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Novel synthesis of the 2-azaanthraquinone alkaloid, scorpinone, based on two microwave-assisted pericyclic reactions

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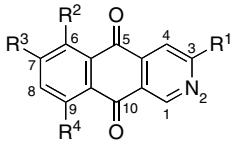
Abstract

The total synthesis of the 2-azaanthraquinone alkaloid, scorpinone (**4**), isolated from the mycelium of a *Bispora*-like tropical fungus, has been completed in nine steps. The two key steps involve a microwave-assisted thermal electrocyclic reaction for the synthesis of an 8-oxygenated isoquinoline skeleton from a 1-aza 6π-hexatriene system, and a regioselective microwave-assisted [4+2] cycloaddition for the construction of a 2-azaanthraquinone framework.

Keywords: Microwave; Electrocyclic reaction; [4+2] Cycloaddition; 2-Azaanthraquinone; Scorpinone

Recently, much attention has been paid to a family of naturally occurring 2-azaanthraquinones having benz[*g*]isoquinoline-5,10-dione (Fig. 1). Several biological activities of this class of compounds have been reported. For example, the simple azaanthraquinone **1**[1] exhibits antimalarial activity and trypanocidal activity against *Trypanosoma congolense*. Bostrycoidin (**2**)[2] also shows antibiotic activity against the tubercle bacillus. In 2001, Miljkovic and co-workers[3] isolated a new 2-azaanthraquinone, scorpinone (**4**), from the mycelium of a *Bispora*-like tropical fungus. The structure was elucidated by the analysis of X-ray and 2D NMR spectral data.

Because of the physiological importance of 2-azaanthraquinones, several methods have been developed for the synthesis of scorpinone (**4**). Cameron[4] attempted a synthetic study of azaanthraquinone derivatives by the cycloaddition of isoquinoline-5,8-dione with 1,1-dimethoxyethene to give scorpinone (**4**) in low yield as a by-product. The same group also developed a synthetic method for the synthesis of scorpinone[5] using the Houben–Hoesch reaction (intermolecular Friedel–Crafts reaction) of 3-cyano-4-benzoylpyridines. Krapcho[6] reported the syntheses of an azaanthraquinone skeleton in which the key step was an intermolecular Friedel–Crafts reaction of a 4-benzylnicotinic acid derivative in the



benz[*g*]isoquinoline-5,10-dione
1: R^1=H, R^2=R^3=R^4=H
bostrycoidin
2: R^1=Me, R^2=OH, R^3=OMe, R^4=OH
6-deoxybostrycoidin
3: R^1=Me, R^2=H, R^3=OMe, R^4=OH
scorpinone
4: R^1=Me, R^2=H, R^3=R^4=OMe

Fig. 1.

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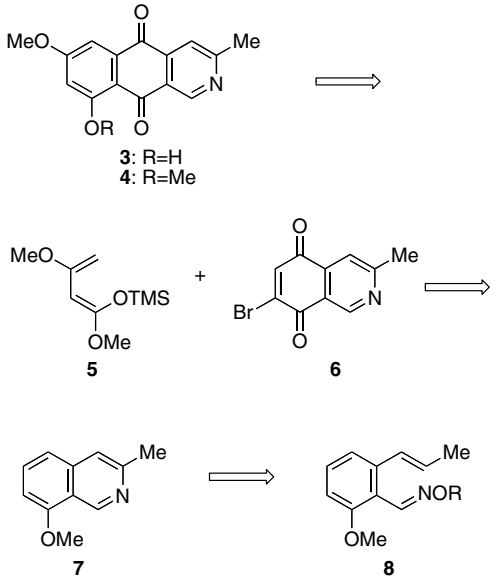
presence of fuming sulfuric acid. De Kimpe published an effective synthesis of 2-azaanthraquinones via the ammonia-induced cyclization of 2-acetonyl-3-bromomethyl-1,4-naphthoquinones[7] or 3-phenoxymethyl-2-acetonyl-1,4-naphthoquinone,[8] where the leaving group is a bromo atom or a phenoxide moiety, respectively.[9,10]

