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# Hypervalent iodine-mediated synthesis of benzoxazoles and benzimidazoles via an oxidative rearrangement

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ABSTRACT

A Beckmann-type rearrangement of *o*-hydroxy and *o*-aminoaryl N–H ketimines has been developed to prepare benzoxazoles and *N*-Ts benzimidazoles, respectively. The ketimine derivatives were easily prepared by condensation of ammonia with the corresponding ketones and (diacetoxyiodo)benzene was found to act as an efficient oxidant to trigger the [1,2]-aryl migration towards the formation of the desired heterocycles. Depending on the substitution pattern, the results revealed another mechanistic pathway through which benzisoxazoles or 1*H*-indazoles could be formed. The Beckmann-type rearrangement strategy was applied to the synthesis of benzimidazole-containing biorelevant targets such as chlormidazole and clemizole.



## 1. Introduction

With the preparation of the first organic hypervalent iodine species, iodobenzene dichloride ($PhICl_2$) in 1886, C. Willgerodt paved the way to what has recently evolved as a thriving field of chemistry.[1] Hypervalent iodine compounds have been developed as oxidants but they can be used as electrophilic reagents as well. These properties, combined with a non-toxic profile and an ease of handling, make hypervalent iodine reagents attractive alternatives to toxic transition metals in a wide range of organic transformations.[2] A profusion of publications that ensued from the discovery of (diacetoxyiodo)benzene (DAIB),[3] 2-iodoxybenzoic acid (IBX)[4] or Dess-Martin periodinane (DMP)[5] relied on the oxidation of various functional groups (i.e., alcohols, amine, thiols)[6] and applications in total synthesis of natural products.[7] Besides such reactivities, breakthroughs in this area have been driven by the implementation of new synthetic methodologies.[8] The electrophilic nature of the iodine atom in hypervalent iodine species associated with the leaving group ability of iodophenyl moiety have been harnessed by several research groups in synthetically interesting new directions. Within this context, oxidative rearrangement processes have been described in literature.[9] Despite great advances in this field, hypervalent iodine-mediated Beckmann rearrangement remains an unexplored territory to prepare benzoxazoles and benzimidazoles. These heterocycles are common structural units in many marketed pharmaceuticals and drug candidates.[10,11] For instance, Tafamidis is a drug marketed for the treatment of transthyretin-associated familial amyloid polyneuropathy, which is a progressive neurodegenerative disease, while Flunoxaprofen was investigated as a non-steroidal anti-inflammatory drug (Fig. 1). The benzimidazole scaffold is found in Esomeprazole and Bendamustine, which are respectively used in the treatment of gastroesophageal reflux disease and lymphocytic

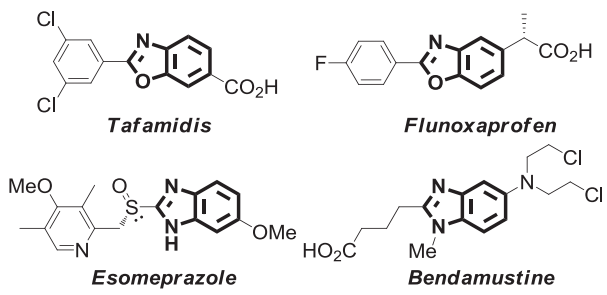


**Fig. 1.** Benzoxazole- and benzimidazole-containing drugs.

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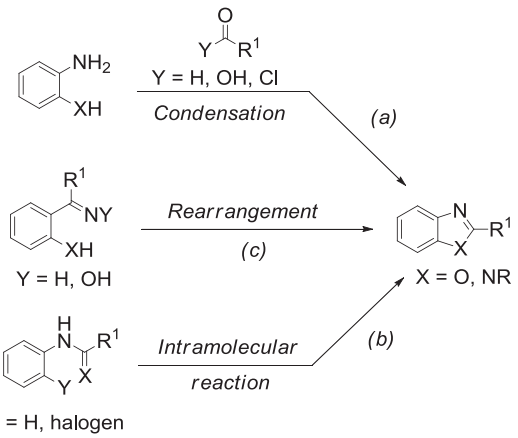
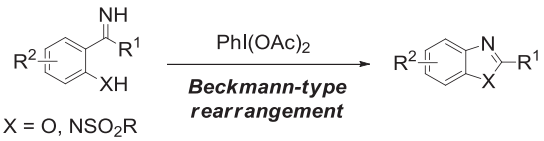
leukemia and lymphomas. Additionally, benzoxazoles and benzimidazoles are found in natural products,[12] polymers,[13] and various functional materials.[14]

The most common synthetic strategies towards the preparation of benzoxazole and benzimidazole structures lie in the condensation of *o*-aminophenols or *o*-phenylenediamines with an aldehyde or carboxylic acid derivatives (Scheme 1, route a)[15] and the intramolecular condensation of anilide or amidine derivatives under oxidative conditions (Scheme 1, route b).[16] Another strategy, which has received less attention by the academic community employs *o*-hydroxy or *o*-aminoaryl N–H ketimine derivatives (Scheme 1, route c). In the presence of various additives, these substrates undergo a Beckmann-type rearrangement to produce the corresponding benzoxazole or benzimidazole units.[17] Strong acids or harsh reaction conditions are often used to promote such rearrangements, while to the best of our knowledge, hypervalent iodine reagents have never been used to trigger the Beckmann-type rearrangement towards the formation of benzoxazole and benzimidazole motifs.




**Scheme 1.** Major synthetic routes towards benzoxazole and benzimidazole scaffolds.

Built upon the interesting features of hypervalent iodine reagents, we surmised that a hypervalent iodine-mediated Beckmann-type rearrangement could be the centerpiece of a strategy devoted to the synthesis of heterocyclic architectures from readily available substrates (Scheme 2). We describe herein a $PhI(OAc)_2$-mediated synthesis of benzoxazoles and benzimidazoles from the corresponding imines and the application of the methodology to the synthesis of biologically relevant targets.

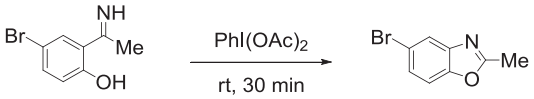



**Scheme 2.** Hypervalent-mediated preparation of benzoxazoles and benzimidazoles.

## 2. Results and discussion

We first investigated the reaction of bromo imine **1a**, readily prepared from the corresponding acetophenone derivative,[17c] in the presence of $PhI(OAc)_2$, in order to get the best reaction conditions (Table 1). The transformation of **1a** into the benzoxazole **2a** was performed at room temperature for 30 min as a model reaction. Our initial investigation concentrated on the study of the effect of the amount of $PhI(OAc)_2$ on the yield (entries 1–5). The best result was obtained by performing the reaction in MeOH with 1.5 equiv of $PhI(OAc)_2$.

**Table 1**
Optimization of the rearrangement of **1a** into **2a**[a]

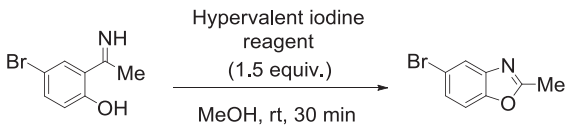



**1a** **2a**

| Entry | $PhI(OAc)_2$ (equiv) | Solvent | Yield %[b] |
|---|---|---|---|
| 1 | 1.1 | MeOH | 77% |
| 2 | 1.3 | MeOH | 81% |
| 3 | 1.5 | MeOH | 82% |
| 4 | 1.7 | MeOH | 75% |
| 5 | 2.0 | MeOH | 78% |
| 6 | 1.5 | EtOH | 80% |
| 7 | 1.5 | *i*-PrOH | 78% |
| 8 | 1.5 | MeOH:$H_2O$ (1:1) | 70% |
| 9 | 1.5 | $Et_2O$ | 43% |
| 10 | 1.5 | THF | 50% |
| 11 | 1.5 | 1,4-Dioxane | 45% |
| 12 | 1.5 | $CH_2Cl_2$ | 55% |
| 13 | 1.5 | $CHCl_3$ | 54% |
| 14 | 1.5 | $CH_3CN$ | 66% |
| 15 | 1.5 | EtOAc | 47% |
| 16 | 1.5 | Toluene | 66% |

[a] Reaction conditions: **1a** (1 mmol), $PhI(OAc)_2$ (see table), solvent (2 mL) for 30 min at room temperature.
[b] Isolated yield of **2a**.

