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Rearrangement of spiro-benzimidazolines: preparation of *N*-alkenyl- and *N*-alkyl-benzimidazol-2-ones

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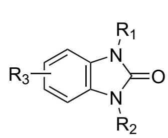
Abstract—A synthetically useful protocol has been developed for the preparation of highly functionalized *N*-alkenyl-benzimidazol-2-ones. Reaction of commercially available *o*-phenylenediamines with variously substituted cyclic ketones provides spiro-benzimidazolines. Treatment of these spiro-benzimidazolines with triphosgene in the presence of potassium carbonate results in rapid rearrangement and formation of *N*-alkenyl-benzimidazol-2-ones in modest to excellent yield for the two-step sequence. Extension of this methodology toward the preparation of a μ opiate receptor antagonist and droperidol, a potent antiemetic and antipsychotic agent, currently a marketed pharmaceutical is also described. Upon treatment of spiro-benzimidazolines with triphosgene in the presence of sodium triacetoxyborohydride, *N*-alkyl-benzimidazol-2-ones were formed.

1. Introduction

The 1,3-dihydro-2*H*-benzimidazole-2-one ring system **1** represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds.[1] Both mono- and disubstituted benzimidazol-2-one derivatives **1** have been identified as potent NK_1 antagonists,[2] CGRP receptor antagonists,[3] farnesyl transfer inhibitors,[4] p38 inhibitors,[5] cathepsin S inhibitors,[6] 5-HT_4 agonists and antagonists,[7] progesterone receptor antagonist,[8] respiratory syncytial virus (RSU) inhibitors,[9] vasopressin 1a receptor antagonists,[10] aldose reductase inhibitors,[11] and neurotransmitter antagonists,[12] and have been reported to display potent neuroleptic activity,[13] enhance pulmonary surfactant secretion,[14] and modulate ion channels.[15] The development of efficient and practical methods for construction of this important heterocycle remains as an active area of synthetic research (Fig. 1).



1

Figure 1.

Preparation of the 1,3-dihydro-2*H*-benzimidazole-2-one ring system of **1** in a regioselective manner with control of the substituents on each nitrogen atom has remained problematic due to the difficulty associated with selectively functionalizing a single nitrogen atom. An inevitable feature of many approaches is the use of protecting group strategies. Conventional approaches to compounds of subclass **1** have typically involved multi-step manipulations beginning with the core benzimidazol-2-one **1**,[16] 1-halo-2-nitrobenzenes,[17] or *o*-phenylenediamines[18,19] and many of these methods have been successfully adapted to solid-phase synthesis.[20] The palladium-catalyzed intramolecular cyclization of *o*-chloroureas has recently emerged as an attractive method for the construction of this important heterocycle.[21] Although each of these methods offers certain advantages, each has limitations including starting material availability, harsh reaction conditions, or inefficient and low yielding transformations.

The preparation of *N*-alkenylbenzimidazol-2-ones of type **4**, developed over 40 years ago, involves the condensation of *o*-phenylenediamines **2** with β-keto esters **3** either in the presence, or absence, of an acid catalyst and currently represents the only known method for the construction of this functionality (Scheme 1).[18,22] Depending on the nature of the β-keto ester (cyclic vs acyclic) and whether the reaction is conducted under neutral or acidic conditions, varying amounts of either diazepinone **6** or benzimidazole **7** are formed as unavoidable by-products of these reactions. While the alkenyl substituent of **4** often serves as a protecting group for the preparation of benzimidazolones of type **5**, the alkenyl group is also found in a number of biologically active compounds including marketed pharmaceuticals. Mild synthetic methods that provide rapid assembly of the benzimidazol-2-one ring system and tolerate a wide range of

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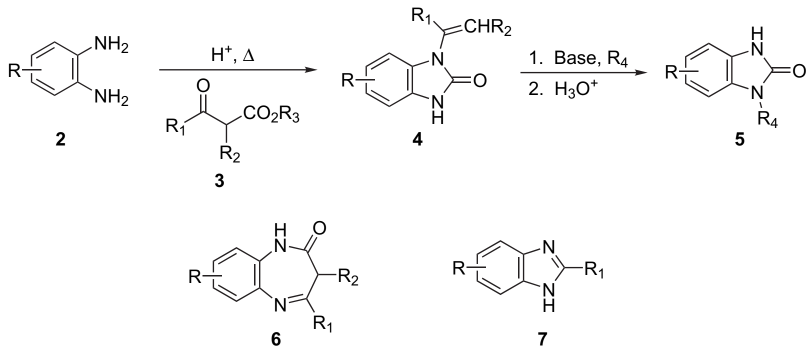
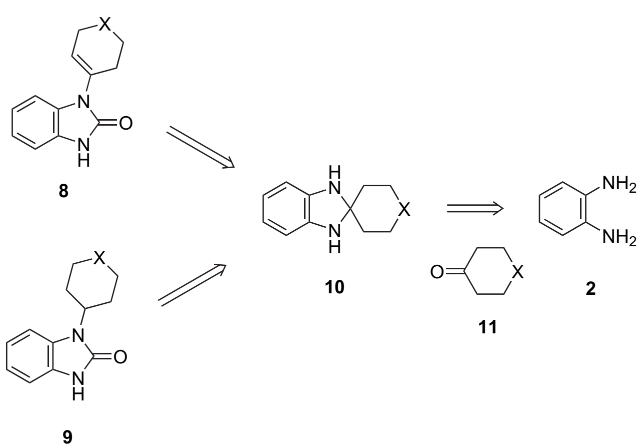


Scheme 1.

functional groups without the need for protecting groups offer significant advantages. In a continuing program to develop new methodologies, which rapidly enhance molecular complexity with better atom economy, we have discovered a new two-step protocol for the preparation of substituted *N*-alkenyl- **8** and *N*-alkylbenzimidazol-2-ones **9**, which involves the rearrangement of readily available spiro-benzimidazolines **10** in the presence of triphosgene (Scheme 2). In this paper we document a complete account of our work in this area and highlight the methodology with an efficient preparation of Droperidol®, an antiemetic and antipsychotic pharmaceutical.[23]

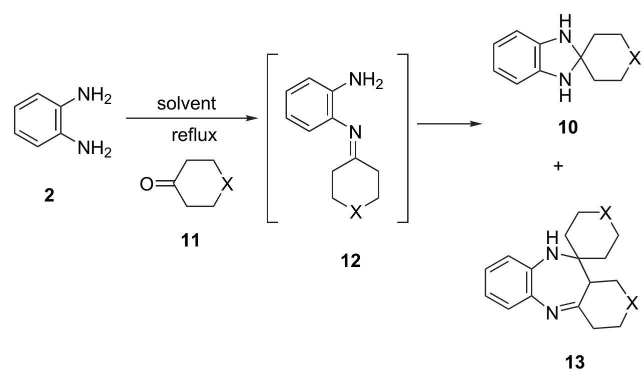


Scheme 2.

2. Results and discussion

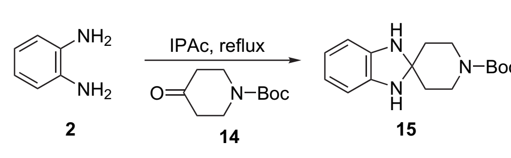
2.1. Preparation of spiro-benzimidazolines

Spiro-benzimidazolines have served as useful protecting groups for 1,2-phenylenediamines due to their ease of hydrolysis.[24] In addition they are readily oxidized to 2-spiro-2*H*-benzimidazole (isobenzimidazoles), which can be selectively elaborated to more functionalized heterocycles.[24,25] Spiro-benzimidazolines of type **10** have typically been prepared by the reaction of *o*-phenylenediamine **2** with ketones under a variety of conditions including refluxing in water,[25a] AcOH,[26] sulfolane,[25c] and acetonitrile (Scheme 3).[24a] The intermediate Schiff's base **12** is not typically isolated and cyclization to **10** is usually rapid. Regardless of the method employed, the desired spiro-benzimidazolines are typically obtained after an aqueous workup followed by chromatography. The preparation of non-spiro-benzimidazolines from aldehydes and acyclic ketones has also been reported.[27] The use of nearly equimolar amounts of **2** and **11** are required in order to minimize the formation of 1,5-benzodiazepine derivatives **13**, which are often reaction by-products. When an excess of the ketone is employed, 1,5-benzodiazepine derivatives **13** can become the sole reaction product.[28] The full synthetic utility of spiro-benzimidazolines has remained unexplored, presumably due to a lack of practical methods for their preparation and the ease with which they are hydrolyzed.



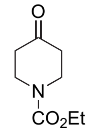
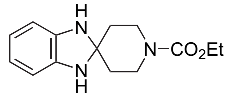
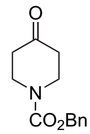
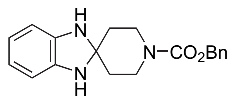
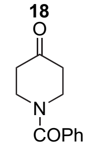
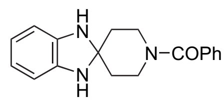
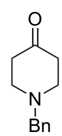
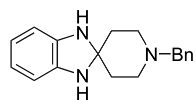
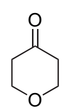
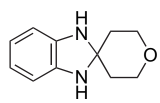
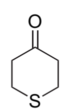
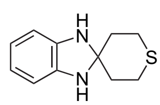
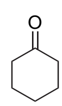
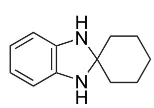
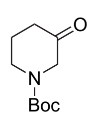
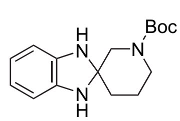
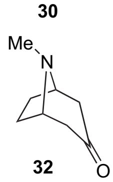
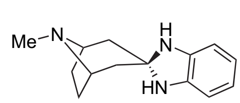
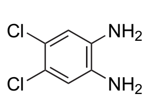
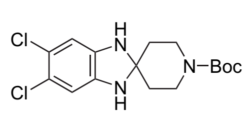
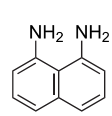
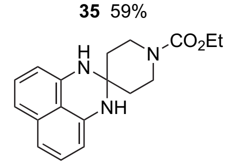
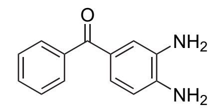
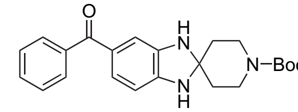
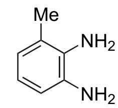
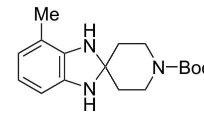
Scheme 3.

