JOC The Journal of Organic Chemistry

Note

Development of a One-Pot Synthetic Method for Multifunctional Oxazole Derivatives Using Isocyanide Dichloride

Takahiro Soeta, Akihiro Matsumoto, Yoko Sakata, and Yutaka Ukaji

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00296 • Publication Date (Web): 12 Apr 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

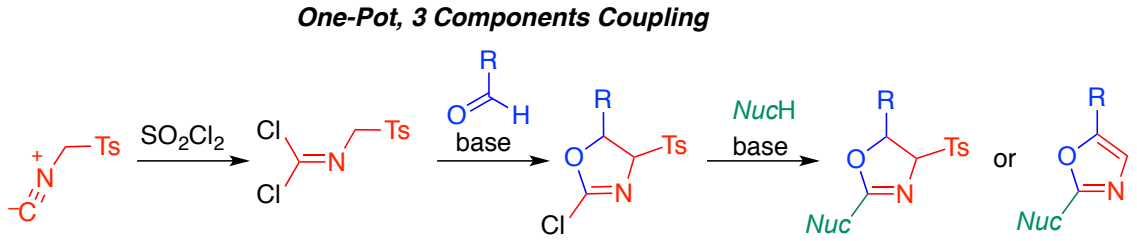
Development of a One-Pot Synthetic Method for Multifunctional Oxazole Derivatives Using Isocyanide Dichloride

Takahiro Soeta*, Akihiro Matsumoto, Yoko Sakata, Yutaka Ukaji*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan.

soeta@se.kanazawa-u.ac.jp; ukaji@staff.kanazawa-u.ac.jp

Abstract

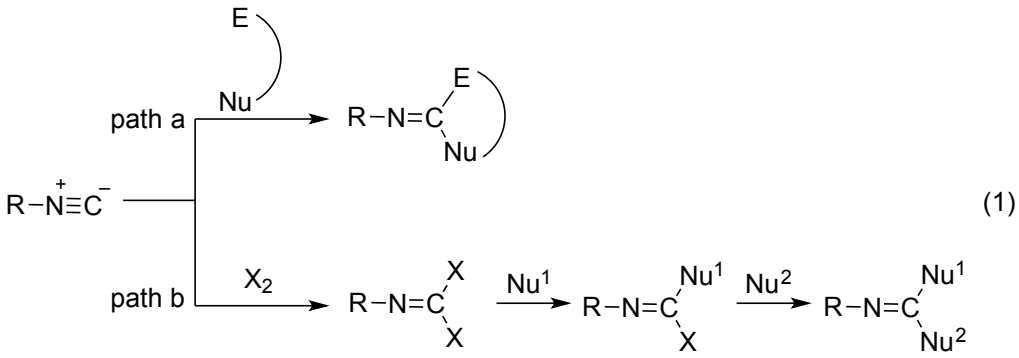


A one-pot synthetic method was developed for multifunctional dihydrooxazole and oxazole derivatives. New reaction sequences were developed involving the formation of isocyanide dichloride, an aldol-type reaction with aldehydes, and a nucleophilic addition-elimination reaction, which efficiently afforded the dihydrooxazole and oxazole scaffolds.

Isocyanides have been found useful as polyfunctional molecules, due to their molecular diversity, in fields such as drug discovery and natural product synthesis.[1] Isocyanide was first synthesized in 1859 by Lieke, in the form of an allyl isocyanide, by alkylation of silver cyanide.[2] These compounds remained laboratory curiosities for decades, as their strong and unpleasant smell discouraged many chemists from working with them. In 1921, a breakthrough achievement by Passerini allowed the use of isocyanide, along with aldehydes and carboxylic acids, to synthesize α-hydroxyamides.[3] After another 40 years, Ugi developed multi-component reactions using isocyanides, aldehydes, amines, and carboxylic acids to afford α-aminoamides.[4] Isocyanides have also been used for their oligo- and polymerization[5] properties, as well as acting as two-electron-donating

ligands in organometallic chemistry.[6] However, the most important application of isocyanides is in the synthesis of versatile heterocycles.[7,8] Zhu and other groups independently developed reactions of α-isocyanoacetamides with aldehydes or imines leading to the corresponding oxazoles, including asymmetric versions.[9] Our research group is involved in extending Ugi-type reactions using 1,n-dipoles (E–Nu), which are composed of an electrophilic moiety (E) and a nucleophilic moiety (Nu), as substrates to afford various types of heterocycle (Eq. 1, path a).[10] We envisioned that isocyanides might be converted to active species which would allow alternative access to heterocycles. Therefore, we focused on the use of isocyanide dihalides, which are relatively stable derivatives readily formed by addition of chlorine or bromine to isocyanides.[11] The existence of the two halogen atoms renders the C=N double bond more reactive toward nucleophiles, with double addition in a sequential manner (Eq. 1, path b). In this work, we demonstrate the use of isocyanide dichloride to afford multifunctional 1,4-dihydrooxazole derivatives from three components in a one-pot reaction.

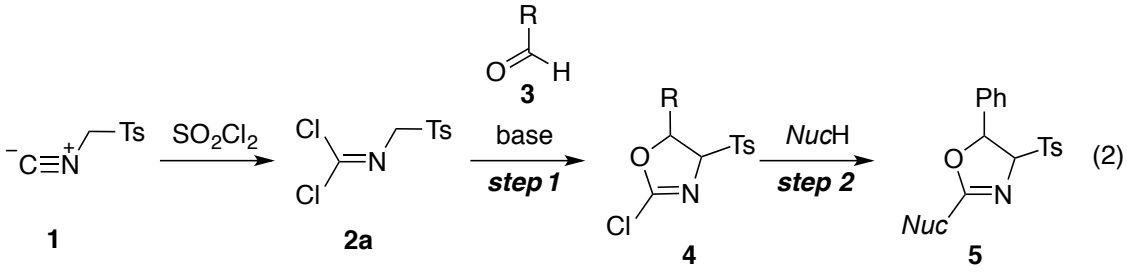
Oxazoles and their derivatives have long attracted attention due to their functionality as chiral ligands for Lewis acids and as building blocks for natural product synthesis, as well as their biological activity.[12] There are many approaches to the synthesis of oxazoles derivatives.[13] Furthermore, dihydrooxazoles can easily be transformed into other functional groups such as carboxylic acids and amines. We sought a strategy that would provide a valuable synthetic method for the preparation of functionalized dihydrooxazoles. The existing method for the synthesis of oxazoles is through dehydration of α-acylaminocarbonyls, as demonstrated by van Leusen[14], Gannesan[15], and Schöllkopf;[16] these strategies have been greatly enriched by the use of isocyanides. General interest in the synthesis and reactivity of dihydrooxazoles is reflected in the extensive works published on this subject over the past few decades.



