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Various approaches for synthesis of some important benzothiaiazepines

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ABSTRACT

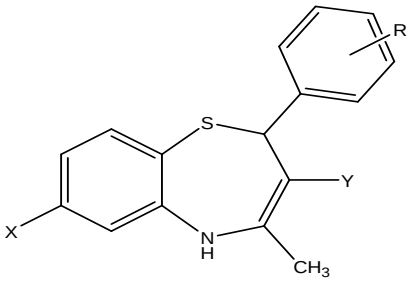
Benzthiazepines are important group of 7- membered heterocyclics which posses hypertensive, cardiovascular, antipsychotic activities.

Key word: Benzothiazepine, hypertension, cardiovascular activity, antipsychotic, Diltiazem.

INTRODUCTION

Benzothiazepines

The versatile application of benzothiazepines in the treatment of ailments of cardiovascular system such as coronary vasodilation, hypertension etc. enthused great interest in a detailed study of this class of compounds. These compounds have various activities such as antimicrobial activity, cytotoxic activity, cardiovascular activities, antipsychotic activity etc.The basic structure of benzothiazepines can be given as –



Benzothiazepines

Fig;1- Benzothiazepine nucleus

There are various benzothiazepines which have been synthesized and tested for biological activities- Diltiazem S(DTZ) is a 1,5 benzothiazepine calcium channel blocker synthesized in 1971[1]. Nicardipine (a dihydropyridine derivative) reduces the three hyperactivities, verapamil (a diphenylalkylamine derivative) reduces only oxolinic acid hyperactivity, and diltiazem (a benzothiazepine derivative) was active except in the MAOI-reserpine test. Levome-promazine used as a reference drug reduced the three hyperactivities[2]. The renal effects of the calcium entry-blocking drugs diltiazem, nifedipine, verapamil and nitrendipine are reviewed. Although nifedipine stimulates plasma renin activity on a short-term basis, none of the calcium entry blockers produces a clinically significant sustained effect on any of the components of the reninangiotensin-aldosterone system.

A series of calcium antagonists were used to study their blocking effect on high potassium-induced calcium uptake into rat cortical synaptosomes; these antagonists were classified into five groups: (1) dihydropyridine group (i.e. nifedipine and nitrendipine), (2) benzothiazepine group (i.e. diltiazem), (3) phenylalkylamine group (i.e. verapamil and D600), (4) phenothiazine group (i.e. trifluoperazine) and (5) diphenylpiperazine group (i.e. flunarizine and cinnarizine)[3].

Although all of the calcium entry blockers effectively lower blood pressure, none adversely affects renal function; glomerular filtration rate and effective renal plasma flow are maintained. Diltiazem may increase glomerular filtration rate via attenuation of the intrarenal effects of angiotensin II or norepinephrine[4].

Diltizem is a non-dihydropyridine (DHP) member of the group of drugs known as benzothiazepines. The structure of Diltizem can be given as[5]-

