HETEROCYCLES, Vol. 90, No. 1, 2015, pp. 690 - 697. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 3rd June, 2014, Accepted, 11th July, 2014, Published online, 23rd July, 2014
DOI: 10.3987/COM-14-S(K)35

DESIGN OF AZA-POLYQUINANES *VIA* FISCHER INDOLE CYCLIZATION UNDER GREEN CONDITIONS†

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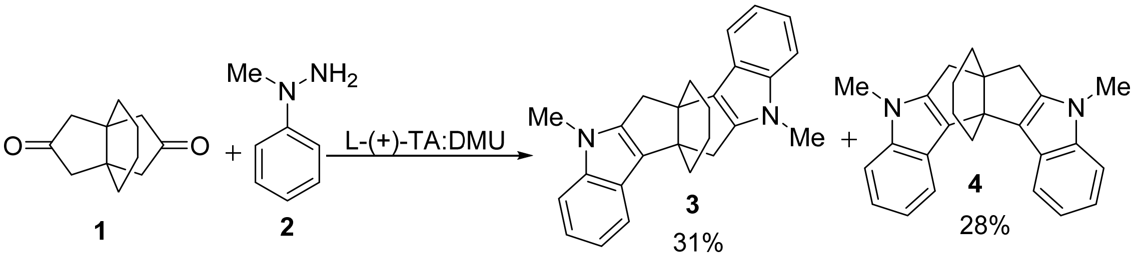
†This paper is dedicated to Prof. Isao Kuwajima on the occasion of his 77th birthday.

Abstract – We have demonstrated a simple and an efficient synthetic route for the synthesis of aza-polyquinane derivatives involving Fischer indole cyclization as a key step under low melting mixture conditions.

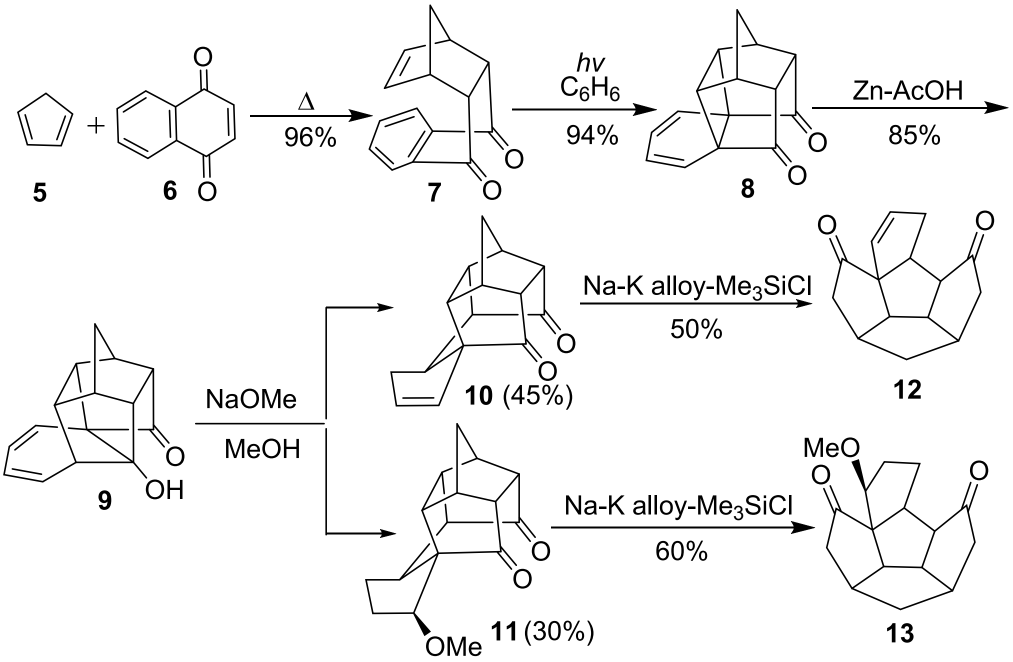
Synthesis and design of polyquinanes is actively pursued during last three decades.[1] Isolation of various natural products and activity in theoretically interesting non-natural products containing quinane systems has fueled the growth of polyquinane area. Recently, various hetero-atom containing polyquinanes appeared in the literature as useful targets.[2] König and co-workers reported low melting mixtures as a green reaction media for promoting the Fischer indole cyclization. These low melting mixture conditions (tartaric acid and dimethyl urea) are considered as green because of mild reaction conditions, ease of handling, simple work up and recycling ability aspects.[3] In connection with our interest in utilizing a readily available building blocks to generate "drug like" molecules in diversity oriented fashion, we studied Fischer indole cyclization of Weiss–Cook diones[4a] in low melting mixtures. To this end, tricyclic [4.3.3]propellane dione **1** was shown to undergo two-fold Fischer indole cyclization to generate bis-indole derivatives. Latter, this methodology has been extended to the synthesis of various other propellane derivatives (Scheme 1).[4b,4c]



