

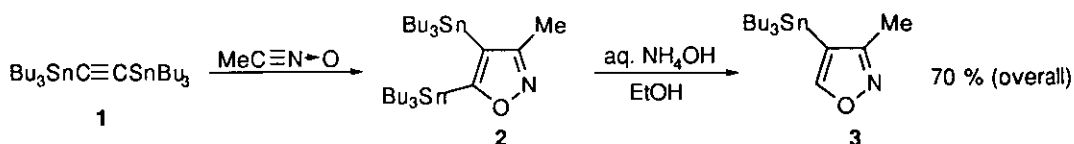
SYNTHESIS AND REACTIONS OF 4-TRIBUTYLSTANNYL-3-METHYLISOXAZOLE

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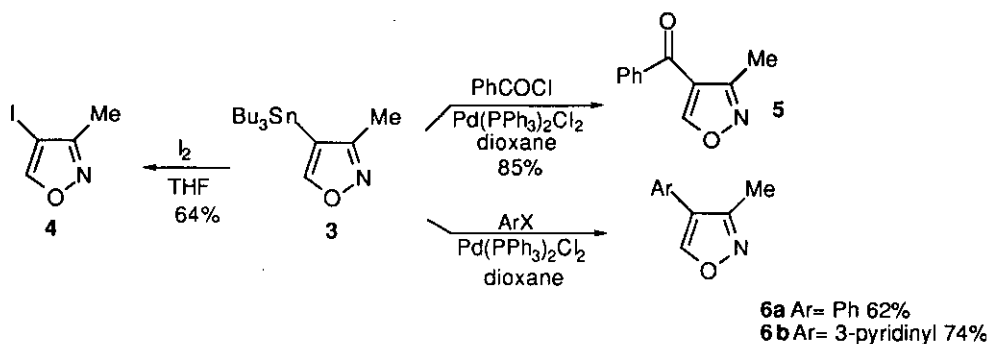
Abstract-1,3-Dipolar cycloaddition reaction of bis(tributylstannyl)acetylene with nitrile oxides, followed by treatment with aqueous ammonia in ethanol in a sealed tube gave 4-tributylstannyl-3-methylisoxazole. The palladium catalyzed cross coupling reaction of the isoxazole with 2-iodonitrobenzene, followed by reductive cyclization afforded 3-acetylindole.

Organotin derivatives have been used as versatile reagents for organic synthesis.¹ We have demonstrated that 5-tributylstannylisoxazole derivatives can be used as 1,3-diketone anion equivalent, and some condensed heterocyclic compounds were synthesized by employing the 5-tributylstannylisoxazole derivatives as 1,3-diketone donors onto aromatic rings.² In connection with our recent studies of stannylazoles,³ we focussed our interest on the synthesis and reaction of 4-tributylstannylisoxazoles with no substituent at 5-position. Since it is well known that treatment of isoxazoles without a substituent at 5-position with butyllithium results in ring cleavage,⁴ preparation of 4-stannylisoxazoles from 4-lithioisoxazoles seemed difficult in the isoxazole derivatives with no substituent at 5-position. So we chose 1,3-dipolar cycloaddition of bis(tributylstannyl)acetylene and subsequent selective destannylation at 5-position as a preparative way for 5-unsubstituted 4-stannylisoxazoles. When bis(tributylstannyl)acetylene (**1**) was treated with acetonitrile oxide generated *in situ* from nitroethane and phenyl isocyanate, 1,3-dipolar cycloaddition proceeded to give 4,5-bis(tributylstannyl)isoxazole (**2**). The isoxazole (**2**) was treated with aq. NH₄OH-EtOH in a sealed tube at 150°C, and 3-methyl-4-tributylstannylisoxazole (**3**) was obtained in 70% overall yield.



