Communication

Cyclization Modes in Anilides of *N*-Protected 3-Oxo-4-phenylaminobutyric Acid Under Knorr Conditions

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Abstract: Anilides of 3-oxo-4-phenylaminobutyric acid with Troc or COOEt protection at the phenylamino group undergo competing cyclization processes in neat polyphosphoric acid at 80 °C. Depending on the protecting group and the duration of the process, three main products in different ratios are formed. Along with the quinolin-2-ones, resulting from the classic Knorr cyclization, an indole derivative and a spirocyclic product have also been obtained from the COOEt-protected substrate. It has been demonstrated that the obtained indole derivative is capable of further dearomative spirocyclization under the studied conditions.

1. Introduction

The methods for construction of quinolin-2-ones [1] and indole [2] ring systems are of utmost importance for synthetic organic chemistry, as both classes of heterocycles are vastly abundant in nature, with many examples of highly bioactive alkaloids [3–5]. The ring closure of oxocarbenium intermediates via intramolecular aromatic electrophilic substitution is an approach applicable to the construction of both quinolin-2-ones and indoles. In the former case, this approach is known as the Knorr synthesis [6], and it has found numerous applications in the preparation of various quinolin-2-one derivatives from β-ketoanilides [7,8]. The mechanism of this reaction has been studied in detail, and it has been shown to proceed via distonic superelectrophilic dications [9]. Indoles have also been prepared in a similar manner from appropriate α-phenylaminocarbonyl precursors [10,11], although the scope of the approach in this case is narrower and it is rarely used in comparison to other methods of indole synthesis [2].

In the course of our studies on the application of functionalized β-keto amides in the synthesis of bioactive heterocycles, we have had the opportunity to realize both modes of cyclization in precursors designed to provide either indole [11] or quinolone [12] derivatives via intramolecular aromatic electrophilic substitution. In view of these results, it was of interest to experiment with substrates that are simultaneously capable of both five- and six-membered ring formation modes (Scheme 1).
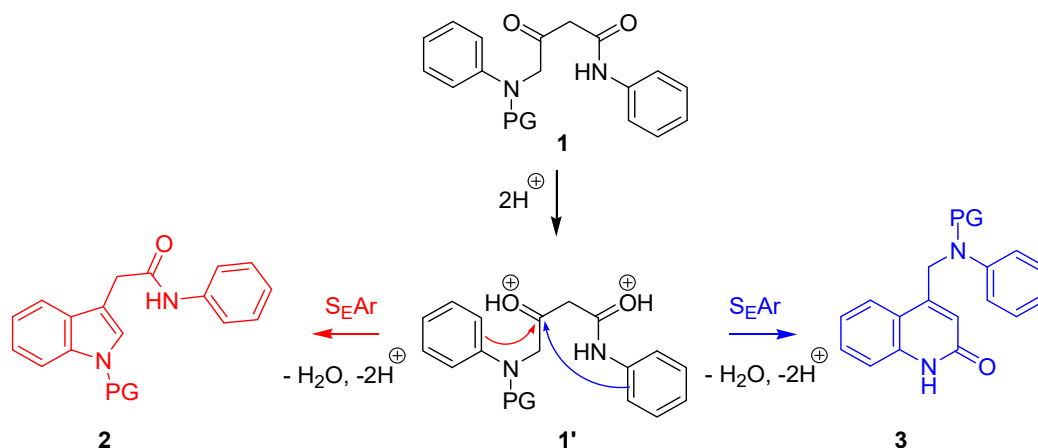
Scheme 1. Possible modes of cyclization in anilides of *N*-protected 3-oxo-4-phenylaminobutyric acid.

