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# REDUCTIVE CLEAVAGE OF FUSED ISOXAZOLES WITH CHLOROTRIMETHYLSILANE/SODIUM IODIDE: A CONVENIENT ROUTE TO 3,4-DISUBSTITUTED ISOXAZOLES

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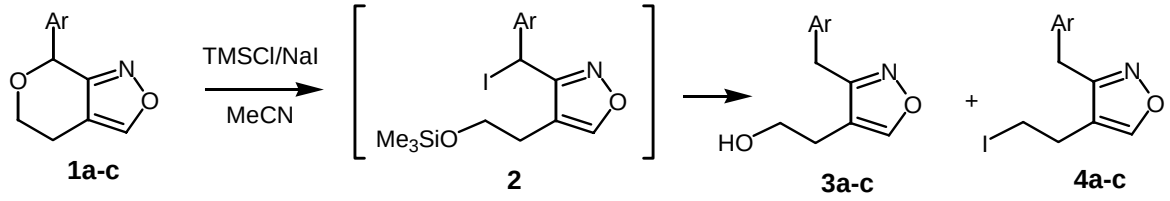
**Abstract** – The reaction of 7-aryl-4,5-dihydro-7*H*-pyrano- and 6-aryl-4*H*,6*H*-furo[3,4-*c*]isoxazoles with a combination of TMSCl/NaI afforded reductively ring cleaved 3,4-disubstituted isoxazoles (**3**, **4**, **6** and **7**). TMSCl/NaI (5/10 equivalents) mediated reductive cleavage of 3,6-disubstituted 4*H*,6*H*-furo[3,4-*c*]isoxazole (**5**) efficiently provided the key intermediates (**6**) and (**7**) leading to new fused isoxazoles, 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (**8**,**9**) *via* further synthetic modification.

The synthesis of isoxazole derivatives with various substituents has garnered many synthetic interests due to their diverse biological activities in pharmaceutical and agricultural areas.[1-3] Originating from the first report by Claisen,[4] the synthetic methods for isoxazoles containing various substituents on the ring are generally classified into two routes such as the condensation reaction of a hydroxylamine with a carbonyl compound and the 1,3-dipolar cycloaddition of a nitrile oxide with an alkyne. These synthetic methods provide easy access to 3,5-disubstitued isoxazoles. Introduction of a substituent at C-4 relied on previously known methods, however, is inconvenient and intermolecular dimerization of nitrile oxides leads undesirably furoxan as a significant byproduct. With such synthetic limits in mind, we reported the selective cleavage of [5,5] or [6,5] fused isoxazoles using boron trihalide for the facile preparation of 3,4-disubstituted isoxazoles.[5] As expanding on methodology for accessing 3,4-disubstitued isoxazoles, we considered a mixture of chlorotrimethylsilane and sodium iodide as an in situ equivalent of iodotrimethylsilane[6] which can cleave C-O bond of allylic or benzylic ether into the corresponding hydroxy and iodo compounds.[7] Herein, we report the first example of reductive cleavage of

4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles and 4*H*,6*H*-furo[3,4-*c*]isoxazole by using a mixture of chlorotrimethylsilane/sodium iodide (TMSCl/NaI) in dry acetonitrile.

To a solution of the corresponding isoxazoles (**1**) or (**5**) (1.0 mmol) and NaI (for specific amounts, see Table 1) in dry MeCN (10 mL) was added TMSCl (for specific amounts, see Table 1). After being refluxed for 24 h, the reaction mixture was diluted with water (10 mL) and was taken up into ether (10 mL x 2). The organic layer was washed successively with sodium thiosulfate solution (10%, 20 mL) and brine, dried ($MgSO_4$) and concentrated. The residue was column chromatographed ($SiO_2$) eluting with a 5:1 mixture of hexane/EtOAc to give ring cleaved isoxazoles (**3**, **4** or **6**, **7**).