Under these conditions, the benzoxazole **2a** was obtained in 82% yield. To study the effect of the medium, various solvents were tested. Alcoholic solvents gave high yields even in the presence of water (entries 6–8) while the use of ethereal or halogenated solvents led to a decrease in reactivity (entries 9–13). Acetonitrile, ethyl acetate and toluene enabled the formation of **2a** in yields ranging from 47 to 66% (entries 14–16). Therefore, methanol turned out to be the best solvent for the Beckmann-type rearrangement (entry 3). This result is in agreement with previous studies about Beckmann rearrangement, which showed that the rate of reaction was increased by using solvents with high dielectric constants.[18] Various hypervalent iodine reagents were then evaluated in order to study their influence on the reaction outcome (Scheme 3). The reaction of **1a** with $PhI(OAc)_2$ or PhIO afforded the benzoxazole **2a** in good yields while no reaction took place by mixing **1a** with the Koser's reagent [PhI(OH)(OTs)] or with $PhI(OTf)_2$. It is worthwhile noting that the use of a catalytic amount of iodobenzene in conjunction with *m*-chloroperbenzoic acid as a stoichiometric terminal oxidant did not allow the synthesis of **2a**. Under these conditions, only degradation products from **1a** were observed.




**1a** **2a**

$PhI(OAc)_2$, 82%
PhIO, 76%
PhI(OH)(OTs), no reaction
$PhI(OTf)_2$, no reaction

**Scheme 3.** Influence of the hypervalent iodine reagent.

The release of acetic acid (vide infra) during the course of the reaction prompted us to investigate the influence of acid and basic additives in the Beckmann-type rearrangement of **1a** in MeOH at room temperature for 30 min using 1.5 equiv of $PhI(OAc)_2$ (Table 2).

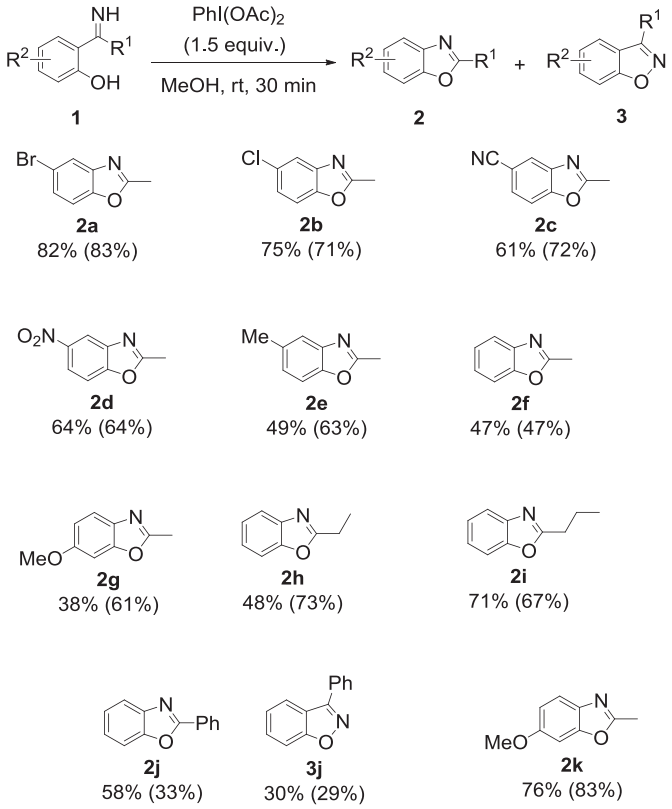
Treatment of **1a** with a mixture of $PhI(OAc)_2$ and different amounts of AcOH led to similar levels of yields for **2a** while the addition of trifluoroacetic acid in the reaction medium had

**Table 2**
Influence of different acid and basic additives[a]

| Entry | Additive | Equiv | Yield **2a** %[b] |
|---|---|---|---|
| 1 | AcOH | 0.2 | 76% |
| 2 | AcOH | 0.5 | 74% |
| 3 | AcOH | 1.0 | 70% |
| 4 | $CF_3CO_2H$ | 1.0 | 38% |
| 5 | $K_2CO_3$ | 1.0 | 78% |
| 6 | $Et_3N$ | 1.0 | 81% |
| 7 | $Et_3N$ | 1.5 | 76% |
| 8 | $Et_3N$ | 0.5 | 83% |
| 9 | $Et_3N$ | 0.2 | 77% |

[a] Reaction conditions: **1a** (1 mmol), $PhI(OAc)_2$ (1.5 mmol), additive (see table), MeOH (2 mL) for 30 min at room temperature.
[b] Isolated yield of **2a**.

a negative impact on the yield (entries 1–4). In order to trap the acetic acid released during the reaction of **1a** with $PhI(OAc)_2$, we screened $K_2CO_3$ and $Et_3N$ as bases. The addition of 1 equiv of $K_2CO_3$ or $Et_3N$ gave similar yields when compared to the reaction without any additive (entries 5 and 6 vs Table 1, entry 3). The study of the influence of the amount of $Et_3N$ showed that the addition of 0.5 equiv of $Et_3N$ gave the best results by producing the benzoxazole **2a** in 83% yield (entries 6–9). In light of the results depicted in Tables 1 and 2, reaction conditions (MeOH, rt, 30 min, 1.5 equiv $PhI(OAc)_2$) with or without 0.5 equiv of $Et_3N$ were investigated to explore the substrate scope (Scheme 4).



