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A MILD AND EFFICIENT THREE COMPONENT ONE- POT SYNTHESIS OF NOVEL 9-ARYL-2-SULFANYL-5, 9-DIHYDRO-1*H*-IMIDAZO[4,5-*H*][4,1] BENZOTHIAZEPIN-6[7*H*]-ONES

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Abstract
A three component one-pot protocol for the synthesis on novel 9-aryl-2-sulfanyl-5,9-dihydro-1*H*-imidazo [4,5-*h*][4,1]benzothiazepin-6[7*H*]-ones from commercially available materials.

Keywords: 5-amino-2-mercapto-benzimidazole, aromatic aldehydes, *p*-TSA and acetonitrile

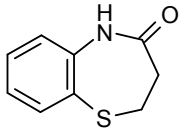
Introduction

Multi-component reaction (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation[1,2], and are of increasing importance in organic and medicinal chemistry[3-5], structural activity relationship of imidazole containing structure have dominated investigations in medicinal chemistry for active biological entities[6]. Benzimidazole a nitrogen containing heterocyclic, provides an interesting building block for the synthesis of various biologically active compounds[7-9].there are several classic examples of benzimidazole derivatives which possess useful pharmaceutical properties and they are marketed as commercial drugs .Benzimidazole derivatives are also reported to possess analgesic[10], antihelmentic[11,12], anti-inflammatory[13], anti-microbial, anti-arthritic, antibacterial, anti-tumour and anti-HIV activities[14]. Heterocycle containing the 1,4-thiazepine moiety are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in a wide number of natural and synthetic biologically active agent[15].

Several derivatives of dihydro-1,5-benzothiazpine-4(5*H*)-one[16], **1** compound have received considerable attention because of their pharmacological activities. Besides their use for the treatment of cardiovascular diseases[17], some members of this class of compounds act as potent bradykinin agonists[18], growth hormone secretegognes[19].

A literature survey revealed that when two heterocyclic moieties are joined together in a single molecule frame work, the resulting compound is expected to possess enhanced bioactivity[20]. Realizing the importance of the above bioynamic heteryl nuclei , and in continuation of our

intrest in designing the synthesis of biologically active benzimidazole linked to thiazepine ring , it was thought worthwhile to undertake the synthesis of novel dihydro-1*H*-imidazole[4,5-][4,1]benzothiazepine-6-ones.



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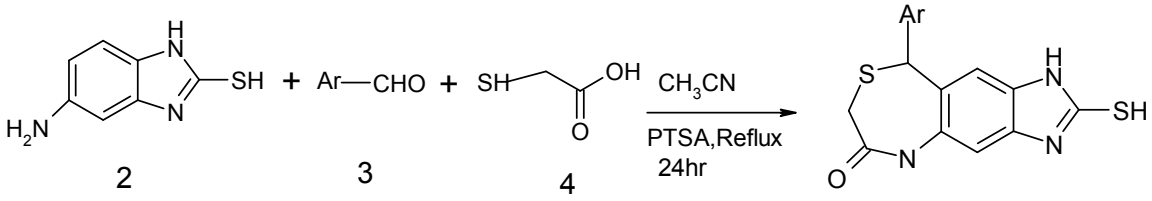
Results and Discussions

The one pot three component reaction of 5-amino- 2-mercapto benzimidazole **2**, various aromatic aldehyde **3**, and mercapto acetic acid **4** was carried out in acetonitrile in presence of catalytic amount of *p*-toluene sulfonic acid under reflex for 24h. After the completion of reaction (monitored by TLC) the reaction mixture was poured onto crushed ice. The solid that separated was filtered, washed with pet ether and recrystallized from ethyl acetate to give corresponding dihydro-1*H*-imidazo[4,5-*h*][4,1] benzothiazepine-6-ones in good yields. A plausible mechanism of action of this three component reaction is presented in **scheme-II**. The first step involves the formation of Baylis-Hilman type adduct **6** by nucleophilic addition of 5-amino-2-mercapto benzimidazole **2** to aromatic aldehyde **3** as a key intermediate, which might occur to afford **7**. Then **7** is attacked *via* Michael addition of thio acid **4** to give intermediate **8** followed by cycloaddition, dehydration to form the desired product **5**.



