CONDENSATION OF 2-AMINO-5-CHLOROBENZOXAZOLE WITH α–BROMOKETONES: A MECHANISTIC STUDY

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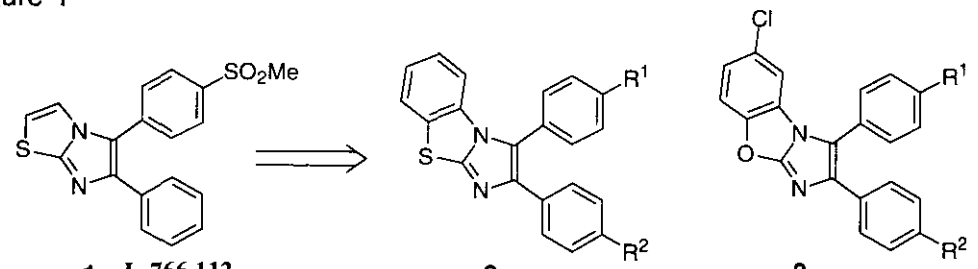
Abstract - The condensation of 2-aminobenzothiazoles with α-bromo ketones produces the fused imidazothiazole (**2**) whereas the analogous reaction with 2-aminobenzoxazoles gives the unexpected carbamate (**10**) or the fused imidazooxazole (**13**), depending on the nature of the starting materials. Isotope labelling studies as well as a proposed mechanism will be discussed.

In a previous paper,[1] we discussed the synthesis and structure-activity relationship for a series of diarylimidazothiazole COX-2 inhibitors as represented by **1** (Figure 1). During the course of that work, we decided to extend the series to include the benzo analogues (**2**) and (**3**).

Figure 1



1 **L-766,112** **2** **3**

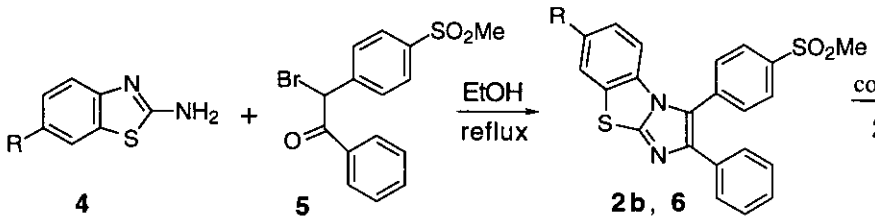
2a,**3a**, R^1=H, R^2= SO_2Me

2b,**3b**, R^1= SO_2Me, R^2=H

Initial results from the condensation of 2-aminobenzothiazole (**4**) with α-bromo ketone (**5**) gave the fused cyclic compound (**6**) , as expected from the literature precedence[2] (Scheme 1). The analogous reaction of 2-amino-5-chlorobenzoxazole (**7**) with **5**, however, was found to give carbamate (**10a**) as confirmed by high resolution mass spectrometry and X-Ray crystallography of its acetate derivative[3] (Figure 2).

Following this observation, we decided to study the condensation of 2-aminobenzoxazole (**7**) with a variety of α-bromo ketones. Werbel and co-workers investigated the condensation of **7** with bromoacetophenone (**11a**) (Scheme 2), and in their hands only the imine salt (**12**) was isolated.[4] However, we found that in refluxing EtOH, **12** was converted to the fused 5,5 system (**13a**) in 18% yield.