Scheme 1. Fischer indole cyclization of dione **1** under low melting mixture conditions

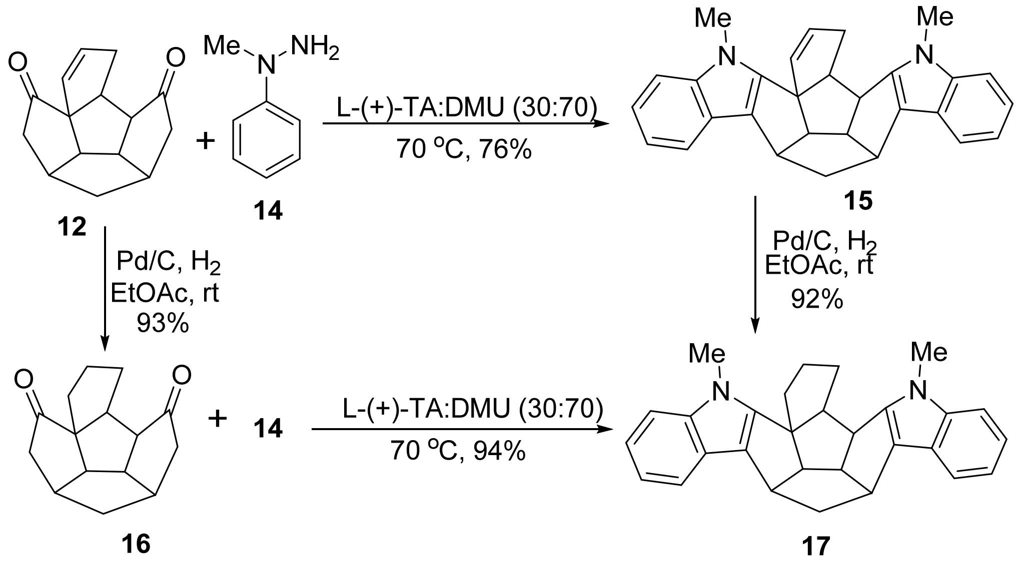
To expand the scope of this methodology here we used intricate polyquinane derivatives to generate polycyclic bis-indole derivatives. Pentaquinanes **12** and **13** used in the present study are easily available by a five step sequence from a readily available starting materials such as cyclopentadiene **5** and 1,4-benzoquinone **6**. These diones **12** and **13** are attractive targets for further synthetic exploitation due to their easy accessibility and stable nature.[5] Some time back Fischer indole cyclization, Friedlander annulation and other benzanulation reactions were studied to design novel molecular entities.[6-9]

Pentaquinane derivative **12** synthesis used here start with Diels–Alder reaction. Thus, cyclopentadiene **5** on Diels–Alder reaction with 1,4-naphthoquinone **6** gave the Diels–Alder adduct **7**, which on [2+2] photocycloaddition delivered the hexacyclic propellane derivative **8**. Latter, the diketone **8** was subjected to reduction in the presence of Zn-AcOH to produce an annulated trishomocubane derivative **9**. The cubane derivative **9** was refluxed under NaOMe-MeOH conditions to generate a mixture of rearranged diones **10** and **11**. Latter, the diones **10** and **11** were subjected to succinyl C-C bond cleavage under Na-K alloy-Me_3SiCl conditions to furnish the pentacyclic diones **12** and **13** respectively (Scheme 2).



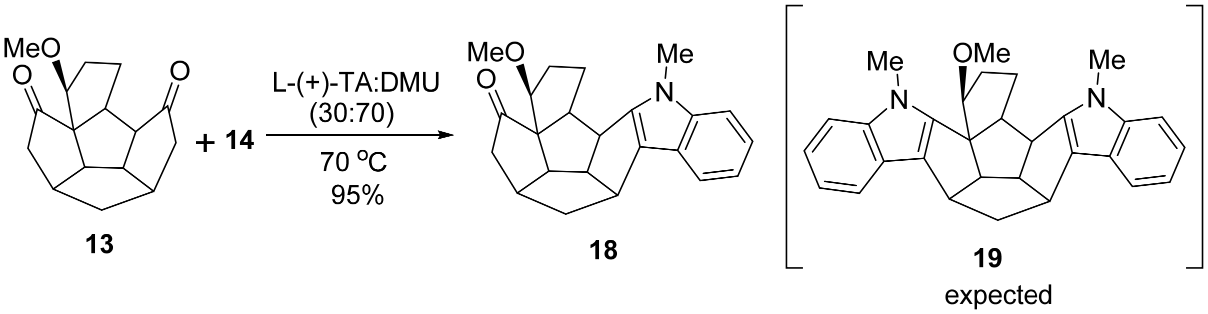
Scheme 2. preparation of pentacyclic dione derivatives **12** and **13**

