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NOVEL SYNTHESIS OF 1,4-PHENYLENE BRIDGED BIS-HETEROCYCLIC TROPONE COMPOUNDS

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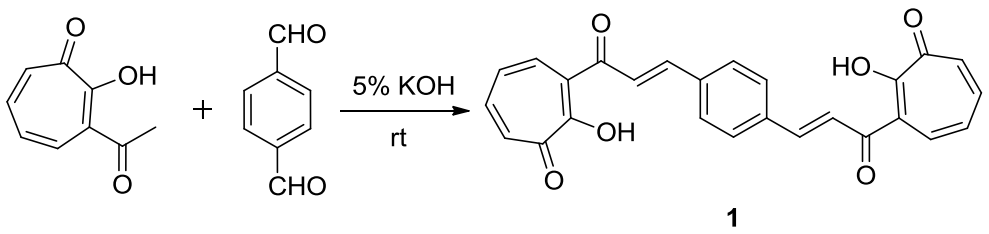
Abstract – A facile synthesis of novel 1,4-phenylene bridged bis-isoxazolo-, pyrazolo-, and pyrano-fused tropone compounds (**2-6**) is described, involving the cyclization reaction of 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}-bis(tropolone) (**1**) with hydroxylamine hydrochloride, aromatic hydrazine hydrochlorides, and I_2/DMSO/H_2SO_4 system, respectively. The substrate **1** was obtained *via* the Claisen-Schmidt condensation reaction between 3-acetyl-tropolone and terephthalaldehyde.

Troponoids with heterocyclic substructures are present in a variety of pharmacologically relevant natural products[1-3] and are attractive targets for synthesis since they often exhibit diverse and important biological activities such as anti-HCV,[4] antifungal,[5] and antimalarial activities.[6] Accordingly, the synthesis of structurally novel heterocycle-containing troponoids continue to receive considerable attention in the field of synthetic organic chemistry.[7-10]

On the other hand, 1,4-phenylene bridged bis-heterocyclic compounds had been widely investigated and reported to display important biological properties such as antiamoebic[11] and antibacterial activities.[12] Therefore, extensive synthetic efforts have been devoted to the development of more novel and interesting 1,4-phenylene-bis-heterocyclic compounds.[13-15] The recent progress in the synthesis of such compounds has been reviewed by Shaker.[16] However, to the best of our knowledge, there has no report of the synthesis of 1,4-phenylene bridged bis-heterocyclic-condensed tropone compounds.

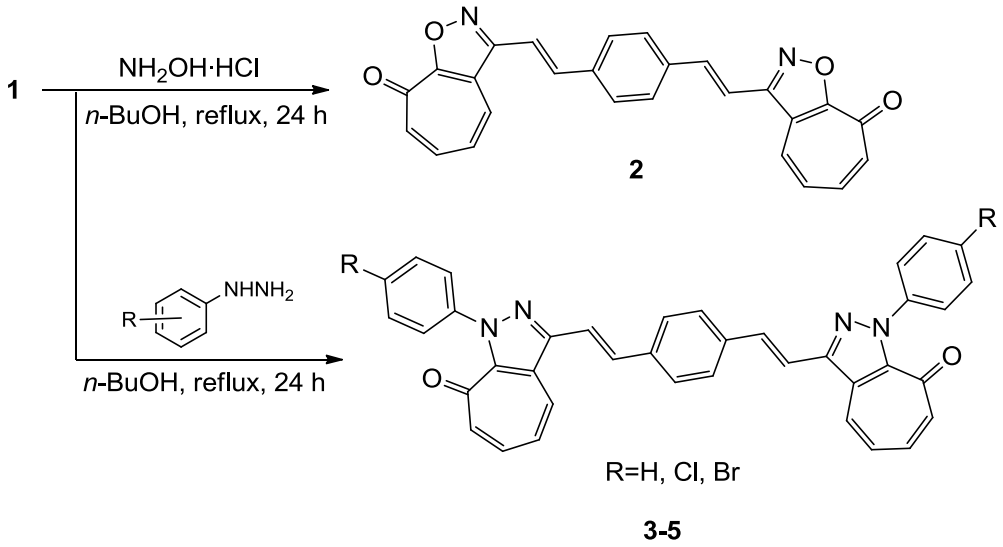
Our research group derives substantial capability in the synthesis of troponoid-based heterocyclic compounds through previous experiences.[17-22] Building on this evolving expertise and in light of the above findings, we wish to report herein the synthesis of novel 1,4-phenylene bridged bis-heterocycle-fused tropone compounds, which could be expected to be vitally important for