Our investigations began by examining the reaction between *o*-phenylenediamine **2** and *N*-Boc-4-piperidone **14** (Scheme 4). Under standard conditions employing refluxing AcOH, significant hydrolysis of the Boc-group was observed and none of the spiro-benzimidazoline **15** was observed. In order to circumvent these harsh conditions and eliminate both water and acid from the reaction, the reaction was conducted under neutral conditions. When a mixture of **2** and **14** (1.2 equiv) was allowed to react in refluxing isopropyl acetate (IPAc) with azeotropic removal of water, product **15** crystallized from the hot solution during the course of the reaction. Upon cooling and filtration, **15** was isolated in



Scheme 4.

Table 1. Preparation of spiro-benzimidazolines

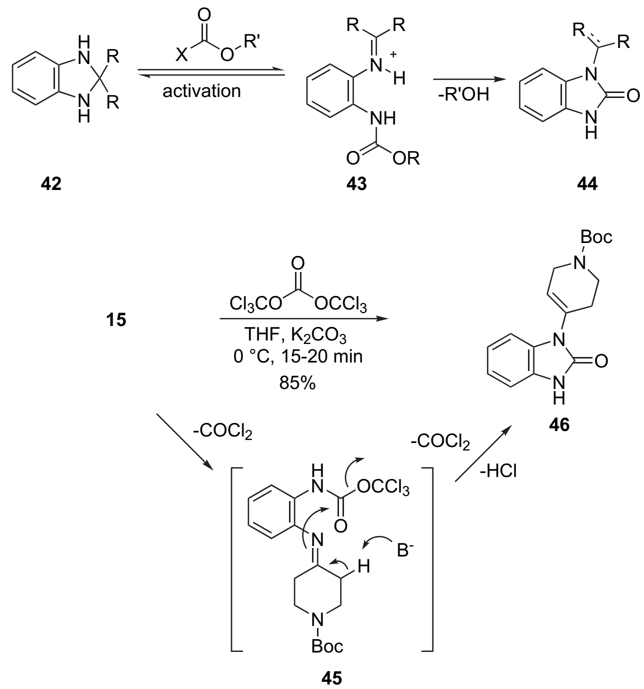
Entry	1,2-Phenylenediamine	Ketone	Spiro-benzimidazoline[a]
1	**2**	 **16**	 **17** 77%
2	**2**	 **18**	 **19** 67%
3	**2**	 **20**	 **21** 92%
4	**2**	 **22**	 **23** 74%
5	**2**	 **24**	 **25** 58%
6	**2**	 **26**	 **27** 72%
7	**2**	 **28**	 **29** 70%
8	**2**	 **30**	 **31** 55%
9	**2**	 **32**	 **33** 40%[c]
10	 **34**	**14**	 **35** 59%
11	 **36**	**16**	 **37** 70%
12	 **38**	**14**	 **39**[b] 60%
13	 **40**	**14**	 **41** 65%

[a] Isolated yield directly from the reaction mixture.
[b] Purified by silica gel chromatography.
[c] The reaction was stopped after 18 h and 45% conversion.

analytically pure form and in 85% isolated yield. Attempts to purify **15** by either aqueous workup or silica gel chromatography resulted in significant decomposition to **2** and **14** suggesting that **15** was unstable to these conditions despite the reported stability of spiro-benzimidazolines.[24–26] The reaction sequence whereby an appropriately substituted *o*-phenylenediamine was allowed to react with a cyclic ketone in refluxing IPAc followed by isolation of the product directly from the reaction mixture without resorting to either workup or chromatography proved to be general, providing access to a diverse array of substituted spiro-benzimidazolines (Table 1). Entry 11 also illustrates that spiro-perimidines can also be prepared.

2.2. Rearrangement of spiro-benzimidazolines: preparation of *N*-alkenylbenzimidazolones

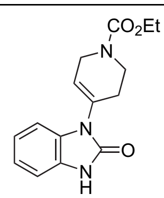
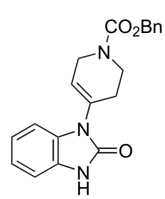
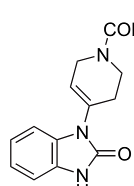
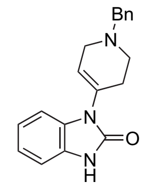
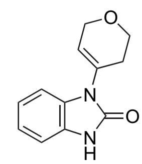
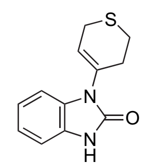
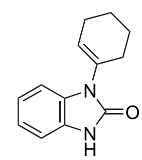
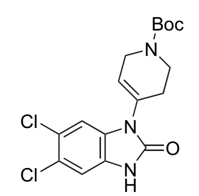
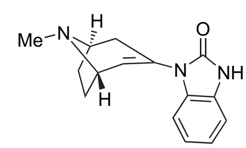
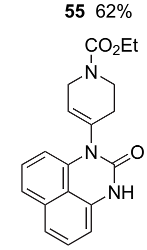
With an array of spiro-benzimidazolines in hand, our attention focused on examining the reactivity of this interesting heterocycle. We reasoned that appropriate activation of a single nitrogen atom of **42** with a suitable acylating agent would facilitate ring opening and formation of an intermediate imine **43** (Scheme 5). While the fate of this intermediate could not be predicted, it was speculated that either capture of the imine or tautomerization followed by cyclization might afford the desired *N*-substituted benzimidazol-2-one **44**. Attempts to initiate the sequence of events outlined in Scheme 5 with spiro-benzimidazoline **15** in the presence of dimethyl carbonate, diethylcarbonate, 1,1′-carbonyldimidazole (CDI), or methyl chloroformate at rt or at reflux did not provide any detectable amounts of **46**. In each case either **15** was recovered unchanged or significant decomposition to unidentified intractable tars resulted. On the other hand, reaction of **15** with 1 equiv of phosgene (20% in toluene) furnished **46** in 52% yield. The only detectable reaction by-products were **2** and ketone **14**, accounting for the mass balance. Encouraged by this result, the reaction was then optimized in terms of solvent, temperature, and phosgene or its equivalent. After extensive experimentation, it was discovered that treatment of **15** with 0.4 equiv of triphosgene in THF at 0 °C in the presence of 2 equiv of K_2CO_3 for 15 min, followed by filtration of the reaction mixture and purification by silica gel chromatography, routinely afforded **46** in 87% yield. The reaction was complete almost instantaneously and the only detectable reaction by-products were **2** and ketone



Scheme 5.

14. These by-products were easily removed by chromatography. We speculate that activation of **15** with triphosgene provides intermediate **45** and phosgene. Rapid tautomerization, followed by intramolecular cyclization affords **46** and phosgene, which can further react with available **15**. The use of anhydrous powdered K_2CO_3 in the reaction mixture was crucial for obtaining high yields and helped to scavenge the HCl liberated during the course of the reaction. Unfortunately, all efforts to eliminate minor amounts of hydrolysis by-products **2** and **14** by performing the reaction in dry THF (KF<20 ppm), in the presence of 4 Å molecular sieves

Table 2

Entry	Spiro-benzimidazoline	Benzimidazole
1	**17**	 **47** 80%
2	**19**	 **48** 71%
3	**21**	 **49** 68%
4	**23**	 **50** 55%
5	**25**	 **51** 85%
6	**27**	 **52** 60%
7	**29**	 **53** 74%
8	**35**	 **54** 57%
9	**33**	 **55** 62%
10	**37**	 **56** 61%

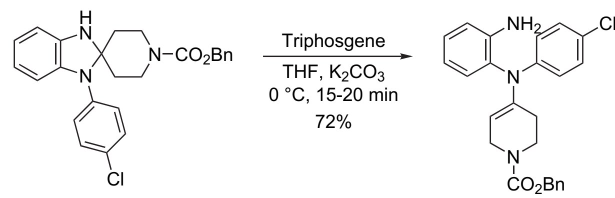
(*continued*)

Table 2. (*continued*)

or $MgSO_4$ were unsuccessful. While the formation of *o*-phenylenediamine and ketone by-products was unavoidable, the overall sequence provided access to a number of intriguing *N*-alkenylbenzimidazolones in good to excellent yield as demonstrated in Table 2.

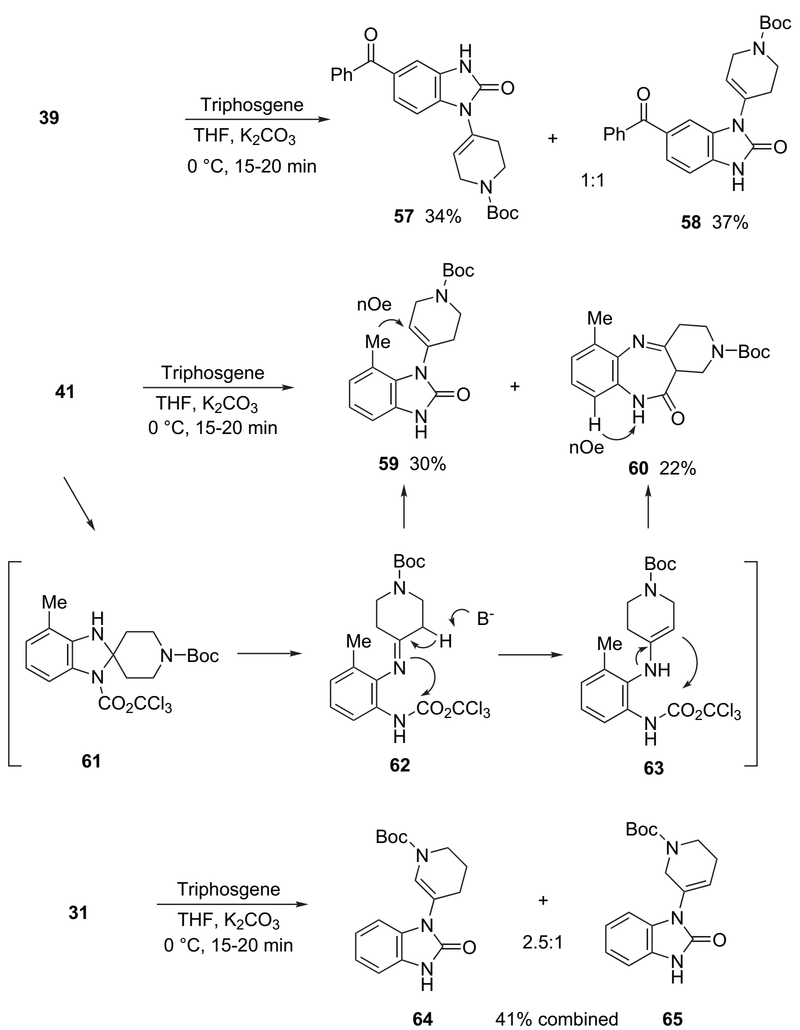
Having established that symmetrical spiro-benzimidazolines rearrange to benzimidazol-2-ones, we next investigated the effect of substitution about the spiro-benzimidazoline ring system on the product distribution (Scheme 6). For example, treatment of **39** with triphosgene afforded a 1:1 mixture of benzimidazoles **57** and **58** in 34% and 37% yields, respectively, where the benzoyl group had little influence on the product distribution. Interestingly, reaction of **41** under the identical reaction conditions afforded a separable mixture of benzimidazole **59** and benzazipinone **60**. There were no detectable amounts of the isomeric benzimidazol-2-one or benzazipinone in the crude NMR of the reaction mixture and the structures of both **59** and **60** were unequivocally established by NMR. It is believed that activation occurred regioselectively at the less sterically demanding nitrogen of **41** to give **61**. Subsequent ring opening, tautomerization, and cyclization gave **59**. Formation of **60** can only be explained by intramolecular cyclization of enamine **63** and represented the only case that any detectable benzazepinones of type **60** were formed in any of the reactions outlined in Table 2. Spiro-benzimidazoline **31** is unsymmetrically substituted in the piperidine portion of the molecule. When **31** was subjected to the reaction conditions, an inseparable 2.5:1 mixture of regioisomeric benzimidazol-2-ones **64** and **65** were obtained.

