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An Efficient Procedure for the Preparation of 3′-Acetyl-2′,3′-dihydrobenzothiazoles by Ring Contraction of 2′,3′-Dihydro-1,5-Benzothiazepines Under Acetylating Conditions

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AN EFFICIENT PROCEDURE FOR THE PREPARATION OF 3'-ACETYL-2',3'-DIHYDROBENZOTHIAZOLES BY RING CONTRACTION OF 2',3'-DIHYDRO-1,5-BENZOTHIAZEPINES UNDER ACETYLATING CONDITIONS

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ABSTRACT : Reaction of 2-benzoyl-6-hydroxy-3-methyl-5-(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl) benzofurans (**4a-f**) with a mixture of acetic anhydride and pyridine afforded 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (**5a-f**) as sole products in good yields. A reaction mechanism for the ring contraction is proposed. All the compounds (**5a-f**) were screened for their antifeedant activity by the "Non-Choice test method" using 6 h prestarved fourth instar larvae of *Spodoptera litura* F. Compounds **5a**, **5c** and **5d** exhibited highest antifeedant activity.

Synthesis and chemical transformations of 1,5-benzothiazepines are well documented in the chemical literature[1-4]. An important group of these compounds are 2-benzoyl-6-hydroxy-3-methyl-5-(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl) benzofurans (**4a-f**) obtained by the reaction of 2-aminothiophenol with 2-benzoyl-5-cinnamoyl-6-hydroxy-3-methyl benzofurans[5] (**3a-f**).

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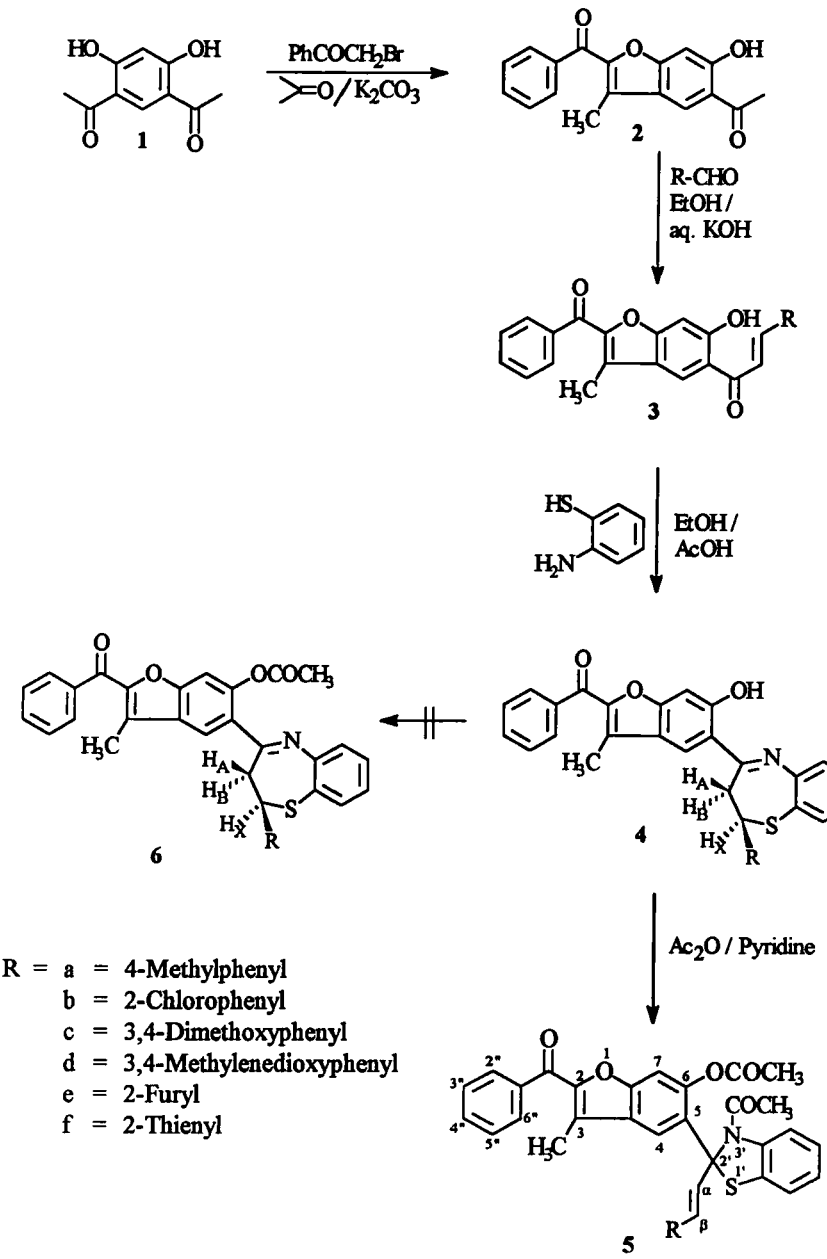
In our present study, we planned to prepare 6-acetoxy-2-benzoyl-3-methyl-5-(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl) benzofurans (**6a-f**) by acetylation of the corresponding monohydroxy derivatives with a mixture of acetic anhydride and pyridine. However, each reaction product was found to contain two acetyl groups. To elucidate these unexpected results, all the 1,5-benzothiazepines (**4a-f**) were subjected to the same treatment. The spectral data revealed that, two acetyl groups had been incorporated into the product isolated. These results have prompted us to synthesise the title compounds. Moreover, literature survey revealed that the synthesis and antifeedant activity of the title compounds have not been reported so far. In order to know the combined effect of both 2'-substitutedstyryl benzothiazole and benzofuran moieties on physiological activity, we have taken up the synthesis of some new 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (**5a-f**).

