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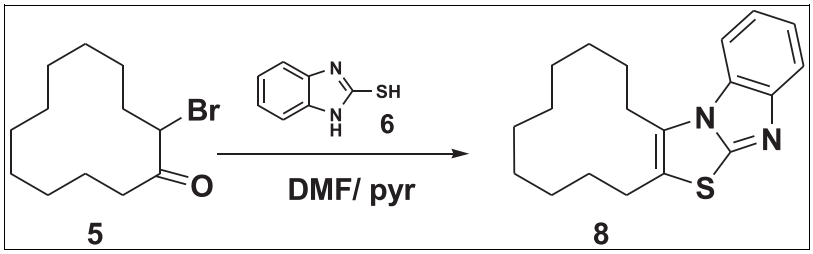

2-Bromocyclododecanone was utilized as precursor to synthesize polyfused heterocyclic cyclododecane ring systems. Transformation of 2-bromocyclododecanone (**5**) with 1*H*-benzimidazole-2-thiole (**6**), benzo [*d*]thiazole-2-thiol (**9**), *2*-naphthol (**12**), and thiophenol (**15**) afforded thiazolo[2,3-b]benzimidazole (**8**), thiazolo[2,3-b]benzothaizole derivative (**11**) naphtho[1,2-d]furan derivative (**14**) and 2-(phenylthio) cyclododecanone (**16**), respectively.

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INTRODUCTION

Cyclododecanone is an important intermediate for the synthesis of natural muscone (**1**) and macrocyclic fragrances of musk-like odor, for example, (*S*)-muscolides: **2** and **3** as well as (*R*)-12-methyltridecanolide **4** [1–5] (Fig. 1).

Cyclododecanone derivatives are important intermediates for synthesis of spiro and fused heterocycles of different classes [6,7]. In view of the aforementioned findings, we report herein the synthesis of some new heterocyclic systems incorporating cyclododecane moiety starting from 2-bromocyclododecanone (**5**) [8].

RESULTS AND DISCUSSION

α-haloketones have been attracting increasing attention in view of their high reactivity as building blocks for the synthesis of compounds of various classes due to their selective transformations with different reagents. They are widely used in construction of different heterocyclic ring systems, such as thiazoles [9,10], quinoxalines [11], indoles [12], furans and their fused derivatives [13,14], thiophenes and their fused derivatives [15], and many other ring systems [16]. This promoted us to explore the validity of 2-bromocyclododecanone (**5**) for construction of heterocyclic systems fused to cyclododecane ring skeleton.

Treatment of 2-bromocyclododecanone (**5**) with 1H-benzimidazole-2- thiole (**6**) in boiling DMF containing one equivalent of pyridine furnished 4,5,6,7,8,9,10, 11,12, 13-decahydrocyclododeca[d]thiazolo[2,3-b]benzimidazole (**8**) in good yield without isolation of the expected open intermediate **7** (Scheme 1).

The substitution product 2-(benzo[d]thiazol-2-ylthio) cyclododecanone (**10**) was isolated in a moderate yield from reaction of **5** with benzo[d]thiazole-2-thiol (**9**) in refluxing ethanol in presence of sodium acetate. The IR spectrum of **10** showed a sharp absorption at 1721 cm^{-1} (CO group). In addition, its ^{1}H NMR spectrum supported its open structure where it displayed a triplet signal for one proton at 5.2 ppm (proton on carbon bearing (benzo [d]thiazol-2-yl)thio moiety) besides the other characteristic signals. Treatment of the cyclododecanone derivative **10** with concentrated sulfuric acid catalyses its transformation into thiazolo[2,3-b]benzothaizole derivative **11** (Scheme 1).

The chemical constitution of **11** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and DEPT 135 spectra. The IR spectrum of **11** revealed its tetracyclic structure due to the absence of the carbonyl absorption besides the presence of a broad band at 3423 cm^{-1} corresponding to OH group. Also, its ^{1}H NMR spectrum supported its tetracyclic structure due to the absence of the triplet signal for one proton at 5.2 ppm characteristic to the open structure. The structure of **11** was also ascertained by ^{13}C NMR spectroscopy where its spectrum displayed a signal at 117.01 ppm corresponding to (S–C–OH) carbon [17] besides the other characteristic signals. Also, its DEPT 135 spectrum disclosed the presence of 10 CH_2 groups and four CH groups.

The transformation of **10** into **11** was proposed to take place via two consecutive nucleophilic additions in a domino's manner as depicted in Scheme 2.