We also briefly explored the consequences of having a substituent on the nitrogen atom of the spiro-benzimidazoline as the case of **66** (Scheme 7). In this case, only a single nitrogen atom could be activated. Reaction of **66** with triphosgene in the presence of K_2CO_3 in THF afforded **67** as the only identifiable product, which was isolated in 72% yield. Although this result was not completely surprising, it represents a new entry to di-functionalized anilines.



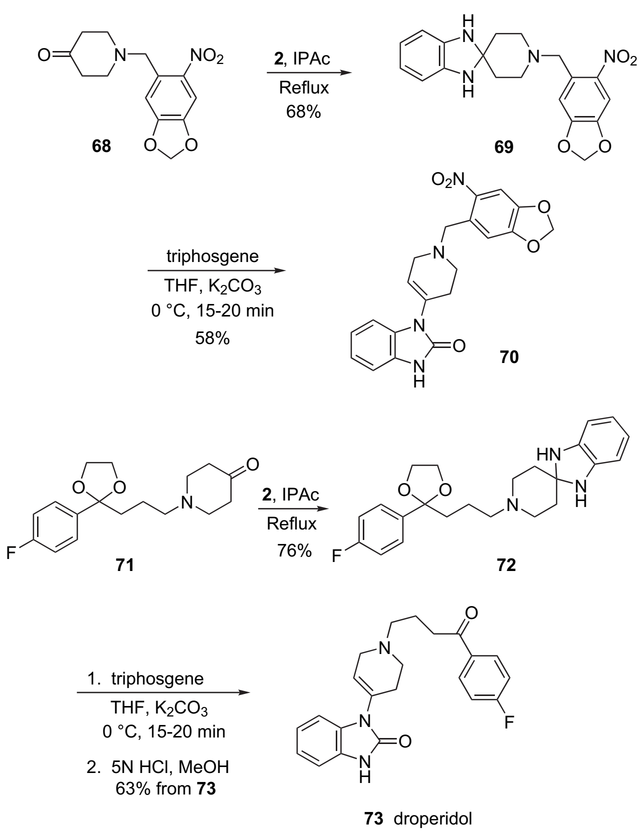
66 **67**

Scheme 7.



Scheme 6.

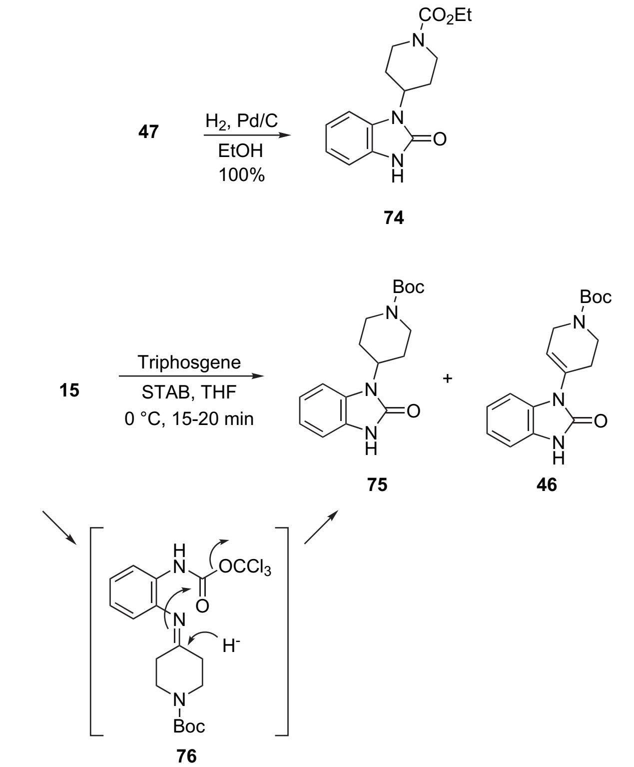
The facility with which spiro-benzimidazolines readily rearrange to benzimidazolones was further highlighted by the synthesis of μ opiate receptor antagonist **70**[29] and Droperidol® **73**,[23] a potent antiemetic and antipsychotic agent, which is marketed under a variety of generic names (Scheme 8). For example, reaction of **68** with **2** in IPAc followed by filtration afforded **69** in 68% yield. Treatment of **69** with triphosgene under the standard reaction conditions described above gave **70** in 58% yield. The synthesis of droperidol **73** began with piperidone **71**,[30] which was readily converted to spiro-benzimidazoline **72** in 76% yield. Rearrangement of **72** in the presence of triphosgene followed by reaction of the crude product with 5 N HCl in MeOH afforded droperidol **73** in 63% overall yield from **72**. The three-step synthesis of **70** and four-step synthesis of **73** demonstrates that complex target molecules can rapidly be assembled from readily available starting materials in a minimum number of synthetic transformations using this methodology.



Scheme 8.

2.3. Rearrangement of spiro-benzimidazolines: preparation of *N*-alkylbenzimidazol-2-ones

The preparation of *N*-alkylbenzimidazol-2-ones from *N*-alkenylbenzimidazol-2-ones is a relatively straight forward reaction involving catalytic hydrogenation over Pd/C (Scheme 9). For example, hydrogenation of **47** over 10% Pd/C furnished **74**[6] in quantitative yield. We became intrigued with the possibility of capturing imine **76** with an appropriate hydride source prior to cyclization to the corresponding *N*-alkenylimidazol-2-one. Treatment of **15** with triphosgene in the presence of a number of hydride sources ($NaBH_4$, $LiBH_4$, LAH, and borane) only led to minor amounts of **75** or **46** and resulted in the formation of multiple reaction products. On the other hand, when **15** was treated with 0.4 equiv of triphosgene (0.4 equiv) in the presence of 1 equiv of sodium triacetoxyborohydride (STAB) in THF, **75** became the major reaction product (50%). Also detected in the crude reaction mixture was **46**, ketone **16**, and **2**. The reaction was then optimized in terms of equivalent charges of triphosgene and STAB. The optimal results involved the addition of 0.7 equiv of triphosgene to a mixture of **15** and 2 equiv of STAB at 0 °C. Under these conditions, **75** was isolated in 73% yield, which was also contaminated with ∼5% of **46**. Attempts to separate **75** from **46** by chromatography were unsuccessful. Due to the high electrophilicity of the trichloromethyl carbamate intermediate and an extremely rapid tautomerization–cyclization, formation of **46** was competitive with hydride capture leading to **75**. Similar results were obtained for variously substituted spiro-benzimidazolines as outlined in Table 3. In each case, contamination of the product with the corresponding *N*-alkenylbenzimidazol-2-ones was observed. Again, the mass balance was made up of the hydrolysis products: ketones and *o*-phenylenediamines.

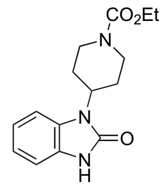
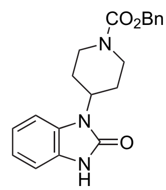
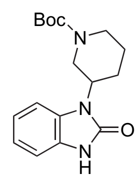
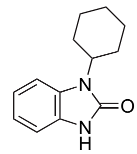
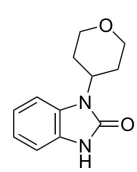


Scheme 9.

3. Conclusion

In conclusion, we have outlined an efficient and practical means of preparing spiro-benzimidazolines by reaction of variously substituted ketones with *o*-phenylenediamines. Treatment of these spiro-benzimidazolines with triphosgene results in rapid rearrangement to provide access to highly functionalized *N*-alkenyl-benzimidazol-2-ones. This methodology was also highlighted by the synthesis of μ opiate receptor antagonist **70** and droperidol **73**. We have also demonstrated that capture of the intermediate imine with STAB is feasible providing direct access to *N*-alkyl-benzimidazol-2-ones.

Table 3

Entry	Spiro-benzimidazoline	*N*-Alkylbenzimidazolone[a,b]
1	**17**	 **77** 70%(4%)
2	**19**	 **78** 64%(3%)
3	**31**	 **79** 73%(1%)
4	**29**	 **80** 64%(3%)
5	**25**	 **81** 60%(4%)

[a] Combined yield.
[b] Yield in parenthesis if for the corresponding *N*-alkenyl-benzimidazol-2-one.

4. Experimental section

4.1. General

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate–hexanes mixture as the eluent unless specified otherwise.

4.2. General procedure for the preparation of 1,3-dihydro-spiro(2*H*-benzimidazoles)

To a stirred solution of 5.00 g (46.24 mmol) of 1,2-phenylenediamine **2** in 100 mL of isopropyl acetate (IPAc) was added 60.11 mmol of the appropriately substituted ketone. The resulting mixture was heated to reflux for 30 min and the water was azeotropically removed by distillation of IPAc at atmospheric pressure for 1.5 h while flushing with additional IPAc. The solvent level was adjusted to a final volume of ~45 mL and the reaction mixture cooled to rt. The product, usually crystallized from the crude reaction mixture, was isolated by filtration and dried under vacuum/N_2 sweep to give the desired 1,3-dihydro-sprio[2*H*-benzimidazole] in analytically pure form. When the product did not crystallize from the crude reaction mixture, the solvent was removed under reduced pressure and the residue was rapidly passed through a short column of silica gel.