2. Results and Discussion

To carry out the experiments, we first prepared two anilides of 3-oxo-4-phenylaminobu
tyric acid, bearing ethoxycarbonyl or 2,2,2-trichloroethyloxycabonyl (Troc) protection at
the phenylamine nitrogen (**1**). For this purpose, we used our previously published pro-
tocol [13]. The substrates **1** were then subjected to Knorr-type conditions via heating in
neat polyphosphoric acid (PPA) at 80 °C. The reaction was checked by TLC on 30 min
intervals and the heating was maintained until full consumption of the starting compounds
1, which took 3 h in both cases. Under these conditions, the Troc-protected substrate **1b**
(PG = Troc) gave only one major product that could be isolated via column chromatography.
Its NMR spectra corresponded to the quinolin-2-one **3b**, and the yield was 72%. On the
other hand, the ethoxycarbonyl protected substrate **1a** (PG = COOEt) gave a mixture of
three products with clear spots on the TLC plate. These products were easily separated via
column chromatography on silica gel, and their spectral characteristics corresponded to the
indolylacetanilide **2a** (8%), the quinolin-2-one **3a** (49%), and the spirocyclic derivative **4a**
(12%) (Scheme 2).
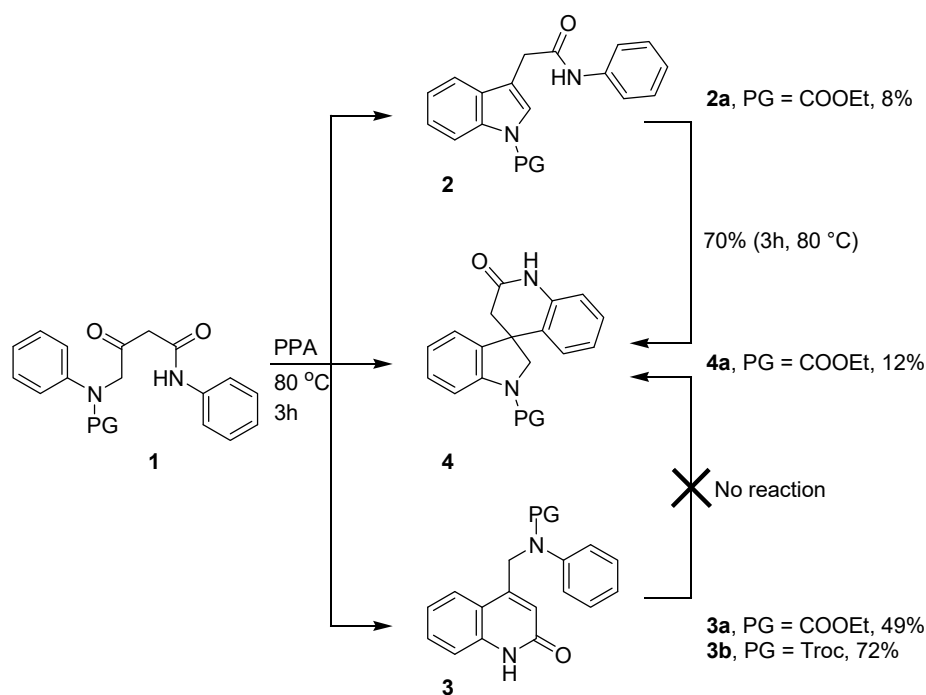
Scheme 2. Products obtained from anilides of *N*-protected 3-oxo-4-phenylaminobutyric acid under
Knorr conditions.