Scheme 1

**Table 1.** Cleavage of 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (**1a-c**) with TMSCl/NaI [a]

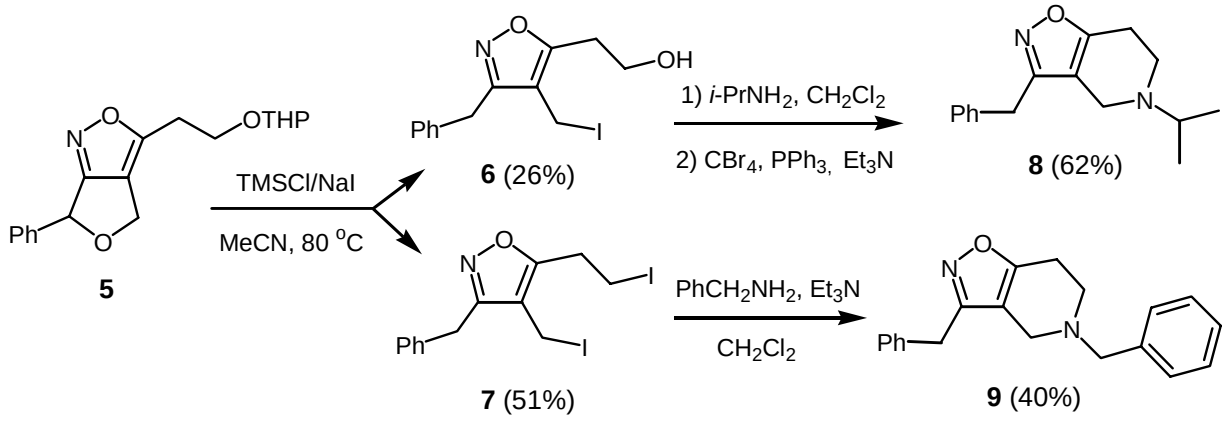
| Entry | Compound | Ar | Ratio of TMSCl/NaI [b] | Product Ratio (%)[c] | | | Isolated Yield (%)[d] |
|---|---|---|---|---|---|---|---|
| | | | | **3** | **4** | **1** | |
| 1 | **1a** | $C_6H_5$ | 5/10 | 10 | 90 | 0 | 10/85/0 |
| 2 | **1b** | 2-$ClC_6H_4$ | 5/10 | 5 | 95 | 0 | 4/87/0 |
| 3 | **1c** | 4-$ClC_6H_4$ | 5/10 | 4 | 96 | 0 | 5/84/0 |
| 4 | **1c** | 4-$ClC_6H_4$ | 5/10[e] | 19 | 77 | 4 | 20/70/4 |
| 5 | **1c** | 4-$ClC_6H_4$ | 2/2 | 33 | 7 | 60 | 27/8/55 |
| 6 | **1c** | 4-$ClC_6H_4$ | 2/3 | 33 | 10 | 57 | 30/8/54 |
| 7 | **1c** | 4-$ClC_6H_4$ | 3/5 | 34 | 22 | 42 | 31/20/40 |
| 8 | **1c** | 4-$ClC_6H_4$ | 5/7 | 35 | 40 | 25 | 31/39/20 |

[a] All the reactions were carried out by heating under reflux in MeCN except in Entry 4. [b] Equivalent amount.
[c] Ratios were determined by $^1$H NMR spectrum before a chromatographic purification. [d] Isolated yields for **3**/**4**/**1**.
[e] The reaction was run at rt.

