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A Microwave Synthesis of the *cis* and *trans* Isomers of 3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one: The influence of Solvent and Power Output on the Diastereoselectivity

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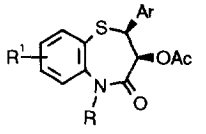
Abstract. A diastereoselective one-pot synthesis of the *trans*- and *cis*-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one nucleus, a key intermediate in the preparation of the calcium channel blocker Diltiazem, is carried out under microwave irradiation in an open vessel. Control of the diastereoselectivity is achieved by varying the reaction time and power output as well as the nature of the solvent.

Calcium channel blockers are important cardiovascular drugs in the management of angina pectoris and hypertension.[1] Most of these agents structurally belong either to the family of 1,4-dihydropyridines, the phenylalkylamines (*e.g.*Verapamil) or to a third class, the 1,5-benzothiazepin-2-ones represented by Diltiazem.[2]

Our interest in the field[3] led us to explore the use of microwave energy for the synthesis of 1,4-dihydropyridines and have found remarkable decreases in the times required to prepare either 3,5-symmetrically substituted[4] or 3,5-unsymmetrically substituted 1,4-dihydropyridines, imidazo[1,5-*a*]pyrimidines and imidazo[1,2-*a*]pyrimidines.[5] Additionally, higher yields have been obtained in most cases with high purity for most compounds.These advantages, which have also been reported for other microwave assisted syntheses,[6] prompted us to investigate the use of the technique for the preparation of the 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **4**, the structural core of Diltiazem and analogues.[7] In this case, the diastereoselective formation of the *cis*- or *trans*-isomers represented an interesting challenge, since chemical selectivity has only rarely been observed in organic syntheses carried out under microwaves conditions, in either open or sealed vessels.[8]



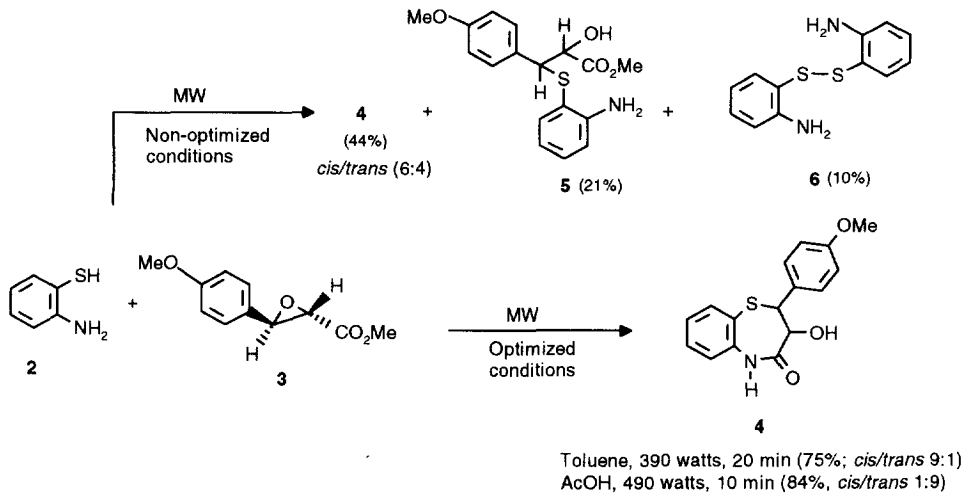
Diltiazem Ar = *p*-MeO-C_6H_4
R = $CH_2CH_2N(CH_3)_2$
R^1 = H

In the present paper, we report on the results of a microwave-assisted preparation of both the *cis*- and the *trans*-isomers of **4**, using one-pot procedure, which was optimized with the aid of a SIMPLEX program OPTIMUS.[9]

The traditional one-pot preparation of racemic **4**, a key intermediate for Diltiazem and analogues, involves the reaction of 2-aminothiophenol **2**, with the epoxide **3** at 160 °C (Scheme 1). Although the method is simple, the yield is only 30% and in some cases even lower, depending on the substituents on the 2-aminothiophenol or on the oxirane aryl moiety.[7a,10,11] These low yields are associated with the prolonged reaction times required, which favour the oxidation of **2** to the corresponding disulphide **6** which, in some cases, can be the main reaction product.

From previous experience, we felt that we could profit from the short reaction times associated with microwave energy in a one-pot synthesis of **4**, as the formation of **6** would be minimized. Initial experiments, whereby a mixture of 2-aminothiophenol **2** and *trans*-3-(4-methoxyphenyl)glycidate **3** in toluene was irradiated in a microwave oven at 350 watts for 10 min gave the disulphide **6** in only low amounts (10%), with the main products being the hydroxy ester **5** (21%) and the benzothiazepin-4(5*H*)-one **4** (44%).

Although the attack of the 2-aminothiophenol on the oxirane ring is usually regioselective, with only a single regioisomer being obtained either under classical[12] or microwave heating, the ^{1}H NMR of the benzothiazepinone **4**, obtained from the non-optimized reaction of **2** and **3**, clearly showed the presence of a mixture of diastereoisomers, with the *cis*-stereoisomer being the major component (6:4). In order to improve the diastereoselectivity we performed a basic SIMPLEX optimization[13] using OPTIMUS. The process was carried out in an open vessel with toluene as solvent, and using power, reaction time and the molar quantities of **3** as variables.

