molbank

MDPI

Short Note

1-(4-Chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3*H*-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-3*H*-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 $PdCl_2$/CuI/Ph_3P catalytic system.

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

check for updates

Citation: Volkov, P.A.; Khrapova, K.O.; Telezhkin, A.A.; Bidusenko, I.A.; Albanov, A.I.; Trofimov, B.A. 1-(4-Chlorophenyl)-2-methyl-2-phenyl-5-(thiophen-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one. *Molbank* **2022**, *2022*, M1520. https://doi.org/10.3390/M1520

Academic Editor: Stefano D'Errico

Received: 11 November 2022
Accepted: 29 November 2022
Published: 6 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

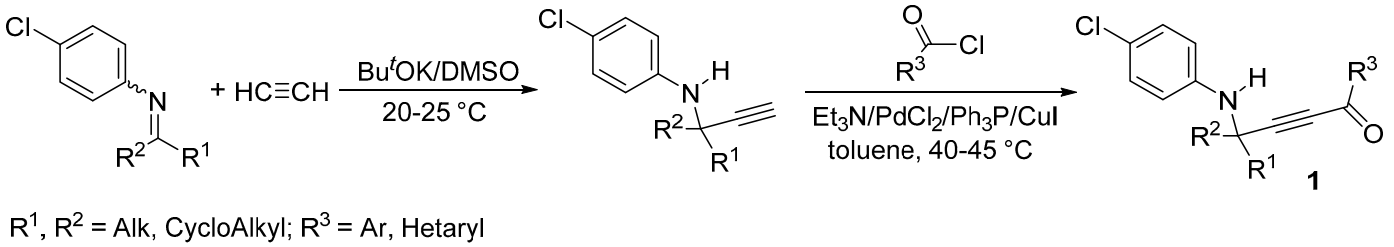
Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

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, tryptanthrin, 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 aminoacylmalononitriles 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.

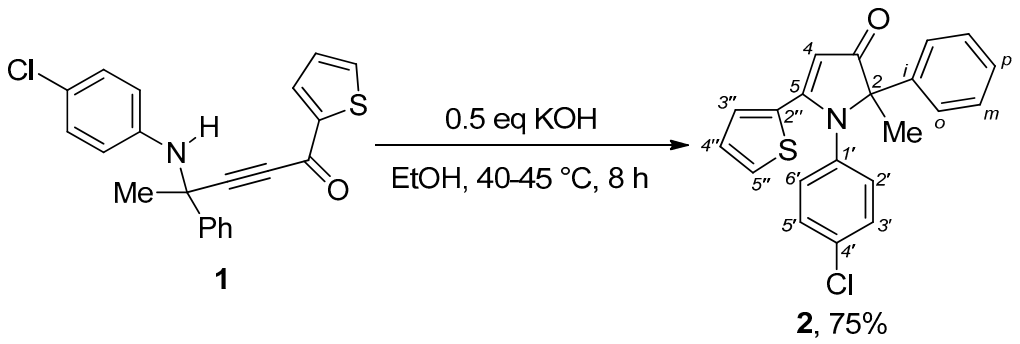
Here, we have reported a direct method for the synthesis of 1-(4-chlorophenyl)-2-methyl-2-phenyl-5-(thiopheno-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one by the base-catalyzed intramolecular cyclization of 4-((4-chlorophenyl)amino)-4-phenyl-1-(thiophen-2-yl)pent-2-yn-1-one under mild reaction conditions. The 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^{t}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-3*H*-pyrrol-3-one (**2**) has been obtained in 75% yield.



Scheme 2. Synthesis of 1,2-dihydro-3*H*-pyrrol-3-one **2**.

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 ^{1}H, ^{13}C NMR, and IR spectroscopy (see Supplementary Materials). The assignment of 1,2-dihydro-3*H*-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 ^{1}H 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 ^{13}C 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 3*H*-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.