As expected, 7-aryl substituted 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (**1a-c**)[8] were readily transformed into a 3,4-disubstituted isoxazoles (**3**, **4**) in 90-96% yield (Table 1) and the isoxazole ring was never damaged in the reaction with a mixture of TMSCl and NaI in refluxing MeCN (Scheme 1). Benzylic C-O bond was selectively cleaved to the corresponding hydroxy and iodo compounds. Five/ten equivalent amounts of TMSCl and NaI were required to complete this cleavage reaction as shown in Table 1. The

reaction of **1c** with less than 5/10 amounts of TMSCl/NaI in refluxing MeCN did not complete the reaction leaving starting material (Entry 5-8 in Table 1) and resulting in the lower yields of the hydroxy compound (**3c**) and the iodo compound (**4c**) than that in case of using 5/10 equivalents. But, the same reaction (Entry 3) with 5/10 equivalents of TMSCl/NaI resulted in that no starting material remained and hydroxyisoxazole (**3c**) in 4% yield and iodoisoxazole (**4c**) in 96% yield were produced. Even though the exact mechanistic explanation for the quantitative amounts of TMSCl/NaI used in the reductive cleavages of fused isoxazoles (**1a-c**) was not available, poor solubility of NaI in MeCN was considered as one of the reasons for excess usage. The reaction was dependent on the temperature. When the reaction was allowed to proceed at room temperature, **4c** was obtained in 77% yield along with **3c** in 19% yield even after the prolonged reaction for 3 days (Entry 4 in Table 1). It is presumed that pyranoisoxazole (**1**) is initially cleaved to the intermediate (**2**), of which benzylic carbon is then reduced leading to **3** and **4**. Although some reductive properties[9] are known for a mixture of TMSCl and NaI in MeCN, this is the first example of the reductive cleavage of dihydropyranoisoxazoles to give isoxazole derivatives functionalized at 3,4-positions. By the use of the above reaction condition (TMSCl/NaI = 5/10 molar ratio), dihydropyranoisoxazoles substituted with phenyl or 2-chlorophenyl groups at C-7 (**1a** and **1b**) were also readily cleaved to produce mainly iodo compound (**4a** and **4b**) in more than 90% yields (Table 1).

The same methodology was applied to cleavage of 4*H*,6*H*-furo[3,4-*c*]isoxazole (**5**) that is substituted at C-3 and C-6 positions (Scheme 2). In case of dihydrofuroisoxazole (**5**)[10] substituted with tetrahydropyranyloxy group, as we expected, carbon atom at C-6 was not only reduced but tetrahydropyranyl group was also removed[11] and the corresponding hydroxy- (**6**) and iodo compound (**7**) were produced in 26% and 51% yields, respectively. In this reaction, it seems likely that the hydroxy compound (**6**) is initially formed to be slowly converted into the iodo compound (**7**) under the reaction condition since only hydroxy compound (**6**) was obtained in 73% yield when the same reaction was run at room temperature.




**5** **6** (26%) **7** (51%) **8** (62%) **9** (40%)

Scheme 2

Indeed, the various functionalities of isoxazoles (**3**, **4**, **6**, and **7**) could provide numerous opportunities for further chemical elaboration. As shown in Scheme 2, attempts were made to prepare new 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine derivatives *via* substitution and ring closing reactions. After displacement reaction with isopropyl amine, isoxazole (**6**) was successively treated with a mixture of $CBr_4/Ph_3P$ and with a base such as $Et_3N$ or $K_2CO_3$ to give the corresponding 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (**8**) in 62% overall yield. In addition, the ring closing of diiodoisoxazole (**7**) was achieved by treating with an equimolar amount of benzylamine and $Et_3N$ to deliver the corresponding 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (**9**) in 40% yield.

In summary, we have demonstrated that 7-aryl substituted 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (**1a**-**c**) and 3,6-disubstituted 4*H*,6*H*-furo[3,4-*c*]isoxazoles (**5**), upon treatment with a mixture of TMSCl/NaI in MeCN, are utilized for the preparation of unusual 3,4-disubstituted isoxazoles (**3**,**4**) and 3,4,5-trisubstitued isoxazoles (**6**) and (**7**), respectively. The latter compounds are readily transformed into another fused isoxazoles such as 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridines (**8**) and (**9**) through nucleophilic substitution and ring closing reactions. Therefore, the chemical transformations described in this paper provide easy access to a variety of isoxazoles.