2 3 4 5 a-h

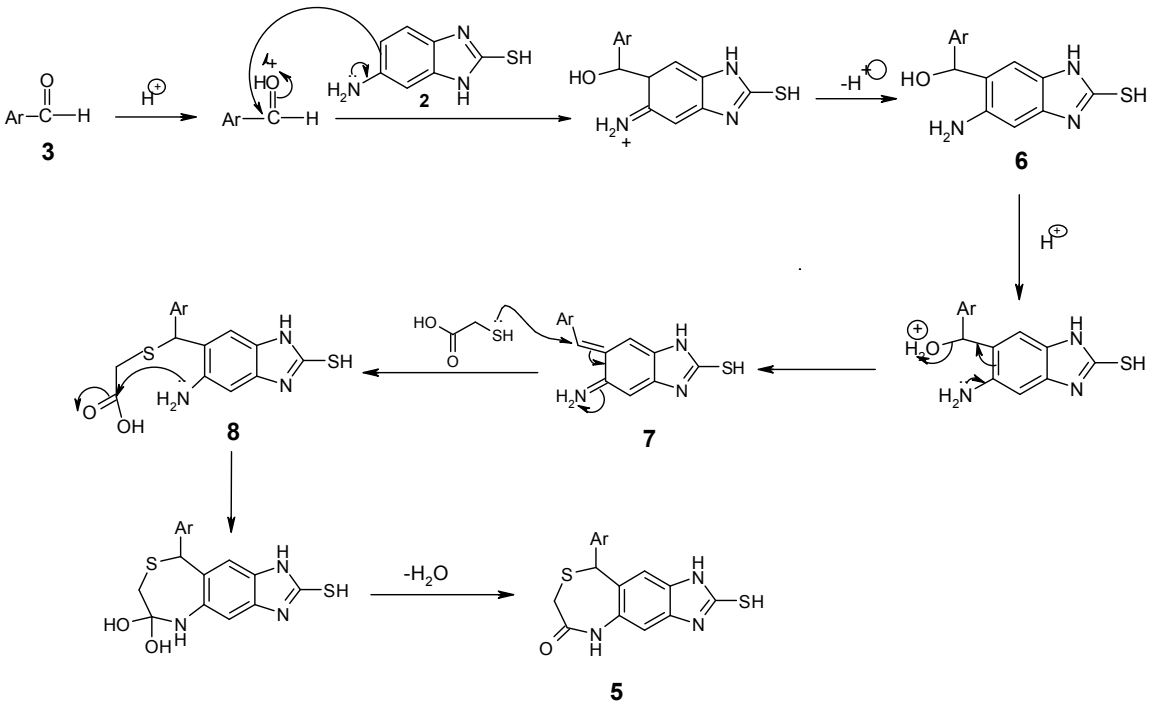
5a, Ar = C_6H_5 **5e**, Ar = 4-$OCH_3C_6H_4$

5b,Ar= 4-Cl C_6H_4 **5f**, Ar = 2-OHC_6H_4

5c,Ar= 4-Br C_6H_4 **5g**, Ar = 4-$N(CH_3)_2C_6H_4$

5d,Ar=4-CH_3 C_6H_4 **5h**, Ar = 4-$NO_2C_6H_4$

Scheme-I



Scheme II

In order to study the scope of this reaction, different substituted aromatic aldehydes were utilized in this multi-component synthesis.The results are good in terms of yield and product purity in the presence of *p*-TSA, while without *p*-TSA the yield of products were trace even after 30 h. To the best of our knowledge, this new procedure provides the first example of an efficient and three-component methods for the synthesis of dihydro-1*H*-imidazo[4,5-*h*][4,1] benzothiazepin-6(7*H*)-ones. This method, based on three-component *p*-TSA catalysed reaction in CH_3CN, is the most simple and convenient and would be applicable for the synthesis of different types of imidazo[4,5-*h*][4,1] benzothiazepin-6-ones

The IR spectra of dihydro-1*H*-imidazo [4, 5-*h*][4,1] benzothiazepine-6-ones **5** exhibited characteristic absorption bands at 3320, 3220 and 1682 cm-1 due to NHCO, NH and C=O groups respectively. The ^{1}H NMR spectra **5** displayed signals at δ 4.4, 4.5 and 9.1 due to Ar-CH, -S-CH_2-CO- and NH protons respectively conforming cyclization process. The mass spectrum of **5a**, showed a molecular ion $[M+H]^+$ peak at m/z **327** supporting the product formation. The structure of compounds **5a-h** have been elucidated by elemental analyses and spectral (IR, ^{1}HNMR, MS) data.

