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RECYCLIZATION OF FURAN IN THE SYNTHESIS OF PYRROLO[1,2-*d*][1,4]DIAZEPINONE

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Pyrrolodiazepines are an important class of heterocyclic compounds due to their broad spectrum of pharmacological activity [1-4]. Additionally, the pyrrolodiazepinone framework is the basic structural fragment of natural anthramycin alkaloids which show antitumor activity [5]. All of this is responsible for the high interest in developing synthetic methods for these compounds. However, the Paal-Knorr reaction has been virtually unused in the preparation of pyrrolodiazepinones. Only two examples of its use have been reported. The first involves successive closing of the pyrrole and diazepinone rings [6] and the second a simultaneous formation of both rings [7]. This is likely associated with the fact that the synthesis of suitable 1,4-dicarbonyl compounds as precursors of the pyrrolodiazepinones is a multistage and laborious process [7].

It is well known that furan derivatives in the presence of acids can serve as precursors of 1,4-diketones [8]. This property of furan compounds allowed us to develop a simple and efficient method for preparing pyrrolo[1,2-*a*][1,4]diazepinones based on the recyclization of N-(furfuryl)anthranilamides [9]. This process is a *one-pot* domino reaction in which opening of the furan ring and the formation of the diazepinone and pyrroles ring occur. We now report the use of this methodology for preparing pyrrolo[1,2-*d*][1,4]diazepinones.

Acylation of the furylethylamine **1** by the 2-phthalimidoacetyl chloride **2** in benzene gave amide **3**, treatment of which with hydrazine hydrate in ethanol led to the removal of the phthalimido protection and formation of the amine **4**. Holding compound **4** in a mixture of acetic and hydrochloric acids for 1 day at room temperature and subsequent work up of the reaction mixture with an aqueous solution of $NaHCO_3$ gave the target compound **6**. Evidently the reaction takes place *via* intermediate formation of the diketone **5**.

The yield of the pyrrolodiazepinone **6** is 21% which compares with the results in the study [6]. However, bearing in mind the simplicity of these procedures in our proposed method, it can be used in the preparation of other pyrrolo[1,2-*d*][1,4]diazepinones and in further work we intend to carry out an optimization of the method.

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 and 75 MHz respectively) using $CDCl_3$ as solvent. The standards used were the residual protons of the deuterated solvent $CDCl_3$ (7.25 ppm for ^1H and 77.0 ppm for ^{13}C). Mass spectra were obtained on a Kratos MS-30 spectrometer by EI with ionizing energy 70 eV and ionization chamber temperature 200ºC.

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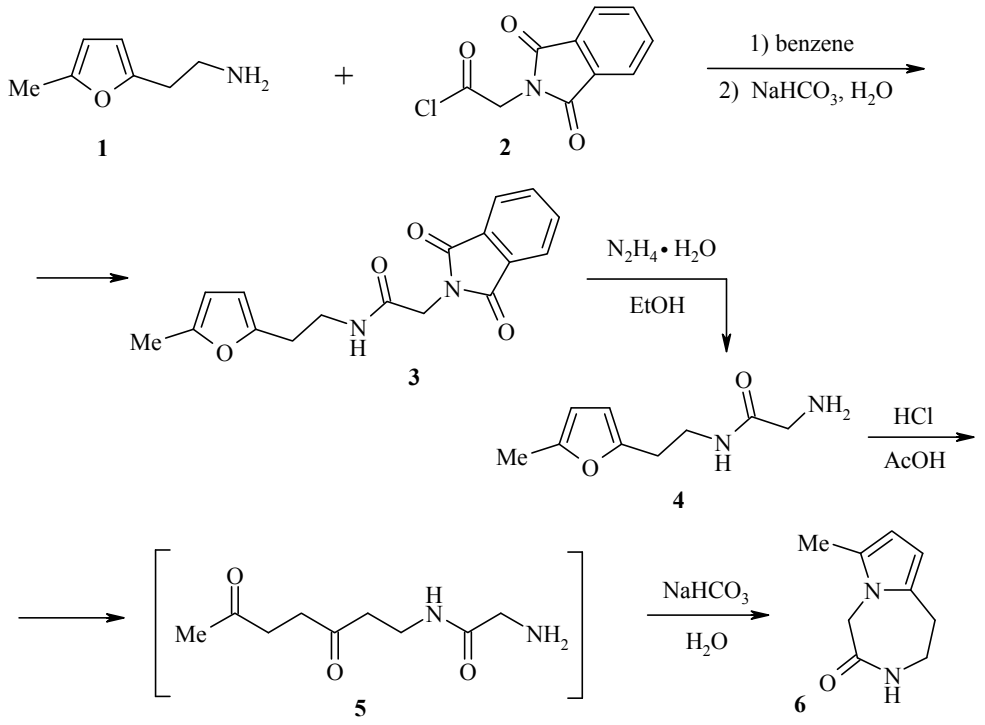

