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Substituted pyrrolizine-bridged bipyrroles synthesis via ring annulation under green conditions

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KEYWORDS
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Ring annulation;
Green condition.

Abstract. Several new substituted 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles were synthesized via ring annulation under green aqueous conditions. In this work, the acid-catalyzed condensation of pyrrole with the different diketones did not produce the expected bisdipyrromethanes. However, new important pyrrolizine-bridged bipyrroles were synthesized in good yields. Ferric hydrogensulfate was used as an environmentally friendly homogeneous acidic catalyst to produce pure products in aqueous conditions. This catalyst has enabled the synthesis of pyrrolizine-bridged bipyrroles with bearing functional groups at designated positions. These synthesized compounds can be used for various unknown and known applications, such as chiral catalysts and essential biological activities.

1. Introduction

Substituted porphyrins, porphyrin analogues such as dipyrrins, calixpyrroles, chlorins, corroles, and polypyrrolic polymers are applicable in science, medicine, and engineering. Dipyrromethanes are important intermediates in the synthesis of these valuable compounds. Besides, dipyrromethanes are commonly used as ligands in organometallic catalysis [1–4]. Therefore, synthetic chemists try to find efficient routes for the synthesis of these molecules under mild reaction conditions. In most of the reported methods, an aldehyde or ketone and pyrrole react in the presence of various combinations of catalysts and solvents [5–12]. Recently, ferric hydrogensulfate prepared from available starting materials was reported to be an environmentally friendly, stable and efficient heterogeneous acidic catalyst [13,14].

While dipyrromethanes are of a convergent type and used as very good building blocks for making strapped calixpyrroles and porphyrinoid macrocycles, the development of bisdipyrromethanes is of growing interest to synthetic chemists [15].

Towards developing the chemistry of bisdipyrromethanes, recently Panda et al. condensed 2,4-pentanedione and pyrrole to obtain the desired bisdipyrromethane under acidic conditions. But, surprisingly, an unexpected ring annulation occurred during the condensation reaction. It was found that 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles were formed through its 1,3-position [16].

Therefore, an effort has been made in this paper to evaluate the reactivity of different diketones with different alkyl and aryl groups with pyrrole using ferric hydrogensulfate as an environmentally friendly acidic catalyst under green conditions. This environmentally

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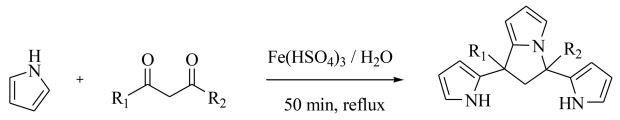
aqueous method was considered to need a stoichiometric amount of pyrrole.

In this study, a catalytic amount of ferric hydrogensulfate was used for the preparation of substituted 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles under aqueous and green conditions without using any organic solvent. It is intended to produce several new compounds with a pyrrolizine nucleus via ring annulation from simple pyrrole. These molecules contain two chiral carbons, which can be used in the designing of chiral sensing. Also, the pyrrolizine derivatives, as bicyclic heterocycles, are present in alkaloid natural products. So, because of their valuable and various biological activities, they have been considered by synthetic chemists [17].

2. Results and discussion

Pyrrolizine derivatives are very good building blocks and show important biological activities. Toward developing the chemistry of these compounds, it is found that in the presence of a catalytic amount of $Fe(HSO_4)_3$ and under an aqueous reflux condition, pyrrole and various diketones react to producea pyrrolizine derivative in 50-70% yields (Scheme 1).