There are two possible mechanistic sequences leading to the formation of the spiro-cyclic product **4a**. This product could be a result of S_EAr cyclization occurring in either of two different cationic intermediates, formed after the first ring closure (Scheme 3, **2-II** and **3-II**). The cationic intermediates **2-II** and **3-II** could either eliminate a proton to give indole **2** and quinolone **3**, respectively, or undergo a second S_EAr process, leading to the spirocyclic product **4a**. Should the proton elimination in **2-II** and **3-II** be reversible, then the spirocyclic product could also be obtained from any of the competing products **2** and **3**. To clarify this, we carried out additional experiments, starting with pure, chromatographically isolated compounds **2a** and **3a**. Both compounds were heated separately in PPA, but only the indole derivative **2a** underwent a dearomative spirocylization to **4a**. The conversion of **2a** to **4a** took 3h at 80 °C and gave an isolated yield of 70%. Compound **3a** on the other hand did not react even after 5h at 100 °C in either PPA or H_3PO_4. This suggests that the protonation of the quinolone **3** occurs preferentially at the amide oxygen, with formation of a stable aromatic 2-hydroxyquinolinium ion **3′** (Scheme 4). Although a protonation at the amide carbonyl is also likely for the indole derivative **2a**, this apparently does not preclude a dearomative protonation in the five-membered ring of this compound.
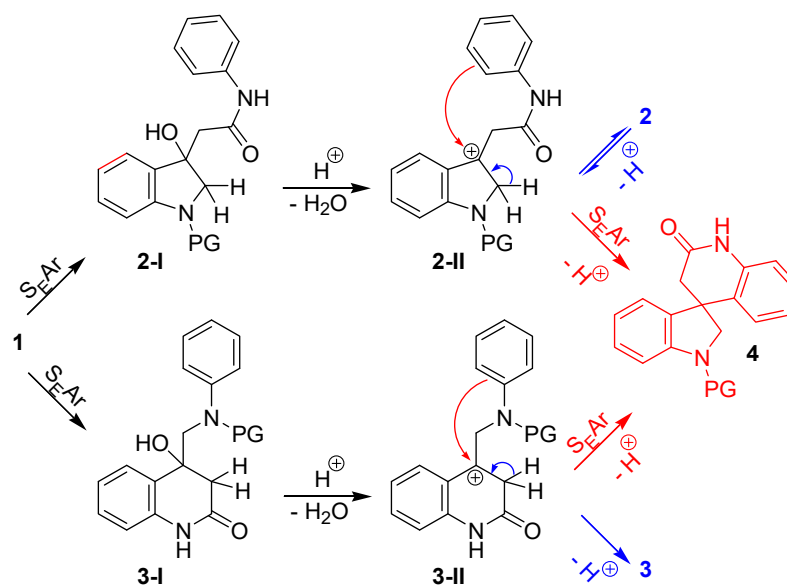
Scheme 3. Alternative pathways to the spirocyclic product **4a**.
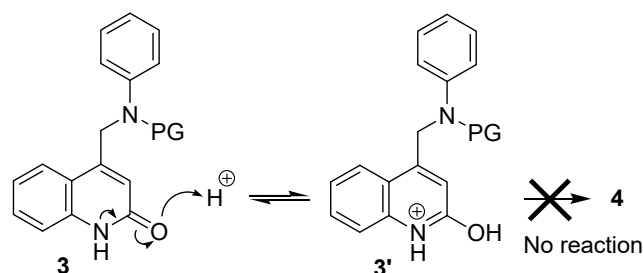
Scheme 4. Protonation of quinolones **3**.

In another experiment, the cyclization of **1a** in PPA was carried out for prolonged period of 5 h, which provided enough time for product **2a** to fully convert to **4a** in the same reaction vessel. In this way, only products **3a** and **4a** were isolated in 50% and 21% yield, correspondingly.

The structures of the obtained products **2**, **3**, and **4** were unequivocally determined on the basis of their NMR spectra. In the ^{1}H NMR spectrum of the spirocyclic product **4**, there are signals for two AB spin systems, arising from the presence of a stereogenic center

