

Short Note

Syn-Ethyl 1-hydroxy-7-methoxy-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolone-3-carboxylate HCl Salt

Marcus Baumann and Ian R. Baxendale *

Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK

* Author to whom correspondence should be addressed; E-Mail: i.r.baxendale@durham.ac.uk.

Academic Editor: Norbert Haider

Received: 12 December 2014 / Accepted: 26 February 2015 / Published: 3 March 2015

Abstract: This short note describes a one-step synthesis of the title compound from commercially available starting materials and reports its full spectroscopic characterization data.

Keywords: heterocycle; quinoline; pyrrolidine

Introduction

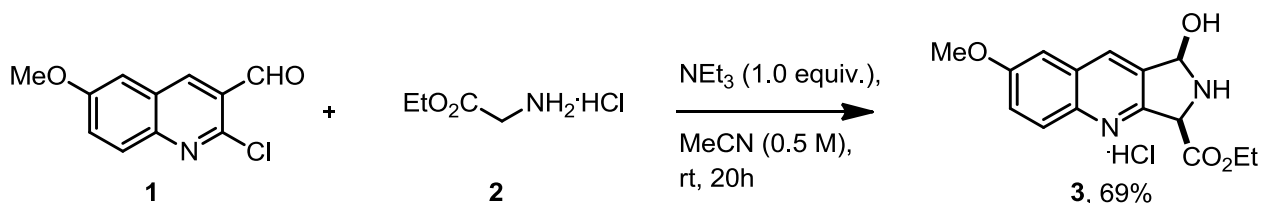
The pharmaceutical and agrochemical industries are under constant pressure to streamline their development cycles to provide new chemical entities required to target human diseases and increase agricultural output [1]. Despite recent breakthroughs in the areas of biologics and protein engineering simple heterocyclic structures still remain principle targets offering rapid modification points, high atom to biological activity ratios, and beneficial pharmacological profiles [2–4]. Consequently many synthesis endeavors are focused on accessing new heterocyclic derivatives. Recently, we [5,6] and others [7] have reviewed the available literature focusing on top-selling drug molecules and were able to confirm and analyse the prevalence of small molecular entities containing five- and six-membered heterocyclic rings. Amongst the heteroaromatic scaffolds indoles, imidazoles and pyridines were found to be most common, whereas pyrrolidines, piperazines and piperidines are most frequently encountered in saturated heterocycles. Consequently, it comes with no surprise that chemists in both industry and academia continue to seek new entries into highly versatile heterocyclic building blocks bearing specific functionalities (*i.e.*, halides, esters, amines, *etc.*) or distinct hydrogen bonding

networks. Over the past ten years one key area of our research has been to devise modern, often flow-based routes towards such interesting heterocyclic architectures [8–11].

In this short note we wish to report on the efficient synthesis of *syn*-ethyl 1-hydroxy-7-methoxy-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolone-3-carboxylate hydrochloride salt, which represents an interesting fused tricyclic system containing several hydrogen bond acceptors and donors.

Experimental Section

To a 100 mL round bottom-flask containing 2-chloro-6-methoxyquinoline-3-carboxaldehyde (**1**, 2.21 g, 10 mmol) and glycine ethyl ester hydrochloride (**2**, 1.39 g, 10 mmol) in acetonitrile (20 mL) was added triethylamine (1.4 mL, 10 mmol) in one portion. The resulting suspension was stirred at room temperature for 20 h. After evaporation of the solvent the resulting residue was redissolved in ethyl acetate and extracted with water (3 × 25 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to yield a waxy solid. This material was recrystallised from dichloromethane to furnish a pale yellow amorphous solid (**3**, 1.95 g, 69% yield, Scheme 1).



Scheme 1. Synthesis of *syn*-ethyl 1-hydroxy-7-methoxy-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolone-3-carboxylate hydrochloride salt **3**.

Initial analysis of the reaction product by LC-MS and high resolution LC-MS had revealed the molecular formula to be $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$. Furthermore IR spectroscopy indicated the presence of a carbonyl stretch (1724.5 cm^{-1}) as well as an amine (3346.8 and 3276.0 cm^{-1}) and a hydroxyl group (2619.2 cm^{-1}) consistent with the tricyclic structure proposed for **3**. In addition elemental analysis was consistent with the proposed HCl salt of the parent compound, and further analysis of the result suggest the presence of a hemihydrate species of **3**.

As the reaction product was isolated as a single diastereoisomer (^1H NMR) further 2-dimensional NMR experiments were used to determine its relative configuration. Crucially, it was found that both methine protons on the pyrrolidine moiety show a correlation in the COSY spectrum with the coupling constant being measured as $J = 2.8\text{ Hz}$, which is indicative of a long-range coupling. NOESY spectral data furthermore revealed a through space coupling of these two methine protons (see Figure 1 and SI for details) indicating the presence of the *cis*-diastereoisomer. By creating an energy-minimised 3D model (ChemDraw 3D, PerkinElmer, Waltham, MA, USA) of the free base form of *cis*-**3** the distance between these two protons was estimated to be $\sim 3.3\text{ \AA}$.

It is believed that this conformationally stable diastereoisomer is due to the presence of the hydrochloride salt.