## EXPERIMENTAL

$^1H$ and $^{13}C$ NMR spectra were recorded at 300 and 75 MHz, respectively, on a Varian Unity 300 plus and were obtained in $CDCl_3$. Mass spectral data were obtained on a Shimadzu GCMS-QP5050 (low resolution) and JEOL JMX-DX303 (high resolution) mass spectrometers using the electron impact mode at 70 eV. Column chromatography was performed using Merck Kieselgel 60 (70-230 mesh) as the stationary phase.

**General procedure for cleavage of fused isoxazoles by chlorotrimethylsilane/sodium iodide**. To a solution of the corresponding pyranoisoxazole or furoisoxazole (1.0 mmol) and NaI (for specific amounts, see Table 1) in dry MeCN (10 mL) was added TMSCl (for specific amounts, see Table 1) with good stirring in dry $N_2$ atmosphere. The reaction mixture was then heated under reflux for 24 h. The reaction mixture was cooled to rt and quenched with water (10 mL). Subsequently, the mixture was taken up in ether (10 mL x 2) and washed successively with $Na_2S_2O_3$ solution (10%, 20 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a residue, which was column chromatographed ($SiO_2$) eluting with a 5:1 mixture of hexane/EtOAc.

**3-Benzyl-4-(2-hydroxyethyl)isoxazole (3a).** Oil; $^1H$ NMR δ 1.90 (br s, OH), 2.43 (td, $J$ = 6.3, 0.9 Hz, 2H), 3.56 (t, $J$ = 6.3 Hz, 2H), 4.03 (s, 2H), 7.25 (m, 5H), 8.22 (br s, 1H); $^{13}C$ NMR δ 25.1, 30.9, 61.3,

115.1, 126.8, 128.6, 128.6, 136.5, 156.2, 161.0; MS *m/z* (%): 203 ($M^+$, 13), 174 (10), 156 (14), 144 (18), 130 (12), 91 (100), 77 (6), 65 (30), 41 (20); HRMS calcd for $C_{12}H_{13}NO_2$ ($M^+$) 203.0946, found 203.0947.

**3-(2-Chlorophenyl)methyl-4-(2-hydroxyethyl)isoxazole (3b).** Oil; $^1$H NMR δ 2.59 (m, 3H), 1.61 (br s, OH), 2.51 (td, *J* = 6.3, 0.9 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 4.17 (s, 2H), 7.18 (m, 3H), 7.41 (m, 1H), 8.29 (bs, 1H); $^{13}$C NMR δ 25.1, 28.1, 61.6, 115.1, 127.3, 128.4, 129.6, 130.4, 156.3, 160.4; MS *m/z* (%): 238 ($M^+$+2, 1.9), 236 ($M^+$, 3.5), 127 (36), 125 (100); HRMS calcd for $C_{12}H_{12}NO_2Cl$ ($M^+$) 237.0557, found 237.0559.

**3-(4-Chlorophenyl)methyl-4-(2-hydroxyethyl)isoxazole (3c).** Oil; $^1$H NMR δ 2.44 (dt, *J* = 6.3, 0.6 Hz, 2H), 3.62 (t, *J* = 6.3 Hz, 2H), 4.00 (s, 2H), 7.15 (d, *J* = 6.6 Hz, 2H), 7.29 (d, *J* = 6.6 Hz, 2H), 8.25 (s, 1H); $^{13}$C NMR δ 25.0, 30.3, 61.4, 115.1, 128.8, 129.9, 132.7, 135.0, 156.4, 160.7; MS *m/z* (%): 222 [($M^+$+2)-16, 4.5], 220 ($M^+$-16, 11.3), 127 (44), 125 (100); HRMS calcd for $C_{12}H_{12}NO_2Cl$ ($M^+$) 237.0557, found 237.0560.