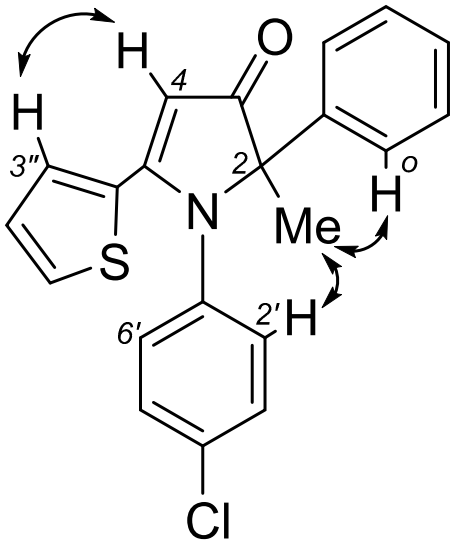
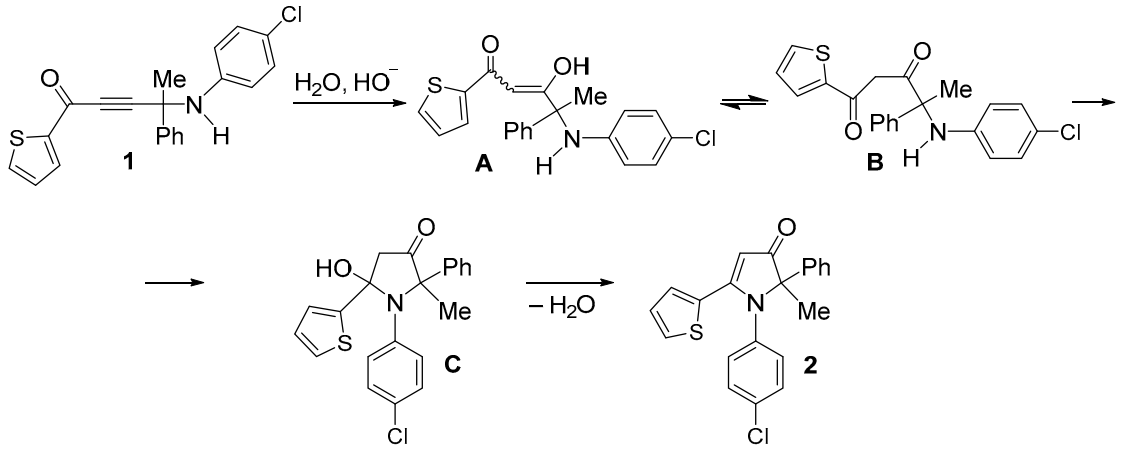


Figure 1. 2D NOESY of 1,2-dihydro-3*H*-pyrrol-3-one **2**.

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 3*H*-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.

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 reaction mixture due to the polymerization 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

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-3*H*-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-3*H*-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_2O, 1:2), the solvent was removed under reduced pressure, the residue was purified by column chromatography on SiO_2 (eluent: toluene/Et_2O, 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_2O = 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, 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, $CDCl_3$): δ 7.46 (dd, $^{3}J_{5''\text{-}4''}$ = 5.0 Hz, $^{4}J_{5''\text{-}3''}$ = 1.6 Hz, 1H, H5″), 7.31–7.38 (m, 5H, H*o*,*m*,*p*), 7.17–7.13 (m, 2H, H3′,5′), 7.16 (d, $^{3}J_{3''\text{-}4''}$ = 3.9 Hz, 1H, H3″), 6.99 (dd, $^{3}J_{4''\text{-}3''}$ = 3.9 Hz, $^{3}J_{4''\text{-}5''}$ = 5.0 Hz, 1H, H4″), 6.78–6.74 (m, 2H, H2′,6′), 5.71 (s, 1H, H4), 1.59 (s, 3H, 2-Me); ^{13}C{^{1}H} NMR (100.62 MHz, $CDCl_3$): δ 201.8 (C=O), 167.3 (C5), 138.7 (C*i*), 137.6 (C4′), 133.3 (C1), 132.0 (C2″), 131.6 (C3″), 131.0 (C5″), 129.6 (C2′,6′), 129.3 (C3′,5′), 128.8 (C*m*), 128.1 (C*p*), 127.8 (C4″), 126.3 (C*o*), 99.1 (C4), 75.7 (C2), 20.3 (2-Me); HRMS (ESI-TOF) calcd for $[C_{21}H_{16}ClNOS + H]^{+}$: 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-3*H*-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 jmod 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 I.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. 121021000199-6).

