Published in final edited form as:

Synth Commun. 2011 ; 41(7): 2615–2623. doi:10.1080/00397911.2010.515335.

SYNTHESIS OF N-SUBSTITUTED CARBONYLAMINO-1,2,3,6-TETRAHYDROPYRIDINES AS POTENTIAL ANTI-INFLAMMATORY AGENTS

Mohammad A. Ghaffari, Tiffany W. Ardley, Madhavi Gangapuram, and Kinfe K. Redda
College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida, USA

Abstract

Several N-substituted carbonyl/sulfonylamino-1,2,3,6-tetrahydropyridines (**5a–i** and **9a, b**) were synthesized via sodium borohydride reduction of the corresponding N-substituted imino-pyridinium ylides (**4a–i** and **8a, b**) in absolute ethanol.

Keywords

Inflammation; tetrahydropyridine (THP)

INTRODUCTION

Inflammation is a local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function. It initiates the elimination of noxious agents and damaged tissue.^[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are generally effective and widely used for treatment of inflammatory conditions.^[2–5] Several compounds consisting of reduced pyridines, such as the 1,2,3,6-tetrahydropyridine (THP) ring system, are known to exhibit a variety of biological activities.^[6] The biological activities of these compounds were dependent on the position and nature of substituents on the THP ring system.^[7–13]

In a new approach, the carbonyl group of the THPs was replaced with a sulfonyl group, which resulted in isolating new derivatives with significant anti-inflammatory activities.^[14,15]

The synthesis of target compounds (**5a–i**) is shown in Scheme 1 and that of compounds (**9a, b**) in Scheme 2. In Scheme 1, 1-chloro-2,4-dinitrobenzene (**1**) was refluxed with substituted pyridines (**2**) in the presence of acetone. This nucleophilic aromatic substitution reaction gave 2,4-dinitrophenyl-substituted pyridinium chloride (**3**). The pyridinium chloride salt and benzoyl/pyridyl sulfonyl or carbonyl hydrazides were reacted at room temperature using methanol as a solvent with excess triethylamine (Et₃N). The resulting residues were hydrolyzed using a *p*-dioxane/water mixture (4:1 v/v) and furnished pyridinium ylides (**4a–i**). Sodium borohydride reduction of the ylides afforded the appropriate tetrahydropyridines (**5a–i**).

In Scheme 2, 3-ethylpyridine (**1**) reacted with O-mesitylenesulfonyl hydroxylamine (**6**)^[16] to furnish N-amino-3-ethylpyridinium mesitylenesulfonate (**7**). The reaction of **7** with substituted acid chlorides in the presence of tetrahydrofuran (THF) and later in saturated sodium bicarbonate furnished the corresponding ylides (**8a, b**). Sodium borohydride reduction of the ylides afforded the appropriate tetrahydro-pyridines (**9a, b**).

RESULTS

The analytical data for the substituted 1,2,3,6-tetrahydropyridines are presented in Table 1.

EXPERIMENTAL

Materials

¹H NMR spectra were determined on a Bruker HX 270-MHz spectrometer using CDCl₃ as a solvent. Elemental analysis was performed by Galbraith Laboratories Inc., Knoxville, TN. Melting points were determined on Gallenkamp capillary melting apparatus and were uncorrected. Chemicals and solvents were purchased from Aldrich Chemical Company Inc., Milwaukee, WI; Fluka Chemical Corporation, Ronkonkoma, NY; and Fisher Scientific Company, Orlando, FL. Separations on column chromatography were performed on silica gel (Porasil silica, 55–105 mesh). Analytical thin-layer chromatography (TLC) was performed on Whatman PE SIL G/UV, 250-mm-layer flexible plates.

