Synthesis of New Pyrazolylisoxazolines *via* 1,3-Dipolar Cycloaddition Reaction of Bicyclic Sydnone with Benzyl Propiolate

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A series of isoxazoline compounds received attentions by their potent herbicidal activities.[1] The compounds possessing a pyrazole moiety also attracted considerable interest by their broad biological activities.[2] In search for new structures with good herbicidal activities, we have extensively studied on the synthesis of diverse types of isoxazolines and pyrazoles.[3] In continuation of our study, we designed some isoxazolines containing bicyclic pyrazole moiety as target molecules (**6b-c** and **9b-c**).

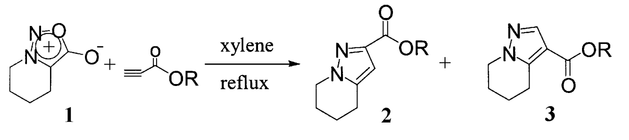
In the 1,3-dipolar cycloaddition reaction of sydnones with propiolates could form two regioisomeric pyrazoles such as 3-carboxypyrazole ester (**2**) and 4-pyrazolecarboxylate (**3**) but 3-pyrazolecarboxylate (**2**) is known to be predominantly formed.[4] Our requirement for tetrahydropyrazolo[1,5-a]-pyridinylcarboxylate (**2** and **3**) prompted us to explore the cycloaddition of tetrahydropyridino[1,2-c][1,2,3]oxadiazolone (**1**) to propiolates.[5] When a mixture of bicyclic sydnone (**1**) and methyl propiolate were refluxed in xylene for 10 h, two regioisomers, 3- and 4-bicyclicpyrazolecarboxylate (**2a** and **3a**) were obtained in a ratio of 2 to 1 as shown in Table. Employing ethyl propiolate as a dipolarophile gave the 3-pyrazolecarboxylate (**2b** and **3b**) with rather improved selectivity (3 to 1). The reaction with a bulky dipolarophile such as *n*-butyl, benzyl, and 1-phenylethyl propiolates led to the less regiospecific formation of 3-pyrazolecarboxylate (**2**) than the reaction of ethyl propiolate. Two regioisomers could be easily separated by silica gel column chromatography, especially in case of benzyl 3- and 4-pyrazolecarboxylate (**2d**, **3d**).

Hydrolysis of **2d** and **3d** by lithium hydroxide in methanol-water followed by acidification to give free acids (**4a**, **7a**), which were converted to the corresponding acid chlorides (**4b**, **7b**) by refluxing in thionyl chloride. The acid chlorides (**4b**, **7b**) were reduced to the corresponding aldehydes (**4d**, **7d**) *via* Weinreb amides (**4c**, **7c**).[5]

The aldehydes (**4d**, **7d**) were converted to the corresponding oximes (**5a**, **8a**) by treating hydroxylamine in pyridine as a base. When **5a** was chlorinated with *N*-chlorosuccinimide (NCS), dichlorinated product **5b** was mainly obtained regardless of the amount of NCS due to the good nucleophilicity of 4-position of pyrazoles, however, **8a** could be converted to **8b** in good yield under the same reaction condition. 1,3-Dipolar cycloaddition reactions of methallyl alcohol with the corresponding nitrile oxides obtained *in situ* from **5b** and **8b** by triethylamine gave the isoxazolines (**6a**, **9a**). Efficient substitution of benzyl group to the hydroxy group of **6a** and **9a** could be performed to give **6b-c** and **9b-c** employing tetrabutyl ammonium iodide as a catalyst in DMF.[6]

