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SHORT COMMUNICATION

REACTION OF NITRILIMINES WITH 1,4-BISMALEIMIDOBENZENE

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ABSTRACT. A series of 1,4-bis(3-aroyl-1-aryl-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazol-4,6-dion-5-yl)benzene was synthesized by the reaction of 1,4-bis-maleimidobenzene with appropriate nitrilimines. The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structures.

KEY WORDS: Fusedpyrazoles, 1,4-Bismaleimidobenzene, Nitrilimines, Cycloaddition

INTRODUCTION

Maleimides are useful reactive moieties in bioorganic chemistry and find significant applications in synthetic chemistry [1] particularly as a source of functional β-lactams [2], as Diels-Alder dienophiles [3], and as Michael acceptors [2, 3]. In addition, they enable highly site-selective conjugation of flurophores and other species to proteins by reaction with cysteine side chains [4, 5]. Several fused pyrazole derivatives have received great attention due to their biological activities as anti-HSV-1 [6], herbicidal [7], antimicrobial [8], anti-inflammatory [9, 10], anti-allergic [9, 10], antiviral [11], and anticancer agents [12]. Numerous synthetic methods for the preparation of pyrazole derivatives have been developed. Among them 1,3-dipolar cycloaddition of nitrilimines with dipolarophiles [13, 14]. Nitrilimines are well-known intermediates generated in *situ* by base-promoted dehydrohalogenation of the corresponding hydrazonoyl halides [15, 16]. In continuation of our studies on the 1,3-dipolar cycloaddition reactions, we describe the synthesis of 1,3-disubstituted 1,4-bis(3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]-pyrazol-4,6-dion-5-yl)benzene through nitrilimines cycloaddition methodology [15, 16].

EXPERIMENTAL

Melting points were determined on an A. Krüss melting point meter and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 mid infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center of Cairo University, Egypt. The hydrazonoyl halides **1** [14-16], 1,4-bismaleimidobenzene **3** [17] were prepared according to literature procedures.

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*Synthesis of title compounds **4a-f***

General procedure. To a mixture of the appropriate hydrazonoyl halide **1** (10 mmol) and 1,4-bismaleimidobenzene **3** (1.34 g, 5 mmol) in dry benzene (100 ml), triethylamine (1.5 mL, 10 mmol) was added and the reaction mixture was heated under refluxing condition. The reaction was followed by TLC ($CHCl_3$) and continued until the starting substrates were completely consumed (6-10 h), then left to cool to room temperature. The triethylammonium chloride salt was filtered off, the solvent was removed under reduced pressure and the residue was triturated with methanol. The solid product formed was collected and crystallized from dimethylformamide.

*Characterization data for title compounds **4a-f***

*Compound **4a***. White solid, yield 51%, m.p. 230-232 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 2.54 (s, 3H), 5.22 (d, 1H, *J* = 10.2), 5.65 (d, 1H, *J* = 10.2), 7.10-7.68 (m, 12H). ^{13}C NMR (300 MHz, DMSO-d_6) = 192.6 (RC=O), 171.5, 170.8 (amide C=O), 147.3 (C=N), 139.6-126.1 (ArC's), 67.2, 54.3 (C-6a and C-3a). IR (KBr disk): 1721 (amide C=O), 1692 (RC=O), 1598 (C=N). MS, (*m/z*): 656/658 $[M]^+$. Analysis (% calculated/found) for $C_{32}H_{22}Cl_2N_6O_6$ (Mw 657.47) C: 58.46/58.55, H: 3.37/3.50, N: 12.78/12.70.

*Compound **4b***. White solid, yield 48%, m.p. 281-283 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 5.40 (d, 1H, *J* = 10.5), 5.81 (d, 1H, *J* = 10.5), 7.12-7.81 (m, 22H). ^{13}C NMR (300 MHz, DMSO-d_6) = 184.6 (RC=O), 171.3, 170.6 (amide C=O), 147.1 (C=N), 139.8-118.8 (ArC's), 66.7, 53.8 (C-6a and C-3a). IR (KBr disk): 1718 (amide C=O), 1665 (RC=O), 1596 (C=N). MS, (*m/z*): 780/782 $[M]^+$. Analysis (% calculated/found) for $C_{42}H_{26}Cl_2N_6O_6$ (Mw 781.62) C: 64.54/64.65, H: 3.35/3.25, N: 10.75/10.67.

*Compound **4c***. White off solid, yield 50%, m.p. 266-268 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 5.15 (d, 1H, *J* = 9.3), 5.55 (d, 1H, *J* = 9.3), 7.10-7.77 (m, 22H), 10.18 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6) = 171.5, 170.8 (amide C=O), 159.3 (RC=O), 147.8 (C=N), 139.8-116.7 (ArC's), 66.2, 53.4 (C-6a and C-3a). IR (KBr disk): 1715 (amide C=O), 1656 (RC=O), 1594 (C=N). MS, (*m/z*): 810/812 $[M]^+$. Analysis (% calculated/found) for $C_{42}H_{28}Cl_2N_8O_6$ (Mw 811.65) C: 62.15/61.95, H: 3.48/3.40, N: 13.81/13.73.

*Compound **4d***. White solid, yield 51%, m.p. 257-259 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 2.65 (s, 3H), 4.78 (d, 1H, *J* = 10.2), 5.35 (d, 1H, *J* = 10.2), 7.04-8.20 (m, 18H). ^{13}C NMR (300 MHz, DMSO-d_6) = 174.6 (RC=O), 171.5, 170.8 (amide C=O), 146.8 (C=N), 139.8-115.6 (ArC's), 66.8, 53.5 (C-6a and C-3a). IR (KBr disk): 1713 (amide C=O), 1660 (RC=O), 1599 (C=N). MS, (*m/z*): 760/762 $[M]^+$. Analysis (% calculated/found) for $C_{38}H_{22}Cl_2N_6O_8$ (Mw 761.54) C: 59.93/60.15, H: 2.91/3.02, N: 11.04/10.97.

