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Synthesis of substituted benzimidazoles via tosylation of *N*-aryl amidoxime

Yuhei Yamamoto *, Takayuki Tsuritani, Toshiaki Mase

Process Research Preclinical Development, Banyu Pharmaceutical Co., Ltd, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan

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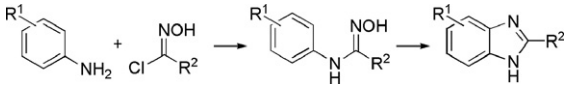
Abstract

Tosylation of *N*-aryl amidoxime in the presence of TEA produces the corresponding benzimidazoles in high yields.

Keywords: Benzimidazoles; *N*-Aryl amidoximes; Imidoyl chlorides; Nitrile oxides

Substituted benzimidazole is a structural motif that is seen in many pharmaceutically and biologically interesting molecules.[1] Although the widespread interest in benzimidazole-containing structures has prompted extensive studies for their synthesis, practical synthetic methods to access this class of molecules are rather limited.[2] The most commonly used starting materials to synthesize these compounds are *ortho*-aminoanilines, and these amines are either condensed with carboxylic acids (or their synthetic equivalents),[3] or reacted with aldehydes in the presence of an oxidant.[4] Recent publications have synthesized these moieties via transition metal catalyzed amination of *ortho*-haloaniline derivatives as the key reaction.[5] The main drawback of these procedures is the requirement of *ortho*-substituted anilines, and thereby limits the diversity of the available starting materials. Despite the importance of useful synthetic methods for benzimidazoles starting from non-*ortho*-substituted anilines, only a few methods have appeared in the literature to date. Herein, we wish to report a new general way to prepare benzimidazoles from amidoximes that are easily obtained from anilines and imidoyl chlorides (Eq. 1).



(1)

It was first reported by Turner and Partridge that 2-substituted benzimidazoles can be prepared by the treatment of *N*-aryl amidoximes with benzenesulfonyl chloride and tertiary amine (Eq. 2).[6] Subsequent work by Grenda and co-workers showed that such products can also be obtained from the parent amidines by oxidation with sodium hypochlorite under basic conditions.[7] The mechanism is believed to involve a nitrene precursor intermediate **1** (Eq. 3).[8] Two modes of reaction can be envisioned for intermediate **1**. Firstly, cyclo-α-elimination which gives the desired benzimidazole (path a), and secondly, rearrangement leading to the carbodiimide (path b). Interestingly, the mode of the reaction (path a vs path b) is influenced by the leaving group on the amidine nitrogen. Based on these observations, we became interested in developing a practical and effective pathway to benzimidazoles which does not rely on substituted anilines. To get further insights into this relationship, we envisioned that *N*-aryl amidoximes are excellent substrates since the hydroxy group of the amidoxime could be easily modified. *N*-Aryl amidoximes can readily be prepared by the reaction of aniline with either imidoyl chlorides or with nitrile oxides.[9]

* Corresponding author. Tel.: +81 29 877 2215; fax: +81 29 877 2173.
E-mail address: yuhei_yamamoto@merck.com (Y. Yamamoto).

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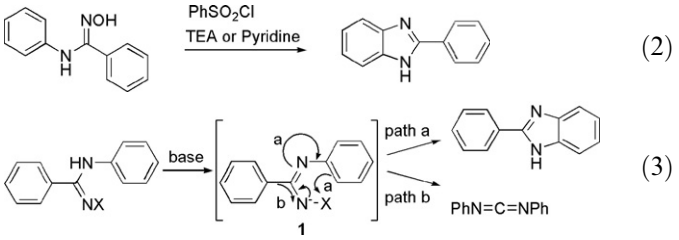
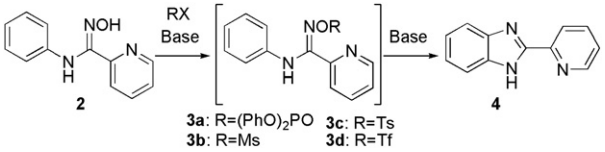