**3-Benzyl-4-(2-iodoethyl)isoxazole (4a).** Oil; $^1$H NMR δ 2.76 (t, *J* = 6.9 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 4.03 (s, 2H), 7.26 (m, 5H), 8.25 (s, 1H); $^{13}$C NMR δ 3.1, 26.23, 30.9, 117.1, 126.9, 128.5, 128.7, 136.2, 155.9, 160.4; MS *m/z* (%): 313 ($M^+$, 4.3), 186 ($M^+$-I, 90), 91 (100); HRMS calcd for $C_{12}H_{12}NOI$($M^+$) 312.9964, found 312.9961.

**3-(2-Chlorophenyl)methyl-4-(2-iodoethyl)isoxazole (4b).** Oil; $^1$H NMR δ 2.84 (t, *J* = 7.2, 2H), 3.05 (t, *J* = 7.2, 2H), 4.16 (s, 2H), 7.18 (m, 3H), 7.41 (m, 1H), 8.30 (s, 1H); $^{13}$C NMR δ 3.2, 26.1, 28.0, 117.1, 127.1, 128.5, 129.6, 130.4, 133.7, 134.8, 156.0, 159.7; MS *m/z* (%): 348 ($M^+$+1, 1.2), 312 ($M^+$-Cl, 100), 220 ($M^+$-I, 9.4), 127 (49); HRMS calcd for $C_{12}H_{11}NOClI$ ($M^+$) 346.9574, found 346.9593.

**3-(4-Chlorophenyl)methyl-4-(2-iodoethyl)isoxazole (4c).** Oil; $^1$H NMR δ 2.78 (t, *J* = 7.2 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 8.28 (s, 1H); $^{13}$C NMR δ 2.8, 26.3, 30.3, 111.1, 128.9, 129.9, 132.9, 134.7, 134.7, 156.0, 160.0; MS *m/z* (%): 349 ($M^+$+2, 11), 347 ($M^+$, 33), 222 [($M^+$+2)-I, 34], 220 ($M^+$-I, 100), 125 (83); HRMS calcd for $C_{12}H_{11}NOClI$ ($M^+$) 346.9574, found 346.9583.

**3-Benzyl-4-(iodomethyl)-5-(2-hydroxyethyl)isoxazole (6).** Oil; $^1$H NMR δ 1.87 (br s, OH), 2.96 (t, *J* = 6 Hz, 2H), 3.941 (s, 2H), 3.98 (t, *J* = 6 Hz, 2H), 4.07 (s, 2H), 7.26-7.33 (m, 5H); $^{13}$C NMR δ -9.3, 29.5, 31.3, 59.3, 113.7, 127.1, 128.8, 128.8, 135.6, 161.2, 167.6; MS *m/z* (%): 344 ($M^+$+1, 0.7), 254 (23), 216 (11), 186 (10), 159 (4), 144 (11), 105 (5), 91 (100), 65 (14), 43 (4); HRMS calcd for $C_{13}H_{14}NO_2$ ($M^+$–I) 216.1025, found 216.1029.

**3-Benzyl-4-(iodomethyl)-5-(2-iodoethyl)isoxazole (7).** Oil; $^1$H NMR δ 3.29 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 3.84 (s, 2H), 4.08 (s, 2H), 7.20-7.35 (m, 5H); $^{13}$C NMR δ -10.3, -2.7, 30.2, 31.3, 113.5,

127.1, 128.7, 128.8, 135.6, 161.2, 167.6; MS *m/z* (%): 454 ($M^+$+1, 1.9), 326 (9.9), 198 (1.6), 144 (16), 91 (100), 80 (3), 65 (14), 63 (3); HRMS calcd for $C_{13}H_{13}NOI_2$ ($M^+$-I) 326.0042, found 326.0054.