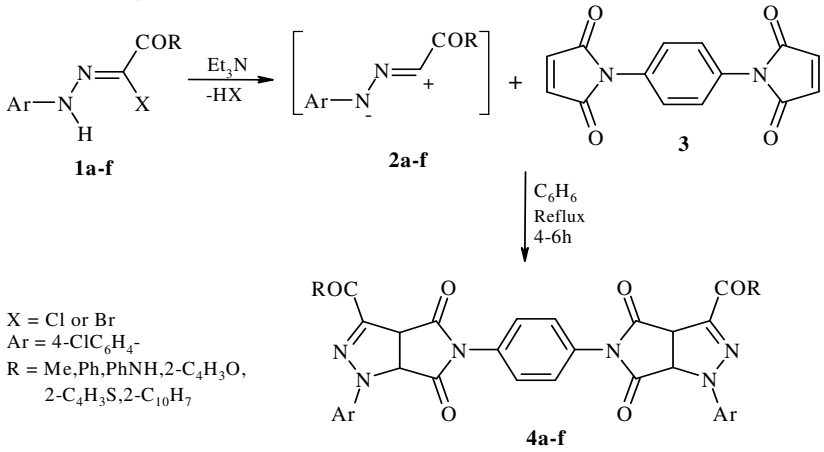
*Compound **4e***. Yellow solid, yield 50%, m.p. 241-243 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 2.65 (s, 3H), 4.81 (d, 1H, *J* = 10.3), 5.44 (d, 1H, *J* = 10.3), 7.06-8.30 (m, 18H). ^{13}C NMR (300 MHz, DMSO-d_6) = 176.7 (RC=O), 171.3, 170.6 (amide C=O), 147.8 (C=N), 139.7-114.9 (ArC's), 66.7, 53.3 (C-6a and C-3a). IR (KBr disk): 1710 (amide C=O), 1665 (RC=O), 1597 (C=N). MS, (*m/z*): 792/794 $[M]^+$. Analysis (% calculated/found) for $C_{38}H_{22}Cl_2N_6O_6S_2$ (Mw 793.67) C: 57.51/57.65, H: 2.79/2.67, N: 10.59/10.67.

*Compound **4f***. Pale yellow solid, yield 47%, m.p. 248-250 ^oC, ^1H NMR (300 MHz, DMSO-d_6, *J*/Hz) = 2.65 (s, 3H), 5.25 (d, 1H, *J* = 10.0), 5.50 (d, 1H, *J* = 10.0), 7.10-8.45 (m, 26H). ^{13}C NMR (300 MHz, DMSO-d_6) = 184.5 (RC=O), 171.1, 170.5 (amide C=O), 147.1 (C=N), 139.1-123.3 (ArC's), 67.4, 54.7 (C-6a and C-3a). IR (KBr disk): 1720 (amide C=O), 1650 (RC=O), 1595

(C=N). MS, (*m/z*): 880/882 $[M]^+$. Analysis (% calculated/found) for $C_{50}H_{30}Cl_2N_6O_6$ (Mw 881.74) C: 68.11/67.95, H: 3.43/3.35, N: 9.53/9.62.

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction of nitrilimines **2a-f**, obtained in *situ* from the corresponding hydrazonoyl halides **1** in presence of triethylamine, with 1,4-bismaleimido-benzene **3** was carried out in refluxing benzene for 4-6h, gave in each case a single product that proved to be 1,4-bis(3-aroyl-1-aryl-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dion-5-yl)benzene **4a-f** (Scheme 1). The purity of obtained compounds was confirmed by TLC and elemental analysis.



Scheme 1. Synthetic pathway for the preparation of compounds **4a-f**.

Spectroscopical data. The structures of the title compounds **4a-f** were deduced from IR, ^1H, ^{13}C NMR and MS spectral data and were further supported by elemental microanalysis. Their IR spectra exhibited characteristic absorption bands at 1780-1640 cm^{-1} region, assignable to a carbonyl groups. All these products **4a-f** gave two doublets signal at 4.8 and 5.8 ppm in their ^1H NMR spectra, assignable to the protons at C-3a and C-6a, respectively. The cycloaddition products **4a-f** were assigned the *cis*-configuration on the basis of the vicinal coupling constant values. It is worth mentioning that the vicinal coupling constants have been shown to be diagnostic, J_{trans} were lower than 6Hz and J_{cis} were in the range 9-12 Hz [17]. The observed values of coupling constants in the title compounds **4a-f** were in the range J = 9.3-10.5 Hz, and they are compatible with the expected *cis*-configuration. Their ^{13}C NMR spectra showed all the signals of the proposed structures, specially the amide carbonyl carbons were found to resonate at about 172 and 171 ppm and the signals at 67 and 53 ppm are assignable to fused carbons C-6a and C-3a, respectively. The signal at about 147-145 ppm was attributed to C=N of the pyrazoline ring. The complete ^1H and ^{13}C NMR data are presented in the experimental section.

CONCLUSIONS

In summary, the 1,3-dipole cycloaddition of several nitrilimines with 1,4-bismaleimido-benzene leads to formation of 1,4-bis(3a,4,6,6a-tetrahydro-1H,5H-pyrrolo-[3,4-c]pyrazol-4,6-dion-5-yl)benzene derivatives.

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