pharmacological studies or in the realization of new medicinal properties. Recently, we have reported on the Claisen-Schmidt condensation reaction of 3-acetyltropolones with aromatic and heteroaromatic aldehydes to synthesize tropolonyl-substituted chalcone derivatives.[17,21,22] According to the reports, we again used the reliable approach in order to achieve the synthesis of the required starting compound 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}bis(tropolone) (**1**) as shown in Scheme 1. Thus, under the same experimental conditions, 3-acetyltropolone (2 equiv.) was reacted readily with terephthalaldehyde (1.5 equv.) in the presence of 5% aqueous KOH as catalyst in 50% aqueous methanol as solvent at room temperature to afford a single product according to TLC analysis (Scheme 1). After workup and recrystallization from methanol, the product was obtained in 63% yield. Based on the spectral data, the structure of the isolated product was identified as the desired substrate (**1**).



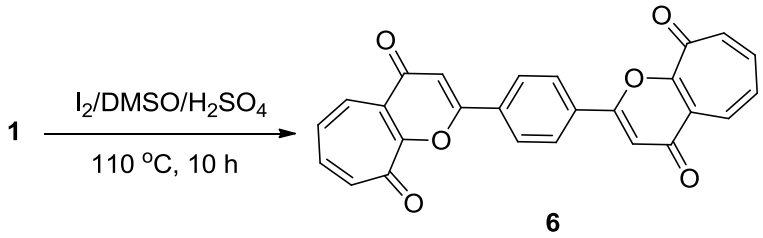
Scheme 1. Synthesis of the substrate **1**

Subsequently, we attempted to conduct the nucleophilic cyclization reaction of substrate **1** with bifunctional agents such as hydroxylamine hydrochloride and substituted phenylhydrazine hydrochloride for the synthesis of the desired 1,4-phenylene bridged bis-heterocyclic-condensed troponoids. Our recent work has demonstrated the reaction of 3-cinnamoyltropolone derivatives with hydroxylamine and aromatic hydrazines in refluxing EtOH to afford the corresponding isoxazolo- and pyrazolo-fused tropones in good yields.[20] Unfortunately, following the reaction conditions, the nucleophilic cyclization reaction in this case did not proceed smoothly, and the products were isolated only in very low yields of 11-20% yields. We deduced that the low reaction temperature might impede the condensation reaction. At this point, we decided to switch the solvent to a high-boiling solvent, such as butanol. When the reaction with hydroxylamine hydrochloride was run in refluxing butanol for 24 hours, the desired 1,4-phenylene bis-isoxazolo-fused tropone (**2**) was obtained in 58% yield. Similarly, the treatment of substrate **1** with aromatic hydrazine hydrochlorides gave the corresponding 3,3'-{1,4-phenylenebis[(*E*)ethene-2,1-diyl]}bis[1-(aryl)cyclohepta[*c*]pyrazol-8(1*H*)-one]s (**3-5**) in 50-53% yields (Scheme 2).



