Short Note

1-(4-Chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one

Pavel A. Volkov, Kseniya O. Khrapova, Anton A. Telezhkin, Ivan A. Bidusenko, Alexander I. Albanov and Boris A. Trofimov *

A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Science, 664033 Irkutsk, Russia
* Correspondence: boris_trofimov@irioch.irk.ru

Abstract: 1-(4-Chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one, was synthesized for the first time in 75% yield by the base-catalyzed intramolecular cyclization of 4-((4-chlorophenyl)amino)-4-phenyl-1-(thiophen-2-yl)pent-2-yn-1-one. The starting aminoacetylenic ketone was prepared by cross-coupling of available propargylamines with acyl chlorides in the presence of the PdCl₂/CuI/Ph₃P catalytic system.

Keywords: aminoacetylenic ketones; cyclization; 3H-pyrrol-3-one; electron-deficient acetylenes

1. Introduction

Pyrrol-3-ones are one of the most attractive classes of heterocyclic compounds [1,2]. Functional pyrrol-3-ones exhibit pronounced anticancer, antihypertensive, anti-HIV, antiviral, and antimalarial activity [1–6]. Their structures are found in such natural compounds as isatin, isatisine, fascaplysin, trypyranthin, and duocarmycin [2,3,7–9]. In addition, pyrrol-3-one derivatives are actively used as flame retardants [10] and ligands for the design of metal complex nanocatalysts [11], as well as building blocks in organic synthesis [2,12].

However, the broader applications of this class of heterocyclic compounds is hampered by the lack of convenient approaches to their synthesis [2], the most synthetically acceptable reactions being intramolecular cyclization [2,13–16]. This includes the cyclization of aminocyclonitrides in the presence of strong acids [2,13], ring-closure of acetylenic ketones containing an amide group with the use of palladium and gold salts [2,14,15], and the aminolysis of chloroenaminines [16]. Therefore, the search for alternative methods for the preparation of pyrrol-3-ones is an important task.

Here, we have reported a direct method for the synthesis of 1-(4-chlorophenyl)-2-methyl-2-phenyl-5-(thiopheno-2-yl)-1,2-dihydro-3H-pyrrol-3-one by the base-catalyzed intramolecular cyclization of 4-((4-chlorophenyl)amino)-4-phenyl-1-(thiophen-2-yl)pent-2-yn-1-one under mild reaction conditions. The latter became available due to the development of a chemoselective palladium/copper-catalyzed cross-coupling reaction of terminal propargylamines (originally obtained by the addition of gaseous acetylene to available ketimines in the Bu’OK/DMSO superbasic system [17]) with aromatic and heteroaromatic acyl chlorides (Scheme 1) [18].
Scheme 1. Synthesis of aminoacetylenic ketones 1.

2. Results and Discussion

The intramolecular cyclization of 4-((4-chlorophenyl)amino)-4-phenyl-1-(thiophen-2-yl)pent-2-yn-1-one (1) is performed in the presence of 0.5 equivalents of KOH in ethanol solution at 40–45 °C for 8 h (Scheme 2). The target 1-(4-chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one (2) has been obtained in 75% yield.

The reaction was monitored by both thin-layer chromatography (TLC) and IR spectroscopy through the disappearance of the absorption band of the triple bond of the starting aminoacetylenic ketone 1 in the region of ~2240 cm\(^{-1}\).

The structure of the target product 2 was confirmed by the use of \(^1H\), \(^13C\) NMR, and IR spectroscopy (see Supplementary Materials). The assignment of 1,2-dihydro-3H-pyrrol-3-one 2 characteristic signals was performed using 2D homo- and heteronuclear HMBC, HSQC, COSY, and NOESY NMR spectroscopy.

The characteristic singlet of the pyrrolone ring H4 is present in the region of 5.71 ppm in the \(^1H\) NMR spectrum, while the signal of the Me group appears in the form of a singlet in the region of 1.59 ppm. In the \(^13C\) NMR spectrum, the pyrrolone ring appears as separate C2, C4, and C5 signals at 75.7, 99.1, and 167.3 ppm, respectively. The C=O group signal has a characteristic shift value of 201.8 ppm.