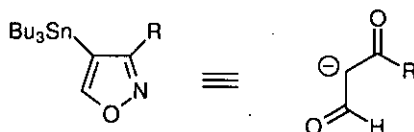
Scheme 1

Treatment of the isoxazole (3) with iodine gave 4-iodoisoxazole (4) in 64%, and the reaction with benzoyl chloride proceeded in the presence of palladium catalyst to give 4-benzoylisoxazole (5) in 85% yield. The cross coupling reaction of the isoxazole (3) with iodobenzene or 3-bromopyridine also proceeded smoothly to give 4-phenyl- and 4-(3-pyridinyl)isoxazoles (6a and 6b) in 62 and 74% yields, respectively.



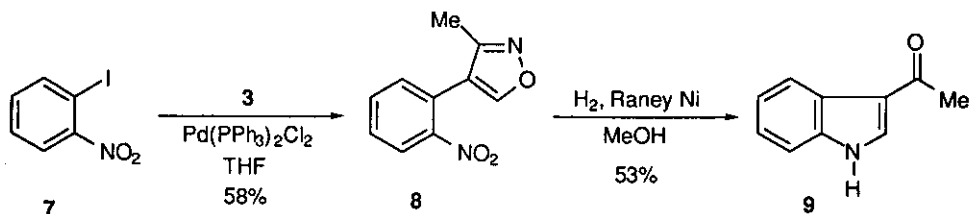
Scheme 2

Isoxazoles have served as important building blocks because of the labile nature of the nitrogen-oxygen bond under appropriate reductive conditions and have been used as key intermediates to construct natural products.⁵ Since 3-substituted 4-stannylisoxazoles are considered to be an effective masked formyl methyl ketone anion equivalent, synthetic application using the stannylisoxazole (3) was investigated.



Scheme 3

In order to confirm the synthetic utility of the stannylisoxazole (3), 3-acetylindole was synthesized using 3 as a formylacetone equivalent. The cross coupling reaction of 3 with 2-nitroiodobenzene (7) proceeded smoothly to give 3-methyl-4-(2-nitrophenyl)isoxazole (8) which was converted into 3-acetylindole (9) by hydrogenation over Raney nickel.



Scheme 4

EXPERIMENTAL

4-Tributylstannyl-3-methylisoxazole (3)

A dry benzene (40 ml) solution of nitroethane (1.05 g, 14 mmol) and phenyl isocyanate (3.33 g, 28 mmol) was stirred at 50°C for 5 min, to which a dry benzene (20 ml) solution of bis(tributylstannyl)acetylene (6.06 g, 10 mmol) and Et_3N (one drop) was added. The whole mixture was stirred at 60-70°C for 15 h, then filtered through a Celite pad. The filtrate was concentrated under reduced pressure. To the residue EtOH (1 ml) and 25% aq. NH_4OH (5 ml) were added and the mixture was heated at 150°C in a sealed tube for 24 h. After cooling, the mixture was extracted with Et_2O . The Et_2O extract was dried over MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on Al_2O_3 column with hexane-AcOEt (10:1) as an eluent to give a colorless liquid (2.60 g, 70%). bp 180°C/2 mmHg. $^1\text{H-Nmr}$ (CDCl_3 , ppm): 0.8-1.6 (27H, m), 2.31 (3H, s), 8.02 (1H, s). *Anal.* Calcd for $\text{C}_{16}\text{H}_{31}\text{NOSn}$: C, 51.47; H, 8.31; N, 3.75. Found: C, 51.52; H, 8.51; N, 3.49.

4-Iodo-3-methylisoxazole(4)

Iodine (300 mg, 1.2 mmol) in THF (10 ml) was added dropwise to a stirred solution of **3** (370 mg, 1.0 mmol) in THF (10 ml) at room temperature, and the mixture was stirred for additional 1 h. After addition of 1N aqueous NaHCO_3 , the mixture was extracted with Et_2O . The extract was washed with 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried over MgSO_4 , and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (10:1) as an eluent to give a colorless liquid (130 mg, 64%). bp 50-60°C/1 mmHg. $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.33 (3H, s), 8.32 (1H, s). *Anal.* Calcd for $\text{C}_4\text{H}_4\text{NOI}$: C, 22.99; H, 1.93; N, 6.70; I, 60.72. Found: C, 22.75; H, 1.92; N, 6.60; I, 60.79.