In conclusion, we report the one-pot protocol for the synthesis of dihydro-1*H*-imidazo [4,5-*h*][4,1] benzothiazepine-6-ones, using commercially available materials. To the best of our knowledge, this is the first report on the fused heterocycles of benzimidazole linked to thiazepine. Prominent among the advantage of this new method are novelty, operational simplicity, good yields and easy work up procedures uses employed. In view of potential biological activity of benzimidazole and thiazepine nuclei, we predict that the newly synthesized compounds may be drug candidates and the activity data will be published else where.

Experimental section

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}HNMR spectra on a Varian Gemini 300 MHz spectrometer using TMS as internal standard and mass spectra on a Jeol JMS-300 spectrometer. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

One-pot synthesis of 9-aryl-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4, 5-*h*][4, 1] benzothiazepine-6-ones 5a-h

A mixture of 5-amino-2-mercapto benzimidazol **2** (0.01mol) aromatic aldehyde **3** (0.01 mol), mercapto acetic acid **4** (0.01 mol) and *p*-TSA (30 mol %) in CH_3CN (5mL) was stirred at 80^{o}C 24 h. After completion of the reaction mixture was poured onto crushed Ice. The separated solid was filtered, washed with pet ether and recrystallized from ethyl acetate.

9-Phenyl-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine-6[7*H*]-one**(5a)** :
IR (KBr): 3320 (NH), 3220 (NHCO), 1682 (C=O) cm^{-1}; ^{1}H NMR (300 MH$_Z$, $CDCl_3$,δ ppm): 3.2 (s, 1H, SH), 4.4 (s, 1H, ArH), 4.5 (s, 2H, CH_2), 6.8 -7.6 (m, 7H, ArH), 9.6 (bs, 1H, NH, D_2O exchangeable), 10.8 (bs, 1H, NH, D_2O exchangeable); MS (EI): *m/z* 328 $[M+H]^+$.

9-(2-Chlorophenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine- 6[7*H*] -one **(5b)** :
IR (KBr): 3340 (NH) , 3218 (NHCO), 1675 (C=O) cm^{-1}; ^{1}H NMR (300 MH$_Z$, $CDCl_3$, δ ppm): 3 .4 (s,1 H, SH), 4..3 (s, 1H, ArH), 4.6 (s, 2H, CH_2), 6.8-7.8 (m, 6H, ArH), 9. 3 (bs, 1H, NH, D_2O exchangeable) , 10.4 (bs, 1H, NH, D_2O exchangeable) ; MS (EI) : m/z 362 $M+H]^+$.

9-(4-Bromo phenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo [4, 5-*h*] [4, 1] benzothiazepine-6[7*H*]-one **(5c) :**
IR (KBr): 3350 (NH), 3210 (NHCO), 1660 (C=O) cm^{-1}; ^{1}H NMR (300 MH$_Z$,$CDCl_3$, δ ppm): 3.2 (s,1H,SH), 4.5 (s,1H,ArH), 4.6 (s,2H,CH_2), 6.8-7.9 (m,6H,ArH), 9.8 (bs,1H,NH,D_2O exchangeable), 10.3 (bs,1H,NH, D_2O exchangeable); MS(EI): m/z 406 $[M+H]^+$.

9-(4-Methylphenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine-6[7*H*]-one **(5d) :**
IR (KBr):3360 (NH), 3220 (NHCO), 1650 (C=O) cm^{-1}; ^{1}H NMR (300 MH$_Z$,$CDCl_3$, δ ppm): 2.8 (s,3H, Ar-CH_3), 3.3 (s, 1H, SH), 4.2 (s,1H,ArH), 4.4 (s,2H,CH_2), 6.9-7.8 (m,6H,ArH), 9.5 (bs,1H,NH,D_2Oexchangeable), 10.4 (bs,1H,NH,D_2O exchangeable); MS(EI): m/z 342 $[M+H]^+$.