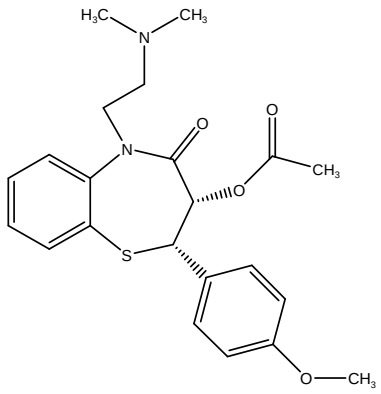


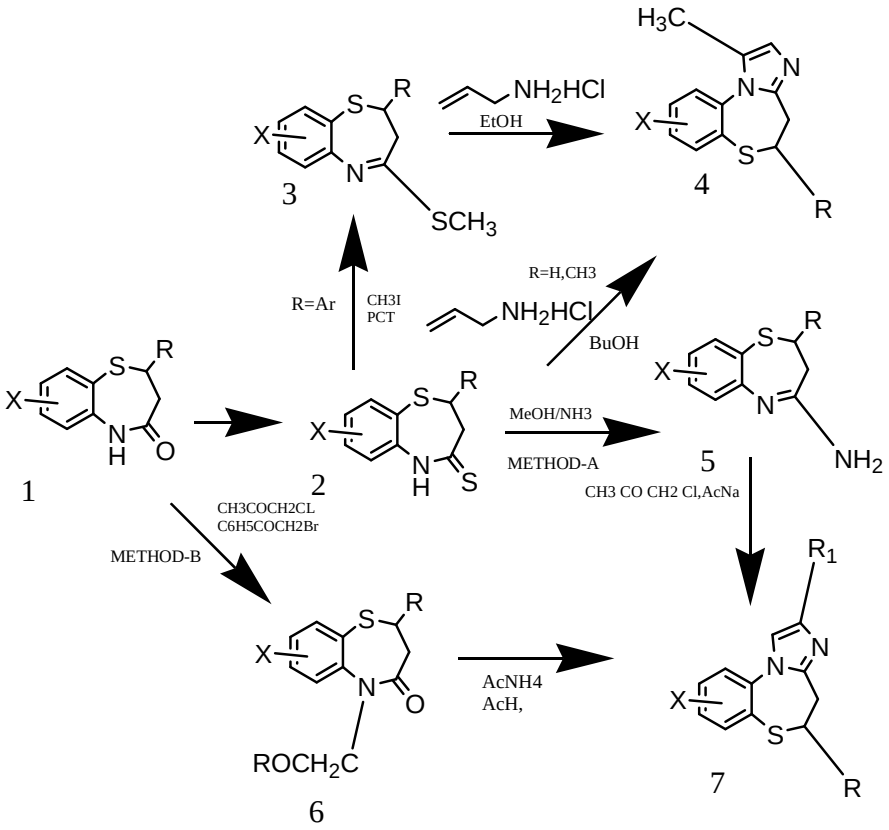
Fig. 2 Diltizem

1.2. Synthesis of benzothiazepines

Different benzothiazepine derivatives have been synthesized by different methods. Few of them can be given as-

1.2.1. Synthesis of 1,5- benzothiazepines annulated with either atriazole and tetrazole ring-

V. Ambrogi et al.(1995) synthesized three series of 1- and 1-substituted imidazo [2,1-d][1,5] benzothiazepine, starting from 1,5-benzothiazepines-4-ones.[6]



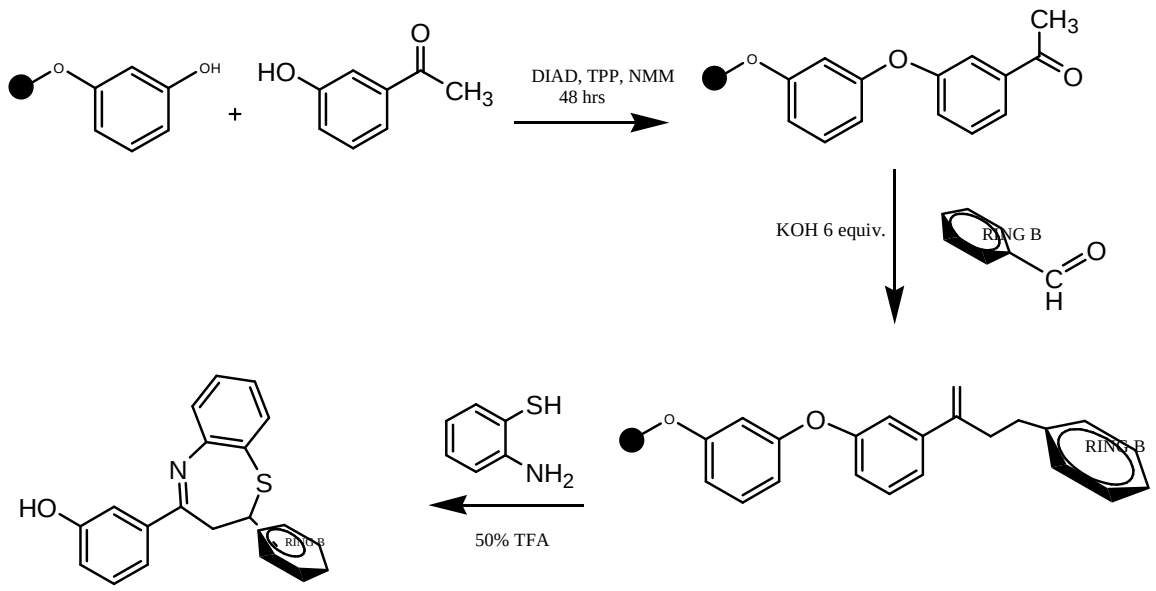
Scheme 1.

