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Synthesis of 2-bromo-7-methyl-3,5-dihydro-imidazo[4,5-*d*]-pyridazin-4-one and 3-alkyl-2-bromo-3,5-dihydro-imidazo-[4,5-*d*]pyridazin-4-one and their selective elaboration

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Abstract

Two synthetic routes to the versatile 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-ones **2** and **5** have been developed that allow the production of multigram quantities without the need of any chromatographic purification. Broad and selective elaboration of the heteroaromatic scaffolds has also been accomplished.

Keywords: Imidazoles; Imidazopyridazinones; Regiocontrol; Combinatorial chemistry

During the course of a project aimed at developing DPP-4 inhibitors for the treatment of type 2 diabetes, we discovered that compounds based on the xanthine scaffold are highly potent inhibitors.[1] Starting our synthetic efforts from the methyl derivatized xanthine **1**, we succeeded in developing the highly potent DPP-4 inhibitor **BI 1356**, which is currently undergoing clinical phase III trials, by consecutively varying the free positions on the xanthine (Fig. 1). The xanthine core proved to be a particularly suited framework for this venture allowing all sites to be varied highly chemoselectively. Thus, we were able to gain rapid insight into structure–activity relationship (SAR) and optimize inhibitory activity. In addition to achieving the optimal decoration around the xanthine core, we were also interested in examining the core itself. Therefore, we became attracted to alternative scaffolds, such as 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-one, that place the various residues in roughly the same spatial locations as that

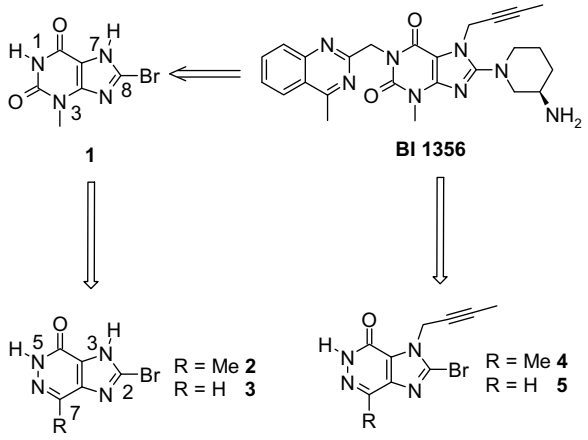

Fig. 1.

achieved by xanthine. Analogous quick and efficient alteration of this alternate scaffold to determine and compare SAR strategically required compounds **2** and **3** as equivalent starting points. While compound **2**, due to its high resemblance, should be eligible for the derivatization process employed for analog **1**, the hydrogen for methyl replacement at C-7 leading to compound **3** may result in

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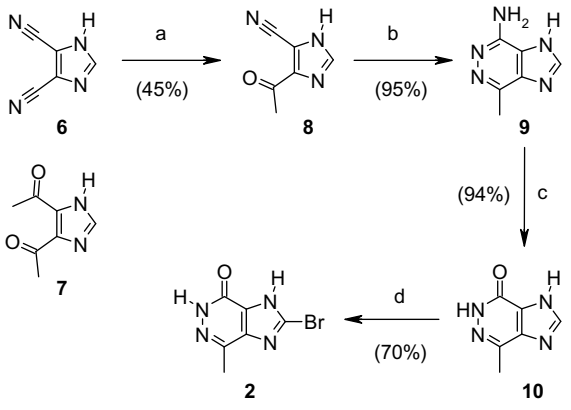
a shift of preference for the attachment of residues to N-3 versus N-1: easier accessiblility of N-1 over N-3 may compromise the selectivity for the latter derivatized regioisomer.[2,3] Hence, we decided to choose for such a scaffold a more elaborated common intermediate that already included the properly positioned substituent on the imidazole substructure as in **5**. Unfortunately, neither compound **2** nor **5** has been described in the literature. Although a few quite competent syntheses of the 3,5-dihydro-imidazo[4,5-*d*]-pyridazin-4-one core have been reported,[4–7] none that would provide the desired scaffolds expediently and quickly in larger quantities has been delineated. In this Letter, we describe the convenient and efficient syntheses of the 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-ones **2, 5** and analogs of **5** and their chemoselective variation at all open sites.

