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CHEMISTRY

A New Method for the Synthesis of α-Aryl-Substituted Pyrrolines and Tetrahydropyridines

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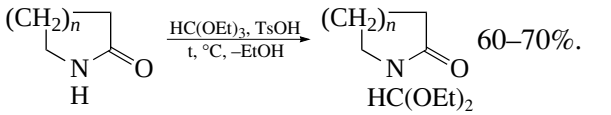
2-Aryl-substituted cyclic imines and amines are important classes of biologically active compounds and are of great interest for biochemistry and medicine [1–3]. The reported methods for the synthesis of similar compounds involve the cyclization of γ-amino ketones resulting from the catalytic hydrogenation of β-cyanoketones [4, 5] and the reaction of organolithium compounds with *N*-vinyl- or *N*-trimethylsilyl-substituted lactams, followed by hydrolysis of the reaction mixtures [6, 7]. 2-Arylpyrrolines were also obtained via Claisen condensation of *N*-vinylpyrrolidone with arylcarboxylic esters, followed by hydrolysis and decarboxylation of the intermediates [8].

However, we found that the above methods of synthesis failed to result in 2-thiazolyl-substituted pyrrolines and tetrahydropyridines. In particular, the reaction of 2-thiazolyllithium with *N*-trimethylsilyl-substituted lactams leads mainly to silylated heterocycles, whereas in the case of *N*-vinyl-substituted lactams, the process is complicated by side reactions of acetaldehyde appearing in the hydrolysis stage.

To overcome the difficulties, we suggested two new heterocyclizing reagents: *N*-diethoxymethylpyrrolidone-2 (**1a**) and *N*-diethoxymethylvalerolactam (**1b**). We found that both reagents could be obtained in large amounts and in high yield merely by refluxing the corresponding unsubstituted lactams with an excess of triethyl orthoformate in the presence of catalytic amounts of *p*-toluenesulfonic acid with simultaneous removal of ethanol.

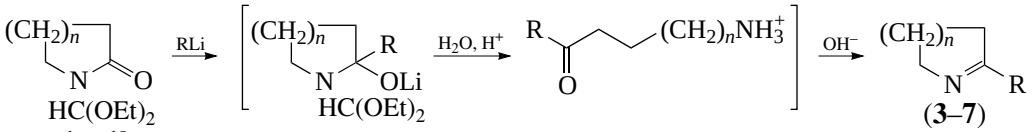


(**1a**, **1b**); a: $n = 1$; b: $n = 2$.

It should be noted that lactams (**1a**, **1b**) were described earlier; however, they were obtained in small amounts by time-consuming chromatographic separation, and the yield was only 25% in the case of **1b** [9].

We found that a series of lithiated aromatic and heteroaromatic compounds react with lactams **1a** and **1b** even at low temperatures, and their subsequent treatment leads to the formation of 2-aryl-substituted pyrrolines and tetrahydropyridines in good yields (table).

It is obvious that the addition of organolithium compound to the carbonyl group of lactams **1a** and **1b** takes place at the first stage, and subsequent acidic hydrolysis gives rise to a salt of ω-amino ketone, which undergoes ring closure upon alkaline treatment to give cyclic imine.



1a, **1b** (**3**–**7**)

It is interesting that the yields of target products do not increase in this reaction as the basicity of organolithium compounds rises. Moreover, the least basic thiazolyllithium, which decomposes at temperatures higher than –50°C, gives the highest yields of cyclic imines **2a** and **2b**. It was also shown experimentally that the yields in ether–hexane solutions are much higher than in tetrahydrofuran as a solvent.

EXPERIMENTAL

All manipulations with organolithium compounds were carried out in an argon atmosphere with the use of anhydrous solvents. The structure of the resulting compounds was confirmed by elemental analysis data and ^{1}H NMR spectra. The yields and boiling and melting points of cyclic imines **3**–**7** are given in the table.

