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NOVEL ROUTE TO QUINOLINES *VIA* RECYCLIZATION OF FURANS

A. V. Butin[1]*, F. A. Tsiunchik[1], O. N. Kostyukova[1], and I. V. Trushkov[2]

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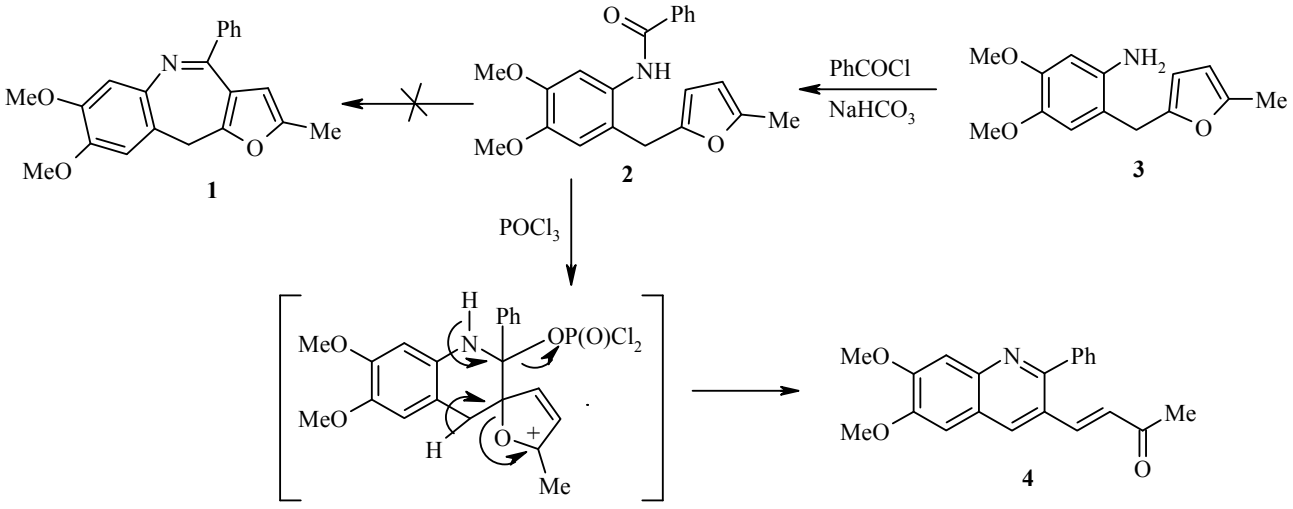
The Bischler-Napieralski reaction is a powerful tool for the construction of nitrogen-containing heterocyclic compounds through the formation of a new C–C bond as the result of the reaction of an electrophilic carbon atom with an aromatic or heterocyclic nucleus. It is generally used in the synthesis of 3,4-dihydroisoquinolines from phenylethylamine amides or β-carbolines from tryptamine amides [1, 2] but it can also be used for the annelation of a pyridine ring to other heterocyclic compounds [3-6]. In addition, variation of the linkage joining the aromatic fragment and the amide function permits the synthesis of a wide range of nitrogen-containing heterocycles. Thus, under the indicated conditions, 2-acylaminodiphenylmethanes give dibenzoazepines [7] and their thienyl analogs yield thienoazepines [8].



* To whom correspondence should be addressed, e-mail: alexander_butin@mail.ru.

[1]Research Institute of Heterocyclic Compounds Chemistry, Kuban State Technological University, Krasnodar 350072, Russia.
[2]M. V. Lomonosov State University, Chemistry Faculty, Moscow 119992, Russia.

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A similar reaction has not been reported for 2-(2-acylaminobenzyl)furans although it is known that 2-[2-(aminocarbamoyl)phenylthio]furans give furo[2,3-*b*][1,5]benzothiazepines when treated with phosphorus oxychloride in the presence of P_2O_5 [9]. In that connection, the aim of this work was to study the possibility of preparing the furo[3,2-*c*]benzazepine **1** under Bischler-Napieralski conditions from the 2-(2-acylaminobenzyl)furan **2**.

When compound **2** (prepared by acylation of the available benzylfuran **3** with benzoyl chloride [10]) was refluxed in benzene in the presence of excess phosphorus oxychloride the quinoline **4** was obtained instead of the expected furoazepine **1**. Evidently, its formation results from electrophilic attack of the formed iminium ion not at the β-position of the furan ring but at the α-carbon atom of the furan. There then occurs an electrophilic opening of the furan ring to form the aromatic quinoline system.