Scheme 1



compd	R	time(h)	yield(%)
2b	H	16	30
6	Cl	48	19

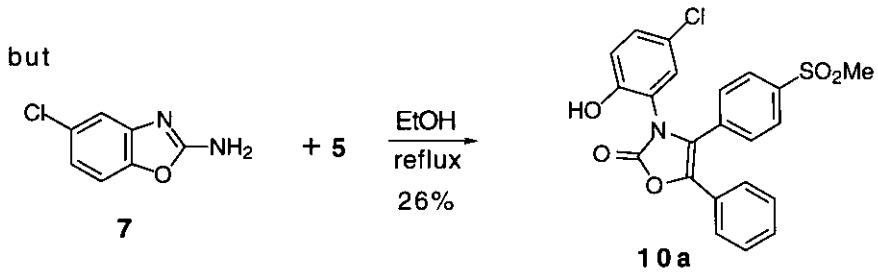
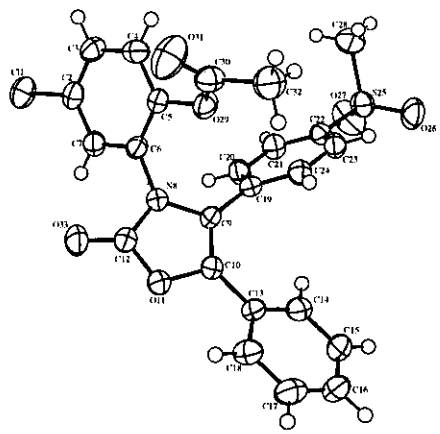
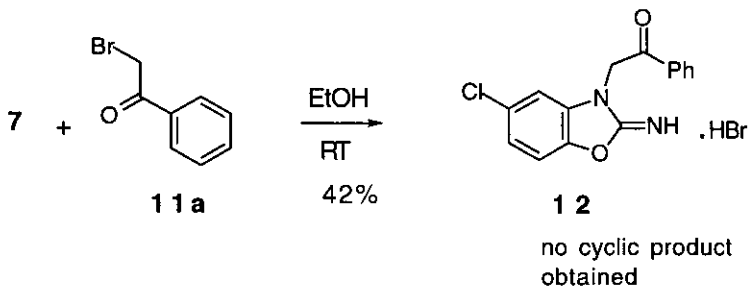


Figure 2 ORTEP perspective view of the acetate of **10a** using 50% thermal ellipsoids for the non-hydrogen atoms.The crystallographic atom-numbering scheme is shown.

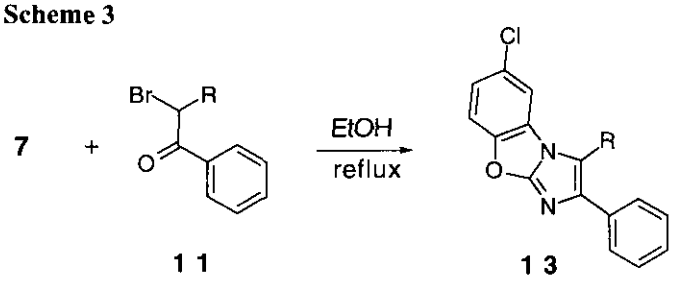


Scheme 2



Further experiments with 2-alkyl substituted acetophenones (Scheme 3) provided only the fused 5,5 system, except when R was isopropyl (**11d**), where no desired product was isolated. The regiochemistry of this reaction was determined by NOE experiments with compound (**13b**) (R=Me).

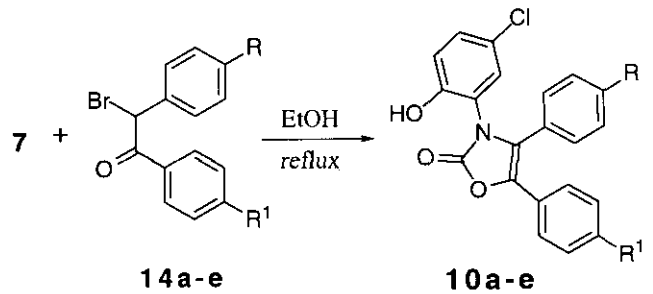
Scheme 3



compd	R	time(h)	yield(%)
13a	H	100	18
13b	Me	16	30
13c	Et	72	14
13d	i-Pr	96	0

These results with the alkyl substituted bromoacetophenones were in contrast with those obtained with aryl substituted acetophenones (Scheme 4), in which case no fused 5,5 product was isolated, giving instead carbamate (**10**). This suggests that a different mechanism is involved for each of the two series.
In both series, no major side-products were isolated. Even though the starting materials were consumed, the low yield appears to result more from the production of very polar baseline material.