TABLE 1.2.1: Table for %yields and melting points of different derevatives-

S.No.	X	R	%Yield	M.P.(*C)
4a	H	H	33	114-115
4b	8-Cl	H	56	47-48
5a	H	H	35	186
5b	8-Cl	H	32	131-135
6a	H	H	70	103-105
6b	8-Cl	H	26	94-96
7	H	H	57	85-87

1.2.2.Solid phase synthesis of 2,3-dihydro-1,5-benzothiazepines-

Farzana Latif Ansari et al. (2008) performed solid phase synthesis of a parallel library of 3'-hydroxy-2,3-dihydrobenzothiazepines through [4+3] annulation of alpha beta unsaturated ketone with aminothiopental, using wang resin as solid support.[7]



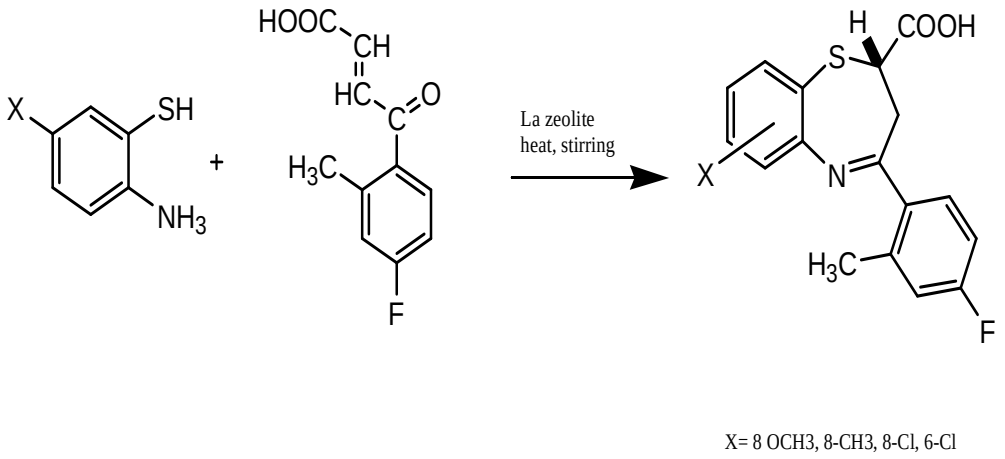
Scheme-2

TABLE 1.2.2- Table of %yield and and melting points of different derivative

Ring b	%Yield	M.P. (*C)
C_6H_5	71	102
2”-Cl C_6H_5	81	45-47
3”-Cl C_6H_5	80	100-101
4”-Cl C_6H_5	87	114
2”-F C_6H_5	87	68-70

1.2.3. Synthesis of 1,5- Benzothiazepine-

Kapil Arya et al.(2008) The expedient synthesis of 1,5-benzothiazepine using zeolite under stirring conditions is reported and synthesized. The reaction produces the product in relatively low yield[8]-