We started our investigation using *N*-hydroxy-*N*′-phenyl-2-pyridinecarboximidamide **2** as the starting material, which was obtained in 92% yield by the reaction of aniline and *N*-hydroxy-2-pyridinecarboximidoyl chloride[10] in the presence of TEA. The hydroxy group of the amidoxime was converted to several leaving groups in situ, and subsequent reaction to yield the benzimidazole proceeded without further treatment. The results are summarized in Table 1. Among the conditions we investigated, tosylation with Ts_2O in the presence of triethylamine was the best, and gave the product in 96% yield (entry 4). Presumably, the reaction proceeded through intermediate **3c**, which was generated immediately after the addition of the reagents at −20 °C.[11] The cyclization of intermediate **3c** that followed, proceeded slowly at room temperature. In the case of MsCl (entry 2) and TsCl (entry 3), the generation of intermediates **3b** and **3c** required a higher temperature and resulted in lower yields. Although phosphorylation with $(PhO)_2POCl$ gave intermediate **3a**,[11] this did not cyclize to the desired compound, but instead decomposed (entry 1). No intermediate **3d** was observed when Tf_2O was used, and the reaction was messy (entry 5).

Having these optimized conditions in hand, the reaction of a number of amidoximes with various functional groups on the phenyl group was examined. The amidoximes (Table 2) in $CHCl_3$ were treated with 2.5 equiv of TEA and 1.05 equiv of Ts_2O at −20 °C. This reaction mixture was then warmed to either room temperature or 35 °C.[12] This method was applied to the synthesis of 2-pyridylbenzimidazoles (entries 1–3), 2-phenylbenzimidazoles (entries 4–9), and 2-cyclohexylbenzimidazoles (entries 10–12). Both *ortho* substituted (entries 3, 8, 9, and 12) and *para* substituted (entries 2, 5–7, 10, and 11) amidoximes gave the benzimidazole products in moderate to good yield. The reaction conditions we use are mild, and do not require strong acids or oxidants, which are often required in condensation reactions starting from diamines. Thus, susceptible functional groups toward acid and oxidants like MeO (entries 2, 3, 6, and 8), MeS (entries 7 and 11), and iodo group (entries 9 and 12) are well tolerated under these reaction conditions.

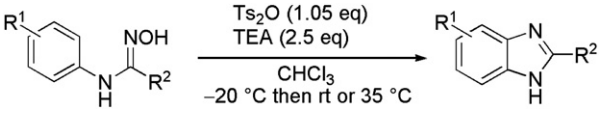
Table 1
Effects of leaving group[a]



Entry	RX	Base	Yield (%)
1	$(PhO)_2POCl$	TEA	<5
2	MsCl	TEA	76
3	TsCl	TEA	81
4	Ts_2O	TEA	96
5	Tf_2O	TEA	<5

[a] Reaction was conducted with 1.05 equiv of RX and 2.5 equiv of base in $CHCl_3$ under N_2 atmosphere at −20 °C followed by warming to room temperature.

Table 2
Synthesis of various benzimidazoles[a]



Entry	R^1	R^2	Temperature (°C)	Time (h)	Yield[b] (%)
1	H	2-Pyridyl	35	2	96
2	*p*-MeO	2-Pyridyl	rt	2	94
3	*o*-MeO	2-Pyridyl	35	2	91
4	H	Ph	rt	7	88
5	*p*-Me	Ph	rt	3	72
6	*p*-MeO	Ph	rt	3	72
7	*p*-MeS	Ph	rt	4	83
8	*o*-MeO	Ph	rt	4	73
9	*o*-I	Ph	rt	4	59
10	*p*-Me	Cyclohexyl	rt	1	94
11	*p*-MeS	Cyclohexyl	rt	1	98
12	*o*-I	Cyclohexyl	rt	1	87

[a] Reaction was conducted with 1.05 equiv of RX and 2.5 equiv of base in $CHCl_3$ under N_2 atmosphere at −20 °C followed by warming to room temperature or to 35 °C.
[b] Isolated yield after silica gel chromatography.

In summary, a new practical method for the synthesis of 2-substituted benzimidazoles via tosylation of *N*-aryl amidoximes, which are readily available from anilines and imidoyl chlorides was demonstrated. Further utilization of the amidoxime chemistry is currently under investigation in our laboratories.

