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SYNTHESIS OF DERIVATIVES OF 8*H*-INDENO[1,2-D]THIAZOL-2-AMINES *VIA* α-BROMO, α,α-DIBROMO AND α-TOSYLOXY CARBONYL COMPOUNDS

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Abstract: The present study described the synthesis of derivatives of 8*H*-indeno[1,2-d]thiazol-2-amines (**5)** by the reaction of thiourea with 2-tosyloxy-1-indanone **(3),** 2-bromo-2,3-dihydroinden-1-ones **(6)** and 2,2-dibromo-2,3-dihydroinden-1-one **(7)** in fairly good to excellent yields (90-95%).

Keywords: 2-Tosyloxy-1-indanones, HTIB, 2,3-dihydroinden-1-one, 2-bromo-2,3-dihydroinden-1-ones, 2,2-dibromo-2,3-dihydroinden-1-ones, 8*H*-indeno[1,2-d]thiazol-2-amines.

Introduction

Thiazoles are interesting building blocks and frequently encountered structural motifs in a variety of natural products and synthetic bioactive compounds useful as pharmaceuticals agents. Among natural products derived from thiazole, thiamine (vitamin B1) is a prominent example. More recently discovered compound classes like epothilones [1], cystothiazoles [2] or thiazolyl peptide antibiotics [3] also contain at least one thiazole ring and show interesting pharmacological properties such as analgesic, antibacterial, anticonvulsant, antiparasitic, anti-inflammatory and herbicidal activities [4-7]. Some derivatives of thiazole are potent anti-HIV agents [8]. As a result, a number of methods have been developed to synthesize these compounds.

The most frequently encountered method for the synthesis of thiazole derivatives is the classical Hantzsch reaction, where an α-haloketone is condensed with thiourea [9-10]. The modified methods of King and Dadson [11], in connection with some other workers [12], have also been reported for the synthesis of thiazole derivatives. However, lachrymatory properties associated with α-halocarbonyl compounds have given way to α, α-dihalocarbonyl compounds which can be used as synthetic equivalents [13-15] to the corresponding α-halocarbonyl compounds as they possess high reactivity in most of reactions. Being non-lachrymatory, generally solid at room temperature and soluble in commonly used reaction solvents, these compounds are easy to work with and can be handled easily [16-17].

Compared with the others, the method using [hydroxy(tosyloxy)iodo]benzene (HTIB) has the advantage of simple experimentation and avoids the use of highly lachrymatory and not readily available α-halocarbonyl compounds [18]. Continuing our studies directed toward the synthesis of some new heterocyclic compounds of potential biological interest, we report here different routes for synthesis of 5/7-alkyl-8*H*-indeno[1,2-d]thiazol-2-amines via α-bromo, α,α-dibromo and α-tosyloxy carbonyl compounds.

Results and Discussion

We described here a convenient approach to the preparation of 5/7-alkyl-8*H*-indeno[1,2-d]thiazol-2-amines **(5a-c)**. For the synthesis of desired compounds, **scheme 1** was followed. Initially, cyclocondensation was carried out following route 'a' starting from 2-tosyloxy-1-indanone (**3a)** and thiourea (**4)** in ethanol to afford the desired product **5a** in 90% yield (**Scheme 1**). α-tosyloxyketones **3a-c** were prepared by the oxidation of 1-indanones (**1a-c**) with HTIB (**2**) in acetonitrile. The structures of all the new α-tosyloxyketones **3a-c** were thoroughly characterized by analyzing their spectral (IR, ^{1}H NMR, ^{13}C NMR) data.

<<**Scheme 1**. Synthesis of 5/7-alkyl-8*H*-indeno[1,2-d]thiazol-2-amines (**5a-c**).>>

Then we carried out the reaction of different 4/6-methyl-2-tosyloxy-1-indanones (**3b-c**) with thiourea (**4**) under similar conditions. It was found that the method in all the cases afforded the desired products **5b-c** in good to excellent yield. The structure of these compounds were confirmed by IR spectra which shows appearance of $-NH_2$ absorption at 3450-3250 cm^{-1} along with disappearance of CO absorption and which was further confirmed by ^{1}H NMR having a broad singlet at 5.3(δ ppm) corresponding to $-NH_2$ protons. The desired products **(5a-c)** were also synthesized following route 'b' and 'c'. The starting materials 2-bromo-2,3-dihydroinden-1-ones **(6)** and 2,2-dibromo-2,3-dihydroinden-1-one **(7)** were prepared using literature method.