(1)

We initially examined whether isocyanide dichloride **2**, which was easily prepared from the corresponding 4-toluenesulfonylmethyl isocyanide (TosMIC) (**1a**) with SO_2Cl_2, was capable of participating in an aldol-type reaction with an aldehyde to afford the 2-chloro-4,5-dihydrooxazole derivatives **4** (Eq. 1, step 1).[17] We further investigated the reaction of the resulting 2-chloro-4,5-dihydrooxazole derivatives **4** with a nucleophile to generate the 4,5-dihydrooxazole derivatives **5** in a one-pot operation (Eq. 2, step 2).

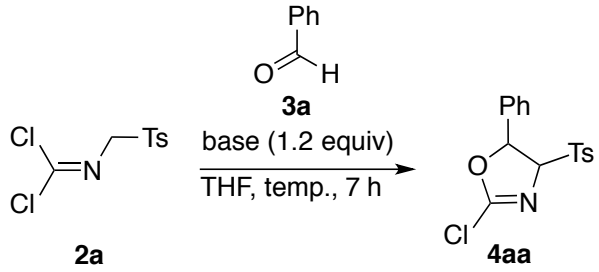
One-Pot?

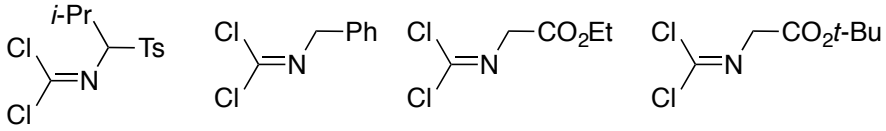


(2)

In our initial studies, we examined the aldol-type reaction of isocyanide dichloride **2a** with benzaldehyde (**3a**) in the presence of LDA as a base using THF as a solvent (Table 1). Fortunately, the reaction proceeded smoothly at room temperature, affording the 2-chloro-4,5-dihydrooxazole **4aa** in 54% yield (Table 1, entry 1). In view of these results, bases other than LDA were evaluated for their ability for an aldol-type reaction in THF (entries 2–4). Thus, with the use of LHMDS, dihydrooxazole **4aa** was obtained in relatively good yield; however, DBU and TBD were not effective in this reaction (entries 3 and 4). A significant increase in yield was observed when 1.2, 1.5, and 2.0 equiv of **2a** were used at –30 °C, and the product **4aa** was isolated in 90%, 85%, and 90% yields, respectively (entry 5–7). Unfortunately, the use of isocyanide dichlorides **2b–2e** resulted in no reaction.

Table 1. Aldol-type reaction of isocyanide dichloride



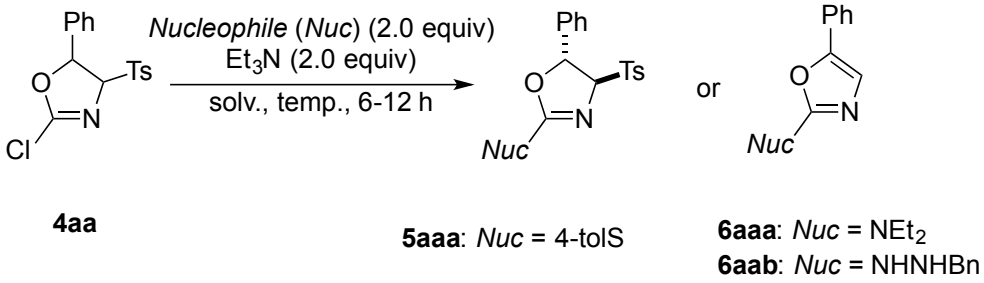


Entry	**2a**/equiv	base	temp.	yield of **4aa**/%
1	1.0	LDA	rt	63
2	1.0	LHMDS	rt	62
3	1.0	DBU	rt	complicated
4	1.0	TBD	rt	40
5	1.2	LDA	–30 °C	90
6	1.5	LDA	–30 °C	85
7	2.0	LDA	–30 °C	90

Next, we set out to evaluate the addition-elimination reaction nucleophiles of various types using 2-chloro-4,5-dihydrooxazole derivatives **4aa**. When 4-toluenethiol (**7a**) was used, the addition-elimination reaction proceeded efficiently to afford the corresponding dihydrooxazole **5aaa** in 95% yield as a single diastereomer. The stereochemistry was determined by X-ray crystallographic analysis of a single crystal of **5aea** (see Table 3, entry 5). However, oxazoles **6** were selectively obtained when the nitrogen nucleophiles

8a and **9** were used (entries 2 and 3). Other nucleophiles such as alcohol, phosphine, and carbanions resulted in no isolable product being obtained (entries 4–8).

Table 2. Results of addition-elimination reaction using various nucleophiles.



