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A convenient synthesis of dihydro- and tetrahydro-1,3-thiazine derivatives from β-aryl-β-amino acids

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Abstract—A facile synthesis of 2-alkyl-4-aryl-5,6-dihydro-4*H*-1,3-thiazines and *cis*-2-alkyl-4-aryl-3,4,5,6-tetrahydro-2*H*-1,3-thiazines with potential therapeutic interest was achieved starting from readily accessible β-aryl-β-amino acids.

The literature for heterocyclic pharmaceutical agents includes sulfur-containing compounds that have been reported as antimalarial agents,[1] HIV-1 inhibitors,[2] and antimicrobial agents.[3] Among these derivatives, several 5,6-dihydro-4*H*-1,3-thiazines were recently reported as cholecystokinin antagonists[4] or antimycobacterial agents.[5]

With the aim to enlarge this chemical family with potential therapeutic interest, we wish to describe herein a facile synthesis of 2-alkyl-4-aryl-5,6-dihydro-4*H*-1,3-thiazines and *cis*-2-alkyl-4-aryl-3,4,5,6-tetrahydro-2*H*-1,3-thiazines starting from readily accessible β-aryl-β-amino acids.

In a first step, β-aryl-β-amino acids **2a**–**c** were readily prepared by applying the Rodionow–Johnson procedure[6] using the appropriate arylcarboxaldehyde **1a**–**c**. The former were then treated with 2 equiv of $LiAlH_4$ in refluxing THF to afford the alcohols **3a**–**c**. The third step consisted of acylation of the amine using acetic anhydride in pyridine, which at the same time led to protection of the hydroxyl function. Lawesson's reagent[7] was used to convert the amide to the corresponding thioamide in excellent yields and the ester group was cleaved under aqueous alkaline conditions to afford derivatives **6a**–**c**.

The Mitsunobu procedure[8,9] was used to perform the internal cyclization of hydroxy substituted thioamides **6a**–**c** using 1.5 equiv of PPh_3/DEAD in toluene. After 48 h at room temperature the reaction was complete, however the expected products **7a**–**c** were isolated only with difficulty by silica gel column chromatography. Alternatively a method involving activation of hydroxyl group with mesyl chloride in the presence of Et_3N[10] led to the isolation of compounds **7a**–**c** after 12 h and with an easier purification step.

The selective reduction of the C=N double bond has been shown to occur with excellent diastereoselectivity to generate stereospecifically *trans*- or *cis*-2,6-disubstituted piperidines[11] and tetrasubstituted piperazines.[12] In our case we observed that the use of the acid-catalyzed $NaBH_3CN$ reduction,[13] at −20 °C in MeOH, afforded *cis*-tetrahydrothiazines **8a**–**c** with high diastereo-selectivity (only one product was detected by ^1H NMR spectroscopy). By extrapolation, the product was assigned as the *cis* isomer because the rear approach of the hydride ion towards the imino π bond was preferred due to the stabilization of the low-lying vacant orbital of the imine through electron delocalization from the sulfur lone-pair electrons into this latter.[11] This hypothesis was confirmed by the coupling constants measured from the ^1H NMR spectra (Scheme 1).

In summary, this procedure can be easily generalized because of the easy access to a large variety of β-aryl-β-amino acid starting materials.[14]

The biological evaluation of these new compounds is now under investigation.