Next, the pentacyclic dione **12** was treated with two equivalents of 1-methyl-1-phenylhydrazine **14** in the presence of a low melting mixture of L-(+)-tartaric acid (TA) and dimethyl urea (DMU) to generate two-fold Fischer indole cyclization product **15**. Hydrogenation of **15** in the presence of 10 mol% Pd/C in EtOAc gave the saturated diindole **17**. In another route pentaquinane derivative **12** was hydrogenated and then subjected to two-fold Fischer indole cyclization to deliver the bis aza-polyquinane derivative **17**. The product **17** obtained by this procedure was found to be identical to that of the compound obtained by the earlier route (Scheme 3).



Scheme 3. Synthesis of aza-polyquinane derivative **15** and **17**

Later, methoxy substituted pentacyclic dione **13** was also subjected to two-fold Fischer indole cyclization in low melting mixture with two equivalents of 1-methyl-1-phenylhydrazine **14** is expected to deliver the bis-indole derivative **19**. Surprisingly, mono-indole derivative **18** was obtained in 95% yield (Scheme 4).



Scheme 4. Synthesis of aza-polyquinane **18**

It appears that only one side pentacyclic dione had undergone Fischer indole cyclization due to the presence of the methoxy group creating the steric barrier. The structure of **18** was unambiguously established by single crystal X-ray diffraction studies (Figure 1).[10]

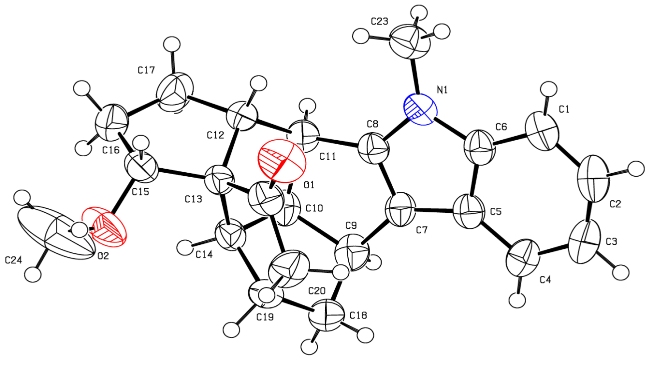


Figure 1. The molecular crystal structure of **18** with 50% probability

In summary, we have developed a new and simple synthetic route towards the synthesis of aza-polyquinane derivatives containing up to nine rings in six step sequence starting with cyclopentadiene and 1,4-naphthaquinanone by using Fischer indole cyclization as a key step. Since macrocyclic indole derivatives are implicated in medicinal chemistry, our results are likely to draw the attention of medicinal chemists and drug discovery persons.

EXPERIMENTAL

NMR spectra were recorded at rt on 400 MHz Bruker NMR spectrometer in $CDCl_3$ solution. Coupling constants (J values) are given in Hertz (Hz). Melting points were recorded with Buchi melting point apparatus. Infrared (IR) spectra were recorded Nicolet Impact-400 FT IR spectrometer in KBr. The high-resolution mass measurements were carried out using a Micromass Q-ToF spectrometer. Analytical thin layer chromatography (TLC) was performed on (10 × 5 cm) glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder). Chromatography was performed using Acme's silica gel (100-200 mesh) using double spray bellows for application of pressure and the column is eluted with EtOAc/petroleum ether mixture. The organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

General procedure for the Fischer indole cyclization.

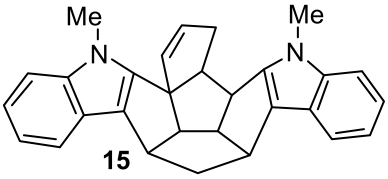
In a typical experiment, 1.5 g of L-(+)-tartaric acid- *N*,*N*′–dimethylurea (30:70) mixture was heated to 70 ^{o}C to obtain a clear melt. To this melt, 2 mmol of 1-methyl-1-phenyl hydrazine and 1 mmol of diketone were added at 70 ^{o}C. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched by adding water while still hot. The reaction mixture was cooled to room temperature and the solid that separated was filtered and washed with water (2 × 5 mL). The crude product was dried under vacuum and then it was purified by silica gel column chromatography.

