A New Approach to the Synthesis of 2-Aryl-4-halomethyl-5-methyl-1,3-oxazoles by Highly Regioselective Direct Halogenation with NBS or NCS/MeCN

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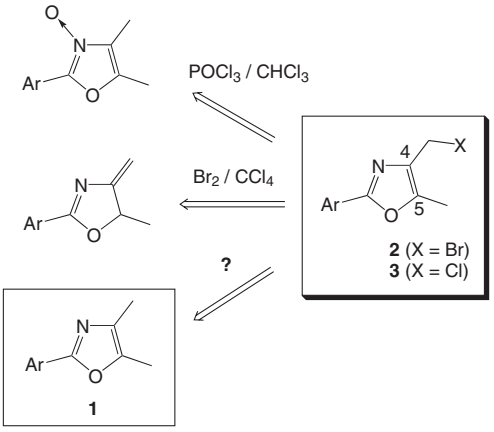
Abstract: A simple and efficient method for the synthesis of 2-aryl-4-bromomethyl-5-methyl-1,3-oxazoles **2** and 2-aryl-4-chloromethyl-5-methyl-1,3-oxazoles **3** is described. The reaction of 2-aryl-4,5-dimethyl-1,3-oxazoles **1** with *N*-bromosuccinimide and *N*-chlorosuccinimide in acetonitrile under mild conditions provides 4-halomethyl isomers with exceptionally high regioselectivity in moderate to good yields.

Key words: oxazoles, halogenation, regioselectivity, heterocycles, drugs

Because of the important pharmacological activity of 1,3-oxazoles (also known simply as oxazoles), general and efficient methods for their preparation are continually being developed and new methods are required to meet the demands to synthesize a wide variety of substituted oxazoles.[1] Among them, 2-aryl-4-halomethyl-5-methyloxazoles **2** and **3** appear as key intermediates in the synthesis of biologically and pharmaceutically useful molecules such as agonists of peroxisome proliferator-activated receptors (PPARs),[2] dipeptidyl peptidase IV (DPP-IV) inhibitors,[3] protein tyrosine phosphatase 1B (PTP1B) inhibitors[4] and 5-lipoxygenase (5-LO) inhibitors.[5]

Despite the versatility of these compounds, only a few methods for the synthesis of **2** and **3** are known (Scheme 1). The most common approach disclosed by Goto et al. involves the use of 2-aryl-4,5-dimethyloxazole *N*-oxides, which upon treatment with $POCl_3$ affords 2-aryl-4-chloromethyl-5-methyloxazoles **3** (77–84% yield). The synthesis of 2-aryl-4,5-dimethyloxazole *N*-oxides was accomplished by the reaction of butane-2,3-dione monoxime with benzaldehyde by bubbling HCl gas in an acetic acid solution (84–90% yield).[6] On the other hand, Overman et al. reported that the bromination of 2-aryl-4-methylene-4,5-dihydrooxazoles, which were synthesized by a two-step sequence from but-3-yn-2-ol (60–90% yield), with bromine furnished **2** (88% yield).[7]

Another technique involves the direct halogenation of 2-aryl-4,5-dimethyloxazoles **1**, however, relatively little attention has been paid to this method. Gompper and Rühle have reported the bromination of 2-aryl-4,5-dimethyloxazoles with bromine in benzene, but it required several steps to afford **2** (33% yield) from 2-aryl-4,5-dimethyloxazoles, the regiochemical outcome of this reaction has not been detailed and it has been reported that the chlorination does not proceed.[8]



Scheme 1 Selected synthetic routes to 2-aryl-4-halomethyl-5-methyloxazoles **2** and **3**

In our pursuit of an efficient method of synthesizing **2** and **3**, we were intrigued with the possibility of the direct halogenation of 2-aryl-4,5-dimethyloxazoles **1**. Previously we have reported the highly C4-methyl regioselective halogenation of 2-aryl-4,5-dimethyl-1,3-thiazoles with NBS or NCS in acetonitrile under mild conditions. The protocol works well with a variety of 2-aryl-4,5-dimethyl-1,3-thiazoles.[9]

As a continuation of our work in this field, we present a general and practical method, which allows a highly C4-methyl regioselective halogenation of readily accessible 2-aryl-4,5-dimethyloxazoles **1**.

The compounds for our studies were a range of 2-aryl-4,5-dimethyloxazoles **1a–l**. These were conveniently prepared in 31–63% yield by esterification of benzoic acids with acetoin using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC-HCl) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in DMF followed by cyclization with NH_4OAc in refluxing acetic acid (Scheme 2).[10,11]

A brief analysis of the reaction conditions for the bromination of **1a** revealed that the reactions with NBS (1.0 equiv) in acetonitrile at 25 °C gave **2a** in a highly regiose-

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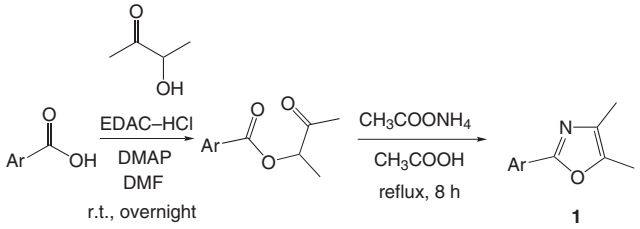
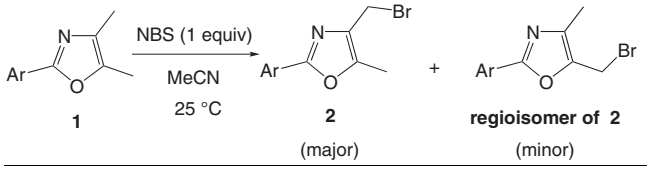


Scheme 2 Preparation of **1**

lective manner[12,13] in 73% yield (Table 1, entry 1). The scope of the reaction was assessed using a structurally diverse set of 2-aryl-4,5-dimethyloxazoles **1b–k**. In all cases, isolation of the product was achieved in a straightforward fashion by adding water to the crude reaction mixture affording precipitates of 2-aryl-4-bromomethyl-5-methyloxazoles **2b–k** in moderate to good yields (Table 1, entry 2–11). The reactions were usually complete within 1–2 hours.