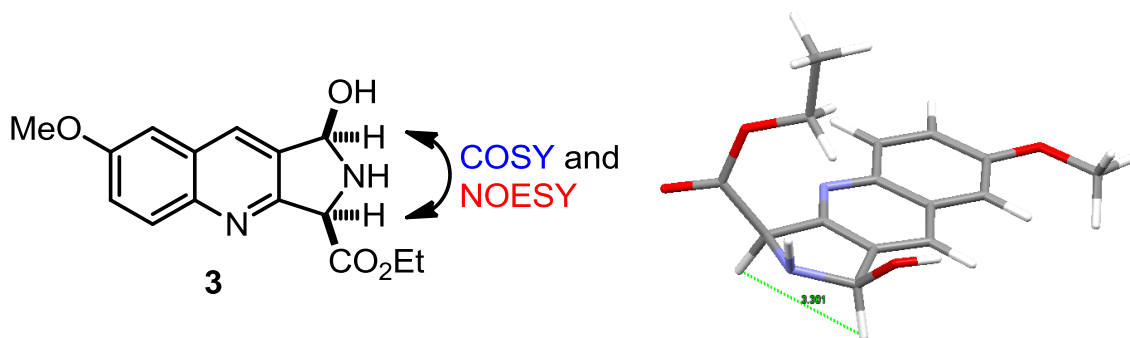


Figure 1. Assignment of the relative configuration of **3** based on 2D NMR data and a modelled 3D structure (free base form).

Spectroscopic Data

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$) δ 8.38 (s, 1H), 7.82 (d, $J = 9.1$ Hz, 1H), 7.46 (d, $J = 2.8$ Hz, 1H), 7.40 (dd, $J = 9.2, 2.8$ Hz, 1H), 5.95 (s, 1H), 5.34 (d, $J = 2.8$ Hz, 1H), 4.14 (m, 2H), 3.88 (s, 3H), 3.68 (d, $J = 2.8$ Hz, 1H), 1.19 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C-NMR}$ (151 MHz, $\text{DMSO-}d_6$) δ 173.8 (C), 158.2 (C), 145.4 (C), 142.6 (C), 137.7 (CH), 134.8 (C), 129.3 (CH), 128.6 (C), 123.2 (CH), 106.4 (CH), 70.7 (CH), 60.9 (CH_2), 58.1 (CH), 56.1 (CH_3), 14.6 (CH_3).

IR (neat, HCl-salt) ν 3346.8 (w), 3276.0 (w), 2619.2 (broad), 1724.5 (s), 1624.4 (m), 1499.3 (m), 1340.9 (m), 1218.3 (s), 1157.4 (s), 1015.8 (s), 876.5 (m), 823.9 (s), 537.9 (m) cm^{-1} .

LC-MS (ESI) $m/z = 289.1$ (M+H). HR-MS (ESI) calculated for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_4$ 289.1188, found 289.1201 (M+H, $\Delta = 4.5$ ppm).

Elemental analysis: calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ C: 53.98%, H: 5.44%, N: 8.39%; measured C: 53.75%, H: 5.18%, N: 8.45%.

Melting range: $\sim 135\text{--}140$ $^\circ\text{C}$ (HCl-salt; CH_2Cl_2 , decomposition).

Acknowledgments

Both authors gratefully acknowledge financial support through the Royal Society.

Author Contributions

Both authors contributed equally to the research outlined in this paper and the writing of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Scannel, J.W.; Blanckley, A.; Boldon, H.; Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Disc.* **2012**, *11*, 191–200.
2. Li, J.J., Ed. *Heterocyclic Chemistry in Drug Discovery*; Wiley: Hoboken, NJ, USA, 2013; ISBN: 978-1-118-14890-7.
3. Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action*; Elsevier Academic Press: Burlington, MA, USA, 2004; ISBN 978-0126437324.
4. Wermuth, C.G., Ed. *The Practice of Medicinal Chemistry*, 3rd ed.; Elsevier Academic Press: Waltham, MA, USA, 2008; ISBN: 978-0-12-374194-3.
5. Baumann, M.; Baxendale, I.R.; Ley, S.V.; Nikbin, N. An overview of the key routes to the best selling 5-membered ring heterocyclic pharmaceuticals. *Beilstein J. Org. Chem.* **2011**, *7*, 442–495.
6. Baumann, M.; Baxendale, I.R. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319.
7. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
8. Baumann, M.; Baxendale, I.R.; Ley, S.V.; Smith, C.D.; Tranmer, G.K. Fully automated continuous flow synthesis of 4,5-disubstituted oxazoles. *Org. Lett.* **2006**, *8*, 5231–5234.
9. Baumann, M.; Baxendale, I.R.; Ley, S.V. Synthesis of 3-Nitropyrrolidines via dipolar cycloaddition reactions using a modular flow reactor. *Synlett* **2010**, *5*, 749–752.
10. Baumann, M.; Baxendale, I.R.; Kirschning, A.; Ley, S.V.; Wegner, J. Synthesis of highly substituted nitropyrrolidines, nitropyrrolizines and nitropyrroles via multicomponent-multistep sequences within a flow reactor. *Heterocycles* **2010**, *82*, 1297–1316.
11. Baumann, M.; Baxendale, I.R.; Kuratli, C.; Ley, S.V.; Martin, R.E.; Schneider, J. Synthesis of a drug-like focused library of trisubstituted pyrrolidines using integrated flow chemistry and batch methods. *ACS Comb. Sci.* **2011**, *13*, 405–415.

© 2015 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 license (<http://creativecommons.org/licenses/by/4.0/>).