In addition, naphthofuran derivative **14** was synthesized in an analogous manner to **11** via the successful substitution, acid catalyzed cyclization reaction sequence. Thus, the

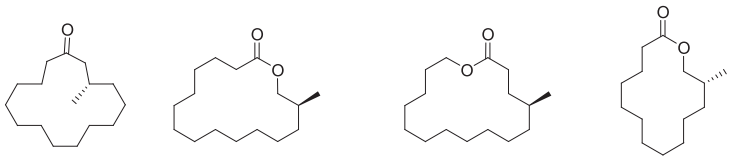
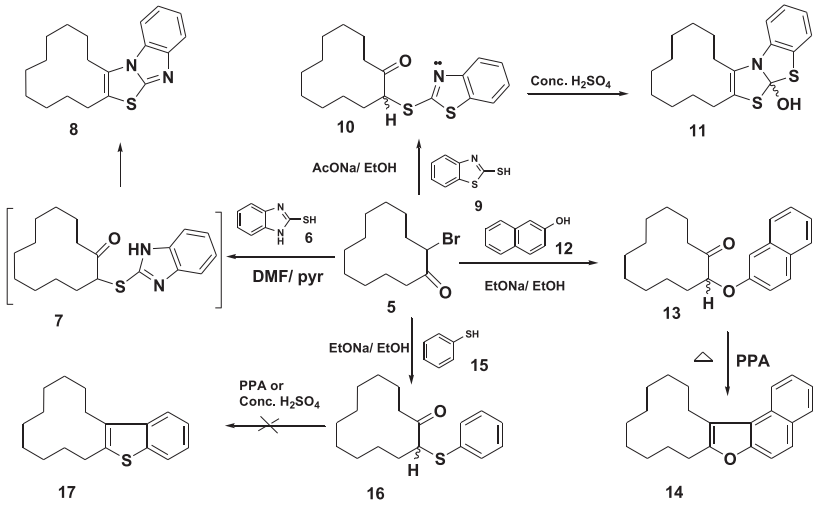
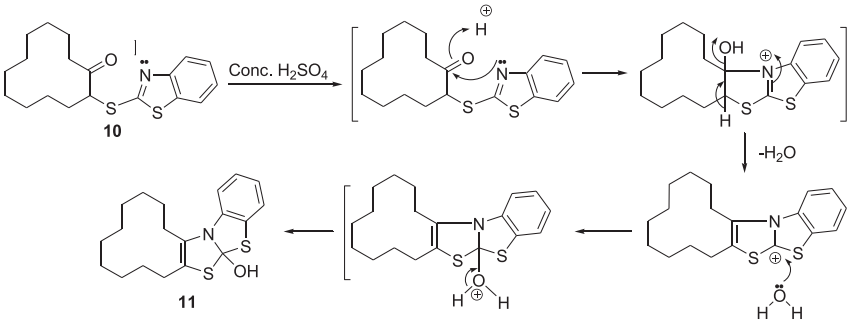


Figure 1. (*S*)-muscone (VII) (*S*)-muscolide (VIII) (*S*)-muscolide (IX) (R)-12-methyltri decanolide (X).

Scheme 1. Reactivity of **5** toward different reagents.



Scheme 2. Proposed mechanism for transformation of **10** into **11**.



reaction of **5** with 2-naphthol (**12**) in EtONa/EtOH afforded 2-(2-naphthyloxy)cyclododecanone (**13**), which then cyclized to 8,9,10,11,12,13,14,15,16,17-decahydrocyclododeca[b] naphtho[1,2-d]furan (**14**) under the influence of polyphosphoric acid (Scheme 1).

Structures of **13** and **14** were supported by IR, ^{1}H NMR, and ^{13}C NMR spectra. Besides, the ^{13}C NMR signals of compound **14**, taken as a typical example of the annulated products of this series are appeared together with signal assignments as shown in Figure 2.

Furthermore, nucleophilic substitution of bromoketone **5** with benzothiolate anion proceeded easily in EtONa/EtOH to afford the 2-(phenylthio)cyclododecanone (**16**) in 76% yield. Whereas, all our trials to synthesize 8,9,10,11,12,13,14,15,16,17-decahydrocyclododeca[b]benzo[1,2-d] thiophene (**17**) via cyclization of **16** under the influence of polyphosporic acid or concentrated sulfuric acid were failed, and **16** was recovered unchanged (Scheme 1).

