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Short Note

1-Benzyl-2-(thien-2-yl)-4,5-dihydro-1*H*-imidazole

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Abstract: Imidazolines are a valuable class of organic compounds, namely ligands of imidazoline receptors, chiral ligands for metal catalysis, synthetic intermediates. The title compound has been prepared through a modified procedure, employing *N*-benzylethylenediamine and thiophene-2-carbaldehyde under the action of *N*-bromosuccinimide (NBS) in dichloromethane (DCM) in a good 78% yield.

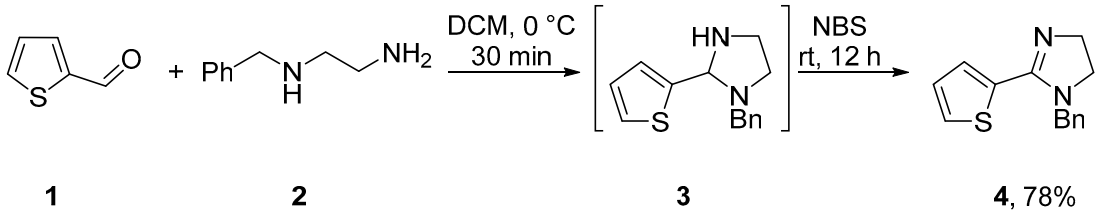
Keywords: imidazoline; NBS; cyclization

1. Introduction

Five-membered heterocycles with two or more heteroatoms find wide application in medicinal chemistry and other fields [1–8]. The innate affinity of imidazolines to imidazoline-type receptors has attracted a significant amount of effort in the synthesis and bioactivity investigations of these compounds. The endeavors in the field resulted in the appearance of marketed drugs clonidine, moxonidine, idazoxane, cirazolline, iodofexidine, efaroxan, and others [9–14]. Moreover, imidazolines are renowned ligands in transition metal catalysis [15–18] and useful synthetic intermediates [19–21]. Numerous syntheses of imidazolines have been published, and common drawbacks include the need for harsh conditions or expensive catalysts [22–27]. A general preparative procedure for the synthesis of imidazolines under mild conditions was developed by Fujioka et al. [28]. In that approach, diamine was mixed with an aldehyde in dichloromethane (DCM) or *tert*-butyl methyl ether (TBME) to form an aminal, which was oxidized by a subsequent treatment with *N*-bromosuccinimide (NBS). Notwithstanding the broad scope and generality of the method, comparatively low yields were obtained for *N*-benzylethylenediamine due to reluctant aminal formation with a more sterically crowded amine. Following our interest in synthesis and chemistry of 1,2-diamines [29–31], herein, we report the synthesis of previously unknown 1-benzyl-2-(thien-2-yl)-4,5-dihydro-1*H*-imidazole through a slightly modified Fujioka's procedure, giving the title compound in a good 78% yield.

2. Results

The reaction of thiophene-2-carbaldehyde (**1**) with *N*-benzylethylenediamine (**2**) was carried out in DCM at 0 °C for 30 min and resulted in the in situ formation of aminal **3**. Subsequent addition of NBS and overnight stirring at rt furnished the target molecule **4** in 78% yield (Scheme 1). The structure determination of the title compound **4** was achieved with ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry (for details, see Supplementary Materials). The brutto formula was devised with the help of high-resolution mass spectrometry.



Scheme 1. Preparation of thienyl-substituted imidazoline **4**.

3. Discussion

Comparing the above procedure to Fujioka's original work, the following differences were noted: Firstly, the use of nitrogen atmosphere does not grant any benefits and the reaction can be performed in a closed vessel without nitrogen; secondly, and more importantly, the use of more concentrated solutions are crucial for the effective reaction. Thus, carrying out the reaction in 0.32 M DCM solution instead of 0.1 M gives the product **4** with 78% yield, comparing to 65% under greater dilution. It is worth noting that the procedure also works excellently for *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde, giving the corresponding imidazolines.

