A FACILE CONSTRUCTION OF THE WOODWARD KETONE BY A ZINC(II) CHLORIDE-CATALYZED STILLE COUPLING REACTION

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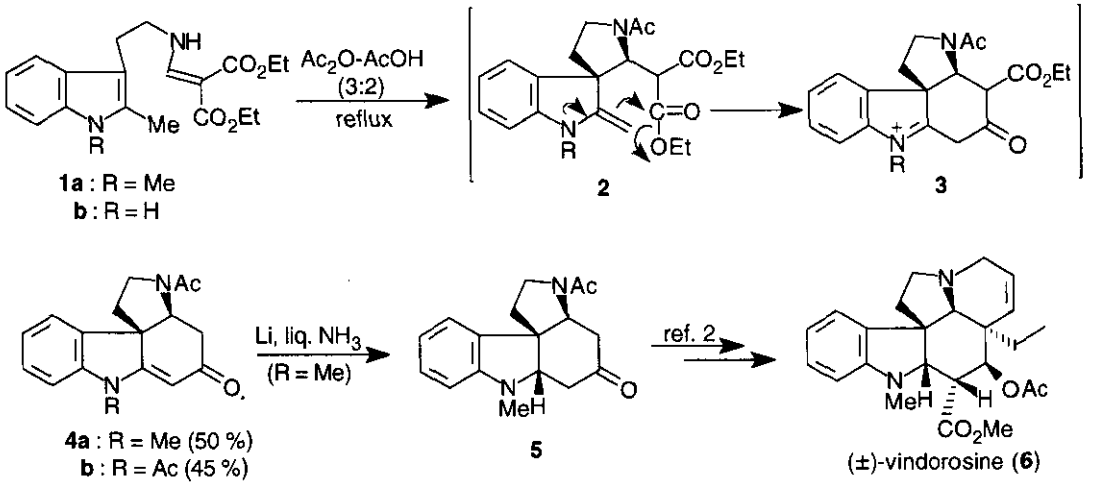
Abstract —— The pentacyclic ketone, obtained by Woodward and co-workers during the first total synthesis of strychnine, has been prepared in a five-step sequence from 2-methyltryptamine by employing a zinc(II) chloride-catalyzed Stille coupling reaction as the key step.

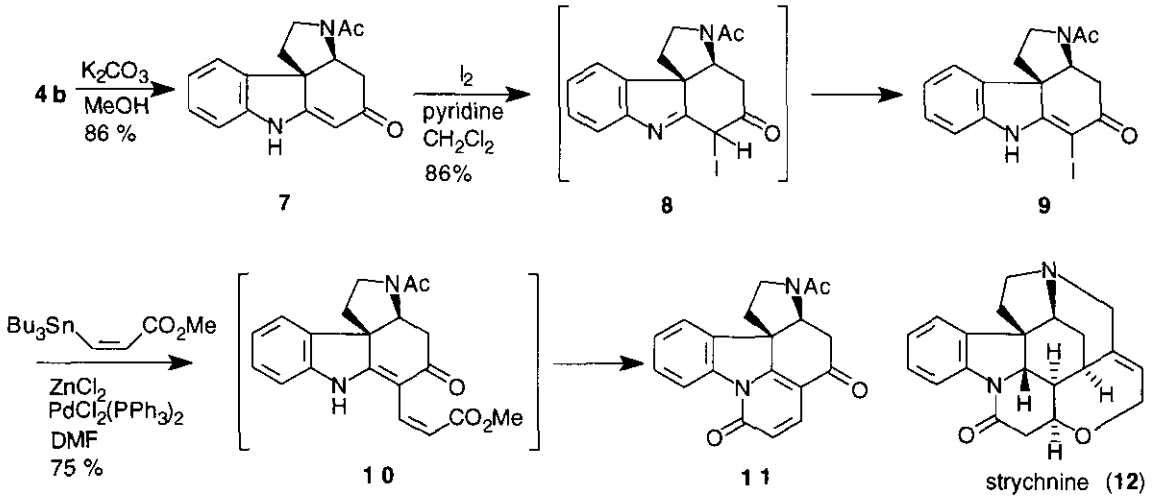
We found that the aminomethylenemalonates (**1**), derived from the 2-methyltryptamines by condensation with diethyl ethoxymethylenemalonate, furnish in one step the tetracyclic amides (**4**) in acceptable yields on reflux with a 3:2 mixture of acetic anhydride and acetic acid.[1] The reaction is presumed to proceed by a consecutive generation of Fischer base type enamines (**2**), their cyclization to one of the malonate ester carbonyl functionalities to generate the tetracyclic indolenium keto esters (**3**), and their collapse into the final products (**4**) by loss of the remaining carboethoxy functionality under the conditions. Of the two products, the *N*-methyl compound (**4a**) was transformed into the tetracyclic β-amino ketone[2] (**5**) serving as the key intermediate for the racemic synthesis of the highly functionalized *Aspidosperma* indole alkaloid vindorosine (**6**) (**Scheme 1**).



