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Intramolecualr cyclization of a dipyrromethane by an electrophilic aromatic substitution reaction producing a new chiral compound

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Abstract Dipyrromethane **2** functionalized with 3-chloropropyl group on the meso carbon undergoes an unusual intramolecular electrophilic aromatic substitution reaction in the presence of NaN_3 instead of a simple nucleophilic substitution reaction. As a result, a new chiral dipyrromethane **1** was synthesized. In this reaction, the β-carbon of the pyrrole ring functions as a nucleophile while the carbon next to the chlorine atom acts as an electrophile. Interestingly, this reaction progresses even in the absence of an acid catalyst. Compound **1** was fully characterized by ^{1}H-^{1}H and ^{1}H-^{13}C COSY NMR spectroscopic analyses and the high resolution EI mass spectrometry.

Keywords pyrrole, dipyrromethane, electrophilic aromatic substitution, nucleophilic substitution, COSY NMR spectroscopy

Introduction

Pyrrole, a building block for the constructions of poly-pyrrolic macrocycles such as porphyrins and calixpyrrole derivatives, undergoes various reactions to afford numerous kinds of products.[1,2] For example, its condensation reactions with aldehydes in the presence of catalytic amount of acid followed by oxidation lead to the production of porphyrins, fully conjugated tetrapyrrolic aromatic macrocycles.[1] In a similar way, the reactions of pyrrole with ketones, instead of with aldehyde, under otherwise same conditions give calix[4]pyrroles which are non-aromatic macrocycles where the α-carbon atoms of the pyrroles are connected via meso carbons bearing dimethyl groups.[2-4] In contrast, the similar condensation reactions using an excess amount of pyrrole produce dipyrromethanes consisting of a meso carbon covalently linked to two pyrroles and two other functional groups.[5] In addition, pyrrole experiences an electrophilic acyl substitutions reaction in the presence of Lewis acid and an acyl chloride to give a pyrrole ester.[6] In all cases of aforementioned reactions, the α-carbon atom of pyrrole functions as a nucleophile attacking the electrophilic carbonyl carbon atom activated by an acid catalyst. By contrast, we reported that the condensation reaction of pyrrole with hydroxyacetone in the presence of methanesulfonic acid led to the formation of hydrofuran-fused calix[4]pyrrole via an intramolecular cyclization reaction.[7] In this case, the β-pyrrolic carbon atom was presumed to act as an electrophile activated by the acid while the hydroxy group works as a nucleophile. Despite these various reactions of pyrrole, it is relatively hard for the β-pyrrolic carbon atom to undergo an electrophilic aromatic substitution reaction with acyl or alkyl halides because of its

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weak reactivity relative to the α-carbon. Therefore, to the best of our knowledge, no electrophilic aromatic substitution reaction of pyrrole via its β-carbon atom has been reported yet. Here, we report a new intramolecular cyclization reaction of pyrrole with an alkyl halide via an electrophilic aromatic substitution mechanism. This reaction gave rise to a new chiral compound (**1**) having three rings presumably as a racemic mixture.

Experimental Methods

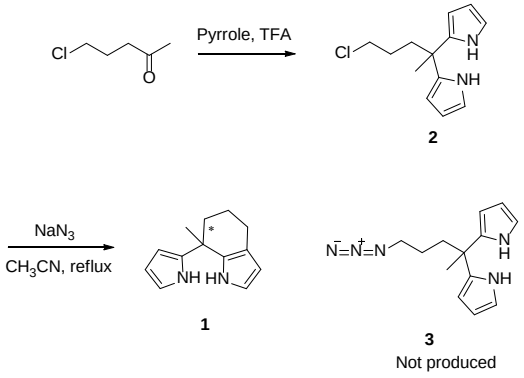
All solvents and chemicals used were purchased from Sigma-Aldrich, TCI, or Acros and used without further purification. TLC analyses were carried out by using Sorbent Technologies silica gel (200 mesh) sheets. Column chromatography was performed on Sorbent silica gel 60 (40-63 μm). NMR spectra were recorded on a Bruker Advance-300 MHz instrument. The NMR spectra were referenced to solvent residue peaks and the spectroscopic solvents were purchased from Cambridge Isotope Laboratories or Sigma-Aldrich. Compound **2** was synthesized by following the literature procedure.[8]