4. Materials and Methods

4.1. General

Starting reagents were purchased from commercial sources and were used without any additional purification. ^{1}H and ^{13}C NMR spectra were acquired on a Jeol JNM-ECA 600 spectrometer (JEOL Ltd., Tokyo, Japan, with operating frequencies of 600 and 150 MHz, respectively) at room temperature and referenced to the residual signals of the solvent. The solvent used for NMR was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Coupling constants (*J*) are reported in Hertz (Hz). The peak patterns are indicated as follows: s, singlet; t, triplet; m, multiplet. Infrared spectra were measured on an Infralum FT-801 FT/IR instrument. The wavelengths are reported in reciprocal centimeters (ν max/cm^{-1}). Mass spectra were recorded with LCMS-8040 Triple quadrupole liquid chromatograph mass spectrometer from Shimadzu (Shimadzu corp., Japan, ESI) and Kratos MS-30 mass-spectrometer (Shimadzu division, Japan, EI, 70 eV). HRMS spectra were recorded on a Bruker MicrOTOF-Q II (Bruker corp., Bremen, Germany). Elemental analysis was performed with a Euro Vector EA-3000 elemental analyzer (EuroVector S.p.A., Milan, Italy). The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Column chromatography was performed using silica gel (60–75 mesh). Melting points were determined on an SMP-10 apparatus and were uncorrected. Solvents were distilled and dried according to standard procedures.

*4.2. 1-Benzyl-2-(thien-2-yl)-4,5-dihydro-1H-imidazole (**4**)*

The mixture of thiophene-2-carbaldehyde (**1**) (3.55 mL, 38 mmol) and *N*-benzylethylenediamine (**2**) (6.00 mL, 40 mmol) in dry CH_2Cl_2 (125 mL) was stirred at 0 °C for 30 min, NBS (7.12 g, 40 mmol) was added to the mixture and the resulting solution was stirred overnight at rt. The reaction was diluted by CH_2Cl_2 (125 mL) and quenched by the addition of a mixture of $Na_2S_2O_5$ aq (140 mL) and 10% NaOH aq (70 mL), the organic layer was washed by 10% NaOH aq (70 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography ($CHCl_3$/MeOH, 100:0 → 99:1). TLC: R_f 0.35 ($CHCl_3$/MeOH/NH_3, 10:1:0.1,). Recrystallization gave the title compound **4** (7.18 g, 78%) as yellow needles; m.p. 52–53 °C (MeCN). ^{1}H NMR ($CDCl_3$) δ 3.50 (t, 2 H, *J* 10.2), 3.93 (t, 2 H, *J* 10.2), 4.57 (s, CH_2, 2 H), 7.02–7.07 (m, 1 H), 7.27–7.32 (m, 3 H), 7.37 (t, 2 H, *J* 7.6), 7.41–7.45 (m, 2 H). ^{13}C NMR δ 160.9 (Cq), 137.5 (Cq), 131.7 (Cq), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.7 (2C, CH), 127.5 (CH), 127.1 (2C, CH), 52.9 (CH_2), 52.2 (CH_2), 51.8 (CH_2). IR (cm^{-1}) ν = 3054 (w), 2930 (w), 2865 (m), 1709 (m), 1597 (m), 1522 (m), 1443 (m), 1358 (m), 1266 (m), 999 (m), 850 (w), 732 (w), 700 (m). EI-MS (*m/z*, M^{+}): 243 (100%), 244 (16), 245 (5). HRMS (TOF ES^{+}): *m/z* [M + H]$^{+}$ calculated for

$C_{14}H_{14}N_2S$: 243.0951; found: 243.0950. Anal. calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.56%; found: C, 69.55; H, 5.78; N, 11.60%.

Supplementary Materials: Copies of the ^1H, ^{13}C NMR, and HRMS spectra are available online.