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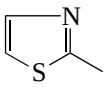
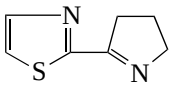
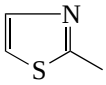
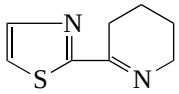
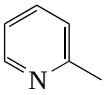
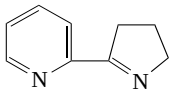
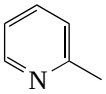
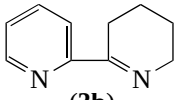
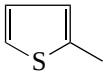
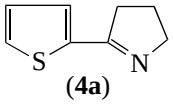
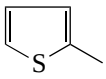
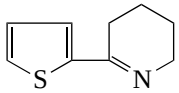
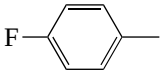
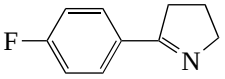
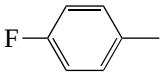
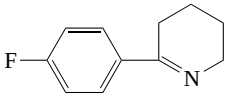
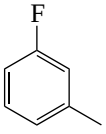
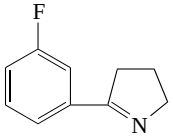
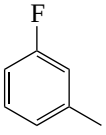
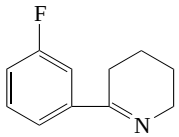
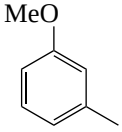
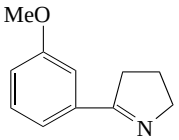
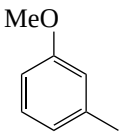
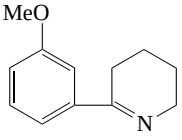
Synthesis of 2-aryl-substituted cyclic amines

R	*n*	Product	T_b, °C (mmHg), T_m, °C	Yield, %
	1	 **(2a)**	72/1 39	79
	2	 **(2b)**	80/1 46	80
	1	 **(3a)**	68/1 38–40	59
	2	 **(3b)**	78/1	64
	1	 **(4a)**	72/1 58	60
	2	 **(4b)**	85–86/1 67	52
	1	 **(5a)**	74/1 38–39	60
	2	 **(5b)**	86/1 30–31	62
	1	 **(6a)**	73/1	56
	2	 **(6b)**	92–93/1	69
	1	 **(7a)**	114/1	48
	2	 **(7b)**	124/1	50

***N*-Diethoxymethylpyrrolidone-2 (1a) and *N*-diethoxymethyl-δ-valerolactam (1b).** A solution of 170 g (2 mol) of 2-pyrrolidone or 198 g (2 mol) of δ-valerolactam was heated at reflux in 1.5 L of triethyl orthoformate in the presence of 2 g of *p*-toluenesulfonic acid hydrate in a flask equipped with a distilling column attached to a descending condenser until ethanol distillation ceased. The temperature of reaction mixture rose to 150–153°C (8–12 h). The reaction mixture was cooled and the major portion of triethyl orthoformate was distilled off in a vacuum of 10–20 mmHg at 50°C. The triethyl orthoformate distillate may be used in the same synthesis again. The residue was cooled, diluted with a triple volume of benzene, and washed quickly in a separating funnel with a cooled 10% K_2CO_3 solution (2×200 mL). The organic layer was separated, dried with Na_2SO_4, concentrated in vacuum, and distilled, a small head fraction being removed, to give 254 g of compound **1a** (68%), bp 84–86°C/1 mmHg, or 250 g of compound **1b** (62%), bp 94°C/1 mmHg.

Preparation of Lithiated Arenes

2-Thiazolyllithium. A 100-mL portion of ether was added dropwise with stirring to 62.5 mL of a 1.6 N *n*-butyllithium solution in hexane (0.1 mol), with a temperature of <0°C maintained. The solution was cooled to –80°C, a solution of 17.8 g (0.105 mol) of thiazole in 20 mL of ether was added dropwise, and the reaction mixture was stirred for 30–40 min at –75°C.

2-Pyridyllithium. A 80-mL portion of ether was added to 62.5 mL of a 1.6 N *n*-butyllithium solution in hexane (0.1 mol) at 0°C, the mixture was cooled to –70°C, a solution of 15.8 g (0.1 mol) of 2-bromopyridine in 20 mL of ether was added dropwise, and the mixture was stirred at –70°C for 40 min.

2-Thienyllithium. Thiophene (9.24 g, 0.11 mol) was added dropwise to a mixture of 62.5 mL of a 1.6 N *n*-butyllithium solution in hexane (0.1 mol) and 80 mL of ether at 0°C, and the mixture was stirred at 20°C for 1 h.

3-Fluorophenyllithium, 4-fluorophenyllithium, and 3-anisyllithium. 3-Bromofluorobenzene (17.5 g, 0.1 mol) was added dropwise with stirring to a mixture of 62.5 mL of a 1.6 N *n*-butyllithium solution in hexane (0.1 mol) and 80 mL of ether at –30°C, the cooling bath was removed, the solution was allowed to warm spontaneously to 20°C, and the mixture was stirred at this temperature for 15 min. 4-Fluorophenyllithium and 3-anisyllithium were obtained similarly.