4.2.1. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid *tert*-butyl ester (15). According to the general procedure, treatment of 8.00 g (74.0 mmol) of **2** with 17.69 g (89.0 mmol) of *tert*-butyl 4-oxo-1-piperidinecarboxylate **14** afforded 16.0 g (75%) of **15** as a colorless solid; mp 174–175 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.80 (t, 4H, J=5.8 Hz), 3.54 (t, 4H, J=5.8 Hz), 3.83 (br s, 2H), 6.60 (m, 2H), 6.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 38.6, 40.9, 78.1, 79.9, 110.2, 120.5, 139.4, 154.7. Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.02; H, 7.99; N, 14.39.

4.2.2. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid ethyl ester (17). According to the general procedure, treatment of 6.00 g (55.5 mmol) of **2** with 12.35 g (72.1 mmol) of ethyl 4-oxo-1-piperidinecarboxylate **16** afforded 9.25 g (64%) of **17** as a light yellow solid; mp 154–155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H, J=7.2 Hz), 1.79 (m, 4H), 3.59 (m, 4H), 3.89 (br s, 2H), 4.15 (q, 2H, J=7.2 Hz), 6.58 (m, 2H), 6.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 38.5, 41.0, 61.6, 78.0, 110.2, 120.5, 139.5, 155.5. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.15; H, 7.22; N, 15.99.

4.2.3. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid benzyl ester (19). According to the general procedure, treatment of 5.00 g (46.24 mmol) of **2** with 12.94 g (55.49 mmol) of benzyl 4-oxo-1-piperidinecarboxylate **18** afforded 10.02 g (67%) of **19** as a colorless solid; mp 139–140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (t, 4H, J=5.2 Hz), 3.63 (t, 4H, J=5.2 Hz), 3.84 (br s, 2H), 5.17 (s, 2H), 6.61 (m, 2H), 6.69 (m, 2H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.5, 41.2, 67.4, 77.9, 110.4, 120.6, 128.0, 128.2, 128.6, 136.7, 139.4, 155.2. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.21; H, 6.48; N, 13.01.

4.2.4. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-phenyl-methanone (21). According to the general procedure, treatment of 3.00 g (27.7 mmol) of **2** with 6.77 g (3.33 mmol) of 1-benzoyl-4-piperidone **20** afforded 7.50 g (92%) of **21** as a colorless solid; mp 165–166 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65–1.95 (br m, 4H), 3.51 (br s, 2H), 3.71–3.92 (br m, 4H), 6.59 (m, 2H), 6.61 (m, 2H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.3, 39.3, 44.6, 78.1, 110.4, 120.7, 127.0, 128.6, 129.9, 135.9, 139.4, 170.5. Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.52; H, 6.44; N, 14.29.

4.2.5. Preparation of 4′-benzyl-1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine] (23). According to the general procedure, treatment of 5.00 g (46.2 mmol) of **2** with 11.37 g (60.1 mmol) of 1-benzyl-4-piperidone **22** afforded 9.56 g (74%) of **23** as a tan solid; mp 113–114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (t, 4H, J=5.6 Hz), 2.55 (m, 4H), 3.85 (s, 2H), 3.85 (br s, 2H), 6.59 (m, 2H), 6.68 (m, 2H), 7.29 (m, 1H), 7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0, 50.7, 63.1, 78.2, 109.9, 120.2, 127.2, 128.4, 129.2, 138.4, 139.5. Anal. Calcd for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 76.99; H, 7.23; N, 14.79.

4.2.6. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-pyranyl] (25). According to the general procedure, treatment of 5.00 g (46.24 mmol) of **2** with 12.94 g (55.49 mmol) of tetrahydro-4*H*-pyran-4-one **24** afforded 5.12 g (58%) of **25** as a colorless solid; mp 117–118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (t, 4H, J=5.6 Hz), 3.80 (t, 4H, J=5.6 Hz), 6.61 (m, 2H), 6.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.7, 65.1, 110.1, 116.7, 120.4, 139.3. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.22; H, 7.31; N, 14.66.

4.2.7. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-thiopyranyl] (27). According to the general procedure, treatment of 2.86 g (26.4 mmol) of **2** with 1.30 g (34.4 mmol) of tetrahydro-4*H*-thiopyran-4-one **26** afforded 3.93 g (72%) of **27** as a light yellow solid; mp 86–87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (m, 4H), 2.74 (m, 4H), 3.81 (br s, 2H), 6.59 (m, 2H), 6.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0, 40.1, 78.4, 110.1, 120.5, 139.4. Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.68; N, 13.58. Found: C, 63.89; H, 6.62; N, 13.47.

4.2.8. Preparation of 1,3-dihydro-spiro[benzoimidazole-2,1′-cyclohexane] (29). According to the general procedure, treatment of 4.00 g (37.0 mmol) of **2** with 17.69 g (48.1 mmol) of cyclohexanone **28** afforded 4.87 g (70%) of **29**[31] as a colorless solid; mp 139–140 °C (lit.[31] 138–139 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (m, 2H), 1.62 (m, 4H), 1.75 (m, 4H), 3.85 (br s, 2H), 6.58 (m, 2H), 6.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 25.1, 39.2, 79.9, 109.7, 120.0, 139.8. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55, H, 8.57; N, 14.88. Found: C, 76.45; H, 8.47; N, 14.69.

4.2.9. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,3′-piperidine]-3′-carboxylic acid *tert*-butyl ester (31). According to the general procedure, treatment of 2.20 g (20.3 mmol) of **2** with 4.86 g (24.4 mmol) of *tert*-butyl 3-oxo-1-piperidinecarboxylate **30** afforded 3.25 g (55%) of **31** as a colorless solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.73 (m, 2H), 1.85 (m, 2H), 3.40 (m, 4H), 3.84 (br s, 2H), 6.58 (m, 2H), 6.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 28.5, 37.3, 43.3, 54.0, 77.6, 80.1, 110.2, 120.6, 139.4, 155.3. Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.29; H, 7.97; N, 14.44.

4.2.10. Preparation of 1,3-dihydro-spiro(2*H*-benzimidazole-8′-methyl-8′-azo-bicyclo[3.2.1]octane) (33). According to the general procedure, treatment of 3.00 g (27.7 mmol) of **2** with 4.63 g (33.3 mmol) of tropinone **32** afforded 2.1 g (33%) of **33** as an amber oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (m, 1H), 1.69 (m, 1H), 1.95 (m, 1H), 2.07 (m, 2H), 2.27 (d, 1H, J=14.9 Hz), 2.39 (d, 1H, J=14.9 Hz), 2.41 (s, 3H), 2.86 (dd, 1H, J=14.9 and 1.8 Hz), 3.18 (d, 1H, J=1.8 Hz), 3.40 (d, 1H, J=1.8 Hz), 3.59 (br s, 2H), 6.47 (d, 1H, J=7.7 Hz), 6.67 (m, 2H), 6.89 (t, 1H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1, 27.3, 37.7, 38.8, 44.3, 47.6, 60.7, 61.3, 115.3, 118.2, 119.7, 124.7, 136.7, 138.0, 173.1.

4.2.11. Preparation of 5,6-dichloro-1,3-dihydro-spiro-[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid *tert*-butyl ester (35). According to the general procedure, treatment of 3.00 g (16.95 mmol) of **34** with 4.39 g (22.03 mmol) of *tert*-butyl 4-oxo-1-piperidinecarboxylate **14** afforded 3.60 g (59%) of **35** as a colorless solid; mp 157–158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.77 (m, 4H), 3.51 (m, 4H), 4.03 (br s, 2H), 6.53 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 38.5, 40.9, 79.6, 80.1, 110.3, 122.1, 139.3, 154.7. Anal. Calcd for $C_{16}H_{21}Cl_2N_3O_2$: C, 53.64; H, 5.91; N, 11.73. Found: C, 53.55; H, 5.89; N, 11.61.

4.2.12. Preparation of 2,3-dihydro-spiro[1*H*-perimidine-2,4′-piperidine]-4′-carboxylic acid ethyl ester (37). According to the general procedure, treatment of 5.20 g (32.9 mmol) of 1,8-diaminonapthalene **36** with 8.46 g (49.4 mmol) of 1-carboethoxy-4-piperidone **16** afforded 7.0 g (70%) of **37** as a light gray solid; mp 199–201 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H, J=7.1 Hz), 1.83 (t, 4H, J=5.7 Hz), 3.61 (t, 4H, J=5.6 Hz), 4.17 (q, 2H, J=7.1 Hz), 6.57 (dd, 2H, J=1.1 Hz), 7.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.76, 36.31, 40.24, 61.61, 64.05, 107.39, 118.11, 127.10, 134.66, 139.00, 155.55. Anal. Calcd for $C_{18}H_{21}N_3$: C, 69.43; H, 6.80; N, 13.49. Found: C, 68.99; H, 6.73; N, 13.05.

4.2.13. Preparation of 5-benzoyl-1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid *tert*-butyl ester (39). According to the general procedure, treatment of 2.5 g (11.8 mmol) of **38** with 3.52 g (89.0 mmol) of *tert*-butyl 4-oxo-1-piperidinecarboxylate **14** afforded 2.79 g (60%) of **39** as a yellow foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.78 (m, 4H), 3.46 (m, 2H), 3.55 (m, 2H), 4.58 (s, 1H), 5.14 (s, 1H), 6.32 (d, 1H, J=7.9 Hz), 7.03 (d, 1H, J=1.5 Hz), 7.09 (dd, 1H, J=7.9 and 1.5 Hz), 7.39 (m, 2H), 7.46 (m, 1H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 38.8, 41.0, 79.4, 79.9, 105.6, 109.2, 127.2, 128.0, 128.4, 129.5, 131.2, 139.1, 139.4, 144.9, 154.7, 195.8. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 69.88; H, 6.81; N, 10.66.

4.2.14. Preparation of 1,3-dihydro-4-methyl-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid *tert*-butyl ester (41). According to the general procedure, treatment of 3.24 g (26.5 mmol) of **40** with 6.34 g (31.8 mmol) of *tert*-butyl 4-oxo-1-piperidinecarboxylate **14** afforded 5.25 g (65%) of **41** as a tan solid; mp 83–84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.79 (t, 4H, J=5.7 Hz), 2.13 (s, 3H), 3.57 (m, 4H), 3.60 (br s, 2H), 6.46 (d, 1H, J=7.5 Hz), 6.52 (d, 1H, J=7.5 Hz), 6.62 (t, 1H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 28.5, 38.7, 41.0, 77.9, 79.8, 107.9, 120.0, 120.6, 122.0, 137.9, 139.1, 154.8. Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.30; H, 8.31; N, 13.85. Found: C, 67.12; H, 7.98; N, 13.66.