The required starting materials, the 1,5-benzothiazepines (**4a-f**) were prepared by the condensation of 4,6-diacetylresorcinol[6] (**1**) with ω-bromo-acetophenone[7] (1:1) in the presence of acetone-anhydrous K_2CO_3 medium to yield 5-acetyl-2-benzoyl-6-hydroxy-3-methyl benzofuran[8] (**2**), which on condensation with aromatic aldehydes in the presence of 60% aq. KOH yielded 2-benzoyl-5-cinnamoyl-6-hydroxy-3-methyl benzofurans[5,9] (**3a-f**). These cinnamoylbenzofurans (**3a-f**) on refluxing with 2-aminothiophenol in presence of few drops of glacial acetic acid in ethanol yielded the corresponding 2-benzoyl-6-hydroxy-3-methyl-5-(2'substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl) benzofurans[5] (**4a-f**). The 1,5-benzothiazepines (**4a-f**) on refluxing with



R = a = 4-Methylphenyl
b = 2-Chlorophenyl
c = 3,4-Dimethoxyphenyl
d = 3,4-Methylenedioxyphenyl
e = 2-Furyl
f = 2-Thienyl

Scheme-1

acetic anhydride and anhydrous pyridine for 7 h yielded the corresponding 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (**5a-f**) in one step in good yields.

The IR spectrum of the product **5a** showed absorption at 1767 (-O-C=O), 1674 (-N-C=O) and 1646 cm^{-1} (benzoyl) is characteristic of three carbonyl groups. The UV absorption data λ_{Max}^{MeOH} nm (log ε) 236 (4.77), 258 (4.67), 320 (4.57) is in good agreement with benzothiazoles[10]. The ^{1}H-NMR spectrum of **5a** exhibited four singlets in aliphatic region at δ 1.92, 2.10, 2.40 and 2.65 integrating for three protons each, which were assigned to N-CO-$\underline{CH_3}$, O-CO-$\underline{CH_3}$, $\underline{CH_3}$-Ar and $\underline{CH_3}$-3 respectively. The spectrum revealed two sharp singlets in the aromatic region at δ 6.82 and 7.68 integrating for one proton each assigned to H-7 and H-4. The spectrum also exhibits two sharp doublets at δ 7.15 (J = 16 Hz) 7.52 (J = 16 Hz) integrating for one proton each is assigned to β and α protons respectively. One sharp doublet observed at δ 8.08 (J = 9.4 Hz) integrating for two protons was assigned to H-2",6". The aromatic region of the spectrum showed a multiplet at δ 7.05 to 7.60 (11H) for the protons of phenyl and styryl groups. The mass spectrum of **5a** showed molecular ion peak at m/z 587 (28%) which is consistent with its molecular formula $C_{36}H_{29}NO_5S$. The prominent fragmentation ions at m/z 545 (36), 527 (12), 502 (51), 469 (9), 410 (18), 379 (58), 252 (16), 105 (100), 77 (63) were highly diagnostic. On the basis of the above analytical and spectral data compound **5a** has been characterised as 6-acetoxy-2-benzoyl-3-methyl-5-[3'-acetyl-2'-(p-methylstyryl)-2',3'-dihydrobenzothiazole-2'-yl] benzofuran (**5a**).