General Procedure for the Synthesis of Cyclic Amines

2-(Δ^1-Pyrrolin-2-yl)thiazole (2a). To a solution of 2-thiazolyllithium obtained from 7.1 mL (8.5 g, 0.1 mol) of thiazole by the above procedure, a solution of 20.6 g (0.11 mol) of compound **1a** in an equal volume of anhydrous ether was added with stirring at –90°C, while the temperature was not allowed to increase above –70°C. The mixture was stirred for 40 min at –70°C and then was allowed to warm to –40°C while remaining in a cooling bath, and a solution of 50 mL of concentrated HCl in 60 mL of water cooled to 0°C was added in one portion. The mixture was shaken vigorously; the aqueous layer was separated, extracted with 50 mL of ether, and allowed to stand for 36–40 h. Then, a solution of 30 g of NaOH in 40 mL of water was added dropwise with stirring to the aqueous layer, with prevention of the temperature growth above 30–40°C. The organic layer was separated, and the aqueous layer was extracted with ether (3×50 mL). The combined extract was dried with potassium carbonate, the ether was distilled off in vacuum, and the residue was distilled in a vacuum. After distillation, the substance became a crystalline solid. The yield of compound **2a** was 12.0 g. 2-(3,4,5,6-Tetrahydropyridin-2-yl)thiazole (**2b**), 2-(Δ^1-pyrrolin-2-yl)pyridine (**3a**), and 2-(3,4,5,6-tetrahydropyridin-2-yl)pyridine (**3b**) were obtained similarly.

2-(2-Thien-2-yl)-Δ^1-pyrroline (4a). A solution of compound **1a** (19.6 g, 0.105 mol) in a double volume of anhydrous ether was added rapidly at –90°C to a solution of 2-thienyllithium prepared from 8.4 mL (8.8 g, 0.105 mol) of thiophene by the above procedure. The mixture was stirred for 40 min at –70°C, allowed to warm spontaneously to –35°C, and poured into a solution of 75 mL of concentrated HCl in 150 mL of water cooled to 0°C. The mixture was stirred for 5 min, the ether and hexane were removed in vacuum, and the residual hydrochloric solution was kept for one day at 20°C. A solution of 66 g (1.65 mol) of NaOH in 166 mL of water was added to the resulting solution with stirring, while the temperature of the mixture was prevented from increasing above 35–40°C. The organic layer was separated, and the aqueous layer was extracted with ether (4×40 mL). The combined extract was dried with potassium carbonate, the ether was removed in vacuum, and the residue was distilled in vacuum. After distillation, the substance became a crystalline solid. The yield of compound **4a** was 8.2 g. 2-(2-Thienyl)-3,4,5,6-tetrahydropyridine (**4b**) was obtained similarly.

2-(4-Fluorophenyl)-Δ^1-pyrroline (5a). A solution of 20.6 g (0.11 mol) of compound **1a** in an equal volume of anhydrous ether was added at –90°C to a solution of 4-fluorophenyllithium obtained from 10.9 mL (17.5 g, 0.1 mol) of 1-bromo-4-fluorobenzene by the above procedure; the mixture was stirred for 40 min at –70°C and allowed to warm spontaneously to –40°C. Then, it was cooled to –60°C, and a solution of 51 mL of concentrated HCl in 51 mL of water was added. The mixture was warmed to ambient temperature, and the solvent was distilled off at atmospheric pressure until the temperatures of the vapor and the distillation residue became 105°C and 108°C, respectively. Then, the mixture was cooled and allowed to stand overnight and a solution of 25 g of NaOH in 30 mL of water was added with stirring, with the mixture temperature main-

tained at not higher than 35°C. The organic layer was separated, and the aqueous layer was extracted with ether (4×40 mL). The extract was dried with potassium carbonate, and the ether was removed in a vacuum. The residue was distilled in vacuum. After distillation, the substance became a crystalline solid. The yield of compound **5a** was 10.6 g. 2-(4-Fluorophenyl)-3,4,5,6-tetrahydropyridine (**5b**), 2-(3-fluorophenyl)-Δ^1-pyrroline (**6a**), 2-(3-fluorophenyl)-3,4,5,6-tetrahydropyridine (**6b**), 2-(3-anisyl)-Δ^1-pyrroline (**7a**), and 2-(3-anisyl)-3,4,5,6-tetrahydropyridine (**7b**) were obtained similarly.

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