General Procedure A

N-(Benzenesulfonylimino)-4-phenylpyridinium ylide (4a)—4-Phenylpyridine (7.25 g, 46.64 mmol) was added to a stirring solution of 1-chloro-2,4-dinitrobenzene (9.45 g, 46.64 mmol) in 125 mL of acetone, and the mixture was refluxed for 17 h. The product was cooled to room temperature and filtered. The residue was washed with acetone and dried under vacuum. The product, N-(2,4-dinitrophenyl)-4-phenyl pyridinium chloride (8.2 g, 49% yield), was collected. The pyridinium salt (2.146 g, 6 mmol) was dissolved and stirred in 35 mL of methanol for about 10 min at 0 °C before 1.03 g (6 mmol) of benzenesulfonyl hydrazide was added. To this solution, 0.5 mL of triethylamine was added, and the mixture was stirred at ice-bath temperature until the ice melted. Stirring and continued at room temperature for 17 h. The solvent was evaporated, and the residue was crystallized with ethyl acetate. The product, a 2,4-dinitroanilo derivative (0.9 g), was isolated as a solid. The product was purified by silica-gel column chromatography. The impurities were eluted starting from 10–35% ethyl acetate/hexane and 100% methylene chloride. The product was eluted in 50% ethyl acetate/methylene chloride. The product was immediately refluxed in water/1,4-dioxane (50 mL, 1:4 v/v) for 10 h. The solution was concentrated, and the dark brown residue was chromatographed on a silicagel column. The product was eluted in 30% ethyl acetate/methylene chloride, which furnished **4a** in 22% yield. Mp 218–219 °C. ¹H NMR (CDCl₃): δ 8.41 (d, *J* = 2.0 Hz, 2H), 7.76 (d, *J* = 2.0 Hz, 2H), 7.72 (d, *J* = 2.0 Hz, 2H), 7.64 (dd, *J* = 1.0, 2.0 Hz, 2H), 7.51–7.58 (m, 3H), 7.35–7.45 (m, 3H).

N-(2-Furoylimino)-4-phenylpyridinium ylide (4b)—The compound **4b** was obtained as solid; 27% yield, mp 228–229 °C. ¹H NMR (CDCl₃): δ 8.83 (d, *J* = 2.0 Hz, 1H), 8.86–8.81 (m, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.86–7.81 (m, 1H), 7.72–7.67 (m, 2H), 7.58–7.53 (m, 3H), 7.51–7.48 (m, 1H), 7.07 (dd, *J* = 1.0, 2.0 Hz, 1H), 6.46 (dd, *J* = 1.0, 2.0 Hz, 1H).

N-(2-Thiophenecarboylimino)-4-phenylpyridinium ylide (4c)—The compound **4c** was obtained as a white solid; 48% yield, mp 210–211 °C. ¹H NMR (CDCl₃): δ 8.84 (d, *J* = 2.0 Hz, 1H), 8.86–8.82 (m, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.85–7.80 (m, 1H), 7.76 (dd, *J* =

1.0, 2.0 Hz, 1H), 7.2–7.67 (m, 2H), 7.59–7.52 (m, 3H), 7.36 (dd, J = 1.0, 2.0 Hz, 1H), 7.06 (dd, J = 1.0, 2.0 Hz, 1H).

N-(4-Methylbenzenesulfonylimino)-4-phenylpyridinium ylide (4d)—The compound **4d** was obtained as white powder; yield 48%, mp 214–215 °C. ^1H NMR (CDCl_3): δ 8.41 (d, J = 2.0 Hz, 2H), 7.71 (d, J = 2.0 Hz, 2H), 7.61–7.66 (m, 4H), 7.51–7.58 (m, 3H), 7.16 (d, J = 3.0 Hz, 2H), 2.34 (s, 3H, CH_3).

N-(4-Methylbenzenesulfonylimino)-5-phenylpyridinium ylide (4e)—The compound **4e** was obtained as solid; 22% yield, mp 157–158 °C. ^1H NMR (CDCl_3): δ 8.60 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 3.0 Hz, 2H), 7.60 (dd, J = 1.0, 2.0 Hz, 1H), 7.46–7.51 (m, 3H), 7.38–7.43 (m, 2H), 7.17 (d, J = 3.0 Hz, 2H), 2.35 (s, 3H, CH_3).