Table 1 Bromination of 2-Aryl-4,5-dimethyloxazoles



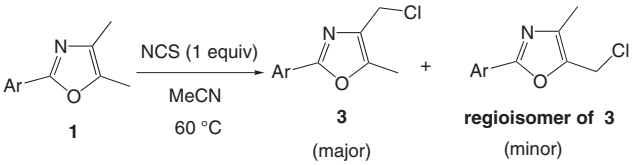
Entry	Substrate (Ar =)	Yield (%)[a]	Regioselectivity (%)[b,c]
1	Ph (**1a**)	73 (**2a**)	>99 (>99)
2	*p*-^{t}BuC$_6$H$_4$ (**1b**)	68 (**2b**)	>99 (>99)
3	*p*-PhC$_6$H$_4$ (**1c**)	70 (**2c**)	>99 (>99)
4	2-naphthyl (**1d**)	71 (**2d**)	>99 (>99)
5	*p*-BrC$_6$H$_4$ (**1e**)	70 (**2e**)	>99 (>99)
6	*p*-ClC$_6$H$_4$ (**1f**)	75 (**2f**)	>99 (>99)
7	*m*-BrC$_6$H$_4$ (**1g**)	78 (**2g**)	98 (98)
8	*m*-ClC$_6$H$_4$ (**1h**)	78 (**2h**)	>99 (>99)
9	3,4-Cl$_2$C$_6$H$_3$ (**1i**)	80 (**2i**)	>99 (>99)
10	2,4-Cl$_2$C$_6$H$_3$ (**1j**)	65 (**2j**)	>99 (>99)
11	*p*-CF$_3$C$_6$H$_4$ (**1k**)	64 (**2k**)	>99 (>99)

[a] Yields refer to single runs and are given for isolated products.
[b] Regioselectivity was determined for isolated products by a HPLC analysis (YMC Pack-SIL A-002 column with 40:1 *n*-hexane/THF as the mobile phase).
[c] Regioselectivity in crude reaction mixtures determined by a HPLC analysis (the same conditions for isolated products) is shown in parentheses.

The regioselectivity of not only the isolated compounds but also the crude reaction mixtures was uniformly high, irrespective of the aryl substituents present in substrate **1**.

Attention was next turned to the chlorination with NCS. Once again, a successful C4-methyl-selective halogenation of 2-aryl-4,5-dimethyloxazole **1a** was achieved using NCS (1 equiv) in acetonitrile at 60 °C and the compound was isolated directly as a crystalline solid of **3a** in 64% yield by just adding water to the reaction mixture (Table 2, entry 1). Similarly, the regioselectivity of the crude reaction mixture as well as the isolated product was also considerably high. As expected, the synthesis worked well for a variety of aryl groups. The chlorides **3b–l** were also isolated with high regioselectivity and moderate to good yield (Table 2, entry 2–12). The reactions were usually complete within 4–8 hours.