Keywords: 5,6-Dihydro-4*H*-1,3-thiazines; 3,4,5,6-Tetrahydro-2*H*-1,3-thiazines; β-Aryl-β-amino acids.
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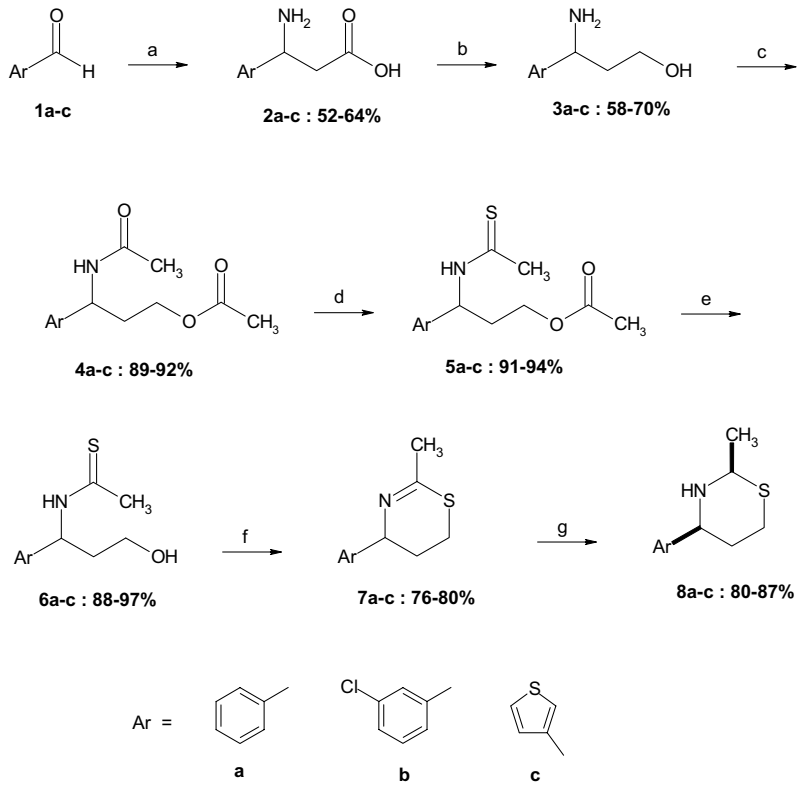

Scheme 1. Reagents and conditions: (a) Ammonium acetate (2 equiv), malonic acid (1 equiv), EtOH, reflux, 6 h; (b) $LiAlH_4$ (2 equiv), THF, reflux, 12 h; (c) Acetic anhydride (5 equiv), pyridine, rt, 12 h; (d) Lawesson's reagent (0.55 equiv), THF, 40 °C, 2 h; (e) NaOH 4 N, THF/H_2O (1:1), rt, 2 h; (f) Method A: PPh_3 (1.5 equiv), DEAD (1.5 equiv), toluene, rt, 48 h; Method B: MsCl (1.05 equiv), Et_3N (2.1 equiv), CH_2Cl_2, rt, 12 h; (g) PPTS (2 equiv), $NaBH_3CN$ (2 equiv), MeOH, −20 °C to rt, 4 h.

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14. All new compounds reported were characterised (IR, ^1H and ^{13}C NMR, HRMS and/or elemental analyses). Typical experimental procedure: To a solution of **3a** (3.30 mmol) in dry pyridine (5 mL) was added dropwise acetic anhydride (16.50 mmol) and the reaction mixture was stirred for 12 h at rt. The solvents were evaporated under reduced pressure and the residue was poured into 10% aqueous solution of K_2CO_3. The resulting mixture was extracted with CH_2Cl_2, dried over calcium chloride and evaporated to dryness. The residue was purified by silica gel chromatography using diethyl ether as eluent to give 3-acetylamino-3-phenylpropyl acetate **4a** (91%) as white crystals. Mp: 90 °C. IR (KBr) 3311, 3060, 3029, 2972, 2923, 2839, 1732, 1650, 1547, 1426, 1370, 1242, 756, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H, H_{arom}), 5.97 (d, $^3J = 7.9$ Hz, 1H, NH), 5.12 (m, 1H,