In synthetic endeavors, it is found that different substituted pyrrolizines were prepared via a one-step reaction in 50-70% yields by the drop-wise addition



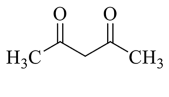
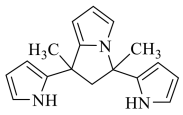
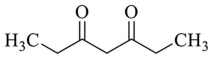
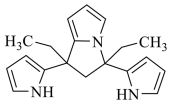
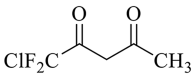
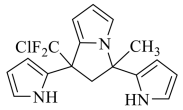
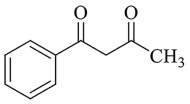
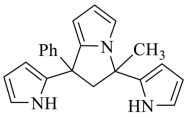
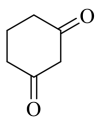
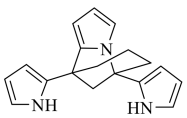
Scheme 1. Preparation of different substituted 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles.

of $Fe(HSO_4)_3$ solution in a water medium containing pyrrole and various diketones under a reflux condition (Table 1).

Therefore, the reaction is an environmentally friendly process without any strong acid and organic solvent. This fact prompted the use of $Fe(HSO_4)_3$ for the electrophilic substitution of pyrrole with various ketones, simply and practically. Also, it is proposed that the procedure occurs at the interface between the aqueous diketone phase and the organic pyrrole phase. This reaction was complete via the release of the product from the aqueous layer [18].

As shown in Figure 1(a), the 1 and 2 carbons of these substituted pyrrolizines bind to four different groups. Also, these two carbons are not identical due to the position of the pyrroles in the molecule leading to a three-dimensional structure in space (Figure 1(b)). So, the chemical position and environment of the CH_3 groups attached to the two carbons 1 and 2 as well the two hydrogens attached to CH_2 are different, which is confirmed by the ^{1}H-NMR spectrum (Figure 2). The structure of the compound was drawn using the

Table 1. Reactions of diketones with pyrrole to give substituted pyrrolizine under green aqueous conditions.[a]

Ketone	Product (number)		Yield (%)[b]
		**(1c)**	68%
		**(2c)**	55%
		**(3c)**	51%
		**(4c)**	57%
		**(5c)**	50%

[a]: The reactions were carried out in 1 mmol of diketone, 4 mmol pyrrole and $Fe(HSO_4)_3$ (20 mol%) in water at reflux conditions;

[b]: Isolated yields.

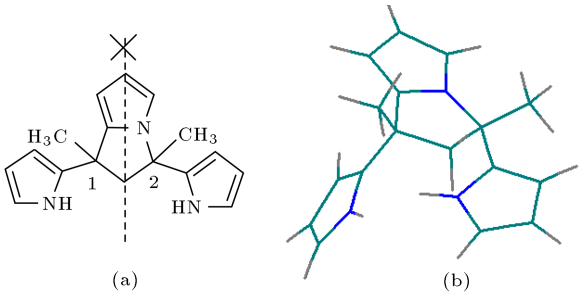


Figure 1. The structure of the compound (**1c**) was drawn using (a) the ChemOffice professional and (b) HyperChem 7.5.

ChemOffice professional (Cambridge software). The output structure files were minimized in HyperChem7.5 under: 1) the molecular mechanic MM+ and: 2) the semi-empirical AM1 method (convergence limit = 1e-5; iteration limit = 100; RMS gradient = 0.05 kcal/mol; in the Fletcher-Reeves optimiser algorithm).

The ^{1}HNMR spectra of the synthetic compounds were quite complicated (Figure 2). Two broad NH peaks appeared at 7.80–7.98 ppm and 5.70–6.80 ppm with eight multiplets. Also, there were two more symmetrical doublets at 2.85 and 3.25 ppm (J = 7.5 Hz) showing geminal coupling, and two peaks at 1.78 and 1.94 ppm for the methyl groups of the compound. The above ^{1}HNMR result confirmed that the desired pyrrolizine has formed and that it is quite unsymmetrical. In the FTIR spectrum of the compound, the band seen at 3334 cm^{-1} was assigned to the stretching vibration of N-H groups. The bands at 3097, 2972, 2929, and 2868 cm^{-1} correspond to the stretch vibration of aromatic and aliphatic C-H groups. The band existing at 1695 cm^{-1} can be assigned to the C=C stretching vibration of the pyrrole rings. Also, the mass spectrum indicated a peak at 265 m/z.