Scheme 2. Synthesis of 1,4-phenylene bridged bis-isoxazolo- and pyrazolo-fused tropones (**2-5**)

Our recent work has proved that the use of I_2/DMSO/H_2SO_4 system for the intramolecular oxidation cyclization reaction of 3-cinnamoyltropolone derivatives is very efficient for the construction of pyranotropone compounds.[17,22] We felt that this approach can be judiciously extended for the synthesis of 1,4-phenylene bridged bis-pyrano-fused tropone. Thus, upon the subjection to the reaction conditions, the oxidation cyclization reaction of **1** proceeded smoothly and became complete in 12 hours. After usual workup followed by purification of the crude products by recrystallization from trifluoroacetic acid, the product 2,2'-(1,4-phenylene)bis(cyclohepta[b]pyran-4,9-dione (**6**) was obtained in 65% yield.



Scheme 3. Synthesis of 2,2'-(1,4-phenylene)biscyclohepta[*b*]pyran-4,9-dione (**6**)

The structures of all the newly synthesized 1,4-phenylene bridged bis-heterocycle-fused tropone compounds **2-6** were established based on the spectral data and elemental analysis as described for **2**. Its ^{1}H NMR spectrum exhibited the absence of the signal at about 9.50 ppm belonging to OH moiety of the precursor **1**, along with the signals for aromatic protons and vinylic protons exactly matching its structure in the range of aromatic region between 7.26-8.39 ppm. The IR spectrum was also devoid of the stretching vibration band resembling the OH moiety of **1**, and exhibited only the typical carbonyl absorption for the tropone ring at 1629 cm^{-1}, supporting the signal of its ^{13}C NMR spectrum at 178.42

ppm. Further, the ESI-MS (positive-ion mode) spectrum showed a characteristic quasi-molecular ion peak $(M+H)^+$ at *m/z* 421.0 suggesting, along with the elemental analysis, a molecular formula $C_{26}H_{16}N_2O_4$.

In summary, the present investigation has demonstrated a facile synthesis of a series of new 1,4-phenylene bridged bis-heterocycle-fused tropone compounds. The structures of all the newly synthesized compounds were confirmed by spectral analysis. All data were fully consistent with the assigned molecular structure (see Experimental Section). We anticipate that this work would arouse more interest in the chemistry of troponoid.

EXPERIMENTAL

The melting points were measured on WRS-1B digital melting points apparatus and are uncorrected. The progress of the reaction was monitored by TLC. Infrared spectra were recorded on KBr pellets on an FT/IR-430 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE NMR spectrometer using DMSO-d_6 as the solvent. The reported chemical shifts (δ values) are given in parts per million downfield from tetrammethylsilane (TMS) as the internal standard. Elemental analyses were estimated on an Elementar Vario EL-III element analyzer. The mass spectra were determined using a MSD VL ESI1 spectrometer. The reaction process was monitored by thin-layer chromatography (TLC) on silica gel GF254 using EtOAc/petroleum ether (1/4).

Procedure for the synthesis of 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}bistropolone (1). To a stirred solution of 3-acetyltropolone (0.33 g, 2.0 mmol) and terephthalaldehyde (0.27 g, 1.5 mmol) in 50% MeOH (8 mL) was added dropwise a solution of 5% aqueous KOH (8 mL) at room temperature. The resulting solution was stirred at room temperature for 24 h. After the reaction was completed, the mixture was acidified with 3 N hydrochloric acid to precipitate yellow solids. The solids were collected and recrystallized from trifluoroacetic acid (TFA) to give **1** as yellow crystals in 72% yield, mp 268-269 °C. IR (KBr) ν/cm^{-1}: 3192 (OH), 1670 (C=O), 1605 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.16-7.21 (m, 2H, ben-H), 7.32 (d, *J*=15.6 Hz, 2H, =CH), 7.46-7.54 (m, 4H, ben-H and =CH), 7.84 (d, 2H, *J*=10.8 Hz, tropolone-H), 8.29-8.36 (m, 4H, tropolone-H), 8.42 (d, *J*=10.8 Hz, 2H, tropolone-H), 9.50 (br s, 2H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 119.57, 124.43, 126.31, 128.82, 131.13, 135.25, 143.72, 144.08, 144.34, 158.19, 177.46, 182.77; ESI-MS *m/z*: 427.1 $(M+1)^+$. Anal. Calcd for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25. Found: C, 73.03; H, 4.42.