**3-Benzyl-5-isopropyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (8).** To a solution of **6** (240 mg, 0.7 mmol) in dry $CH_2Cl_2$ (10 mL) was slowly added a solution of *i*-$PrNH_2$ (91 mg, 11.54 mmol) in $CH_2Cl_2$ (5 mL), and the mixture was stirred at rt for 2 h. Water (20 mL) was added and the resulting mixture was extracted with ether (20 mL x 2). The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified using column chromatography ($SiO_2$) eluting with a 3:1 mixture of hexane/EtOAc to afford 3-benzyl-4-[(isopropylamino)methyl]-5-(2-hydroxyethyl)isoxazole, as a brown oil: 150 mg (78%); $^1$H NMR δ 1.20 (d, *J* = 6.6 Hz, 6H), 1.25 (br s, OH), 3.05 (t, *J* = 5.4 Hz, 2H), 3.16 (m, 1H), 3.52 (s, 2H), 3.82 (t, *J* = 5.4 Hz, 2H), 4.29 (s, 2H), 5.97 (br s, NH), 7.30 (m, 5H); $^{13}$C NMR δ 19.88, 29.41, 31.44, 36.90, 50.49, 58.94, 108.86, 127.12, 128.71, 128.90, 136.44, 161.81, 171.54; MS *m/z* (*%*): 273 ($M^+$-1, 0.6), 260 (1.8), 246 (1.2), 229 (23), 214 (5.4), 202 (5.9), 186 (44), 174 (12), 158 (45), 140 (100), 105 (62), 91 (14), 77 (57), 55 (17), 43 (42). To a stirred mixture of this isoxazole (141 mg, 0.51 mmol) and $Ph_3P$ (202 mg, 0.77 mmol) dissolved in dry $CH_2Cl_2$ (10 mL) were slowly added $CBr_4$ (257 mg, 0.77 mmol) and $Et_3N$ (101 mg, 1.0 mmol) at 0 $^o$C. After being stirred for 2 h at rt, ether (20 mL) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* to give a residue which was purified using column chromatography ($SiO_2$) eluting with a 3:1 mixture of hexane/EtOAc to afford isoxazolopyridine (**8**), as an oil: 105 mg (80%); $^1$H NMR δ 1.12 (d, *J* = 6.6 Hz, 6H), 2.75 (s, 4H), 2.87 (m, 1H), 3.10 (s, 2H), 3.96 (s, 2H), 7.27 (m, 5H); $^{13}$C NMR δ 18.5, 24.2, 31.6, 42.7, 44.7, 53.6, 111.5, 126.8, 128.6, 128.8, 136.4, 159.2 166.9; MS *m/z* (%): 256($M^+$, 7.4), 255(7.5), 241 (39), 201 (4.9), 165 (11), 123 (9.4), 107 (3.3), 91 (100), 77 (7.4), 56 (19), 41 (14); HRMS calcd for $C_{16}H_{20}N_2O$ ($M^+$) 256.1576, found 256.1575.

**3-Benzyl-5-benzyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (9).** To a stirred mixture of **8** (193 mg, 0.43 mmol) and $PhCH_2NH_2$ (53 mg, 0.49 mmol) dissolved in dry $CH_2Cl_2$ (5 mL) was added $Et_3N$ (98 mg, 0.97 mmol), and the mixture was stirred for 2 h at rt. Water (5 mL) was added and the resulting mixture was extracted with $CH_2Cl_2$ (10 mL x 2). The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was column chromatographed ($SiO_2$) eluting with a 5:1 mixture of hexane/EtOAc to afford isoxazolopyridine (**9**), as an oil: 52 mg (40%); $^1$H NMR δ 2.74 (s, 4H), 3.06 (s, 2H), 3.60 (s, 2H), 3.93 (s, 2H), 7.12-7.31 (m, 10H); $^{13}$C NMR δ 23.4, 31.6, 47.3, 48.7, 61.3, 121.2, 126.8, 127.3, 128.4, 128.6, 128.7, 128.9, 136.35, 159.2, 166.7; MS *m/z* (%): 304 ($M^+$, 13), 213 (13), 168 (27), 149 (18), 117(5.6), 97(9), 84 (79), 69 (13), 57 (29), 43 (100); HRMS calcd for $C_{20}H_{20}N_2O$ ($M^+$) 304.1576, found 304.1563.

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