The IR spectrum of **16** showed a strong absorption band at 1699 cm^{-1} corresponding to carbonyl group. The ^{1}H NMR spectrum showed a signal for one proton at 4.0 (1H, dd) corresponding to the proton of cyclododecanone carbon bearing the thiophenyl moiety, besides the other characteristic signals. In addition, the ^{13}C NMR signals

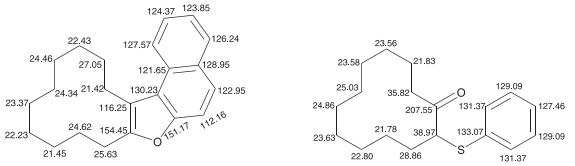


Figure 2. ^{13}C NMR signals of naphtho[1,2-d]furan (**14**) and 2-(phenylthio) cyclododecanone (**16**).

of compound **16**, taken as a typical example of the open products of this series, are appeared together with signal assignments in Figure 2. In addition, the DEPT 135 spectrum of **16** revealed the presence of 10 CH_2 groups and six CH groups.

In conclusion, 2-bromocyclododecanone is a valuable synthetic building block used for construction of different heterocyclic ring systems fused to the macrocyclic cyclododecane ring skeleton via sequence of nucleophilic substitution followed by cyclization reaction.

EXPERIMENTAL

All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. The IR spectra were recorded (KBr) on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science; Mansoura University. The ^{1}H NMR data were obtained in DMSO-d_6 using TMS as internal standard, and chemical shifts were reported in ppm (δ) downfield from internal TMS. The ^{1}H NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 MHz; Billerica, MA) in Bioorganic Chemistry Department, University of Saarland, Saarbrüken, Germany. ^{13}C NMR spectra at 125 MHz were performed on a Bruker Avance 500 spectrometer in Bioorganic Chemistry department, University of Saarland, Saarbrüken, Germany. Mass spectra were recorded on a Finnigan MAT 212 mass spectrometer instrument, Microanalytical Unit, Cairo University, Egypt. Elemental analyses were carried out in Microanalytical Unit, Cairo University, Egypt. Reactions were monitored by TLC using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp.

2-Bromocyclododecanone (**5**) was prepared according to literature method [8].

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododeca[1′,2′:4,5]thiazolo [3,2-a]benzoimidazole (8). 2-Bromocyclododecanone (**5**) (0.65 g, 2.5 mmol) was added to a solution of 1H-benzo[d]imidazol-2-thiol (**6**) (0.37 g, 2.5 mmol) in DMF (7 mL) containing pyridine (0.21 mL, 2.5 mmol). The reaction mixture was heated under reflux for 4 h, left to cool over night and diluted with methanol (20 mL) whereby a crystalline material was formed within 30 min then filtered off and washed with methanol to give **8**, (0.58 g; 74%). This product was satisfactorily pure without recourse to chromatography as confirmed by TLC. mp 126–128°C; IR: 2933, 2850, 1617, 1473, 1447 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.3–1.85 (16H, m), 2.8 (2H, t), 3.15 (2H, t), 7.25 (1H, t), 7.3 (1H, t), 7.65 (1H, d), 7.85 ppm (1H, d); MS (70 eV): *m/z* = 312 (14.6, M^+), 93 (100) [base peak]. *Anal*. Calcd for $C_{19}H_{24}N_2S$: C, 73.03; H, 7.74; N, 8.97. Found: C, 73.12; H, 7.76; N, 8.99.

2-(Benzo[d]thiazol-2-ylthio)cyclododecanone (10). 2-Bromocyclododecanone (**5**) (0.3 g, 1.65 mmol) was added to a mixture of benzo[d]thiazole-2-thiol (**9**) (0.28 g, 1.65 mmol) and sodium acetate (0.62 g, 7.6 mmol) in absolute methanol (15 mL). The reaction mixture was refluxed over a steam bath for 2 h, left to cool overnight whereby a pale yellow precipitate was formed, filtered off, washed with cold water, air dried, and recrystallized from absolute ethanol to furnish **10**, (0.3 g; 53%); mp 112–114°C; IR: 2939, 2863, 1721, 1451 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.0–1.8 (18H, m), 2.0–2.2 (2H, m), 5.2 (1H, t), 7.18–8 ppm (4H, m). *Anal*. Calcd for $C_{19}H_{25}NOS_2$: C, 65.66; H, 7.25; N, 4.03. Found: C, 65.77; H, 7.26; N, 4.04.