Scheme 4

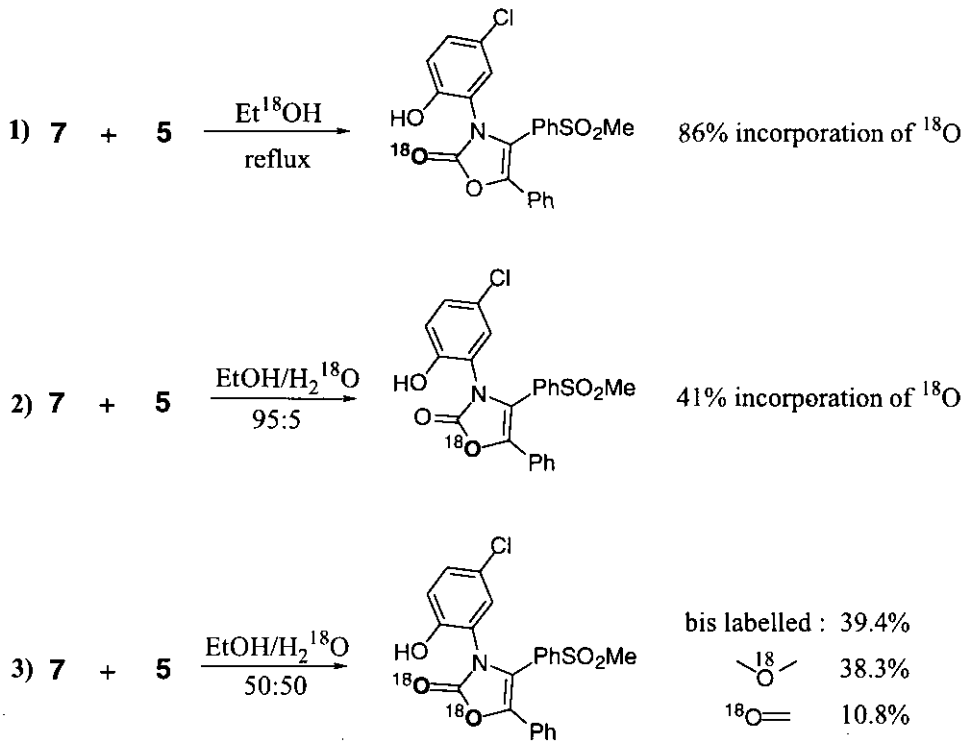


compd	R	R^1	time(h)	yield(%)
10a	SO_2Me	H	16	26
10b	CO_2Me	H	16	13
10c	H	H	16	31
10d	H	SO_2Me	16	24
10e	SMe	H	96	0

In order to determine the source of the extra oxygen, the reaction was carried out in anhydrous EtOH, degassed anhydrous EtOH, and anhydrous acetonitrile. Formation of carbamate (**10a**) was noted in both ethanol experiments, but no reaction took place in the acetonitrile. This led us to conclude that the ethanol must be the source of the extra oxygen, since product formation occurred in the absence of O_2 and H_2O. Experiments were then carried out with ^{18}O labelled solvents[5] to aid in elucidating the mechanism (see Scheme 5).
Using EI mass spectrometry, one of the major fragments observed was the acylium ion $(Ph\text{-}C{\equiv}O)^+$. The measurement of the isotopic ratios of this and other fragments relative to the parent peak allowed us to conclude that in experiment **1)**, labelling occurred at the carbonyl oxygen, with 86% incorporation of ^{18}O . This again pointed to EtOH as being the source of O. To eliminate the possibility that exchange was occurring between $Et^{18}OH$ and trace H_2O to give $H_2{}^{18}O$, experiment **2)** was carried out with EtOH and 5% $H_2{}^{18}O$. Incorporation of ^{18}O occurred in the ring, suggesting that water is exchanging with the bromo ketone or an intermediate ketone species. When the percentage of $H_2{}^{18}O$ was increased to 50% in

experiment **3)** the $H_2{}^{18}O$ was then able to compete with the EtOH as a nucleophile and an appreciable amount of labelling at the carbonyl position was observed.