Table-1

Analytical and spectral data of title compounds (5a-f)

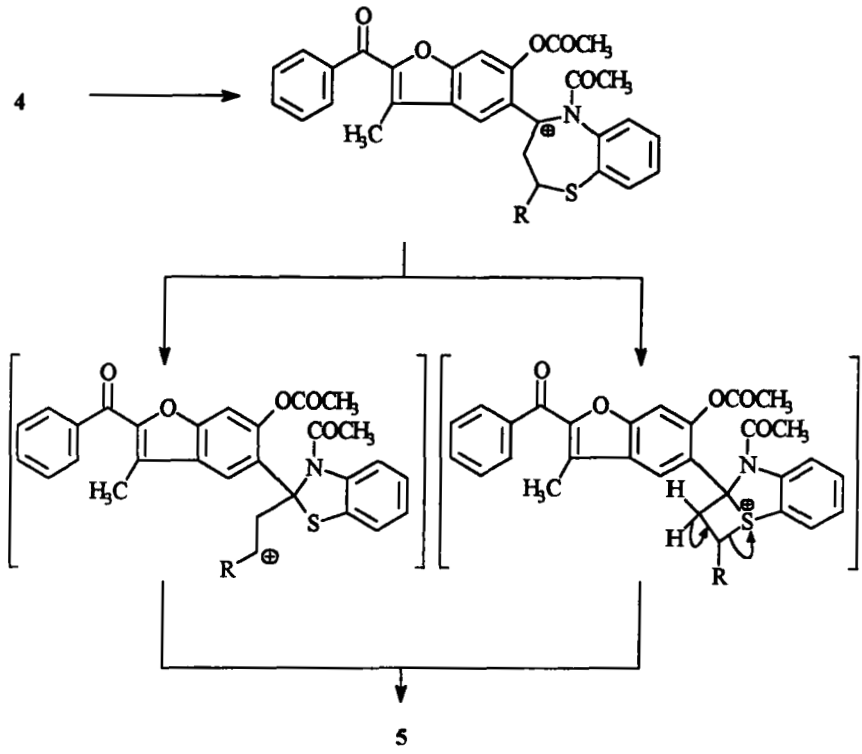
Compd.	M^+	m.p (°C)	Yield (%)	ν IR KBr cm^{-1}			UV(MeOH) nm (log ε)	Antifeedant activity
				O-C=O	N-C=O	benzoyl		
5a	587	220	72	1767	1674	1646	320 (4.57)	94.60
5b	607	163	81	1769	1670	1647	318 (4.48)	86.50
5c	633	170	85	1771	1672	1637	317 (4.66)	94.25
5d	617	148	68	1769	1670	1648	317 (4.47)	98.00
5e	563	136	70	1767	1668	1644	318 (4.63)	91.25
5f	579	178	75	1768	1669	1644	318 (4.66)	92.55

2-Styrylbenzothiazoles have previously been prepared by thermal or proton-catalyzed ring contraction of 2,3-dihydro-1,5-benzothiazepines.[1,11-13] However in such cases the 1,5-benzothiazepines possessed good leaving groups at their C-4 atoms, in contrast to our 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (**5a-f**). Previously published 2,3-dihydro-1,5-benzothiazepine → 2-styrylbenzothiazole conversions[1,11-13] involved either a thermally mediated or an acid-catalyzed contraction of the seven-membered ring. Each compound possessed a good leaving group at the C-4 atom, making possible the formation of a benzothiazole structure[13]. Cleavage of the C-4 substituent and nucleophilic attack of the sulfur atom may have occured in a concerted manner. In this study, conversions of compounds **4** into **5** may

start with acetylation of the nitrogen atom, followed either by heterolytic S-(C-2) bond scission and subsequent nucleophilic attack of the sulfur atom at C-4 affording an allyl cation, or by a nucleophilic attack of sulfur as mentioned above giving rise to a cyclic sulfonium salt, deprotonation of which furnishes **5** (Scheme-2). Despite the ring strain involved, the route via the cyclic sulfonium ion seems to be energitically favourable[14].

In summary, we have described a simple and convenient procedure for the preparation of previously unknown 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (**5a-f**) by ring contraction of the readily available 2-benzoyl-6-hydroxy-3-methyl-5-(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl) benzofurans (**4a-f**) under acetylating conditions. Few examples of N-acetyl derivatives of 2,2-disubstituted 2,3-dihydrobenzothiazoles have previously been prepared by acetylation of the appropriate 2,3-dihydrobenzothiazoles[15,16].