4.3. General procedure for the triphosgene-mediated rearrangement of 1,3-dihydro-spiro[2*H*-benzimidazoles]

To a stirred solution of 1.00 mmol of the appropriately substituted 1,3-dihydro-spiro(2*H*-benzimidazole) in 10 mL of THF was added 691 mg (5.00 mmol) of powdered K_2CO_3. The resulting slurry was cooled to 0 °C and 119.0 mg (0.40 mmol) of triphosgene in 2 mL of THF was added dropwise. The mixture was stirred for 15–30 min and quenched with 15 mL of water. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

4.3.1. Preparation of 4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (46). According to the general procedure, treatment of 1.50 g (5.18 mmol) of **15** with 615 mg (2.07 mmol) of triphosgene in the presence of 3.56 g (25.9 mmol) of K_2CO_3 afforded 1.39 g (85%) of **46** as a colorless solid; mp 201–202 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.45 (s, 9H), 2.45 (m, 2H), 3.61 (t, 2H, J=5.3 Hz), 4.07 (m, 2H), 7.01 (m, 3H), 7.05 (m, 1H), 10.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.8, 28.4, 41.1, 42.2, 49.4, 79.5, 108.8, 109.3, 121.0, 121.7, 122.5, 128.9, 130.1, 130.7, 153.2, 154.2. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.55; H, 6.62; N, 13.29.

4.3.2. 4-(2-Oxo-2,3-dihydro-benzimidazol-1-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid ethyl ester (47). According to the general procedure, treatment of 500 mg (1.91 mmol) of **17** with 227 mg (0.77 mmol) of triphosgene in the presence of 1.32 g (9.55 mmol) of K_2CO_3 afforded 440 mg (80%) of **47** as a colorless solid; mp 197–198 °C. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.19 (t, 3H, J=7.1 Hz), 2.47 (m, 2H), 3.60 (t, 2H, J=5.7 Hz), 4.06 (m, 4H), 5.89 (s, 1H), 6.96 (m, 3H), 7.01 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.8, 27.1, 40.5, 42.8, 61.7, 108.8, 110.0, 121.5, 122.1, 123.1, 128.3, 130.1, 131.1, 154.6, 155.7. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.55; H, 5.87; N, 14.57.

4.3.3. Preparation of 4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid benzyl ester (48). According to the general procedure, treatment of 1.00 g (3.09 mmol) of **19** with 367 mg (1.24 mmol) of triphosgene in the presence of 2.14 g (15.5 mmol) of K_2CO_3 afforded 767 mg (71%) of **48** as a colorless solid; mp 150–151 °C. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.63 (m, 2H), 3.85 (t, 2H, J=5.0 Hz), 4.28 (m, 2H), 5.22 (s, 2H), 5.97 (br s, 1H), 7.07 (m, 4H), 7.40 (m, 5H), 10.56 (br s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 27.1, 40.5, 42.9, 67.4, 108.9, 109.9, 121.5, 122.1, 123.1, 128.1, 128.2, 128.3, 128.6, 130.0, 136.6, 154.4, 155.1. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.44; H, 5.41; N, 11.92.

4.3.4. Preparation of 1-(1-benzoyl-1,2,3,6-tetrahydro-pipridin-4-yl)-1,3-dihydro-benzimidazol-2-one (49). According to the general procedure, treatment of 1.00 g (3.41 mmol) of **21** with 405 mg (1.36 mmol) of triphosgene in the presence of 2.36 g (17.04 mmol) of K_2CO_3 afforded 740 mg (68%) of **49** as a tan solid; mp 251–252 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.51 (br m, 2H), 3.56 and 3.86 (br m, 2H, due to rotamers), 4.10 and 4.30 (br m, 2H, due to rotamers), 5.82 and 5.99 (br s, 1H, due to rotamers), 6.97 (br m, 3H), 7.07 (br m, 1H, due to rotamers), 7.44 (m, 5H), 10.94 (br s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 26.9 and 27.1 (due to rotamers), 41.8 and 44.1 (due to rotamers), 46.4 and 48.7 (due to rotamers), 109.1, 109.5, 121.2, 121.9, 122.2, 127.2 and 127.3 (due to rotamers), 129.0, 130.1, 130.2, 136.5, 153.5, 169.6, 169.7. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.22; H, 5.31; N, 13.01.

4.3.5. Preparation of 1-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1,3-dihydro-benzimidazol-2-one (50). According to the general procedure, treatment of 2.40 g (8.59 mmol) of **24** with 1.02 g (3.44 mmol) of triphosgene in the presence of 5.94 g (43.0 mmol) of K_2CO_3 afforded 1.70 g (65%) of **50** as a colorless solid; mp 159–160 °C (lit.[18b] 160–162 °C). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.64 (m, 2H), 2.86 (t, 2H, J=5.7 Hz), 3.30 (m, 2H), 3.74 (s, 2H), 5.97 (s, 1H), 7.12 (m, 4H), 7.28 (m, 1H), 7.33 (m, 2H), 7.42 (m, 2H), 10.54 (br s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 27.5, 49.4, 51.8, 62.2, 109.0, 109.9, 121.3, 121.8, 124.5, 127.3, 128.3, 128.4, 129.2, 130.3, 130.8, 137.9, 154.7. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.38; H, 6.22; N, 13.67.

4.3.6. Preparation of 1-(3,6-dihydro-2*H*-pyran-4-yl)-1,3-dihydro-benzimidazol-2-one (51). According to the general procedure, treatment of 470 mg (2.70 mmol) of **25** with 293 mg (0.99 mmol) of triphosgene in the presence of 1.71 g (12.4 mmol) of K_2CO_3 afforded 454 mg (85%) of **51** as a colorless solid; mp 233–234 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.43 (m, 2H), 3.82 (t, 2H, J=5.4 Hz), 4.24 (m, 2H), 5.93 (s, 1H), 6.97 (m, 3H), 7.03 (m, 1H), 10.91 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.1, 64.1, 64.6, 109.0, 109.5, 121.2, 121.9, 124.0, 129.0, 129.9, 130.2, 153.4. Anal. Calcd for $C_{12}H_{12}N_2O_2\cdot 1/2H_2O$: C, 63.42; H, 6.65; N, 12.33. Found: C, 63.35; H, 6.44; N, 12.11.

4.3.7. Preparation of 1-(3,6-dihydro-2*H*-thiopyran-4-yl)-1,3-dihydro-benzimidazol-2-one (52). According to the general procedure, treatment of 740 mg (3.59 mmol) of **27** with 426 mg (1.44 mmol) of triphosgene in the presence of 2.48 g (18.0 mmol) of K_2CO_3 afforded 500 mg (60%) of **52** as a colorless solid; mp 235 °C (decomp.) (lit[32] 236 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.51 (m, 2H), 2.83 (t, 2H, J=5.4 Hz), 3.32 (m, 2H), 6.03 (s, 1H), 6.94 (m, 4H), 10.88 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.9, 25.1, 28.0, 108.6, 109.4, 121.1, 121.7, 124.5, 129.0, 130.6, 133.3, 153.5. Anal. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 61.93; H, 5.19; N, 11.98.

4.3.8. Preparation of 1-cyclohex-1-enyl-1,3-dihydro-benzimidazol-2-one (53). According to the general procedure, treatment of 750 mg (3.98 mmol) of **29** with 473 mg (1.59 mmol) of triphosgene in the presence of 2.75 g (19.9 mmol) of K_2CO_3 afforded 630 mg (74%) of **53** as a colorless solid; mp 180–181 °C (lit.[18b] 182–183 °C). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.77 (m, 2H), 1.89 (m, 2H), 2.32 (m, 2H), 2.42 (m, 2H), 5.99 (s, 1H), 7.05 (m, 3H), 7.14 (m, 1H), 10.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 22.7, 24.8, 26.9, 108.7, 109.9, 121.2, 121.6, 127.8, 128.4, 130.7, 132.2, 155.0. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.93; H, 6.58; N, 12.92.

4.3.9. Preparation of 4-(5,6-dichloro-2-oxo-2,3-dihydro-benzimidazol-1-yl)-2,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (54). According to the general procedure, treatment of 616 mg (1.55 mmol) of **35** with 184 mg (0.62 mmol) of triphosgene in the presence of 1.07 g (7.75 mmol) of K_2CO_3 afforded 339 mg (57%) of **54** as a colorless solid; mp 208–209 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 2.54 (m, 2H), 3.73 (t, 2H, J=5.0 Hz), 4.17 (m, 2H), 5.93 (s, 1H), 7.08 (s, 1H), 7.19 (s, 1H), 10.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.9, 28.4, 41.0, 42.3, 80.3, 110.2, 111.4, 123.9, 125.1, 125.5, 127.6, 129.3, 131.0, 154.4, 154.6. Anal. Calcd for $C_{17}H_{19}Cl_2N_3O_3$: C, 53.14; H, 4.98; N, 10.94. Found: C, 52.76; H, 4.65; N, 10.91.

4.3.10. Preparation of (1*S5*R**)-1-(8-methyl-8-aza-bicyclo[3.2.1]oct-2-en-3-yl)-1,3-dihydro-benzimidazol-2-one (55).** According to the general procedure, treatment of 500 mg (2.18 mmol) of **33** with 259 mg (3.44 mmol) of triphosgene in the presence of 1.51 g (10.9 mmol) of K_2CO_3 afforded 345 mg (62%) of **55** as a tan solid; mp 203 °C (decomp.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (m, 1H), 2.09 (m, 1H), 2.16–2.32 (m, 3H), 2.58 (s, 3H), 2.86 (d, 1H, J=17.5 Hz), 3.46 (m, 1H), 3.56 (t, 1H, J=5.4 Hz), 6.04 (d, 1H, J=5.4 Hz), 7.03 (m, 4H), 10.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.1, 32.4, 34.5, 36.0, 57.3, 58.7, 108.6, 109.8, 121.3, 121.8, 128.6, 128.8, 129.4, 130.4, 154.7. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.51; H, 6.66; N, 16.43.

4.3.11. Preparation of 4-(2-oxo-2,3,3a,9b-tetrahydro-perimidin-1-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid ethyl ester (56). According to the general procedure, treatment of 1.00 g (3.21 mmol) of **37** with 760 mg (2.56 mmol) of triphosgene in the presence of 1.33 g (9.63 mmol) K_2CO_3 afforded 659 mg (61%) of **56** as a light gray solid; mp 199–201 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J=7.1 Hz), 2.46 (m, 2H), 3.87 (br m, 2H), 4.24 (m, 4H), 5.95 (s, 1H), 6.54 (m, 2H), 7.24 (m, 4H), 8.39 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.79, 43.00, 61.67, 104.80, 105.36, 114.73, 119.43, 119.90, 127.86, 127.91, 134.79, 135.42, 137.98, 149.95. Anal. Calcd for $C_{19}H_{19}N_3O_3\cdot 1/3H_2O$: C, 66.46; H, 5.77; N, 12.24. Found: C, 66.66; H, 5.57; N, 12.14.

