Micowave Assisted Synthesis of Benzo-Substituted Macrocyclic Diamides and Their Corresponding Macrocyclic Dithiodiamides

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A synthesis of a series of macrocyclic diamides **3** in good yields by reacting the corresponding bis phenols **4** with the appropriate dihalo alkanes **6** either in solvent or in dry media under microwave irradiation. Thiation of **3** with P_2S_5 or Lawesson's reagent in solvent free conditions under microwave irradiation is also described.

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Introduction.

In the last decades macrocyclic polyether dilactams and their benzo-derivatives have attracted much attention [1] not only for being valuable intermediates for the synthesis of azacrowns and related compounds but also for their wide applications in selective noble metal complexing [2,3] and as metal ion selective electrodes [4-7]. Also macrocyclic diamides are precursors in the preparation of diazocrown compounds which are used as molecular receptors and for the synthesis of cryptands and related compounds [8,9]. Moreover some macrocyclic diamides have been recently used as new catalysts in the highly regioselective halogenation cleavage of epoxides with elemental halogens [10]. In addition, insertion of aromatic rings into the macrocyclic ring facilitate the modification of macrocyclic hosts with various UV and/or fluorescent active groups [11], proton ionizable fragments [12] and functional groups, which can be attached to proteins to provide radionuclide carriers for medicals diagnosis and therapy [13].

Recently there has been a growing interest in the use of microwave irradiation in chemical reaction enhancement [14]. The use of such reaction conditions has several advantages such as short reaction times compared to conventional heating, ease of work up, reduction in the usual thermal degradation and better selectivity. Furthermore many solvent free reactions using microwaves have been developed since it reduces the risk of hazards by pressure build up in the reaction vessel and the scale-up is made easier [15-16].

In connection with these findings and in continuation of our interest in synthesizing macrocyclic crown compounds [17-22] and their precursors, we report here the first employment of microwave in the synthesis of a series of benzo-substituted macrocyclic diamides.

Results and Discussion.

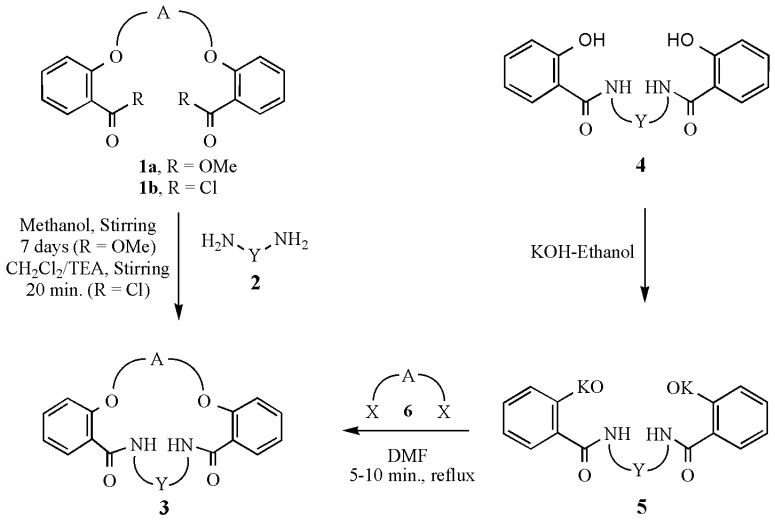
Several synthetic methods have been reported for the synthesis of macrocyclic diamides in which the carbonyl group of the amide moiety is attached directly to the aromatic ring. These methods include either reaction of α,ω-dicarboxylic acid derivatives (diester, or diacid dichloride) with various diamines or reaction of bis phenol (containing amide moieties) with the appropriate dihalo or ditosylate compounds as outlined in Scheme 1. For example, Jurczak and co-workers [23] reported the synthesis of some benzomacrocyclic diamides **3** by stoichiometric condensation of a series of diesters **1a** with diamines **2**. Sodium methoxide was found by the same group to be an effective catalyst in these reactions [24]. The high dilution technique is often used as the most versatile procedure.

On the other hand Sharghi and co-workers [10,25] recently reported the synthesis of some macrocyclic dibenzotrioxadiamides **3** by reacting the appropriate dicarboxylic acid dichloride **1b** with the corresponding diamines **2** in CH_2Cl_2. The cyclization does not require high dilution technique or template metal ions and provides the expected dilactams in high yields ranging from 80-90%. It is noteworthy to mention that some derivatives of **3** were obtained in only 6-8% yields using a similar approach [17].