Two fold Fischer indole cyclization of 15

The pentacyclic dione **12** (100 mg, 0.44 mmol) reacted with 1-methyl-1-phenylhydrazine (118 mg, 0.96 mmol) in the presence of low melting mixture by following the general procedure. At the conclusion of the reaction (TLC monitoring), the reaction mixture was workup according to the general procedure. The crude product obtained was purified by column chromatography on a silica gel (EtOAc/petroleum ether, 10:90) to provide diindole derivative **15** (134 mg, 76%) as a colorless solid.

R_f = 0.38 (Silica gel, 10% EtOAc/petroleum ether).

mp 152-153 ^{o}C.



15

IR (KBr): v_{max} 3019, 2952, 2855, 1406, 1216, 1155 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.26-2.31 (m, 1H), 2.35-2.42 (m, 1H), 2.51-2.57 (m, 1H), 2.93-3.00 (m, 1H), 3.02-3.06 (m, 1H), 3.46 (s, 3H), 3.56 (s, 3H), 3.71-3.78 (m, 2H), 3.82-3.92 (m, 2H), 4.19-4.26 (m, 1H), 5.82-5.83 (d, J = 6.28 Hz, 2H), 6.82-6.88 (m, 2H), 6.91-6.93 (m, 2H), 6.96-6.99 (m, 2H), 7.27-7.29 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.54, 30.50, 36.64, 40.34, 44.94, 45.87, 52.88, 52.99, 62.38, 69.21, 71.07, 108.91, 108.97, 118.21, 118.24, 118.72, 119.85, 119.97, 121.76, 122.30, 123.40, 123.60, 129.14, 137.19, 141.96, 142.20, 145.49, 146.28

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{27}N_2$: 403.2169; found: 403.2169.

Synthesis of Compound 17

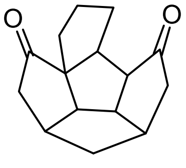
Method A

To a solution of diindole **15** (50 mg, 0.12 mmol) in dry EtOAc (10 mL), 10% Pd/C (10 mg, 0.09 mmol) was added and the reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 4 h. At the end of the reaction (TLC monitoring), the reaction mixture was filtered through a pad of celite and washed with EtOAc (20 mL). Evaporation of the solvent in vacuo gave the crude product. Further purification by silica-gel column chromatography (5% EtOAc/petroleum ether) afforded the hydrogenated product **17** (46 mg, 92%) as a colorless solid.

Method B

Hydrogenation of Compound 12

To a solution of dione **12** (50 mg, 0.22 mmol) in dry EtOAc (10 mL), 10% Pd/C (10 mg, 0.09 mmol) was added and the reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 4 h. At the end of the reaction (TLC monitoring), the reaction mixture was filtered through a pad of celite and washed with ethyl acetate (20 mL). Evaporation of the solvent in vacuo gave the crude product. Further purification by silica-gel column chromatography (5% EtOAc/petroleum ether) afforded the hydrogenated product **16** (47 mg, 93%) as a colorless solid.



16

R_f = 0.37 (Silica gel, 10% EtOAc/petroleum ether).

mp 94-96 °C.

IR (KBr): v_{max} 3020, 2928, 2855, 1730, 1216, 1045 cm^{-1}.

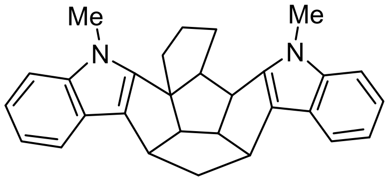
^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.76 (q, J = 11.89 Hz, 1H), 1.57-1.71 (m, 3H), 1.75-1.85 (m, 2H), 1.87-1.96 (m, 1H), 2.14-2.21 (m, 1H), 2.23-2.33 (m, 2H), 2.28-2.54 (m, 4H), 2.66-2.77 (m, 2H), 3.08 (t, J = 8.33 Hz, 1H), 3.39-3.45 (q, J = 8.44 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.85, 35.67, 38.98, 39.62, 41.00, 41.37, 44.98, 45.90, 54.58, 57.16, 61.25, 62.37, 70.37, 221.06, 223.58.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{19}O_2$: 231.1380; found: 231.1375.

Fischer indole cyclization of 16

The pentacyclic dione **16** (50 mg, 0.22 mmol) reacted with 1-methyl-1-phenylhydrazine (59 mg, 0.48 mmol) in the presence of low melting mixture by following the general procedure. At the conclusion of the reaction (TLC monitoring), the reaction mixture was workup by according to the general procedure. The crude product obtained was purified by column chromatography on silica gel (EtOAc/petroleum ether, 10:90) to provide diindole derivative **17** (83 mg, 94%) as a colourless solid.