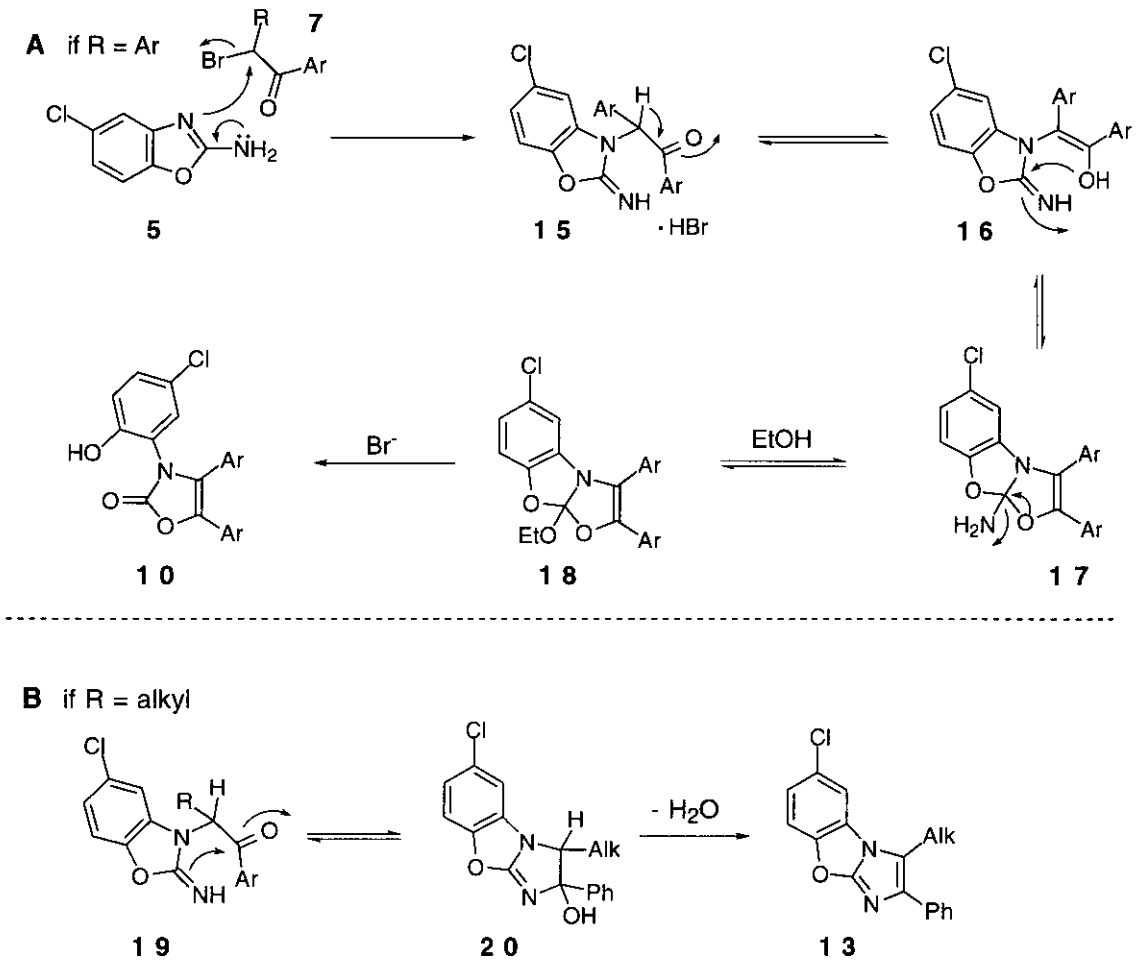
Scheme 5 ^{18}O Labelling experiments



With these results in hand, we proposed a mechanism for the formation of the carbamate, in the case of the diaryl substituted bromo ketones (see Scheme 6). Initial attack of the ring nitrogen of **5** gives ketone (**15**) which undergoes enolization to give the highly conjugated enol ether (**16**). Cyclisation occurs to provide amine (**17**) which is in equilibrium with **18** *via* the oxonium ion. Attack of bromide anion then gives the observed carbamate (**10**). Also shown is a route leading to the formation of the fused imidazyloxazoles in the acetophenone series. In this case, enolization is less favoured, and ring closure occurs on ketone (**19**) to afford alcohol (**20**) which undergoes dehydration to give the observed 5,5 fused system (**13**). In addition, the reduced steric bulk in **20** compared to the analogous diaryl compound should facilitate this dehydration. Based on our results, the diaryl sulfur containing analogues (Figure 1) might have reduced ring strain due to the longer C-S bond, and therefore dehydration *via* pathway **B** would be energetically more favoured compared to the oxygen containing diaryl series (Figure 1).

In conclusion, we have observed that the condensation of 2-amino-5-chlorobenzoxazole with α-bromo ketones provides either the tricyclic system (**13**) or the carbamate (**10**), depending on the nature of the α-bromo ketone. In the case of the carbamate system (**10**), isotope labelling studies with ^{18}O have shown that the extra oxygen incorporated into the ring is from the solvent, ethanol.

Scheme 6 Mechanistic Considerations



EXPERIMENTAL SECTION