Synthesis of compound 1 - Sodium azide (1.86g, 28.6 mmol) was added to a solution of compound **2** (3.39 g, 14.3 mmol) in acetonitrile (50 mL). After the reaction mixture was refluxed for 24 h under an N_2 atmosphere and allowed to cool to room temperature, the solvent was removed *in vacuo*. To the resulting sticky solid, CH_2Cl_2 (100 mL) and water (100 mL) were added. The organic layer was separated off and washed three times with 100 mL of water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo* to give a yellowish sticky solid. Column chromatography over silica gel using ethyl acetate/hexane (1/9) as the eluent followed by recrystallization from hexane gave 0.35g (12.2%) of compound **1** as a yellowish solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (broad s, 2H), 6.59 (t, *J* = 2.7 Hz, 1H), 6.54 (q, *J* = 2.6, 1.5 Hz, 1H), 6.14 (q, *J* = 3.4, 2.7 Hz, 1H), 6.03-6.00 (m, 1H), 5.99 (t, *J* = 2.7 Hz, 1H), 2.64-2.50 (m, 2H), 1.96-1.80 (m, 3H), 1.80-1.64 (m, 2H), 1.61 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.87, 131.49, 117.66, 116.74, 116.15, 108.17, 108.04, 106.99, 103.67, 40.96, 35.79, 27.24, 23.09, 20.96 ppm. HRMS (EI) *m/z* 200.1314 [M^+] calcd for $C_{13}H_{16}N_2$, found 1003.44003

Results and Discussion

The synthesis of the chiral dipyrromethane (**1**) is depicted in Scheme 1. First, compound **2** was synthesized by following the standardized synthetic method of dipyrromethanes. Specifically, 5-chloro-2-pentanone was condensed with pyrrole in excess in the presence of 1.0 equiv of trifluoroacetic acid (TFA) to give dipyrromethane **2** in 61% yield.[8] The subsequent reaction of compound **2** with sodium azide (NaN_3) was expected to produce the azide-substituted dipyrromethane **3** by a simple nucleophilic substitution reaction. However, the reaction led to the synthesis of the chiral tricyclic dipyromethane (**1**) rather than compound **3**. This reaction is presumed to take place via an unprecedented intramolecular electrophilic aromatic substitution reaction of pyrrole with the 3-chloropropyl group to give an additional six-membered ring. It is interesting that this reaction progresses without any acid catalysts that are usually required for the electrophilic aromatic substitution reaction. Compound **1** was completely characterized by standard spectroscopic techniques.

Scheme 1. Synthesis of compound **1**



Initial evidence for the formation of the chiral dipyrromethane **1** came from high resolution EI (Electron Ionization) mass spectrum. For instance, the peak corresponding to the exact molecular weight of 200.1314 calculated for compound **1**, $C_{13}H_{16}N_2$, appears at 200.1318 m/z.

It was proved by ^{1}H-^{1}H homonuclear and ^{1}H-^{13}C heteronuclear COSY NMR spectroscopic analysis that compound **1** has a chirality. Specifically, the signals of the aliphatic protons (H_a, H_b and H_c) appeared significantly split into multiplets, which is attributable to the protons placed in a chiral environment. In the ^{1}H-^{1}H COSY NMR spectrum shown in Figure 1, the proton signal showing up at δ = 2.57 ppm could be assigned to the proton (H_a) because such protons located closely to the aromatic pyrrole resonate in relatively downfield region as compared with other aliphatic protons (Fig. 1). This peak was found to have two cross peaks resonating at δ = 1.78 ppm and 1.69 ppm, respectively. This finding suggests that the protons corresponding to H_b's are diastereotopic because they are located in magnetically different environment. In addition, the protons (H_c) of the carbon (C3) directly connected to the chiral center (C5) also give rise to two distinguishable peaks having noticeably different chemical shifts (Figs. 1 and 2). This finding was taken as an additional evidence for the formation of the chiral compound (**1**).

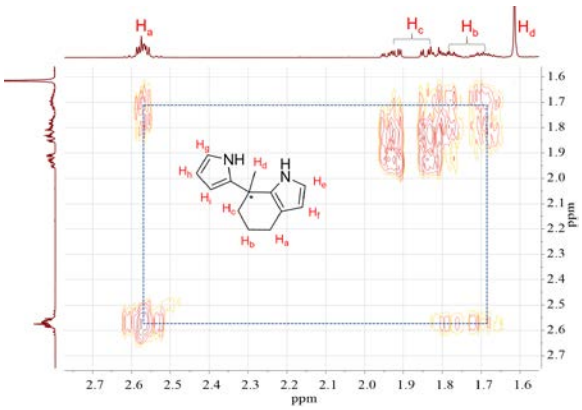


Figure 1. Partial ^{1}H-^{1}H homonuclear COSY NMR spectrum of compound **1** recorded in $CDCl_3$.

Further support for the proposition that compound **1** has two pairs of diasterotopic protons came from ^{1}H-^{13}C COSY NMR spectrum. For instance, the peaks corresponding to the aliphatic carbons (C3 and C2) in close proximity to the chiral center of the quaternary carbon (C5) have two cross peaks, respectively (Fig. 2). In detail, the carbon signal of C2 appearing δ = 21.0 ppm is coupled with two proton signals having chemical shifts of δ = 1.78 ppm and δ = 1.69 ppm, respectively, which are assigned to the protons (H_b's). Similarly, the carbon peak of C3 at δ = 41.0 ppm shows two cross peaks with the proton peaks of H_c's appearing at δ = 1.93 ppm and δ = 1.83 ppm (Fig. 2). These observations are consistent with the conclusion that the hydrogens attached to C2 and C3 are diastereotopic protons and that compound **1** has a chirality.