Moreover, Ibrahim and Elwahy [17,18] reported the synthesis of some derivatives of **3** in moderate to good yields (35-90%) by reacting dipotassium salts **5** (obtained upon treatment of **4** with ethanolic KOH) with the appropriate dihaloalkanes or ditosylates **6** in DMF.

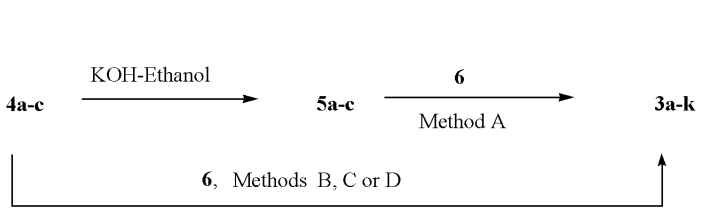
In the search for a more facile method for the synthesis of macrocyclic diamides of type **3**, we decided to investigate the reaction of the bis phenol **4** with the corresponding dibromide **6** under microwave conditions. Several types of conditions were considered involving either the performed potassium salt **5** (Method A) or the generation *in situ* of the same salt from **4** and potassium hydroxide (Methods B, C or D) and subsequent alkylation. The progress of reaction was monitored by TLC. To find the best conditions, the reaction mixture was irradiated for variable times and microwave power. It was observed that the reaction was complete in a short period of time (30 sec.) by irradiation of the reaction mixture using a microwave oven of power 350 W. In our first experiments (Methods A, B) a small amount of *N,N*-dimethylformamide, an excellent energy

Scheme 1



transfer solvent with a high dielectric constant, was added to the reaction mixture in order to increase the energy input in a shorter time and providing a uniform heating [26]. The rate enhancement in such reactions is belived to be due to rapid superheating of the polar solvents [27]. Thus, the reaction of **5a-c** with **6** using (method A) gave **3a-k** in 72-98% yields. Compounds **3a-d** and **3g-i** were alternatively obtained from the corresponding bis-phenols **4** in 87-92% yields (Method B). When the alkylation of **4a,b** with the appropriate dihalo compounds **6** was carried out in the presence of diglyme as a solvent as well as as a catalytic amount of tetrabutyl ammonium bromide (TBAB) and KOH/K_2CO_3 adsorbed in Al_2O_3, and then by irradiating in an open vessel in a domestic microwave oven (350 W, 30 sec.). Comparing the yields of entries **3a-d** and **3g-i** (Table 1), it can be found that method A gave better yields than methods B, C or D. Although conventional heating methods can be used to synthesize **3** from **5** in good yields [18], however, repeated attempts to synthesize **3** directly from **4** under these conditions using similar mixtures to that described in methods B, C or D, were unsuccessful.

Scheme 2



Method A, DMF, MW (350 W), 30 sec.
Method B, KOH, DMF, MW (350 W), 30 sec.
Method C, KOH, Diglyme, MW (350 W), 30 sec.
Method D, KOH-K_2CO_3-Al_2O_3 (300 m), TBAB (catalytic amount), MW (350 W), 30 sec.

4a, **5a**, Y = $(CH_2)_2$, **4b**, **5b**, Y = $(CH_2)_3$, **4c**, **5c**, Y = $(CH_2)_4$

Entry	Y	A
3a	$(CH_2)_2$	$(CH_2)_2$
3b	$(CH_2)_2$	$(CH_2)_3$
3c	$(CH_2)_2$	$(CH_2)_4$
3d	$(CH_2)_2$	CH_2-CH=CH-CH_2
3e	$(CH_2)_3$	$(CH_2)_3$
3f	$(CH_2)_3$	$(CH_2)_4$
3g	$(CH_2)_3$	$(CH_2)_5$
3h	$(CH_2)_3$	$(CH_2)_6$
3i	$(CH_2)_3$	CH_2-CH=CH-CH_2
3j	$(CH_2)_4$	$(CH_2)_5$
3k	$(CH_2)_4$	$(CH_2)_6$

transfer agent [28] (Method C) the reaction yield of **3** was reduced to 45-76%.