The synthetic route we developed to access scaffold **2** is outlined in Scheme 1.[8] Starting out with the commercial and inexpensive dicyanoimidazole **6**, monoketone **8** was acquired in 45% yield by the addition of three equivalents of methylmagnesium halide to the imidazole dissolved in tetrahydrofuran.[9,10] Besides the desired product, diketone **7** was isolated in about 5–10% yield. We did not spend much effort on optimizing the yield of this transformation since the product was obtained in high purity after simple precipitation from ethyl acetate and ether. Subsequently, monoketone **8** was reacted with hydrazine hydrate in ethanol at elevated temperature, which resulted in a clean conversion to compound **9** in nearly quantitative yield. Diazotization of **9** using sodium nitrite and sulfuric acid in acetic acid and water followed by hydrolysis of the diazo intermediate at reflux temperature furnished the 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-one core **10** in excellent yield and purity after precipitation from water. Bromination of compound **10** was conducted in the presence of potassium carbonate with bromine in acetonitrile. After the aqueous work-up and precipitation from water, the desired relay compound **2** was obtained in 70% yield.[11] This route appeals by its conciseness and efficiency. All

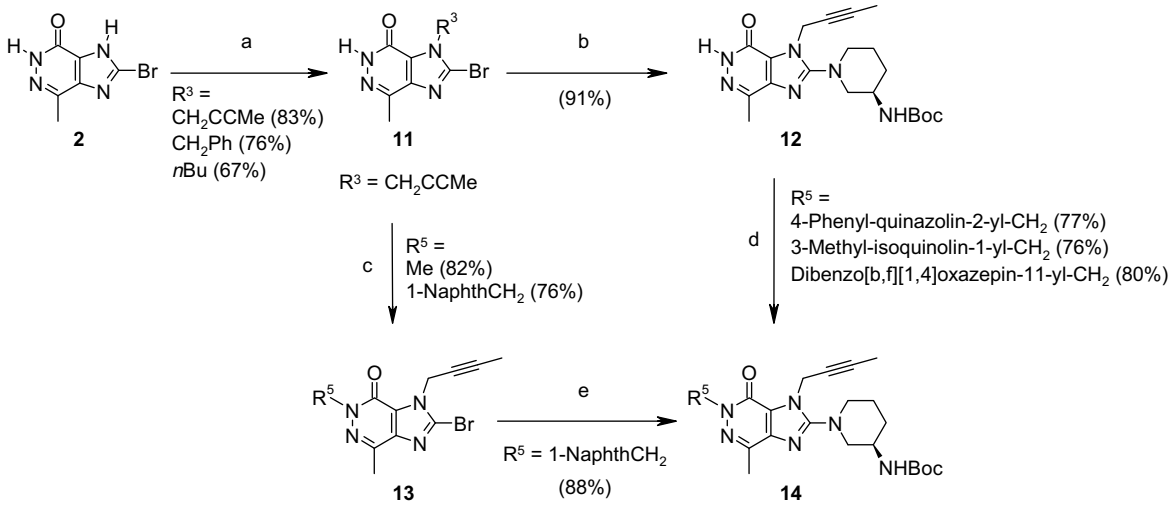


Scheme 1. Reagents and conditions: (a) MeMgCl (3 equiv, 3 mol/L in Et_2O), THF, 5–10 °C; (b) $H_2NNH_2{\cdot}H_2O$ (4 equiv), EtOH, reflux; (c) $NaNO_2$ (4 equiv), H_2SO_4 (0.6 equiv), HOAc, H_2O, 50 °C (0.5 h), then 95 °C; (d) Br_2 (1.1 equiv), K_2CO_3 (1.2 equiv), MeCN, 60 °C.

