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Microwave Assisted, Rapid Synthesis of Novel Benzothiazepine

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Abstract

The 1, 5-benzothiazepine moiety is a privileged class of pharamacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities. Owing to their well known bioactivities, the synthesis and chemical transformations of various groups of benzothiazepines have been studied and the procedures used have also been summarized. A series of novel substituted benzothiazepines were prepared by the reaction of substituted sufanyl derivatives with 2-amino phenol. The structures of the synthesised products were confirmed by NMR.

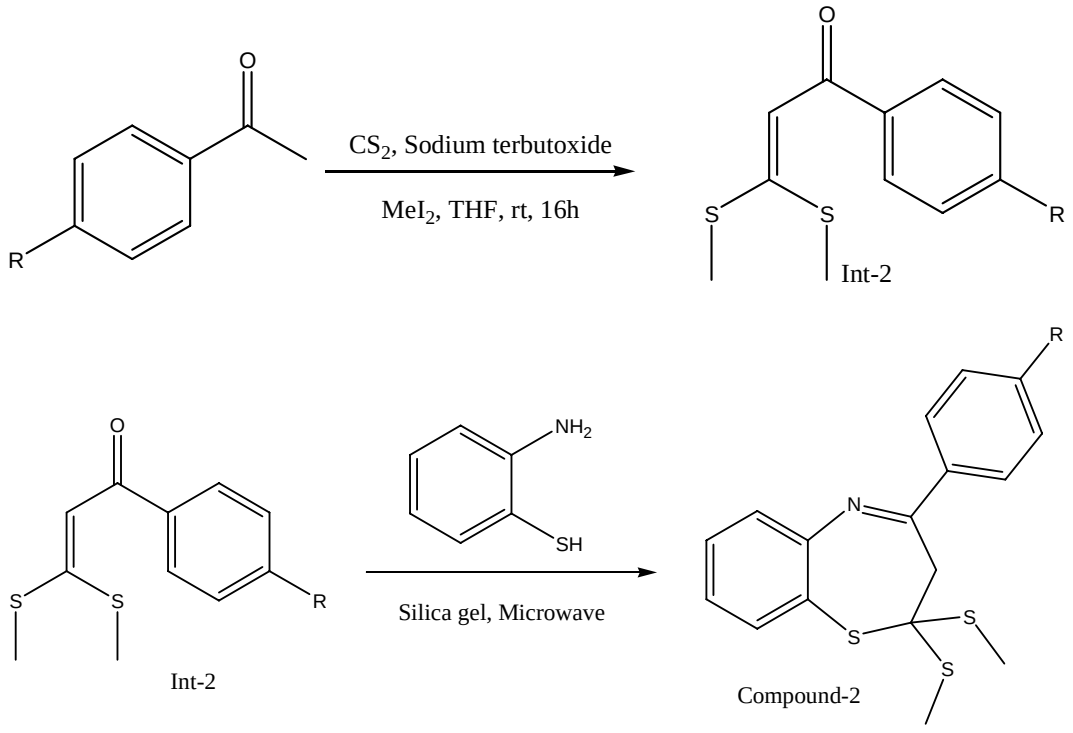
Keywords: Benzothiazepines, Bioactivities, Pharamacophore, 2-amino Phenol

Introduction

Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with low rate of new therapeutic discovery. Information on the human genome, its sequence and what it encodes has been hailed as a potential windfall for drug discovery, promising to virtually eliminate the bottleneck in therapeutic targets that has been one limiting factor on the rate of therapeutic discovery. However, data indicates that "new targets" as opposed to "established targets" are more prone to drug discovery project failure in general. This data corroborates some thinking underlying a pharmaceutical industry trend beginning at the turn of the twenty-first century and continuing today which finds more risk aversion in target selection among multi-national pharmaceutical companies. It is very unlikely that a perfect drug candidate will emerge from these early screening runs. It is more often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical

features, one or more pharmacophores can then be developed. At this point, medicinal chemists will attempt to use structure-activity relationships (SAR) to improve certain features of the lead compound.

Several naturally occurring and synthetic benzofuran derivatives are known to be associated with biological and pharmacological activities such as anti-inflammatory, anti-implantation etc. The 1, 5-benzothiazepines scaffold is extremely versatile and features in a great number of famous drugs. Currently 1, 5-benzothiazepines are being used as coronary vasodilators, as calcium antagonists and as antidepressants. The 1, 5-benzothiazepine moiety is a privileged class of pharamacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities. The high biological activity of these molecules prompted us to study the synthesis of novel molecules of these class. In the present study, we report the synthesis of novel benzothiazepines in Green chemical approach. The overall scheme is given below.