17

R_f = 0.40 (Silica gel, 10% EtOAc/petroleum ether).

mp 208-210 °C.

IR (KBr): v_{max} 3165, 3021, 2942, 2293, 2254, 1442, 1374, 1219, 1038 cm^{-1}.

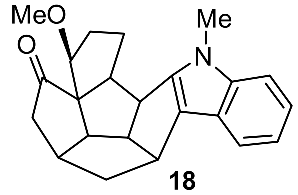
^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.57-1.61 (m, 1H), 1.76-1.80 (m, 1H), 1.83-1.93 (m, 1H), 1.96-2.08 (m, 3H), 2.11-2.19 (m, 1H), 2.72-2.75 (m, 1H), 2.88-2.91 (m, 1H), 3.39 (s, 3H), 3.44 (s, 3H), 3.46-3.48 (m, 1H), 3.66-3.69 (m, 3H), 3.96-4.01 (m, 1H), 6.60-6.67 (m, 6H), 7.13-7.19 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.16, 29.94, 30.39, 34.15, 34.54, 38.71, 43.20, 44.33, 50.68, 51.94, 60.95, 63.15, 70.85, 108.38, 108.46, 117.87, 118.08, 118.46, 119.52, 121.90, 121.96, 123.41, 123.45, 141.94, 142.19, 144.98, 146.32.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{28}N_2Na$: 427.2149; found: 427.2145.

Compound 18

The pentacyclic dione **13** (50 mg, 0.19 mmol) reacted with 1-methyl-1-phenylhydrazine (52 mg, 0.42 mmol) in the presence of low melting mixture by following the general procedure. At the conclusion of the reaction (TLC monitoring), the reaction mixture was workup by according to the general procedure. The crude product obtained was purified by column chromatography on silica gel (EtOAc/petroleum ether, 10:90) to provide indole derivative **18** (63 mg, 95%) as a colorless solid.



18

R_f = 0.36 (Silica gel, 10% EtOAc/petroleum ether).

mp 196-198 °C.

IR (KBr): v_{max} 3006, 2929, 2874, 2826, 1719, 1466, 1174, 1104 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.50-1.57 (dd, J_1 = 7.65 Hz, J_2 = 2.41 Hz, 1H), 1.58-1.67 (m, 1H), 1.75-1.83 (m, 1H), 2.04-2.10 (m, 1H), 2.12-2.19 (m, 1H), 2.20-2.28 (m, 2H), 2.44-2.46 (d, J = 13.21 Hz, 1H), 2.80-2.90 (m, 1H), 3.04-3.05 (m, 1H), 3.18 (s, 3H), 3.49-3.56 (m, 2H), 3.58 (s, 3H), 3.77-3.80 (t, J = 7.01 Hz, 1H), 4.01-4.04 (t, J = 7.90 Hz, 1H), 4.07-4.12 (m, 1H), 7.06-7.09 (m, 1H), 7.13-7.18 (m, 1H), 7.20-7.22 (m, 1H), 7.47-7.49 (d, J = 7.80 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.53, 30.41, 31.08, 37.72, 39.35, 43.56, 45.60, 50.98, 53.06, 58.14, 58.29, 63.32, 73.57, 88.22, 109.84, 118.49, 119.16, 120.92, 121.47, 123.15, 142.90, 144.83, 225.35.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{25}NNaO_2$: 370.1777; found: 370.1777.

ACKNOWLEDGMENT

We thank CSIR and Department of Science and Technology (DST), New Delhi for the financial support. SK thanks DST for the award of a J. C. Bose fellowship. AKC thanks University Grant Commission, New Delhi for the award of a research fellowship.

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10. CCDC-1005894 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif. Crystal data: (**18**): $C_{23}H_{25}NO_2$, M^+ = 347, monoclinic, space group P 2_1/n, unit cells dimensions a = 9.2592 (9) A° α = 90 deg, b = 9.559 (11), c = 19.72 1 (2) A° γ = 90 deg, β = 91.251 (9)°, Z = 4, D_c = 1.323 g cm^{-3}, F(000) = 744, λ (Mo-Kα) = 0.71 cm^{-1}; 1812 observed reflections [$|F| \geq 3\sigma(|F|)$, $2\Theta \leq 50°$] were measured on high resolution single crystal X-ray diffraction data at 293 K and the structure was solved by MULTAN 78 and refined by full-matrix least-square method to R 0.064. The figure shows a prospective view of the molecule.