Scheme 1

We report here a utilization of the other diamide product (**4b**) for the construction of the pentacyclic ketone (**11**) by employing a zinc(II) chloride-catalyzed Stille coupling reaction. This ketone was first obtained by Woodward and co-workers[3] as a by-product during their total synthesis of the representative *Strychnos* indole alkaloid strychnine (**12**) some thirty years ago and was anticipated to be a promising intermediate for an alternative synthesis of the same alkaloid. The present synthesis provides a new route to this ketone (**11**) in a facile three-step sequence from the tetracyclic diamide (**4b**).

Treatment of the diamide (**4b**) with methanolic potassium carbonate at room temperature allowed a chemoselective deacylation of the aromatic amide to give the mono-amide (**7**) in excellent yield. The observed facile deacylation under the methanolysis conditions was apparently due to the imide-like nature of one of two amide functionalities by conjugation to the cyclohexene carbonyl group. Owing to the selective deacylation, it was possible to carry out the direct α-iodination of the enone functionality using iodine in the presence of pyridine in dichloromethane.[4] Thus, exposure of **7** to a little excess of iodine (1.8 equiv.) in dichloromethane containing pyridine (30 % v/v) at room temperature afforded the α-iodo-enone (**9**) in excellent yield, presumably through an iodo-indolenine intermediate (**8**). The conditions employed were followed by the procedure reported by Johnson and co-workers[4] for α-iodination of cycloalkenones and were now found to be well applicable to this intractable β-amino ketone (**7**). Having introduced iodine at the α position of the enone functionality, we next examined the Stille coupling[5] of **9** with methyl (*Z*)-3-tributylstannylacrylate[6] to give the α-substituted enone (**10**). We first examined the reaction in the presence of tris(dibenzylideneacetone)dipalladium(0) chloroform adduct [$(dba)_3Pd_2{\cdot}CHCl_3$] (2.5 mol %) and triphenylarsine[7] (15 mol %) in THF[8] at 55 °C. However, the cross-coupling reaction did not occur at all and the dehalogenated enone (**7**) was obtained as the only isolable product.



Scheme 2

Negishi and co-workers[9] reported that cyclic α-iodo enones smoothly react with dialkenylzinc in the presence of a catalytic amount of a palladium-phosphine complex to give the corresponding α-alkenylenones in good yields. As it was practically difficult to prepare a dialkenylzinc[10] having a carbomethoxy functionality in the molecule, we examined the cross-coupling reaction using methyl (*Z*)-3-tributylstannylacrylate in the presence of an additional $ZnCl_2$ expecting an *in situ* generation of di[(*Z*)-3-carbomethoxyvinyl]zinc under the conditions. Thus, a mixture of the iodide (**9**), 2.2 equiv. of methyl (*Z*)-3-tributylstannylacrylate, and 2.2 equiv. of zinc(II) chloride in DMF was refluxed in the presence of a catalytic amount (10 mol %) of dichlorobis(triphenylphosphine)palladium(II)[$PdCl_2(PPh_3)_2$] for 3 h expecting to obtain the α-substituted enone (**10**) serving as the penultimate intermediate for the Woodward ketone (**11**). The reaction proceeded more than as expected to furnish directly the Woodward ketone (**11**) in 75 % yield by spontaneous cyclization of the initially formed **10** under the conditions accompanied with a minor amount (14 %) of the dehalogenated product (**7**). Since the yield of **11** was reduced to 43 % yield accompanied with the dehalogenated **7** (11 %) and the unchanged iodide (**9**) (19 %) when 1.1 equiv. of the 3-tributylstannylacrylate was used under the same conditions, it was assumed that a transient dialkenylzinc intermediate may be involved in the reaction pathway. When zinc(II) chloride was absent, none of the Woodward ketone (**11**) but the dehalogenated **7** was produced (**Scheme 2**).
In summary, we have developed a facile route to the Woodward ketone (**11**) by employing a zinc(II) chloride-catalyzed Stille coupling reaction as the key step.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hotstage instrument and are uncorrected. UV spectra were recorded on a HITACHI 320 spectrophotometer. IR spectra were recorded on a JASCO-IR 700 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 M Hz) spectrometer.