Based on earlier work [16], however, the proposed mechanism for formation of the desired products (Scheme 2) proceeds via acid-catalyzed condensation of one of the carbonyl groups of diketone to form **2**, which condenses with a pyrrole to form the hydroxyl derivative **3**. The protonated hydroxyl derivative **3**, loses a water molecule to form the carbonium ion **5** and/or intermediate **6**, which condenses with another pyrrole to form **7**. The protonated carbonyl group of **8** condenses with another pyrrole via the acid-catalyzed condition to form the hydroxyl derivative **9**. The protonated hydroxyl derivative **10** loses a water molecule to form the carbonium ion **11**. The carbonium ion **11** and/or intermediate **12** undergo intramolecular nucleophilic substitution to form the product **13**, which, upon the subsequent loss of a proton, results in the formation of the pyrrolizine-bridged bipyrroles **1**. Though the yield is moderate, the presence of two 1- and 5- unsubstituted positions of pyrroles in the final product makes this molecule attractive for the desired su bstitution.

3. Conclusions

In this study, an environmentally efficient homogeneous acidic catalyst, ferric hydrogensulfate, was used in a condensation reaction of pyrrole with different diketones in the presence of an aqueous non-toxic medium. This reaction formed 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles through a ring annulation. The ^{1}H-NMR, FT-IR, mass spectroscopy, and elemental analysis confirmed the structure of the compounds. The selective formation of these compounds

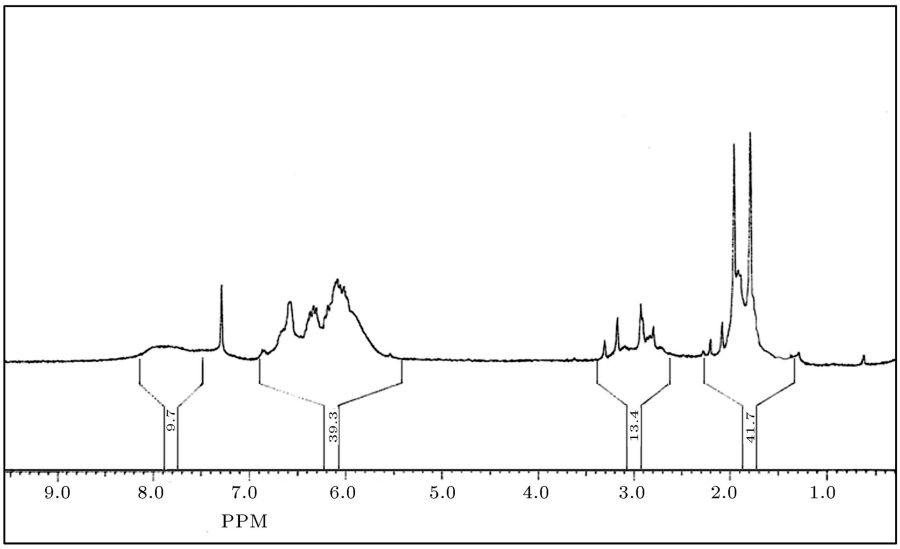
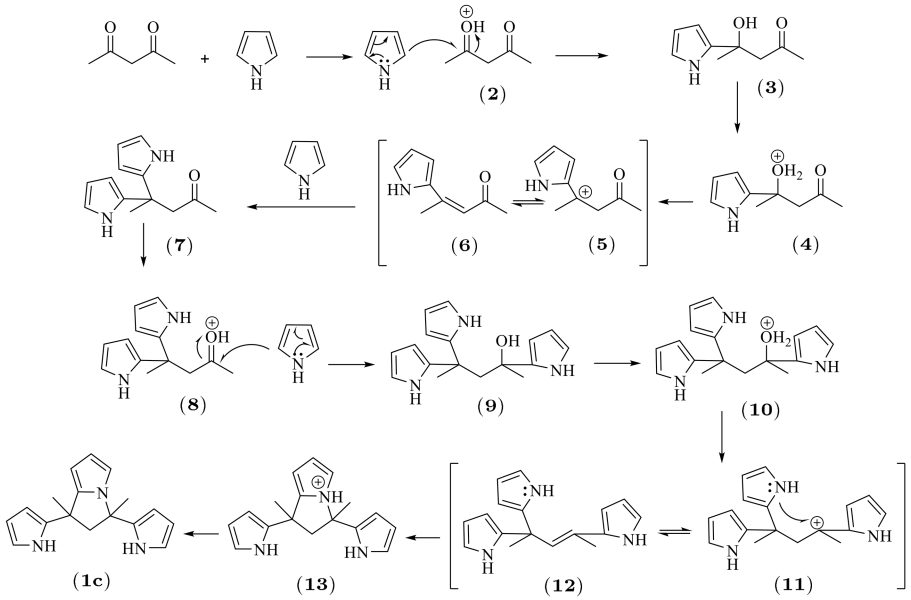