R= H, OMe, Me, Cl, Ph

Materials

Reaction vessels and other glass equipment used for the experiments were thoroughly dried in an oven and cooled under a stream of dry nitrogen just prior to use. All reagents, solvents were purchased from Sigma-Aldrich and were used as supplied. Thin-layer chromatography (TLC) was performed on 0.25 mm pre coated silica gel 60 F254 aluminum sheets and column chromatography on silica gel 60 (0.063-0.2 mm) as well as silica gel 60 (<0.063 mm), products of Merck & Co. (Darmstadt, Germany).

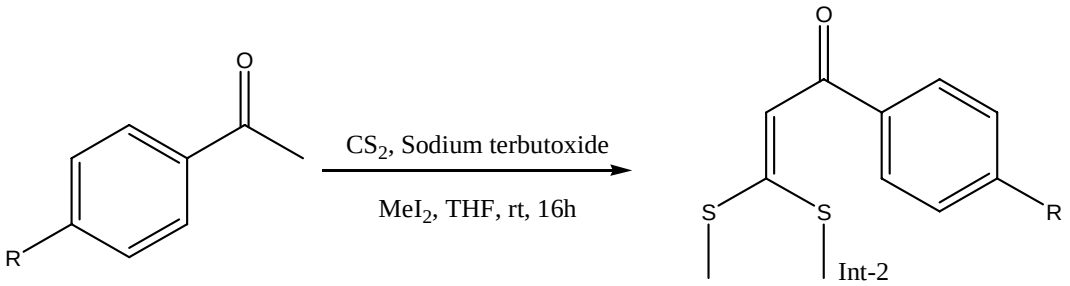
Experimental

General

All bp's and mp's were uncorrected. The IR spectra were scanned with a Perkin-Elmer 783 spectrophotometer and only the pertinent values were expressed, in cm^{-1}. The C^{13} & H^{1}NMR spectra were recorded, with a Bruker (500 MHz) spectrometer, with TMS as internal standard.$CDCl_3$ was used as the solvent. The chemicalshift (d) and coupling constant (J) values were expressed in ppm and Hz only. The GLC analyses were carried out on a Shimadzu GC-7A chromatograph fitted with a flame ionization detector and glass packed column for routine analysis and a capillary column for the determination of isomeric compositions. The mass spectra (EI) was recorded at 70 eV with a Shimadzu GC-MS QP-1000A spectrometer. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

Synthesis of Sufanyl Derivative of Acetophenone

Sodium tert-butaoxide (10mmol) was taken in a dried round bottom flask with side arm adaptor and septum. The flask was purged three times with Nitrogen and subsequently immersed into an ice bath (0 ^{o}C). 100ml of dry THF was added and stirred. Acetophenone was added and followed by CS_2, then MeI_2 added and allowed to stirred at rt for 16 hrs. The reaction was monitored by TLC. After the completion of the reaction, the solvents were distilled out and the product obtained as crystalline solid. The melting point was determined, which was matching with the literature value.