in the molecule. These signals correspond to the diastereotopic protons in the methylene groups that are adjacent to the stereogenic center. One of the methylene groups gives two doublets with ^2J = 16 Hz at δ_A = 2.69 ppm and δ_B = 3.05 ppm. The protons of this AB system are bonded to a carbon with ^{13}C δ = 42.2 ppm according to the observed HSQC correlation. This, along with the HMBC correlation of the same protons to the amide carbonyl (δ = 168.5 ppm), is sufficient to assign that methylene group to the the six-membered ring. The other methylene group appears in the ^{1}H NMR spectrum as two doublets with ^2J = 12 Hz at δ_A = 3.89 and δ_B = 4.03 ppm. These doublets correlate to a carbon with ^{13}C δ = 60.7 ppm in the HSQC spectrum and show no correlation to the amide carbonyl in the HMBC spectrum, which assigns the corresponding methylene group to the five-membered indoline ring. Both, the five- and the six-membered-ring methylene groups, show HMBC correlation to the quaternary carbon at the spiro ring juncture, which appears at δ = 46.1 ppm in the ^{13}C NMR spectrum. The ^{1}H signals of the ethoxycarbonyl group in **4a** are broad and unresolved, most likely due to a rotameric exchange. With regard to products **2** and **3**, the most significant difference in their NMR spectra is observed in the chemical shifts of the methylene signals—δ ^{1}H/^{13}C = 3.79/34.7 for **2a**, where the CH$_2$ is neighbored by an indole ring and an amide carbonyl, compared to δ ^{1}H/^{13}C = 5.15/50.7 for **3a**, where the CH$_2$ is allylic and next to a nitrogen. In both cases, the ^{1}H methylene signals appear as narrow doublets due to allylic coupling to a CH in the neighboring ring (^4J = 1.0 and 0.9 Hz respectively). The new sp^2-CH signals in **2a**/**3a** that appear as a result of the cyclization are easily identifiable by COSY and HSQC. In the indole ring of **2a**, this is the aromatic C2-H signal at δ ^{1}H/^{13}C = 7.68/124.4 ppm, while in the quinolone **3a**, this is the C3-H at δ ^{1}H/^{13}C = 6.29/119.4 ppm. Here, the ^{1}H signals are unresolved triplets because of the weak ^4J coupling.

In conclusion, we have shown that the competing reaction pathways of anilides of *N*-protected 3-oxo-4-phenylaminobutyric acids under Knorr-conditions are influenced by the nature of the protecting group in the substrates. While the Troc-protected substrate is preferentially converted to a quinolin-2-one derivative, the COOEt-protected one gives a mixture of quinolone, indole, and spirocyclic products. Although the latter variant is of little preparative value, it revealed an interesting possibility of dearomative spirocyclization in indolylacetanilides, which may be useful in other contexts.

3. Materials and Methods

The anilides of N-protected 3-oxo-4-phenylaminobutyric acid **1** were synthesized according to our previously published protocol [13]. All other reagents and solvents were purchased from Sigma-Aldrich, Darmstadt, Germany, and were used as supplied. PPA refers to polyphosphoric acid (115% H$_3$PO$_4$ basis, CAS No. 8017-16-1). NMR spectra were measured on a Bruker NEO 400 (400/100 MHz ^{1}H/^{13}C) spectrometer. Chemical shifts (δ, ppm) are reported downfield from TMS. TLC was performed on aluminium-backed Silica gel 60 sheets (Merck, Darmstadt, Germany), with KMnO$_4$ staining. Melting point measurements were carried out in capillary tubes on KRÜSS M5000 automatic mp meter (KRÜSS, Hamburg, Germany) and were not corrected. Mass spectral measurements were performed on a Thermo Fisher Scientific Q Exactive high-resolution mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). IR spectra were measured on a Bruker Alpha II FT IR spectrometer (Bruker, Billerica, MA, USA).

Cyclization of compounds **1** in polyphosphoric acid, general procedure: The corresponding compound **1a,b** (1 mmol) was mixed with PPA (6–8 g, 3–4 mL) in a glass vial, and the mixture was stirred intensely at 80 °C until full homogenization. The homogenous mixture was kept at 80 °C for 3 h; then, the vial was cooled to r.t. with tap water. The contents were rinsed with water (50–70 mL) and poured into a separatory funnel. The reaction products were extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic layers were dried with anhydrous Na$_2$SO$_4$, and the solvent was removed on a rotary evaporator. The residue was separated via column chromatography on silica gel using diethyl ether as the eluent (increasing polarity to Et$_2$O:MeOH 20:1 for product **3a**).

3-Phenylcarbamoylmethylindole-1-carboxylic acid ethyl ester (**2a**): m.p. 131–132 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm, *J* Hz): 1.40 (t, *J* = 7.0, 3H), 3.79 (d, *J* = 0.9, 2H), 4.45 (q, *J* = 7.0, 2H), 7.04 (m, 1H), 7.26–7.33 (m, 3H), 7.36 (m, 1H), 7.61 (m, 2H), 7.67–7.70 (m, 2H), 8.10 (d, J = 8.2, 1H), 10.21 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 14.64, 33.47, 63.64, 115.11, 116.02, 119.61, 120.12, 123.22, 123.73, 124.41, 125.04, 129.19, 130.63, 135.22, 139.61, 150.75, 168.86; HRMS *m/z* (ES+): calcd. for $C_{19}H_{19}N_2O_3^+$ [M+H]$^+$ 323.1390, found 323.1385.