Tetracyclic Diacetamide (4b)

To a solution of 2-methyltryptamine[11] (17.4 g, 0.1 mol) in EtOH (50 mL) was added diethyl ethoxymethylenemalonate (21.6 g, 0.1 mol) dropwise with stirring. An exothermic reaction occurred and a crystalline precipitate was separated on standing. The crystals were collected by filtration and recrystallized from EtOH to give the aminomethylenemalonate (**1b**) (32.8 g, 95 %), mp 107-108 °C, IR (Nujol): ν= 3270, 1680, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.18 (6H, t, *J*=7 Hz) , 2.26 (3H, s), 2.94 (2H, t, *J*=6 Hz), 3.54 (2H, t, *J*=6 Hz), 4.10 (2H, q, *J*=7 Hz), 4.15 (2H, q, *J*=7 Hz), 7.00-7.50 (4H, m), 7.68 (1H, d, *J*=14 Hz), 8.00 (1H, br s, exchangeable with D_2O), 9.10 (1H, br s, exchangeable with D_2O), Anal. Calcd For $C_{19}H_{24}N_2O_2$: C 66.26, H 7.02, N 8.13. Found: C 65.95, H 7.03, N 8.02.
A solution of **1b** (34.4 g, 0.1 mol) in a mixture of AcOH (150 mL) and Ac_2O (200 mL) was refluxed for 50 h. After evaporation of the mixture under reduced pressure, the residue was treated with acetone to leave a brown solid which was recrystallized from a mixture of acetone and EtOH to give the diacetamide (**4b**) (14.0 g, 45 %) as pale brown prisms, mp 232-233 °C. IR (Nujol): ν=1700, 1640, 1600 cm^{-1}; 1H NMR ($CDCl_3$): δ=2.12-2.27 (1.5H, m), 2.17 (1.5H, s), 2.20 (1.5H, s), 2.33 (0.5H, dd, *J*=9.9, 18.1 Hz), 2.48-2.73 (1H, m), 2.57 (1.5H, s), 2.58 (1.5H, s), 3.05 (0.5H, dd, *J*=6.9, 17.6 Hz), 3.35 (0.5H, dd, *J*=7.1, 18.1 Hz), 3.70-3.93 (2H, m), 4.45 (0.5H, dd, *J*=6.9, 10.2 Hz), 4.86 (0.5H, dd, *J*=7.4, 10.2

Hz), 6.12 (0.5H, s), 6.17 (0.5H, s), 7.06 (1H, td, *J*=1.4, 6.3 Hz), 7.13-7.22 (1H, m), 7.31-7.42 (1H, m), 8.08 (1H, dd, *J*=6.0, 8.2 Hz).

Tetracyclic Monoacetamide (7)

To a stirred solution of the diacetamide (**4b**) (3.0 g, 9.68 mmol) in MeOH (50 mL) was added K_2CO_3 (6.69 g, 48.4 mmol) at rt and the stirring was continued for 1.5 h at the same temperature. After addition of water (30 mL), the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (75 g, elution with MeOH-$CHCl_3$ 7:93) to give the monoacetamide (**7**, 2.23 g, 86 %) as colorless crystals, mp 262-264 °C (from $CHCl_3$-hexane). IR (Nujol): ν=3128, 1644 cm^{-1}; 1H NMR ($CDCl_3$): δ=2.04-2.70 (m, 3H), 2.19 (s, 1.7H), 2.22 (s, 1.30H), 2.97 (dd, 0.57H, *J*=7.6, 18.0 Hz), 3.20 (dd, 0.43H, *J*=7.7, 18.1 Hz), 3.72-3.98 (m, 2H), 4.43 (t, 0.57H, *J*=8.2 Hz), 4.82 (t, 0.43H, *J*=8.2 Hz), 5.54 (s, 0.43H), 5.56 (s, 0.57H), 6.90-7.50 (m, 3H), 7.20-7.30 (m, 1H), 9.75 (s, 0.43H), 9.76 (s, 0.57H); MS: *m/z*=268 (M^+), 170 (100 %); HRMS: Calcd for $C_{16}H_{16}N_2O_2$: 268. 1212. Found: 268. 1185.