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

References

1. Soni, J.; Sethiya, A.; Sahiba, N.; Agarwal, D.K.; Agarwal, S. Contemporary Progress in the Synthetic Strategies of Imidazole and its Biological Activities. *Curr. Org. Syn.* **2019**, *16*, 1078–1104. [CrossRef]
2. Cho, S.H.; Kim, S.H.; Shin, D. Recent applications of hydantoin and thiohydantoin in medicinal chemistry. *Eur. J. Med. Chem.* **2019**, *164*, 517–545. [CrossRef] [PubMed]
3. Kaur, R.; Palta, K.; Kumar, M.; Bhargava, M.; Dahiya, L. Therapeutic potential of oxazole scaffold: A patent review (2006–2017). *Expert Opin. Ther. Pat.* **2018**, *28*, 783–812. [CrossRef] [PubMed]
4. De Oliveira Silva, A.; McQuade, J.; Szostak, M. Recent Advances in the Synthesis and Reactivity of Isothiazoles. *Adv. Synth. Catal.* **2019**, *361*, 3050–3067. [CrossRef]
5. Maftei, C.V.; Fodor, E.; Jones, P.G.; Daniliuc, C.G.; Franz, M.H.; Kelter, G.; Fiebig, H.H.; Tamm, M.; Neda, I. Novel 1,2,4-oxadiazoles and trifluoromethylpyridines related to natural products: Synthesis, structural analysis and investigation of their antitumor activity. *Tetrahedron* **2016**, *72*, 1185–1199. [CrossRef]
6. Shaik, A.; Bhandare, R.R.; Palleapati, K.; Nissankararao, S.; Kancharlapalli, V.; Shaik, S. Antimicrobial, antioxidant, and anticancer activities of some novel isoxazole ring containing chalcone and dihydropyrazole derivatives. *Molecules* **2020**, *25*, 1047. [CrossRef]
7. Kotian, S.Y.; Mohan, C.D.; Merlo, A.A.; Rangappa, S.; Nayak, S.C.; Rai, K.M.L.; Rangappa, K.S. Small molecule based five-membered heterocycles: A view of liquid crystalline properties beyond the biological applications. *J. Mol. Liq.* **2020**, *297*, 111686. [CrossRef]
8. Kadyrov, A.; Neda, I.; Kaukorat, T.; Sonnenburg, R.; Fischer, A.; Jones, P.G.; Schmutzler, R. New Phospholene and Phosphepine Derivatives from λ^3-Phosphorus Compounds and Hexafluoroacetone or Perfluorinated α-Diketones. *Chem. Ber.* **1996**, *129*, 725–732. [CrossRef]
9. Regunathan, S.; Reis, D.J. Imidazoline receptors and their endogenous ligands. *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 511–544. [CrossRef]
10. Khan, Z.P.; Ferguson, C.N.; Jones, R.M. Alpha-2 and imidazoline receptor agonists therapeutic role. *Anaesthesia.* **1999**, *54*, 146–165. [CrossRef]
11. Li, J.X. Imidazoline I2 receptors: An update. *Pharmacol. Ther.* **2017**, *178*, 48–56. [CrossRef] [PubMed]
12. Jones, B.D.; Tochowicz, A.; Tang, Y.; Cameron, M.D.; McCall, L.I.; Hirata, K.; Siqueira-Neto, J.L.; Reed, S.L.; McKerrow, J.H.; Roush, W.R. Synthesis and Evaluation of Oxyguanidine Analogues of the Cysteine Protease Inhibitor WRR-483 against Cruzain. *ACS Med. Chem. Lett.* **2016**, *7*, 77–82. [CrossRef] [PubMed]
13. Krasavin, M. Biologically active compounds based on the privileged 2-imidazoline scaffold: The world beyond adrenergic/imidazoline receptor modulators. *Eur. J. Med. Chem.* **2015**, *97*, 525–537. [CrossRef] [PubMed]
14. Bousquet, P.; Hudson, A.; García-Sevilla, J.A.; Li, J.X. Imidazoline receptor system: The past, the present, and the future. *Pharmacol. Rev.* **2020**, *72*, 50–79. [CrossRef] [PubMed]
15. Huang, H.; Peters, R. A highly strained planar-chiral platinacycle for catalytic activation of internal olefins in the Friedel-crafts alkylation of indoles. *Angew. Chem. Int. Ed.* **2009**, *48*, 604–606. [CrossRef] [PubMed]
16. Hyodo, K.; Nakamura, S.; Shibata, N. Enantioselective aza-Morita-Baylis-Hillman reactions of acrylonitrile catalyzed by palladium(II) pincer complexes having C 2-symmetric chiral bis(imidazoline) ligands. *Angew. Chem. Int. Ed.* **2012**, *51*, 10337–10341. [CrossRef]
17. Awata, A.; Arai, T. PyBidine/copper catalyst: Asymmetric exo'-selective [3+2] cycloaddition using imino ester and electrophilic indole. *Angew. Chem. Int. Ed.* **2014**, *53*, 10462–10465. [CrossRef]

