IMPACT OF MICROWAVE RADIATIONS ON MACROCYCLIZATION REACTIONS: SOLVENT FREE SYNTHESIS OF 1,4-BENZOTHIAZIN-3-ONE DERIVATIVES ON BASIC ALUMINA

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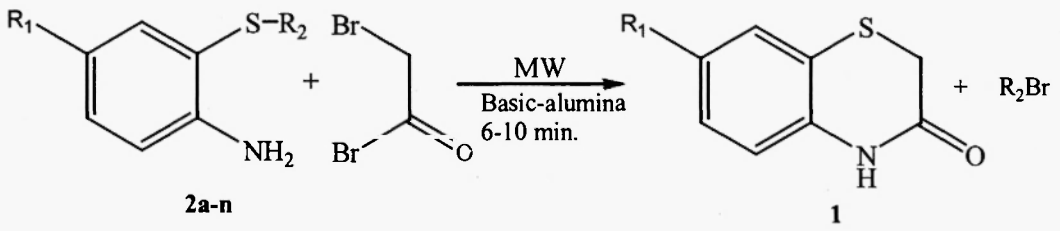
Abstract

A rapid transformation of alkyl and arylalkyl amino phenyl thioethers (2-alkylsulphanyl-phenylamine) into 7-substituted 1,4-benzothiazines in presence of basic-alumina under solvent free conditions using microwave irradiation has been described. The specific microwave effects are due to increase in polarity during the course of reaction.

Introduction

Microwave assisted organic synthesis has attracted a substantial amount of attention in recent years. The practical advantages associated with microwave-assisted reaction are enhanced reaction rates, high yields, improved selectivity and environment-friendly reaction conditions (1). Several methods have been developed for performing reaction with microwave irradiation in solution and under solvent free conditions (2). Applications of microwave irradiation in organic synthesis have seen considerable growth to improve the selectivity, rate enhancement and reduction of thermal degradative by-product. Furthermore, the combination of microwave and inexpensive mineral solid supports such as alumina, silica and clay allows the rapid and high yield of various organic molecules (3,4).

The 3-oxo-3,4-dihydro-2H-1,4-benzothiazine **1** is an important intermediate for the synthesis of various biologically active compounds (5). 2-substituted and N-alkyl bridgehead cyclo-aza derivatives of 3-oxo-3,4-dihydro-2H-1,4-benzothiazine are potential antimicrobial and antifungal agents (6). The 1,4-benzothiazine has also been reported to be central motif for various molecules which has found to posses potential Aldose Reductase inhibition (7), Ca^{2+} antagonism (8) immunomodulating properties, antagonism of α^2-andrenoreceptor (9) and anti-inflammatory activity (10). Various methods have been reported for the synthesis of 1,4-benzothiazines such as from 2-aminothiophenol (11), α-(o-Nitrophenylthio) acids (12), o-aminophenyl sulphide (13). In this paper synthesis of 1,4-benzothiazines from various 2-alkylsulphanylphenylamines (**2a-n**) under microwave radiations on basic alumina (Scheme1) are repotred.