Table 2 Chlorination of 2-Aryl-4,5-dimethyloxazoles

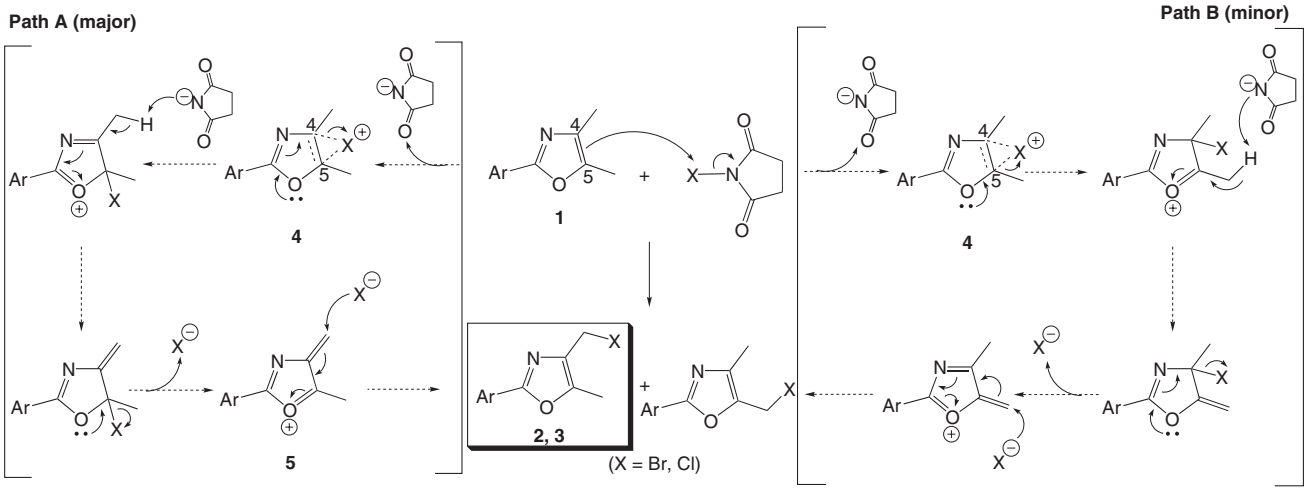


Entry	Substrate (Ar =)	Yield (%)[a]	Regioselectivity (%)[b,c]
1	Ph (**1a**)	64 (**3a**)	>99 (>99)
2	*p*-^{t}BuC$_6$H$_4$ (**1b**)	68 (**3b**)	>99 (>99)
3	*p*-PhC$_6$H$_4$ (**1c**)	47 (**3c**)	>99 (97)
4	2-naphthyl (**1d**)	71 (**3d**)	98 (98)
5	*p*-BrC$_6$H$_4$ (**1e**)	76 (**3e**)	97 (97)
6	*p*-ClC$_6$H$_4$ (**1f**)	63 (**3f**)	>99 (>99)
7	*m*-BrC$_6$H$_4$ (**1g**)	52 (**3g**)	>99 (>99)
8	*m*-ClC$_6$H$_4$ (**1h**)	57 (**3h**)	>99 (>99)
9	3,4-Cl$_2$C$_6$H$_3$ (**1i**)	45 (**3i**)	>99 (>99)
10	2,4-Cl$_2$C$_6$H$_3$ (**1j**)	70 (**3j**)	>99 (>99)
11	*p*-CF$_3$C$_6$H$_4$ (**1k**)	54 (**3k**)	>99 (>99)
12	3,4,5-(MeO)$_3$C$_6$H$_2$ (**1l**)	48 (**3l**)	>99 (>99)

[a] Yields refer to single runs and are given for isolated products expect for entry 8 (recrystallized from MeCN–H$_2$O).
[b] Regioselectivity was determined for isolated products by a HPLC analysis (YMC Pack-SIL A-002 column with 40:1 *n*-hexane/THF as the mobile phase).
[c] Regioselectivity in crude reaction mixtures determined by a HPLC analysis (the same conditions for isolated products) is shown in parentheses.

Although the reactions required a higher temperature (60 °C) and longer reaction time (4–8 h) than the bromination (25 °C, 1–2 h), identical reactivity trends as for the bromination were observed.

A plausible explanation of the regioselective halogenation is depicted in Scheme 3. One possibility is that the reaction proceeds via the formation of an addition product **4** to the 4,5-double bond of an oxazole ring.[14]



Scheme 3 Plausible reaction mechanism for the formation of **2** and **3** and their regioisomers

According to this hypothesis, the halogenation occurs at the 4,5-double bond of compound **1** in the first step of the reaction to generate a halonium intermediate **4**, which is much more likely to give a C5-halogenated derivative (Path A) than a C4-halogenated derivative (Path B) via a ring opening reaction of the halonium 3-membered ring. Loss of a proton and a halogen anion and subsequent attack of a halogen anion to a C4 exomethylene site of an oxonium intermediate **5** might furnish the compound **2** or **3** predominantly. However, none of the foregoing intermediates was detected by either a HPLC analysis or ^{1}H NMR spectroscopy.

The facile preparation of **2** and **3** is of interest to synthetic and medicinal chemists. In this paper, we have presented a highly regioselective and efficient method that allows for the synthesis of 2-aryl-4-bromomethyl-5-methyloxazoles **2** and 2-aryl-4-chloromethyl-5-methyloxazoles **3** utilizing the 2-aryl-4,5-dimethyloxazoles **1** readily prepared from aryl carboxylic acid and acetoin. Since this process involves no complicated operation, it should frequently be the method of choice for the preparation of 2-aryl-4-halomethyl-5-methyloxazoles.

Melting points were determined on a Büchi 530 melting point apparatus in open capillaries, and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DPX–300 300 MHz spectrometer at r.t. ^{1}H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from tetramethylsilane as an internal standard, multiplicity, integration and coupling constants spectra (Hz). ^{13}C NMR spectra are reported in ppm (δ) relative to the central line of the triplet for $CDCl_3$ at 77 ppm. All commercial chemicals and solvents used were of reagent grade and were used without further purification.

2-Aryl-4,5-dimethyloxazoles 1; General Procedure

To a solution of aryl carboxylic acid (74.6 mmol) and acetoin (7.23 g, 82.1 mmol) in DMF (× 6.7 v/w of aryl carboxylic acid) was added EDAC-HCl (21.45 g, 111.9 mmol) and DMAP (0.916 g, 7.5 mmol) at r.t. After stirring the reaction mixture overnight at 25 °C, H_2O was added to the mixture. The mixture was extracted with EtOAc, the organic layer was dried (Na_2SO_4) and evaporated in vacuo. To a solution of the residual brown liquid in AcOH (× 6.7 v/w of aryl carboxylic acid) was added NH_4OAc (28.75 g, 0.373 mol) and the mixture was refluxed for 8 h and evaporated in vacuo. H_2O (× 10 v/w of aryl carboxylic acid) was added dropwise at r.t. to give a white to pale yellow precipitation (**1c–l**). The precipitate was filtered, washed with H_2O (× 3 v/w of aryl carboxylic acid) and dried to afford the corresponding 4,5-dimethyl-2-phenyloxazoles **1**. [In the case of **1a** and **1b**, H_2O and EtOAc were added to the evaporated residue. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give brown oil. The residue was purified by column chromatography on silica gel using EtOAc and *n*-hexane (3:7) to give **1a** or **1b** as pale yellow oil.]

Bromides 2; General Procedure

To a solution of 2-aryl-4,5-dimethyl-1,3-oxazole **1** (22.1 mmol) in MeCN (× 10 v/w of **1**) was added NBS (3.93 g, 22.1 mmol) and the reaction mixture was stirred at 25 °C for 1–2 h. To the mixture was added H_2O (× 5–10 v/w of **1**) dropwise at r.t. to give a white to pale yellow precipitation. The mixture was stirred at 0–5 °C for 1 h. The precipitate was filtered and washed with H_2O (× 3 v/w of **1**) to afford the corresponding bromides **2**.

Chlorides 3; General Procedure

To a solution of 2-aryl-4,5-dimethyl-1,3-oxazole **1** (22.1 mmol) in MeCN (× 10 v/w of **1**) was added NCS (2.95 g, 22.1 mmol) and the reaction mixture was stirred at 60 °C for 4–8 h. To the mixture was added H_2O (× 5–10 v/w of **1**) dropwise at r.t. to give a white to pale yellow precipitation. The mixture was stirred at 0–5 °C for 1 h. The precipitate was filtered and washed with H_2O (× 3 v/w of **1**) to afford the corresponding chlorides **3**.