2-Amino-5-chlorobenzoxazole (**7**), α-bromoacetophenone (**11a**), desyl bromide (**14c**), 2-aminobenzothiazole and 2-amino-6-chlorobenzothiazole were all purchased from the Aldrich Chemical Company Inc. Solvents enriched in ^{18}O were obtained from CDN ISOTOPES, Pointe Claire, Québec. The HBr salt (**12**),[2] α-bromopropiophenone (**11b**),[6] and α–bromobutyrophenone (**11c**),[6] 2-bromo-1-phenyl-2-(4-methylsulfonylphenyl)ethanone (**14a**),[7] 2-bromo-1-(4-methylsulfonylphenyl)-2-phenylethanone (**14d**),[7] and 2-bromo-1-(4-methylthiophenyl)-2-phenylethanone (**14e**)[7] were all prepared by previously described methods. α-Bromoisovalerophenone (**11d**) was prepared following the procedure described in reference 6.

Typical procedure for the formation of the fused imidazobenzothiazole (2b,6): To a round bottom flask was added 2-amino-5-chlorobenzothiazole (0.200 g, 1.0 mmol), 2-bromo-2-(4-methylsulfonylphenyl)-1-phenylethanone (**5**) (0.323 g, 0.92 mmol) and ethanol (5 mL). The reaction mixture was stirred at reflux for 48 h. The solvent was then removed and the residue was partitioned

between water and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and evaporated. Purification was effected by flash chromatography (1:4 EtOAc:toluene) to yield 74.9 mg (19 %) of a yellow solid, mp>245°C. **7-Chloro-3-(4-methylsulfonylphenyl)-2-phenylbenzo[*d*]imidazo[2,1-*b*][1,3]thiazole (6)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-8.14 (m, 2H), 7.73-7.78 (m, 2H), 7.69 (d, J=2.0 Hz, 1 H), 7.42-7.48 (m, 2H), 7.22-7.29 (m, 5H), 7.18 (dd, J= 8.8, 2.1 Hz, 1H), 6.83 (d, J=8.8 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.42, 113.81, 122.13, 124.24, 126.33, 127.46, 127.75, 128.32, 128.52, 130.46, 131.24, 132.02, 133.22, 135.67, 141.29, 145.11, 148.16; HRMS Calcd for $C_{22}H_{16}N_2O_2ClS_2$ $(M+H)^+$ 439.0342. Found 439.0342.