4.3.12. Rearrangement of spiro-benzimidazoline 39. According to the general procedure, treatment of 650 mg (1.65 mmol) of **39** with 196 mg (0.661 mmol) of triphosgene in the presence of 1.14 g (8.26 mmol) of K_2CO_3 was followed by chromatography on silica gel. The first product to elute from the column (236 mg, 34%) was identified as 4-(5-benzoyl-2,3-dihydro-benzimidazol-1-yl)-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (**57**), which was obtained as a colorless solid; mp 231–232 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.41 (s, 9H), 2.46 (m, 2H), 3.58 (m, 2H), 4.04 (m, 2H), 5.97 (s, 1H), 7.17 (d, 1H, J=8.2 Hz), 7.34 (s, 1H), 7.42 (m, 1H), 7.44 (m, 2H), 7.49–7.67 (m, 3H), 11.2 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.9, 28.6, 41.0, 42.3, 79.7, 108.6, 110.7, 123.2, 124.8, 128.9, 129.0, 129.8, 130.5, 130.8, 132.5, 134.1, 138.5, 153.6, 154.4, 195.4. Anal. Calcd for $C_{29}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.69; H, 5.98; N, 9.95.

The second product to elute from the column (256 mg, 37%) was identified as 4-(6-benzoly-2,3-dihydro-benzimidazol-1-yl)-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (**58**) and was obtained as a colorless solid; mp 237 °C (decomp.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.39 (s, 9H), 2.46 (m, 2H), 3.58 (m, 2H), 4.03 (m, 2H), 5.98 (s, 1H), 7.09 (d, 1H, J=8.1 Hz), 7.39 (m, 2H), 7.49 (m, 2H), 7.64 (m, 3H), 11.42 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.9, 28.6, 41.0, 42.3, 79.7, 108.9, 109.6, 123.6, 126.0, 128.9, 129.8, 130.2, 130.4, 130.6, 132.5, 133.3, 138.4, 153.6, 154.4, 195.3. Anal. Calcd for $C_{29}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.47; H, 5.83; N, 9.86.

4.3.13. Rearrangement of spiro-benzimidazoline 41. According to the general procedure, treatment of 1.00 g (3.30 mmol) of **41** with 391 mg (1.32 mmol) of triphosgene in the presence of 2.28 g (16.5 mmol) of K_2CO_3 was followed by chromatography on silica gel. The first product to elute from the column (330 mg, 30%) was identified as 4-(7-methyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (**59**) and was obtained as a colorless foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 2.35 (s, 3H), 2.40 (m, 1H), 2.67 (m, 1H), 3.77 (m, 3H), 4.17 (m, 2H), 6.81 (s, 1H), 6.81 (d, 1H, J=7.1 Hz), 6.98 (m, 2H), 10.82 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 28.5, 29.4, 39.9, 43.2, 80.2, 108.0, 119.7, 121.8, 124.5, 126.5, 128.2, 128.8, 132.4, 154.9, 155.4. Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.48; H, 6.73; N, 12.56.

The second product to elute from the column (235 mg, 22%) was identified as 6-methyl-11-oxo-1,3,4,10,11,11a-hexahydro-pyrid[4,3-*b*]benzodiazepine-2-carboxylic acid *tert*-butyl ester (**60**) and was obtained as a colorless solid; mp 201–202 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 2.41 (s, 3H), 2.89 (m, 3H), 3.52–3.87 (m, 3H), 4.35 (m, 1H), 6.92 (m, 1H), 7.09 (m, 2H), 8.87 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 28.5, 33.8, 39.1, 41.5, 46.4, 80.1, 119.5, 124.5, 126.1, 126.4, 128.6, 135.7, 137.7, 155.1, 167.7. Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.23; H, 6.77; N, 12.55.

4.3.14. Rearrangement of spiro-benzimidazoline 31. According to the general procedure, treatment of 500 mg (1.73 mmol) of **31** with 205 mg (0.691 mmol) of triphosgene in the presence of 1.19 g (8.64 mmol) of K_2CO_3 was followed by chromatography on silica gel to afford 223 mg (41%) of an inseparable 2.5:1 mixture of 5-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-2,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (**64**) and 5-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (**65**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H, **65**) 1.50 (s, 9H, **64**), 2.07 (m, 2H, **64**), 2.42 (m, 2H, **64** and **65**), 3.67 (m, 2H, **64** and **65**), 6.99–7.10 (m, 6H, **64** and **65**); ^{13}C NMR of **64** and **65**:

21.3, 21.5, 24.1, 24.4, 24.6, 29.7, 39.2, 41.1, 42.2, 44.0, 80.2, 81.4, 81.7, 108.6, 108.7, 110.0, 110.1, 112.0, 112.8, 121.4, 121.5, 121.9, 122.2, 126.1, 127.5, 128.0, 128.3, 128.4, 130.3, 131.2, 151.9, 154.9, 155.0, 155.7. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.55; H, 6.55; N, 13.29.

4.3.15. Preparation of 1,3-dihydro-1-(4-chlorophenyl)-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-carboxylic acid benzyl ester (66). According to the general procedure, treatment of 2.50 g (11.4 mmol) of *N*-(4-chlorophenyl)-1,2-phenylenediamine with 3.20 g (13.7 mmol) of benzyl 4-oxo-1-piperidinecarboxylate **18** afforded 3.77 g (76%) of **66** as a colorless solid; mp 163–164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (br m, 2H), 1.92 (br m, 2H), 3.05 (br m, 2H), 4.03 (br s, 1H), 4.23 (br m, 2H), 5.12 (s, 2H), 6.36 (d, 1H, J=7.7 Hz), 6.73 (m, 3H), 7.25 (d, 2H, J=8.7 Hz), 7.38 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.0, 40.9, 67.3, 82.9, 107.6, 111.4, 119.3, 121.3, 128.0, 128.1, 128.5, 129.8, 132.0, 136.6, 137.9, 139.1, 141.2, 155.0. Anal. Calcd for $C_{25}H_{24}ClN_3O_2$: C, 69.20; H, 5.57; N, 9.68. Found: C, 68.92; H, 5.47; N, 9.61.

4.3.16. Preparation of 4-[(2-aminophenyl)-(4-chlorophenyl)-amino]-piperidine-1-carboxylic acid benzyl ester (67). According to the general procedure, treatment of 600 mg (1.38 mmol) of **66** with 164 mg (0.552 mmol) of triphosgene in the presence of 953 mg (6.90 mmol) of K_2CO_3 was followed by chromatography on silica gel to afford 432 mg (72%) of **67** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (m, 2H), 2.02 (m, 2H), 3.04 (m, 2H), 3.48 (m, 1H), 4.07 (br m, 4H), 5.14 (s, 2H), 6.61 (d, 2H, J=8.6 Hz), 6.73 (m, 2H), 7.12 (m, 4H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.3, 42.8, 44.7, 67.2, 111.8, 116.3, 117.6, 124.0, 125.9, 126.8, 127.9, 128.1, 128.6, 129.2, 129.5, 136.9, 142.8, 144.6, 155.3. Anal. Calcd for $C_{25}H_{26}ClN_3O_2$: C, 68.88; H, 6.01; N, 9.64. Found: C, 69.01; H, 6.23; N, 9.70.

4.3.17. Preparation of 1-(6-amino-1,3-benzodioxol-5-ylmethyl)-piperidin-4-one (68). To a solution of 3.04 g (19.8 mmol) of 4-piperidone monohydrate hydrochloride in 40 mL of DMF were added 6.31 g (45.7 mmol) of K_2CO_3 and 3.96 g (15.23 mmol) of 5-bromomethyl-6-nitro-benzo[1,3]-dioxole.[33] The resulting mixture was heated to 50 °C for 8 h, cooled to rt, and diluted with 50 mL of water. The aqueous layer was extracted with 75 mL of EtOAc and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography to give 3.00 g (71%) of **68** as a bright yellow solid; mp 99–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.47 (t, 4H, J=6.1 Hz), 2.80 (t, 4H, J=6.1 Hz), 3.91 (s, 2H), 6.14 (s, 2H), 7.23 (s, 1H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.2, 53.1, 58.2, 102.9, 105.7, 109.2, 113.2, 143.2, 146.9, 151.7, 208.5. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.06; H, 4.86; N, 9.89.

4.3.18. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-(6-nitro-1,3-benzodioxol-5-yl)-methane (69). According to the general procedure, treatment of 1.00 g (9.25 mmol) of **2** with 3.41 g (10.78 mmol) of **68** afforded 2.50 g (68%) of **69** as a light yellow solid; mp 145–146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (t, 4H, J=6.1 Hz), 2.55 (t, 4H, J=6.1 Hz), 3.81 (s, 2H), 3.89 (br s, 2H), 6.11 (s, 2H), 6.57 (m, 2H), 6.64 (m, 2H), 7.21 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0, 50.9, 78.0, 102.8, 105.7, 109.3, 109.9, 120.2, 131.8, 139.4, 143.2, 146.7, 151.7. Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.11; H, 5.55; N, 15.29.

4.3.19. Preparation of 1-{1-[(6-nitrobenzo[1,3]dioxol-5-yl)methyl]-1,2,3,6-tetrahydropyridin-4-yl}-1,3-dihydrobenzimidazol-2-one (70). According to the general procedure, treatment of 525 mg (1.43 mmol) of **69** with 169 mg (0.57 mmol) of triphosgene in the presence of 985 mg (7.13 mmol) of K_2CO_3 afforded 325 mg (58%) of **70** as a light yellow solid; mp 219–220 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.45 (s, 2H), 2.67 (s, 2H), 3.18 (s, 2H), 3.86 (s, 2H), 5.84 (s, 1H), 6.24 (s, 2H), 6.99 (s, 4H), 7.27 (s, 1H), 7.58 (s, 1H), 10.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.4, 49.6, 51.9, 57.9, 103.7, 105.8, 108.9, 109.4, 109.9, 121.1, 121.7, 123.3, 129.0, 130.3, 130.9, 143.4, 147.1, 151.7, 153.4. Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.87; H, 4.55; N, 14.11.

