A ONE-STEP SYNTHESIS OF 2,3-DIHYDRO-1,4-BENZOTHIAZINES AND PHENOTHIAZINES FROM 1,3-THIAZOLIDINE DERIVATIVES OF CYCLOHEXANONES

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Abstract - *N*-Acetyl-1,3-thiazolidine derivatives of cyclohexanones, when treated with a threefold excess *N*-bromosuccinimide in anhydrous chloroform at room temperature, smoothly afford *N*-acetyl-2,3-dihydro-1,4-benzothiazines. This represents the first general route to such heterocyclic system in one step from aliphatic precursors. The synthesis of optically active *N*-acetyl-2,3-dihydro-1,4-benzothiazines is also reported.

As a part of our current work on halogen-promoted rearrangements of ethanediyl *O*, *S*- and *S*, *S*-acetals,[1,2] we report in this paper a one-step general synthesis of *N*-acylated 2,3-dihydro-1,4-benzothiazines and phenothiazines. This procedure exploits a novel rearrangement of *N*-acetyl-1,3-thiazolidine derivatives of cyclohexanones that, under our conditions, undergo the heterocyclic ring expansion and concurrent aromatization of the carbocyclic ring.

The starting *N*-acetyl-1,3-thiazolidines are readily prepared by reaction of either cyclohexanone or substituted cyclohexanones with the proper 1,2-aminothiol under the conditions already reported in the literature.[3] Optically active cysteines are conveniently used for introducing a chiral center at C-3'. For the preparation of 1,3-benzothiazolidines, *o*-mercaptoaniline is used under the same conditions. The acylation of the nitrogen atom in the starting materials is necessary to avoid reaction with bromine during the rearrangement. The conversions take place under mild conditions –treatment with a threefold excess *N*-bromosuccinimide in anhydrous chloroform at room temperature for minutes– and the 2,3-dihydro-1,4-benzothiazines are obtained in high yields (see experimental). The regiochemistry of the heterocyclic ring expansion is determined by the sulfur atom migration that occurs quantitatively toward the less substituted vicinal position in the carbocyclic ring. It is

Table *N*-Acetylated 2,3-Dihydro-1,4-benzothiazines and Phenothiazines: Relevant Nmr Signals.

Compound	R^1	R^2	R^3	^1H Nmr
2a	H	H	H	2.15 (*s*, 3H, MeCO), 3.13 (*t*, 2H, *J* = 6.0 Hz, CH_2S), 4.17 (*t*, 2H, *J* = 6.0 Hz, CH_2N), 7.06-7.22 (*m*, 4H, aromatic Hs).
2b	H	H	CO_2Me	2.10 (*s*, 3H, MeCO), 3.08 and 3.41 (2 *m*, 2H, CH_2S), 3.63 (*s*, 3H, CO_2Me), 5.67 (*m*, 1H, CHN), 7.10-7.31 (*m*, 4H, aromatic Hs).
2c	H	Me	H	2.10 (*s*, 3H, MeCO), 2.30 (*s*, 3H, aromatic Me), 3.05 (*m*, 2H, CH_2S), 3.47 (*m*, 2H, CH_2N), 7.15 (*m*, 3H, aromatic Hs).
2d	Bu^t	H	H	1.24 (*s*, 9H, Bu^t), 2.10 (*s*, 3H, MeCO), 3.14 (*t*, 2H, *J* = 6.0 Hz, CH_2S), 3.89 (*t*, 2H, *J* = 6.0 Hz, CH_2N), 7.00-7.16 (*m*, 3H, aromatic Hs).
4	--	--	--	2.01 (*s*, 3H, MeCO), 2.15 (*s*, 3H, aromatic Me), 3.55 (*m*, 2H, CH_2S), 3.72 (*s*, 3H, CO_2Me), 5.85 (*m*, 1H, CHN), 7.36 (*s*, 1H, aromatic H).
6a	H	--	--	2.18 (*s*, 3H, MeCO), 6.75-7.35 (*m*, 8H, aromatic Hs).
6b*	Me	--	--	2.15 (*s*, 3H, MeCO), 2.36 (*s*, 3H, aromatic Me), 6.80-7.22 (*m*, 7H, aromatic Hs).