We have also described a rapid bis-alkylation of **4** in 50-78% yields in dry media under microwave irradiation (Method D). The reactions were carried out by simple mixing of bis phenol **4a,b**, dibromo compound **6**, a

The novel macrocyclic diamides, now available, prompted us to study their possible transformation to other functionallized derivatives (Scheme 3). For example, the conversion of oxo group to thioxo group should provide precursors for side-armed macroheterocycles as well as fused macroheterocycles. Thiation of heterocycles usually

Table 1

Yields (%), Methods A, B, C, D

Entry	A	B	C	D
*3a	93	87	64	52
*3b	96	90	62	60
*3c	98	91	61	66
3d	93	91	45	50
3g	90	88	75	77
3h	97	92	76	78
3i	92	89	-	-

*3a-c were obtained from 5a in 93-95% yield under conventional heating method [18].

requires the use of a large amount of P_2S_5 in toxic pyridine [29]. In some cases the thiation proceeds more readily with Lawesson's reagent in non-polar solvent [30]. The reactions under these conditions proceeds at high temperature and requires long reaction times [30-32].

Recently [17,32], we reported the synthesis of some macrocyclic dithiodiamide derivatives **7** in 50-90% yields by reacting the corresponding macrocyclic diamides **3** with Lawesson's reagent in refluxing toluene for 2-3 h. On the other hand, thiation of **3** with P_2S_5 in refluxing pyridine was unsuccessful even after prolonged heating [32].

In connection with our interest in using microwave to increase the rates of reactions as well as to reduce the reaction time, we have also investigated the thiation of **3** under microwave conditions. The reaction was carried out by crushing together P_2S_5 or Lawesson's reagent and a weight equivalent of silica gel (silica gel 60, particle size 0.2-0.6 mm) so as to form an intimate mixture. In a typical reaction 2-3 equivalents of supported P_2S_5 or Lawesson's reagent was mixed with the appropriate macrocyclic diamides **3** in a beaker. The beaker was exposed to microwave irradiation (700 W) for 15-30 minutes. The residue was extracted with boiling, ethanol, acetic acid or DMF. The solvent was then removed and the crude product was crystallized from an appropriate solvent to afford the corresponding macrocyclic dithiodiamides **7**. The thiation results are presented in Table 2.

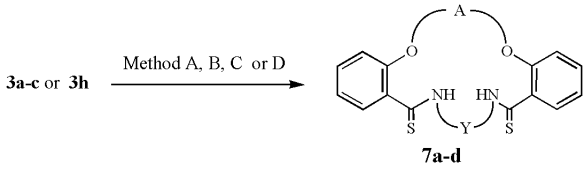
Although there is still some debate over the mode of action of microwave assisted chemistry, the most recent observations suggest that the high tempertaure that can be quickly achieved in such systems are responsible for the acceleration of chemical reactions [33].

In conclusion we have developed a simple, remarkable fast and environmentally friendly procedure for the first synthesis of macrocyclic diamides and their corresponding macrocyclic dithiodiamides under microwave conditions. All the reactions were carried out in an open vessels using a household microwave oven for a very short time. The successful synthesis of these macrocycles should open a new access for the use of microwave irradiation as a powerful tool for enhanced generation of novel macroheterocycles.

Table 2

Entry	Y	A	Yield %			
			A	B	C	D
7a	$(CH_2)_2$	$(CH_2)_2$	86	89	83 [32]	0
7b	$(CH_2)_2$	$(CH_2)_3$	78	86	85 [32]	0
7c	$(CH_2)_2$	$(CH_2)_4$	82	84	90 [32]	0
7d	$(CH_2)_3$	$(CH_2)_6$	86	85	-	0

Scheme 3



Method A: P_2S_5, Silica gel 60 (particle size 0.2-0.6 mm), MW (700 W), 30 min.
Method B: Lawesson's reagent, Silica gel 60 (particle size 0.2-0.6 mm), MW (700 W), 15 min.
Method C [32]: Lawesson's reagent, Toluene, reflux 2-3h.
Method D [32]: P_2S_5, Pyridine, reflux 6 h.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were measured with a Varian GEMINI 200 spectrometer (200 MHz ^{1}H NMR) or Brucker WM-300 insrtument in $CDCl_3$ or DMSO and chemical shift are given in ppm from TMS. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were recorded on DCMS-QP 1000 EX (EI, 70 eV). The reactions were carried out in a domestic microwave oven (LG Microwave 700 W). 1,2-Dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane, 1,6-dibromohexane and 1,4-dibromo-2-butene were used as purchased from Aldrich. The dipotassium salts **5a-c** were prepared as reported [17,18].

Preparation of Macrocyclic Diamides **3**.

General Procedures.

Method A.