Acknowledgments

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11. Reactions were monitored by HPLC and intermediates are not isolated.
12. *Synthesis of benzimidazoles* (Table 2, entry 11): To the mixture of amidoxime (517 mg, 2 mmol) in $CHCl_3$ (5 mL) was added TEA (0.697 mL, 5 mmol). The mixture was cooled to −20 °C, Ts_2O was added (685 mg, 2.1 mmol), and the mixture was stirred at −20 °C for 5 min. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was then quenched with H_2O (2.5 mL). The aqueous layer was discarded and the organic layer was dried over Na_2SO_4 and filtered. The filtered solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the benzimidazole product as white crystals (471 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 7.40 (br s, 2H), 7.08 (d, $J = 9.5$ Hz, 1H), 2.82 (tt, $J = 11.5$ Hz, 3.4 Hz 1H), 2.47 (s, 3H), 1.99 (br d, $J = 12.9$ Hz, 2H) 1.76 (dt, $J = 12.9$ Hz, $J = 3.7$ Hz, 2H), 1.63–1.66 (m, 1H), 1.59 (qd, $J = 12.4$ Hz, $J = 3.0$ Hz, 2H), 1.37 (qt, $J = 12.2$ Hz, $J = 3.2$ Hz, 2H), 1.26 (tt, $J = 12.2$ Hz, $J = 3.2$ Hz, 1H).
^{1}H NMR data for selected compounds (Table 2, entry 2) H NMR (400 MHz, DMSO-d_6) δ 12.98 (br s, 1H), 8.69 (d, $J = 4.6$ Hz, 1H), 8.28 (d, $J = 8.0$ Hz, 1H), 7.95 (td, $J = 7.6$ Hz, 1.4 Hz 1H), 7.44–7.65 (br m, 1H), 7.46 (dd, $J = 6.6$ Hz, $J = 4.9$ Hz, 1H), 7.00–7.25 (br m, 1H), 6.86 (br s, 1H), 3.77 (s, 3H).
(Table 2, entry 3) Mixture of tautomers (9:1): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (br s, 0.1H), 13.07 (br s, 0.9H), 8.71 (d, $J = 4.6$ Hz, 0.9H), 8.70–8.73 (m, 0.1H), 8.30 (d, $J = 8.1$ Hz, 0.9H), 8.28–8.31 (m, 0.1H), 8.00 (td, $J = 7.6$, $J = 1.5$, 0.9H), 7.94–8.00 (m, 0.1H), 7.49 (ddd, $J = 7.3$ Hz, $J = 4.9$ Hz, $J = 1.0$ Hz, 0.9H), 7.47–7.53 (m, 0.1H), 7.29 (d, $J = 8.1$ Hz, 0.1H), 7.08–7.18 (m, 1.9H), 6.80 (d, $J = 7.8$ Hz, 0.1H), 6.70 (dd, $J = 7.3$ Hz, $J = 1.2$ Hz, 0.9H), 3.96 (s, 2.7H), 3.93 (s, 0.3H).
(Table 2, entry 7) ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 8.15 (d, $J = 6.1$ Hz, 2H), 7.44–7.59 (br m, 5H),7.16 (dd, $J = 8.6$ Hz, $J = 2.0$ Hz, 1H), 2.53 (s, 3H).
(Table 2, entry 8) Mixture of tautomers (55:45): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 0.45H), 12.87 (br s, 0.55H), 8.30 (d, $J = 7.1$ Hz, 0.9H), 8.15 (d, $J = 7.3$ Hz, 1.1H), 7.44–7.58 (m, 3H), 7.26 (d, $J = 8.0$ Hz, 0.45H), 7.07–7.17 (m, 1.55H), 6.79 (d, $J = 7.8$ Hz, 0.45H), 6.70 (dd, $J = 6.3$ Hz, $J = 2.4$ Hz 0.55H), 3.97 (s, 1.35H), 3.96 (s, 1.65H).
(Table 2, entry 10)^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 7.13–7.41 (br m, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 2.80 (tt, $J = 11.5$ Hz, 3.4 Hz 1H), 2.37 (s, 3H), 2.00 (br d, $J = 12.9$ Hz, 2H) 1.76 (dt, $J = 12.9$ Hz, $J = 3.7$ Hz, 2H), 1.63–1.74 (m, 1H), 1.60 (qd, $J = 12.4$ Hz, $J = 3.0$ Hz, 2H), 1.37 (qt, $J = 12.2$ Hz, $J = 3.2$ Hz, 2H), 1.26 (tt, $J = 12.2$ Hz, $J = 3.2$ Hz, 1H).
(Table 2, entry 12) Mixture of tautomers (3:1): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (br s, 0.75H), 12.08 (br s, 0.25H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.47 (d, $J = 7.0$ Hz, 0.25H), 7.41 (d, $J = 7.8$ Hz, 0.75H) 6.92 (t, $J = 7.8$ Hz, 0.75H), 6.91 (t, $J = 7.8$ Hz, 0.25H), 2.81–2.94 (m, 1H), 1.93–2.04 (m, 2H), 1.75–1.86 (m, 2H), 1.52–1.75 (m, 3H), 1.24–1.50 (m, 3H).