All the compounds (**5a-f**) were tested for their antifeedant activity by "Non-Choice test method"[17] using 6 h prestarved fourth instar larvae of tobacco caterpillar (*Spodoptera litura* F.). The tobacco caterpillars were reared on fresh castor leaves (*Ricinus communis*) grown on the Osmania University Campus at 28 ±1°C, relative humidity 70 ±5% and 12:12 light/dark photo period. Freshly molted fourth instar larvae were used in the assays. The assays were conducted as described by Ascher and Rones[17] in arenas constructed from plastic Petri dishes (15 x 120 mm). A circle of moistened filter paper (12 cm diameter) was placed on the floor of each arena. Castor leaf disks (10 cm diameter) were cut with a cork borer from leaves with well-



Scheme-2

developed primary leaflets. Treated leaf disks were coated on the upper surface with 100 μL of solution having 5% Triton X-100 of the test compound in acetone, control leaf disks coated with 100 μL of acetone having 5% Triton X-100 only. Acetone was allowed to evaporate before assays were initiated. For these non-choice assays, 10 treated and 10 untreated control disks were run for each test and each test was replicated three times. In each Petri dish one prestarved fourth-instar larva was placed. Assays began 4-5 h after the start of the photophase. Arenas were placed in

clear plastic vantilated Crisper boxes containing moist paper toweling and placed in an environmental chambers at 28 ±1°C. The time period of the experiment was 48 h. Leaf consumption (damaged areas) was measured with the help of Planimeter and the percentage of protection was calculated using the following formula by adopting the method of Singh and Panth[18].

$$\% \text{ of antifeedant activity} = \left[\frac{(\% \text{ protection in treated} - \% \text{ protection in control})}{(100 - \% \text{ protection in control})} \right] \times 100$$

Compounds **5a,5c and 5d** exhibited highest antifeedant activity. The present study revealed that the introduction of substituents like 4-methyl, 3,4-dimethoxy and 3,4-methylenedioxy in the phenyl group increased the antifeedant activity of benzothiazoles.

Experimental Section

Melting points were taken in open capillary tubes in sulfuric acid-bath and are uncorrected. FT-IR spectra were obtained on Perkin-Elmer 1605 spectrophotometer. UV spectra were obtained on a Hitachi U-3410 spectrometer. ^{1}H-NMR spectra were taken in $CDCl_3$ on Varian Gemini 200 MHz spectrometer with TMS as internal standard (chemical shifts in δ, ppm). EI mass spectra were obtained on V.G. Micromass 7070H instrumcnt. Column chromatography was carried out using acme silica gel (200 mesh).

Cinnamoylbenzofurans(3a-f) - General procedure

An equimolar mixture of 1 (1.94g) and ω-bromoacetophenone (1.97g) was refluxed in presence of acetone and anhydrous K_2CO_3 for 6 h. After

acetone evaporation yielded residue was poured over crushed ice. The separated solid was filtered, washed with water and extracted with hot 5% NaOH solution. The crude product obtained on neutralisation with dil. HCl, crystallised from MeOH to afford compound **2**. A mixture of **2** (2.94g, 0.01 mol) and appropriate aldehyde (0.01 mol) in ethanol (40 mL) and aq. KOH (60%, 20 mL) was kept at room temperature for 24 h. The product obtained on dilution and acidification with dil. HCl was purified by column chromatography over silica gel (200 mesh) using benzene : chloroform (6:4 v/v) followed by concentration to afford compound **3**.

Synthesis of 2-benzoyl-6-hydroxy-3-methyl-5-(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl)benzofurans(4a-f) : General procedure

Ethanolic solution of monochalcone (**3a-f**) (0.001 mol) was refluxed with 2-aminothiophenol (0.001 mol) and few drops of glacial acetic acid for 4h. At the end of the reaction, the ethanolic solution was concentrated to about half of its volume under reduced pressure. The solid that separated from the concentrate was filtered and recrystallised from benzene : pet ether (8:2 v/v) to yield (**4a-f**).

Synthesis of 6-acetoxy-2-benzoyl-3-methyl-5-(3'-acetyl-2'-substitutedstyryl-2',3'-dihydrobenzothiazole-2'-yl) benzofurans (5a-f) : General Procedure

A mixture of 1,5-benzothiazepine (**4a-f**) (0.001 mol), acetic anhydride (15.0 mL) and anhydrous pyridine (5.0 mL) was refluxed for 7 h and then poured into water. The precipitated material was filtered off, washed with water, dried and recrystallised from methanol to afford compounds (**5a-f**).