A mixture of the potassium salt **5** (1 mmol), the appropriate dihalo compound **6** (1 mmol) and DMF (3 mL) in an open Erlenmeyer flask was irradiated in a domestic microwave oven at power level (350 W) for 30 sec. The precipitate obtained upon cooling and dilution with water was collected and crystallized from ethanol to give **3** as colorless crystals.

Method B.

A mixture of the bis phenols **4** (1 mmol), KOH (2 mmol), the appropriate dihalo compound **6** (1 mmol) and DMF (3 mL) in an open Erlenmeyer flask was irradiated in a domestic microwave oven at power level (350 W) for 30 sec. The precipitate obtained upon cooling and dilution with water was collected and crystallized from ethanol to give **3** as colorless crystals.

Method C.

The same procedure like method B except that diglyme (3 mL) was used instead of DMF.

Method D.

A mixture of the bis phenols **4** (5 mmol), the appropriate dihalo compound **6** (5 mmol), 0.16 g TBAB (0.5 mmol), and KOH (10 mmol)/ K_2CO_3 (5 mmol) adsorbed on 2 gm Al_2O_3 (300 m) was introduced into a domestic microwave oven at power level (350 W) in a 25 mL beaker for 30 sec. The precipitate obtained upon cooling and dilution with water was collected and crystallized from ethanol to give **3** as colorless crystals.

Compounds **3a**-**3c** were obtained as colorless crystals; **3a**, mp. 246-248 °C lit. [18] mp. 246-248 °C; **3b** mp. 210-212 °C lit. [18] mp. 208-210 °C; **3c**, mp. 227-229 °C lit. [18] mp. 226-228 °C.

Compound **3d** was obtained as colorless crystals; mp. 204-206 °C, MS (EI): m/z (%) 352 [M^+, 2%], 310 (1.3 %), 275 (1.6 %), 189 (23.8 %), 121 (100%); IR (cm^{-1}) 3396, 3312 (NH), 1633 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.53 (s, 4H, CH_2NH), 4.70 (s, 4H, CH_2O), 6.31 (s, 2H, CH=), 7.06-7.82 (m, 8H, aryl H), 8.29 (br, 2H, NH).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.90 ; H, 6.00 ; N, 8.10.

Compound **3e** was obtained as colorless crystals (72%, Method A); mp. 128-130 °C, MS (EI): m/z (%) 354 [M^+, 25%], 298 (22%), 161 (27%), 121 (100%); IR (cm^{-1}) 3398 (NH), 1641 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.83 (quintet, 2H, *J* = 6 Hz, CH_2CH$_2$NH), 2.24 (quintet, 2H, *J* = 5.4 Hz, CH_2CH$_2$O), 3.39 (m, 4H, CH_2NH), 4.31 (t, 4H, *J* = 5.4 Hz, CH_2O), 6.96-7.67 (m, 8H, aryl H), 8.16 (br, 2H, NH).

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.90 ; H, 6.40 ; N, 8.20.

Compound **3f** was obtained as colorless crystals (83%, Method A); mp. 188-190 °C, MS (EI): m/z (%) 368 [M^+, 7.8%], 340 (67.1 %), 312 (12.4 %), 298 (23.9 %), 266 (29.2 %), 239 (11.1 %), 192 (25.4 %), 147 (100%); IR (cm^{-1}) 3397, 3317 (NH), 1640 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.77 (quintet, 2H, *J* = 6 Hz, CH_2CH$_2$NH), 2.00 (s, 4H, CH_2CH$_2$O), δ 3.40 (m, 4H, CH_2NH), 4.16 (br, 4H, CH_2O), 7.00-7.72 (m, 8H, aryl H), 8.18 (br, 2H, NH).

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.60 ; H, 6.60 ; N, 7.40.

Compound **3g** was obtained as colorless crystals; mp. 213-215 °C, MS (EI): m/z (%) 382 [M^+, 14.1%], 326 (10.4 %), 189 (16.8 %), 121 (100%); IR (cm^{-1}) 3397, 3318 (NH), 1640 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.69-1.88 (m, 8H, CH_2CH$_2$NH, CH_2CH$_2$O), 3.36 (m, 4H, CH_2NH), 4.12 (t, 4H, *J* = 5.4 Hz, CH_2O), 6.98-7.68 (m, 8H, aryl H), 8.08 (br, 2H, NH).

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.80 ; H, 6.70 ; N, 7.50.

