hz. ESI(+) high-resolution mass spectra (HRMS) were obtained on a Waters Q-Tof Ultima directly connected with micro HPLC 1100 Agilent [14].

CONCLUSION

In conclusion, a study on the ACHD on deactivated bromopyrroles has been reported and an hypothetical mechanism has been suggested. A different behavior was observed when considering singly deactivated pyrrole alkylcarboxamides, or doubly deactivated pyrrole-keto-lactams (aldisines). While less electron deficient pyrrole alkylcarboxamides suffered from ACHD, the double deactivation on keto-lactams disfavored protonation thus preventing halogen scrambling. Moreover, in the carboxamides series, scrambling was faster when bromine atom was in the 2-position rather than on 3-carbon. In addition, during the conversion of pyrrole alkylcarboxamides **7** and **9** into aldisines, cyclization occurred, respectively, after scrambling and at a competitive velocity.

EXPERIMENTAL

General procedure for ACHD. P_2O_5 (2 eq) and PPA (28 eq) were mechanically stirred and heated at 120°C for 50 min, to obtain a clear solution. The substrate was then added and the mixture was heated at 105°C for 1 h. The mixture was poured into ice water and stirred for 1 h. The solid was filtered off, washed with water, and dried. A second aliquot of reaction mixture was recovered from the aqueous phase as follow: the water solution was cooled, neutralized with concentrated sodium hydroxide, and extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, concentrated, and combined with the solid.

2,3-Dibromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione (6). To a suspension of **5** (414 mg, 1.21 mmol) in dry CH_2Cl_2 (15 mL) oxalyl chloride (0.21 mL, 2.43 mmol) and DMF_{cat} (0.015 mL) were added. The mixture was stirred under nitrogen until completion of gas evolution. The solvent was removed under reduced pressure and the crude was dissolved in 1,2-dichloroethane (40 mL). 4-Å molecular sieves and aluminium trichloride (0.65 g, 4.87 mmol) were subsequently added. The red solution was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved in water, made alkaline by addition of 2*N* sodium hydroxide and then acidified to pH 2 with conc. HCl. The precipitate was filtered, washed with water, and dried under vacuum. **6** was isolated as white solid (334 mg, 85%). mp: 270–272°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (m, 2 H) 3.34 (m, 2 H) 8.47 (br. s., 1 H) 13.46 (br. s., 1 H). ^{13}C NMR (125.7 and 75.4 MHz, DMSO-d_6) δ 36.0, 44.3, 99.0, 110.3, 120.5, 130.6, 161.5, 192.6. HRMS calcd for $C_8H_7Br_2N_2O_2$ [M+H$^+$] 320.8869 found 320.8853.

3-Bromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione (8). The general procedure for ACHD was performed on **9** (170 mg, 0.65 mmol). One hundred thirty milligram of crude were purified by prep-HPLC (eluant 0,05% NH_3 in H_2O/Acetonitrile 95:5 as a mobile phase A and Acetonitrile as mobile phase B), affording **8** (102 mg, 64%) as a white solid. The separation was achieved using a rapid gradient increasing 0–25% B in 15 min followed by a hold at 100% B for 2 min at a flow rate of 20 mL/min. mp: 248–250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (m, 2 H, CH_2CO) 3.35 (m, 2 H, C*H*$_2$NH) 7.20 (s, 1 H, C*H*NH) 8.45 (t, J = 5.12 Hz, 1 H, N*H*CH$_2$) 12.52 (br. s., 1 H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 35.6, 44.6, 96.7, 118.9, 124.0, 128.8, 161.5, 193.8, HRMS calcd for $C_8H_8BrN_2O_2$ [M+H$^+$] 242.9764 found 242.9759.