In summary, novel pyrazolylisoxazolines were prepared

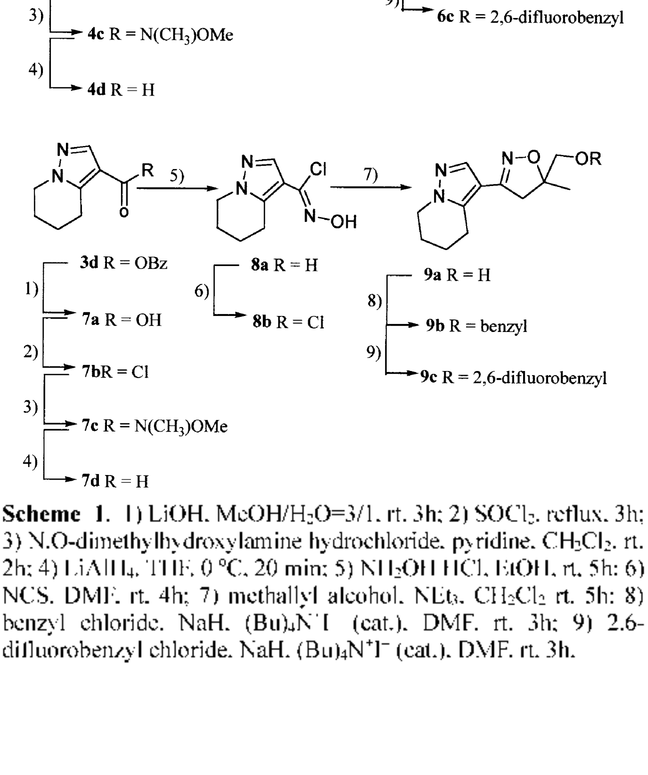
Table 1. 1,3-Dipolar Cycloaddition Reaction of Tetrahydropyridino[1,2-c][1,2,3]oxadiazolone (**1**) to Propiolates



a R = Me **b** R = Et **c** R = n-Bu **d** R = benzyl **e** R = 1-phenylethyl

Entry	R	Yield (%)[a]	Ratio (2:3)[b]
1	Me	60	2:1
2	Et	75	3:1
3	*n*-Bu	72	1.7:1
4	benzyl	59	2.2:1
5	1-phenylethyl	60	1.9:1

[a]Isolated yield of product mixture (2+3) after silica gel chromatography. [b]Regioselectivity (2/3 ratio) was determined by ^{1}H NMR analysis.



Scheme 1. 1) LiOH, MeOH/H_2O=3/1, rt, 3h; 2) $SOCl_2$, reflux, 3h; 3) N,O-dimethylhydroxylamine hydrochloride, pyridine, CH_2Cl_2, rt, 2h; 4) $LiAlH_4$, THF, 0 °C, 20 min; 5) NH_2OH·HCl, EtOH, rt, 5h; 6) NCS, DMF, rt, 4h; 7) methallyl alcohol, NEt_3, CH_2Cl_2 rt, 5h; 8) benzyl chloride, NaH, $(Bu)_4N^+I^-$ (cat.), DMF, rt, 3h; 9) 2,6-difluorobenzyl chloride, NaH, $(Bu)_4N^+I^-$ (cat.), DMF, rt, 3h.

by the procedure involving two types of 1,3-dipolar cycloaddition reactions. Bicyclic pyrazoles were prepared from the reaction of sydnone with benzyl propiolate, and isoxazoline moieties were derived from the reactions of their corresponding hydroximoyl chlorides with methallyl alcohol. Further studies of other pyrazolylisoxazolines and their herbicidal activity evaluation are in progress.