Conclusion

In conclusion, we demonstrated a useful thiazole synthesis by reaction of α-bromo and α,α-dibromo and α-tosyloxy derivatives of carbonyl compounds with thiourea. It can also be added that the method adopted during this effort is significant since the reaction involve very simple experimentation under mild conditions. The study also revealed the behavioral analogy of α,α-dibromo and α-tosyloxy derivatives with α-bromo derivatives in the present work.

Experimental section

Melting points were taken on slides in an electrical apparatus Labindia visual melting range apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 FT-IR spectrophotometer.^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300 MHz and 75 MHz instrument respectively, using TMS as an internal standard. All other chemicals used as such as were procured from supplier.

***Synthesis of 2,3-dihydro-4/6-alkyl-1-oxo-1H-inden-2-yl 4-methylbenzenesulfonates* (3a-c).**

Typical procedure: To a stirred solution of 1-indanone **(1a,** 5g, 38 mmol) in 100 ml acetonitrile, HTIB (**2**, 16.45g, 41.9 mmol) was added and the reaction mixture was refluxed for 5 hrs. After that excess of acetonitrile was distilled off under reduced pressure and residual mass was crystallized from ethanol. The product was further washed with cold ethanol and dried to give pure 2-tosyloxy-1-indanone (**3a**, 9.72g, 83%).

2-Tosyloxy-1-indanone (3a).

Dark brown; mp 110-111^{0}C; yield 83%; IR (ν_{max}, cm^{-1}): 1728(C=O), 1597, 1466, 1404, 1373, 1296, 1188, 1057; ^{1}HNMR (δ, $CDCl_3$, 300 MHz, ppm): 2.484 (s, 3H, CH_3), 3.247-3.320 (dd, 1H, J_1 = 4.5Hz, J_2 = 17.4 Hz), 3.628-3.712 (dd, 1H, J_2 = 17.4 Hz, J_3 = 7.8 Hz), 5.127-5.169 (dd, 1H, J_1 = 4.5 Hz, J_3 = 7.8 Hz), 7.391-7.462 (m, 4H), 7.642-7.690 (m, 1H), 7.735-7.760 (d, 1H, J = 7.5), 7.929-7.955 (d, 2H, J = 7.8 Hz); ^{13}C NMR: 21.70, 30.88, 33.89, 124.68, 126.66, 128.21, 128.42, 129.87, 133.28, 133.64, 136.33, 145.19, 149.95, 197.52.

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.54; H, 4.65.

The other derivatives **3b-c** were synthesized by adopting the similar procedure.

6-Methyl-2-tosyloxy-1-indanone (3b).

Light brown; mp 113-114^{0}C; yield 81%; IR (ν_{max}, cm^{-1}): 1728 (C=O), 1597, 1489, 1427, 1381, 1281, 1180, 1065; ^{1}HNMR (δ, $CDCl_3$, 300 MHz, ppm): 2.402 (s, 3H, CH_3), 2.485 (s, 3H, CH_3), 3.192-3.262 (dd, 1H, J_1 = 3.9 Hz, J_2 = 16.8 Hz), 3.578-3.661 (d, 1H, J_2 = 16.8 Hz, J_3 = 7.8 Hz), 5.107-5.148 (m, 1H), 7.317-7.344 (d, 1H, J = 8.1 Hz), 7.389-7.416 (d, 2H, J = 8.1 Hz), 7.469-7.541 (m, 2H), 7.927-7.954 (d, 2H, J = 8.1 Hz); ^{13}CNMR: 21.14 (CH_3), 21.74 (CH_3), 33.58, 78.57, 124.55, 126.34, 128.23, 129.88, 133.71, 137.63, 138.57, 145.17, 147.30, 197.62 (CO).

Anal. Calcd. for $C_{17}H_{16}O_4S$: C, 64.54; H, 4.67. Found: C, 64.52; H, 4.65.

4-Methyl-2-tosyloxy-1-indanone (3c).

