SYNTHESIS AND ELABORATION OF 3-SUBSTITUTED 4-NITROISOXAZOLES

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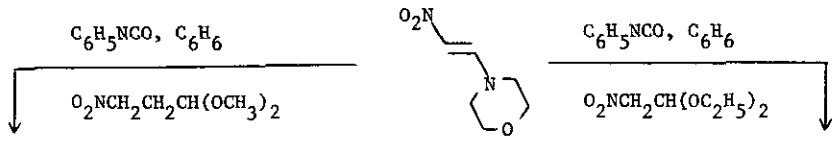
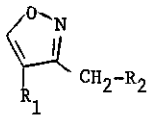
Abstract — A regioselective Mukaiyama reaction involving nitroacetals 1 and 9, phenyl isocyanate and 1-morpholino-2-nitroethene 2 in benzene provided, respectively, the 4-nitroisoxazole acetals 3 and 10 in excellent yield. These acetals in turn served as convenient synthetic entries into the series of 3,4-difunctionalized isoxazoles of structures 4-8 and 11-13, respectively.

Isoxazoles[1] are versatile synthetic intermediates[2] which incorporate latent functionality[3] corresponding to γ-amino alcohols, α,β-unsaturated ketones, β-hydroxy ketones, cyano and imino ketones, as well as other combinations of juxtaposed functional groups. We required a series of 3-substituted 4-nitroisoxazoles which could be further elaborated while maintaining the isoxazole ring intact. Direct nitration[4] of 3-methylisoxazole, for example, requires vigorous conditions not compatible with sensitive substituents. We therefore chose to adapt methodology[5] which has led to 4-nitroisoxazoles by the Mukaiyama reaction[6] of nitrile oxides with nitro enamines.[7]

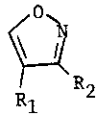
Reaction of nitro acetal 1[8] with a ten-fold excess of phenyl isocyanate in benzene containing 1-morpholino-2-nitroethene 2[9] gave 4-nitroisoxazole 3 regiospecifically and in excellent yield. This compound in turn could be converted under standard conditions into the functionalized derivatives 4-8 while keeping the isoxazole ring intact. Noteworthy is the selective reduction of the nitro group to give amine 6 without fission or reduction of the isoxazole ring. Also, the conversion of acetal 3 into thioacetal 5 allows for the possibility of further elaboration at the terminal carbon atom through umpolung[10] alkylation chemistry.

The generality of this approach is illustrated by the synthesis of the next lower homolog isoxazoles 10-13 starting with nitro acetal 9.[11]





	R_1	R_2
3	NO_2	$CH(OCH_3)_2$
4	NO_2	CHO
5	NO_2	
6	NH_2	$CH(OCH_3)_2$
7	$NHCOCH_3$	$CH(OCH_3)_2$
8	$NHCOCH_3$	



	R_1	R_2
10	NO_2	$CH(OC_2H_5)_2$
11	NH_2	$CH(OC_2H_5)_2$
12	$NHCOC_6H_5$	$CH(OC_2H_5)_2$
13	$NHCOC_6H_5$	CHO

EXPERIMENTAL SECTION

3-(2,2-Dimethoxyethyl)-4-nitroisoxazole (3). To dry benzene (50 ml) containing phenyl isocyanate (23.8 g, 200 mmol) and 2[9] (3.08 g, 20.0 mmol) was added with stirring a solution of 1[8] (6.72 g, 45.4 mmol) and Et_3N (350 mg, 3.48 mmol) in benzene (20 ml). After a 2 h reflux period, the mixture was filtered and the filtrate was concentrated in vacuo. Flash chromatography over silica gel (ether-hexane, 1:9) gave 3 (3.63 g, 90%) as an oil: NMR ($CDCl_3$) δ 3.20 (s, 6), 3.20 (d, 2), 4.86 (t, 1), 9.25 (s, 1). Anal. Calcd for $C_7H_{10}N_2O_5$: C, 41.59; H, 4.99; N, 13.86. Found: C, 41.64; H, 4.65; N, 13.51.

3-(2-Oxoethyl)-4-nitroisoxazole (4). Acetal 3 (32 mg, 0.16 mmol) was dissolved in HOAc (4 ml) containing CF_3CO_2H (10 drops) and water (10 drops) and then heated at 95°C for 30 min. Evaporation of the solvent in vacuo gave the sensitive aldehyde 4 (25 mg, 100%; >90% pure by NMR) as an oil which tended to undergo decomposition during attempted purification. NMR ($CDCl_3$) δ 3.42 (s, 2), 9.32 (s, 1), 9.86 (s, 1); MS m/e 156.016 (M^+, calcd for $C_5H_4N_2O_4$, 156.017) (9), 128 (49), 91 (67), 86 (82), 53 (74), 43 (100).

