1,3-DIPOLAR CYCLOADDITION OF N-OXIDE WITH 2-METHYLENE-1,3-DITHIANE

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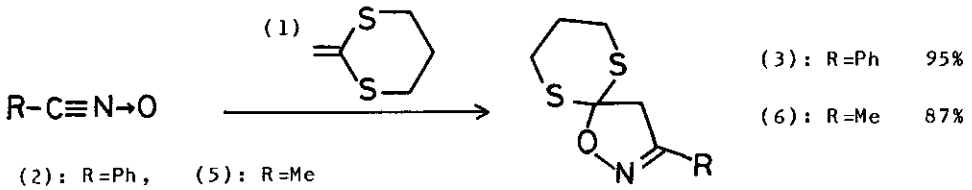
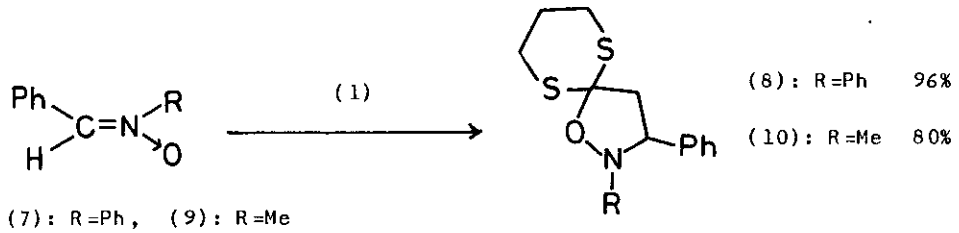
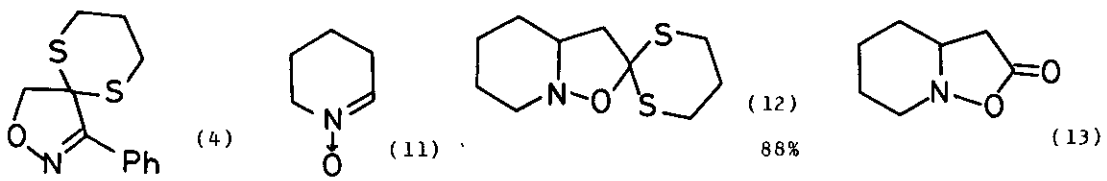
Abstract ——— 1,3-Dipolar cycloaddition of nitrile oxides and nitrones with 2-methylene-1,3-dithiane gave 5-substituted isoxazolines and isoxazolidines in good yield. By treatment with mercuric chloride or NBS isoxazolidine (12) was converted to corresponding lactone (13) which was a precursor of β-amino acid.

Houk and co-workers reported in their application of perturbation theory to 1,3-dipolar cycloadditions that nitrile oxides reacted with both electron rich and defficient dipolarophiles to give mostly 5-substituted isoxazolines[1].
In the case of nitrones with dipolarophiles the products gave a mixture of 4- and 5-substituted isoxazolidines[2].
On the other hand the reaction of 2-methylene-1,3-dithiane (1) with a nucleophile showed the regioselectivity which was attacked by an electrophile on the β-carbon atom to give α-carbanion intermediate[3].
In the course of our seeking novel synthetic method using a heterocycle, we have desired to form an isoxazolin- or isoxazolidin-5-ones.
The addition of benzonitrile oxide (2)[4] with (1) was carried out in THF at -70°C for 1 h to give spiro compound (3) in 95% yield. The other isomer (4) could not be detected in this reaction. Addition of acetonitrile oxide (5)[5] with (1) also gave a sole 5-spiro product (6) in 87% yield.
The addition of nitrone (7)[6] to (1) in refluxing THF for 5 h gave a sole 5-spiro compound (8)(96%) whose attacking position was exclusively at α-carbon atom of (1). This selectivity was revealed in the addition of (1) with nitrones (9) and (11)[7]. The 5-spiro isoxazolidines (10) and (12) were obtained regioselectively in 80 and







88% yields respectively. The structures of the products were determined by compaison of its spectral data with those of similar compounds[8].

The regioselectivity of the cycloaddition of a nitrone with an olefin is known that dipole LUMO-dipolarophile HOMO interaction favors formation of 5-substituted adduct. As the case of enol ethers[7] and thio enol ethers[8] the regioselectivity of (8), (10) and (12) must be controlled by this interaction.

We also tried to hydrolyze the spiro compounds (3) and (12) with various methods such as NBS[9], mercuric chloride[10], silver nitrate[11], sodium metaperiodate[12], and chloramine T[13]. Although the compound (3) gave only decomposed products, (12) gave the desired lactone (13) by treatment with NBS or mercuric chloride. These results suggest that this method can apply for the synthesis of various β-amino acids.