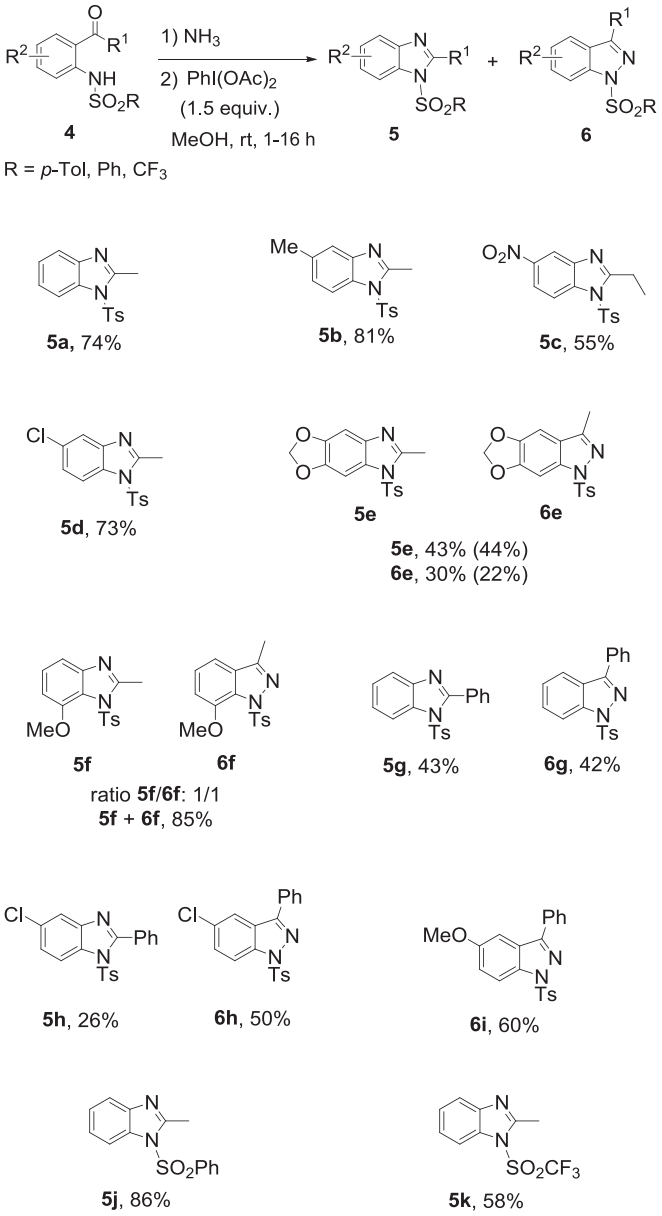

**Scheme 4.** Substrate scope. *Reaction conditions*: **1** (1 mmol), $PhI(OAc)_2$ (1.5 mmol), MeOH (2 mL) for 30 min at room temperature. Isolated yield of **2** without addition of $Et_3N$ and the yields in brackets were obtained in the presence of 0.5 mmol of $Et_3N$. Unless otherwise noted, $^1H$ NMR of the crude showed less than 15% of the benzisoxazole regioisomer **3**.

In the absence of $Et_3N$, good yields of benzoxazole **2** were obtained starting from imines **1a**–**d** bearing halogens or electron-withdrawing groups on the phenyl ring. With imine **1c**, a better yield of 72% (vs 61% without $Et_3N$) was obtained by performing the reaction in the presence of 0.5 equiv of $Et_3N$. This feature has also been observed for the formation of benzoxazoles **2e** and **2g** while the addition of $Et_3N$ did not modify the reaction outcome starting from imine **1f**. An electron-donating group on the phenyl ring has a negative impact on the reactivity and benzoxazole **2g** was produced in 38% yield without $Et_3N$. The same reaction performed in the presence of 0.5 equiv of $Et_3N$ gave better results by producing **2g** in 61% yield. Starting from imines bearing an ethyl (**1h**) or a propyl group (**1i**) produced the corresponding heterocycles in 48% and 71% yield, respectively. A dramatic increase of the yield of **2h** was achieved by adding 0.5 equiv of $Et_3N$ (73% vs 48% without $Et_3N$). The desired target **2j** was obtained in 58% yield along with the benzisoxazole regioisomer **3j** in 30% yield while **2k** was obtained in pure form in 76% yield. It is interesting to note that **1j** ($R^1$=Ph) is less prone to the rearrangement by producing a mixture of **2j**/**3j**. Such a result has already been observed in Beckmann-type rearrangements towards benzoxazole motifs.[17c]

We next set out to determine whether benzimidazoles could be obtained through the route developed for the synthesis of benzoxazoles (Scheme 2). Preliminary results showed that the *o*-aminoaryl N–H ketimines could be obtained in quantitative yields from the corresponding ketones **4** without any further purification. These results prompted us to consider a synthetic strategy whereby benzimidazoles **5** would be prepared over two steps from **4** by just removing the solvent after the imine formation. Based on the conditions optimized for the synthesis of benzoxazoles **2**, imines derived from **4** underwent cyclization in the presence of 1.5 equiv of $PhI(OAc)_2$ in MeOH (Scheme 5).

A screening of nitrogen protecting group borne by **4** suggested that sulfonamide derivatives are the most suitable substrates to give the corresponding benzimidazole **5**.[19] Treatment of **4a** with ammonia followed by the reaction in the presence of $PhI(OAc)_2$ in MeOH gave rise to **5a** in 74% overall yield. The heterocyclic structures **5b** and **5d** were obtained in good yields while a decrease of the yield was noted when **4c** was subjected to the reaction conditions. The results obtained with substrates bearing electron-donating groups stand in striking contrast to those obtained previously and a modification of the protocol was required to enable the reactions. Both increasing the temperature and reaction time for the first step while conducting the $PhI(OAc)_2$-mediated transformation for 16 h produced various ratio of products **5** and **6** depending on the nature of the substrates. While a mixture of the two regioisomers **5e**/**6e**, **5f**/**6f** was obtained, the indazole **6i** was selectively formed in 60% yield. Similarly to the benzoxazole series, a separable mixture of **5g**/**6g** and **5h**/**6h** was obtained starting from the imine **4g** and **4h** bearing a phenyl group. Different sulfonyl groups can be introduced on the heterocyclic framework and compounds **5j** and **5k** were obtained in 86% and 58%, respectively. It is interesting to note that the synthetic strategy developed for the benzimidazole synthesis, which did not involve the isolation and characterization of the imine intermediate has been applied to the formation of **2a**. Applying conditions described in Scheme 5, benzoxazole **2a** has been prepared over two steps from 1-(5-bromo-2-hydroxyphenyl)ethanone by just removing the solvent after the imine formation. Under these conditions, benzoxazole **2a** was formed in 73% yield. Based on the above results and literature data, a plausible mechanism is depicted below to explain the formation of the different products (Scheme 6).[17e]

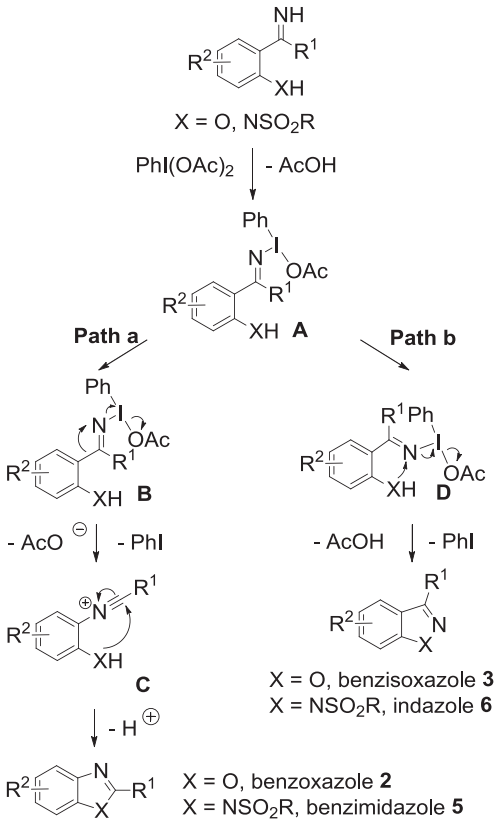
The imine would react with $PhI(OAc)_2$ to produce the corresponding hypervalent iodine species **A**. Following the *path a*, a Beckmann-type [1,2]-migration of the aryl moiety would afford the intermediate **C**, which would then undergo an intramolecular cyclization to give rise to the benzoxazole **2** or benzimidazole **5**. The benzisoxazole **3** and indazole **6** would be formed through the intermediate **D** via intramolecular cyclization of the phenol or amine onto the imine nitrogen following the *path b*. It is worthwhile




**Scheme 5.** Heterocyclic synthesis from **4**. *Reaction conditions*: For starting materials **4a**–**d**, **4i**–**k**: **4** (0.25 mmol), $NH_3$ 7 M in MeOH (1 mL), rt, 2 h and after removal of the solvent, the solid was dissolved in MeOH (0.5 mL) to react with $PhI(OAc)_2$ (0.375 mmol) for 1 h at room temperature. For starting materials **4e**–**h**: **4** (0.2 mmol), $NH_3$ 7 M in MeOH (1.5 mL), 50 °C, 20 h and after removal of the solvent, the solid was dissolved in MeOH (0.4 mL) to react with $PhI(OAc)_2$ (0.3 mmol) for 16 h at room temperature. Unless otherwise noted, $^1H$ NMR of the crude showed less than 15% of the benzisoxazole regioisomer for **4a**–**d**, **4j** and **4k**. Yields in brackets were obtained by using the general procedure with 0.1 mmol of $Et_3N$.