3-(1,3-Dithiacyclohex-2-ylmethyl)-4-nitroisoxazole (5). To a refluxing solution of $BF_3 \cdot Et_2O$ (123 mg, 0.86 mmol) and propane dithiol (39 mg, 0.36 mmol) in dry $CHCl_3$ (10 ml) was added over 1 h acetal 3 (59 mg, 0.29 mmol) in $CHCl_3$ (10 ml). After 5 h at reflux, the usual workup gave an oil which was filtered through silica gel ($CHCl_3$) giving dithiane 5 (52 mg, 72%) as an oil: NMR

($CDCl_3$) δ 1.90-2.20 (m, 2), 2.78-3.02 (m, 4), 3.60 (d, 2), 4.46 (t, 1), 9.29 (s, 1); MS m/e 246.013 (M^+, calcd for $C_8H_{10}N_2O_3S_2$, 246.013) (50), 229 (13), 165 (26), 149 (14), 132 (13), 119 (100).

3-(2,2-Dimethoxyethyl)-4-aminoisoxazole (6). Isoxazole 3 (320 mg, 1.58 mmol) and NH_4Cl (2.0 g, 37 mmol) were dissolved in water (8 ml) at 0°C. Then zinc dust (3.2 g, 49 mg-atom) was added in portions over 15 min with stirring. After 30 min at 0°C, the mixture was filtered and the cake was washed with MeOH (20 ml). The combined filtrate was evaporated in vacuo to give amine 6 (224 mg, 82%) as an oil of suitable purity for the next reaction: NMR ($CDCl_3$) δ 2.98 (d, 2), 3.42 (s, 6), 3.42 (s, 2), 4.58 (t, 1), 7.95 (s, 1).

3-(2,2-Dimethoxyethyl)-4-acetamidoisoxazole (7). To a stirred solution of 6 (224 mg, 1.30 mmol) in CH_2Cl_2 (12 ml) was added pyridine (364 mg, 4.38 mmol) and Ac_2O (248 mg, 2.43 mmol). After 2 h the solution was diluted with water and extracted with ether. The extract was dried (K_2CO_3) and concentrated in vacuo to give amide 7 (275 mg, 98%) as an oil of suitable purity for the next reaction: NMR ($CDCl_3$) δ 2.16 (s, 3), 3.10 (d, 2), 3.51 (s, 6), 4.57 (t, 1), 8.37-8.60 (s, 1), 9.04 (s, 1).

3-(1,3-Dithiacyclohex-2-ylmethyl)-4-acetamidoisoxazole (8). To a refluxing solution of $BF_3 \cdot Et_2O$ (156 mg, 1.1 mmol) and propane dithiol (119 mg, 1.1 mmol) in $CHCl_3$ (10 ml) was added dropwise 7 (235 mg, 1.1 mmol) in $CHCl_3$ (10 ml). After 2 h the usual workup followed by crystallization from CH_2Cl_2-hexane gave 8 (245 mg, 87%) as colorless needles: mp 111-112°C; NMR ($CDCl_3$) δ 1.72-2.30 (m, 2), 2.20 (s, 3), 2.78-3.00 (m, 4), 3.15 (d, 2), 4.36 (t, 1), 8.48 (s, 1), 9.00 (s, 1). Anal. Calcd for $C_{10}H_{14}N_2O_2S_2$: C, 46.49; H, 5.46; N, 10.84. Found: C, 46.41; H, 5.57; N, 10.61.

3-(Diethoxymethyl)-4-nitroisoxazole (10). Following the procedure used to prepare 3, crude 10 was obtained (from 9) as an oil of suitable purity for the next reaction: NMR ($CDCl_3$) δ 1.28 (t, 6), 3.65-3.96 (m, 4), 6.10 (s, 1), 9.24 (s, 1).

3-(Diethoxymethyl)-4-aminoisoxazole (11). A solution of 10 (150 mg) in MeOH (7 ml) containing 10% Pd/C (150 mg) was stirred under H_2 (1 atm.) until 3 equivalents of H_2 were absorbed. Filtration followed by evaporation gave amine 11 (128 mg, 100%) as an oil suitably pure for the next reaction: NMR ($CDCl_3$) δ 1.26 (t, 6), 3.44-3.84 (m, 4), 3.64 (s, 2), 5.59 (s, 1), 7.92 (s, 1).

3-(Diethoxymethyl)-4-benzamidoisoxazole (12). Benzamide 12 was obtained as an oil by benzoylation of 11 with benzoyl chloride and pyridine under standard conditions: NMR ($CDCl_3$) δ 2.32 (t, 6), 3.60-3.94 (m, 4), 5.80 (s, 1), 7.40-7.64 (m, 3), 7.80-7.96 (m, 2), 8.96 (s, 1), 9.28 (s, 1); MS m/e 290.127 (M^+, calcd for $C_{15}H_{18}N_2O_4$, 290.127) (2), 122 (47), 105 (100), 103 (27), 91 (24), 77 (60).

3-Formyl-4-benzamidoisoxazole (13). Acetal 12 (10 mg) was stirred in THF (4 ml) containing 3 N HCl (4 ml) for 22 h at 25°C. After the usual workup 8 mg (100%) of crude 13 was isolated which could be recrystallized from CH_2Cl_2-hexane to give aldehyde 13 as colorless, fluffy microcrystals, mp 125° (dec). NMR ($CDCl_3$) δ 7.50-7.64 (m, 3H), 7.84-7.98 (m, 2H), 9.36 (s, 1H), 9.45 (s, 1H), 10.35 (s, 1H); MS m/e 216.054 (M^+, calcd for $C_{11}H_8N_2O_3$, 216.053) (2), 105 (100), 91 (2), 77 (78), 51 (38).

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