4aa

5aaa: *Nuc* = 4-tolS

6aaa: *Nuc* = NEt_2
6aab: *Nuc* = NHNHBn

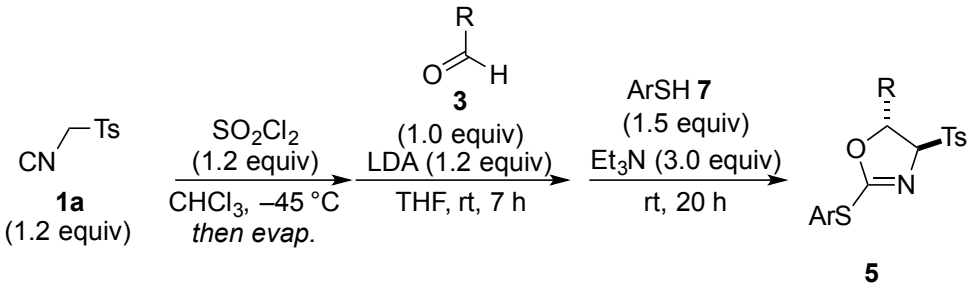
entry	Nucleophile	solv.	temp.	results
1	4-tolSH (**7a**)	CH_2Cl_2	rt	95% (**5aaa**)
2	Et_2NH (**8a**)	THF	rt	96 % (**6aaa**)
3[a]	$BnNHNH_2{\cdot}HCl$ (**9**)	THF	rt	40 % (**6aab**)
4[b]	Guanidine (**10**)	toluene	reflux	complicated
5	MeOH (**11**)	CH_2Cl_2	rt	no reaction
6	Ph_2PH (**12a**)	THF	rt	complicated
7[b]	H_3PO_2 (**12b**)	CH_2Cl_2	rt	no reaction
8[c]	EtMgBr (**13**)	THF	rt to 60 °C	no reaction

[a] 4.0 equiv of Et_3N were used. [b] NaH (2.0 equiv) was used as a base instead of Et_3N. [c] Et_3N was not used.

Having established an efficient method for an aldol-type reaction of isocyanide dichloride **2a** and benzaldehyde (**3a**), followed by an addition-elimination reaction, we

then attempted to expand the range of aldehydes and nucleophiles, particularly in one-pot reactions, as detailed in Table 3. Throughout these experiments, optimal amounts of TosMIC (**1a**) (1.2 equiv), sulfenyl chloride (1.2 equiv), aldehydes **3** (1.0 equiv), LDA (1.2 equiv), thiophenol derivatives **7** (1.5 equiv), and triethylamine (3.0 equiv) were used. The results demonstrate that these conditions allowed the reaction to proceed with a wide variety of aldehydes and thiophenols, and that most reactions were completed smoothly in a one-pot manner. Benzaldehyde (**3a**), 1-naphthaldehyde (**3b**), and 2-naphthaldehyde (**3c**) were found to be good substrates, and the products **5aaa**, **5aba**, and **5aca** were obtained in 95%, 62% and 76% yields (entries 1–3). 4-Tolualdehyde (**3d**) was also a good substrate, and the product **5ada** was obtained in 78% yield (entry 4). We examined substituted aldehydes bearing an electron-withdrawing group at the 2- and 4-position of the phenyl group. The reactions of 4-bromobenzaldehyde (**3e**), 4-chlorobenzaldehyde (**3f**), 2-chlorobenzaldehyde (**3g**) and 4-nitrobenzaldehyde (**3h**) gave the corresponding dihydrooxazolines **5aea**–**5aha** in good yields (entries 5–8). The structure of the product was confirmed by X-ray crystallographic analysis of a single crystal of **5aea**. The reactions of **3i** and **3j**, containing a heterocyclic 2-furyl and a heterocyclic 2-thienyl group, respectively, gave **5aia** and **5aja** in 89% and 69% yields (entries 9 and 10). In the case of cinnamaldehyde (**3k**), the reactivity of the aldol-type reaction was slightly lower, furnishing the corresponding product **5aka** in 48% yield (entry 11). Aliphatic aldehydes **3l**–**3o** were also applicable to this reaction, affording the products in moderate to good yields (entries 12–15). Other aromatic thiols, such as 2-toluenethiol (**7b**), 4-chlorobenzenethiol (**7c**), and thiophenol (**7d**) were also good nucleophiles for the formation of the dihydrooxazoles in good yields (entries 16–18).

Table 3. One-pot synthesis of 3,4-dihydrooxazoles using various aldehydes.



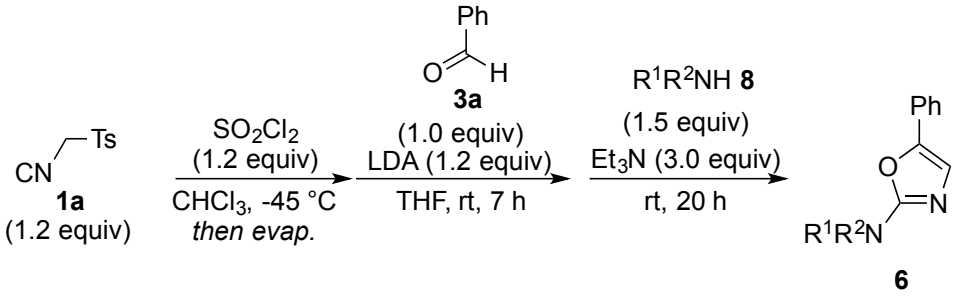
entry	R	Ar	yield/%[a]
1	C_6H_5 (**3a**)	4-tol (**7a**)	95 (**5aaa**)
2	1-naphthyl (**3b**)	4-tol (**7a**)	62 (**5aba**)
3	2-naphthyl (**3c**)	4-tol (**7a**)	76 (**5aca**)
4	4-MeC_6H_4 (**3d**)	4-tol (**7a**)	78 (**5ada**)
5	4-BrC_6H_4 (**3e**)	4-tol (**7a**)	53 (**5aea**)
6	4-ClC_6H_4 (**3f**)	4-tol (**7a**)	69 (**5afa**)
7	2-ClC_6H_4 (**3g**)	4-tol (**7a**)	73 (**5aga**)
8	4-$O_2NC_6H_4$ (**3h**)	4-tol (**7a**)	63 (**5aha**)
9	2-furyl (**3i**)	4-tol (**7a**)	89 (**5aia**)
10	2-thienyl (**3j**)	4-tol (**7a**)	69 (**5aja**)
11	2-phenylethenyl (**3k**)	4-tol (**7a**)	48 (**5aka**)
12	*t*-Bu (**3l**)	4-tol (**7a**)	35 (**5ala**)
13	*i*-Pr (**3m**)	4-tol (**7a**)	81 (**5ama**)
14	*c*-Hex (**3n**)	4-tol (**7a**)	94 (**5ana**)

15	2-phenylethyl (**3o**)	4-tol (**7a**)	59 (**5aoa**)
16	C_6H_5 (**3a**)	2-tol (**7b**)	87 (**5aab**)
17	C_6H_5 (**3a**)	4-ClC_6H_4 (**7c**)	60 (**5aac**)
18	C_6H_5 (**3a**)	C_6H_5 (**7d**)	78 (**5aad**)

[a] The stereochemistries of **5** were assigned as *trans* based on analogous reactions.