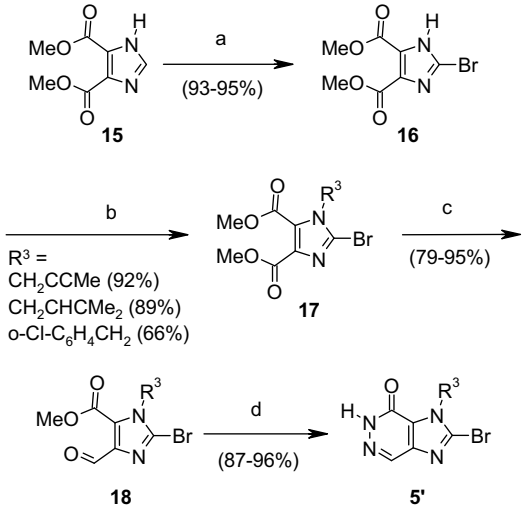
reaction steps have been carried out on 5–20 g-scale without the use of any chromatographic purification. In addition, the route may be employable for further C-7 carbon derivatized 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-ones provided that the selective monoaddition to **6** of carbon nucleophiles other than methyl is workable.

Opportunely, relay compound **2** could be selectively derivatized at N-3 and N-5 by reacting with an alkyl electrophile and at C-2 by displacing the bromine with a nitrogen nucleophile using the conditions applied in the variation of xanthine **1** (Scheme 2). Reaction of **2** with one equivalent of an alkyl halide in the presence of a weak amine base, such as triethylamine or ethyldiisopropylamine, in dimethylformamide gave the monoalkylated product selectively derivatized at N-3 in high yield; neither the competing N-1 nor the N-5 alkylated product was detected. Alkylation of N-5 was then carried out using the stronger base potassium carbonate in dimethylformamide affording product **13** in good yield; O-alkylation at C-4 instead of N-alkylation was not observed. Replacement of the bromine at C-2 for 3-*tert*-butoxycarbonylaminopiperidine (→**14**) was accomplished in high yield using sodium carbonate in dimethylsulfoxide at elevated temperature; however, dimethylformamide or *N*-methylpyrrolidinone could be employed with similar success. The order of introduction of the last two substituents could be reversed allowing specific variations at either site at a very late stage of the reaction sequence. However, initial introduction of the residue at C-2 required longer reaction times for the nucleophilic displacement to be complete due most likely to the abstraction of the proton at N-5 by the base that renders the scaffold less electrophilic. Additionally, it was also feasible to carry out the last two steps in one pot to streamline the reaction sequence. Accordingly, compound **11** was reacted first with the alkyl halide in the presence of potassium carbonate in dimethylformamide. After complete consumption of the starting material, determined by HPLC or TLC, the nucleophile was added and the temperature increased to 80 °C to deliver the product within 8–10 h in yields comparable to those obtained for the step-by-step procedure. In a first trial, we also succeeded in attaching all three substituents successively to **2** in one pot using dimethylformamide as the solvent and ethyldiisopropylamine followed by potassium carbonate as the bases achieving a yield of 56% for the purified product bearing 2-butynyl at N-3, methyl at N-5, and 3-*tert*-butoxycarbonylaminopiperidinyl at C-2.

The syntheses of scaffold **5** and analogs were accomplished in four steps from the commercial imidazole **15** (Scheme 3).[12] The sequence started with the bromination of **15** furnishing **16** in excellent yield using either bromine in combination with potassium carbonate in a solvent mixture of dichloromethane and acetonitrile or *N*-bromosuccinimide in acetonitrile.[13] At this stage, the residue at N-3 of the eventual scaffold **5′** was attached via alkylation of one imidazole nitrogen. Allyl, propargyl, and benzyl residues were introduced via their corresponding halides by



Scheme 2. Reagents and conditions: (a) alkyl halide (1 equiv), EtN*i*Pr$_2$ (1.2 equiv), DMF, 40–60 °C; (b) (*R*)-3-(BocNH)-piperidine (1.2 equiv), Na_2CO_3 (1.5 equiv), DMSO, 80 °C; (c) alkyl halide (1.2 equiv), K_2CO_3 (1.2 equiv), DMF, rt or 60 °C; (d) alkyl chloride (1.2 equiv), K_2CO_3 (1.2 equiv), DMF, 60 °C; (e) (*R*)-3-(BocNH)-piperidine (1.2 equiv), Na_2CO_3 (1.5 equiv), DMSO, 80 °C.