N-(2-Furoylimino)-5-phenylpyridinium ylide (4f)—The compound **4f** was obtained as an oil; 30% yield. ^1H NMR (CDCl_3): δ 9.04 (s, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.07 (d, J = 2.5 Hz, 1H), 7.73 (dd, J = 2.5, 2.0 Hz, 1H), 7.46–7.61 (m, 6H), 7.07 (d, J = 1.0 Hz, 1H), 6.46 (dd, J = 1.2, 0.6 Hz, 1H).

N-(2-Thiophenecarboylimino)-5-phenylpyridinium ylide (4g)—The compound **4g** was obtained as an oil; 35% yield. ^1H NMR (CDCl_3): δ 9.04 (s, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 2.5 Hz, 1H), 7.76 (dd, J = 1.0, 0.5 Hz, 1H), 7.70 (dd, J = 2.0, 2.5 Hz, 1H), 7.47–7.63 (m, 5H), 7.36 (dd, J = 2.0, 0.5 Hz, 1H), 7.07 (dd, J = 1.2, 1.7 Hz, 1H).

N-(2-Furoylimino)-4-*tert*-butylpyridinium ylide (4h)—The compound **4h** was obtained as a solid; 20% yield, mp 228–229 °C. ^1H NMR (CDCl_3): δ 8.64 (d, J = 2.0 Hz, 2H), 7.60 (d, J = 2.0 Hz, 2H), 7.47 (s, 1H), 7.04 (d, J = 1.0 Hz, 1H), 6.44 (dd, J = 1.0, 2.0 Hz, 1H), 1.38 (s, 9H, $3 \times \text{CH}_3$).

N-(2-Thiophenecarboylimino)-4-*tert*-butylpyridinium ylide (4i)—The compound **4i** was obtained as white solid; 20% yield, mp 229–230 °C. ^1H NMR (CDCl_3): δ 8.64 (d, J = 2.0 Hz, 2H), 7.73 (dd, J = 1.0, 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 2H), 7.34 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 1.0, 2.0 Hz, 1H), 1.37 (s, 9H, $3 \times \text{CH}_3$).

General Procedure B

N-(2-Furoylimino)-5-ethyl-pyridinium ylide (8a)—To an ice-cooled solution of 3-ethyl pyridine (2.36 g, 22 mmol) in 10 ml of methylene chloride was added dropwise *O*-mesitylenesulfonylhydroxamine^[11] (4.73 g, 22 mmol) in 10 ml methylene chloride over 5 min with stirring. After 15 min, the ice bath was removed, and stirring continued for 1 h at room temperature. The reaction mixture was concentrated to half the volume. Ether and hexane were added. The oil that formed was separated, decanted from the solvent, and dried under high vacuum to give 3-ethyl pyridinium-mesitylenesulfonate (6.12 g, 86%). The *N*-aminopyridinium salt (6.12 g, 19 mmol) in 25 ml anhydrous tetrahydrofuran (THF) was added to 2-furoyl chloride (2.48 g, 19 mmol) at low temperature (ice bath). It was warmed to room temperature and stirred at 70 °C for 14–16 h, and then 50 ml of saturated sodium bicarbonate (NaHCO_3) solution was added to quench the reaction. The product was extracted with 3×50 ml of methylene chloride and dried over sodium sulfate. After filtration, the solvent was evaporated, and the residue was purified by column chromatography using silica gel (200–425 mesh). The product *N*-(2-furoylimino)-5-ethyl-pyridinium ylide **8a** was eluted with 40% ethyl acetate/methylene chloride as an oil in 65% yield. ^1H NMR (CDCl_3): δ 8.59 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H),

7.56 (t, 1H), 7.46 (s, 1H), 7.03 (d, $J = 1.0$ Hz, 1H), 6.43 (dd, $J = 1.0, 2.0$ Hz, 1H), 2.76 (q, $J = 3.0$ Hz, 2H, CH_2CH_3), 1.29 (t, $J = 3.0$ Hz, 3H, CH_2CH_3).