9-(4-Methoxyphenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine-6[7*H*]-one **(5e):**
IR (KBr):3380 (NH), 3205 (NHCO), 1660(C=O) cm^{-1}; ^{1}H NMR (300 MH$_Z$,$CDCl_3$, δ ppm): 3.8 (s,3H, OCH_3), 3.2 (s,1H,SH), 4.3 (s,1H,ArH), 4.4 (s,2H,CH_2), 6.7-7.9 (m,6H,ArH), 9.6 (bs,1H,NH,D_2Oexchangeable), 10.6 (bs,1H,NH,D_2O exchangeable);
MS (EI): m/z 358$[M+H]^+$.
9-(2-Hydroxyphenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine-6[7*H*]-one **(5f):**

IR (KBr):3365 (NH), 3215 (NHCO), 1655 (C=O) cm^{-1}; ^1H NMR (300 MH_Z,$CDCl_3$, δ ppm): 3.3 (s,1H, SH), 4.3 (s,1H, ArH), 4.5 (s, 2H, CH_2), 6.8-7.5 (m, 6H, ArH), 9.2 (bs, 1H, NH, D_2Oexchangeable), 9.8 (bs,1H,NH,D_2Oexchangeable), 10.3 (bs,1H,NH,D_2O exchangeable);MS(EI): m/z 344$[M+H]^+$.

9-(4-(Dimethylamino)phenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzo thiazepine-6[7*H*]-one **(5g):**
IR (KBr): 3365 (NH), 3220 (NHCO), 1651 (C=O) cm^{-1}; ^1H NMR (300 MH_Z,$CDCl_3$, δ ppm): 3.1 (s, 6H, $N(CH_3)_2$), 3.3 (s, 1H, SH), 4.4 (s, 1H, ArH), 4.6 (s, 2H, CH2), 6.6-7.7 (m, 6H, ArH), 9.7 (bs, 1H, NH, D_2Oexchangeable), 10.0 (bs, 1H, NH, D_2O exchangeable);MS(EI): m/z 371 $[M+H]^+$.

9-(4-(Nitrophenyl)-2-sulfanyl-5,9-dihydro-1*H*-imidazo[4,5-*h*][4,1]benzothiazepine-6[7*H*]-one **(5h):**
IR(KBr): 3355 (NH), 3210 (NHCO), 1660 (C=O), 1570,1360 ($=N^+-O^-$)cm^{-1}; ^{1}HNMR (300 MH_Z,$CDCl_3$, δ ppm): 3.2 (s, 1H, SH), 4.3 (s, 1H, ArH), 4.5 (s, 2H, CH_2), 6.7-7.8 (m, 6H, ArH), 9.6 (bs, 1H, NH, D_2Oexchangeable), 10.3 (bs, 1H, NH, D_2O exchangeable);MS(EI): m/z 373$[M+H]^+$.

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Table-I Characterization data of 9-aryl-2-sulfanyl -5,9-dihydro-1*H*-imidazo[4, 5-*h*][4, 1] benzothiazepin-6[7*H*]-ones 5a-h.

Compd	Ar	M.P (^oC)	Yield (%)	Mol .formula	Found (%) (Calcld)		
					C	H	N
5a	C_6H_5	165	65	$C_{16}H_{12}N_3OS_2$	(58.64 58.69	4.04 4.00	12.87 12.83)
5b	4-ClC_6H_4	170	70	$C_{16}H_{12}ClN_3OS_2$	(53.15 53.11	3.30 3.34	11.58 11.61)
5c	4-Br C_6H_4	190	64	$C_{16}H_{12}BrN_3OS_2$	(47.28 47.30	2.99 2.98	10.30 10.34)
5d	4-CH_3 C_6H_4	200	60	$C_{17}H_{15}N_3OS_2$	(59.79 59.80	4.40 4.43	12.28 12.31)
5e	4-OCH_3 C_6H_4	204	63	$C_{17}H_{15}N_3O_2S_2$	(57.10 57.12	4.20 4.23	11.72 11.76)
5f	2-OH C_6H_4	185	68	$C_{16}H_{13}N_3O2S_2$	(55.94 55.96	3.87 3.82	12.20 12.24)
5g	4-$N(CH_3)_2$ C_6H_4	207	75	$C_{18}H_{18}N_4OS_2$	(58.31 58.35	4.89 4.90	15.15 15.12)
5h	4-$NO_2C_6H_4$	210	72	$C_{16}H_{12}N_4O_3S_2$	(51.65 51.60	3.21 3.25	15.01 15.04)