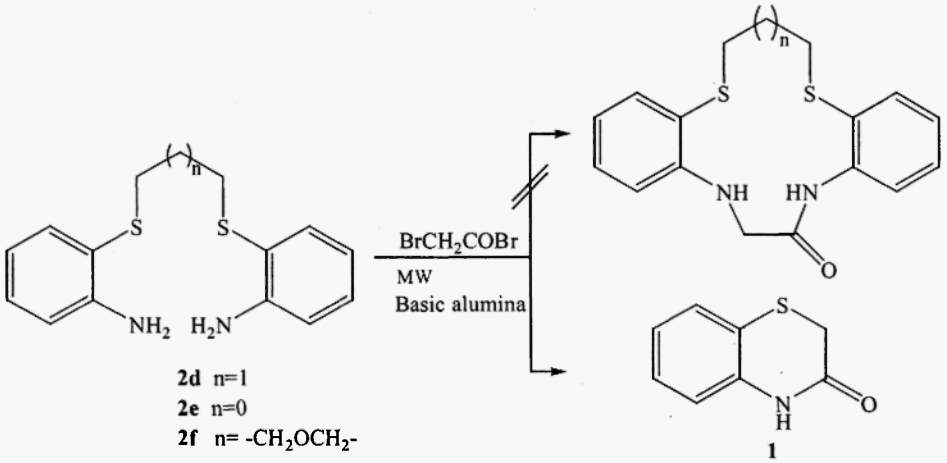


2a-n **1**

Scheme 1

Result and Discussion

The cyclization of S,S'-di(2-aminophenyl)-1,3-dithiopropane with bromoacetyl bromide using basic alumina as solid support under microwave irradiations, gave 3-oxo-3,4-dihydro-2H-1,4-benzothiazine **1** in 74% yield without forming cyclized product (Scheme 2). At the end of microwave reaction the temperature of the alumina was found be 90-100°C. The structure of **1** was characterised on the basis of spectral analysis (IR, NMR and mass spectroscopy (14). The strong peak at 1662 cm^{-1} was assigned to carbonyl (C=O) stretching vibration and N-H stretching region, due to presence of three medium to weak peaks of secondary amide moiety. Although from IR it was difficult to distinguish between the macrocycle and benzothiazine structure, a single peak at 3.4 ppm in ^{1}H NMR and ^{13}C-NMR in aliphatic region confirmed the benzothiazine structure. Which was further evidenced by El-mass spectra (m/z 164 (M-1). Beside spectral studies the final product was in agreement to reported (11) data (melting point 180-181°C found (179-180°C reported). We studied the reaction of different alkyl and aralalkylsulphanyl phenyl amines and good to excellent yields of 1,4-benzothiazines were obtained under microwave irradiations. The yield of 1,4-benzothiazines was also compared with conventional heating and low yield was obtained under similar conditions. Further use of organic bases such as Et_3N (triethylamine) in conventional method did not result in increased yield. Formations of benzyl bromide as another product from the reaction of 2f suggest that the reaction took place by cyclic mechanism as shown in Scheme 3.

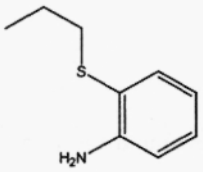
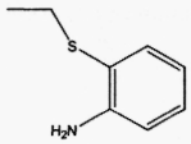
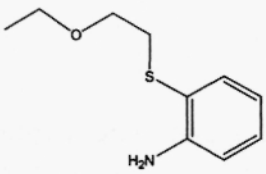


2d n=1
2e n=0
2f n= $-CH_2OCH_2-$

1

Scheme 2

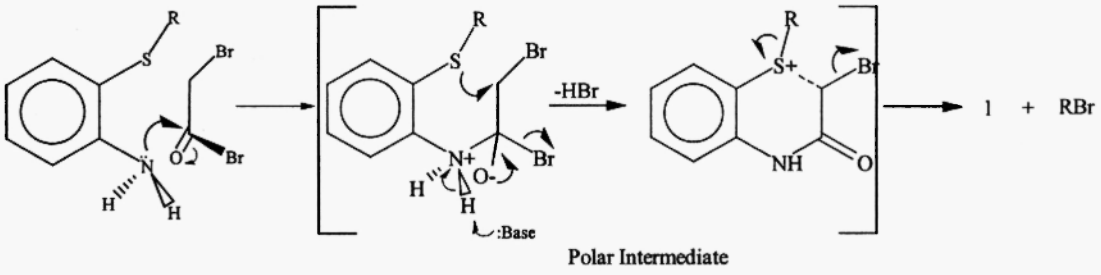
Table 1: Synthesis of 1 from 2-alkyl/arylalkyl sulphanylphenylamines

ent			Equiv. of	Microwave reaction		Conventional Method	
ry	R_2	R_1	$BrCH_2COBr$	% Yield[a]	Time min	% Yield[a]	Time h
a	CH_3	H	1.1	80	6	67	5
b	CH_2CH_3	H	1.12	78	7	64	5
c	$CH_2CH_2CH_3$	H	1.2	78	8	60	6
d	CH_3	CH_3[d]	1.15	79	7	64	6
e	$CH_2(CH_2)CH_3$	H	1.25	76	7	59	5
f	$CH_2C_6H_5$	H	1.24	72	8	62	6
g		H	2.4	74	9	64 (62)[c]	7
h		H	2.45	73	8	62	7
i		H	2.24	74	9	60	7
j	CH_3	OCH_3	1.12	75[b]	8	66	5
k	CH_2CH_3	CH_3	1.1	77[b]	6	65	5
l	CH_2CH_3	OCH_3	1.2	74[b]	5	62	5
m	$CH_2CH_2CH_3$	CH_3	1.2	72[b]	7	60	6
n	$CH_2CH_2CH_3$	OCH_3	1.24	71[b]	8	60	6