In the 2D NOESY spectrum (Figure 1), the protons of the methyl group in position 2 of the pyrrolone ring give cross peaks both with the ortho-protons of the phenyl group in the same 2-position and with the H2',6' of protons the aromatic group at the nitrogen atom. This indicates that the Me and aryl groups are on the same side of the five-membered 3H-pyrrol-3-one cycle. In addition, the NOESY spectrum contains a cross peak between the H4 of the pyrrolone ring and the H3″ of the thienyl ring.
The IR spectrum reveals the characteristic bands of the C-Cl group (1092 and 836 cm$^{-1}$), a C=O bond (1680 cm$^{-1}$), and a C=C double aromatic and heteroaromatic ring (1650–1504 cm$^{-1}$). Symmetric and asymmetric C-N stretching bands cannot be assigned because they overlap with the absorption bands of the aromatic and heteroaromatic rings. Moreover, in the IR spectrum of the resulting 3H-pyrrol-3-one 2, there are no characteristic absorption bands of the C=C and N-H bonds of the starting 4-((4-chlorophenyl)amino)-pent-2-yn-1-one 1 in the regions of 3309 and 2216 cm$^{-1}$, respectively.

The cyclization of aminoacetylenic ketone 1 probably starts with the addition of a water molecule to afford the rearrangement of enol A to 1,3-diketone B (Scheme 3). The latter undergoes ring closure by the attack of NH moiety at the remote carbonyl group to give hydroxypyrrolidinone C, which produces pyrrolone 2 after the elimination of water.

![Scheme 3. Plausible reaction mechanism.](image)

It should be noted that the reaction does not occur without potassium hydroxide. At the same time, an increase in the amount of the base to one equivalent led to a decrease in the preparative yield of the target product 2 because of more intense resinification of the initial electron-deficient acetylene 1.

In aprotic solvents such as dioxane, DMSO, and MeCN, the reaction proceeded too slowly (96 h in dioxane, 50 h in MeCN) or resulted in a much lower yield (40% in dioxane and MeCN, 62% in DMSO) than in aqueous ethanol. In ethyl acetate, the reaction did not give the target product at all. These results confirm that the presence of water is

![Figure 1. 2D NOESY of 1,2-dihydro-3H-pyrrol-3-one 2.](image)
required for the successful synthesis of pyrrolone 2 and that in the “anhydrous” medium, the reaction proceeded only with the participation of the trace water always present in the aforementioned solvents.

In conclusion, using the base-catalyzed cyclization of 4-((4-chlorophenyl)amino)-4-phenyl-1-(thiophen-2-yl)pent-2-yn-1-one, we implemented a convenient method for the synthesis of 1-(4-chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one, a representative of a highly in-demand class of heterocyclic compounds with promising pharmacological activity.

3. Materials and Methods

General. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 400 and Bruker AV-400 spectrometer (400.13 and 100.62 MHz, respectively) in CDCl$_3$ solution and referenced to HMDS ($^1$H, $^{13}$C). The assignment of signals in $^1$H spectra was performed using 2D homonuclear correlation methods COSY and NOESY. Resonance signals of $^{13}$C were assigned by applying 2D heteronuclear correlation methods HSQC and HMBC. FT-IR spectra were obtained with a Varian 3100 FT-IR spectrometer in vaseline oil. Mass spectra were recorded on an Agilent 6210 HRMS−TOF−ESI mass spectrometer with electrostatic sputtering and registration of positive ions. Sample solvent was MeCN with the addition of 0.1% HCOOH and with the addition of calibration mixture for mass spectrometer. Melting points were determined on a Kofler hot stage apparatus.