N-(2-Thiophenecarboylimino)-5-ethyl-pyridinium ylide (8b)—The compound **8b** was obtained as a solid; 60% yield, mp 111–112 °C. ^1H NMR (CDCl_3): δ 8.64 (s, 1H), 8.63 (d, $J = 2.0$ Hz, 1H), 7.76–7.71 (m, 2H), 7.55 (t, 1H), 7.34 (dd, $J = 1.0, 2.0$ Hz, 1H), 7.05 (dd, $J = 1.0, 2.0$ Hz, 1H), 2.78 (q, $J = 3.0$ Hz, 2H, CH_2CH_3), 1.31 (t, $J = 3.0$ Hz, 3H, CH_2CH_3).

General Procedure for Reduction

N-(2-Furoylamino)-5-ethyl-1,2,3,6-tetrahydropyridine (9a)—Sodium borohydride (1.9 g, 50 mmol) was added in small portions to a solution of **8a** (1 g, 5 mmol) in 75 mL of absolute ethanol over a period of 1 h at 0 °C. The reaction mixture was stirred at the same temperature for 2 h, then placed into a refrigerator, and left for 15 h. The reaction was quenched by adding cold water and extracted with methylene chloride (3×50 mL). It was then dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified over a silica-gel column. The product **9a** was eluted in 30% ethyl acetate/hexane. It was crystallized with ethyl acetate/hexane as a white solid in 60% yield, mp 122–123 °C. ^1H NMR (CDCl_3): δ 7.40 (br, s, 1H, C_5' -H), 7.32 (s, NH, D_2O exchangeable), 7.15 (d, $J = 1.0$ Hz, 1H, C_3' -H), 6.48 (dd, $J = 0.5, 1.0$ Hz, 1H, C_4' -H), 5.47 (m, 1H, C_4 -H), 3.37 (br, s, 2H, C_6 -H), 3.03 (t, $J = 2.0$ Hz, 2H, C_2 -H), 2.28 (m, 2H, C_3 -H), 1.94 (q, $J = 2.5$ Hz, 2H, CH_2CH_3), 0.99 (t, $J = 2.5$ Hz, 3H, CH_2CH_3). Anal. calc. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ (220.12): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.43; H, 7.50; N, 12.67.

N-(2-Thiophenecarboylimino)-5-ethyl-1,2,3,6-tetrahydropyridine (9b)—The compound **9b** was obtained as a white crystalline solid; 80% yield, mp 110–111 °C. ^1H NMR (CDCl_3): δ 8.07 (brs, 1H, C_5' -H), 7.51 (d, $J = 1.5$ Hz, 1H, C_3' -H), 7.08 (t, $J = 1.5$ Hz, 1H, C_4' -H), 6.52 (s, NH, D_2O exchangeable), 5.51 (m, 1H, C_4 -H), 3.48 (d, $J = 5.0$ Hz, 1H), 3.11 (m, 1H), 3.03 (d, $J = 5.0$ Hz, 1H), 2.72 (m, 1H), 2.50 (m, 1H), 2.18 (d, $J = 5.0$ Hz, 1H), 1.95 (q, $J = 2.5$ Hz, 2H, CH_2CH_3), 1.01 (t, $J = 2.5$ Hz, 3H, CH_2CH_3). Anal. calc. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS}$ (236.1): C, 60.99; H, 6.82; N, 11.85. Found: C, 60.88; H, 6.99; N, 11.73.