4,5-Dimethyl-2-phenyl-1,3-oxazole (1a)

Yield: 61%; pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.16 (d, 3 H, *J* = 0.6 Hz), 2.31 (d, 3 H, *J* = 0.6 Hz), 7.38–7.45 (m, 3 H), 7.96–7.99 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 9.97, 11.1, 125.8, 127.7, 128.6, 129.6, 131.8, 143.3, 159.0.

LRMS (EI): *m*/*z* = 173 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}NO$: 173.0841; found: 173.0838.

2-(4-*tert*-Butylphenyl)-4,5-dimethyl-1,3-oxazole (1b)

Yield: 63%; pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 2.15 (d, 3 H, *J* = 0.7 Hz), 2.30 (d, 3 H, *J* = 0.7 Hz), 7.43 (dd, 2 H, *J* = 6.7 Hz, 1.9 Hz), 7.90 (dd, 2 H, *J* = 6.7 Hz, 1.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 31.2, 34.8, 125.1, 125.5, 125.6, 131.6, 143.0, 152.9, 159.2.

LRMS (EI): *m*/*z* = 229 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}NO$: 229.1467; found: 229.1471.

2-Biphenyl-4-yl-4,5-dimethyl-1,3-oxazole (1c)
Yield: 58%; white solid; mp 145–147 °C.

^{1}H NMR ($CDCl_3$): δ = 2.18 (d, 3 H, *J* = 0.8 Hz), 2.33 (d, 3 H, *J* = 0.8 Hz), 7.37–7.48 (m, 3 H), 7.62–7.69 (m, 4 H), 8.05 (dd, 2 H, *J* = 6.7, 1.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.1, 11.3, 126.3, 126.7, 127.0, 127.3, 127.7, 128.8, 132.0, 140.3, 142.3, 143.5, 159.0.

Anal. Calcd for $C_{17}H_{15}NO$ (+1/10 H_2O): C, 81.31; H, 6.10; N, 5.58. Found: C, 81.31; H, 6.05; N, 5.59.

4,5-Dimethyl-2-(2-naphthyl)-1,3-oxazole (1d)
Yield: 58%; pale yellow solid; mp 81–82 °C.

^{1}H NMR ($CDCl_3$): δ = 2.18 (d, 3 H, *J* = 0.8 Hz), 2.32 (d, 3 H, *J* = 0.8 Hz), 7.46–7.51 (m, 2 H), 7.80–7.90 (m, 3 H), 8.07 (dd, 1 H, *J* = 8.6, 0.7 Hz), 8.46 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.1, 11.3, 123.1, 125.1, 125.3, 126.5, 126.8, 127.7, 128.4, 128.5, 132.1, 133.1, 133.8, 143.6, 159.2.

Anal. Calcd for $C_{15}H_{13}NO$ (+1/10 H_2O): C, 80.05; H, 5.91; N, 6.22. Found: C, 80.07; H, 5.87; N, 6.20.

2-(4-Bromophenyl)-4,5-dimethyl-1,3-oxazole (1e)
Yield: 43%; white solid; mp 132–134 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (d, 3 H, *J* = 0.8 Hz), 2.31 (d, 3 H, *J* = 0.8 Hz), 7.55 (dd, 2 H, *J* = 6.8, 1.8 Hz), 7.84 (dd, 2 H, *J* = 6.8, 1.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 123.9, 126.7, 127.2, 131.8, 132.1, 143.7, 158.2.

Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.18; H, 4.00; N, 5.65.

2-(4-Chlorophenyl)-4,5-dimethyl-1,3-oxazole (1f)
Yield: 38%; pale yellow solid; mp 122–124 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.31 (s, 3 H), 7.39 (d, 2 H, *J* = 8.6 Hz), 7.91 (d, 2 H, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 126.3, 127.0, 128.8, 132.1, 135.5, 143.6, 158.1.

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.55; H, 4.81; N, 6.81.

2-(3-Bromophenyl)-4,5-dimethyl-1,3-oxazole (1g)
Yield: 38%; white solid; mp 71–73 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.31 (s, 3 H), 7.28 (t, 1 H, *J* = 8.0 Hz), 7.49–7.53 (m, 1 H), 7.88–7.91 (m, 1 H), 8.13–8.14 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 122.7, 124.2, 128.7, 129.6, 130.1, 132.3, 132.4, 144.0, 157.6.

Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.35; H, 3.96; N, 5.59.

2-(3-Chlorophenyl)-4,5-dimethyl-1,3-oxazole (1h)
Yield: 31%; pale yellow solid; mp 63–65 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (d, 3 H, *J* = 0.8 Hz), 2.32 (d, 3 H, *J* = 0.8 Hz), 7.35–7.36 (m, 2 H), 7.84–7.87 (m, 1 H), 7.97–7.98 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 123.8, 125.8, 129.4, 129.5, 129.9, 132.2, 134.7, 143.9, 157.7.

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.54; H, 4.79; N, 6.80.

2-(3,4-Dichlorophenyl)-4,5-dimethyl-1,3-oxazole (1i)
Yield: 45%; white solid; mp 125–126 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.32 (s, 3 H), 7.49 (d, 1 H, *J* = 8.5 Hz), 7.80 (dd, 1 H, *J* = 2.0, 8.5 Hz), 8.07 (d, 1 H, *J* = 2.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 124.8, 127.5, 127.6, 130.7, 132.5, 133.0, 133.6, 144.2, 156.9.

Anal. Calcd for $C_{11}H_9Cl_2NO$: C, 54.57; H, 3.75; N, 5.79. Found: C, 54.42; H, 3.71; N, 5.81.