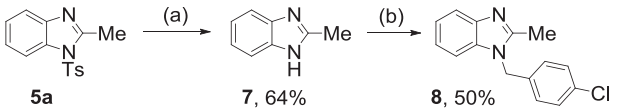
noting that electron-donating groups at the *para*- or *ortho*-position of amino group (X=$NSO_2R$) increase the amount of indazoles **6** due to a higher nucleophilicity of the heteroatom. For instance, the presence of a methoxy group at the *para* position of the amino group induces the selective formation of indazole **6i** while a 1/1 mixture of benzimidazole/indazole **5f**/**6f** was obtained (Scheme 5). In addition, the inclusion of a phenyl group ($R^1$=Ph) in compounds **1** and **4** increases the amount of benzisoxazole **3** or indazole **6** compared to substrates bearing an alkyl group ($R^1$=Me, Et, Pr). This feature has already been observed in other articles dealing with Beckmann-type rearrangement.[17c]

We next moved toward the application of the sequence to the preparation of two biologically active benzimidazole products,




**Scheme 6.** Suggested mechanism.

chlormidazole and clemizole. Chlormidazole is a chlorobenzyl azole derivative developed and marketed as an antifungal drug.[20] This product was synthetized in two steps from benzimidazole **5a** (Scheme 7).




**Scheme 7.** Synthesis of chlormidazole **8**. Reagents and conditions: (a) **5a** (1 equiv), KOH (5 equiv), CTAB (5 mol%), $THF/H_2O$ (3/1), 20 h, 75 °C; (b) **7** (1 equiv), 4-$ClC_6H_4CH_2Br$ (1.2 equiv), $K_2CO_3$ (2.5 equiv), DMF, 100 °C, 3.5 h.

The sulfonamide cleavage was carried out with KOH in THF and water in the presence of a phase transfer catalyst.[21] Under these conditions, benzimidazole **7** was obtained in 64% yield after 20 h of reaction at 75 °C. The treatment of **7** with 4-chlorobenzyl bromide under basic conditions furnished the desired target chlormidazole **8** in an unoptimized isolated yield of 50%. Clemizole **11** or its hydrochloride counterpart are usually used for the treatment of allergic disorders and elicit interesting biological responses as an antiviral agent.[22,23] In addition, recent studies have shown promising responses to prevent seizures in children with Dravet syndrome.[24] The synthesis started with the radical halogenation of benzimidazole **5j** in the presence of *N*-bromosuccinimide and benzoyl peroxide (Scheme 8). The bromo derivative **9** was obtained in 61% yield while starting from the tosyl analog **5a** gave rise to a complex reaction mixture. Next, the compound **9** reacted with 5 equiv of pyrrolidine in the presence of sodium carbonate. Under these conditions, both cleavage of the sulfonamide and substitution of the bromine by the pyrrolidine occurred. Benzimidazole **10** was obtained in 64% yield along with the corresponding *N*-Ts pyrrolidine in 57% yield. Benzylation of the nitrogen atom with 4-chlorobenzyl bromide furnished clemizole **11** in a 65% yield.

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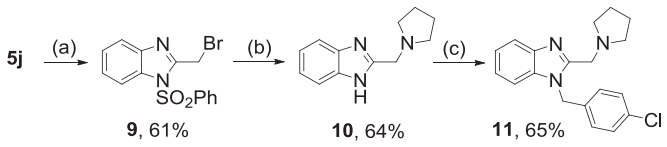


**Scheme 8.** Application to the synthesis of clemizole **11**. Reagents and conditions: (a) **5j** (1 equiv), *N*-bromosuccinimide (1.3 equiv), benzoyl peroxide (10 mol %), $CCl_4$, reflux, 24 h; (b) **9** (1 equiv), pyrrolidine (5 equiv), TBABr, $Na_2CO_3$, MeCN, reflux, 18 h; (c) **10** (1 equiv), 4-$ClC_6H_4CH_2Br$ (1.1 equiv), NaH (1.5 equiv), $Bu_4NI$ (10 mol %), THF, rt, 16 h.

## 3. Conclusion

In summary, we have reported a $PhI(OAc)_2$-mediated Beckmann-type rearrangement towards the preparation of functionalized benzoxazoles and *N*-Ts benzimidazoles. This strategy was applied to a range of *o*-hydroxy and *o*-aminoaryl N–H ketimines easily prepared by condensation of the corresponding ketones with ammonia. The results outlined herein demonstrate the importance of the substitution pattern at the aromatic ring on the mechanistic pathway. Depending on the substituents, the [1,2]-migration of the aryl moiety leading to benzoxazoles or benzimidazoles can compete with the formation of benzisoxazoles or indazoles through an intramolecular cyclization. From a synthetic standpoint, the strategy was applied to the preparation of biologically relevant compounds such as chlormidazole and clemizole.

## 4. Experimental section

### 4.1. General

$^1H$ NMR (200, 300 or 500 MHz) and $^{13}C$ (75 or 125 MHz) spectra were recorded with 200, 300 or 500 MHz spectrometers in chloroform-d or DMSO-$d_6$ with the residual peak solvent or tetramethylsilane as an internal standard. Chemical shifts ($\delta$) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument. Samples (solubilized in ACN at 1 mg/mL and then diluted by 1000) were introduced into the MS via an UHPLC system whilst a Leucine Enkephalin solution was co-injected via a micro pump. Infrared spectra were recorded with a FT spectrometer. Melting points were measured with a Köfler apparatus. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040–0.060 mm). Unless otherwise specified, all solvents were purchased from commercial suppliers and used as received. The *ortho*-hydroxyaryl N–H ketimines **1** were prepared according to reported procedures.[17c,25]

### 4.2. General procedure for the hypervalent iodine-mediated synthesis of benzoxazoles 2 and benzoisoxazoles 3

To a stirred solution of *ortho*-hydroxyaryl N–H ketimines **1** (1 mmol) in solvent (2 mL) was added an additive if specified (0.2–1.0 mmol) and $PhI(OAc)_2$ (1.1–2.0 mmol). The resulting mixture was stirred at room temperature for 30 min and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica gel (pentane/ethyl acetate, 30–100:1) to furnish the desired products **2**/**3**.

*4.2.1. 5-Bromo-2-methylbenzo[d]oxazole (**2a**).* Colorless solid. Yield=82% (174 mg). Mp 61–62 °C; previously reported 67–69 °C.[26] $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$=2.0 Hz, 1H), 7.39 (dd, $J$=8.5 Hz, $J$=2.0 Hz, 1H), 7.32 (d, $J$=8.5 Hz, 1H), 2.63 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 165.2, 150.1, 143.3, 127.6, 122.6, 116.9, 111.5, 14.7; HRMS (ESI) Calcd for $C_8H_7BrNO$ $[M+H]^+$: 211.9711, Found 211.9707; FTIR (neat) $cm^{-1}$ 3066, 2920, 2850, 1583, 1445, 1420, 1269, 1252, 1157, 1042, 929, 896, 840, 798, 683. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.2. 5-Chloro-2-methylbenzo[d]oxazole (**2b**).* Colorless solid. Yield=75% (126 mg). Mp 51.6–53.0 °C; previously reported 53.5–54.7 °C.[28] $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$=1.0 Hz, 1H), 7.38 (d, $J$=8.5 Hz, 1H), 7.26 (dd, $J$=8.5 Hz, $J$=1.5 Hz, 1H), 2.64 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 165.5, 149.7, 142.8, 129.7, 124.9, 119.6, 111.1, 14.7; HRMS (ESI) Calcd for $C_8H_7ClNO$ $[M+H]^+$: 168.0216, Found 168.0210; FTIR (neat) $cm^{-1}$ 3442, 2954, 2929, 2875, 2858, 1729, 1633, 1457, 1286, 1269, 1123, 1070, 742. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.3. 5-Cyano-2-methylbenzo[d]oxazole (**2c**).* Colorless oil. Yield=61% (96 mg). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (s, 1H), 7.61 (dd, $J$=8.5 Hz, $J$=1.5 Hz, 1H), 7.57 (d, $J$=8.5 Hz, 1H), 2.70 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 166.4, 153.5, 142.2, 128.9, 124.3, 119.0, 111.7, 108.3, 14.7; HRMS (ESI) Calcd for $C_9H_7NO_2$ $[M+H]^+$ 159.0558, Found 159.0554; FTIR (neat) $cm^{-1}$ 3111, 3066, 2954, 2926, 2228, 1729, 1628, 1577, 1476, 1431, 1386, 1280, 1259, 1173, 1120, 907, 815, 618.