Compound **3h** was obtaiend as colorless crystals; mp. 233-35 °C, MS (EI): m/z (%) 396 [M^+, 12.8%], 340 (7.2%), 203 (10.8%), 121 (100%); IR (cm^{-1}) 3400, 3377 (NH), 1643 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.44-1.89 (m, 10H, CH_2CH$_2$NH, (CH$_2$)$_4$CH$_2$O), 3.36 (m, 4H, CH_2NH), 4.11 (t, 4H, *J* = 5.1 Hz, CH_2O), 6.90-7.76 (m, 8H, aryl H), 8.06 (br, 2H, NH).

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.80 ; H, 6.90 ; N, 7.30.

Compound **3i** was obtained as colorless crystals (75%, Method A); mp. 200 °C, MS (EI): m/z (%) 366 [M^+, 22%], 314 (22%), 173 (100%), 121 (48%); IR (cm^{-1}) 3403 (NH), 1649 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.79 (quintet, 2H, *J* = 6.6 Hz, CH_2CH$_2$NH), 3.73 (m, 4H, CH_2NH), 4.67 (s, 4H, CH_2O), 6.25 (s, 2H, C*H*=C*H*), 7.02-7.64 (m, 8H, aryl H), 8.16 (br, 2H, NH).

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.90 ; H, 6.20 ; N, 7.40.

Compound **3j** was obtained as colorless crystals; mp. 214-216 °C, IR (cm^{-1}) 3397(NH), 1640 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.63-1.93 (m, 10H, CH_2CH$_2$NH, (CH_2)$_3$CH$_2$O), 3.45 (m, 4H, CH_2NH), 4.14 (t, 4H, *J* = 5.1 Hz, CH_2O), 6.99-7.76 (m, 8H, aryl H), 8.08 (br, 2H, NH).

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.80 ; H, 6.90 ; N, 7.30.

Compound **3k** was obtained as colorless crystals (85%, Method A); mp. 180-182 °C, MS (EI): m/z (%) 410 [M^+, 6.8%], 393 (2.3%), 323 (2%), 203 (7.8%), 121 (100%); IR (cm^{-1}) 3399, 3340 (NH), 1647 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.23-1.83 (m, 12H, CH_2CH$_2$NH, (CH_2)$_4$CH$_2$O), 3.47 (m, 4H, CH_2NH), 4.10 (t, 4H, *J* = 5.4 Hz, CH_2O), 6.84-7.83 (m, 8H, aryl H), 8.08 (br, 2H, NH).

Anal. Calcd. for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.90 ; H, 7.70 ; N, 7.00.

Synthesis of the Macrocyclic Dithiodiamides **7a-d**.

General Procedure.

Phosphorus pentasulfide (Method A) or Lawesson's reagent (Method B) and a weight equivalent of Silica gel (Silica gel 60, particle size 0.2-0.6 mm) were crushed together so as to form an intimate mixture. 2-3 Equivalents of the latter was mixed with on equivalent of the appropriate macrocyclic diamides **3** in a beaker. The beaker was then exposed to microwave irradiation (700 W) for 30 min. [Method A] or for 15 min. [Method B]. The residue was extracted with boiling acetic acid. After cooling and dilution with water the precipitate formed was collected and crestallized from the proper solvent to give yellow crystals of **7**.

Compounds **7a**-**7c** were obtained as yellow crystals; **7a**, mp. 222-223 °C lit. [32] mp. 220 °C; **7b**, mp. 217-219 °C lit. [32] mp. 216-218 °C; **7c**, mp. 198-200 °C lit. [32] mp. 191-193 °C.

Compound **7d** was obtained as yellow crystals (recrystallized from dil. acetic acid); mp. 222-24 °C, MS (EI): m/z (%) 428 [M^+, 6%], 395 (56%), 363 (13%), 178 (28%), 137 (100%); IR (cm^{-1}) 3314 (NH), 1543 (C=S); ^{1}H NMR ($CDCl_3$): δ 1.47-2.22 (m, 10H, CH_2CH$_2$NH, OCH$_2$(CH_2)$_4$CH$_2$O), 3.97 (br, 4H, CH_2NH), 4.13 (br, 4H, CH_2O), 6.98-8.52 (m, 8H, aryl H), 9.49 (br, 2H, NH).

Anal. Calcd. for $C_{23}H_{28}N_2O_2S_2$: C, 64.45; H, 6.58; N, 6.54. Found: C, 64.70 ; H, 6.40 ; N, 6.30.

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