Next, we examined amines as nucleophiles for the synthesis of multi-substituted oxazoles **6** (Table 4). Diethylamine (**8a**) and benzylhydrazine (**8b**), which had already been examined (Table 2), proved also to be acceptable substrates in the one-pot reaction (entries 1 and 2). Although the cyclic secondary amines **8c** and **8d** were not effective in this reaction, oxazoles **6aac** and **6aad** were obtained in 20% and 17% yields, respectively (entries 3 and 4). Aniline (**8e**), which is a weaker nucleophile, gave the product **6aae** in 25% yield (entry 5). Benzylamine derivatives **8f**–**8i** were good nucleophiles for this reaction, affording aminoxazoles **6aaf**–**6aai** in moderate to good yields (entries 6–9).

Table 4. One-pot synthesis of oxazoles using various amines



entry	R^1R^2NH/**8**	yield/%
1	Et_2NH (**8a**)	96 (**6aaa**)
2[a]	$BnNHNH_2$ HCl (**8b** = **9**)	39 (**6aab**)
3	piperidine (**8c**)	20 (**6aac**)
4	pyrrolidine (**8d**)	17 (**6aad**)
5	aniline (**8e**)	25 (**6aae**)
6	$BnNH_2$ (**8f**)	65 (**6aaf**)
7	4-$MeOC_6H_4CH_2NH_2$ (**8g**)	87 (**6aag**)
8	2-$MeOC_6H_4CH_2NH_2$ (**8h**)	46 (**6aah**)
9	4-$O_2NC_6H_4CH_2NH_2$ (**8i**)	37 (**6aai**)

[a] 4.0 equiv of Et_3N were used.

Conclusion

In summary, we developed a one-pot synthetic method for multifunctional dihydrooxazole and oxazole derivatives. These included new synthetic sequences involving the formation of isocyanide dichloride, aldol-type reactions of isocyanide dichloride, and nucleophilic addition-elimination reactions, affording the products efficiently in one-pot reactions. Based on these studies, isocyanide dihalides may be considered as isocyanide surrogates suitable for construction of various kinds of multifunctionalized heterocycles with easy operation. Further work is under investigation to extend this work to multifunctionalized heterocycles.

Experimental Section

General Method

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J) and integration. ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (FAB positive, DART) was measured with a quadrupole mass spectrometer and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation.

General procedure

2-Chloro-5-phenyl-4-tosyl-4,5-dihydrooxazole (4aa)

To a solution of the **2a** (0.36 mmol) in THF (1.0 mL), benzaldehyde (**3a**) (0.30 mmol) in THF (2.0 mL) and LDA (0.36 mmol) in THF (3.0 mL) were subsequently added at –30 °C, then the whole was stirred at –30 °C for 7 h. The reaction mixture was filtered through silica gel and the filtrate was concentrated. Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **4aa** (96 mg, 90% yield) as a white solid of mp = 87–90 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.44 (s, 3H), 5.01 (d, J = 5.6 Hz, 1H), 6.22 (d, J = 5.6 Hz, 1H), 7.31–7.44 (m, 7H), 7.83 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.7, 83.2, 91.9, 125.2, 129.3, 129.6, 130.0, 132.6, 136.6, 145.9, 158.7. IR (KBr): 2980, 2250, 1740, 1460, 1370, 1250, 1150 cm^{-1}. HRMS–ESI (*m/z*): Calcd for $C_{16}H_{15}ClNO_3S$ $[M+H]^+$: 336.0461. Found: 336.0456.

To a solution of **1a** (0.36 mmol) in $CHCl_3$ (1.0 mL), SO_2Cl_2 in $CHCl_3$ (1.0 mL) was added dropwise at –45 ℃. The reaction mixture was stirred for 10 min at –45 ℃, then allowed to warm to room temperature. After removing the solvents, **2a** was obtained and was used without further purification. To a solution of the obtained **2a** in THF (1.0 mL), aldehyde **3** (0.30 mmol) in THF (2.0 mL) and LDA (0.36 mmol) in THF (3.0 mL)

were subsequently added at 0 °C, then the whole was stirred for 7 h at room temperature. To the reaction mixture, nucleophile (0.45 mmol) in THF (1.0 mL) and Et_3N (0.90 mmol) were subsequently added and the whole was stirred at room temperature. After 20 h, the reaction mixture was filtered through silica gel and the filtrate was concentrated. The crude product was purified by silica gel column chromatography.

5-Phenyl-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aaa)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aaa** (121 mg, 95% yield) as a white solid of mp = 110–111 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.31 (s, 3H), 2.41 (s, 3H), 4.94 (dd, *J* = 1.6, 4.8 Hz, 1H), 6.11 (d, *J* = 4.8 Hz, 1H), 7.19–7.26 (m, 6H), 7.30–7.37 (m, 3H), 7.50 (d, *J* = 6.4 Hz, 2H), 7.70 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.4, 21.7, 82.1, 93.4, 123.1, 125.2, 129.0, 129.6, 129.7, 130.1, 133.0, 135.0, 137.7, 140.4, 145.3, 172.6. IR (KBr): 2950, 1580, 1490, 1450, 1400, 1320, 1230, 1150, 1090, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{22}NO_3S_2$ $[M+H]^+$: 424.1041. Found: 424.1039.

