molbank

Short Note

2-Amino-5-chloro-1*H*-pyrrole-3,4-dicarbonitrile

Andreas S. Kalogirou [1,*] **and Panayiotis A. Koutentis** [2]

[1] Department of Life Sciences, School of Sciences, European University Cyprus, 6 Diogenis Str., Engomi, P.O. Box 22006, 1516 Nicosia, Cyprus
[2] Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus; koutenti@ucy.ac.cy
* Correspondence: A.Kalogirou@euc.ac.cy; Tel.: +357-22559655

Abstract: The reaction of tetracyanoethylene (TCNE) with HCl (g) in the presence of Sn (1 equiv) and AcOH resulted in 2-amino-5-chloro-1*H*-pyrrole-3,4-dicarbonitrile in a 74% yield. The compound was fully characterized.

Keywords: TCNE; heterocycle; polyfunctionalized; pyrrole; cyano group

Citation: Kalogirou, A.S.; Koutentis, P.A. 2-Amino-5-chloro-1*H*-pyrrole-3,4-dicarbonitrile. *Molbank* **2021**, *2021*, M1191. https://doi.org/10.3390/M1191

Academic Editor: Luke R. Odell

Received: 6 February 2021
Accepted: 11 February 2021
Published: 13 February 2021

1. Introduction

Pyrroles are important aromatic *N*-heterocycles that exist in nature, for example, as components of the well-known ligand heme (Figure 1). Pyrroles also have wide pharmaceutical applications with examples of pyrrole containing drugs being the nonsteroidal anti-inflammatory drug tolmetin and the lipid-lowering agent atorvastatin (Figure 1). Other uses of pyrroles include insecticides [1], dyes [2] and polymers [3]. The chemistry of pyrroles has been reviewed [4].

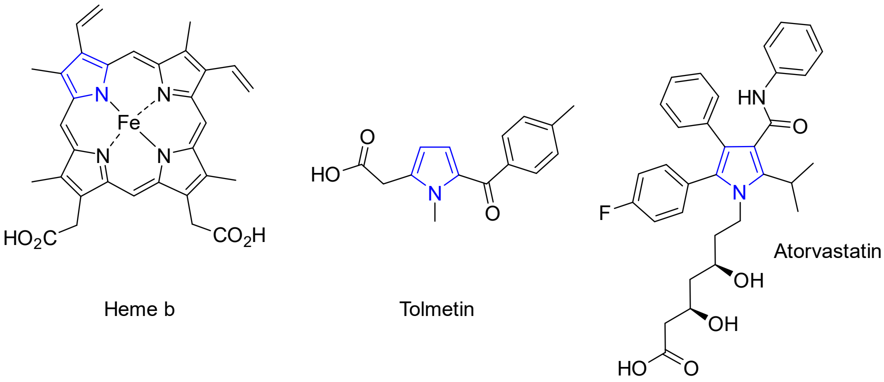
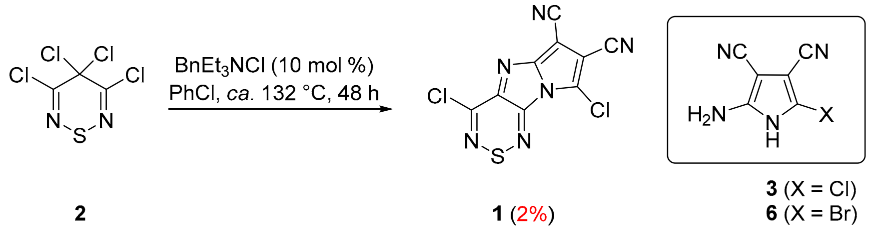


Figure 1. Pyrroles in nature and in drugs.