Figure 2. ^{1}H-NMR of this structure claims two types of C**H**$_3$ (1.78 (s, 3H, CH$_3$), 1.94 (s, 3H, C**H**$_3$)) and two types of H in CH$_2$ (2.85 (d, 1H, J = 7.5 Hz, C**H**$_2$), 3.25 (d, 1H, J = 7.5 Hz, C**H**$_2$)).



Scheme 2. The proposed mechanism of the synthesis of substituted 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles.

and the asymmetric three pyrrole units in the molecules make them useful as interesting building blocks in porphyrinoid chemistry. Also, these molecules contain two chiral carbons, which can be used in designing chiral sensing.

4. Experimental

4.1. Materials and physical methods

All compounds were purchased from Merck. Melting points were measured by an electrothermal melting point tool (type 9100). The FT-IR spectra were obtained on an FT-IR Therma Nicolet spectrometer (Avatar 370), and the 1H NMR (100 MHz) spectra were recorded on a Bruker spectrometer (AC100). Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer.

4.2. Synthesis of substituted 2,3-dihydro-1H-pyrrolizine-bridged bipyrroles

In a typical experiment, a suspension of acetylacetone (0.18 ml, 1 mmol) was prepared in 5 ml of water. Pyrrole (0.5 ml, 4 mmol) was added to the fresh prepared suspension upon stirring. Then, $Fe(HSO_4)_3$ (72 mg, 0.2 mmol) was added slowly to the mixture. After refluxing for 50 min, the reaction was completed and the mixture was extracted with chloroform and washed with water. The organic phase containing the desired product was dried over anhydrous Na_2SO_4 and the solvent was evaporated under a high vacuum. The relatively pure residue appeared as brown, which can be further purified by recrystallization with hexane/ethylacetate (9:1).

2,3-dihydro-1,3-dimethyl-1,3-bipyrrole-1H-pyrrolizine (1c)

The free base was obtained at 68% yield as a yellow solid; ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.78 (s, 3 H, C**H**$_3$), 1.94 (s, 3 H, C**H**$_3$), 2.85 (d, 1 H, J = 7.5 Hz, C**H**$_2$), 3.25 (d, 1 H, J = 7.5 Hz, C**H**$_2$), 5.7–6.8 (m, 9 H), 7.80–7.98 (br s, 2 H, N**H**); FT-IR (cm^{-1}; group): (3334, 3097, 2972, 2929, 2868, 1695, 1291, 669); mp: 117-118°C; Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.90; H, 7.22; N, 15.81; M$^+$ for $C_{17}H_{19}N_3$: 265.

2,3-dihydro-1,3-diethyl-1,3-bipyrrole-1H-pyrrolizine (2c)

The free base was obtained at 55% yield as a yellow solid; ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.95 (m, 6 H, C**H**$_3$), 1.55–2.55 (m, 4 H, C**H**$_2$CH$_3$ and 1 H, C**H**$_2$), 2.70–3.05 (m, 1 H, C**H**$_2$), 5.55–6.82 (m, 9 H), 7.45–8.28 (br s, 2 H, N**H**); FT-IR (cm^{-1}; group): (3381, 2967, 2934, 2880, 1691, 1459, 1040, 718); mp: 105-108°C; Anal. Calcd for $C_{19}H_{23}N_3$: C, 77.78; H, 7.90; N, 14.32. Found: C, 77.79; H, 7.88; N, 14.32; M$^+$ for $C_{19}H_{23}N_3$: 292.