5-(Naphthalen-1-yl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aba)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aba** (88 mg, 62% yield) as a white solid of mp = 178–179 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H), 2.35 (s, 3H), 4.99 (d, *J* = 4.0 Hz, 1H), 6.79 (d, *J* = 4.0 Hz, 1H), 7.13–7.19 (m, 4H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.45–7.49 (m, 3H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 21.7, 80.4, 92.3, 122.8, 123.1, 123.4, 125.1, 126.2, 127.2, 129.0, 129.4, 129.5, 129.7, 129.8, 130.1, 132.0, 133.3, 133.9, 135.2, 140.4, 145.3, 173.3. IR (KBr): 2920, 1580, 1490, 1400, 1300, 1290, 1230, 1200, 1160, 1080, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{27}H_{24}NO_3S_2$ $[M+H]^+$: 474.1198. Found: 474.1207.

5-(Naphthalen-2-yl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aca)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aca** (108 mg, 76% yield) as a white solid of mp = 147–149 °C (hexane/ethyl acetate). ^{1}H NMR

($CDCl_3$): 2.40 (s, 3H), 2.42 (s, 3H), 5.03 (d, J = 4.4 Hz, 1H), 6.27 (d, J = 4.4 Hz, 1H), 7.22–7.34 (m, 5H), 7.49–7.55 (m, 4H), 7.71–7.86 (m, 6H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 82.3, 93.4, 122.2, 123.2, 124.8, 126.7, 126.8, 127.8, 128.2, 129.3, 129.6, 129.7, 130.1, 132.9, 133.1, 133.4, 134.8, 135.1, 140.4, 145.3, 172.7. IR (KBr): 2940, 1590, 1490, 1380, 1310, 1290, 1230, 1160, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{27}H_{24}NO_3S_2$ $[M+H]^+$: 474.1198. Found: 474.1184.

5-(*p*-Tolyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5ada)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5ada** (106 mg, 78% yield) as a yellow solid of mp = 136–137 °C (hexane/ethyl acetate) ^{1}H NMR ($CDCl_3$): 2.32 (s, 3H), 2.38 (s, 3H), 2.41 (s, 3H), 4.93 (d, J = 4.4 Hz, 1H), 6.06 (s, J = 4.4 Hz, 1H), 7.11–7.26 (m, 8H), 7.49 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H) .^{13}C NMR ($CDCl_3$): 21.2, 21.3, 21.7, 82.2, 93.4, 123.2, 125.3, 129.5, 129.7, 129.8, 130.0, 133.1, 134.7, 135.0, 139.1, 140.3, 145.3, 172.6. IR (KBr): 2920, 1590, 1490, 1450, 1400, 1310, 1230, 1160, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{24}H_{24}NO_3S_2$ $[M+H]^+$: 438.1198. Found: 438.1179.

5-(4-Bromophenyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aea)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aea** (81 mg, 53% yield) as a white solid of mp = 132–133 °C (hexane/ethyl acetate) ^{1}H NMR ($CDCl_3$): 2.37 (s, 3H), 2.41 (s, 3H), 5.04 (d, J = 4.8 Hz, 1H), 6.39 (d, J = 4.8 Hz, 1H), 7.16–7.31 (m, 7H), 7.37–7.39 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 80.2, 92.1, 123.0, 127.4, 128.3, 129.5, 129.7, 130.1, 130.4, 130.6, 132.5, 133.2, 134.3, 135.1, 140.4, 145.3, 172.7. IR (KBr): 2950, 1590, 1490, 1450, 1410, 1310, 1290, 1240, 1150, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{21}BrNO_3S_2$ $[M+H]^+$: 502.0146. Found: 502.0149.

5-(4-Chlorophenyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5afa)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5afa** (95 mg, 69% yield) as a white solid of mp = 147–148 °C (hexane/ethyl acetate) ^{1}H NMR ($CDCl_3$): 2.38 (s, 3H), 2.42 (s, 3H), 4.87 (d, J = 4.8 Hz, 1H), 6.06 (d, J = 4.8 Hz, 1H), 7.18–7.27 (m, 6H), 7.30 (d, J = 8.4 Jz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.4, 21.7, 81.4, 93.4, 123.0, 126.5, 129.3, 129.6, 129.7, 130.1, 132.9,

134.9, 135.0, 136.2, 140.5, 145.5, 172.5. IR (KBr): 2940, 1590, 1490, 1420, 1380, 1230, 1150, 1010 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{21}ClNO_3S_2$ $[M+H]^+$: 458.0651. Found: 458.0639.

5-(2-Chlorophenyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aga)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aga** (103 mg, 73% yield) as a white solid of mp = 123–124 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 2.38 (s, 3H), 2.41 (s, 3H), 5.05 (d, *J* = 4.8 Hz, 1H), 6.39 (d, *J* = 4.8 Hz, 1H), 7.19–7.30 (m, 7H), 7.31–7.39 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 80.2, 92.1, 123.0, 127.4, 128.3, 129.5, 129.7, 130.1, 130.4, 130.6, 132.5, 133.2, 134.3, 135.1, 140.4, 145.3, 172.7. IR (KBr): 2920, 1580, 1490, 1470, 1440, 1400, 1310, 1230, 1150, 1080, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{21}ClNO_3S_2$ $[M+H]^+$: 458.0651. Found: 458.0662.

5-(4-Nitrophenyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aha)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aha** (89 mg, 63% yield) as a white solid of mp = 209–210 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 2.34 (s, 3H), 2.41 (s, 3H), 5.04 (d, *J* = 4.8 Hz, 1H), 6.39 (d, *J* = 4.8 Hz, 1H), 7.17–7.30 (m, 7H), 7.37–7.40 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.4, 21.7, 80.2, 92.2, 123.0, 127.4, 128.3, 129.5, 129.7, 130.1, 130.4, 130.6, 132.6, 133.2, 134.3, 135.1, 140.4, 145.3, 172.7. IR (KBr): 2950, 1580, 1490, 1350, 1230, 1160, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{21}N_2O_5S_2$ $[M+H]^+$: 469.0892. Found: 469.0895.