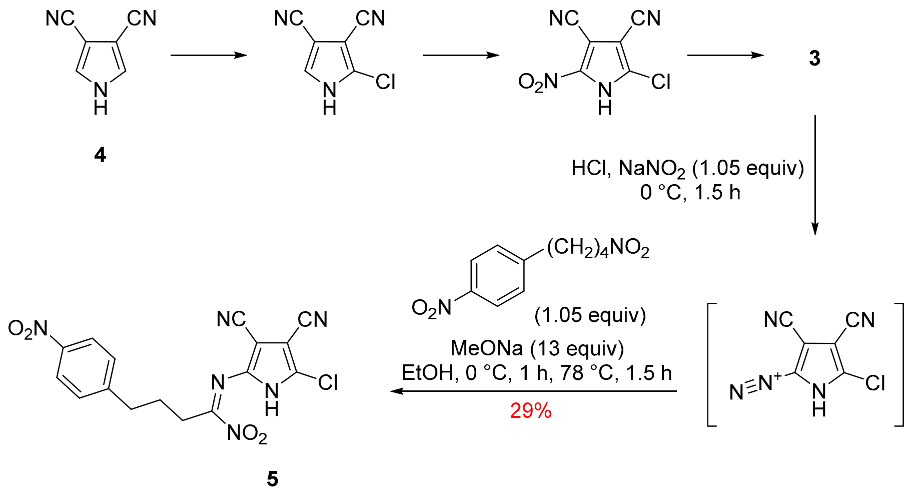
2. Results and Discussion

Our interest in pyrroles began with 4,8-dichloropyrrolo [2′,1′:2,3]imidazo [4,5-*c*]-[1,2,6]thiadiazine-6,7-dicarbonitrile (**1**), a compound that was isolated in low yield from the chloride-catalyzed degradation of tetrachlorothiadiazine (**2**) [5] (Scheme 1). We believed that the formation of tricycle **1** in this reaction involved the in situ generation of 2-amino-5-chloro-1*H*-pyrrole-3,4-dicarbonitrile (**3**) under the reaction conditions.

The chloropyrrole **3** appears in the patent literature where it is claimed to be synthesized in a three-step synthesis starting from 1*H*-pyrrole-3,4-dicarbonitrile (**4**) (Scheme 2), but no experimental details or characterization data are reported [6–14]. Interestingly, the chloropyrrole **3** was used as a scaffold for the synthesis of dyes, such as ylidene **5** (Scheme 2), used in color photography [6–14], while it is also commercially available (CAS: 152586-70-4).



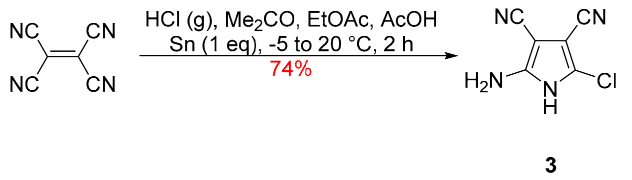
Scheme 1. Isolation of dicyanopyrrole **1** from tetrachlorothiadiazine **2**.



Scheme 2. The claimed patented synthesis of chloropyrrole **3** and its use to prepare ylidene **5**.

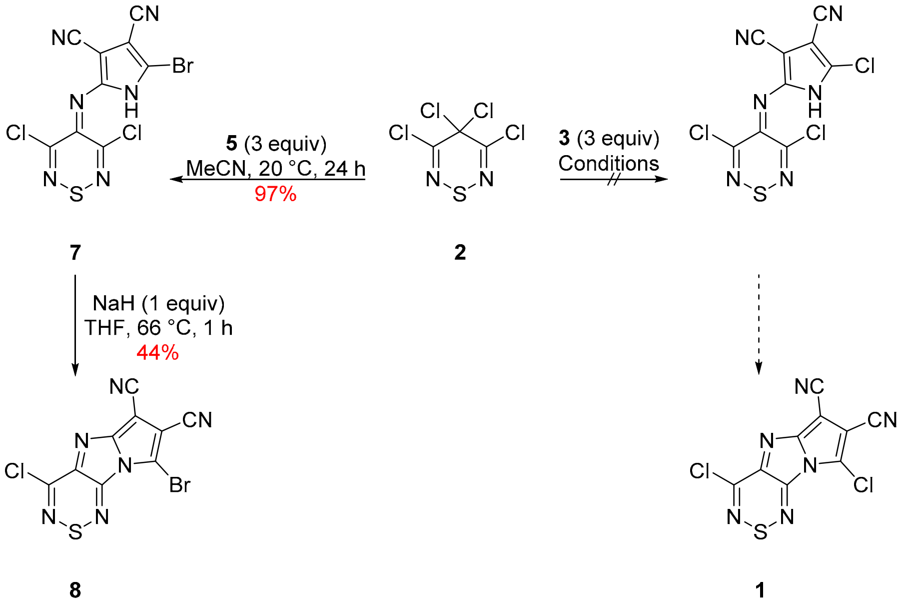
To attempt a higher yielding semi-independent synthesis of tricycle **1**, we decided to develop a simpler synthesis of chloropyrrole **3**. Since the full synthesis and experimental data of analogous 2-amino-5-bromo-1*H*-pyrrole-3,4-dicarbonitrile (**6**) (Scheme 1) from tetracyanoethylene (TCNE) and HBr (g) are known [15], we chose to attempt this route for the analogous chloropyrrole **3**.