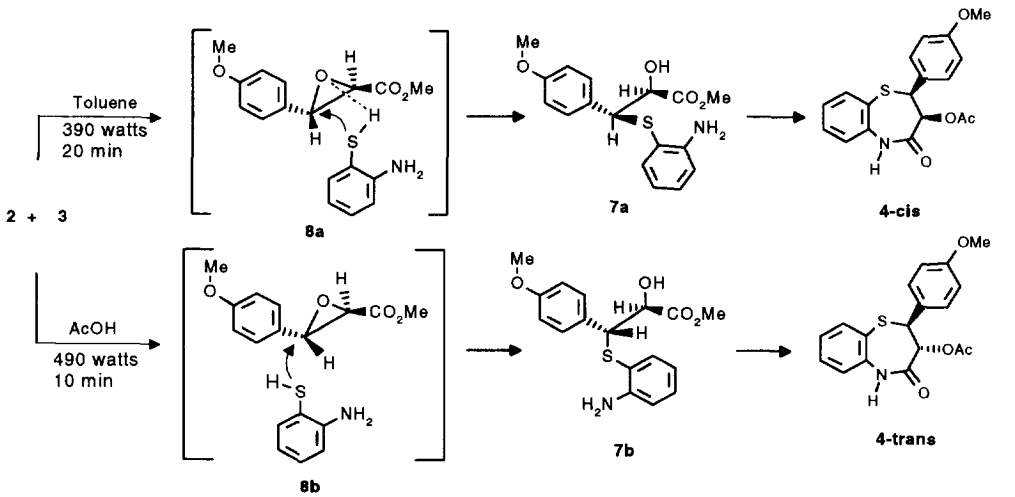


Scheme 1

After optimization the diastereoselective preparation of **4** was achieved in a yield of 75% and a *cis/trans* ratio of 9:1, by irradiating for 20 min at a power output of 390 watts.[14a,15] Although the power could be raised up to 500 watts without appreciable decomposition of the products, increasing amounts of the *trans*-isomer were observed.

The reaction was also examined in the presence of catalytic amounts of acetic acid, since the tendency for acid catalysis to predominantly give the *cis*-isomer is well known.[12] The ^{1}H NMR of the crude however, showed an unexpected appreciable change in the diastereoselectivity (*cis*: $J_{H2\text{-}H3}$=7 Hz; *trans*: $J_{H2\text{-}H3}$=11 Hz), with the *trans*-stereoisomer now being the main product (6:4). Optimization of the process as described, gave an 84% yield of the benzothiazepinone and a 1:9 ratio for the *cis/trans* diastereoisomers when the reaction mixture was irradiated at 490 watts for 10 min.[14b] Longer reaction times or higher power output resulted in partial decomposition of the reaction products, with concomitant lowering of yields.

The effect of the different reaction conditions can be rationalised by refeering to Scheme 2. As has been described for related procedures,[16] the reaction variables, in our case mainly solvent and microwave energy, direct the stereochemistry of the ring opening of the glycidic ester **3**. Thus, when the process is carried out in a nonpolar solvent such as toluene, a hydrogen bond between the thiophenol and the oxygen of epoxy group is formed, and hence in complex **8a** cis-opening predominates, yielding the *threo*-ester **7a** which cyclizes producing the *cis*-isomer. On the contrary, when the reaction is performed in the presence of acetic acid, a trans-attack, as represented in complex **8b**, is likely to predominate. In such case the *erythro*-ester **7b** would form, which on cyclizing would give the *trans*-isomer. High energy irradiation, would also favour this process.



Scheme 2

In conclusion, we have demonstrated that microwave irradiation is synthetically useful in the one-pot synthesis of the Diltiazem related 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one. The diastereoselectivity of the process is achieved by varying the reaction time and the power output and time, as well as the nature of solvent. Furthermore, the possibility of performing the stereocontrolled process in an open flask using a domestic microwave oven makes it a cheap and efficient alternative to conventional procedures.

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14. (a) **4-cis**: A mixture of **2** (0.13 g, 1.04 mmol) and **3** (0.20 g, 0.96 mmol) in toluene (0.5 mL) was purged with argon and irradiated in a microwave oven in an open erlenmeyer flask for 22 min at 390 watts. The solvent was then evaporated under reduced pressure and the residue chromatographed on silica gel. Elution with CH_2Cl_2:EtOAc:hexane (6:0.5:3.5) afforded 0.21 g (75%) of a 9:1 mixture of *cis/trans* isomers (HPLC, Spherisorb ODS, 4.6 mm; eluent: MeOH/H_2O (7:3); flow rate: 0.5 mL/min; absorbance: 244 nm; time from injection: *trans* (10.19 min), *cis* (13.17 min).

    (b) **4-trans**: A mixture of **2** (0.35 g, 2.8 mmol) and **3** (0.45 g, 2.16 mmol) in glacial AcOH (0.5 mL) was purged with argon and irradiated in a microwave oven in an open erlenmeyer flask for 10 min at 490 watts. Work-up as indicated above for **4-cis** afforded 0.58 g (83%) of a 9:1 mixture of *trans/cis* isomers.
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