4-Benzoyl-3-methylisoxazole (5)

A mixture of **3** (270 mg, 0.72 mmol), benzoyl chloride (140 mg, 1.0 mmol), and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (10 mg) in dioxane (6 ml) was refluxed for 3 h. After cooling, the mixture was diluted with water and extracted with Et_2O . The Et_2O extract was dried over MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (10:1) as an eluent to give a colorless liquid (110 mg, 85%). bp 150°C/3mmHg. The liquid crystallized on cooling was recrystallized from pentane to give colorless scales, mp 49-50°C. $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.58 (3H, s), 7.5-8.0 (5H, m), 8.75 (1H, s); ir (KBr) ν_{max} : 1641 cm^{-1} . *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{NO}_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.41; H, 4.85; N, 7.65.

3-Methyl-4-phenylisoxazole (6a)

A mixture of iodobenzene (260 mg, 1.2 mmol), **3** (370 mg, 1.0 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (35 mg) in dioxane (10 ml) was refluxed for 24 h. After removal of the dioxane under reduced pressure, the residue was diluted with water and extracted with Et_2O . The extract was dried over MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (10:1) as an eluent to give a colorless liquid (100 mg, 62%). bp 90-100°C/1mmHg (lit.,⁶ bp 68-70°C/0.02Torr). $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.33 (3H, s), 7.38 (5H, s), 8.42 (1H, s). *Anal.* Calcd for $\text{C}_{10}\text{H}_9\text{NO}$: C, 75.47; H, 5.66; N, 8.81.

Found: C, 75.42; H, 5.58; N, 8.86.

3-Methyl-4-(3-pyridinyl)isoxazole(6b)

A mixture of 3-bromopyridine (600 mg, 3.8 mmol), **3** (1.17 g, 3.2 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (110 mg) in dioxane (30 ml) was refluxed for 36 h. After removal of the dioxane under reduced pressure, the residue was diluted with water and extracted with Et_2O . The extract was dried over MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (2:1) as an eluent to give a colorless liquid (380 mg, 74%). The liquid crystallized on cooling was recrystallized from pentane, mp 39–40°C. $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.31 (3H, s), 7.2–7.9 (2H, m), 8.5–8.8 (3H, m). *Anal.* Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 4.95; N, 17.53.

3-Methyl-4-(2-nitrophenyl)isoxazole(8)

A mixture of **3** (1.66 g, 4.5 mmol), 2-iodonitrobenzene (1.66 g, 6.7 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (160 mg) in dioxane (50 ml) was refluxed for 4 h under N_2 atmosphere. The dioxane was removed under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (5:1) as an eluent to give pale yellow liquid (610 mg, 66%). bp 135–145°C/3 mmHg. $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.18 (3H, s), 7.2–8.1 (4H, m), 8.35 (1H, s); ir (KBr) ν_{max} : 1528, 1350 cm^{-1} . High Resolution ms Calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_3$: 204.0534. Found: 204.0492.

3-Acetyllindole(9)

A solution of **8** (410 mg, 2 mmol) in MeOH (10 ml) was hydrogenated at 5 atm pressure over Raney nickel W-1 prepared from Ni-Al alloy (2.5 g) for 3 h. The catalyst was filtered off and washed with MeOH, and the MeOH solution was concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-AcOEt (2:1) as an eluent to give colorless solid (170 mg, 53%), mp 186–188°C (lit.,⁷ mp 188–189°C), which recrystallized from EtOH; $^1\text{H-Nmr}$ (CDCl_3 , ppm): 2.56 (1H, s), 7.26–7.32 (2H, m), 7.39–7.44 (1H, m), 7.87 (1H, d, $J=2.9$ Hz), 8.37–8.42 (1H, m), 8.67 (1H, br s); ir (KBr) ν_{max} : 1624 cm^{-1} .

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