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6. The spectral data of key intermediary products are as follows: **2d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.27 (m, 5H), 6.52 (s, 1H), 5.36 (s, 2H), 4.19 (t, J = 5.7 Hz, 2H), 2.05-1.83 (m, 6H); ^{13}C NMR (75 MHz) 218.44, 162.24, 140.35, 136.05, 128.38, 128.27, 128.02, 106.01, 66.20, 48.57, 23.14, 22.50, 20.12; MS (20 eV) m/z (rel intensity) 257 (M^+, 6.5), 150 (44.6), 122 (100), 91 (31.8); HRMS calcd for $C_{15}H_{16}N_2O_2$ 256.1211, found 256.1213. **3d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.42-7.26 (m, 5H), 5.26 (s, 1H), 4.14 (t, J = 5.7 Hz, 2H), 2.08-1.80 (m, 4H); 13C NMR (75 MHz) 218.43, 162.25, 142.02 140.16, 135.88, 128.24, 127.81, 127.70, 65.13, 47.79, 22.78, 22.29, 19.23; MS (20 eV) m/z (rel intensity) 256 (M^+, 20.0), 149 (100), 91 (34.6); HRMS calcd for $C_{15}H_{16}N_2O_2$ 256.1211, found 256.1211. **4a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.06-6.60 (br, 1H), 6.54 (s, 1H), 4.14 (t, J = 5.90 Hz, 2H), 3.04 (t, J = 6.10 Hz, 2H), 2.02-1.86 (m, 4H); ^{13}C NMR (75 MHz) 197.94, 168.54, 144.71, 141.48, 48.05, 22.99, 22.67, 19.35. MS (20 eV) m/z (rel intensity) 166 (M^+, 100), 149 (25.9), 138 (44.0), 121 (44.0). **4c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.44 (s, 1H), 4.16 (t, J = 6.10 Hz, 2H), 3.72 (s, 3H), 3.39 (s, 3H). 2.78 (t, J = 6.51 Hz, 2H), 2.05-1.90 (m, 2H), 1.87-1.77 (m, 2H); ^{13}C NMR (75 MHz) 164.45, 151.24, 142.03, 105.49, 61.29, 50.78, 48.29, 23.19, 22.41, 20; MS (20 eV) m/z (rel intensity) 209 (M^+, 3.3) 178 (2.5), 149 (100), 79 (6.7). **4d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.91 (s, 1H), 6.51 (s, 1H), 4.23 (t, J = 5.9 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 2.20-2.01 (m, 2H), 1.99-1.90 (m, 2H); ^{13}C NMR (75 MHz) 197.99, 186.87, 150.96, 102.96, 48.77, 23.22, 22.68, 20.18; MS (20 eV) m/z (rel intensity) 150 (M^+, 100), 121 (39.3), 94 (37.3), 66 (38.6). **5a**: ^{1}H NMR (200 MHz, $CDCl_3$); δ 8.17 (s, 1H), 6.52 (s, 1H), 4.13 (t, J = 5.9 Hz, 2H), 2.74 (t, J = 6.5 Hz, 2H), 2.17-1.92 (m, 4H); ^{13}C NMR (75 MHz) 158.48, 151.21, 127.94, 125.88, 48.05, 29.40, 22.84, 20.93; MS (20 eV) m/z (rel intensity) 166 (M^++1, 5.2), 165 (M^+, 45.5), 148 (100.0), 121 (24.4), 120 (23.6), 93 (14.8). **6a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.04 (t, 1H), 4.39-4.28 (m, 1H), 4.04-3.87 (m, 1H), 3.78-3.56 (m, 3H), 3.08 (dd, J = 2.84 Hz, 1H), 2.44-2.07 (m, 4H), 1.61 (s, 3H); ^{13}C NMR (75 MHz) 151.79, 139.27, 138.88, 108.61, 86.71, 68.68, 59.77, 48.76, 42.61, 30.94, 22.61, 18.35; MS (20 eV) m/z (rel intensity) 269 (M^+, 4.23), 230 (100.0), 231 (72.5), 194 (40.4), 43 (15.3). **6b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 6.51-6.45 (m, 1H), 6.16-6.07 (m, 1H), 4.60 (s, 2H), 4.17 (t, J = 7.52 Hz, 2H), 3.75-3.46 (m, 3H), 3.11 (d, J = 16.5 Hz, 1H), 2.71-2.61 (m, 2H), 