1H-Pyrrole-2-carboxylic acid methyl amide (10). To a solution of 2-trichloroacetylpyrrole (2.12 g, 9.98 mmol) in 40 mL of dry CH_3CN, a 2*M* solution of $MeNH_2$ in THF was added (12.5 mL, 25 mmol). The mixture was stirred under nitrogen, at room temperature for 48 h, until HPLC revealed the disappearance of the starting material. The solvent was removed under reduced pressure to give **10** as white solid. mp: 151–152°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72–2.74 (d, 3 H, J = 5 Hz, CH_3) 6.06 (dt, J = 3.63, 2.40 Hz, 1 H, CHC*H*CH) 6.70 (ddd, J = 3.69, 2.41, 1.46 Hz, 1 H, CHC*H*C) 6.82 (td, J = 2.69, 1.46 Hz, 1 H, CHC*H*N) 7.89 (br. s., 1 H, N*H*CH$_3$) 11.37 (br. s., 1 H, NH).

5-Bromo-1H-pyrrole-2-carboxylic acid methylamide (11). To a stirred solution of **10** (500 mg, 4.03 mmol) in dry MeOH (84 mL) and dry THF (168 mL) at 0°C, *N*-bromosuccinimide (NBS) (323 mg, 1.81 mmol) was added. The cold bath was removed and the reaction mixture was allowed to warm to room temperature under stirring. After 3 h, a HPLC control revealed a 50% conversion of **10–11**. The mixture was recooled to 0°C and more NBS (323 mg, 1.81 mmol) was added. The ice bath was removed and the reactants were stirred for further 2 h at room temperature. The solvent was then removed under vacuum and the residue was purified by flash chromatography (eluant Et_2O/Hexane 2:1) to give **11** in mixture with **14** as side product. **11** was isolated as white solid by reverse-phase chromatography (eluant 0.1% trifluoroacetic

acid in H_2O/acetonitrile 95/5 as mobile phase A and Acetonitrile as mobile phase B) (490 mg, 60%). mp: 173–175°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 (d, J = 4.64 Hz, 3 H, CH_3) 6.11 (dd, J = 3.72, 2.38 Hz, 1 H, CHC*H*CBr) 6.69 (dd, J = 3.78, 2.69 Hz, 1 H, CHC*H*C) 7.93 (q, J = 3.99 Hz, 1 H, N*H*CH_3) 12.15 (br. s., 1 H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 25.0, 102.1, 110.5, 111.2, 128.8, 160.5. HRMS calcd for $C_6H_8BrN_2O$ [M+H$^+$] 202.9815 found 202.9821.

4-Bromo-2-(trichloroacetyl)pyrrole (12). 2-(Trichloroacetyl)pyrrole (10 g, 0.05 mol) in $CHCl_3$ (50 mL) was treated with Br_2 (9.5 g, 0.06 mol) in $CHCl_3$ (3 mL) at 5°C. The ice bath was removed and the reactants were stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with H_2O, $NaHCO_3$, and brine. The organic layer was dried (over Na_2SO_4) and concentrated under vacuum. The crude was then crystallized from hexane-CH_2Cl_2 affording **12** (11.3 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.34 (dd, J = 2.68, 1.46 Hz, 1 H, CC*H*C) 7.56 (dd, J = 3.29, 1.46 Hz, 1 H, C*H*N) 12.85 (br. s., 1 H).

4-Bromo-1H-pyrrole-2-carboxylic acid methylamide (13). Compound **12** (575 mg, 1.98 mmol) was treated with a 2*M* solution of $MeNH_2$ in THF (2.45 mL, 4.95 mmol) delivering **13** (400 mg, quantitative) as white solid after removal of the solvent. mp: 178–180°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.70 (d, J = 4.69 Hz, 3 H, CH_3) 6.75 (dd, J = 2.64, 1.47 Hz, 1 H, CHCBr) 6.92 (dd, J = 2.93, 1.47 Hz, 1 H, CHN) 8.01 (q, 1 H, N*H*CH_3) 11.75 (br. s., 1 H, NH).

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