4.3.20. Preparation of 1,3-dihydro-spiro[2*H*-benzimidazole-2,4′-piperidine]-4′-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]}-propane (72). According to the general procedure, treatment of 1.03 g (9.49 mmol) of **2** with 3.25 g (9.49 mmol) of **71**[30] afforded 3.12 g (76%) of **72** as a light yellow solid; mp 135–136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (m, 2H), 1.85 (m, 6H), 2.34 (t, 2H, J=7.5 Hz), 2.46 (m, 4H), 3.76 (m, 2H), 3.83 (br s, 2H), 4.01 (t, 2H, J=7.5 Hz), 6.55 (m, 2H), 6.64 (m, 2H), 7.01 (m, 2H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 38.5, 38.9, 50.7, 58.3, 64.6, 78.2, 109.8, 110.1, 114.9 (d, J=21.0 Hz), 115.1, 120.2, 127.6 (d, J=10.0 Hz), 138.5, 139.5, 162.1 (d, J=244.0 Hz). Anal. Calcd for $C_{23}H_{28}FN_3O_2$: C, 69.50; H, 7.10; N, 10.57. Found: C, 69.13; H, 6.89; N, 10.44.

4.3.21. Preparation of 1-{1-[4-(4-fluorophenyl)-4-oxobutyl]-3,6-dihydro-2*H*-pyrdin-4-yl}-3*H*-benzoimidazol-2-one (Droperidol®) (73). According to the general procedure, treatment of 500 mg (1.26 mmol) of **72** with 149 mg (0.50 mmol) of triphosgene in the presence of 870 mg (6.30 mmol) of K_2CO_3 gave protected droperidol. The resulting crude product was treated with aqueous 5 N HCl in MeOH for 1.5 h and the reaction mixture was neutralized to pH 9 with 2 N NaOH. The aqueous layer was extracted with EtOAc (2×25 mL) and the combined extracts were washed with 15 mL of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography to afford 300 mg (63%) of **73** as a colorless solid; mp 144–145 °C (lit.[23] 145–146.5 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (m, 2H), 2.61 (m, 4H), 2.81 (t, 2H, J=5.6 Hz), 3.05 (t, 2H, J=7.1 Hz), 3.26 (m, 2H), 5.92 (s, 1H), 7.00 (m, 3H), 7.12 (m, 3H), 8.02 (m, 2H), 10.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 27.4, 36.2, 49.7, 51.8, 57.0, 109.0, 109.9, 115.6 (d, J=21.0 Hz), 121.2, 121.8, 124.1, 128.4, 130.3, 130.7 (d, J=10.0 Hz), 131.0, 133.7, 154.8, 162.1 (d, J=244.0 Hz), 198.5; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −106.2. Anal. Calcd for $C_{22}H_{22}FN_3O_2$: C, 69.64; H, 5.84; N, 11.07. Found: C, 69.58; H, 5.79; N, 11.01.

4.4. General procedure for the preparation of *N*-alkylbenzimidazol-2-ones

To a stirred mixture of 1.00 mmol of the appropriately substituted spiro-benzimidazoline and 425 mg (2.00 mmol) of sodium triacetoxyborohydride in 5 mL of THF was added dropwise a solution of 208 mg (0.70 mmol) of triphosgene in 5 mL of THF. After stirring for 15 min the reaction was quenched with 10 mL of water. The aqueous layer was extracted with 10 mL of EtOAc (2×) and the combined extracts were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

4.4.1. Preparation of 4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (75). According to the general procedure, treatment of a mixture of 288 mg (0.995 mmol) of **15** and 425 mg (2.00 mmol) of sodium triacetoxyborohydride with 208 mg (0.70 mmol) of triphosgene gave 230 mg (73%) of **75**[34] contaminated with ~5% of **46** as a colorless solid; mp 156–159 °C (lit.[33] 165–166 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 1.85 (m, 2H), 2.35 (m, 2H), 2.88 (m, 2H), 4.35 (m, 2H), 4.50 (m, 2H), 7.05 (m, 2H), 7.15 (m, 2H), 10.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 29.3, 43.4, 50.9, 80.0, 109.4, 110.0, 121.0, 121.1, 128.4, 129.0, 154.8, 155.4.

4.4.2. Preparation of 4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid ethyl ester (77). According to the general procedure, treatment of a mixture of 535 mg (2.00 mmol) of **17** and 847 mg (4.00 mmol) of sodium triacetoxyborohydride with 415 mg (1.40 mmol) of triphosgene gave 404 mg (70%) of **77**[6] contaminated with ~4% of **47** as a colorless solid; mp 174–175 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J=7.4 Hz), 1.88 (m, 2H), 2.35 (m, 2H), 2.94 (m, 2H), 4.19 (q, 2H, J=7.3 Hz), 4.39 (br m, 2H), 4.41 (m, 1H), 7.08 (m, 3H), 7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 29.3, 43.7, 50.8, 61.7, 109.4, 110.0, 121.1, 121.5, 128.3, 129.0, 155.3, 155.6.

4.4.3. Preparation of 4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid benzyl ester (78). According to the general procedure, treatment of a mixture of 502 mg (1.56 mmol) of **19** and 375 mg (1.77 mmol) of sodium triacetoxyborohydride with 293 mg (0.99 mmol) of triphosgene gave 296 mg (64%) of **78** contaminated with ~3% of **48** as a colorless solid; mp 145–148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (m, 2H), 2.32 (m, 2H), 2.94 (m, 2H), 4.42 (br m, 2H), 4.50 (m, 1H), 5.19 (s, 2H), 7.05 (m, 4H), 7.41 (m, 5H), 9.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3, 43.9, 50.7, 64.5, 109.4, 110.1, 121.2, 121.5, 128.1, 128.2, 128.4, 128.6, 128.9, 136.8, 155.3, 155.4.

4.4.4. Preparation of 3-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (79). According to the general procedure, treatment of a mixture of 281 mg (1.00 mmol) of **31** and 424 mg (2.00 mmol) of sodium triacetoxyborohydride with 214 mg (0.72 mmol) of triphosgene gave 231 mg (73%) of **79** contaminated with ~1% of **64/65** as a colorless solid; mp 160–161 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.63 (m, 1H), 1.88 (m, 1H), 2.07 (m, 1H), 2.43 (m, 1H), 2.76 (m, 1H), 3.49 (m, 1H), 4.25 (m, 3H), 7.08 (m, 2H), 7.12 (m, 2H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 27.9, 28.5, 42.2, 44.2, 50.3, 80.1, 108.8, 109.9, 121.2, 121.5, 128.2, 129.5, 154.9, 155.2. Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.66; H, 7.41; N, 13.42.

4.4.5. Preparation of 1-cyclohexyl-1,3-dihydro-benzimidazol-2-one (80). According to the general procedure, treatment of a mixture of 381 mg (2.02 mmol) of **29** and 852 mg (4.02 mmol) of sodium triacetoxyborohydride with 415 mg (1.41 mmol) of triphosgene gave 279 mg (64%) of **80** contaminated with ~3% of **53** as a colorless solid; mp 165–168 °C (lit.[18b] 169–171 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (m, 1H), 1.50 (m, 2H), 1.80 (m, 1H), 1.95 (m, 4H), 2.21 (m, 2H), 4.35 (m, 1H), 7.05 (m, 2H), 7.15 (s, 1H), 7.25 (s, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 26.1, 30.3, 52.7, 109.6, 110.0, 120.8, 121.0, 128.5, 129.4, 155.7.

4.4.6. Preparation of 1-(tetrahydropyran-4-yl)-1,3-dihydro-benzimidazol-2-one (81). According to the general procedure, treatment of a mixture of 381 mg (2.00 mmol) of **25** and 847 mg (4.00 mmol) of sodium triacetoxyborohydride with 420 mg (1.42 mmol) of triphosgene gave 260 mg (60%) of **81** contaminated with ~4% of **51** as a colorless solid; mp 204–206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (m, 2H), 2.55 (m, 2H), 3.60 (m, 2H), 4.15 (m, 2H), 4.59 (m, 1H), 7.10 (m, 3H), 7.25 (m, 1H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.2, 49.6, 67.3, 109.5, 110.1, 121.4, 122.4, 128.4, 129.0, 155.5. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.39; H, 6.58; N, 13.01.

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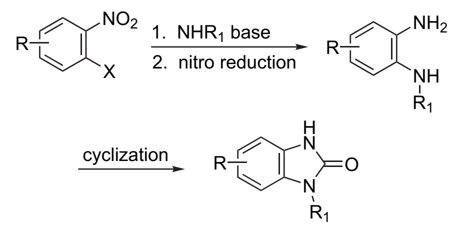
References and notes

1. Preston, R. M. *Chemistry of Heterocyclic Compounds*; Preston, P. M., Ed.; Wiley Interscience: New York, NY, 1980; Vol. 40, Part 2, Chapter 10, pp 531–542.
2. Rémond, G.; Portevin, B.; Bonnet, J.; Cnaet, E.; Regoli, D.; De Nanteuil, G. *Eur. J. Med. Chem.* **1997**, *32*, 843–868.
3. Zuev, D.; Michne, J. A.; Huang, H.; Beno, B. R.; Wu, D.; Gao, Q.; Torrente, J. R.; Xu, C.; Conway, C. M.; Macor, J. E.; Dobowchik, G. M. *Org. Lett.* **2005**, *7*, 2465–2468.
4. Li, Q.; Li, T.; Woods, K. W.; Gu, W.-Z.; Cohen, J.; Stoll, V. S.; Galicia, T.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2918–2922.
5. (a) Dombroski, M. A.; Letavic, M. A.; McClure, K. F.; Barberia, J. T.; Carty, T. J.; Cortina, S. R.; Csiki, C.; Dipesa, A. J.; Elliott, N. C.; Gabel, C. A.; Jordan, C. K.; Labasi, J. M.; Martin, W. H.; Pesse, K. M.; Stock, I. A.; Svensson, L.; Sweeney, F. J.; Yu, C. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 919–923; (b) McClure, K. F.; Abramov, Y. A.; Laird, E. R.; Barberia, J. T.; Cai, W.; Carty, T. J.; Cortina, S. R.; Danley, D. E.; Dipesa, A. J.; Donahue, K. M.; Dombroski, M. A.; Elliot, N. C.; Gabel, C. A.; Han, S.; Hynes, T. R.; LeMotte, P. K.; Mansour, M. N.; Marr, E. S.; Letavic, M. A.;