3-(4-Methylsulfonylphenyl)-2-phenylbenzo[*d*]imidazo[2,1-*b*][1,3]thiazole (2b). mp 230-235 °C (decomp). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.18-8.22 (m, 2H), 7.94-8.00 (m, 3H), 7.51-7.56 (m, 2H), 7.35-7.41 (m, 1H), 7.20-7.31 (m, 4H), 6.96 (d, J=8.5 Hz, 1H), 3.25 (s, 3H). HRMS Calcd for $C_{22}H_{16}N_2O_2S_2$ $(M+H)^+$ 405.07302. Found 405.073147.

Typical procedure for the preparation of the carbamate structure (10): A mixture of 2-amino-5-chlorobenzoxazole (0.300 g, 1.79 mmol), 2-bromo-2-(4-methylsulfonylphenyl)-1-phenylethanone (**1**) (0.524 g, 1.49 mmol) in ethanol (9 mL) was brought to reflux overnight. The solvent was removed and the residue was partitioned between 25% NH_4OAc and EtOAc. The organic layer was then dried over $MgSO_4$, filtered, and evaporated. Purification was effected by flash chromatography (1:50 $MeOH:CH_2Cl_2$) to afford 0.207g (26%) of **3-(5-chloro-2-hydroxyphenyl)-4-(4-methylsulfonylphenyl)-5-phenyl-2,3-dihydro-1,3-oxazol-2-one (10a)** as a beige solid, mp 198-200°C(decomp). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.30 (br s, 1H), 7.93-7.97 (m, 2H), 7.66-7.70 (m, 2H), 7.51 (d, J= 2.6 Hz, 1H), 7.30-7.37 (m, 5H), 7.25 (dd, J=8.8, 2.6 Hz, 1H), 6.93 (d, J=8.8 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 43.91, 118.82, 122.65, 124.22, 124.28, 125.78, 128.11, 128.48, 129.27, 129.61, 130.94, 131.46, 131.74, 133.34, 136.26, 142.88, 153.54, 153.73; *Anal.* Calcd for $C_{22}H_{16}NO_5ClS$: C, 59.86; H, 3.63; N, 3.17. Found: C, 59.48; H, 3.84; N, 3.11; HRMS Calcd for $C_{22}H_{17}NO_5ClS$ $(M+H)^+$ 442.0516, found 442.0516; IR (KBr) 3380, 1765, 1600, 1500 cm^{-1}.

3-(5-Chloro-2-hydroxyphenyl)-4-(4-methoxycarbonylphenyl)-5-phenyl-2,3-dihydro-1,3-oxazol-2-one (10b). mp 220-223 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 9.35 (br s, 1H), 7.99 (d, J= 8.8 Hz, 2H), 7.55 (d, J= 8.8 Hz, 2H), 7.46 (d, J= 2.6 Hz, 1H), 7.28-7.40 (m, 5H), 7.23 (dd, J= 8.8, 2.6 Hz, 1H), 6.91 (d, J= 8.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 52.54, 118.82, 122.89, 124.32, 124.85, 125.60, 128.63, 129.11, 129.58, 130.54, 131.07, 131.24, 131.42, 131.97, 132.84, 135.88, 153.52, 153.92, 166.53; *Anal.* Calcd for $C_{23}H_{16}NO_5Cl$: C, 65.56; H, 3.80; N, 3.32. Found: C, 65.62; H, 3.86; N, 3.29; HRMS Calcd for $C_{23}H_{17}NO_5Cl$ $(M+H)^+$ 442.0795, found 442.0794; IR (KBr) 3600-3000, 1740, 1600, 1500 cm^{-1}; Purified by 1:20 $MeOH:CH_2Cl_2$.