N-(Benzenesulfonylimino)-4-phenyl-1,2,3,6-tetrahydropyridine (5a)—The compound **5a** was obtained as a white solid; 30% yield, mp 159–160 °C. ^1H NMR (CDCl_3): δ 7.97 (d, $J = 2.5$ Hz, 2H), 7.60 (m, 1H), 7.52 (d, $J = 2.5$ Hz, 2H), 7.22–7.33 (m, 5H), 5.85 (m, 1H, C_5 -H), 5.54 (s, 1H, NH, D_2O exchangeable), 3.33 (m, 2H, C_6 -H), 2.87 (t, $J = 2.0$ Hz, 2H, C_2 -H), 2.50 (m, 2H, C_3 -H). Anal. calc. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (314.40): C, 64.94; H, 5.77; N, 8.91. Found: C, 64.82; H, 5.92; N, 8.87.

N-(2-Furoylamino)-4-phenyl-1,2,3,6-tetrahydropyridine (5b)—The compound **5b** was obtained as a white solid; 83% yield, mp 193–194 °C. ^1H NMR (CDCl_3): δ 7.22–7.43 (m, 7H, NH, D_2O exchangeable), 7.18 (d, $J = 1.0$ Hz, 1H, C_3' -H), 6.49 (dd, $J = 0.5, 1.0$ Hz, 1H, C_4' -H), 6.02 (m, 1H, C_5 -H), 3.68 (m, 2H, C_6 -H), 3.24 (t, $J = 2.0$ Hz, 2H, C_2 -H), 2.73 (m, 2H, C_3 -H). Anal. calc. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ (268.12): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.49; H, 6.12; N, 10.38.

N-(2-Thiophenecarboylimino)-4-phenyl-1,2,3,6-tetrahydropyridine (5c)—The compound **5c** was obtained as a white crystalline solid; 73% yield, mp 202–204 °C. ^1H NMR (CDCl_3): δ 8.10 (s, 1H), 7.25–7.55 (m, 6H), 7.08 (t, $J = 1.5$ Hz, 1H), 6.74 (s, 1H, NH, D_2O exchangeable), 6.06 (m, 1H, C_4' -H), 3.80 (d, $J = 5.0$ Hz, 1H, C_6 , H), 3.33 (m, 2H), 2.92–3.10 (m, 2H), 2.60 (d, $J = 5.0$ Hz, 1H). Anal. calc. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS}$ (284.1): C, 67.58; H, 5.67; N, 9.85. Found: C, 67.72; H, 5.71; N, 9.78.

N-(4-Methylbenzenesulfonylimino)-4-phenyl-1,2,3,6-tetrahydropyridine (5d)—

The compound **5d** was obtained as a white solid; 48% yield, mp 164–165 °C. ¹H NMR (CDCl₃): δ 7.84 (d, *J* = 2.7 Hz, 2H), 7.22–7.33 (m, 7H), 5.85 (m, 1H, C₅-H), 5.49 (s, 1H, NH, D₂O exchangeable), 3.32 (m, 2H, C₆-H), 2.87 (t, *J* = 2.0 Hz, 2H, C₂-H), 2.50 (m, 2H, C₃-H), 2.42 (s, 3H, C₄'-CH₃). Anal. calc. for C₁₈H₂₀N₂O₂S (328.12): C, 65.83; H, 6.14; N, 8.53. Found: C, 65.96; H, 6.30; N, 8.59.

N-(4-Methylbenzenesulfonylimino)-5-phenyl-1,2,3,6-tetrahydropyridine (5e)—

The compound **5e** was obtained as a white solid; 25% yield, mp 149–150 °C. ¹H NMR (CDCl₃): δ 7.85 (d, *J* = 2.7 Hz, 2H), 7.29 (d, *J* = 2.7 Hz, 2H), 7.14–7.27 (m, 5H), 6.05 (m, 1H, C₄-H), 5.59 (s, 1H, NH, D₂O exchangeable), 3.52 (m, 2H, C₆-H), 2.78 (t, *J* = 2.0 Hz, 2H, C₂-H), 2.42 (s, 3H, C₄'-CH₃), 2.28 (m, 2H, C₃-H). Anal. calc. for C₁₈H₂₀N₂O₂S 0.1 H₂O (330.239): C, 65.47; H, 6.10; N, 8.48. Found: C, 65.27; H, 6.29; N, 8.33.