(2-Oxo-1,2-dihydroquinolin-4-ylmethyl)-phenylcarbamic acid ethyl ester (**3a**): m.p. 172–173 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm, *J* Hz): 1.15 (t, *J* = 7.0, 3H), 4.14 (q, *J* = 7.0, 2H), 5.15 (d, *J* = 1.0, 2H), 6.29 (s, 1H), 7.20 (m, 2H), 7.29–7.37 (m, 5H), 7.52 (m, 1H), 7.78 (dd, *J* = 8.0, *J* = 1.1, 1H), 11.73 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 14.84, 50.76, 62.14, 116.16, 117.94, 119.44, 122.28, 124.31, 126.50, 126.62, 129.29, 131.01, 139.33, 141.82, 147.08, 155.22, 161.79; HRMS *m/z* (ES+): calcd. for $C_{19}H_{19}N_2O_3^+$ [M+H]$^+$ 323.1390, found 323.1392.

(2-Oxo-1,2-dihydroquinolin-4-ylmethyl)-phenylcarbamic acid 2,2,2-trichloroethyl ester (**3b**): m.p. 185–186 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm, *J* Hz): 4.97 (s, 2H), 5.23 (s, 2H), 6.36 (s, 1H), 7.19 (m, 1H), 7.25 (m, 1H), 7.32–7.39 (m, 5H), 7.52 (m, 1H), 7.79 (dd, *J* = 8.1, *J* = 1.1, 1H), 11.73 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 51.18, 74.92, 96.14, 116.19, 117.89, 122.27, 124.36, 126.90, 127.03, 127.35, 127.39, 129.37, 131.07, 139.34, 146.27, 153.61, 161.70; HRMS *m/z* (ES+): calcd. for $C_{19}H_{16}Cl_3N_2O_3^+$ [M+H]$^+$ 425.0221, found 425.0226.

Ethyl 2′-oxo-2′,3′-dihydro-1′H-spiro[indole-3,4′-quinoline]-1(2H)-carboxylate (**4a**): m.p. 214–215 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$, δ ppm, *J* Hz): 1.25 (br s, 3H), 2.69 (d, ^2J = 16.0, 1H), 3.05 (d, ^2J = 16.0, 1H), 3.89 (d, ^2J = 11.0, 1H), 4.03 (d, ^2J = 11.0, 1H), 4.18 (br s, 2H), 6.61 (dd, *J* = 7.7, *J* = 1.3, 1H), 6.89 (td, *J* = 7.6, *J* = 1.3, 1H), 6.99 (dd, *J* = 7.9, *J* = 1.1, 1H), 7.06 (td, *J* = 7.5, *J* = 1.0, 1H), 7.18–7.23 (m, 2H), 7.32 (m, 1H), 7.80 (br s, 1H), 10.44 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d$_6$, δ ppm): 14.84, 42.26, 46.10, 60.73, 61.91, 114.84, 116.36, 123.14, 123.66, 124.48, 125.98, 128.73, 129.24, 129.47, 137.58, 152.78, 168.49; HRMS *m/z* (ES+): calcd. for $C_{19}H_{19}N_2O_3^+$ [M+H]$^+$ 323.1390, found 323.1394.

Supplementary Materials: Figures S1–S17: ^{1}H and ^{13}C NMR spectra of the synthesized compounds; Figures S18–S21: IR spectra of the synthesized compounds.

Data Availability Statement: The data presented in this study are available in this article and the Supplementary Materials. The raw NMR data of all compounds, including COSY, HSQC, and HMBC spectra, are available for download at https://doi.org/10.5281/zenodo.14175517 (accessed on 18 November 2024). Further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

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