Light brown; mp 141-142^{0}C; yield 83%; IR (ν_{max}, cm^{-1}): 1728 (C=O), 1597, 1489, 1435, 1358, 1281, 1180, 1095; ^{1}HNMR (δ, $CDCl_3$, 300 MHz, ppm): 2.352 (s, 3H, CH_3), 2.486 (s, 3H, CH_3), 3.149-3.221 (dd, 1H, J_1 = 4.2Hz, J_2 = 17.4 Hz), 3.594-3.678 (d, 1H, J_2 = 17.4 Hz, J_3 = 7.8 Hz), 5.116-5.157 (dd, 1H, J_1 = 4.2 Hz, J_3 = 7.8 Hz), 7.307-7.357 (m, 1H), 7.393-7.420 (d, 2H, J = 8.1 Hz), 7.468-7.493 (d, 1H, J = 7.5 Hz), 7.573-7.598 (d, 1H, J = 7.5 Hz); 7.939-7.966 (d, 2H, J = 8.1 Hz) ^{13}CNMR: 17.80, 21.14, 32.75, 78.26, 122.03, 128.25, 128.50, 129.89, 133.12, 133.46, 136.04, 136.83, 145.22, 149.07, 197.94 (CO).

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 64.54; H, 4.67. Found: C, 65.53; H, 4.64.

Synthesis of 2-bromo-2,3-dihydroinden-1-ones (6a).

Typical procedure: To a stirred solution of 1-indanone **(1a,** 2g, 9 mmol) in 50 ml dichloromethane (DCM), bromine (Br_2) (1.6g, 10 mmol) was added and the reaction mixture was stirred continuously for 10 hrs. Reaction mixture was monitored by tlc. After completion of reaction the reaction mixture was poured on ice. Organic layer was washed with sodium bisulphite solution to remove excess bromine, then with brine and cold water. Then organic layer was dried over sodium sulphate and filtered, after that excess of DCM was distilled off under reduced pressure and residual mass was crystallized on cooling at room temperature (**6a**, 2.4g, 88%).

2-bromo-2,3-dihydroinden-1-one (6a).

mp. 36-37 ^{0}C (lit. mp. 37-38 ^{0}C). [19]

2-bromo-2,3-dihydro-4-methylinden-1-one (6b).

mp. 55-57 ^{0}C.

The derivative **6b** was prepared adopting the above procedure.

Synthesis of 2,2-dibromo-2,3-dihydro-4-alkylinden-1-ones (7a-b).
Typical procedure: To a stirred solution of 1-indanone **(1a,** 2g, 9 mmol) in 50 ml acetic acid (AcOH), bromine (Br_2) (3.05g, 19 mmol) was added and the reaction mixture was refluxed for 30 min. Reaction mixture was monitored by tlc. After completion of reaction the reaction mixture was poured on ice, a solid was formed, filtered and washed with cold water. (**7a**, 3.2g, 93%).

2,2-dibromo-2,3-dihydroinden-1-one (7a).
mp. 132-133 ^{0}C (lit mp. 133-134 ^{0}C) [20]

Synthesis of 5/7-alkyl-8H-indeno[1,2-d]thiazol-2-amines (5a-c).
To a solution containing equimolar amounts of **3 or 6 or 7** in ethanol was added equimolar amount of thiourea and reaction mixture was refluxed for 4-5 hrs. On cooling, a crystalline product was separated out which was filtered, washed with water and recrystallized from aqueous ethanol to afford pure 8,8a-dihydro-5/7-alkyl-8H-indeno[1,2-d]thiazol-2-amine (**5).**

8H-indeno[1,2-d]thiazol-2-amine (5a).
mp. 220-222 ^{0}C (lit. mp 220-223 ^{0}C) [21]

5-methyl-8H-indeno[1,2-d]thiazol-2-amine (5b).
mp. 200-201^{0}C; IR (ν_{max}, cm^{-1}): 3456, 3263 (NH_2 stretching), 1620, 1528, 1443, 1404, 1366, 1304, 1234, 1180, 1103, 1065, 1034; ^{1}HNMR (δ, $CDCl_3$, 300 MHz, ppm): 2.432 (s, 3H, CH_3), 3.676 (s, 2H, CH_2), 5.272 (s, 2H, NH_2), 7.010-7.034 (d, 1H, J=7.2 Hz), 7.329-7.354 (d, 1H, J=7.2 Hz), 7.531 (s, 1H); ^{13}C NMR: 19.01, 21.63, 32.28, 56.49, 118.61, 123.72, 124.70, 125.06, 136.04, 142.92, 173.26