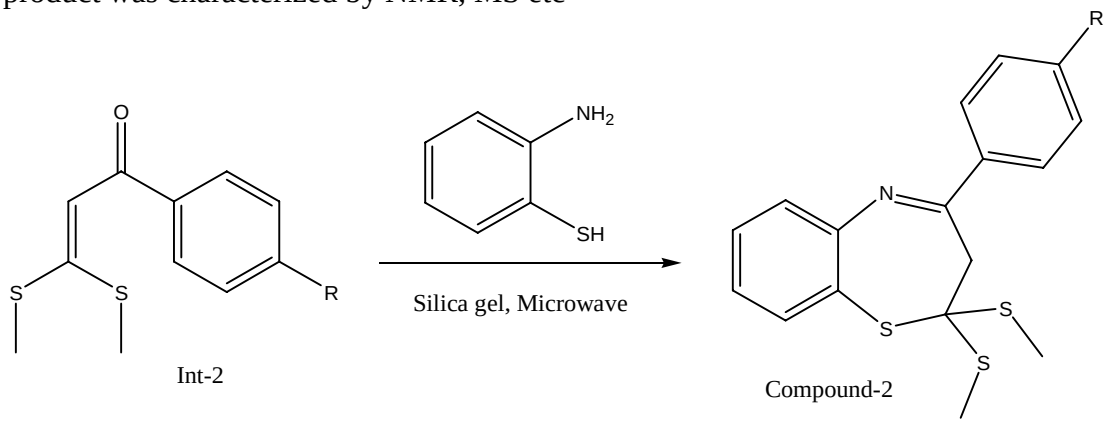


R= H, OMe, Me, Cl, Ph

Synthesis of Substituted Benzothiazepines

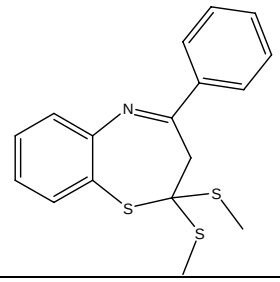
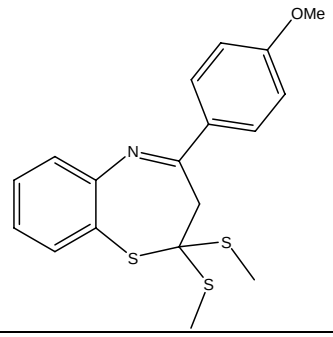
The substituted sulfanyls (10mmol) were taken in a dried round bottom flask with side arm adaptor and septum. The flask was purged with nitrogen and connected to a mercury bubbler and 10g of dry silica gel was added to the flask. 2-amino benzothiol was added through the side arm, using a solid addition funnel. Both reactant was taken in same equalent. The reaction mixture was kept under microwave irradiation, at 70^{o}C for half an hour. The reaction was further monitored with TLC and after completion of reaction, crude product extracted in chloroform. The organic layer was separated and the aqueous layer extracted two times with ethyl acetate. The organic portions combined and dried with anhydrous sodium sulphate. The product was concentrated by rotary evaporator and purified by column chromatography. The

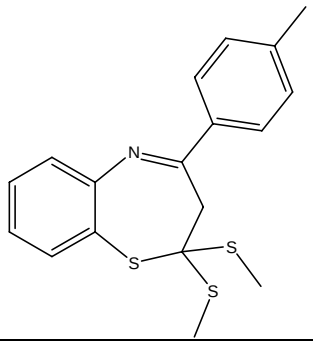
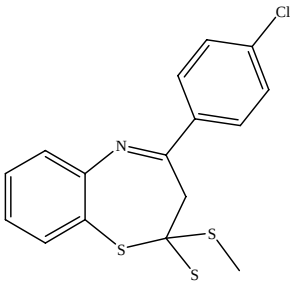
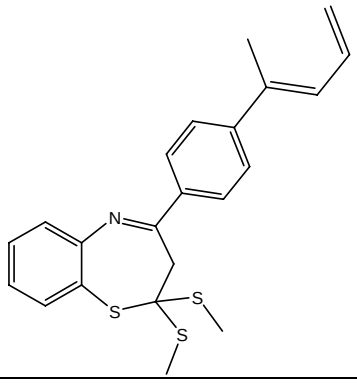
product was characterized by NMR, MS etc



R= H, OMe, Me, Cl, Ph

Synthesised Compounds

Structure	NMR
	^{13}C (CDCl3)- 164.1, 127.9, 122.2, 115.9, 129.1, 128.9, 116.3, 21.8, 9.9 ^{1}H -7.57, 7.20, 6.57, 5.2, 6.49, 2.11
	^{13}C (CDCl3)- 164.6, 152.9, 127.9, 122.2, 115.9, 129.1, 128.9, 116.3, 21.8, 9.9 ^{1}H -7.57, 7.20, 6.57, 5.2, 6.49, 2.09

	^{13}C (CDCl3)- 164.5, 155.7, 127.9, 122.2, 115.9, 129.1, 128.9, 116.3, 21.8, 9.9 ^{1}H -7.89, 7.28, 6.57, 5.2, 6.49, 2.07
	^{13}C (CDCl3)- 164.3, 154.3 127.9, 122.2, 115.9, 129.1, 116.4, 21.8, 9.9 ^{1}H -7.37, 7.22, 6.57, 5.21, 6.49, 2.09
	^{13}C (CDCl3)- 164.1, 127.9, 122.2, 115.9, 129.1, 128.9, 116.3, 21.8, 9.9 ^{1}H -7.57, 7.20, 6.57, 5.2, 6.49, 2..09

Result and Discussion

Several naturally occurring and synthetic benzofuran derivatives are known to be associated with biological and pharmacological activities such as anti-inflammatory, anti-implantation etc. The 1, 5-benzothiazepines scaffold is extremely versatile and features in a great number of famous drugs. We have developed a general solid-phase route to benzothiazepine derivatives which allows the incorporation of a wide variety of substituents on the benzene ring of benzothiazepine. In summary, we have developed a new methodologies for the synthesis of 1, 5-benzothiazepines by microwave irradiation. Our method has many advantages over existing methods, including moderate yield, simple work-up, shorter reaction span, no side reactions no critical purification method. This procedure represents a convenient, economic and environmentally friendly process for the synthesis of 1, 5-benzothiazepines.

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