3-(5-Chloro-2-hydroxyphenyl)-4,5-diphenyl-2,3-dihydro-1,3-oxazol-2-one (10c). mp 207-209 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 9.40 (br s, 1H), 7.50-7.15 (complex m, 12 H), 6.90 (d, J= 8.5 Hz, 1H); ^{13}C NMR (75, MHz, acetone-d_6) δ 118.67, 122.45, 122.87, 124.02, 125.08, 128.03, 128.54, 128.83, 129.30, 129.56, 130.39, 130.93, 131.00, 131.12, 135.20, 153.41, 153.99; *Anal.* Calcd for $C_{21}H_{14}NO_3Cl$: C, 69.42; H, 3.86; N, 3.86. Found: C, 69.30; H, 3.86; N, 4.00; HRMS Calcd for $C_{21}H_{15}NO_3Cl$ $(M+H)^+$ 364.0740. Found 364.0740; IR (KBr) 3300, 1740, 1600, 1500 cm^{-1}; Purified by

1:100 MeOH:CH_2Cl_2.

3-(5-Chloro-2-hydroxyphenyl)-5-(4-methylsulfonylphenyl)-4-phenyl-2,3-dihydro-1,3-oxazol-2-one (10d.) mp 240-244 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 9.30 (br s, 1H), 7.83-7.87 (m, 2H), 7.51-7.55 (m, 2H), 7.42-7.51 (m, 6 H), 7.24 (dd, J=8.8, 2.6 Hz, 1H), 6.94 (d, J=8.8 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 44.10, 118.83, 122.54, 124.20, 125.25, 127.50, 128.55, 128.83, 129.94, 130.96, 131.03, 131.10, 131.49, 133.64, 133.83, 140.71, 153.18, 154.04; *Anal.* Calcd for $C_{22}H_{16}NO_5Cl$ $(M+H)^+$ 442.0516. Found 442.0516; IR (KBr) 3320, 1760, 1660, 1600, 1500 cm^{-1}; Purified by 1:50 MeOH:CH_2Cl_2.

Typical procedure for the formation of the fused imidazobenzoxazole (13): To a round bottom flask was added 2-amino-5-chlorobenzoxazole (0.600 g, 3.6 mmol), α-bromopropiophenone (0.636 g, 3.0 mmol) and ethanol (15 mL). The reaction was brought to reflux overnight, and the solvent was then removed under vacuum. The residue was partitioned between 25% NH_4OAc and EtOAc, and the organic layer was then dried over $MgSO_4$, filtered, and evaporated. The crude material was purified by flash chromatography (1:5 EtOAc: hexane) to afford 198 mg (23%) of **6-chloro-3-methyl-2-phenylbenzo[*d*]imidazo[2,1-*b*][1,3]oxazole (13b)** as a pink solid. mp 152-155°C (ethanol); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.92 (d, J= 2.0 Hz, 1H), 7.73-7.78 (m, 2H), 7.76 (d, J= 8.7 Hz, 1H), 7.39-7.46 (m, 3H), 7.26-7.31 (m, 1H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 10.92, 112.40, 114.03, 116.17, 124.69, 127.39, 127.81, 128.77, 129.15, 129.72, 137.53, 139.37, 150.21, 155.04; *Anal.* Calcd for $C_{16}H_{11}N_2OCl$: C, 68.08; H, 3.90; N, 9.93. Found: C, 68.05; H, 3.80; N, 10.06; HRMS Calcd for $C_{16}H_{12}N_2OCl$ $(M+H)^+$ 283.0638. Found 283.0637; IR (KBr) 3380, 1640, 1590, 1490 cm^{-1}; Purified by 1:5 EtOAc:hexane.