5-(Furan-2-yl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aia)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aia** (110 mg, 89% yield) as a yellow solid of mp = 129–131 °C (hexane/ethyl acetate) ^1H NMR ($CDCl_3$): 2.32 (s, 3H), 2.36 (s, 3H), 5.18 (d, *J* = 4.8 Hz, 1H), 6.03 (d, *J* = 4.8 Hz, 1H), 6.29–6.30 (m, 1H), 6.40 (d, *J* = 3.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.34 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 75.6, 89.6, 110.7, 110.8, 123.1, 129.5, 129.7, 130.0, 132.8, 134.9, 140.2, 144.2, 145.4, 148.8, 172.1. IR (KBr): 2960, 1580, 1490, 1400, 1300, 1230, 1180, 1150, 1080, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{21}H_{20}NO_4S_2$ $[M+H]^+$: 414.0834. Found:

414.0840.

5-(Thiophen-2-yl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aja)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aja** (89 mg, 69% yield) as a white solid of mp = 133–134 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.38 (s, 3H), 2.42 (s, 3H), 5.10 (d, J = 4.4 Hz, 1H), 6.32 (d, J = 4.4 Hz, 1H), 6.97 (dd, J = 3.2, 5.2 Hz, 1H), 7.08 (d, J = 3.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 1.6, 5.2 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 78.5, 92.9, 123.0, 126.5, 127.0, 127.2, 129.6, 129.7, 130.0, 132.9, 135.0, 139.8, 140.3, 145.4, 172.3. IR (KBr): 2930, 1580, 1490, 1440, 1310, 1250, 1230, 1190, 1150, 1080, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{21}H_{20}NO_3S_3$ $[M+H]^+$: 430.0605. Found: 430.0616.

5-Styryl-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aka)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aka** (65 mg, 48% yield) as a white solid of mp = 130–132 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.38 (s, 3H), 2.42 (s, 3H), 4.89 (d, J = 4.4 Hz, 1H), 5.73–5.76 (m, 1H), 6.10 (dd, J = 7.2, 15.6 Hz, 1H), 6.68 (d, J = 15.6 Hz, 1H), 7.19–7.36 (m, 9H), 7.46 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.4, 21.7, 82.0, 91.3, 123.1, 123.5, 126.9, 128.6, 128.7, 129.6, 129.7, 130.0, 133.1, 134.6, 135.0, 135.1, 140.3, 145.3, 172.4. IR (KBr): 2930, 1590, 1490, 1450, 1400, 1310, 1200, 1150, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{25}H_{24}NO_3S_2$ $[M+H]^+$: 450.1198. Found: 450.1192.

5-(*tert*-Butyl)-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5ala)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5ala** (42 mg, 35% yield) as a white solid of mp = 103–106 °C (hexane/ethyl acetate) ^{1}H NMR ($CDCl_3$): 0.80 (s, 9H), 2.33 (s, 3H), 2.36 (s, 3H), 4.71 (d, J = 4.8 Hz, 1H), 4.77 (d, J = 4.8 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 20.3, 20.7, 23.4, 33.4, 86.3, 88.1, 122.3, 128.5, 128.7, 128.9, 132.3, 134.1, 139.2, 144.1, 171.9. IR (KBr): 2970, 1590, 1490, 1460, 1400, 1310, 1240, 1180, 1160, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{21}H_{26}NO_3S_2$ $[M+H]^+$: 404.1354. Found: 404.1352.

5-Isopropyl-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5ama)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5ama** (95 mg, 81% yield) as a white solid of mp = 106–108 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.92 (d, J = 7.6 Hz, 3H), 0.97 (d, J = 7.6 Hz, 3H), 1.89 (m, 1H), 2.38 (s, 3H), 2.41 (s, 3H), 4.73 (d, J = 4.4 Hz, 1H), 4.94 (dd, J = 4.4, 5.2 Hz, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 16.5, 17.1, 21.3, 21.7, 32.0, 86.3, 88.5, 123.3, 129.5, 129.6, 129.9, 133.2, 135.0, 140.1, 145.1, 172.7. IR (KBr): 2960, 1590, 1490, 1470, 1380, 1300, 1250, 1170, 1150, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{24}NO_3S_2$ $[M+H]^+$: 390.1198. Found: 390.1191.

5-Cyclohexyl-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5ana)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5ana** (121 mg, 94% yield) as a white solid of of mp = 108–109 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.96–1.77 (m, 11H), 2.39 (s, 3H), 2.42 (s, 3H), 4.78 (d, J = 4.4 Hz, 1H), 4.95 (dd, J = 4.4, 6.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 25.4, 25.5, 26.0, 26.9, 27.6, 41.5, 85.7, 88.6, 123.4, 129.4, 129.6, 129.9, 133.2, 135.0, 140.1, 145.1, 172.6. IR (KBr): 2920, 1590, 1490, 1450, 1400, 1380, 1310, 1220, 1170, 1080, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{28}NO_3S_2$ $[M+H]^+$: 430.1511. Found: 430.1502.

5-Phenethyl-2-(*p*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aoa)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **52aoa** (80 mg, 59% yield) as a white solid of mp = 138–140 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.88–1.94 (m, 2H), 2.33 (s, 3H), 2.36 (s, 3H), 2.59–2.64 (m, 2H), 4.68 (d, J = 5.2 Hz, 1H), 5.10 (ddd, J = 1.2, 5.2, 6.4, 1H), 7.07–7.23 (m, 9H), 7.39 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 21.7, 30.5, 36.4, 81.2, 90.6, 123.2, 126.3, 128.4, 128.6, 129.5, 129.6, 129.9, 132.9, 135.0, 140.0, 140.3, 145.2, 172.5. IR (KBr): 2920, 1600, 1490, 1450, 1400, 1310, 1230, 1180, 1160, 1090, 1010 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{25}H_{26}NO_3S_2$ $[M+H]^+$: 452.1354. Found: 452.1336.

5-Phenyl-2-(*o*-tolylthio)-4-tosyl-4,5-dihydrooxazole (5aab)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aab** (111 mg, 87% yield) as a white solid of mp = 94–96 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.40 (s, 3H), 2.52 (s, 3H), 4.92 (d, J = 5.2 Hz, 1H), 6.11 (d, J = 5.2 Hz, 1H), 7.20–7.38 (m, 10H), 7.62 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.1, 21.6, 82.0, 93.5, 125.1, 126.2, 126.7, 129.1, 129.5, 130.7, 130.8, 133.1, 136.6, 137.7, 142.9, 145.3, 171.9. IR (KBr): 2920, 1600, 1490, 1450, 1400, 1380, 1310, 1290, 1230, 1170, 1140, 1080, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{23}H_{22}NO_3S_2$ $[M+H]^+$: 424.1041. Found: 424.1040.