The reaction involved bubbling HCl (g) through a solution of TCNE in Me_2CO, EtOAc and AcOH, followed by the addition of powdered Sn (1 equiv) (Scheme 3). The choice of this solvent mixture was inspired by a reported preparation of the bromopyrrole **6** [16], as it dissolves the reagents effectively but does not dissolve the HCl salt of the product **3**, thereby allowing for a facile purification of the product after the end of the reaction by filtration and subsequent treatment with base and acid (see materials and methods below). The addition of the reductant Sn (in the presence of AcOH) was required to bring the product to the correct oxidation state. In contrast, no reductant was required in the reported synthesis of bromopyrrole **6** [15], tentatively, due to a redox reaction involving loss of Br_2. Subsequent stirring for 2 h resulted in a yellow precipitate, presumably the HCl salt of aminopyrrole **3**. An acid/base treatment involving first 2 M NaOH and then AcOH resulted in the desired compound **3** in a 74% yield (see Supplementary Materials for the complete spectra).



Scheme 3. Synthesis of 2-amino-5-chloro-1*H*-pyrrole-3,4-dicarbonitrile (**3**).

Chloropyrrole **3** was subsequently reacted with tetrachlorothiadiazine **2** in attempts to synthesize tricycle **1**. However, while the respective reaction of bromopyrrole **6** with tetrachlorothiadiazine **2** was clean and resulted in thiadiazinimine **7** in excellent yield, which was subsequently converted to tricycle **8** [5], the reaction of chloropyrrole **3** in a number of different conditions [MeCN at 20–82 °C; MeCN, 2,6-lutidine (1 eq) at 20 °C; DCE at 83 °C; THF at 20–66 °C; PhCl at 132 °C] only resulted in a complex mixture of products that could not be resolved (Scheme 4).



Scheme 4. Reactions of bromopyrrole **6** and chloropyrrole **3**.

3. Materials and Methods

The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass backed TLC plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner and Munz, Kofler Hotstage Microscope apparatus (Wagner and Munz, Munich, Germany). The solvent used for recrystallization is indicated after the melting point. The UV-vis spectrum was obtained using a Perkin-Elmer Lambda-25 UV-vis spectrophotometer (Perkin-Elmer, Waltham, MA, USA); inflections are identified by the abbreviation “inf”. The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with a Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA); strong, medium and weak peaks are represented by s, m and w, respectively. A Bruker Avance 500 machine (Bruker, Billerica, MA, USA) was used at 500 and 125 MHz to record the ^{1}H and ^{13}C NMR spectra, respectively. Deuterated solvents were used for the homonuclear lock; the signals are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies were used for the assignment of the ^{13}C peaks as CH_3, CH_2, CH and Cq (quaternary). The ES-API$^-$ mass spectrum was recorded on a Model 1260 Infinity II Quadrupole MSD (Agilent Technologies). The elemental analysis was run by the London Metropolitan University Elemental Analysis Service. Tetracyanoethylene was prepared according to the literature [17].

2-Amino-5-chloro-1H-pyrrole-3,4-dicarbonitrile (**3**)

A stirred mixture of TCNE (384 mg, 3.00 mmol) in Me_2CO (2 mL), EtOAc (4 mL) and AcOH (2 mL) at ca. −5 °C was purged with HCl (g) for 2 min. Then, powdered Sn (356 mg, 3.00 mmol) was added, and the mixture was left to warm to ca. 20 °C. After 2 h, the yellow precipitate was filtered and washed with Et_2O (5 mL). The solid was then dissolved in H_2O (5 mL) and the pH adjusted to 11 by addition of 2 M NaOH. AcOH was then added dropwise until pH = 5, and a new colorless precipitate formed. The precipitate was filtered and dried in vacuo to give the title compound **3** (371 mg, 74%) as colorless plates, mp > 300 °C (from PhH); R_f 0.37 (DCM/MeOH 90:10); (found: C, 43.45; H, 1.71; N, 33.56. $C_6H_3ClN_4$ requires C, 43.27; H, 1.82; N, 33.64%); λ_{max}(MeOH)/nm 215 (log ε 3.90), 259 (3.63), 283 (3.70); v_{max}/cm^{-1} 3439m, 3339m, 3223m and 3169w (N–H), 2236s and 2234s (C≡N), 1639s, 1632s, 1601s, 1557m, 1479m, 1408w, 1350w, 1242m, 1092w, 1067w, 932m, 903m, 702m; δ_H(500 MHz; DMSO-d_6) 12.35 (1H, partially exchanged, br s, N*H*), 6.50 (2H, br s, NH_2); δ_C(125 MHz; DMSO-d_6) 148.1 (Cq), 116.9 (Cq), 114.6 (Cq), 113.1 (Cq), 89.0 (Cq), 69.4 (Cq); *m/z* (ES-API$^-$) 167 ($M - H^+ + 2$, 33%), 165 ($M - H^+$, 100).