Procedure for the synthesis of 3,3'-((1*E*,1'*E*)-1,4-phenylenebis(ethene-2,1-diyl))bis(8*H*-cyclohepta-[*d*]isoxazol-8-one) (2). To a solution of 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}bistropolone **(1)** (0.43 g, 1 mmol) in 10 mL of *n*-BuOH was added hydroxylamine hydrochloride (0.14 g, 2 mmol). The resulting mixture was heated at reflux for 24 h. After the reaction was completed (TLC), the mixture was cooled to room temperature, and then poured into some water, filtered to give the

crude products, which were further purified by recrystallization from TFA. This compound was obtained as pale yellow powder in 58% yield, mp >300 °C. IR (KBr) ν/cm^{-1}: 1629 (C=O), 1433 (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.26 (d, J=15.6 Hz, 2H, =CH), 7.33-7.46 (m, 6H, ben-H and =CH), 7.52 (dd, J=10.8, 10.8 Hz, 2H, tropolone-H), 7.79-7.87 (m, 2H, tropone-H), 8.13 (d, J=10.8 Hz, 2H, tropone-H), 8.39 (d, J=10.8 Hz, 2H, tropone-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 116.74, 122.30, 122.94, 126.17, 126.84, 131.98, 140.32, 141.27, 143.79, 152.27, 158.69, 178.42; ESI-MS *m/z*: 421.0 $(M+1)^+$. Anal. Calcd for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.44; H, 3.64; N, 6.49.

General procedure for the synthesis of 3,3'-{1,4-phenylenebis[(*E*)ethene-2,1-diyl]}bis[1-(aryl)-cyclohepta[*c*]pyrazol-8(1*H*)-one]s (3-5). To a solution of 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}bistropolone **(1)** (0.43 g, 1 mmol) in 10 mL of *n*-BuOH was added the corresponding phenylhydrazine hydrochloride (2 mmol). The resulting mixture was heated at reflux for 24 hours. After the reaction was complete (TLC), the mixture was cooled to room temperature, and then poured into some water, filtered to give the crude products, which were further purified by recrystallization from TFA.

3,3'-{1,4-Phenylenebis[(*E*)ethene-2,1-diyl]}bis[1-(phenyl)cyclohepta[*c*]pyrazol-8(1*H*)-one] (3). This compound was obtained as yellow crystals in 53% yield, mp >300 °C. IR (KBr) ν/cm^{-1}: 1644 (C=O), 1485 (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.39 (d, J=15.6, 2H, =CH), 7.47-7.51 (m, 6H, ben-H), 7.58-7.69 (m, 4H, ben-H and =CH), 7.83-7.87 (m, 6H, ben-H and tropone-H), 8.07-8.12 (m, 4H, ben-H and tropone-H), 8.38 (d, J=10.8 Hz, 2H, tropone-H), 8.54 (d, J=10.8 Hz, 2H, tropone-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 113.96, 115.37, 123.53, 123.89, 124.15, 127.57, 129.88, 132.09, 133.40, 135.68, 136.10, 136.56, 149.07, 151.17, 153.21, 178.82; ESI-MS *m/z*: 571.1 $(M+1)^+$. Anal. Calcd for $C_{38}H_{26}N_4O_2$: C, 79.98; H, 4.59; N, 9.82. Found: C, 80.20; H, 4.40; N, 9.83.