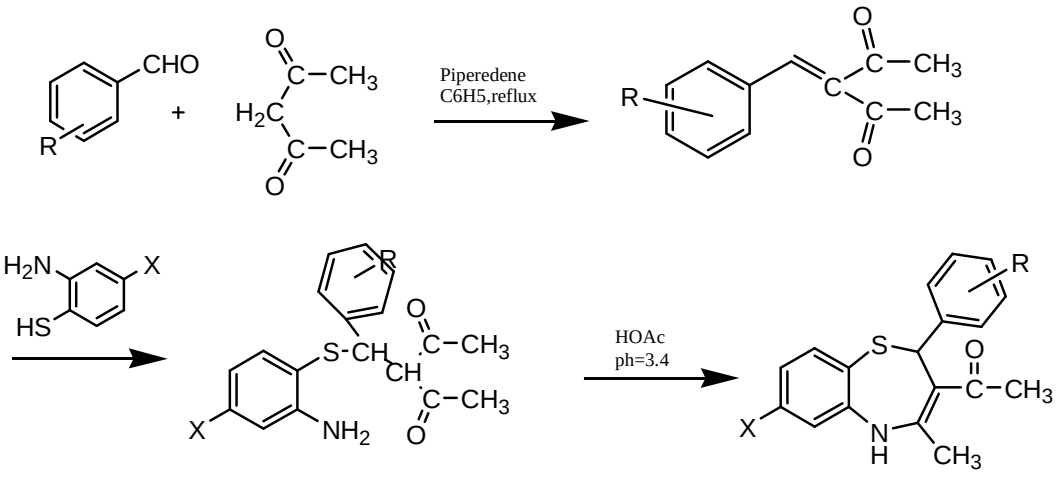


X= 8 OCH3, 8-CH3, 8-Cl, 6-Cl

Scheme 3

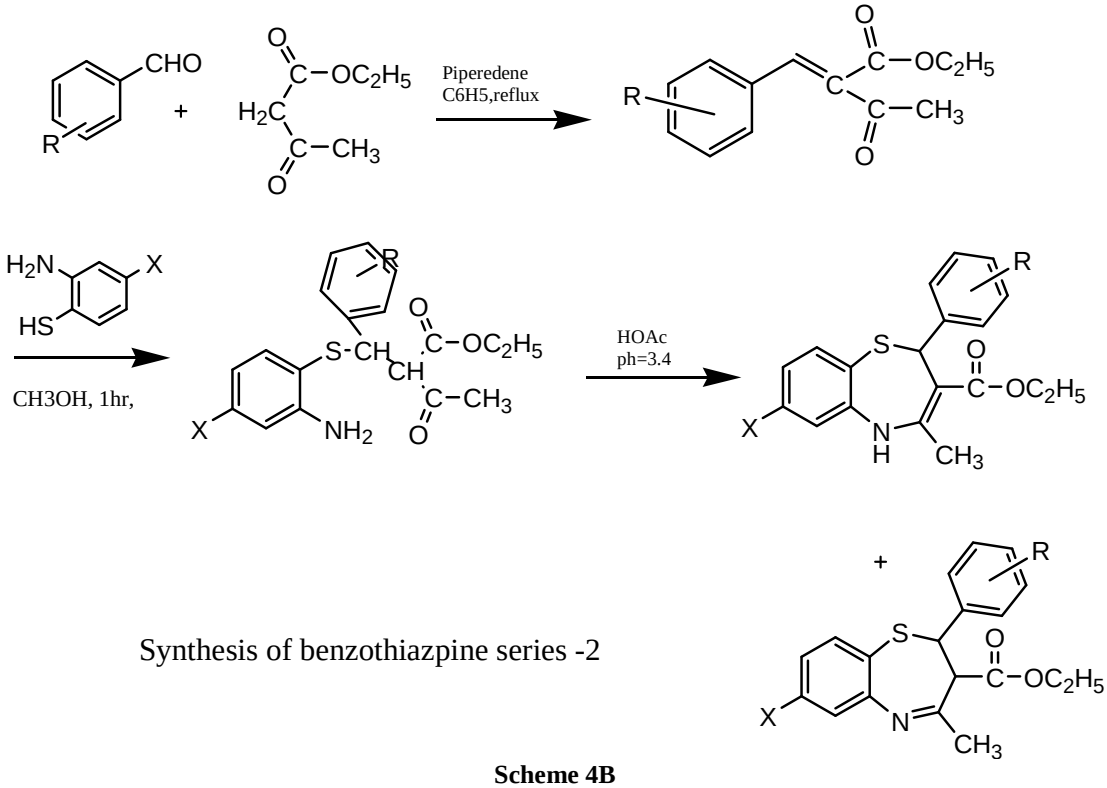
1.2.4. Synthesis of noval series of 1,5-benzothiazepine derevatives-

Lanzhi Wang et al. (2008) they synthesized two series of 1,5-benzothiazepine derivatives (23) compounds by different reactions can be illustrated as below as in scheme 4A and 4B[9]-