Supplementary Materials: The following are available online: mol file, ^1H, ^{13}C NMR, IR, UV-Vis and mass spectra.

Author Contributions: P.A.K. and A.S.K. conceived the experiments; A.S.K. designed and performed the experiments, analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Cyprus Research Promotion Foundation, grant numbers ΣΤΡΑΤΗΙΙ/0308/06, ΝΕΚΥΡ/0308/02 ΥΓΕΙΑ/0506/19 and ΕΝΙΣΧ/0308/83.

Acknowledgments: The authors thank the following organizations and companies in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture, MedoChemie Ltd., Medisell Ltd. and Biotronics Ltd. Furthermore, we thank the A. G. Leventis Foundation for helping to establish the NMR facility at the University of Cyprus.

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

References

1. Loughlin, W.A.; Murphy, M.E.; Elson, K.E.; Henderson, L.C. Synthesis of a Novel Pyrrole Oxazole Analogue of the Insecticide Pirate. *Aust. J. Chem.* **2004**, *57*, 227–232. [CrossRef]
2. Chou, S.-S.P.; Hsu, G.-T.; Lin, H.-C. Synthesis and second-order nonlinearities of sulfonyl-substituted pyrrole imino dyes. *Tetrahedron Lett.* **1999**, *40*, 2157–2160. [CrossRef]
3. Wuang, S.C.; Neoh, K.G.; Kang, E.-T.; Pack, D.W.; Leckband, D.E. Polypyrrole Nanospheres with Magnetic and Cell-Targeting Capabilities. *Macromol. Rapid Commun.* **2007**, *28*, 816–821. [CrossRef]
4. Trofimov, B.A.; Nedolya, N.A. Pyrroles and their Benzo Derivatives: Reactivity. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K., Eds.; Pergamon Press: Oxford, UK, 2008; Volume 3, pp. 45–268.
5. Kalogirou, A.S.; Manoli, M.; Koutentis, P.A. Reaction of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine with benzyltriethylammonium chloride. *Tetrahedron Lett.* **2018**, *59*, 3589–3593. [CrossRef]
6. Hayashi, H. Processing Method for Color Photographic Material. Japan Patent 05,341,470, 24 December 1993.
7. Asami, M. Color Photographic Photosensitive Material and Color Image-Forming Method Using Same. Japan Patent 05,297,537, 12 November 1993.
8. Kawai, K. Method for Forming a Color Image. European Patent 556,858, 25 August 1993.
9. Morigaki, M.; Yoshioka, Y.; Seto, N. Silver Halide Color Photographic Material. European Patent 544,317, 2 June 1993.
10. Hayashi, H. Method for Processing Color Photographic Material. European Patent 557,851, 1 September 1993.
11. Naruse, H.; Suzuki, M.; Sato, T. Silver Halide Color Photographic Material. European Patent 544,319, 2 June 1993.
12. Suzuki, M.; Naruse, H.; Sato, T. Silver Halide Color Photographic Material. European Patent 544,323, 2 June 1993.
13. Naruse, H.; Suzuki, M. Silver Halide Color Photographic Material. European Patent 544,322, 2 June 1993.
14. Seto, N.; Yoshioka, Y.; Suzuki, M.; Morigaki, M. Silver Halide Color Photographic Material. European Patent 544,316, 2 June 1993.
15. Middleton, W.J.; Engelhardt, V.A.; Fisher, B.S. Cyanocarbon Chemistry. VIII. Heterocyclic Compounds from Tetracyanoethylene. *J. Am. Chem. Soc.* **1958**, *80*, 2822–2829. [CrossRef]
16. Wilding, B.; Winkler, M.; Petschacher, B.; Kratzer, R.; Glieder, A.; Klempier, N. Nitrile Reductase from *Geobacillus kaustophilus*: A Potential Catalyst for a New Nitrile Biotransformation Reaction. *Adv. Synth. Catal.* **2012**, *354*, 2191–2198. [CrossRef]
17. Carboni, R.A. Tetracyanoethylene. *Org. Synth.* **1959**, *39*, 64. [CrossRef]