EXPERIMENTAL

Synthesis of (3): To a solution of benzhydroxamoyl chloride (360 mg, 2.73 mmol) in 20 ml of dry THF, 1.3 ml of n-BuLi (1.6M solution in hexane) was added and the mixture was stirred at -70°C for 1 h. The resulting benzonitrile oxide (2) was added 325 mg(2.09 mmol) of (1) in 10 ml of dry THF and the mixture was stirred at -70°C for additional 3 h under nitrogen. After quenching with 10%-NH_4Cl aqueous solution the reaction mixture was worked up as usual to give a crude product which was re-

Table: Physical Data of the Spiro Compounds

Comp. No:	mp(°C)	IR(cm^{-1})	NMR(ppm)	Elemental Analysis(%)
(3)	154-155	1600, 1550, 1280, 990	3.93(s)[a]	C: 57.03, H: 5.15, N: 5.62[e] Calcd for $C_{12}H_{13}NOS_2$ C: 57.34, H: 5.21, N: 5.57[f]
(6)	92-93	1670, 1550 1465, 770	3.12(s)[a] 2.05(s)[b]	-------
(8)	138-139	1600, 1495 1050, 920	4.95(t)[c] (8.6Hz) 3.5-3.8(m)[a]	C: 65.35, H: 5.79, N: 4.28[e] Calcd for $C_{18}H_{19}NOS_2$ C: 65.62, H: 5.81, N: 4.25[f]
(10)	oil	1605, 1580, 1025, 700	3.65(t)[c] (9.0Hz) 2.30(m)[b]	------
(12)	oil	1100, 1010, 910	3.03-3.80[d] (m)	MS(m/z) M^+: 231.3728[e] Calcd for $C_{10}H_{17}NOS_2$ M: 231.3704[f]

a: C_4-H, b: N-CH_3, c: C_3-H and coupling constant in parenthesis, d: C_3-H and C_4-H, e: observed data, f: calculated data

crystallized from CCl_4 to give 498 mg(95%) of (3), mp 154-155°C.

Synthesis of (6): The solution of 561 mg(6 mmol) of acetohydroxamoyl chloride in 20 ml of dry THF was treated with 3.75 ml of n-BuLi. To the resulting acetonitrile oxide solution was added 792 mg(6 mmol) of (1) in 5 ml of dry THF at -70°C. After 4 h stirring the reaction mixture was worked up as the case of (3), the crude product was crystallized from n-hexane-benzene to give 991 mg(87%) of (6), mp 92-93°C. The reaction was also carried out at 40°C for 1 h (78% yield).

Synthesis of (8): To a solution of 700 mg(3.55 mmol) of (7) in 20 ml of dry THF was added 500 mg(3.79 mmol) of (1) in 10 ml of dry THF and the reaction mixture was refluxed for 5 h. After working up as usual the crude product was crystallized from $CHCl_3$-MeOH to give 1.16 g(96%) of (8), mp 138-139°C.

Synthesis of (10): This compound was obtained by the similar procedure as (8) from 534 mg(3.96 mmol) of (9) and 573 mg(4.34 mmol) of (1). Purification was carried out by silica gel column chromatography with benzene. Yield 886 mg(80%).

Synthesis of (12): To a solution of 1.74 g(17.5 mmol) of piperidine-N-oxide (11) in 10 ml of dry THF was added 2.78 g(21 mmol) of (1) in 20 ml of dry THF. The mixture was stirred at rt for 60 h. After working up as usual treatment the obtained

paste was purified by silica gel column chromatography with benzene-ethyl acetate (4 : 1) to give 3.95 g(88%) of (12) as colorless oil.

Synthesis of (13): The mixture of 4.2 g(18.2 mmol) of (12), 10.9 g(40 mmol) of mercuric chloride, 4.0 g(40 mmol) of calcium carbonate in 270 ml of 80% aqueous acetonitrile was heated to reflux for 7 h. After washing with 5M-aqueous ammonium acetate solution (3 40 ml) the organic layer was dried over anhydrous magnesium sulfate, concentrated to give pure (13)(1.09 g, 43%)(one spot on TLC: solvent; benzene-ethyl acetate = 4 : 1). IR(neat): 1785 and 1310 cm^{-1}. NMR(in $CDCl_3$): 1.10-2.20(m, 6H), 2.45-3.00(m, 4H) and 3.56 ppm(m, 1H).

Desulfurization was also carried out as follows: the mixture of 1.39 g(6.0 mmol) of (12), 6.4 g(36 mmol) of NBS in 60 ml of 80% aqueous acetonitrile was reacted at -10°C for 30 min. The reaction mixture was quenched with 300 ml of 0.1M-Na_2SO_3 solution, then extracted with benzene-ethyl acetate mixed solvent (1 : 1). The organic layer was treated as usual and 123 mg(14.5%) of (13) was obtained.

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