1-(4-Chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one (2). To a solution of aminoacetylenic ketone 1 (0.365 g, 1.0 mmol) in EtOH (2 mL), KOH (0.033 g, 0.5 mmol) was added. The mixture was stirred under an argon atmosphere at 40–45 °C for 8 h (see also Scheme 2). After completion of the reaction (TLC monitoring, eluent: toluene/Et$_2$O, 1:2), the solvent was removed under reduced pressure, the residue was purified by column chromatography on SiO$_2$ (eluent: toluene/Et$_2$O, 1:2), and the solution was dried in vacuo to obtain the corresponding pyrrolone 2 (0.273 g, 75%) as a light-brown solid. $R_f$ = 0.50 (toluene/Et$_2$O = 1:2); m.p. 117–118 °C; IR (oil): 3087, 3051, 2953, 2923, 2854, 2725, 2360, 1898, 1666, 1650, 1540, 1529, 1489, 1460, 1407, 1377, 1365, 1339, 1293, 1262, 1247, 1225, 1205, 1143, 1089, 1064, 1013, 973, 921, 879, 846, 833, 793, 784, 769, 756, 722, 699, 652, 578, 553, 520, 494, 480, 461 cm$^{-1}$; $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ 7.46 (dd, $^3$J$_{3'-4'}$ = 5.0 Hz, $^4$J$_{3'-5'}$ = 1.6 Hz, 1H, H$_5$), 7.31–7.38 (m, 5H, H$_2$, H$_3$, H$_4$), 7.16 (d, $^3$J$_{3'-4'}$ = 3.9 Hz, 1H, H$_5$), 6.99 (dd, $^3$J$_{3'-4'}$ = 3.9 Hz, $^4$J$_{4'-5'}$ = 5.0 Hz, 1H, H$_5$), 6.78–6.74 (m, 2H, H$_2'$, H$_6$), 5.71 (s, 1H, H$_4$), 1.59 (s, 3H, 2-Me); $^{13}$C($^1$H) NMR (100.62 MHz, CDCl$_3$): $\delta$ 201.8 (C=O), 167.3 (C$_5$), 138.7 (C$_i$), 137.6 (C$_4'$), 133.7 (C$_3$), 132.0 (C$_2'$), 131.6 (C$_3'$), 131.0 (C$_5'$), 129.6 (C$_2'$, H$_6$), 129.3 (C$_3'$, H$_5$), 128.8 (C$_m$), 128.1 (C$_p$), 127.8 (C$_4'$), 126.3 (C$_o$), 99.1 (C$_4$), 75.7 (C$_2$), 20.3 (2-Me); HRMS (ESI-TOF) calcd for [C$_{21}$H$_{16}$CNOS + H]$^+$: 366.0719, found 366.0717.

Supplementary Materials: The following supporting information for the characterization of 1-(4-chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3H-pyrrol-3-one (2) can be downloaded online. Figure S1: $^1$H NMR spectrum (400.13 MHz); Figure S2: $^{13}$C NMR spectrum (100.62 MHz); Figure S3: $^{13}$C m mod NMR spectrum (100.62 MHz); Figure S4: $^1$H-$^1$H COSY NMR spectrum; Figure S5: $^1$H-$^1$H NOESY NMR spectrum; Figure S6: $^1$H-$^{13}$C HMBC NMR spectrum; Figure S7: $^1$H-$^{13}$C HSQC NMR spectrum; Figure S8: IR spectrum (oil); Figure S9: HRMS (ESI-TOF) spectrum; Figure S10: HRMS (ESI-TOF) spectrum of compound 2.

Author Contributions: Conceptualization, P.A.V.; investigation, P.A.V., K.O.K., A.A.T., A.I.A. and L.A.B.; data curation, P.A.V.; writing—original draft preparation, P.A.V.; writing—review and editing, A.A.T.; supervision, B.A.T.; project administration, P.A.V.; funding acquisition, P.A.V.; resources, K.O.K.; performed synthesis, A.A.T. All authors have read and agreed to the published version of the manuscript.

Funding: This work has been funded by the Ministry of Science and Higher Education of the Russian Federation (State Registration no. 12021000199-6).

Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors thank the Baikal Analytical Centre of collective use and Shared Research Facilities for Physical and Chemical Ultramicroanalysis, Limnological Institute, SB RAS (HRMS-TOF Spectra) for the equipment.

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

References


2. Sharma, P.; Kumar, R.; Bhargava, G. Recent development in the synthesis of pyrrolin-4-ones/pyrrolin-3-ones. J. Heterocycl. Chem. 2020, 57, 4115–4135. [CrossRef]