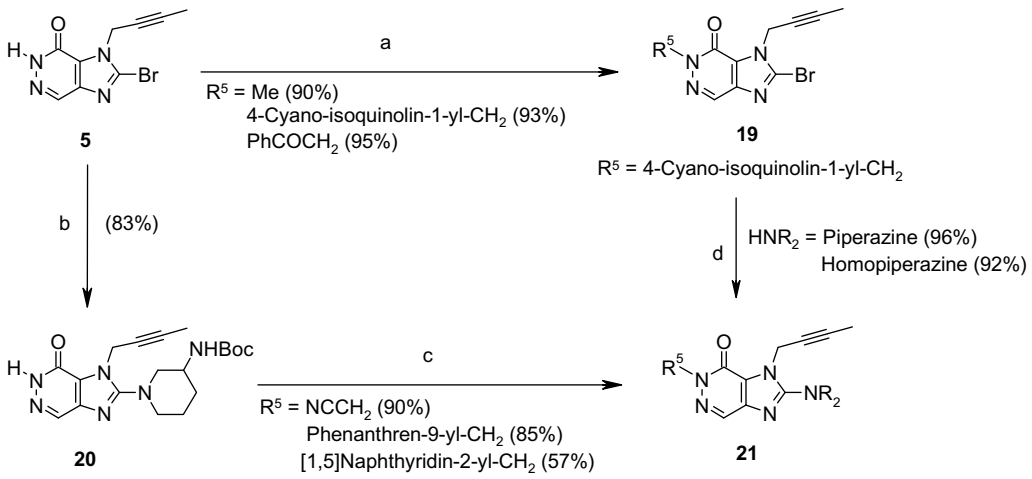


Scheme 3. Reagents and conditions: (a) NBS (1.1 equiv), MeCN, rt or Br_2 (1.1 equiv), K_2CO_3 (1 equiv), DCM/MeCN, rt; (b) alkyl halide (1 equiv), K_2CO_3 (1.1 equiv), DMF, rt or 60 °C; (c) DIBAl-H (1.5 equiv, 1 mol/L in toluene), THF, −70 °C; (d) $H_2NNH_2{\cdot}H_2O$ (1.2 equiv), EtOH, rt (15 min), then HOAc (4 equiv), 80 °C.

the treatment of **16** with potassium carbonate in dimethylformamide or ethyldiisopropylamine in tetrahydrofuran. The respectively derivatized products were isolated in reasonable to superb yield and high purity after crystallization. Installing the carbonyl function of the final bicyclic structure (**5′**) next to the alkyl residue at N-3 required chemoselective reduction of the 4-carboxy ester function to the carbaldehyde. Using 1.5 equiv of DIBAl-H in tetrahydrofuran and toluene at −70 °C afforded the desired aldehyde **18** in high yield with complete regioselectivity;[14] no reduction of the 5-carboxy function was observed and only small amounts of the alcohol derived from the 4-carbaldehyde could be detected. Pure **18** was yielded after crystallization from methylcyclohexane and little toluene. Reaction of imidazole **18** with hydrazine concluded the preparation of **5′**. Accordingly, **18** was treated with hydrazine in ethanol for 15 min to give the hydrazone intermediate that was cyclized to pyridazone **5′** at elevated temperature after the addition of acetic acid. Separation and purification of **5′** was conveniently conducted by precipitation from the reaction mixture by cooling in an ice bath and washing the precipitate with ethanol. The entire reaction sequence to compound **5**[15] could be repeated on a multigram-scale using only extraction and crystallization procedures to isolate the products in high purity; the diethylester analog of compound **15** has also been submitted to the reaction sequence furnishing similar yields and selectivities.

Since scaffold **5′** already bears a substituent at N-3, no selectivity issues had to be considered in subsequent alkylation reactions. In analogy to our previously established procedure for xanthine **1** and scaffold **2**, different alkyl residues were attached to N-5 and amino nucleophiles to C-2 of compound **5** (Scheme 4). Either way around the two residues could be introduced delivering compounds **21** in comparable and decent yield. Attachment of both residues in one pot as described for the methyl derivative **11** proved to be feasible as well.

In summary, we have developed two expedient synthetic routes to the versatile 3,5-dihydro-imidazo[4,5-*d*]pyridazin-4-ones **2** and **5**. The compounds have been prepared in multigram quantities with routes that require no chromatographic purification and thus qualify for large scale preparations. In addition, we have shown that the substituents on the scaffolds can be varied selectively, broadly, and with high efficiency allowing quick access to a series of analogous compounds. Hence, we consider frameworks **2** and **5** as useful platforms for combinatorial chemistry and SAR-based approaches.