*4.2.4. 2-Methyl-5-nitrobenzo[d]oxazole (**2d**).* Colorless solid. Yield=64% (114 mg). Mp 152.5–154.5 °C; previously reported 154.7–155.5 °C.[28] $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$=2.5 Hz, 1H), 8.28 (dd, $J$=9.0 Hz, $J$=2.0 Hz, 1H), 7.59 (d, $J$=9.0 Hz, 1H), 2.72 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 167.3, 154.7, 145.3, 142.1, 120.9, 116.0, 110.6, 14.9; HRMS (ESI) Calcd for $C_8H_7N_2O_2$ $[M+H]^+$ 179.0457, Found 179.0452; FTIR (neat) $cm^{-1}$ 3111, 3063, 2872, 1616, 1515, 1457, 1351, 1255, 1171, 1067, 910, 826, 736. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.5. 2,5-Dimethylbenzo[d]oxazole (**2e**).* Colorless oil. Yield=49% (72 mg). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.42 (s, 1H), 7.31 (d, $J$=8.5 Hz, 1H), 7.07 (d, $J$=8.0 Hz, 1H), 2.59 (s, 3H), 2.43 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 164.0, 149.3, 141.8, 133.9, 125.5, 119.4, 109.6, 21.5, 14.6; HRMS (ESI) Calcd for $C_9H_{10}NO$ $[M+H]^+$ 148.0762, Found 148.0765; FTIR (neat) $cm^{-1}$ 3024, 2926, 2861, 1614, 1577, 1476, 1429, 1381, 1274, 1255, 1173, 1115, 1036, 918, 865, 837, 803, 764, 657. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.6. 2-Methylbenzo[d]oxazole (**2f**).* Colorless oil. Yield=47% (62.5 mg). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$=5.0 Hz, 1H), 7.46–7.45 (m, 1H), 7.28–7.27 (m, 2H), 2.62 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 163.9, 151.0, 141.6, 124.5, 124.1, 119.5, 110.3, 14.6; HRMS (ESI) Calcd for $C_8H_8NO$ $[M+H]^+$ 134.0606, Found 134.0612; FTIR (neat) $cm^{-1}$ 3055, 2959, 2929, 2850, 1622, 1577, 1468, 1451, 1431, 1384, 1269, 1247, 1165, 1143, 1103, 1036, 1005, 924, 882, 834, 758, 742. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.7. 6-Methoxy-2-methylbenzo[d]oxazole (**2g**).* Colorless solid. Yield=61% (99 mg). Mp 52–53 °C; previously reported 51.5–53 °C.[29] $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J$=8.5 Hz, 1H), 6.99 (s, 1H), 6.89 (d, $J$=8.5 Hz, 1H), 3.84 (s, 3H), 2.59 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 162.8, 157.7, 151.8, 135.2, 119.3, 112.0, 95.3, 55.9, 14.4; HRMS (ESI) Calcd for $C_9H_{10}NO_2$ $[M+H]^+$ 164.0712, Found 164.0713; FTIR (neat) $cm^{-1}$ 2923, 2842, 1616, 1583, 1498, 1437, 1381, 1299, 1204, 1115, 1025, 910, 854, 812. All physical and spectroscopic data were in complete agreement with the reported ones.[26]

*4.2.8. 2-Ethylbenzo[d]oxazole (**2h**).* Colorless oil. Yield=73% (107 mg). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$=4.5 Hz, 1H), 7.47 (d, $J$=4.0 Hz, 1H), 7.292–7.287 (m, 2H), 2.96 (q, $J$=7.0 Hz, 2H), 1.45 (t,

$J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.2, 150.9, 141.5, 124.5, 124.2, 119.7, 110.4, 22.3, 11.0; HRMS (ESI) Calcd for $C_9H_{10}NO$ $[M+H]^+$ 148.0762, Found 148.0759; FTIR (neat) $cm^{-1}$ 3057, 2982, 2940, 2878, 1616, 1572, 1451, 1372, 1238, 1168, 1148, 1008, 921, 823, 764, 742. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.9. 2-Propylbenzo[d]oxazole (**2i**).* Colorless oil. Yield=71% (114 mg). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.68–7.66 (m, 1H), 7.48–7.46 (m, 1H), 7.29–7.27 (m, 2H), 2.91 (t, $J$=7.5 Hz, 2H), 1.92 (sext, $J$=7.5 Hz, 2H), 1.05 (t, $J$=7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.3, 151.0, 141.6, 124.5, 124.2, 119.7, 110.4, 30.7, 20.4, 13.9; HRMS (ESI) Calcd for $C_{10}H_{12}NO$ $[M+H]^+$ 162.0919, Found 162.0912; FTIR (neat) $cm^{-1}$ 3057, 2965, 2929, 2875, 1608, 1566, 1463, 1429, 1381, 1269, 1241, 1157, 1145, 1098, 1000, 932, 865, 834, 767, 742. All physical and spectroscopic data were in complete agreement with the reported ones.[30]

*4.2.10. 2-Phenylbenzo[d]oxazole (**2j**).* Colorless solid. Yield=58% (113 mg). Mp 100–101 °C; previously reported 101–103 °C.[16g] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.29–8.26 (m, 2H), 7.82–7.75 (m, 1H), 7.62–7.57 (m, 1H), 7.55–7.51 (m, 3H), 7.39–7.33 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 163.2, 150.9, 142.2, 131.7, 129.0 (2C), 127.8 (2C), 127.2, 125.2, 124.7, 120.1, 110.7; HRMS (ESI) Calcd for $C_{13}H_{10}NO$ $[M+H]^+$ 196.0762, Found 196.0758; FTIR (neat) $cm^{-1}$ 1616, 1551, 1446, 1240, 1051, 923, 779, 684, 626, 485. All physical and spectroscopic data were in complete agreement with the reported ones.[27]

*4.2.11. 3-Phenyl-1,2-benzisoxazole (**3j**).* Colorless oil. Yield=30% (59 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.01–7.95 (m, 3H), 7.68–7.50 (m, 5H), 7.39 (t, $J$=7.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 163.9, 157.4, 130.4, 129.9, 129.3 (2C), 129.1, 128.2 (2C), 124.0, 122.3, 120.6, 110.3; HRMS (ESI) Calcd for $C_{13}H_{10}NO$ $[M+H]^+$ 196.0762, Found 196.0755; FTIR (neat) $cm^{-1}$ 1610, 1490, 1446, 1372, 1237, 895, 873, 746, 693, 659. All physical and spectroscopic data were in complete agreement with the reported ones.[31]