5a : (200 MHz, $CDCl_3$) : δ 1.92 (3H, s, N-CO-$\underline{CH_3}$), 2.10 (3H, s, O-CO-$\underline{CH_3}$), 2.40 (3H, s, $\underline{CH_3}$-Ar), 2.65 (3H, s, $\underline{CH_3}$-3), 6.82 (1H, s, H-7), 7.05-7.60 (11H, m, aromatic protons), 7.15 (1H, d, J = 16 Hz, H-β), 7.52 (1H, d, J = 16 Hz, H-α), 7.68 (1H, s, H-4), 8.08 (2H, d, J = 9.4 Hz, H-2",6"); Anal: Calcd. for $C_{36}H_{29}NO_5S$: C, 73.59; H, 4.94; N, 2.38, found : C, 73.55; H, 5.01; N, 2.35.

5b : (200 MHz, $CDCl_3$) : δ 1.88 (3H, s, N-CO-$\underline{CH_3}$), 2.08 (3H, s, O-CO-$\underline{CH_3}$), 2.62 (3H, s, $\underline{CH_3}$-3), 6.95 (1H, s, H-7), 7.15-7.70 (11H, m, aromatic protons), 7.30 (1H, d, J = 16 Hz, H-β), 7.68 (1H, d, J = 16 Hz, H-α), 7.80 (1H, s, H-4), 8.20 (2H, d, J = 10 Hz, H-2",6"); Anal : Calcd. for $C_{35}H_{26}NO_5SCl$: C, 69.19; H, 4.28; N, 2.30, found : C, 69.25; H, 4.30; N, 2.22.

5c : (200 MHz, $CDCl_3$) : δ 1.95 (3H, s, N-CO-$\underline{CH_3}$), 2.05 (3H, s, O-CO-$\underline{CH_3}$), 2.68 (3H, s, $\underline{CH_3}$-3), 3.88 (6H, s, 2 x OCH_3), 6.80-7.60 (11H, m, aromatic protons), 6.88 (1H, s, H-7), 7.10 (1H, d, J = 16 Hz, H-β), 7.75 (1H, d, J = 16 Hz, H-α), 8.10 (2H, d, J = 12 Hz, H-2",6"); Anal. Calcd. for $C_{37}H_{31}NO_7S$: C, 70.14; H, 4.89; N, 2.21, found : C, 70.20; H, 4.85; N, 2.19.

5d : (200 MHz, $CDCl_3$) : δ 1.94 (3H, s, N-CO-$\underline{CH_3}$), 2.12 (3H, s, O-CO-$\underline{CH_3}$), 2.62 (3H, s, $\underline{CH_3}$-3), 6.0 (2H, s, O-$\underline{CH_2}$-O), 6.75-7.60 (11H, m, aromatic protons), 6.80 (1H, s, H-7), 7.10 (1H, d, J = 16 Hz, H-β), 7.68 (1H, s, H-4), 8.05 (2H, d, J = 12.2 Hz, H-2",6"); Anal : Calcd. for $C_{36}H_{27}NO_7S$: C,70.01; H, 4.37; N, 2.26, found : C, 70.05; H, 4.35; N, 2.24.

5e : (200 MHz, $CDCl_3$) : δ 1.82 (3H, s, N-CO-$\underline{CH_3}$), 2.0 (3H, s, O-CO-$\underline{CH_3}$), 2.68 (3H, s, $\underline{CH_3}$-3), 6.40-7.58 (11H, m, aromatic protons), 6.84 (1H,

s, H-7), 7.08 (1H, d, J = 16 Hz, H-β), 7.75 (1H, s, H-4), 8.05 (2H, d, J = 12 Hz, H-2",6"); Anal : Calcd. for $C_{33}H_{25}NO_6S$: C, 70.33; H, 4.44; N, 2.48, found : C, 70.30; H, 4.42; N, 2.53.

5f : (200 MHz, $CDCl_3$) : δ 1.88 (3H, s, N-CO-$\underline{CH_3}$), 2.10 (3H, s, O-CO-$\underline{CH_3}$), 2.62 (3H, s, $\underline{CH_3}$-3), 6.84-7.56 (10H, m, aromatic protons), 6.98 (1H, s, H-7), 7.18 (1H, d, J = 16 Hz, H-β), 7.70 (1H, d, J = 16 Hz, H-α), 7.80 (1H, s, H-4), 8.18 (2H, d, J = 12 Hz, H-2",6"); Anal: Calcd. for $C_{33}H_{25}NO_5S_2$: C, 68.39; H, 4.31; N, 2.41, found : C, 68.45; H, 4.32; N, 2.34.

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