2-((4-Chlorophenyl)thio)-5-phenyl-4-tosyl-4,5-dihydrooxazole (5aac)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aac** (80 mg, 60% yield) as a white solid of mp = 140–142 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.40 (s, 3H), 4.93 (d, J = 5.2 Hz, 1H), 6.14 (d, J = 5.2 Hz, 1H), 7.24–7.39 (m, 9H), 7.56 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.7, 82.3, 93.2, 125.2, 125.3, 129.1, 129.2, 129.4, 129.5, 129.6, 133.1, 136.2, 136.5, 137.5, 145.5, 171.7. IR (KBr): 2970, 1610, 1450, 1400, 1380, 1320, 1220, 1140, 1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{22}H_{19}ClNO_3S_2$ $[M+H]^+$: 444.0495. Found: 444.0490.

5-Phenyl-2-(phenylthio)-4-tosyl-4,5-dihydrooxazole (5aad)

Silica gel column chromatography (hexane/diethyl ether = 6/1) gave **5aad** (98 mg, 78% yield) as a white solid of mp = 116–117 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.41 (s, 3H), 4.93 (d, J = 4.8 Hz, 1H), 6.13 (d, J = 4.8 Hz, 1H), 7.24–7.43 (m, 10H), 7.62–7.65 (m, 2H), 7.70 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.6, 82.1, 93.4, 125.2, 126.8, 129.1, 129.3, 129.5, 129.6, 129.9, 133.1, 135.0, 137.6, 145.3, 172.2. IR (KBr): 2930, 1580, 1490, 1470, 1390, 1320, 1230, 1170, 1150, 1090, 1010 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{22}H_{20}ClNO_3S_2$ $[M+H]^+$: 410.0885. Found: 410.0878.

***N*,*N*-Diethyl-5-phenyloxazol-2-amine (6aaa)**

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aaa** (62 mg, 96% yield) as a brown oil. ^{1}H NMR ($CDCl_3$): 1.18 (t, J = 7.6 Hz, 6H), 3.44 (q, J = 7.6 Hz, 4H), 6.97 (s, 1H), 7.08–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.4, 42.8, 122.3, 126.3, 128.7, 129.0, 144.6, 161.0. IR (KBr): 2970, 1610, 1450, 1450, 1380, 1320, 1220, 1140,

1080, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{17}N_2O$ $[M+H]^+$: 217.1341. Found: 217.1335.

2-(2-Benzylhydrazineyl)-5-phenyloxazole (6aab)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aab** (31 mg, 39% yield) as a white solid of mp = 74–75°C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 4.09 (brs, 1H), 4.69 (s, 2H), 7.03 (s, 1H), 7.16–7.31 (m, 8H), 7.44 (d, J = 7.6 Hz, 2H). NH proton was not appear clearly.^{13}C NMR ($CDCl_3$): 56.9, 122.2, 122.7, 127.0, 127.8, 128.4, 128.5, 128.7, 128.8, 136.4, 146.5, 162.9. IR (KBr): 2920, 1580, 1490, 1450, 1360, 1300, 1220, 1150, 1050, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$: 266.1293. Found: 266.1292.

5-Phenyl-2-(piperidin-1-yl)oxazole (6aac)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aac** (14 mg, 20% yield) as a brown oil. ^1H NMR ($CDCl_3$): 1.34–1.66 (m, 6H), 3.46–3.48 (m, 4H), 6.99 (s, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 24.0, 25.0, 46.7, 122.2, 122.5, 126.5, 128.6, 128.9, 144.8, 161.2. IR (KBr): 2940, 1600, 1490, 1450, 1400, 1300, 1260, 1150, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1341. Found: 229.1336.

5-Phenyl-2-(pyrrolidin-1-yl)oxazole (6aad)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aad** (11 mg, 17% yield) as a brown oil. ^1H NMR ($CDCl_3$): 1.92–1.96 (m, 4H), 3.49–3.53 (m, 4H), 6.99 (s, 1H), 7.11 (t *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 25.6, 47.3, 122.2, 122.3, 126.3, 128.6, 128.9, 144.8, 160.0. IR (KBr): 2970, 1620, 1490, 1460, 1400, 1350, 1300, 1230, 1190, 1140, 1050, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$: 215.1184. Found: 215.1181.

***N*,5-Diphenyloxazol-2-amine (6aae)**

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aae** (18 mg, 25% yield) as a white solid of mp = 170–172 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 1.84 (brs, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.29–7.35 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 117.5,

120.4, 122.8, 123.1, 127.6, 127.9, 128.9, 129.4, 138.0, 145.4. IR (KBr): 2930, 1660, 1590, 1500, 1390, 1300, 1210, 1140, 1050, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$: 237.1028. Found: 237.1025.

***N*,*N*-Dibenzyl-5-phenyloxazol-2-amine (6aaf)**

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aaf** (55 mg, 65% yield) as a white solid of mp = 130–131 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 4.50 (d, J = 4.8 Hz, 2H), 5.41 (brs, 1H), 6.94 (s, 1H), 7.13–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$): 47.3, 121.8, 122.6, 126.7, 127.6, 127.7, 128.6, 128.7, 128.8, 138.1, 145.1, 160.6. IR (KBr): 2950, 1640, 1490, 1450, 1390, 1350, 1300, 1250, 1190, 1160, 1070, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{15}N_2O$ $[M+H]^+$: 251.1184. Found: 251.1178.

