SYNTHESIS AND REACTIONS OF 4-TRIBUTYLSTANNYL-3-METHYLISOXAZOLE

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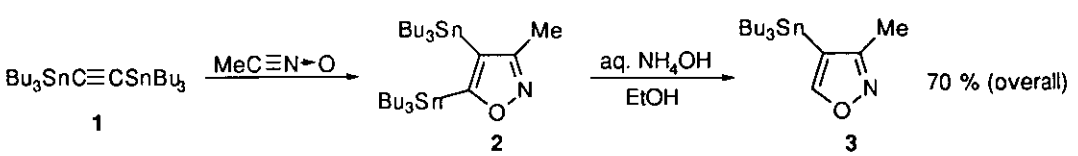
Abstract-1,3-Dipolar cycloaddition reaction of bis(tributylstannyl)acetylene with nitrile oxides, followed by treatment with aqueous ammonia in ethanol in a sealed tube gave 4-tributylstannyl-3-methylisoxazole. The palladium catalyzed cross coupling reaction of the isoxazole with 2-iodonitrobenzene,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

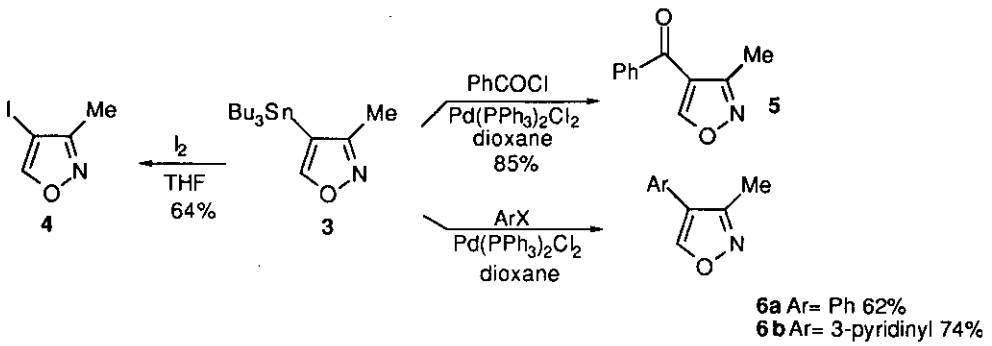
Since it is well known that treatment of isoxazoles without a substituent at 5-position with butyllithium results in ring cleavage,[4] preparation of 4-stannylisoxazoles from 4-lithioisoxazoles seemed difficult in the isoxazole derivatives with no substituent at 5-position. So we chose 1,3-dipolar cycloaddition of bis(tributylstannyl)-acetylene and subsequent selective destannylation at 5-position as a preparative way for 5-unsubstituted 4-stannylisoxazoles. When bis(tributystannyl)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. NH_4OH-EtOH in a sealed tube at 150℃, and 3-methyl-4-tributylstannylisoxazole (**3**) was obtained in 70% overall yield.



1 **2** **3**

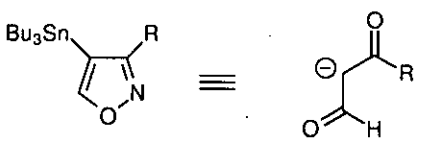
Scheme 1

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.



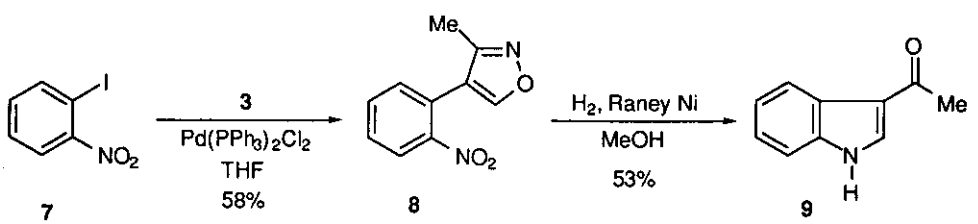
Scheme 2

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℃ 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℃ 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℃ 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 coloress liquid (2.60 g, 70%). bp 180℃/2 mmHg. ^{1}H-Nmr ($CDCl_3$, ppm): 0.8-1.6 (27H, m), 2.31 (3H, s), 8.02 (1H, s). *Anal.* Calcd for $C_{16}H_{31}NOSn$: 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 temprature, 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 $Na_2S_2O_3$, 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℃/1 mmHg. ^{1}H-Nmr ($CDCl_3$, ppm): 2.33 (3H, s), 8.32 (1H, s). *Anal.* Calcd for C_4H_4NOI: 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 $Pd(PPh_3)_2Cl_2$ (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℃/3mmHg. The liquid crystallized on cooling was recrystallized from pentane to give colorless scales, mp 49-50℃. ^{1}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 $C_{11}H_9NO_2$: 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 $Pd(PPh_3)_2Cl_2$ (35 mg) in dioxane (10 ml) was refluxed for 24 h. After removal of the dioxane under reduceed 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℃/1mmHg (lit.,[6] bp 68-70℃/0.02Torr). ^{1}H-Nmr ($CDCl_3$, ppm): 2.33 (3H, s), 7.38 (5H, s), 8.42 (1H, s). *Anal.* Calcd for $C_{10}H_9NO$; 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 $Pd(PPh_3)_2Cl_2$ (110 mg) in dioxane (30 ml) was refluxed for 36 h. After removal of the dioxane under reduceed 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 recrestallized from pentane, mp 39-40℃. ^{1}H-Nmr ($CDCl_3$, ppm): 2.31 (3H, s), 7.2-7.9 (2H, m), 8.5-8.8 (3H, m). *Anal.* Calcd for $C_9H_8N_2O$: 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), $Pd(PPh_3)_2Cl_2$ (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℃/3 mmHg. ^{1}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 $C_{10}H_8N_2O_3$: 204.0534. Found: 204.0492.

3-Acetylindole(9)

A solution of **8** (410 mg, 2 mmol) in MeOH (10 ml) was hydrogenerated 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℃ (lit.,[7] mp 188-189℃), which recrystallized from EtOH; ^{1}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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Received, 8th April, 1996