Synthesis of benzothiazpine series -1

Scheme-4A

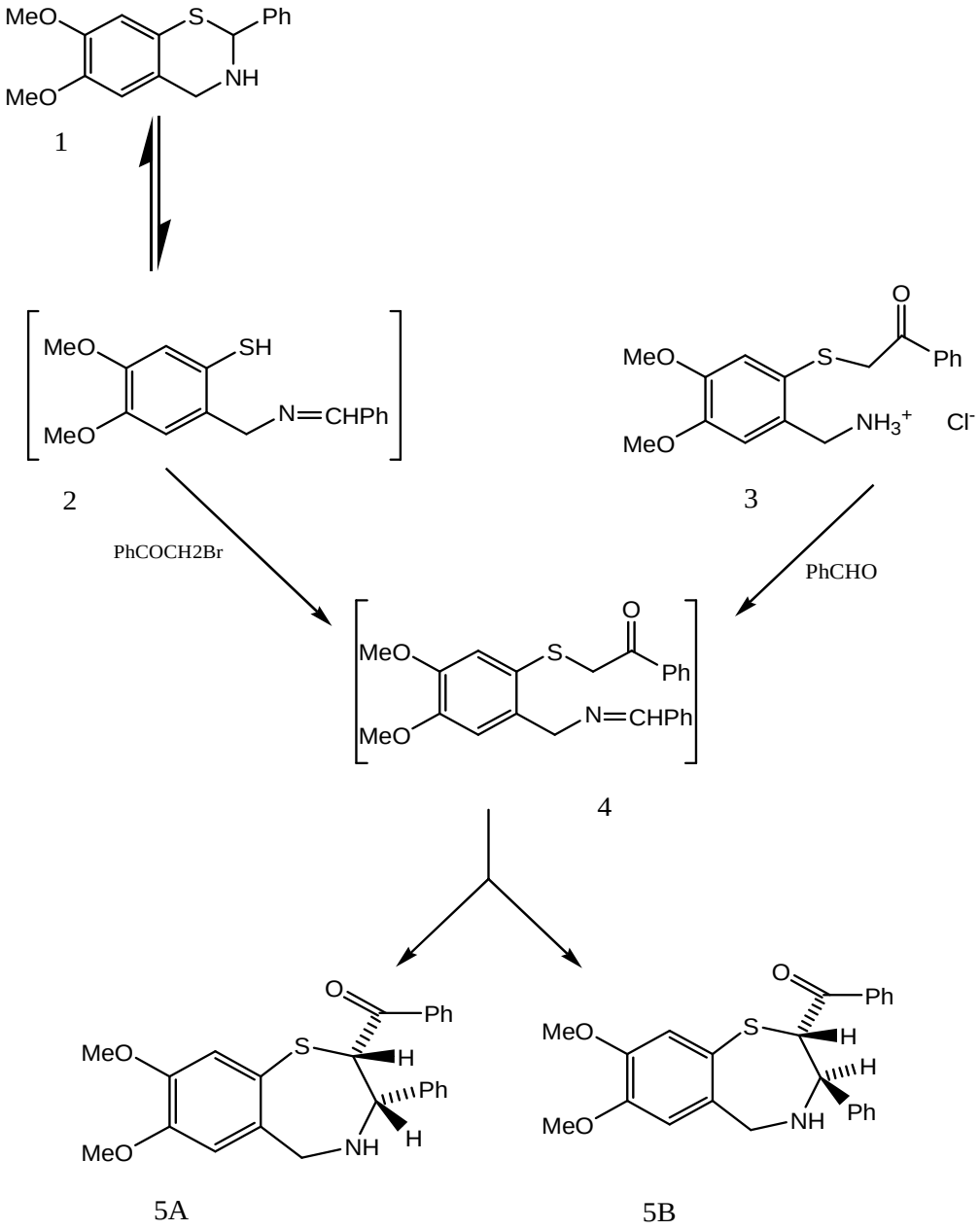


Synthesis of benzothiazpine series -2

Scheme 4B

TABLE 1.2.4:Table for %yields and melting points of different derevatives of 4A and 4B

R	% Yield	M.P.
2-Cl	40	149
4-Cl	42	117
4-CH_3	47	139
2-NO_2	31	127
4-NO_2	32	161



Scheme 5

1.2.5. New conventional synthesis of 1,4-Benzothiazepines-

Lajos Fodor et al. (1995) 1,4-benzothiazepine diastereomers 5a,b were prepared by ring expansion of 1,3-benzothiazene derivative 1 and from 2-benzoylm-ethylthio-4,5-dimethoxybenzalamene hydrochloride(5) with benzaldehyde[10].

The product 5, obtained in 75% yield , was a mixture of two diastereomers: a slight excess of the cis isomer 5A having melting point 166-167^{o}C, over the trans isomer 5B having melting point 159-160^{o}C.

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