N-(2-Furoylamino)-5-phenyl-1,2,3,6-tetrahydropyridine (5f)—

The compound **5f** was obtained as a solid; 67% yield, mp 145–146 °C. ¹H NMR (CDCl₃): δ 7.45 (s, 1H, NH, D₂O exchangeable), 7.41 (s, 1H), 7.23–7.32 (m, 5H), 7.17 (d, *J* = 1.0 Hz, 1H, C₃'-H), 6.49 (dd, *J* = 0.6, 1.2 Hz, 1H, C₄'-H), 6.15 (m, 1H, C₄-H), 3.87 (m, 2H, C₆-H), 3.16 (t, *J* = 2.0 Hz, 2H, C₂-H), 2.50 (m, 2H, C₃-H). Anal. calc. for C₁₆H₁₆N₂O₂ (268.12): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.19; N, 10.28.

N-(2-Thiophenecarboylamino)-5-phenyl-1,2,3,6-tetrahydropyridine (5g)—The compound **5g** was obtained as a white solid; 54% yield, mp 154–155 °C. ¹H NMR (CDCl₃): δ 8.10 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.22–7.34 (m, 5H), 7.08 (t, *J* = 1.5 Hz, 1H), 6.80 (s, 1H, NH, D₂O exchangeable), 6.19 (m, 1H, C₄'-H), 4.00 (d, *J* = 5.0 Hz, 1H, C₆-H), 3.49 (d, *J* = 5.0 Hz, 1H, C₆-H), 3.22 (m, 1H), 2.68–2.93 (m, 2H), 2.34–2.47 (m, 1H). Anal. calc. for C₁₆H₁₆N₂OS (284.1): C, 67.58; H, 5.67; N, 9.85. Found: C, 67.16; H, 5.82; N, 9.69.

N-(2-Furoylamino)-4-*t*-butyl-1,2,3,6-tetrahydropyridine (5h)—The compound **5h** was obtained as a white solid; 80% yield, mp 174–175 °C. ¹H NMR (CDCl₃): δ 7.40 (s, 1H, C₅'-H), 7.19 (s, 1H, NH, D₂O exchangeable), 7.15 (d, *J* = 1.0 Hz, 1H, C₃'-H), 6.48 (dd, *J* = 0.5, 1.0 Hz, 1H, C₄'-H), 5.37 (m, 1H, C₅-H), 3.46 (brs, 2H, C₆-H), 3.04 (t, *J* = 2.0 Hz, 2H, C₂-H), 2.33 (m, 2H, C₃-H), 1.03 (s, 9H, 3CH₃). Anal. calc. for C₁₄H₂₀N₂O₂ (248.15): C, 67.71; H, 8.12; N, 11.28. Found: C, 67.68; H, 8.32; N, 11.16.

N-(2-Thiophenecarboylamino)-4-*t*-butyl-1,2,3,6-tetrahydropyridine (5i)—The compound **5i** was obtained as a white solid; 73% yield, mp 168–169 °C. ¹H NMR (CDCl₃): δ 8.07 (s, 1H, C₅'-H), 7.52 (d, *J* = 1.5 Hz, 1H, C₃'-H), 7.08 (t, *J* = 1.5 Hz, 1H, C₄'-H), 6.45 (s, 1H, NH, D₂O exchangeable), 6.38 (m, 1H, C₅-H), 3.62 (d, *J* = 6.0 Hz, 1H), 3.14 (m, 2H), 2.75 (m, 1H), 2.56 (m, 1H), 2.20 (d, *J* = 6.0 Hz, 1H), 1.06 (s, 9H, 3CH₃). Anal. calc. for C₁₄H₂₀N₂OS (264.13): C, 63.60; H, 7.62; N, 10.60. Found: C, 63.75; H, 7.86; N, 10.54.