2-(2,4-Dichlorophenyl)-4,5-dimethyl-1,3-oxazole (1j)
Yield: 41%; white solid; mp 108–109 °C.

^{1}H NMR ($CDCl_3$): δ = 2.18 (d, 3 H, *J* = 0.7 Hz), 2.33 (d, 3 H, *J* = 0.7 Hz), 7.30 (dd, 1 H, *J* = 8.5, 2.1 Hz), 7.49 (d, 1 H, *J* = 2.1 Hz), 7.89 (d, 1 H, *J* = 8.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.2, 125.2, 127.1, 130.8, 131.2, 132.2, 132.6, 135.6, 144.2, 156.1.

Anal. Calcd for $C_{11}H_9Cl_2NO$: C, 54.57; H, 3.75; N, 5.79. Found: C, 54.35; H, 3.88; N, 6.23.

4,5-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazole (1k)
Yield: 36%; white solid; mp 99–101 °C.

^{1}H NMR ($CDCl_3$): δ = 2.17 (d, 3 H, *J* = 0.6 Hz), 2.33 (d, 3 H, *J* = 0.6 Hz), 7.67 (d, 2 H, *J* = 8.2 Hz), 8.08 (d, 2 H, *J* = 8.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.1, 122.1, 125.6 (q, *J* = 3.8 Hz), 125.7, 125.9, 131.2 (d, *J* = 33 Hz), 132.6, 144.4, 157.7.

Anal. Calcd for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.64; H, 4.12; N, 5.85.

4,5-Dimethyl-2-(3,4,5-trimethoxyphenyl)-1,3-oxazole (1l)
Yield: 53%; white solid; mp 91–93 °C.

^{1}H NMR ($CDCl_3$): δ = 2.15 (d, 3 H, *J* = 0.9 Hz), 2.31 (d, 3 H, *J* = 0.9 Hz), 3.89 (s, 3 H), 3.93 (s, 6 H), 7.22 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.0, 11.1, 56.2, 60.9, 103.1, 123.1, 131.7, 139.6, 143.3, 153.4, 159.0.

Anal. Calcd for $C_{14}H_{17}NO_4$ (+4/3 H_2O): C, 58.53; H, 6.90; N, 4.88. Found: C, 58.64; H, 6.81; N, 4.73.

4-(Bromomethyl)-5-methyl-2-phenyl-1,3-oxazole (2a)
Pale yellow solid; mp 101–103 °C.

^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 4.44 (s, 2 H), 7.40–7.45 (m, 3 H), 7.97–8.01 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.9, 126.2, 127.2, 128.7, 130.2, 133.1, 146.4, 159.9.

Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.40; H, 3.95; N, 5.61.

4-(Bromomethyl)-2-(4-*tert*-butylphenyl)-5-methyl-1,3-oxazole (2b)
White solid; mp 121–123 °C.

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 2.39 (s, 3 H), 4.44 (s, 2 H), 7.45 (dd, 2 H, *J* = 6.7, 1.9 Hz), 7.92 (dd, 2 H, *J* = 6.7, 1.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.9, 31.2, 34.9, 124.4, 125.6, 126.0, 132.9, 146.1, 153.7, 160.1.

Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.54. Found: C, 58.34; H, 5.90; N, 4.59.

2-Biphenyl-4-yl-4-(bromomethyl)-5-methyl-1,3-oxazole (2c)
White solid; mp 125–127 °C.

^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3 H), 4.45 (s, 2 H), 7.34–7.39 (m, 1 H), 7.43–7.48 (m, 2 H), 7.62–7.68 (m, 4 H), 8.06 (d, 2 H, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.9, 24.2, 126.4, 127.1, 127.5, 127.8, 128.2, 129.3, 133.6, 140.6, 143.4, 146.9, 160.2.

Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.18; H, 4.43; N, 4.08.

4-(Bromomethyl)-5-methyl-2-(2-naphthyl)-1,3-oxazole (2d)
Pale yellow solid; mp 118–120 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 4.47 (s, 2 H), 7.50–7.53 (m, 2 H), 7.83–7.92 (m, 3 H), 8.09 (dd, 1 H, *J* = 8.6, 1.7 Hz), 8.49 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.5, 23.8, 123.2, 124.5, 126.0, 126.7, 127.2, 127.8, 128.6, 128.6, 133.0, 133.3, 134.1, 146.6, 160.1.

Anal. Calcd for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64. Found: C, 59.46; H, 4.06; N, 4.67.

4-(Bromomethyl)-2-(4-bromophenyl)-5-methyl-1,3-oxazole (2e)
White solid; mp 116–118 °C.

^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 4.42 (s, 2 H), 7.55–7.58 (m, 2 H), 7.83–7.87 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.5, 124.7, 126.1, 127.6, 131.9, 133.3, 146.7, 159.0.

Anal. Calcd for $C_{11}H_9Br_2NO$: C, 39.91; H, 2.74; N, 4.23. Found: C, 39.86; H, 2.90; N, 4.28.

4-(Bromomethyl)-2-(4-chlorophenyl)-5-methyl-1,3-oxazole (2f)
White solid; mp 98–100 °C.

^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 4.43 (s, 2 H), 7.41 (dd, 2 H, *J* = 6.7, 2.0 Hz), 7.93 (dd, 2 H, *J* = 6.7, 2.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.5, 125.7, 127.4, 129.0, 133.3, 136.3, 146.6, 158.9.

Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.14; H, 3.17; N, 4.95.

4-(Bromomethyl)-2-(3-bromophenyl)-5-methyl-1,3-oxazole (2g)
White solid; mp 102–104 °C.

^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 4.42 (s, 2 H), 7.30 (t, 1 H, *J* = 7.9 Hz), 7.53–7.57 (m, 1 H), 7.90–7.94 (m, 1 H), 8.15–8.16 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.4, 122.8, 124.6, 129.0, 129.1, 130.3, 133.1, 133.4, 146.9, 158.4.