2-(1,3-Dioxo-1,3-dihydro-2H-2-isoindolyl)-N-[2-(5-methyl-2-furyl)ethyl]acetamide (3). Acid chloride **2** (9.9 g, 50 mmol) in benzene (50 ml) was added dropwise with stirring over 30 min to a solution of amine **1** (5 g, 40 mmol) in benzene (50 ml). The reaction mixture was stirred for a further hour at room temperature, a saturated aqueous solution of $NaHCO_3$ (100 ml) was added, and the mixture was vigorously stirred for 30 min. The precipitate formed was filtered off, the benzene layer removed, and the aqueous extracted with benzene (3×30 ml). The combined organic phases were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. The residue and the filtered precipitate were combined and purified through KSK grade silica gel (Sorbpolymer, 5-40 μm fraction) using methylene chloride and petroleum ether (1:1) as eluent. Recrystallization from a mixture of methylene chloride and petroleum ether gave compound **3** (9.86 g, 79%) as colorless crystals with mp 135-136ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, CH_3); 2.77 (2H, t, *J* = 6.6, CH_2); 3.48-3.56 (2H, m, CH_2); 4.31 (2H, s, CH_2); 5.78 (1H, d, *J* = 3.0, H furan); 5.90 (1H, br. s, NH); 5.91 (1H, d, *J* = 3.0, H furan); 7.71-7.77 (2H, m, H Ar); 7.84-7.91 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.4, 27.8, 38.3, 40.7, 105.9, 107.2, 123.5 (2C), 131.9 (2C); 134.2 (2C); 150.7; 151.1, 166.0, 167.7 (2C). Mass spectrum, *m/z* (I_{rel}, %): 312 $[M]^+$ (20), 205 (44), 164 (17), 160 (56), 133 (28), 120 (17), 109 (56), 96 (18), 77 (24), 59 (100), 45 (76). Found, %: C 65.54; H 5.11; N 8.82. $C_{17}H_{16}N_2O_4$. Calculated, %: C 65.38; H 5.16; N 8.97.

N-[2-(5-Methyl-2-furyl)ethyl]-2-aminoacetamide (4). Hydrazine hydrate (5 ml) was added to a solution of amide **3** (5 g, 16 mmol) in ethanol (20 ml). The reaction mixture was held for 1 h at room temperature (TLC monitoring) and evaporated to dryness *in vacuo*. The residue obtained was treated with chloroform (20 ml). The insoluble solid was filtered off and washed with cold chloroform (2×20 ml). The filtrate was washed with saturated aqueous NaCl solution and then water, dried over Na_2SO_4, and evaporated to dryness *in vacuo* to give compound **4** as a light-yellow oil (2.51 g, 86%) which was used in the following stage without additional purification.

7-Methyl-2,3-dihydro-1H-pyrrolo[1,2-*d*][1,4]diazepin-4(5H)-one (6). Conc. HCl (3 ml) was added to a solution of compound **4** (1 g, 0.55 mmol) in glacial acetic acid (10 ml) and held at room temperature for 1 day

(TLC monitoring). The reaction mass was poured into water (50 ml) and neutralized to pH ~ 7 using $NaHCO_3$. The reaction solution was heated to reflux and left overnight at room temperature. The precipitate formed was filtered off, dried, and purified on KSK grade silica gel (Sorbpolymer, 5-40 μm fraction) using benzene as eluent. The purified solution was evaporated to dryness *in vacuo* and the residue was recrystallized from a mixture of acetone and petroleum ether to give compound **6** (0.19 g, 21%) as colorless crystals with mp 141-142ºC (mp 137-138ºC [6]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, CH_3); 3.05-3.09 (2H, m, CH_2); 3.45-3.50 (2H, m, CH_2); 4.61 (2H, s, CH_2); 5.79 (1H, d, *J* = 3.3, H pyrrole); 5.83 (1H, d, *J* = 3.3, H pyrrole); 6.55 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 164 $[M]^+$ (93), 136 (17), 121 (43), 108 (71), 106 (100), 94 (40), 77 (32), 66 (72), 59 (36), 52 (56), 43 (29).

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