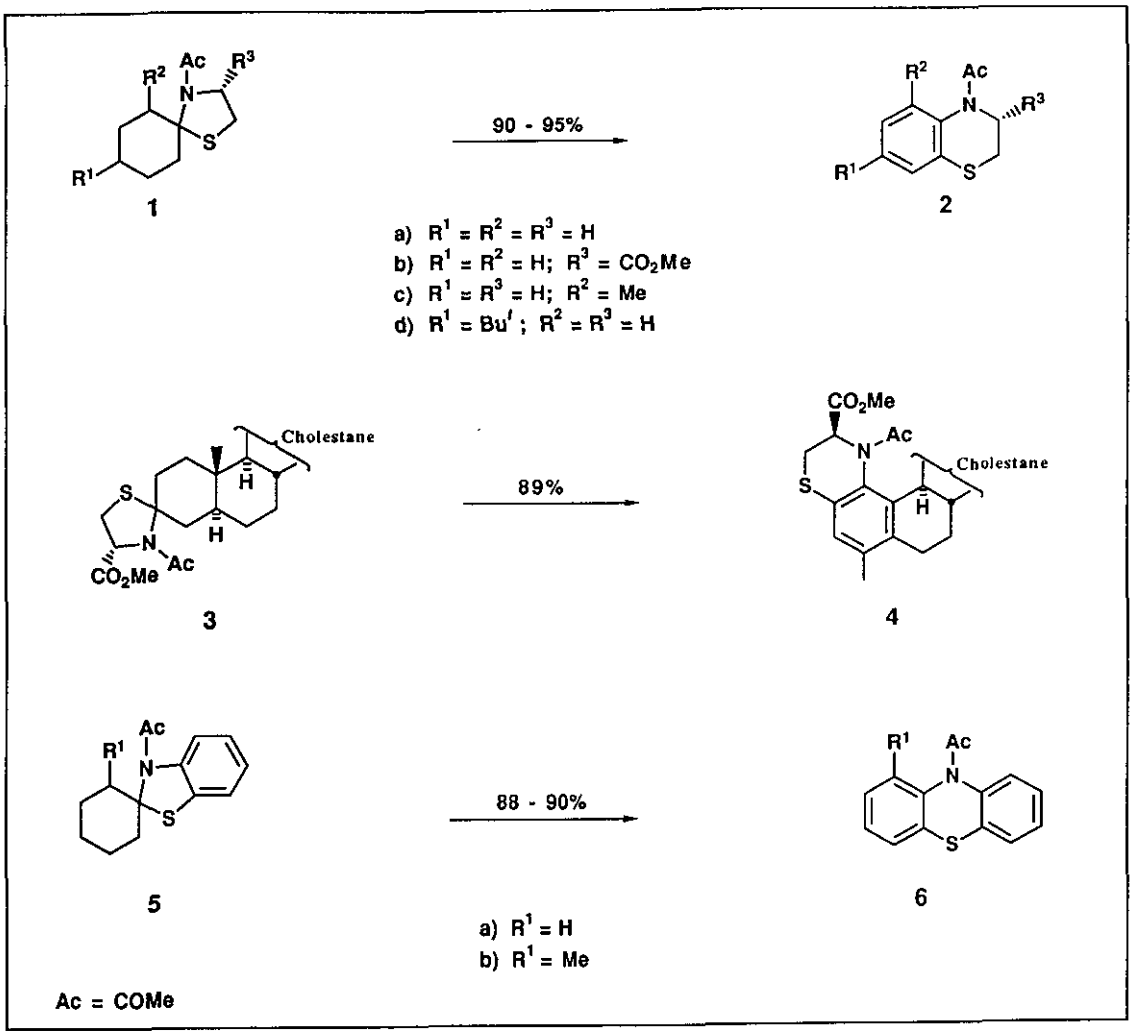
*Characterized after acid hydrolysis.

noteworthy that, under such conditions, no racemization occurs and chirality, if present on the heterocyclic ring of the starting 1,3-thiazolidines, is preserved in the final products.

EXPERIMENTAL

Commercially available *N*-bromosuccinimide (Carlo Erba) was crystallized from water and dried before use. ^1H Nmr spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solutions.

Reaction of cyclohexanone N-*acetyl-1,3-thiazolidine derivative with* N-*bromosuccinimide. Typical procedure.* To a solution of the title compound (**1a**) (1.00 g; 4.6 mmol) in anhydrous chloroform (70 ml), at room temperature and under magnetic stirring, *N*-bromosuccinimide (2.94 g; 13.8 mmol) dissolved in the same



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solvent (20 ml) is added slowly. Stirred for 30 min at room temperature (tlc monitoring), the reaction mixture is then quenched by adding excess solid sodium carbonate and then water: the chloroform layer is washed with 5 N aq. sodium thiosulfate (25 ml), and then with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. The oily crude residue, after chromatography on silica gel (chloroform), affords the pure *N*-acetyl-2,3-dihydro-1,4-benzothiazine (**2a**) (0.76 g; 92 % yield), oil; ^{1}H nmr: see Table; m/z = 193 (M^+). *Anal.* Calcd for $C_{10}H_{11}NOS$: C, 53.32; H, 4.92. Found: C, 53.15; H, 4.86.

Under the same conditions the following conversions were performed:

1b into **2b** (92% yield) oil; $[\alpha]_D^{25}$ = -28° (c = 10.8, chloroform); ^{1}H nmr: see Table; m/z = 251 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21. Found: C, 57.49; H, 5.15.

1c into **2c** (90% yield) oil; ^{1}H nmr: see Table; m/z = 207 (M^+). *Anal.* Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32. Found: 63.89; H, 6.26.

1d into **2d** (95% yield) mp 110-112° C (from *n*-hexane); ^{1}H nmr: see Table; m/z = 249 (M^+). *Anal.* Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68. Found: C, 67.29; H, 7.73.

3 into **4** (89% yield) mp 69-71° C (from methanol); $[\alpha]_D^{25}$ = +13° (c = 8.1, chloroform); ^{1}H nmr: see Table (for the rearrangement of the steroidal skeleton, see ref. 4); m/z = 539 (M^+). *Anal.* Calcd for $C_{33}H_{49}NO_3S$: C, 73.42; H, 9.14. Found: C, 73.31; H, 9.18.

Preparation of N-acetylphenothiazines. Under the conditions reported above, the *N*-acetylphenothiazines (**6a**) and (**6b**) were obtained from their corresponding 1,3-benzothiazolidines. The compound(**6a**)(88% yield) was a crystalline solid, mp 198-199° C (from ethanol) (lit.,[5] 197-198° C); ^{1}H nmr: see Table; m/z = 241 (M^+). *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59. Found: C, 69.80; H, 4.63.

The compound **6b** (90% yield) was a semicrystalline low-melting solid which was hydrolyzed[6] to afford its *N*-deacetyl derivative, mp 139-140° C (from methanol) (lit.,[7] 137.5-138.5); ^{1}H nmr: see Table; m/z = 269 (M^+). *Anal.* Calcd. for $C_{15}H_{13}NOS$: C,70.56; H, 5.13. Found: C,70.45; H, 4.09.

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