[a]yield of the isolated product. [b]yield based on gc analysis. [c]yield with $(ch_3ch_2)_3n$ base. [d]reference (15) [e]reference (16)

Increase in yield of **1** under microwave irradiation condition compared to conventional heating method is attributed to the specific polar microwave effects. These effects are due to microwave activation by the dipole–dipole interactions and increase in polarity of the system during the progress of reaction. The base partially abstracts a proton from amine and generates a partial negative charge on nitrogen. This negatively charged polar nitrogen forms an amide bond with bromoacetyl bromide. After the microwave exposure, there is significant enhancement in polarity with the formation of polar intermediates and with increased polarity of material the radiations strongly interacts with reaction intermediates and the radiation energy is transferred

rapidly to the reaction system. Subsequently with the substitution of bromide by sulfur, alkyl halide is knocked off and this strongly favours the reaction to give more polar benzothiazine during the course of reaction.



Scheme 3

Conclusion

In summary, the synthesis of 7-substituted 3-oxo-3,4-dihydro-2*H*-1,4 benzothiazine **1** from various 2-alkyl/arylalkyl sulfanyl-phenylamines under microwave irradiations on basic-alumina is convenient and fast process and it will be a better substitute to the conventional methods.

Experimental

Material and method

The 5-methyl/5-methoxy-2-alkyl/arylalkyl sulfanyl-phenylamines (**2a-n**) were prepared from respective 2-aminothiophenols and alkyl halide using sodium methoxide in methanol with slight modification of literature procedure (17). Gas Chromatograms were recorded on Shimadzu GC-14B on packed column. IR were recorded on Perkin Elmer Spectrum BX. NMR were recorded on Bruker 300MHz Instrument using tetramethylsilane as internal standard reference.

Typical Procedure For Microwave irradiation method:

2-methylsulfanyl-phenylamine (1 mmol) and $BrCH_2COBr$ (1.2 mmol) were adsorbed on the activated basic-alumina (2g) and the solid mixture in a Pyrex bottle was irradiated with domestic microwave radiations at 320 W for 6 min. at an interval of 20s. After end of the reaction cycle, ethanol was added to reaction mixture and filtered. The filtrate was concentrated and residue on purification by column chromatography using silica gel yielded 80% of compound **1**. In similar way other substituted derivatives were synthesized (Table 1).

Typical Procedure For Conventional Method:

2-methylsulfanyl-phenylamine (1.0mmol), K_2CO_3 (1.0mmol) in acetonitrile (30ml) were refluxed at the boiling point of acetonitrile and a solution of $BrCH_2COBr$ (1.2mmol) in acetonitrile (10ml.) was added drop-wise. Reaction mixture was refluxed with constant stirring for 5hrs. On completion of reaction acetonitrile was

removed under reduced pressure, obtained product was taken in water, floating solid was filtered, dried and purified by flash chromatography over silica gel. Pure crystalline fine needle shaped product was obtained in 67% yield.

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14 Analytical data for 3-oxo-3,4-dihydro-2*H*-1,4 benzothiazine (1a):
White crystalline solid. mp 181°C. IR (KBr pallets, ν/cm^{-1}): 3313-3114w (N-H sec-amide str.), 3057w (Ar-H str.), 2971,2911w (AliphaticC-H asym. & sym. str.), 1662s (C=O str.), 1583m(Ar ring puckering), 1479s, 1385m (Alphatic C-H bending), 740s (Ar-H bending). ^{1}H NMR ($CDCl_3$, 400MHz, δ ppm): 9.2 (s, 1H, N-H), 7.31 (d, 1H, J=7.69, Ar C5-H), 7.1 (t, 1H J=7.55, Ar C6-H), 7.0 (t, 1H J=7.55, Ar C7-H), 6.92 (d, 1H J=7.55, Ar C8-H), 3.4 (s, 2H, -CH_2-). ^{13}C NMR ($CDCl_3$, δ ppm): 166.5 (C3), 136.4 (C10), 127.7 (C6), 127.2 (C7),

123.9 (C8), 120 (C9), 117.4 (C5) and 21.9 (C2). EI-MS (m/z): 164, 135 (100%). Elemental analysis (%) calculated for C_8H_7NOS; C 58.18, H 4.24, N 8.4, S 19.39, O 9.6 found C 58.29, H 4.23, N 8.22.

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