Anal. Calcd for $C_{11}H_9Br_2NO$: C, 39.91; H, 2.74; N, 4.23. Found: C, 39.95; H, 2.75; N, 4.35.

4-(Bromomethyl)-2-(3-chlorophenyl)-5-methyl-1,3-oxazole (2h)
White solid; mp 90–92 °C.

^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3 H), 4.43 (s, 2 H), 7.34–7.42 (m, 2 H), 7.86–7.89 (m, 1 H), 7.99–8.01 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 23.4, 124.2, 126.2, 128.8, 130.0, 130.2, 133.4, 134.9, 146.9, 158.6.

Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.11; H, 3.04; N, 4.97.

4-(Bromomethyl)-2-(3,4-dichlorophenyl)-5-methyl-1,3-oxazole (2i)
White solid; mp 103–105 °C.

^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3 H), 4.42 (s, 2 H), 7.51 (d, 1 H, *J* = 8.4 Hz), 7.82 (dd, 1 H, *J* = 2.0, 8.4 Hz), 8.09 (d, 1 H, *J* = 2.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.5, 23.2, 125.2, 127.0, 127.9, 130.8, 133.2, 133.6, 134.5, 147.1, 157.8.

Anal. Calcd for $C_{11}H_8BrCl_2NO$ (+1/5 H_2O): C, 40.70; H, 2.61; N, 4.32. Found: C, 40.69; H, 2.48; N, 4.40.

4-(Bromomethyl)-2-(2,4-dichlorophenyl)-5-methyl-1,3-oxazole (2j)
White solid; mp 94–96 °C.

^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 4.45 (s, 2 H), 7.32 (dd, 1 H, *J* = 8.5, 2.0 Hz), 7.50 (d, 1 H, *J* = 2.0 Hz), 7.92 (d, 1 H, *J* = 8.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.9, 23.7, 125.1, 127.6, 131.4, 132.0, 133.5, 133.7, 136.8, 147.6, 157.4.

Anal. Calcd for $C_{11}H_8BrCl_2NO$: C, 41.16; H, 2.51; N, 4.36. Found: C, 41.20; H, 2.63; N, 4.44.

4-(Bromomethyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazole (2k)
White solid; mp 106–108 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 4.44 (s, 2 H), 7.69 (d, 2 H, *J* = 8.1 Hz), 8.11 (d, 2 H, *J* = 8.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.5, 23.3, 122.0, 125.7 (q, *J* = 4 Hz), 126.4, 130.3, 131.8 (d, *J* = 33 Hz), 133.7, 147.3, 158.5.

Anal. Calcd for $C_{12}H_9BrF_3NO$: C, 45.03; H, 2.83; N, 4.38. Found: C, 45.11; H, 2.89; N, 4.51.

4-(Chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (3a)
White solid; mp 81–83 °C.

^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3 H), 4.52 (s, 2 H), 7.38–7.42 (m, 3 H), 7.95–8.00 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.1, 37.0, 125.9, 126.9, 128.5, 130.1, 132.6, 146.4, 159.8.

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.20; H, 4.78; N, 6.77.

4-(Chloromethyl)-2-(4-*tert*-butylphenyl)-5-methyl-1,3-oxazole (3b)
White solid; mp 99–101 °C.

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 2.41 (s, 3 H), 4.54 (s, 2 H), 7.45 (d, 2 H, *J* = 8.7 Hz), 7.92 (d, 2 H, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.3, 31.3, 34.9, 37.3, 124.4, 125.6, 126.0, 132.7, 146.2, 153.6, 160.2.

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 67.91; H, 6.78; N, 5.26.

2-Biphenyl-4-yl-4-(chloromethyl)-5-methyl-1,3-oxazole (3c)
Pale yellow solid; mp 108–111 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 4.56 (s, 2 H), 7.37–7.48 (m, 3 H), 7.62–7.68 (m, 4 H), 8.05–8.08 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 37.3, 126.0, 126.6, 127.0, 127.3, 127.8, 128.9, 133.0, 140.1, 142.9, 146.6, 159.9.

Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.90; H, 4.88; N, 5.10.

4-(Chloromethyl)-5-methyl-2-(2-naphthyl)-1,3-oxazole (3d)
Pale yellow solid; mp 105–107 °C.

^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3 H), 4.58 (s, 2 H), 7.50–7.53 (m, 2 H), 7.83–7.93 (m, 3 H), 8.09 (dd, 1 H, *J* = 8.6, 1.7 Hz), 8.50 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 37.3, 123.2, 124.5, 126.0, 126.7, 127.2, 127.8, 128.5, 128.6, 133.0, 133.1, 134.1, 146.7, 160.2.

Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.53; H, 4.56; N, 5.55.

2-(4-Bromophenyl)-4-(chloromethyl)-5-methyl-1,3-oxazole (3e)[2e]
White solid; mp 97–99 °C.

^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 4.54 (s, 2 H), 7.55–7.58 (m, 2 H), 7.85–7.87 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.3, 37.1, 124.7, 126.1, 127.6, 132.0, 133.2, 146.8, 159.1.

Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.13; H, 3.14; N, 5.03.

4-(Chloromethyl)-2-(4-chlorophenyl)-5-methyl-1,3-oxazole (3f)[5]
White solid; mp 90–92 °C.

^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 4.54 (s, 2 H), 7.41 (dd, 2 H, *J* = 6.8, 1.8 Hz), 7.93 (dd, 2 H, *J* = 6.8, 1.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.3, 37.1, 125.7, 127.4, 129.0, 133.1, 136.3, 146.8, 159.1.

Anal. Calcd for $C_{11}H_9Cl_2NO$: C, 54.57; H, 3.75; N, 5.79. Found: C, 54.61; H, 3.78; N, 5.71.