Scheme 4. Reagents and conditions: (a) alkyl halide (1.1 equiv), K_2CO_3 (1.5 equiv), DMF, rt or 60 °C; (b) 3-(BocNH)-piperidine (1.2 equiv), Na_2CO_3 (2 equiv), DMSO, 80 °C; (c) alkyl halide (1.1 equiv), K_2CO_3 (1.5 equiv), DMF, rt or 60 °C; (d) piperazine or homopiperazine (6 equiv), DMSO, 80 °C.

Acknowledgement

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References and notes

1. Eckhardt, M.; Langkopf, E.; Mark, M.; Taddayon, M.; Thomas, L.; Nar, H.; Pfrengle, W.; Guth, B.; Lotz, R.; Sieger, P.; Fuchs, H.; Himmelsbach, F. *J. Med. Chem.* **2007**, *50*, 6450.
2. Beljean-Leymarie, M.; Pays, M.; Richer, J. C. *Can. J. Chem.* **1983**, *61*, 2563.
3. Kelley, J. L.; Thompson, J. B.; Styles, V. L.; Soroko, F. E.; Cooper, B. R. *J. Heterocycl. Chem.* **1995**, *32*, 1423.
4. Carbon, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 6083.
5. Martin, S. F.; Castle, R. N. *J. Heterocycl. Chem.* **1969**, *6*, 93.
6. Groziak, M. P.; Wei, L. *J. Org. Chem.* **1992**, *57*, 3776.
7. Yutilov, Y. M.; Svertilova, I. A. *Russ. J. Org. Chem.* **1999**, *35*, 583.
8. Eckhardt, M.; Hauel, N.; Langkopf, E.; Himmelsbach, F.; Kauffmann-Hefner, I.; Tadayyon, M.; Mark, M. WO 2004111051, 2004; *Chem. Abstr.* **2004**, *142*, 74585.
9. Apen, P. G.; Rasmussen, P. G. *J. Heterocycl. Chem.* **1992**, *29*, 1091.
10. Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Shimoji, Y.; Fujimoto, K.; Kitahara, Y.; Sada, T.; Mizuno, M.; Ikeda, M.; Miyamoto, S.; Furukawa, Y.; Koike, H. *J. Med. Chem.* **1996**, *39*, 323.
11. *Characteristic data of compound* **2**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H), 12.51 (br s, 1H), 14.41 (very br s, 1H); IR (KBr): 1654, 1640, 1591, 1495, 1419, 1363, 1292, 1238, 1208, 1147, 958, 861, 791 cm^{-1}; MS *m*/*z* 229/231 (Br) $(M+H)^+$; HRMS (ES^+) calcd for $C_6H_6BrN_4O$ $(M+H)^+$ *m*/*e* 228.9725, found *m*/*e* 228.9723.
12. Hauel, N.; Himmelsbach, F.; Langkopf, E.; Eckhardt, M.; Maier, R.; Mark, M.; Tadayyon, M.; Kauffmann-Hefner, I. WO 2004050658, 2004; *Chem. Abstr.* **2004**, *141*, 54352.
13. Rhee, Y.-S.; Jones, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 8174.
14. Eckhardt, M. WO 2005110999, 2005; *Chem. Abstr.* **2005**, *144*, 6797.
15. *Characteristic data of compound* **5**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (incompletely resolved t, $J = 2.1$ Hz, 3H), 5.27 (incompletely resolved q, $J = 2.2$ Hz, 2H), 8.36 (s, 1H), 12.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 2.9, 36.7, 72.4, 82.1, 127.1, 132.0, 132.6, 141.1, 154.3; IR (KBr) 1666, 1553, 1396, 1371, 1331, 1320, 1258, 1214, 1138, 1081, 895, 755 cm^{-1}; MS *m*/*z* 267/269 (Br) $(M+H)^+$; HRMS (ES^+) calcd for $C_9H_8BrN_4O$ $(M+H)^+$ *m*/*e* 266.9881, found *m*/*e* 266.9896.