2,3-dihydro-1-(chlorodifluoromethyl)-3-methyl-1,3-bipyrrole-1H-pyrrolizine (3c)

The free base was obtained at 51% yield as a yellow solid; ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.65 (s, 3 H, C**H**$_3$), 2.50-2.65 (m, 1 H, C**H**$_2$), 2.80-3.10 (m, 1 H, C**H**$_2$), 5.65–6.90 (m, 9 H), 7.65–8.20 (br s, 2H, N**H**); FT-IR (cm^{-1}; group): (3392, 2966, 2933, 2872, 1695, 1124, 722); mp: 121–123°C; Anal. Calcd for $C_{17}H_{16}ClF_2N_3$: C, 60.81; H, 4.80; N, 12.51. Found: C, 60.78; H, 4.83; N, 12.54; M$^+$ for $C_{17}H_{16}ClF_2N_3$: 334.

2,3-dihydro-3-methyl-1-phenyl-1,3-bipyrrole -1H-pyrrolizine (4c)

The free base was obtained at 57% yield as a yellow solid; ^{1}H-NMR (100 MHz, $CDCl_3$): δ 2.25 (s, 3 H, C**H**$_3$), 2.30-3.95 (m, 2 H, C**H**$_2$), 5.45–6.90 (m, 9 H), 6.95–7.70 (m, 5 H-arom.), 7.72–8.15 (br s, 2 H, N-H); FT-IR (cm^{-1}; group): (3305, 2987, 2955, 2921, 2868, 1695, 1583, 1292, 668); mp: 111–112°C; Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.46; N, 12.83. Found: C, 80.72; H, 6.40; N, 12.83; M^+ for $C_{22}H_{21}N_3$: 326.

Bicyclo[0,1,4]heptanyl-1,3-bipyrrole-1H-pyrrolizine (5c)

The free base was obtained at 50% yield as a yellow solid; ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.50–2.90 (m, 8 H, C**H**$_2$), 6.34 (m, 2 H, pyrrole-H), 5.75–7.1 (m, 7 H), 7.85 (br s, 1 H, N**H**), 9.50 (br s, 1 H, N**H**); FT-IR (cm^{-1}; group): (3351, 3109, 2933, 2860, 1691, 1584, 1043, 723); mp: 109–110°C; Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 77.93; H, 6.90; N, 15.18; M^+ for $C_{18}H_{19}N_3$: 277.

Acknowledgements

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Biographies

Neda Attaran obtained her BS degree in Chemistry from Ferdowsi University of Mashhad (FUM), Iran, in 2006, where she also received her MSc and PhD Degree, in 2008 and 2013, respectively. Her research activities lie in the area of developing Nanotechnology in cancer therapy through new synthetic organo-metallic compounds. She is currently Assistant Professor at the

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Mohammad Rahimizadeh received his BS degree in Chemistry from Ferdowsi University of Mashhad (FUM), Iran, in 1972, and MS and PhD degrees in Organic Chemistry from Imperial College London, England, in 1979. He also obtained a Postdoctoral fellowship from Pennsylvania State University, USA, in 1985 and the University of Delaware, USA, in 1991. He was Professor of Chemistry at Ferdowsi University of Mashhad (FUM), Iran. His research interests include drug composition, preparation of heterocyclic compounds, production of benzoic acid, natural composition.

Mehdi Bakavoli obtained his BS degree in Physics from Ferdowsi University of Mashhad (FUM), Iran, in 1971, and MS and PhD degrees in Organic Chemistry from the University of Salford, Manchester, England, in 1979. His research interests include the area of preparation of heterocyclic compounds with biological activities. He was Professor of Chemistry at Ferdowsi University of Mashhad (FUM), Iran.