1.45 (s, 3H); MS (20 eV) m/z (rel intensity) 358.9 (0.5), 355.2 (2.3), 284.2 (3.3), 236.1 (2.3), 235.1 (2.8), 194.1 (10.7), 192 (20.0), 152.1 (14.3), 91.0 (100.0), 65.1 (19.1). **6c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30-7.19 (m, 1H), 6.87 (t, J = 7.73 Hz, 2H), 6.49 (d, J = 9.97 Hz, 1H), 6.17-6.08 (m, 1H), 4.68 (s, 2H); HRMS calcd for $C_{19}H_{20}N_3O_2F_2Cl$ 395.1212, found 395.1216; MS (20 eV) m/z (rel intensity) 395 (M^++1, 0.8), 394 (M^+, 1.0), 391 (9.5), 338 (4.3), 233 (25.8), 192 (84.0), 127 (100.0), 43 (42.4). **7a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 (s, 1H), 4.72-4.98 (br, 1H), 4.15 (t, J = 5.70 Hz, 2H), 3.05 (t, J = 6.30 Hz, 2H), 2.10-1.84 (m, 4H); ^{13}C NMR (75 MHz) 218.98, 197.97, 150.94, 140.72, 47.97, 22.92, 22.74, 19.44; HRMS calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0743; MS (20eV) m/z (rel intensity) 165 (M^+, 22.2), 149 (100.0), 121 (16.8) **7c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (s, 1H), 4.14 (t, J = 6.10 Hz, 2H), 3.69 (s, 3H), 3.29 (s, 3H), 3.11 (t, J = 6.50 Hz, 2H), 2.05-1.95 (m, 2H), 1.91-1.87 (m, 2H); ^{13}C NMR (75 MHz) 218.98, 165.34, 145.02, 139.765, 60.92, 48.10, 32.67, 23.59, 22.81, 19.70; HRMS calcd for $C_{10}H_{15}N_3O_2$ 209.1164, found 209.1161; MS (20 eV) m/z (rel intensity) 209 (M^+, 2.0), 149 (100.0), 121 (7.7). **7d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.85 (s, 1H), 4.13 (t, J = 5.9 Hz), 3.05 (t, J = 6.5 Hz), 2.01-1.81 (m, 4H); ^{13}C NMR (75 MHz) 183.99, 135.47, 134.96, 105.19, 47.60, 22.37, 20.00, 19.02; MS (20eV) m/z (rel intensity) 149 (M^+, 100.0), 135 (16.9), 121 (18.8), 94 (16.0). **8a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.21 (s, 1H), 4.15 (t, J = 6.1 Hz, 2H), 2.85 (t, J = 6.5 Hz, 2H), 2.07-1.87 (m, 4H); MS (20 eV) m/z (rel intensity) 165 (M^+, 54.8), 148 (100.0), 120 (19.5). **9a**: ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.58 (d, J = 4.68 Hz, 1H), 5.67 (s, 1H), 4.44 (dd, J = 6.10 Hz, 1H), 4.18-3.96 (m, 1H), 3.76-3.39 (m, 3H), 3.00 (dd, J = 6.92 Hz, 1H), 2.73-1.91 (m, 6H), 1.42 (d, J = 4.07, 3H). **9b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.24 (m, 6H), 4.60 (s, 1H), 4.16 (t, J = 7.7 Hz, 2H), 3.54-3.43 (m, 3H), 3.07 (d, J = 16 Hz, 1H), 2.71-2.63 (m, 2H), 2.42-2.03 (m, 4H); MS (20 eV) m/z (rel intensity) 326.2 (3.17), 300.2 (5.9), 284.2 (13.8), 236.2 (28.3), 235.2 (18.7), 194.1 (100.0), 91.1 (81.9). **9c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54 (d, J = 10.9 Hz, 1H), 7.31-7.23 (m, 1H), 6.88 (t, J = 7.9 Hz, 2H), 4.67 (s, 1H), 4.17 (t, J = 7.8 Hz, 2H), 3.55-3.46 (m, 3H), 3.07 (d, J = 17 Hz, 1H), 2.70-2.61 (m, 2H), 2.40-2.03 (m, 4H); HRMS calcd for $C_{19}H_{21}N_3O_2F_2$ 361.1601, found 361.1603; MS (20 eV) m/z (rel intensity) 361 (M^++1, 31.1), 234.2 (51.5), 204.2 (12.9), 202.1 (31.4), 162.2 (20.8), 160.1 (20.6), 127.1 (100.0), 100.9 (5.8), 43.1 (23.0).