Acknowledgments

We are grateful to the National Institute of Health, the National Institute of General Medical Sciences, Research Center at Minority Institutions Grant (RCMI) RR 03020, and Pharmaceutical Research Center NIH/NCRR Grant 1 C06RR12512-01.

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Figure 1.
Structure and numbering of synthesized tetrahydropyridines.

Scheme 1.

Reaction conditions: (a) acetone, reflux; (b) carbonyl/sulfonyl hydrazide, Et₃N, CH₃OH, rt; (c) H₂O/dioxane (1:4), reflux; (d) NaBH₄, abs. EtOH, 0 °C, 7 h. R = 3- and 4- Phenyl, 4-tert-butyl; R₁ = benzyl, 4-methylbenzyl, 2-furyl, 2-thiophenyl; X=CO, SO₂.

Scheme 2.

Reaction conditions: (a) dry CH₂Cl₂, 0 °C; (b) acyl chloride, dry THF, reflux; (c) NaBH₄, abs. EtOH, 0 °C, 7 h. R= C₂H₅, R₁ = 2-furyl, 2-thiophenyl, X=CO.

Table 1

Elemental analysis of 1,2,3,6-tetrahydropyridines (**5a–i**, **9a**, **b**)

Compound	R	R ₁	X	Molecular formula	Molecular weight	Analysis (%) calcd./found			
						C	H	N	
5a	4-C ₆ H ₅	C ₆ H ₅	SO ₂	C ₁₇ H ₁₈ N ₂ O ₂ S	314.40	64.94 64.82	5.77 5.92	8.91 8.87	
5b	4-C ₆ H ₅	2-Furyl	CO	C ₁₆ H ₁₆ N ₂ O ₂	268.12	71.62 71.49	6.01 6.12	10.44 10.38	
5c	4-C ₆ H ₅	2-Thiophenyl	CO	C ₁₆ H ₁₆ N ₂ OS	284.10	67.58 67.72	5.67 5.71	9.85 9.78	
5d	4-C ₆ H ₅	4-CH ₃ -C ₆ H ₄	SO ₂	C ₁₈ H ₂₀ N ₂ O ₂ S	328.12	65.83 65.96	6.14 6.30	8.53 8.59	
5e	3-C ₆ H ₅	4-CH ₃ -C ₆ H ₄	SO ₂	C ₁₈ H ₂₀ N ₂ O ₂ S 0.1 H ₂ O	330.24	65.47 65.27	6.10 6.29	8.48 8.33	
5f	3-C ₆ H ₅	2-Furyl	CO	C ₁₈ H ₂₀ N ₂ O ₂ S	268.12	71.62 71.51	6.01 6.19	10.44 10.28	
5g	3-C ₆ H ₅	2-Thiophenyl	CO	C ₁₆ H ₁₆ N ₂ OS	284.10	67.58 67.16	5.67 5.82	9.85 9.69	
5h	4- <i>tert</i> -Butyl	2-Furyl	CO	C ₁₄ H ₂₀ N ₂ O ₂	248.15	67.71 67.68	8.12 8.32	11.28 11.16	
5i	4- <i>tert</i> -Butyl	2-Thiophenyl	CO	C ₁₄ H ₂₀ N ₂ OS	264.13	63.60 63.75	7.62 7.86	10.60 10.54	
9a	5-Ethyl	2-Furyl	CO	C ₁₂ H ₁₆ N ₂ O ₂	220.12	65.43 65.43	7.32 7.50	12.72 12.67	
9b	5-Ethyl	2-Thiophenyl	CO	C ₁₂ H ₁₆ N ₂ OS	236.10	60.99 60.88	6.82 6.99	11.85 11.73	