7-methyl-8H-indeno[1,2-d]thiazol-2-amine (5c).
mp. 215-216^{0}C; IR (ν_{max}, cm^{-1}): 3425, 3271, (NH_2 stretching), 1628, 1520, 1427, 1389, 1327, 1288, 1203, 1180, 1134, 1088; ^{1}HNMR (δ, $CDCl_3$, 300 MHz, ppm): 2.385 (s, 3H, CH_3), 3.582 (s, 2H, CH_2), 5.327 (bs, 2H, NH_2), 7.021-7.041 (d, 1H, J= 7.8 Hz), 7.248 (m, 1H), 7.427-7.450 (m, 1H); ^{13}C NMR: 23.07, 36.22, 120.42, 128.21, 130.43, 131.71, 138.14, 142.26, 148.63, 161.18, 177.84

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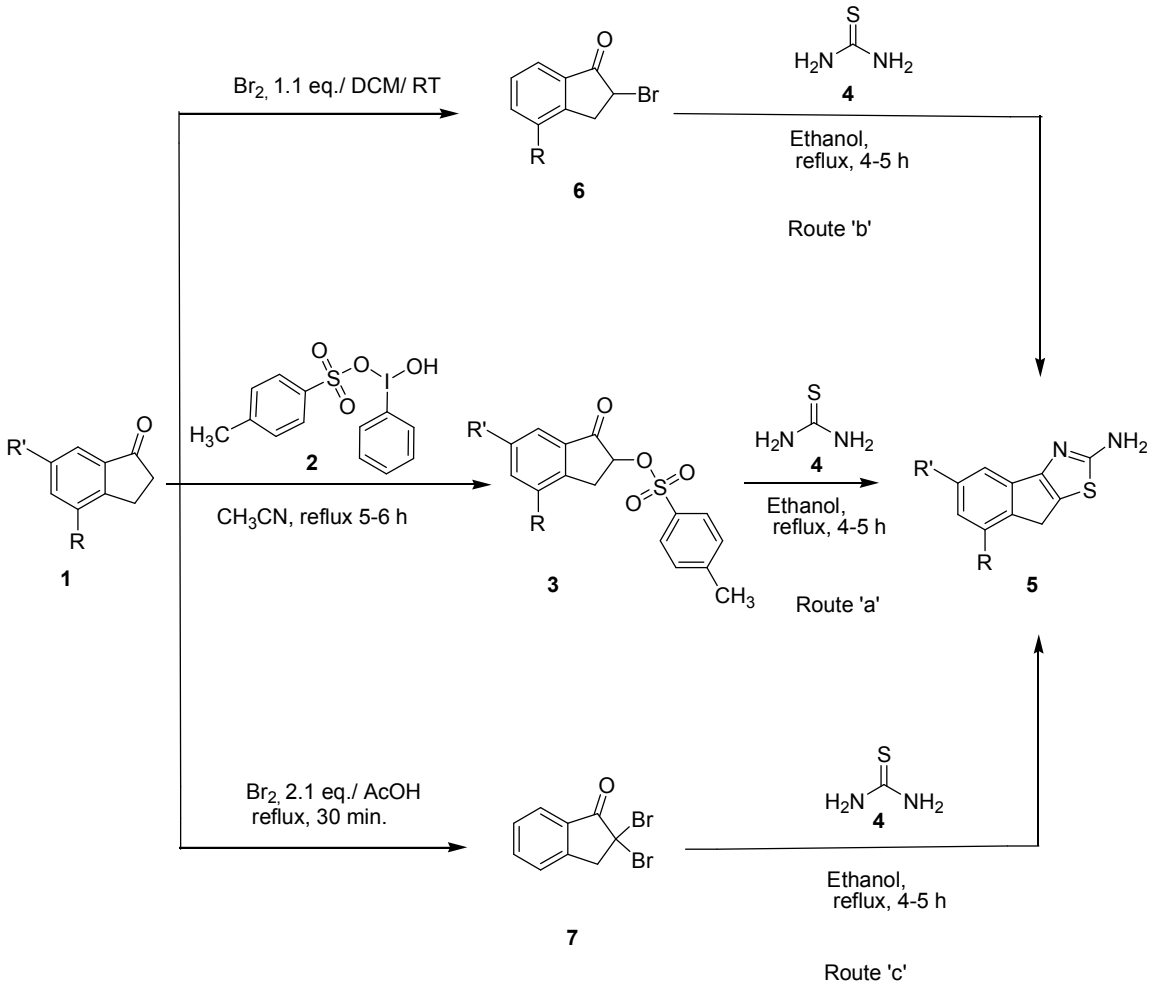

Scheme 1. Synthesis of 5/7-alkyl-8*H*-indeno[1,2-d]thiazol-2-amines (**5**).