4-(Chloromethyl)-2-(3-bromophenyl)-5-methyl-1,3-oxazole (3g)
White solid; mp 87–89 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 4.54 (s, 2 H), 7.31 (t, 1 H, *J* = 7.9 Hz), 7.54–7.57 (m, 1 H), 7.93 (d, 1 H, *J* = 7.9 Hz), 8.16 (t, 1 H, *J* = 1.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 37.0, 122.8, 124.6, 129.0, 129.1, 130.3, 133.2, 133.2, 147.1, 158.5.

Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89. Found: C, 45.93; H, 3.08; N, 5.09.

4-(Chloromethyl)-2-(3-chlorophenyl)-5-methyl-1,3-oxazole (3h)
White solid; mp 77–79 °C.

^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 4.53 (s, 2 H), 7.33–7.40 (m, 2 H), 7.85–7.89 (m, 1 H), 7.98–8.00 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.3, 37.0, 124.2, 126.2, 128.8, 130.0, 130.2, 133.2, 134.8, 147.0, 158.7.

Anal. Calcd for $C_{11}H_9Cl_2NO$ (+1/5 H_2O): C, 53.77; H, 3.86; N, 5.70. Found: C, 53.91; H, 3.67; N, 5.92.

4-(Chloromethyl)-2-(3,4-dichlorophenyl)-5-methyl-1,3-oxazole (3i)
White solid; mp 85–87 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 4.53 (s, 2 H), 7.51 (d, 1 H, *J* = 8.4 Hz), 7.82 (dd, 1 H, *J* = 1.9, 8.4 Hz), 8.10 (d, 1 H, *J* = 1.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 36.9, 125.2, 127.0, 127.9, 130.8, 133.2, 133.4, 134.5, 147.3, 158.0.

Anal. Calcd for $C_{11}H_8Cl_3NO$: C, 47.77; H, 2.92; N, 5.06. Found: C, 47.54; H, 2.96; N, 5.25.

4-(Chloromethyl)-2-(2,4-dichlorophenyl)-5-methyl-1,3-oxazole (3j)
White solid; mp 95–97 °C.

^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H), 4.57 (s, 2 H), 7.32 (dd, 1 H, *J* = 8.5, 2.1 Hz), 7.50 (d, 1 H, *J* = 2.1 Hz), 7.92 (d, 1 H, *J* = 8.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 37.0, 124.7, 127.2, 130.9, 131.6, 133.1, 133.1, 136.4, 147.4, 157.1.

Anal. Calcd for $C_{11}H_8Cl_3NO$: C, 47.77; H, 2.92; N, 5.06. Found: C, 47.69; H, 2.84; N, 5.12.

4-(Chloromethyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazole (3k)
White solid; mp 90–92 °C (Lit.[4] mp 84–85 °C).

^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H), 4.56 (s, 2 H), 7.70 (d, 2 H, *J* = 8.1 Hz), 8.12 (d, 2 H, *J* = 8.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.4, 37.0, 122.0, 125.7 (q, *J* = 4 Hz), 126.4, 130.3, 131.8 (d, *J* = 33 Hz), 133.5, 147.5, 158.6.

Anal. Calcd for $C_{12}H_9ClF_3NO$: C, 52.29; H, 3.29; N, 5.08. Found: C, 52.03; H, 3.13; N, 5.03.

4-(Chloromethyl)-5-methyl-2-(3,4,5-trimethoxyphenyl)-1,3-oxazole (3l)
White solid; mp 110–112 °C.

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 6 H), 4.55 (s, 2 H), 7.24 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.3, 37.2, 56.3, 60.9, 103.5, 122.6, 132.9, 140.1, 146.5, 153.5, 159.8.

Anal. Calcd for $C_{14}H_{16}ClNO_4$: C, 56.48; H, 5.42; N, 4.70. Found: C, 56.21; H, 5.38; N, 4.72.

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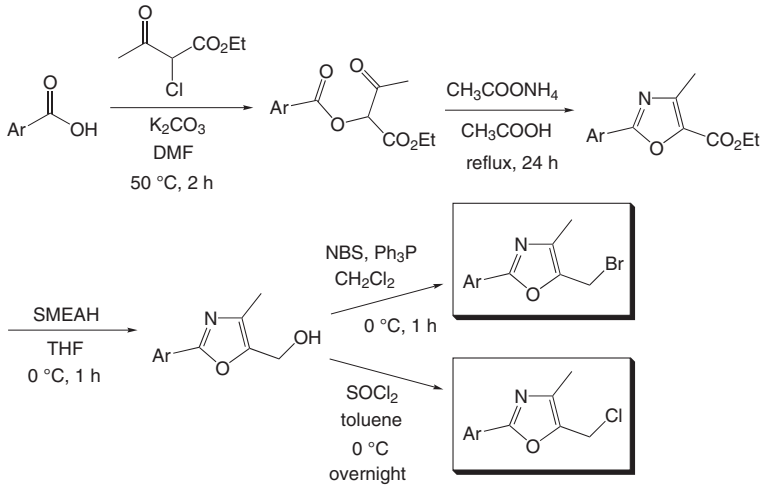
(11) Unoptimized results.