Pandit, J.; Ripin, D. B.; Sweeney, F. J.; Tan, D.; Tao, Y. *J. Med. Chem.* **2005**, *48*, 5728–5737.
6. Gustin, D. J.; Sehon, C. A.; Wei, J.; Cai, H.; Meduna, S. P.; Khatuya, H.; Sun, S.; Gu, Y.; Jiang, W.; Thurmond, R. L.; Karlsson, L.; Edwards, J. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1687–1691.
7. Tapia, I.; Alonso-Cires, L.; Lópes-Tudanca, P. L.; Mosquera, R.; Labeaga, L.; Innerárity, A.; Orjales, A. *J. Med. Chem.* **1999**, *42*, 2870–2880.
8. (a) Zhang, P.; Terefenko, E. A.; Wrobel, J.; Zhang, Z.; Zhu, Y.; Cohen, J.; Marschke, K. B.; Mais, D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2747–2750; (b) Terefenko, E. A.; Kern, J.; Fensome, A.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3600–3603.
9. (a) Yu, K.-L.; Zhang, Y.; Civiello, R. L.; Trehan, A. K.; Pearce, B. C.; Yin, Z.; Combrink, K. D.; Gulgeze, H. B.; Wang, X. A.; Kadow, K. F.; Cianci, C. W.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1133–1137; (b) Yu, K.-L.; Wang, X. A.; Civiello, R. L.; Trehan, A. K.; Pearce, B. C.; Yin, Z.; Combrink, K. D.; Gulgeze, H. B.; Zhang, Y.; Kadow, K. F.; Cianci, C. W.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Wyde, P. R.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem.* **2006**, *16*, 1115–1122.
10. Guillaume, M. *Org. Process Res. Dev.* **2006**, *10*, 1227–1230 and referenced cited therein.
11. Howard, H. R.; Sarges, R.; Siegel, T. W.; Beyer, T. A. *Eur. J. Med. Chem.* **1992**, *27*, 779–789.
12. (a) Turconi, M.; Nicola, M.; Gil Qunitero, M.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. *J. Med. Chem.* **1990**, *33*, 2101–2108; (b) Flynn, D. L.; Moormann, A. D. U.S. Patent 5,300,512, April 5, 1994; (c) Köppe, H.; Mestrup, A.; Reath, E.-O.; Schromm, K.; Hoefke, W.; Muacevic, C. U.S. Patent 4,381,309, April 26, 1983.
13. Henning, R.; Lattrell, R.; Gerhards, H. J.; Leven, M. *J. Med. Chem.* **1987**, *30*, 814–819.
14. Hara, H.; Maruyama, T.; Saito, M.; Takeuchi, M.; Toshiyasu, M. U.S. Patent 5,162,318, November 10, 1992.
15. (a) McKay, M. C.; Dworetzky, S. I.; Meanwell, N. A.; Olesen, S.-P.; Reinhart, P. H.; Levitan, I. B.; Adelman, J. P.; Gribkoff, V. K. *J. Neurophysiol.* **1994**, *71*, 1873–1882; (b) Gribkoff, V. K.; Champigny, F.; Barbry, P.; Dworetzky, S. I.; Meanwell, N. A.; Lazdunski, M. *J. Biol. Chem.* **1994**, *269*, 10983–10986; (c) Olesen, S.-P.; Munch, E.; Wätjen, F.; Drejer, J. *NeuroReport* **1994**, *5*, 1001–1004; (d) Olesen, S.-P.; Munch, E.; Moldt, P.; Drejer, J. *Eur. J. Pharmacol.* **1994**, *251*, 53–98; (e) See Ref. 2 (f) Baragatti, B.; Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Martinotti, E.; Scartoni, V. *Eur. J. Med. Chem.* **2000**, *35*, 949–955.
16. For an excellent discussion, see: Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; St. Laurent, D. R.; Balasubramanian, N. *J. Org. Chem.* **1995**, *60*, 1565–1582 and references cited therein.
17. This general approach involves nucleophilic displacement of a 2-fluoro(or chloro)-nitrobenzene with an amine or aniline followed by reduction of the nitro group and cyclization to the benzimidazol-2-one ring system. For a few leading references, see Refs. 4,5b,6,7,13. For an approach to benzimidazol-2-thiones employing these general conditions, see: Sato, M.; Arimoto, M.; Ueno, K.; Kojima, H.; Yamasaki, T.; Sakauai, T.; Kasahara, A. *J. Med. Chem.* **1978**, *21*, 1116–1120;



18. (a) Davoll, J.; Laney, D. H. *J. Chem. Soc.* **1960**, 314–318; (b) Rossi, A.; Hunger, A.; Kebrle, J.; Hoffmann, K. *Helv. Chim. Acta* **1960**, *43*, 1298–1313; (c) Rossi, A.; Hunger, A.; Kebrle, J.; Hoffmann, K. *Helv. Chim. Acta* **1960**, *43*, 1046–1056.
19. For additional references, see: (a) De Risi, C.; Pollini, G. P.; Trapella, C.; Peretto, I.; Ronzoni, S.; Giardina, G. A. M. *Bioorg. Med. Chem.* **2001**, *9*, 1871–1877; (b) Barreca, M. L.; Rao, A.; De Luca, L.; Zappalà, M.; Monforte, A.-M.; Maga, G.; Rannecouque, C.; Balzarini, J.; De Clercq, E.; Chimirri, A.; Monforte, P. *J. Med. Chem.* **2005**, *48*, 3433–3437; (c) See Ref 8a.
20. For leading references, see: (a) Xu, X.-J.; Zong, Y.-X. *Tetrahedron Lett.* **2007**, *48*, 129–132; (b) Wang, C.-C.; Li, W.-R. *J. Comb. Chem.* **2004**, *6*, 899–902; (c) Pan, P.-C.; Sun, C.-M. *Tetrahedron Lett.* **1999**, *40*, 6443–6446; (d) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668; (e) Raju, B.; Nguyen, N.; Holland, G. W. *J. Comb. Chem.* **2002**, *4*, 320–328; (f) Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201–204; (g) Yeh, C.-M.; Tung, C.-L.; Sun, C.-M. *J. Comb. Chem.* **2000**, *2*, 341–348; (h) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179–182; (i) Yeh, C.-M.; Sun, C.-M. *Tetrahedron Lett.* **1999**, *40*, 7247–7250; (j) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2000**, *41*, 5419–5422; (k) Lee, B. S.; Makajan, S.; Chapman, B.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 3319–3329.
21. McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311–3314.
22. For additional references, see: (a) Israel, M.; Jones, L. C.; Modest, E. J. *Tetrahedron Lett.* **1968**, *9*, 4811–4814; (b) Israel, M.; Jones, L. C. *J. Heterocycl. Chem.* **1969**, *6*, 735–738; (c) Israel, M.; Jones, L. C. *J. Heterocycl. Chem.* **1971**, *8*, 797–802; (d) Israel, M.; Tinter, S. K.; Trites, D. H.; Modest, E. J. *J. Heterocycl. Chem.* **1970**, *7*, 1029–1035; (e) Israel, M.; Jones, L. C.; Joullié, M. M. *J. Heterocycl. Chem.* **1971**, *8*, 1015–1018; (f) Meth-Cohn, O.; Smith, D. I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 261–268; (g) Van den Branden, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1992**, *48*, 9753–9766; (h) Baens, N. P.; Compernolle, F.; Toppert, S. M.; Hoornaert, G. J. *Tetrahedron* **1993**, *49*, 3193–3202; (i) Rodgers, J. D.; Caldwell, G. W.; Gauthier, A. D. *Tetrahedron Lett.* **1992**, *33*, 3273–3276; (j) Taniguchi, K.; Shigenaga, S.; Ogahara, T.; Fujitsu, T.; Matsuo, M. *Chem. Pharm. Bull.* **1993**, *41*, 301–309.
23. Janssen, P. A. J. U.S. Patent 3,161,645, December 15, 1964.
24. (a) Hazelton, J. C.; Iddon, B.; Redhouse, A. D.; Suschitzky, H. *Tetrahedron* **1995**, *51*, 5597–5608; (b) Hazelton, J. C.; Iddon, B.; Suschitzky, H.; Wolley, L. H. *Tetrahedron* **1995**, *51*, 10771–10794.
25. For leading references, see: (a) Davies, K. E.; Domany, G. E.; Farhat, M.; Herbert, J. A. L.; Jefferson, A. M.; Guttierrez Martin, M. de los A.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2465–2475; (b) Iddon, B.; Robinson, A. G.;

Suschitzky, H. *Synthesis* **1988**, 871–876; (c) Herbert, J. A. L.; Iddon, B.; Robinson, A. G.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 991–997; (d) Hazelton, J. C.; Iddon, B.; Suschitzky, H.; Woolley, L. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 685–691; (e) Iddon, B.; Kutschy, P.; Robinson, A. G.; Suschitzky, H.; Kramer, W.; Neugebauer, F. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3129–3134; (f) Schwoch, S.; Kramer, W.; Neidlein, R.; Suschitzky, H. *Helv. Chim. Acta* **1994**, *77*, 2175–2190.

26. Reddy, G. M.; Prasunamba, P. L.; Reddy, P. S. N. *Tetrahedron Lett.* **1996**, *37*, 3355–3358.
27. For leading references, see: (a) Prakash, G. K.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A. *Org. Lett.* **2007**, *9*, 179–182; (b) Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2006**, *245*, 8–11; (c) Itoh, K.; Hideaki, I.; Chikashita, H. *Chem. Lett.* **1982**, 1117–1118; (d) Smith, J. G.; Ho, I. *Tetrahedron Lett.* **1971**, *12*, 3541–3544.
28. (a) Morales, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, *24*, 135–139; (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193–3195; (c) Wang, Z.-X.; Qin, H.-L. *J. Heterocycl. Chem.* **2005**, *42*, 1001–1005; (d) Varala, R.; Enugala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, 1009–1014 and references cited therein.
29. Poulain, R.; Horvath, D.; Bonnet, B.; Eckhoff, C.; Chapelain, B.; Bodinier, M.-C.; Déprez, B. *J. Med. Chem.* **2001**, *44*, 3378–3390.
30. Sui, Z.; De Voss, J. J.; DeCamp, D. L.; Li, J.; Craik, C. S.; Ortiz de Montellano, P. R. *Synthesis* **1993**, 803–808.
31. Garner, R.; Garner, G. V.; Suschitzky, H. *J. Chem. Soc. C* **1970**, 825–829.
32. Eiden, F.; Schulte, E. *Arch. Pharmacol.* **1976**, *309*, 675–678.
33. Scalzo, M.; Massa, S.; De Martino, G.; Giuliano, R.; Artico, M.; Dolfini, E.; Morasca, L. *Farmaco* **1974**, *39*, 459–472.
34. Obase, H.; Takai, H.; Teranishi, M.; Nobuhiro, N. *J. Heterocycl. Chem.* **1983**, *20*, 565–573.