*4.2.12. 6-Methoxy-2-phenylbenzo[d]oxazole (**2k**).* Colorless solid. Yield=76% (334 mg). Mp 58–59 °C; previously reported 66–69 °C.[26] $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19–8.17 (m, 2H), 7.62 (d, $J$=9.0 Hz, 1H), 7.49–7.47 (m, 3H), 7.08 (d, $J$=2.0 Hz, 1H), 6.94 (dd, $J$=8.5 Hz, $J$=2.5 Hz, 1H), 3.84 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 162.3, 158.4, 151.7, 136.0, 131.2, 129.0, 127.5, 127.3, 120.1, 112.9, 95.5, 56.0; HRMS (ESI) Calcd for $C_{14}H_{12}NO_2$ $[M+H]^+$ 226.0868, Found 226.0862; FTIR (neat) $cm^{-1}$ 2923, 2842, 1616, 1583, 1498, 1437, 1381, 1299, 1204, 1115, 1025, 910, 854, 812. All physical and spectroscopic data were in complete agreement with the reported ones.[26]

### 4.3. General procedure for the hypervalent iodine-mediated synthesis of benzimidazoles 5 and indazoles 6

**Method A**: An oven-dried vial was charged with the *ortho*-aminoaryl ketones **4a**–**d** or **4i**–**k** (0.25 mmol) and a solution of $NH_3$ 7 M in MeOH (1 mL) was added. The vial was capped and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure to give a yellow solid. $^1$H NMR analyses of the crude showed complete disappearance of the starting materials and formation of the desired *ortho*-aminoaryl N–H ketimines. The crude ketimine was dissolved in 0.5 mL of MeOH and $PhI(OAc)_2$ (0.375 mmol, 121 mg) was added to the reaction mixture. After stirring at room temperature for 1 h, the solvent was removed under reduced pressure and the crude was purified by chromatography on silica gel (eluent: pentane/EtOAc).

**Method B**: An oven-dried vial was charged with the *ortho*-aminoaryl ketones **4e**–**h** (0.2 mmol) and a solution of $NH_3$ 7 M in MeOH (1.5 mL) was added. The vial was capped and the reaction mixture was stirred at 50 °C for 20 h. The solvent was removed under reduced pressure to give a yellow solid. $^1$H NMR analyses of the crude showed complete disappearance of the starting materials and formation of the desired *ortho*-aminoaryl N–H ketimines. The crude ketimine was dissolved in 0.4 mL of MeOH and $PhI(OAc)_2$ (0.3 mmol, 97 mg) was added to the reaction mixture. After stirring at room temperature for 16 h, the solvent was removed under reduced pressure and the crude was purified by chromatography on silica gel (eluent: pentane/EtOAc).

*4.3.1. 2-Methyl-1-tosyl-benzo[d]imidazole (**5a**).* Compound **5a** was obtained as a colorless solid according to general procedure 4.3, method A. Yield=74% (53 mg). Mp 110–112 °C; previously reported 113–114 °C.[32] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06–8.00 (m, 1H), 7.81 (d, $J$=8.4 Hz, 2H), 7.66–7.61 (m, 1H), 7.37–7.31 (m, 2H), 7.29 (d, $J$=8.4 Hz, 2H), 2.82 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.5, 146.2, 141.9, 135.5, 133.3, 130.4 (2C), 129.9 (2C), 124.9, 124.8, 119.7, 113.6, 21.8, 17.0; HRMS (ESI) Calcd for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 287.0854, Found 287.0858; FTIR (neat) $cm^{-1}$ 2924, 1543, 1492, 1370, 1245, 1187, 1160, 1087, 1052, 1015, 913, 810, 661, 541. All physical and spectroscopic data were in complete agreement with the reported ones.[33]

*4.3.2. 2,5-Dimethyl-1-tosyl-benzo[d]imidazole (**5b**).* Compound **5b** was obtained as a colorless solid according to general procedure 4.3, method A. Yield=81% (61 mg). Mp 150 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$=8.4 Hz, 1H), 7.81 (d, $J$=8.2 Hz, 1H), 7.42 (s, 1H), 7.29 (d, $J$=8.2 Hz, 2H), 7.17 (d, $J$=8.4 Hz, 1H), 2.81 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.5, 146.0, 142.1, 135.5, 134.7, 131.2, 130.3 (2C), 126.9 (2C), 126.1, 119.7, 113.1, 21.8, 21.5, 17.0; HRMS (ESI) Calcd for $C_{16}H_{16}N_2O_2S$ $[M+H]^+$ 301.1011, Found 301.1016; FTIR (neat) $cm^{-1}$ 2923, 2856, 1541, 1370, 1258, 1171, 1087, 1055, 1014, 907, 810, 666, 542.

*4.3.3. 2-Ethyl-5-nitro-1-tosyl-benzo[d]imidazole (**5c**).* Compound **5c** was obtained as a colorless oil according to general procedure 4.3, method A. Yield=55% (47 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.56 (d, $J$=2.2 Hz, 1H), 8.26 (d, $J$=9.0 Hz, $J$=2.2 Hz, 1H), 8.17 (d, $J$=9.0 Hz, 1H), 7.80 (d, $J$=8.5 Hz, 2H), 7.34 (d, $J$=8.5 Hz, 2H), 3.19 (q, $J$=7.3 Hz, 2H), 2.42 (s, 3H), 1.46 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.6, 146.9, 145.3, 141.9, 137.5, 134.9, 130.7 (2C), 127.1 (2C), 120.3, 116.1, 113.8, 23.7, 21.9, 11.5; HRMS (ESI) Calcd for $C_{16}H_{16}N_3O_4S$ $[M+H]^+$ 346.0862, Found 346.0859; FTIR (neat) $cm^{-1}$ 2978, 2937, 1521, 1381, 1342, 1274, 1161, 1088, 1045, 992, 754, 709, 665, 581, 539.

*4.3.4. 5-Chloro-2-methyl-1-tosyl-benzo[d]imidazole (**5d**).* Compound **5d** was obtained as a colorless solid according to general procedure 4.3, method A. Yield=73% (58.5 mg). Mp 160–162 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.94 (d, $J$=8.7 Hz, 1H), 7.78 (d, $J$=8.4 Hz, 2H), 7.60 (d, $J$=2.0 Hz, 1H), 7.34–7.27 (m, 3H), 2.79 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.9, 146.5, 142.8, 135.2, 131.8, 130.5 (2C), 130.4, 126.9 (2C), 125.2, 119.7, 114.4, 21.8, 17.0; HRMS (ESI) Calcd for $C_{15}H_{13}ClN_2O_2S$ $[M+H]^+$ 321.0465, Found 321.0462; FTIR (neat) $cm^{-1}$ 2922, 1536, 1400, 1289, 1261, 1172, 1054, 1009, 900, 811, 719, 664, 541.

*4.3.5. 6-Methyl-5-(methylsulfonyl)-5H-[1,3]dioxolo[4,5-f]benzimidazole (**5e**).* Compound **5e** was obtained as a colorless oil according to general procedure 4.3, method B. Yield=43% (28 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$=8.2 Hz, 2H), 7.50 (s, 1H), 7.30 (d, $J$=8.2 Hz, 2H), 7.02 (s, 1H), 6.01 (s, 2H), 2.75 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.2, 146.4, 146.3, 146.1, 136.0, 135.3, 130.5 (2C), 127.4, 126.9 (2C), 101.8, 99.4, 94.9, 21.8, 16.9; HRMS (ESI) Calcd for $C_{16}H_{15}N_2O_4S$ $[M+H]^+$ 331.0753, Found 331.0751; FTIR (neat) $cm^{-1}$ 2903, 2774, 2627, 1471, 1348, 1213, 1155, 1056, 1007, 938, 813, 679, 562.