IR spectra were taken on a Shimadzu IR Prestige-21 instrument for KBr tablets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 and 75 MHz respectively) using DMSO-d_6 (for compound **2**) or $CDCl_3$ (compound **4**). The standards used were the residual protons of the deuterated solvent $CDCl_3$ (7.25 ppm for ^{1}H and 77.0 ppm for ^{13}C) or DMSO-d_6 (2.50 ppm for ^{1}H and 39.5 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.

N-{2-[(5-Methyl-2-furyl)methyl]-4,5-dimethoxyphenyl}benzamide (2). A solution of benzoyl chloride (2.1 g, 15 mmol) in benzene (25 ml) was added dropwise with stirring to a solution of compound **3** (2.47 g, 10 mmol) in benzene (30 ml), stirred at room temperature for 1 h (TLC monitoring), and then poured into water (100 ml). The mixture obtained was neutralized with $NaHCO_3$ and left for 2 h. The benzene layer was separated and the aqueous extracted with ethyl acetate (2×30 ml). The combined organic fractions were dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue was dissolved in a mixture of methylene chloride and petroleum ether (1:8). The obtained solution was passed through a layer of silica gel and the solvent was evaporated. Recrystallization from a mixture of methylene chloride and petroleum ether (1:5) gave compound **2** (2.53 g, 72%) as a white powder with mp 110ºC. IR spectrum, ν, cm^{-1}: 3260, 1644, 1612, 1516, 1468, 1308, 1284, 1260, 1220, 1092, 712. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 3.87 (6H, s, OCH_3); 3.90 (2H, s, CH_2); 5.89 (1H, d, *J* = 3.3, H furan); 5.94 (1H, d, *J* = 3.3, H furan); 6.75 (1H, s, Ph); 7.44-7.58 (3H, m, Ph); 7.61 (1H, s, Ph); 7.85-7.87 (2H, m, Ph); 8.38 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.5, 31.2, 55.9, 56.0, 106.4, 106.9, 108.1, 112.9, 122.0, 127.0 (2C), 128.6 (2C), 128.9, 131.7, 134.7, 146.3, 147.8, 151.3, 151.5, 165.5. Mass spectrum, *m/z* (I_{rel}, %): 351 $[M]^+$ (78), 247 (24), 246 (76), 106 (12), 105 (95), 95 (13), 77 (100), 59 (48), 43 (55). Found, %: C 71.61; H 6.11; N 3.81. $C_{21}H_{21}NO_4$. Calculated, %: C 71.78; H 6.02; N 3.99.

(3*E*)-4-(6,7-Dimethoxy-2-phenylquinolin-3-yl)but-3-en-2-one (4). $POCl_3$ (25 ml) was added to a solution of compound **2** (0.53 g, 1.5 mmol) in benzene (10 ml) and refluxed for 1.5 h (TLC monitoring). The reaction mixture was then poured onto crushed ice (500 g), neutralized with aqueous NaOH solution (3.5 M, 350 ml), and extracted with methylene chloride (3×150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The reaction product was separated by column chromatography on 50-160 μm silica gel using methylene chloride and petroleum ether (1:3) as eluent. Recrystallization from a mixture of methylene chloride and petroleum ether (1:4) gave quinoline **4** (0.31 g, 61%) as a light-yellow powder with mp 200-201ºC. IR spectrum, ν, cm^{-1}: 1664, 1616, 1588, 1496, 1432, 1392, 1260, 1228, 1212, 1132, 1008, 704. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 4.03 (3H, s, OCH_3); 4.04 (3H, s, OCH_3); 6.73 (1H, d, *J* = 16.2 =CH); 7.10 (1H, s, H Ar); 7.46-7.54 (4H, m, H Ar); 7.58-7.62 (2H, m, H Ar); 7.66 (1H, d, *J* = 16.2, =CH); 8.30. (1H, s, H Py). ^{13}C NMR spectrum, δ, ppm: 26.9, 56.0, 56.2, 104.8, 107.9, 122.5, 124.8, 128.3 (3C), 128.6, 129.7 (2C), 132.8, 139.3, 142.0, 145.6, 150.2, 153.7, 157.1, 198.2. Mass spectrum, *m/z* (I_{rel}, %): 333 $[M]^+$ (27), 290 (100), 275 (31), 274 (38), 246 (30), 217 (26), 101 (29), 59 (55), 43 (57). Found, %: C 75.37; H 5.60; N 4.19. $C_{21}H_{19}NO_3$. Calculated, %: C 75.66; H 5.74; N 4.20

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