CH), 4.05 (m, 2H, CH_2O), 2.14 (m, 2H, CH_2), 2.01 (s, 3H, CH_3CO_2), 1.98 (s, 3H, CH_3CONH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.3, 141.2, 128.7, 127.6, 126.4, 61.3, 50.6, 34.7, 23.3, 20.9. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.44; N, 5.81. To a solution of **4a** (2.10 mmol) in dry THF (10 mL) was added Lawesson's reagent (1.155 mmol) in one portion. After stirring for 2 h at 40 °C, the reaction mixture was quenched with water and extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography on silica gel eluting with Et_2O/petroleum ether (8:2) to give the pure 3-thioacetylamino-3-phenylpropyl acetate **5a** (94%) as a colourless oil. IR (KBr) 3302, 3240, 3030, 2953, 1738, 1720, 1534, 1456, 1384, 1368, 1242, 1172, 1039, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d; $^3J = 6.2$ Hz, 1H, NH), 7.38–7.30 (m, 5H, H_{arom}), 5.76 (m, 1H, CH), 4.08 (m, 2H, CH_2O), 2.54 (s, 3H, $CH_3C{=}S$), 2.37 (m, 1H, C*H*H), 2.23 (m, 1H, CH*H*), 2.01 (s, 3H, $CH_3C{=}O$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 171.1, 139.2, 128.9, 128.1, 126.8, 61.2, 56.7, 34.4, 33.4, 20.9. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 61.89; H, 6.68; N, 5.73. To a stirred solution of **5a** (1.90 mmol) in THF (5 mL) was added an aqueous NaOH (4 M) solution (5 mL). After stirring for 2 h at rt, the solution was neutralized with an aqueous HCl (4 M) solution and extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with Et_2O to give the pure *N*-(3-hydroxy-1-phenylpropyl)thioacetamide **6a** (97%) as white crystals. Mp: 126 °C. IR (KBr) 3280, 3225, 3048, 2955, 2929, 2881, 1659, 1549, 1452, 1391, 1364, 1246, 1020, 724, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $^3J = 6.4$ Hz, 1H, NH), 7.39–7.30 (m, 5H, H_{arom}), 5.87 (m, 1H, CH), 3.68 (m, 2H, CH_2OH), 2.89 (br s, 1H, OH), 2.58 (s, 3H, $CH_3C{=}S$), 2.21 (m, 1H, C*H*H), 2.04 (m, 1H, CH*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 139.3, 128.7, 127.8, 126.8, 58.5, 57.0, 36.9, 34.0. Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.25; H, 7.29; N, 6.80. Synthesis of 2-methyl-4-phenyl-5,6-dihydro-4*H*-1,3-thiazine **7a**, Method A: To a stirred solution of **6a** (2.20 mmol) in dry toluene (5 mL), cooled in an ice bath, were added successively PPh_3 (3.30 mmol) and DEAD (3.30 mmol). The reaction mixture was stirred for 48 h at rt and a white precipitate of diethyl hydrazine-*N*,*N*′-dicarboxylate was formed. The precipitate was filtered off and the solvent was removed in vacuo. The crude mixture was chromatographed on silica gel using Et_2O/petroleum ether (1:1) to afford the pure compound **7a** (76%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H, H_{arom}), 4.58 (d, $^3J = 6.8$ Hz, 1H, CH), 3.06 (ddd, $^2J = 12.2$ Hz, $^3J = 4.0$, 10.0 Hz, 1H, C*H*HS), 2.85 (ddd, $^2J = 12.2$ Hz, $^3J = 3.9$, 6.6 Hz, 1H, CH*H*S), 2.22 (d, $^4J = 1.2$ Hz, 3H, CH_3), 2.10 (m, 1H, C*H*H), 1.69 (m, 1H, CH*H*). ^{13}C (100 MHz, $CDCl_3$) δ 157.8, 143.7, 128.2, 126.6, 126.5, 59.4, 28.1, 26.7, 24.6. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.81; H, 6.80; N, 7.42. Method B: To a stirred solution of **6a** (2.20 mmol) in dry dichloromethane, cooled in an ice bath, were added successively Et_3N (4.62 mmol) and mesyl chloride (2.31 mmol). The reaction mixture was stirred for 12 h at rt. After addition of water, the solution was extracted twice with dichloromethane. The combined organic layers were dried over calcium chloride and evaporated to dryness. The residue was purified by silica gel chromatography to afford **7a** (79%). To a solution of **7a** (1.30 mmol) in dry methanol (5 mL), cooled at −20 °C, were added successively PPTS (2.60 mmol) and sodium cyanoborohydride (2.60 mmol). The reaction mixture was slowly allowed to warm to rt over 4 h and then quenched with a saturated aqueous $NaHCO_3$ solution. The solution was extracted twice with $CHCl_3$, the combined organic layers were dried over calcium chloride and evaporated to dryness. The residue was purified by silica gel chromatography using Et_2O to afford the pure 2-methyl-4-phenyltetrahydro-2*H*-1,3-thiazine **8a** (82%) as white crystals. Mp: 59 °C. IR (KBr) 3288, 3056, 3025, 2966, 2926, 2888, 1469, 1424, 1364, 1249, 1131, 812, 736, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H, $H_{arom.}$), 4.34 (q, $^3J = 6.5$ Hz, 1H, C*H*CH_3), 3.77 (dd, $^3J = 2.2$, 11.7 Hz, 1H, CHPh), 3.19 (m, 1H, C*H*HS), 2.93 (m, 1H, CH*H*S), 2.03 (m, 1H, C*H*H), 1.67 (m, 1H, CH*H*), 1.45 (d, $^3J = 6,5$ Hz, 3H, CH_3). Anal. Calcd for $C_{11}H_{15}NS$: C, 68.35; H, 7.82; N, 7.25. Found: C, 68.44; H, 8.01; N, 7.21.