6-Chloro-2-phenylbenzo[*d*]imidazo[2,1-*b*][1,3]oxazole (13a). mp 191-193°C (ethanol); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.03 (s, 1H), 7.85-7.92 (m, 3H), 7.70 (d, J= 8.7 Hz, 1H), 7.38-7.45 (m, 3H), 7.25-7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.30, 111.65, 113.35, 124.32, 125.12, 127.35, 127.68, 128.72, 129.65, 133.57, 144.53, 149.25, 156.23; *Anal.* Calcd for $C_{15}H_9N_2OCl$: C, 67.16; H, 3.36; N, 10.45. Found: C, 66.70; H, 3.23; N, 10.37; HRMS Calcd for $C_{15}H_{10}N_2OCl$ $(M+H)^+$ 269.0482. Found 269.0483; IR (KBr) 3420, 1640, 1590, 1490 cm^{-1}; Purified by 1:10 EtOAc:hexane.

6-Chloro-3-ethyl-2-phenylbenzo[*d*]imidazo[2,1-*b*][1,3]oxazole (13c). mp 147-148°C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65-7.73 (m, 2H), 7.39-7.54 (m, 4H), 7.26-7.38 (m, 2H), 3.13 (q, J= 7.7 Hz, 2H), 1.48 (t, J=7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.25, 18.26, 111.16, 113.21, 121.02, 123.86, 127.12, 127.37, 127.70, 128.56, 129.48, 131.01, 134.49, 138.78, 149.32; *Anal.* Calcd for $C_{17}H_{13}N_2OCl$: C, 68.90; H, 4.43; N, 9.46. Found: C, 68.78; H, 4.35; N, 9.37; HRMS Calcd for $C_{17}H_{14}N_2OCl$ $(M+H)^+$ 297.0795. Found 297.0794; IR (KBr disk) 3425, 2970, 2940, 2880, 1635, 1590, 1485 cm^{-1}; Purified by 1:10 EtOAc:hexane.

Typical procedure for the preparation of α-bromo ketones (14): To a solution of methyl 4-(2-oxo-phenylethyl)benzoate (made according to the procedure described in reference 8) (2.00 g, 7.87 mmol) in $CHCl_3$ (12 mL) was added 4 drops of 30% HBr/HOAc at rt. Bromine (0.41 mL, 7.87 mmol) in $CHCl_3$ (3 mL) was then added dropwise to the solution. When the colour of the bromine persisted for several

minutes, the solvent was evaporated and the crude α-bromo ketone was dissolved in ethyl acetate and washed with aqueous 10% sodium sulfite, aqueous 10% K_2CO_3 and finally H_2O. After drying over $MgSO_4$, the solvent was removed and the crude was purified by flash chromatography (1:10 ethyl acetate:hexane) to yield 1.52 g (58%) of **methyl 4-(1-bromo-2-oxo-phenylethyl)benzoate (14b)** as a white solid, mp 59-61°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95-8.10 (m, 4H), 7.41-7.68 (complex m, 5H), 6.39 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ .49.20, 52.05, 128.69, 128.91, 129.07, 129.90, 130.49, 133.73, 133.77, 140.40, 166.14, 190.44. HRMS Calcd for $C_{16}H_{14}O_3Br$ $(M+H)^+$ 333.01256. Found 333.012631

Typical Procedure for ^{18}O Experiments.

To a Reacti-Vial was added aminobenzoxazole (**7**) (10 mg, 0.059 mmol), bromo ketone (**5**) (17 mg, 0.049 mmol), anhydrous EtOH (50 μL), and ^{18}O H_2O(50 μL). The vial was sealed and the mixture was heated for 24 h at 80°C. The solvent was removed under vacuum, and the residue was partitioned between EtOAc and saturated NH_4OAc solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Purification was effected by preparatory TLC (1:50 MeOH:CH_2Cl_2) to give 2 mg of the product which had an identical ^{1}H NMR spectrum to that of **10a**.

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