*4.3.6. 3-Methyl-1-(methylsulfonyl)-1H-[1,3]dioxolo[4,5-f]indazole (**6e**).* Compound **6e** was obtained as a colorless solid according to

general procedure 4.3, method B. Yield=30% (20 mg). Mp 232–234 °C; previously reported 227–230 °C.[34] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80 (d, $J$=8.4 Hz, 2H), 7.57 (s, 1H), 7.22 (d, $J$=8.4 Hz, 2H), 6.82 (s, 1H), 6.06 (s, 2H), 2.41 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.7, 150.5, 146.2, 145.2, 137.9, 134.7, 129.9 (2C), 127.6 (2C), 120.8, 102.3, 97.9, 94.1, 21.8, 12.4; HRMS (ESI) Calcd for $C_{16}H_{15}N_2O_4S$ $[M+H]^+$ 331.0753, Found 331.0754; FTIR (neat) cm$^{-1}$ 2920, 1454, 1368, 1339, 1209, 1182, 1170, 1034, 830, 668, 542. All physical and spectroscopic data were in complete agreement with the reported ones.[35]

*4.3.7. Non separable mixture of 7-methoxy-2-methyl-1-tosyl-benzo[d]imidazole (**5f**) and 7-methoxy-3-methyl-1-tosyl-1H-indazole (**6f**).* Non separable compounds **5f**/**6f** were obtained according to general procedure 4.3, method B. ratio **5f**/**6f**, 1/1. Yield=85% (54 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.86 (d, $J$=8.2 Hz, 2H), 7.78 (d, $J$=8.2 Hz, 2H), 7.35–7.15 (m, 8H), 6.88 (dd, $J$=6.3 Hz, $J$=2.2 Hz, 1H), 6.72 (d, $J$=7.9 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 2.99 (s, 3H), 2.57 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 153.5, 148.7, 146.9, 146.8, 144.9, 144.9, 144.1, 137.3, 136.3, 131.1, 129.6 (2C), 129.5 (2C), 129.3, 128.1 (2C), 127.4 (2C), 125.3, 124.9, 122.7, 112.7, 112.5, 110.3, 107.8, 56.1, 55.9, 21.8, 21.7, 18.8, 12.4; HRMS (ESI) Calcd for $C_{16}H_{17}N_2O_3S$ $[M+H]^+$ 317.0960, Found 317.0959.

*4.3.8. 2-Phenyl-1-tosyl-benzo[d]imidazole (**5g**).* Compound **5g** was obtained as a colorless oil according to general procedure 4.3, method B. Yield=43% (30 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$=7.4 Hz, 1H), 7.73 (dd, $J$=6.5 Hz and $J$=1.2 Hz, 1H), 7.63–7.58 (m, 2H), 7.57–7.50 (m, 1H), 7.51–7.37 (m, 4H), 7.33 (d, $J$=8.2 Hz, 2H), 7.09 (d, $J$=8.2 Hz, 2H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 154.2, 145.8, 142.7, 135.1, 133.9, 130.9 (2C), 130.7, 130.1, 129.8 (2C), 127.8 (2C), 127.1 (2C), 125.6, 125.4, 120.5, 115.3, 21.8; HRMS (ESI) Calcd for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 349.1011, Found 349.1010; FTIR (neat) cm$^{-1}$ 2924, 1447, 1386, 1307, 1175, 1118, 1083, 1009, 668, 564, 540. All physical and spectroscopic data were in complete agreement with the reported ones.[33]

*4.3.9. 3-Phenyl-1-tosyl-1H-indazole (**6g**).* Compound **6g** was obtained as a colorless solid according to general procedure 4.3, method B. Yield=42% (29 mg). Mp 122–123 °C; previously reported 126–128 °C.[36] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$=8.4 Hz, 1H), 7.98–7.89 (m, 5H), 7.59 (m, 1H), 7.54–7.47 (m, 3H), 7.38 (t, $J$=7.6 Hz, 1H), 7.23 (d, $J$=7.9 Hz, 2H), 2.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.8, 145.4, 141.9, 134.8, 131.6, 129.9 (2C), 129.7 (2C), 129.2, 128.9, 128.4 (2C), 127.8 (2C), 124.6, 124.5, 121.8, 113.8, 21.8; HRMS (ESI) Calcd for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 349.1011, Found 349.1013; FTIR (neat) cm$^{-1}$ 2922, 1366, 1307, 1172, 1066, 947, 720, 576, 536. All physical and spectroscopic data were in complete agreement with the reported ones.[37]

*4.3.10. 5-Chloro-2-phenyl-1-tosyl-benzo[d]imidazole (**5h**).* Compound **5h** was obtained as a colorless solid according to general procedure 4.3, method B. Yield=26% (39 mg). Mp 129–131 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J$=9.0 Hz, 1H), 7.68 (s, 1H), 7.62–7.51 (m, 3H), 7.45 (t, $J$=7.4 Hz, 1H), 7. 41–7.35 (m, 1H), 7.27 (d, $J$=8.0 Hz, 2H), 7.09 (d, $J$=8.0 Hz, 2H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 155.5, 146.2, 143.6, 134.8, 132.6, 131.0 (3C), 130.1, 129.9 (2C), 129.7, 127.9 (2C), 127.1 (2C), 125.9, 120.4, 116.1, 21.8; HRMS (ESI) Calcd for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 383.0621, Found 383.0623. FTIR (neat) cm$^{-1}$ 3063, 1425, 1375, 1297, 1174, 1086, 819, 572, 544.

*4.3.11. 5-Chloro-3-phenyl-1-tosyl-1H-indazole (**6h**).* Compound **6h** was obtained as a colorless solid according to general procedure 4.3, method B. Yield=50% (75 mg). Mp 118–120 °C; previously reported 128 °C–129 °C.[38] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J$=8.4 Hz, 1H), 7.95–7.85 (m, 5H), 7.60–7.45 (m, 4H), 7.25 (m, 2H), 2.36 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.1, 145.7, 140.4, 134.5, 131.0, 130.5, 130.1 (2C), 129.9, 129.7, 129.1 (2C), 128.3 (2C), 127.8 (2C), 125.5, 121.2, 21.8; HRMS (ESI) Calcd for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 383.0621, Found 383.0626; FTIR (neat) cm$^{-1}$ 2915, 1377, 1357, 1175, 1284, 1214, 1083, 1025, 792, 659, 580, 536 All physical and spectroscopic data were in complete agreement with the reported ones.[38]

*4.3.12. 5-Methoxy-3-methyl-1-tosyl-1H-indazole (**6i**).* Compound **6i** was obtained as a colorless solid according to general procedure 4.3, method A. Yield=60% (47.5 mg).Mp 180–182 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$=9.1 Hz, 1H), 7.76 (d, $J$=7.2 Hz, 2H), 7.26–7.07 (m, 3H), 6.86 (s; 1H), 3.81 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.9, 150.7, 145.1, 136.5, 134.7, 129.8 (2C), 127.5 (2C), 127.2, 119.9, 114.6, 101.0, 55.9, 21.7, 12.5; HRMS (ESI) Calcd for $C_{16}H_{17}N_2O_3S$ $[M+H]^+$ 317.0960, Found 317.0964; FTIR (neat) cm$^{-1}$ 2950, 2914, 1478, 1445, 1367, 1232, 1171, 1056, 1027, 884, 824, 694, 578, 538. All physical and spectroscopic data were in complete agreement with the reported ones.[35]

*4.3.13. 2-Methyl-1-(phenylsulfonyl)-1H-benzo[d]imidazole (**5j**).* Compound **5j** was obtained as a colorless solid according to general procedure 4.3, method A. Yield=86% (59 mg). Mp 95–96 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06–8.00 (m, 1H), 7.96–7.90 (m, 2H), 7.67–7.59 (m, 2H), 7.51 (app. t, $J$=7.9 Hz, 2H), 7.40–7.28 (m, 2H), 2.82 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.9, 141.9, 138.5, 134.8, 133.3, 129.8 (2C), 126.9 (2C), 125.0, 124.9, 119.8, 113.5, 17.1; HRMS (ESI) Calcd for $C_{14}H_{13}N_2O_2S$ $[M+H]^+$ 273.0698, Found 273.0698; FTIR (neat) cm$^{-1}$ 2934, 1445, 1366, 1243, 1119, 1031, 725, 685, 595, 552. All physical and spectroscopic data were in complete agreement with the reported ones.[32]

*4.3.14. 2-Methyl-1-(trifluoromethylsulfonyl)-1H-benzo[d]imidazole (**5k**).* Compound **5k** was obtained as a colorless oil according to general procedure 4.3, method A. Yield=58% (38 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.84–7.76 (m, 1H), 7.75–7.67 (m, 1H), 7.47–7.35 (m, 2H), 2.80 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.7, 141.8, 132.9, 126.3, 126.0, 120.5, 119.6 (q, $^1J_{C\text{-}F}$=324 Hz), 113.6, 16.7; HRMS (ESI) Calcd for $C_9H_8N_2O_2F_3S$ $[M+H]^+$ 265.0259, Found 265.0262; FTIR (neat) cm$^{-1}$ 2930, 1574, 1447, 1251, 1207, 1152, 1135, 1046, 996, 741, 633, 581, 525.