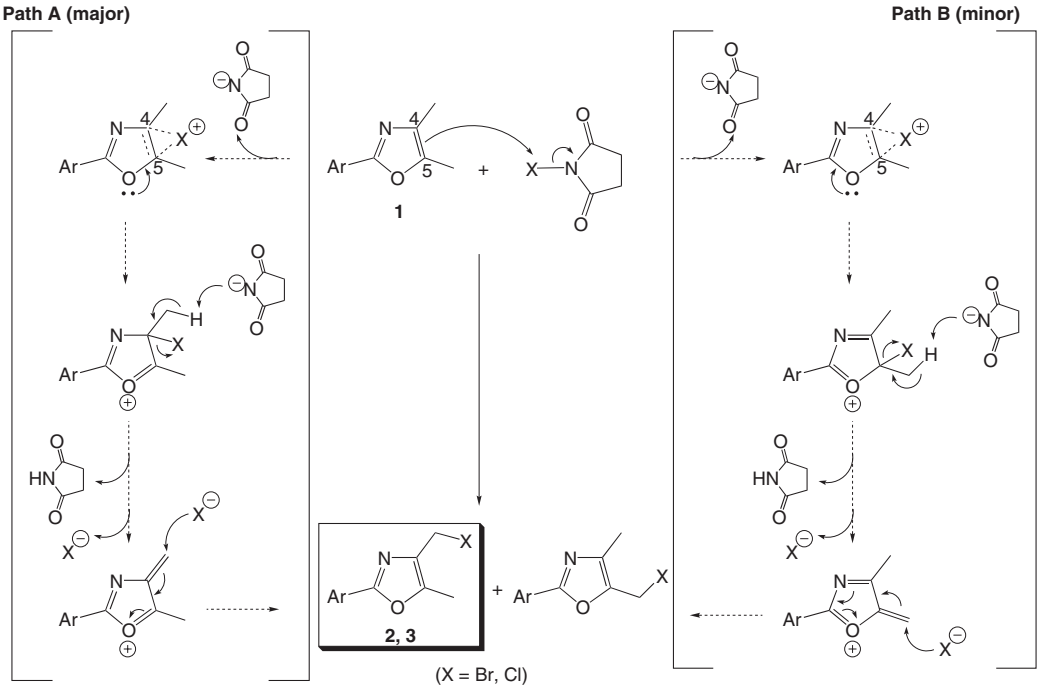
(12) (a) The structures of **2** and **3** were confirmed by synthesizing the 2-aryl-5-halomethyl-4-methyloxazoles (the regioisomers of **2** and **3**) according to a known procedure (Scheme 4) and comparing them with the help of $^{1}H/^{13}C$ NMR spectroscopy and HPLC analysis. Compounds **2** or **3** and their regioisomers are distinguishable clearly by chemical shifts on $^{1}H/^{13}C$ NMR and retention time on a HPLC analysis. (b) See: Fink, C. A.; Firoozina, F. Patent WO 9955723, **1999**; *Chem. Abstr.* **1999**, *131*, 322913. (c) See also: Chao, E. Y.-H.; Haffner, C. D.; Lambert, M. H. III; Maloney, P. R.; Sierra, M. L.; Sternbach, D. D.; Sznaidman, M. L.; Willson, T. M.; Xu, H. E.; Gellibert, F. J. Patent WO 0100603, **2001**; *Chem. Abstr.* **2001**, *134*, 86235; and references cited therein.

(13) The regioselectivity was determined by HPLC analysis (HPLC conditions; YMC Pack-SIL A-002 column with 40:1–10:1 *n*-hexane–THF as the mobile phase). To investigate regioselectivity, we used HPLC with the normal phase, while the 5-halomethyl-4-methyl regioisomers easily decomposed during a HPLC analysis with the reverse phase.

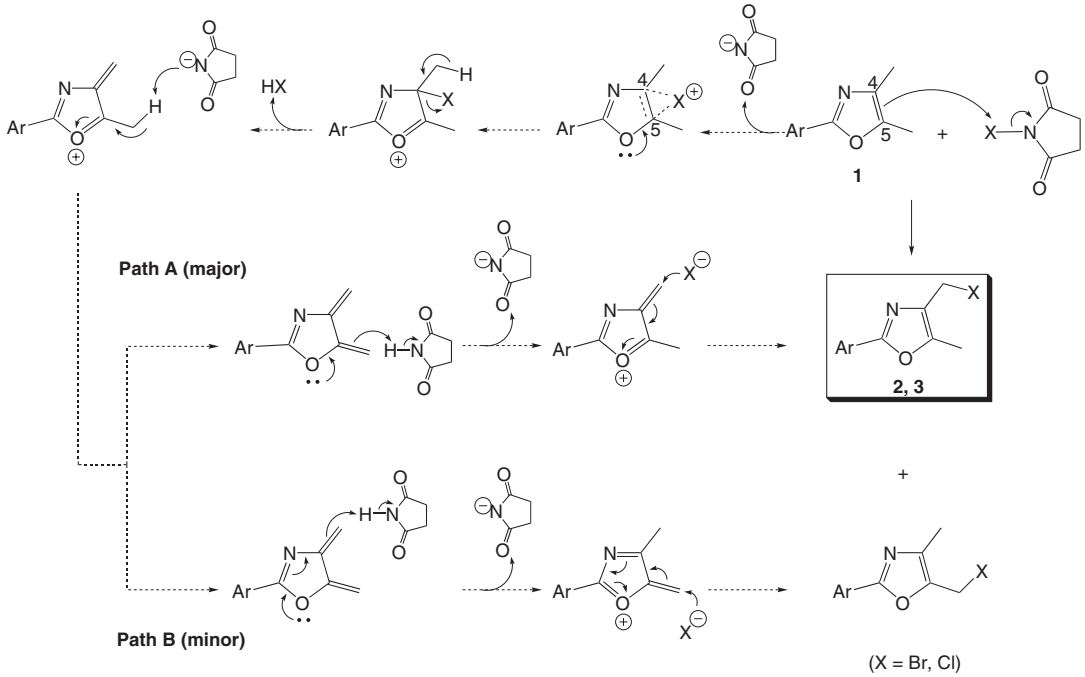
(14) One referee kindly suggested other plausible mechanisms (Schemes 5 and 6).



Scheme 4 Synthesis of regioisomers of **2** and **3**



Scheme 5 Another plausible mechanism for the formation of 2-aryl-4-halomethyl-5-methyl-1,3-oxazoles



Scheme 6 A new mechanism suggested for the formation of 2-aryl-4-halomethyl-5-methyl-1,3-oxazoles