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododeca[1′,2′:4,5]thiazolo [2,3-b]benzothiazole (11). A mixture of **10** (0.2 g, 0.58 mmol) and conc. H_2SO_4 (2.5 mL, 1.84 g/cm^3) was heated over steam bath for 5 h. Cooled, basified with sodium bicarbonate solution then extracted with chloroform (3 × 10 mL). The combined chloroform extract was dried over anhydrous sodium sulfate, filtered off, and solvent removed under vacuum to give **11** as white crystalline solid (52.6%), which was satisfactorily pure as confirmed by TLC. mp 138–140°C; IR: 4372, 2919, 2847, 1469 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.12–1.95 (16H, m), 3.0 (2H, t), 3.2 (2H, t), 7.8 (2H, m), 8.45 ppm (2H, d); ^{13}C NMR (125 MHz, DMSO): δ 20.97, 22.42, 22.51, 22.87, 23.70, 23.97, 24.80, 25.18, 25.52, 28.71, 117.01, 125.03, 127.69, 128.15, 134.16, 135.70, 138.35, 139.80 ppm; ^{13}C NMR (DEPT 135, T = 60 °C, DMSO): indicates the presence of 10 CH_2 and four CH groups. *Anal*. Calcd for $C_{19}H_{25}NOS_2$: C, 65.66; H, 7.25; N, 4.03. Found: C, 65.76; H, 7.26; N, 4.04.

2-(2-Naphthyloxy)cyclododecanone (13). 2-Bromocyclododecanone (**5**) (0.65 g, 2.5 mmol) was added to a solution of sodium naphthalen-2-olate [prepared by dissolving sodium metal (0.058 g, 2.5 mmol) in absolute ethanol (15 mL) containing 2-naphthol (0.36 g, 2.5 mmol)]. The homogeneous mixture was heated under reflux over steam bath for 2 h and then left to cool overnight. The white precipitate that formed was filtered off, washed with cold water and air dried, then recrystallized from ethanol, to give **13** (0.65 g; 80%); mp 118–120°C; IR: 2942, 2865, 1713, 1628, 1598 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.2–1.35 (14H, m), 1.52–1.7 (2H, m), 2.1 (4H, m), 5.05 (1H, t), 7.1 (1H, d), 7.17 (1H, dd), 7.35 (1H, m), 7.45 (1H, m), 7.75 (1H, d), 7.85 ppm (2H, m). *Anal*. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.53; H, 8.72.

8,9,10,11,12,13,14,15,16,17-Decahydrocyclododeca[1′,2′:2,3] furo[4,5-a] naphthalene (14). 2-(2-Naphthyloxy)cyclododecanone (**13**) (0.15 g, 0.46 mmol) was heated for 3 h at 130°C in polyphosporic acid [prepared by stirring P_2O_5 (4.5 g) and H_3PO_4 (2.5 mL) at 60°C overnight] for 3 h, poured into ice-cold water and left overnight. The white precipitate that formed was filtered off and air dried to afford **14** (0.71 g, 50%), which was satisfactorily pure as confirmed by TLC. mp 96–98°C; IR: 2934, 2857 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.3–1.8 (16H, m), 2.85 (2H, t), 2.98 (2H, t), 7.5 (1H, t), 7.6 (1H, t), 7.68 (1H, d), 7.75 (1H, d), 8.0 (1H, d), 8.57 ppm (1H, d); ^{13}C NMR (125 MHz, DMSO): δ 21.42, 21.45, 22.23, 22.43, 23.37, 24.34, 24.46, 24.62, 25.63, 27.05, 112.16, 116.25, 121.65, 122.95, 123.85, 124.37, 126.24, 127.57, 128.95, 130.23, 151.17 and 154.45 ppm. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55%. Found: C, 86.35; H, 8.57%.

2-(Phenylthio)cyclododecanone (16). 2-Bromocyclododecanone (**5**) (0.5 g, 1.9 mmol) was added to ethanolic solution of sodium benzenethiolate [prepared by dissolving sodium metal (0.044 g, 1.9 mmol) in absolute ethanol (10 mL) containing thiophenol

(0.21 g, 0.2 mL, 1.9 mmol)]. The homogeneous mixture was heated under reflux over steam bath for 2 h. The reaction mixture was cooled in ice bath, a light yellow precipitate that formed, was filtered off, washed with cold water and air dried, then recrystallized from ethanol to afford **14** (0.42 g, 76%); mp 56–58°C; IR: 3288, 2926, 2860, 1709, 1581 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.0–1.8 (18H, m), 2.4 (2H, t), 5.0 (1H, dd), 7.1–7.3 ppm (5H, m); ^{13}C NMR (125 MHz, DMSO): δ 21.42, 21.45, 22.23, 22.43, 23.37, 24.34, 24.46, 24.62, 25.63, 27.05, 112.16, 116.25, 121.65, 122.95, 123.85, 124.37, 126.24, 127.57, 128.95, 130.23, 151.17 and 154.45 ppm. ^{13}C NMR (DEPT 135, T = 60°C, DMSO): showed 10 CH_2 and six CH groups. *Anal*. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02. Found: C, 74.53; H, 9.04.

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