### 4.4. Chlormidazole (8)

To a solution of *N*-Tosyl benzimidazole **5a** (0.70 mmol, 200 mg) in THF (1 mL) and water (0.35 mL) was added CTAB (0.035 mmol, 12.8 mg) and KOH (3.5 mmol, 196 mg). The mixture was stirred for 20 h at 75 °C. Water and dichloromethane were added to the reaction mixture upon cooling to room temperature. The aqueous layer was separated and extracted twice with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (eluent: EtOAc) and the unprotected benzimidazole **7** was obtained in 64% yield ($m$=59 mg) as a brownish solid. All the physical and spectroscopic data were in complete agreement with the reported ones.[39]

To a solution of the benzimidazole **7** (0.38 mmol, 50 mg) in anhydrous DMF (0.5 mL) was added 4-chlorobenzyl bromide (0.45 mmol, 93 mg) and $K_2CO_3$ (0.95 mmol, 131 mg). The reaction mixture was stirred at 100 °C for 3.5 h and then cooled down to room temperature. EtOAc and water were added to the reaction mixture and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel (eluent: EtOAc) and chlormidazole **8** was obtained in 50% yield ($m$=48 mg) as a colorless oil. $^1$H NMR

(300 MHz, $CDCl_3$) $\delta$ 7.75 (d, $J$=7.7 Hz, 1H), 7.32–7.16 (m, 5H), 6.99 (d, $J$=8.2 Hz, 2H), 5.29 (s, 2H), 2.57 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 151.8, 142.7, 135.3, 134.4, 133.9, 129.3 (2C), 127.7 (2C), 122.6, 122.3, 119.4, 109.3, 46.6, 14.1; HRMS (ESI) Calcd for $C_{15}H_{14}N_2Cl$ $[M+H]^+$ 257.0846 Found 257.0845; FTIR (neat) $cm^{-1}$ 2928, 1490, 1462, 1328, 1154, 1012, 853, 735, 494.

### 4.5. 2-(Bromomethyl)-1-(phenylsulfonyl)-1*H*-benzo[*d*]imidazole (9)

To a solution of *N*-benzenesulfonyl benzimidazole **5j** (2 mmol, 544 mg) in $CCl_4$ (26 mL) was added *N*-bromosuccinimide (2.6 mmol, 463 mg) and benzoyl peroxide (0.1 mmol, 24 mg) at room temperature under inert atmosphere. The mixture was heated under reflux for 6 h at which point an extra amount of benzoyl peroxide (0.1 mmol, 24 mg) was added to the reaction mixture. After further stirring under reflux for 18 h, the reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (eluent, pentane/EtOAc: 85/15) to afford the desired bromo derivative **9** in 61% yield ($m$=428 mg) as a colorless solid. Mp 107–109 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.15–8.06 (m, 2H), 7.98–7.89 (m, 1H), 7.77–7.66 (m, 1H), 7.68–7.60 (m, 1H), 7.59–7.47 (m, 2H), 7.46–7.31 (m, 2H), 5.05 (s, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 149.4, 141.7, 137.7, 135.1, 132.9, 129.7 (2C), 127.6 (2C), 126.3, 125.4, 120.9, 113.8, 22.8; HRMS (ESI) Calcd for $C_{14}H_{12}N_2O_2SBr$ $[M+H]^+$ 350.9803, Found 350.9812; FTIR (neat) $cm^{-1}$ 3051, 2994, 1444, 1376, 1172, 1117, 1087, 1050, 754, 726, 574, 557, 538.

### 4.6. 2-(Pyrrolidin-1-ylmethyl)-1*H*-benzo[*d*]imidazole (10)

The bromo benzimidazole **9** (0.66 mmol, 232 mg), pyrrolidine (3.3 mmol, 235 mg) and anhydrous acetonitrile (3.3 mL) were mixed in a 10 mL flask. Then $Na_2CO_3$ (0.58 g) and tetrabutylammonium bromide (13 mg) were added directly as solids and the resulting mixture was heated at reflux under argon for 18 h. After cooling to room temperature, the mixture was filtered over Celite and the filter cake was washed with $CH_2Cl_2$. The combined filtrates were evaporated under reduced pressure. To the resulting residue, 1 M NaOH (15 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3×15 mL). The combined organic layers were washed successively with saturated aqueous solutions of $NaHCO_3$ and brine. The organic layers were dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica gel (eluent, pentane/EtOAc: 85/15 then DCM/MeOH: 90/10) to yield 85 mg of **10** (yield=64%) as a light brown solid. Mp 140–142 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.89 (br s, 1H), 7.53 (dd, $J$=5.8 Hz, $J$=3.2 Hz 2H), 7.25–7.15 (m, 2H), 3.97 (s, 2H), 2.71–2.61 (m, 4H), 1.80 (app. dt, $J$=6.3 Hz, $J$=3.1 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 152.8, 138.6, 122.0, 122.3 (2C), 115.1 (2C), 54.5 (2C), 53.9, 23.8 (2C); HRMS (ESI) Calcd for $C_{12}H_{16}NO$ $[M+H]^+$ 202.1344, Found 202.1340; FTIR (neat) $cm^{-1}$ 2953, 2906, 2791, 1453, 1390, 1269, 1224, 750, 741.

### 4.7. Clemizole (11)

Under a nitrogen atmosphere, compound **10** (0.24 mmol, 49 mg) was dissolved in freshly distilled THF (0.75 mL), then cooled to 0 °C. To this solution was added 60% NaH in oil (0.36 mmol, 14.4 mg) and the mixture was stirred at 0 °C for 5 min. 4-Chlorobenzyl bromide (0.26 mmol, 54 mg) was added followed by the addition of tetrabutylammonium iodide (0.024 mmol, 9 mg). The mixture was stirred at rt overnight, then diluted with water (2 mL) and EtOAc (5 mL). The aqueous phase was separated and extracted twice with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was purified by chromatography on silica gel (eluent: EtOAc) to afford the desired target **11** in 65% yield ($m$=51 mg) as a colorless solid. Mp 101–102 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.83–7.77 (m, 1H), 7.32–7.22 (m, 5H), 7.06 (d, $J$=8.7 Hz, 2H), 5.58 (s, 2H), 3.90 (s, 2H), 2.58 (m, 4H), 1.76 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 152.3, 142.5, 135.9, 135.3, 133.6, 129.1 (2C), 128.1 (2C), 122.9, 122.7, 120.0, 109.7, 54.8 (2C), 53.2, 46.8, 23.7 (2C); HRMS (ESI) Calcd for $C_{19}H_{21}N_3Cl$ $[M+H]^+$ 326.1424, Found 326.1427; FTIR (neat) $cm^{-1}$ 2958, 2927, 2875, 2810, 1488, 1463, 1403, 1294, 1088, 1034, 1014, 742, 487.

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## Supplementary data

Copies of $^1H$, $^{13}C$ NMR and a crystallographic structure for **5b** are provided in the Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.11.066.

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