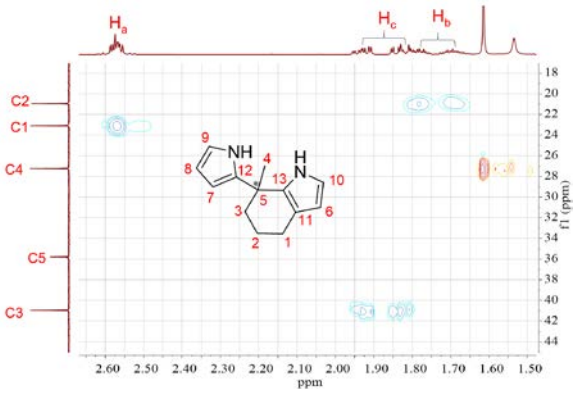


Figure 2. Partial ^{1}H-^{13}C heteronuclear COSY NMR spectrum of compound **1** recorded in $CDCl_3$.

Aromatic protons of the pyrrole rings were also successfully assigned to peaks appearing in lower field region (Fig. 3). For example, the α-pyrrolic protons, in this case, H_e and H_g, generally resonates at downfield relative to the β-pyrrolic proton presumably because the former is more acidic.[9] The proton signal appearing at δ = 6.54 ppm has a cross peak with the one at δ = 6.14 ppm which has two cross peaks. This finding could be interpreted for the latter proton to have two different protons in the neighboring carbon atoms. Therefore, the proton signal showing up δ = 6.14 ppm could be assigned to H_h with the peaks at δ = 6.54 ppm and δ = 6.02 ppm

to H_g and H_i, respectively (Fig. 3). In a similar way, the proton signals of the other pyrrole ring of compound **1** were also assigned to H_e and H_f (Fig. 3). All carbon signals in the ^{13}C NMR spectrum were also assigned to carbon atoms of compound **1** based on ^{1}H-^{13}C COSY NMR spectrum (Figs. 2 and 4). For example, the signals having no cross peak could be assigned to the quaternary carbons C5, C11, C12, and C13, respectively (Figs. 2 and 4). The other signals were assigned to the carbon atoms according to their cross peaks with the proton signal in ^{1}H-^{13}C COSY NMR spectrum.

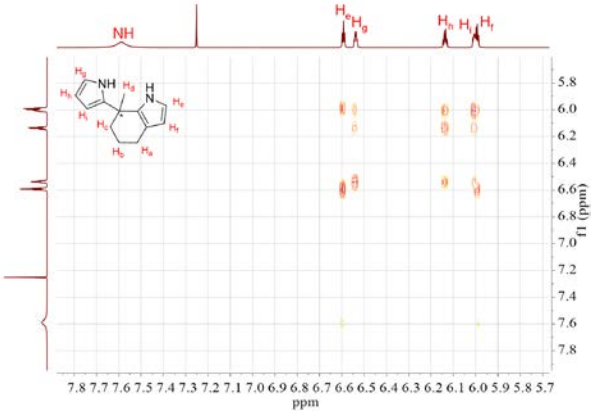


Figure 3. Partial ^{1}H-^{1}H COSY NMR spectrum of compound **1** recorded in $CDCl_3$.

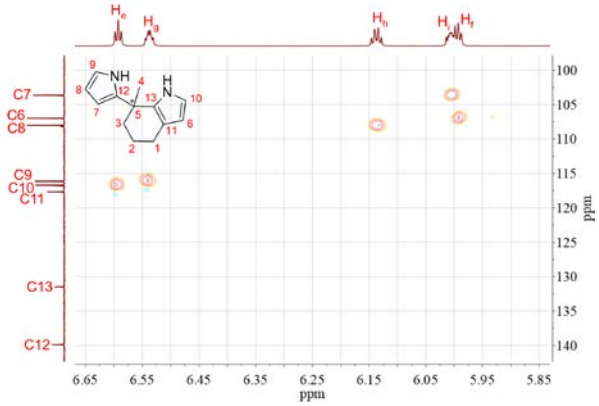


Figure 4. Partial ^{1}H-^{13}C COSY NMR spectrum of compound **1** recorded in $CDCl_3$.

Conclusions

A new chiral tricyclic dipyrromethane **1** was synthesized by an intramolecular electrophilic aromatic substitution reaction of pyrrole with an alkyl chloride via the β-pyrrolic carbon atom. This reaction took place without any acid catalyst which is needed in general electrophilic aromatic substitution reactions. The structure of compound **1** was completely characterized by ^{1}H-^{1}H and ^{1}H-^{13}C COSY NMR spectroscopic analyses as well as the high resolution EI mass spectrometry.

Acknowledgements

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