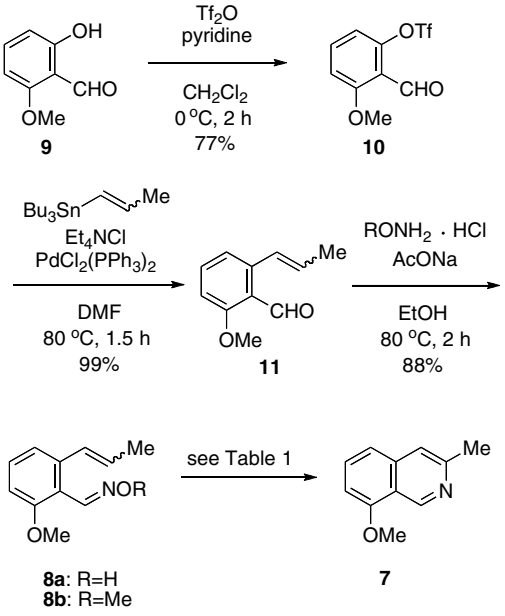
In the course of our studies, we have developed the syntheses of biologically active condensed heterocyclic compounds, including natural products, based on a thermal electrocyclic reaction[11–13] of either hexatriene[14–16] or azahexatriene[14,15,17] systems incorporating a principal aromatic or heteroaromatic moiety. In this Letter, we present a new approach to the synthesis of scorpinone (**4**) using two pericyclic reactions as a key step. In a retro-synthetic analysis (Scheme 1), we envisaged that scorpinone (**4**) could be derived from the known 6-deoxybostrycoidin (**3**), which can be obtained by a regioselective Diels–Alder reaction of an oxygenated diene **5**[18] with a 7-bromoisoquinoline-5,8-dione **6**. An 8-oxygenated isoquinoline **7** as a precursor of the isoquinoline-5,8-dione **6** might be obtained by a thermal electrocyclic reaction of *o*-alkenylbenzaldoxime **8** derived from the cleavage of the 2,3-bond of isoquinoline frameworks by using an 1-azahexatriene system.

As shown in Scheme 2, the 2-propenylbenzaldoxime **8a** was prepared from 2-hydroxy-6-methoxybenzaldehyde (**9**)[19] in three steps as follows. The treatment of 2-hydroxybenzaldehyde **9** with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine afforded triflate **10**,[20] which was subjected to Stille reaction with propenyl tributylstannane[21] in the presence of $PdCl_2(PPh_3)_2$ to give the 3-propenylbenzaldehyde **11**. Aldoxime **8a** was obtained by treating **11** with hydroxylamine.

Next, a thermal electrocyclic reaction of an isomeric mixture of the propenyl group of benzaldoxime **8a** (cis:trans = 2:1)[21] was examined in 1,2-dichlorobenzene at 180 °C to afford the desired isoquinoline **7** in low yield together with oxazepine **12** as a major product (Table 1, entry 1). The same compounds were also obtained from a thermal electrocyclic reaction using an isomeric mixture of the propenyl group of **8a** (cis:trans = 1:5.7)[21] by employing identical reaction conditions (entry 2). Thus, the generation of oxazepine **12** is not based on the geometry of the propenyl group. We attempted to perform the same cyclization using the benzaldoxime methyl ether **8b**, prepared from aldehyde **11** with hydroxylamine. As depicted in entries 3 and 4, these reactions provided isoquinoline **7** in moderate yield without the formation of **12**. Recently, we have achieved the total synthesis of furoisoquinoline alkaloid, TMC-120B[22] using a microwave-assisted thermal electrocyclic reaction as a key step. In a similar way, the microwave-assisted electrocyclic reaction of benzaldoxime methyl ether **8b** was performed to study the effects of microwave irradiation using the same substrate. Initially, we examined the effect of reaction temperature (entries 5–8). The best result was obtained when the reaction was performed at 180 °C for 10 min in 1,2-dichlorobenzene (entry 7). Next, we examined the effect of replacing 1,2-dichlorobenzene with a different solvent, that is, toluene, bromobenzene or DMF (entries 9–17). Furthermore, the reaction was performed using a conventional procedure under optimal conditions determined from the microwave irradiation reaction for each solvent (entries 7, 11, 14 and 17). These reactions did not go to completion and the starting material **11** was recovered with isoquinoline **7**. Based on these results, 1,2-dichlorobenzene was the best solvent for the reaction. Furthermore, microwave-assisted conditions were more effective than conventional conditions in terms of increasing the yield (54→71%) and decreasing the reaction time (30→10 min).

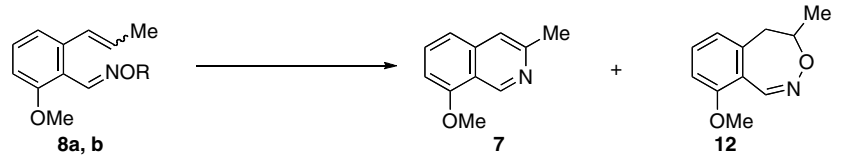


Scheme 1.