Tetracyclic α-Iodo-enone (9)

To a stirred solution of the monoacetamide (**7**) (2.0 g, 7.46 mmol) in a mixture of pyridine and dichloromethane (30 % v/v, 70 mL) was added I_2 (3.41 g, 13.4 mmol) at 0 ℃ and the stirring was continued for 30 min at the same temperature and for 1 h at rt. The mixture was treated with 10 % aqueous $Na_2S_2O_3$ and was extracted with $CHCl_3$. The extract was washed successively with 10 % aqueous $Na_2S_2O_3$, 5 % aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave a colorless solid which was washed well with $CHCl_3$ and MeOH to give the iodide (**9**) (2.53 g, 86 %), mp 225-227 °C. IR (Nujol): ν=3130, 1613, 1580cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=2.10-2.76 (m, 3H), 2.17 (s, 1.5H), 2.20 (s, 1.5 H), 3.23 (dd, 0.5H, *J*=7.4, 17.9 Hz), 3.49 (dd, 0.5H, *J*=7.8, 18.3 Hz), 3.74-3.99 (m, 2H), 4.47 (t, 0.5H, *J*=8.1 Hz), 4.90 (t, 0.5H, *J*=8.4 Hz), 6.98-7.08 (m, 3H), 7.22-7.36 (m, 1H), 7.65-7.73 (m, 0.5H, *J*=1.9, 7.7 Hz), 8.59-8.66(m, 0.5H); MS: *m/z*=394 (M^+), 352 (100 %); HRMS: Calcd for $C_{16}H_{15}N_2O_2I$: 394. 0180. Found: 394. 0152.

The Woodward Ketone (11)

A mixture of the iodide (**9**) (41 mg, 0.10 mmol), methyl (*Z*)-3-tributylstannylacrylate (86 mg, 0.22 mmol) and dried $ZnCl_2$ (31 mg, 0.22 mmol) in DMF (4 mL) was stirred at rt for 1 h. To the mixture was then added $PdCl_2(PPh_3)_2$ (7.2 mg, 10 mol %) and the mixture was refluxed for 3 h. After cooling, the mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (7 g) to give the Woodward ketone (**11**) (25 mg, 75 %) as colorless crystals from a MeOH-$CHCl_3$ (3:97) eluent and the dehalogenated amide (**7**) (4 mg, 14 %) from a MeOH-$CHCl_3$ (10:90) eluent.

The Woodward ketone (**11**): mp 251-253 °C (MeOH) (lit.[3], mp 234-236 °C). UV (MeOH):λ max=236, 294, 318, 332, 348 nm (lit.[3], λ max=237, 294, 319, 332, 347 nm); IR (Nujol): ν=1661, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=2.16-2.32 (m, 1H), 2.21 (s, 1.5H), 2.25 (s, 1.5H), 2.50 (dd, 0.5H, *J*=8.5, 19.2 Hz), 2.58-2.83 (m, 1.5H), 3.22 (dd, 0.5H, *J*=7.4, 18.7 Hz), 3.46 (dd, 0.5H, *J*=7.8, 19.1 Hz), 3.78-4.14(m, 2H), 4.61 (t, 0.5H, *J*=8.0 Hz), 4.97 (t, 0.5H, *J*=8.0 Hz), 6.59 (d, 1H, *J*=9.6 Hz), 7.21-7.40 (2H, m), 7.45-7.75 (m, 1H), 7.78(d, 1H, *J*=9.6 Hz), 8.59 (dd, 1H, *J*=2.5, 8.0 Hz); MS: *m/z*=320 (M^+), 278 (100 %); HRMS: Calcd for $C_{19}H_{16}N_2O_3$=320.1161. Found: 320. 1172.

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