18. Kondo, M.; Nishi, T.; Hatanaka, T.; Funahashi, Y.; Nakamura, S. Catalytic Enantioselective Reaction of α-Aminoacetonitriles Using Chiral Bis(imidazoline) Palladium Catalysts. *Angew. Chem. Int. Ed.* **2015**, *54*, 8198–8202. [CrossRef]
19. Dar'in, D.; Krasavin, M. The Chan-Evans-Lam N-Arylation of 2-Imidazolines. *J. Org. Chem.* **2016**, *81*, 12514–12519. [CrossRef]
20. Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. Intramolecular bromo-amination of 1,4-cyclohexadiene aminal: One-pot discrimination of two olefins and concise asymmetric synthesis of (−)-γ-lycorane. *Chem. Commun.* **2006**, 832–834. [CrossRef]
21. Lathrop, S.P.; Pompeo, M.; Chang, W.T.T.; Movassaghi, M. Convergent and Biomimetic Enantioselective Total Synthesis of (−)-Communesin F. *J. Am. Chem. Soc.* **2016**, *138*, 7763–7769. [CrossRef] [PubMed]
22. Winkel, A.; Wilhelm, R. New chiral ionic liquids based on imidazolinium salts. *Tetrahedron Asymmetry* **2009**, *20*, 2344–2350. [CrossRef]
23. Ishihara, M.; Togo, H. Facile preparation of 2-imidazolines from aldehydes with tert-butyl hypochlorite. *Synthesis (Stuttg)* **2007**, 1939–1942. [CrossRef]
24. Bai, G.Y.; Xu, K.; Chen, G.F.; Yang, Y.H.; Li, T.Y. A facile and efficient synthesis of 2-imidazolines from aldehydes using hydrogen peroxide and substoichiometric sodium iodide. *Synthesis (Stuttg)* **2011**, 1599–1603. [CrossRef]
25. Busacca, C.A.; Bartholomeyzik, T.; Cheekoori, S.; Grinberg, N.; Lee, H.; Ma, S.; Saha, A.; Shen, S.; Senanayake, C.H. On the Racemization of Chiral Imidazolines. *J. Org. Chem.* **2008**, *73*, 9756–9761. [CrossRef]
26. Chen, J.Q.; Yu, W.L.; Wei, Y.L.; Li, T.H.; Xu, P.F. Photoredox-Induced Functionalization of Alkenes for the Synthesis of Substituted Imidazolines and Oxazolidines. *J. Org. Chem.* **2017**, *82*, 243–249. [CrossRef]
27. Aksenov, A.V.; Aksenov, N.A.; Arutiunov, N.A.; Malyuga, V.V.; Ovcharov, S.N.; Rubin, M. Electrophilically activated nitroalkanes in reaction with aliphatic diamines en route to imidazolines. *RSC Adv.* **2019**, *9*, 39458–39465. [CrossRef]
28. Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. One-pot synthesis of imidazolines from aldehydes: Detailed study about solvents and substrates. *Tetrahedron* **2007**, *63*, 638–643. [CrossRef]
29. Golantsov, N.E.; Festa, A.A.; Karchava, A.V.; Yurovskaya, M.A. Marine indole alkaloids containing an 1-(indol-3-yl)ethane-1,2-diamine fragment (Review). *Chem. Heterocycl. Compd.* **2013**, *49*, 203–225. [CrossRef]
30. Golantsov, N.E.; Festa, A.A.; Varlamov, A.V.; Voskressensky, L.G. Revision of the Structure and Total Synthesis of Topsentin C. *Synthesis (Stuttg)* **2017**, *49*, 2562–2574. [CrossRef]
31. Golantsov, N.E.; Festa, A.; Golubenkova, A.S.; Nguyen, K.M.; Yakovenko, E.A.; Varlamov, A.V.; Voskressensky, L.G. Total synthesis of hamacanthin B class marine bisindole alkaloids. *Chem. Heterocycl. Compd.* **2020**, *56*, 331–338. [CrossRef]