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

1. Jiang, M.; Chen, S.; Li, J.; Liu, L. The Biological and Chemical Diversity of Tetramic Acid Compounds from Marine-Derived Microorganisms. *Mar. Drugs* **2020**, *18*, 114. [CrossRef] [PubMed]
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]
3. Karadeolian, A.; Kerr, M.A. Total Synthesis of (+)-Isatisine A. *J. Org. Chem.* **2010**, *75*, 6830–6841. [CrossRef]
4. Murugesan, D.; Mital, A.; Kaiser, M.; Shackleford, D.M.; Morizzi, J.; Katneni, K.; Campbell, M.; Hudson, A.; Charman, S.A.; Yeates, C.; et al. Discovery and Structure–Activity Relationships of Pyrrolone Antimalarials. *J. Med. Chem.* **2013**, *56*, 2975–2990. [CrossRef] [PubMed]
5. Murugesan, D.; Kaiser, M.; White, K.L.; Norval, S.; Riley, J.; Wyatt, P.G.; Charman, S.A.; Read, K.D.; Yeates, C.; Gilbert, I.H. Structure–Activity Relationship Studies of Pyrrolone Antimalarial Agents. *ChemMedChem* **2013**, *8*, 1537–1544. [CrossRef] [PubMed]
6. Zhang, D.B.; Yu, D.G.; Sun, M.; Zhu, X.X.; Yao, X.J.; Zhou, S.Y.; Chen, J.J.; Gao, K. Ervatamines A–I, Anti-inflammatory Monoterpenoid Indole Alkaloids with Diverse Skeletons from *Ervatamia hainanensis*. *J. Nat. Prod.* **2015**, *78*, 1253–1261. [CrossRef] [PubMed]
7. Searcey, M. Duocarmycins–Natures Prodrugs? *Curr. Pharm. Des.* **2002**, *8*, 1375–1389. [CrossRef] [PubMed]
8. Bharate, S.B.; Manda, S.; Mupparapu, N.; Battini, N.; Vishwakarma, R.A. Chemistry and Biology of Fascaplysin, a Potent Marine-Derived CDK-4 Inhibitor. *Mini-Rev. Med. Chem.* **2012**, *12*, 650–664. [CrossRef] [PubMed]
9. Kaur, R.; Manjal, S.K.; Rawal, R.K.; Kumar, K. Recent synthetic and medicinal perspectives of tryptanthrin. *Bioorg. Med. Chem.* **2017**, *25*, 4533–4552. [CrossRef] [PubMed]
10. Younis, A.A.; Faheim, A.A.; Elsawy, M.M.; El-Wahab, H.A. Novel flame retardant paint based on Co (II) and Ni (II) metal complexes as new additives for surface coating applications. *Appl. Organomet. Chem.* **2021**, *35*, e6070. [CrossRef]
11. Sobhani, S.; Moghadam, H.H.; Derakhshan, S.R.; Sansano, J.M. Tandem imine formation via auto-hydrogen transfer from alcohols to nitro compounds catalyzed by a nanomagnetically recyclable copper catalyst under solvent-free conditions. *RSC Adv.* **2021**, *11*, 19121–19127. [CrossRef] [PubMed]
12. Gondi, S.R.; Shaik, A.; Westover, K.D. Acid-Catalyzed Synthesis of Isatoic Anhydride-8-Secondary Amides Enables IASA Transformations for Medicinal Chemistry. *J. Org. Chem.* **2022**, *87*, 125–136. [CrossRef] [PubMed]
13. Hamilakis, S.; Tsolomitis, A. An efficient synthesis of 2-amino-3-cyano-2-pyrrolin-4-ones, via the corresponding open chain tautomers (aminoacetylmalononitriles). *Tetrahedron Lett.* **2003**, *44*, 3821–3823. [CrossRef]
14. Gouault, N.; Le Roch, M.; Cornée, C.; David, M.; Uriac, P. Synthesis of Substituted Pyrrolin-4-ones from Amino Acids in Mild Conditions via a Gold-Catalyzed Approach. *J. Org. Chem.* **2009**, *74*, 5614–5617. Available online: https://pubs.acs.org/action/showCitFormats?doi=10.1021%2Fjo900693a&href=/doi/10.1021%2Fjo900693a (accessed on 1 November 2022). [CrossRef] [PubMed]
15. Spina, R.; Colacino, E.; Gabriele, B.; Salerno, G.; Martinez, J.; Lamaty, F. Synthesis of Pyrrolin-4-ones by Pt-Catalyzed Cycloisomerization in PEG under Microwaves. *J. Org. Chem.* **2013**, *78*, 2698–2702. [CrossRef] [PubMed]
16. Grošelj, U.; Ciber, L.; Gnidovec, J.; Testen, Ž.; Požgan, F.; Štefane, B.; Tavčar, G.; Svete, J.; Ričko, S. Synthesis of Spiro-Δ^2-Pyrrolin-4-One Pseudo Enantiomers via an Organocatalyzed Sulfa-Michael/Aldol Domino Sequence. *Adv. Synth. Catal.* **2019**, *361*, 5118–5126. [CrossRef]
17. Schmidt, E.Y.; Bidusenko, I.A.; Protsuk, N.I.; Demyanov, Y.V.; Ushakov, I.A.; Trofimov, B.A. Superbase-promoted addition of acetylene gas to the C=N bond. *Eur. J. Org. Chem.* **2019**, *2019*, 5875–5881. [CrossRef]
18. Volkov, P.A.; Khrapova, K.O.; Bidusenko, I.A.; Telezhkin, A.A.; Schmidt, E.Y.; Albanov, A.I.; Trofimov, B.A. Chemoselective cross-coupling of terminal propargylamines with (het)aroyl chlorides: Synthesis of β-aminoacetylene ketones bearing aromatic and heteroaromatic substituents. *Russ. Chem. Bull.* **2022**, *71*, 1514–1518. [CrossRef]