3,3'-{1,4-Phenylenebis[(*E*)ethene-2,1-diyl]}bis[1-(4-chlorophenyl)cyclohepta[*c*]pyrazol-8(1*H*)-one] (4). This compound was obtained as yellow crystals in 51% yield, mp >300 °C. IR (KBr) ν/cm^{-1}: 1644 (C=O), 1485 (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.36 (d, J=15.6, 2H, =CH), 7.43 (d, J=7.2 Hz, 4H, ben-H), 7.61-7.70 (m, 6H, ben-H and =CH), 7.81-7.92 (m, 6H, ben-H and tropone-H), 8.11-8.15 (m, 2H, tropone-H), 8.40 (d, J=10.8 Hz, 2H, tropone-H), 8.55 (d, J=10.8 Hz, 2H, tropone-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 115.55, 116.18, 122.43, 123.48, 124.61, 126.57, 131.68, 132.26, 134.30, 135.85, 136.81, 142.56, 148.92, 150.34, 152.94, 179.36; ESI-MS *m/z*: 639.3 $(M+1)^+$. Anal. Calcd for $C_{38}H_{24}Cl_2N_4O_2$: C, 71.37; H, 3.78; N, 8.76. Found: C, 71.53; H, 3.76; N, 8.81.

3,3'-{1,4-Phenylenebis[(*E*)ethene-2,1-diyl]}bis[1-(4-bromophenyl)cyclohepta[*c*]pyrazol-8(1*H*)-one] (5). This compound was obtained as yellow crystals in 50%, mp >300 °C. IR (KBr) ν/cm^{-1}: 1642 (C=O), 1484 (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): δ 7.41 (d, J=15.6 Hz, 2H, =CH), 7.45 (d, J=7.2 Hz, 4H, ben-H), 7.49-7.55 (m, 4H, ben-H), 7.63-7.71 (m, 4H, =CH and tropone-H), 7.81 (d, J=7.2 Hz, 4H,

ben-H), 7.89 (dd, *J*=10.8, 10.8 Hz, 2H, tropone-H), 8.28 (d, *J*=10.8 Hz, 2H, tropone-H), 8.45 (d, *J*=10.8 Hz, 2H, tropone-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 115.39, 116.63, 123.01, 123.74, 130.35, 131.60, 133.72, 135.38, 135.95, 137.39, 140.86, 141.97, 148.28, 150.16, 153.23, 178.81; ESI-MS *m/z*: 727.1, 728.9, 731.0 $(M+1)^+$. Anal. Calcd for $C_{38}H_{24}Br_2N_4O_2$: C, 62.66; H, 3.32; N, 7.69. Found: C, 62.49; H, 3.41; N, 7.80.

Procedure for the synthesis of 2,2'-(1,4-phenylene)bis(cyclohepta[*b*]pyran-4,9-dione) (6). To a stirred solution of 3,3'-{1,4-phenylenebis[(1*E*)-3-oxoprop-1-ene-1,3-diyl]}bistropolone (**1**) (0.43 g, 1 mmol) in 8 mL of DMSO was added 3-4 drops of concd. H_2SO_4. After 15 min of magnetic stirring at 110 °C, I_2 was added carefully and the resulting reaction mixture was reacted under the temperature for 12 h. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and added with 5 mL of H_2O slowly. And then the resulting precipitate was collected by filtration and recrystallized from TFA. This compound was obtained as yellow crystals in 65% yield, mp >300 °C. IR (KBr) ν/cm^{-1}: 1649 (C=O), 1586 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.43 (d, *J*=8.4 Hz, 2H, ben-H), 7.75 (d, *J*=8.4 Hz, 2H, ben-H), 7.90 (d, *J*=10.8 Hz, 2H, tropone-H), 8.03 (dd, *J*=10.8, 10.8 Hz, 2H, tropone-H), 8.28-8.32 (m, 2H, tropone-H), 8.39 (s, 2H, pyran-H), 8.49 (d, *J*=10.8 Hz, 2H, tropone-H); ^{13}C NMR (150 MHz, DMSO-d_6): 117.12, 122.91, 123.74, 125.78, 126.16, 133.11, 137.51, 138.50, 145.75, 160.16, 178.42, 180.82; ESI-MS *m/z*: 422.9 $(M+1)^+$. Anal. Calcd for $C_{26}H_{14}O_6$: C, 73.93; H, 3.34. Found: C, 74.09; H, 3.48.

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