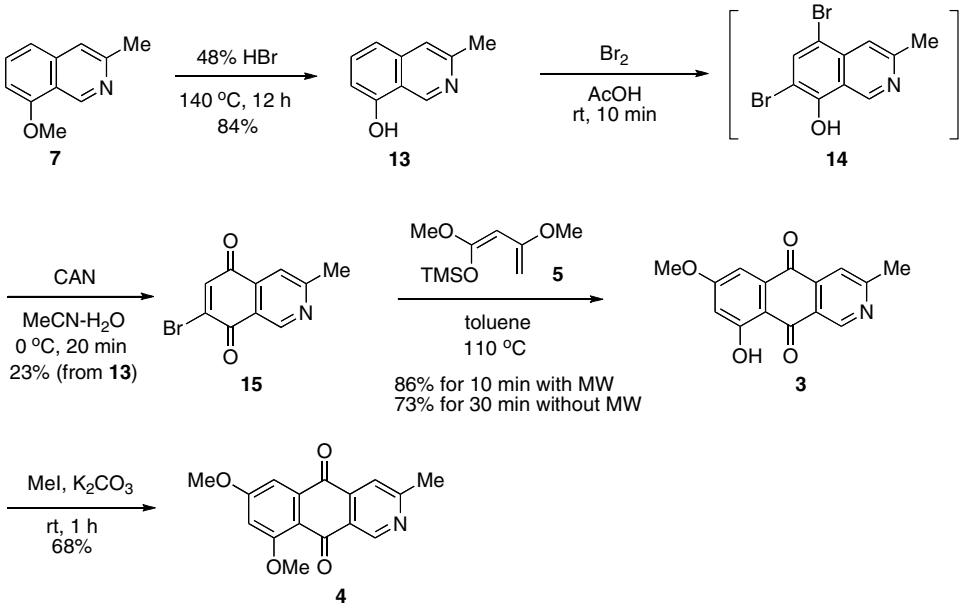
Scheme 2.

Table 1
Effect of the microwave on the thermal electrocyclic reaction



Entry	R[a]	Solvent	Temp (°C)	Time (min)	Microwave irradiation		Conventional method	
					Yield (%) of isoquinoline	Yield (%) of SM	Yield (%) of isoquinoline	Yield (%) of SM[c] or **12**[d]
1	H		180	30			23	0(61[d])
2	H[b]		180	30			23	0(61[d])
3	Me	1,2-Dichlorobenzene	180	30			54	—
4	Me[b]		180	30			41	—
5	Me		150	10	46	5	—	—
6	Me	1,2-Dichlorobenzene	150	15	48	—	—	—
7	Me		180	10	71	—	41	7
8	Me		210	10	59	—	—	—
9	Me		150	10	25	61	—	—
10	Me	Toluene	150	75	56	—	—	—
11	Me		180	10	59	—	0	100
12	Me		150	10	44	9	—	—
13	Me	Bromobenzene	150	20	51	—	—	—
14	Me		180	10	64	—	21	31
15	Me		150	10	32	15	—	—
16	Me	DMF	150	20	51	—	—	—
17	Me		180	10	67	—	34	21

[a] Cis:trans ratio of propenyl group = 2:1.
[b] Cis:trans ratio of propenyl group = 1:5.7.
[c] SM: starting material.
[d] Yield (%) of oxazepine **12**.



Scheme 3.

The obtained 8-methoxyisoquinoline **7** was heated at 140 °C in 48% HBr to give the 8-hydroxyisoquinoline **13** (Scheme 3). The bromination of **13**, based upon the procedure of Choi,[23] was performed to give the 5,7-dibromoisoquinoline **14**. However, compound **14** was very unstable. Therefore, 5,7-dibromoisoquinoline **14** was immediately oxidized with cerium ammonium nitrate (CAN)[24] to afford the isoquinoline-5,8-dione **15**. Subsequently, Diels–Alder reaction of **15** with diene **5** in toluene at 110 °C gave the known 6-deoxybostrycoidine (**3**)[25] with the elimination of a methoxy group. In addition, the microwave-assisted cycloaddition reaction of **15** with diene **5** was attempted. The microwave-irradiated condition was more effective than the conventional condition for improving the yield (73→86%) and decreasing the reaction time (30→10 min) as reported previously in a review.[26] Finally, the alkylation of **3** with MeI in the presence of K_2CO_3 afforded scorpinone (**4**). Physical and spectroscopic analysis of synthetic scorpinone[27] (**4**) agreed with those of natural scorpinone[3] in all respects.

In conclusion, we achieved the total synthesis of scorpinone (**4**) using a novel nine-step reaction scheme via the construction of an 8-oxygenated isoquinoline skeleton based on the microwave-assisted thermal electrocyclic reaction of a 1-azahexatriene system. Regioselective cycloaddition using microwave irradiation then afforded the azaanthraquinone framework. Furthermore, we demonstrated that microwave irradiation plays a useful supporting role for both pericyclic reactions in terms of improving yield and reducing the reaction time.

Acknowledgement

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27. Synthetic scorpinone, mp 193–194 °C (MeOH) (lit.,[3] 195 °C). IR (ATR) ν: 1673, 1654, 1592 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.75 (3H, s), 4.00 (3H, s), 4.03 (3H, s), 6.84 (1H, d, $J = 2.6$ Hz), 7.43 (1H, d, $J = 2.6$ Hz), 7.82 (1H, s), 9.41 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 183.4, 180.5, 165.0, 164.1, 162.7, 149.7, 137.5, 137.0, 117.5, 115.6, 105.4, 103.5, 56.6, 56.0, 25.0. MS (EI) *m*/*z*: 283 (M^+). HR-MS (EI) *m*/*z*: 283.0840, calcd for $C_{16}H_{13}NO_4$: 283.0845.