2-(4-Methoxybenzyl)-5-phenyloxazole (6aag)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aag** (74 mg, 87% yield) as a white solid of mp = 113–114 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 3.78 (s, 3H), 4.05 (s, 2H), 5.55 (brs, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.03 (s, 1H), 7.20–7.34 (m, 5H), 7.45 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 46.8, 55.3, 114.1, 121.8, 122.6, 126.7, 128.6, 128.7, 129.0, 130.2, 145.0, 159.1, 160.5. IR (KBr): 3010, 2870, 1620, 1510, 1470, 1440, 1370, 1300, 1250, 1150, 1100, 1050, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$: 281.1290. Found: 281.1291.

2-(2-Methoxybenzyl)-5-phenyloxazole (6aah)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aah** (39 mg, 46% yield) as a white solid of mp = 106–107 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 3.86 (s, 3H), 4.54 (d, *J* = 6.0 Hz, 2H), 5.27 (brs, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 7.16–7.35 (m, 5H), 7.44 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 43.5, 55.3, 110.3, 120.6, 121.9, 122.6, 126.2, 126.7, 128.7, 128.8, 129.1, 129.6, 144.9, 157.6, 160.8. IR (KBr): 2940, 1650, 1490, 1460, 1380, 1340, 1280, 1250, 1160, 1120, 1050, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$: 281.1290. Found: 281.1286.

2-(4-Nitrobenzyl)-5-phenyloxazole (6aai)

Silica gel column chromatography (hexane/diethyl ether = 5/1) gave **6aai** (33 mg, 37% yield) as a white solid of mp = 101–103 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$):

4.59 (s, 2H), 6.17 (brs, 1H), 6.89 (s, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H). 8.10 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 46.2, 121.2, 122.6, 123.8, 127.1, 127.9, 128.1, 128.7, 145.4, 145.9, 147.3, 160.1. IR (KBr): 3030, 1620, 1520, 1450, 1400, 1350, 1220, 1150, 1050, 1020 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{14}N_3O_3$ $[M+H]^+$: 296.1035. Found: 296.1031.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Young Scientists (B) (24750037), a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science (24350022), Kanazawa University CHOZEN Project, and Kanazawa University SAKIGAKE.Project.

SUPPORTING INFORMATION Copies of ^{1}H NMR and ^{13}C NMR spectra of products.

REFERENCES:

[1] Ito, Y. *J. Synth. Org. Chem., Jpn*. **2010**, *68*, 1239–1248.

[2] Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316–321.

[3] (a) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140. (b) Passerini, M. *Gazz. Chim. Ital*. **1921**, *51*, 126–129. (c) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181–189.

[4] (a) Ugi, I.; Steinbrückner, C. *Angew. Chem*. **1960**, *72*, 267–268. (b) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem*. **1959**, *71*, 386.

[5] Suginome, M.; Ito, Y. *Adv. Polym. Sci*. **2004**, *171*, 77–136.

[6] (a) Singleton, E.; Oosthuizen, H. E. *Adv. Organomet. Chem.* **1983**, *22*, 209–310. (b)

Treichel, P. M. *Adv. Organomet. Chem*. **1973**, *11*, 21–86. (c) Yamamoto, Y.; Yamazaki, H. *Coord. Chem. Rev.* **1972**, *8*, 225–239.

[7] (a) Lygin, A. V.; Meijere, A. *Angew. Chem., Int. Ed*. **2010**, *49*, 9094–9124. (b) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141–208.

[8] (a) Tokuyama, H.; Fukuyama, T. *Chem. Rec.* **2002**, *2*, 37–45. (b) van Leusen, D.; van Leusen, A. M. *Org. React.* **2001**, *57*, 417–666. (c) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587–7598. (d) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73–84.

[9] (a) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 8396–8399. (b) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2009**, *131*, 8384–8385. (c) Scheffelaar, R.; Paravidino, M.; Muilwijk, D.; Lutz, M.; Spek, A. L.; de Kanter, F. J. J.; Orru, R. V. A.; Ruijter, E. *Org. Lett*. **2009**, *11*, 125–128. (d) Elders, N.; Ruijter, E.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem.-Eur. J*. **2008**, *14*, 4961–4973. (e) Pirali, T.; Tron, G. C.; Masson, G.; Zhu, J. *Org. Lett*. **2007**, *9*, 5275–5278 and references cited therein.

[10] (a) Soeta, T.; Miyamoto, Y.; Fujinami, S.; Ukaji, Y. *Tetrahedron* **2014**, *70*, 6623–6629. (b) Soeta, T.; Tamura, K.; Ukaji, Y. *Org. Lett.* **2012**, *14,* 1226–1229.

[11] (a) El Kaim, L.; Grimaud, L.; Patil, P. *Org. Lett.* **2011**, *13*, 1261–1263. (b) Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem., Int. Ed*. **1969**, *8*, 20–34.

[12] (a) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero,

M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778–4791. (b) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506–9509. (c) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812–6815. (d) For a review of the synthesis of naturally occurring oxazoles, see: Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995–12042. (e) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389–437. (f) Chemistry of Heterocyclic Compounds, Oxazoles: Synthesis, Reactions, and Spectroscopy Parts A & B, Ed. Palmer, D. C. John Wiley & Sons, New York, 2004, vol. 60.

[13] (a) Thalhammer, A.; Mecinović, J.; Schofield, C. J. *Tetrahedron Lett.* **2009**, *50*, 1045–1047. (b) Pulici, M.; Quartieri, F.; Felder, E. R. *J. Comb. Chem.* **2005**, *7*, 463–473. (c) Wipf, P.; Fletcher, J. M.; Scarone, L. *Tetrahedron Lett.* **2005**, *46*, 5463–5466. (d) Robinson, R. *J. Chem. Soc., Trans.* **1909**, *95*, 2167–2174.

[14] (a) van Leusen, D.; van Leusen, A. M. *Org. React*. **2001**, *57*, 417–666. (b) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett*. **1972**, *13*, 2369–2372.

[15] Kulkarni, B. A. Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5637–5638.

[16] (a) Schöllkopf, U.; Schröder, R. *Synthesis* **1972**, 148. (b) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed., Engl.* **1971**, *10*, 333.

[17] Gober, C. M.; Le, H. V.; Ganem, B. *Tetrahedron Lett*. **2012**, *53*, 4536–4537.