Regioselective Preparation of Diethyl 3,4-Disubstituted 1,5-Dihydro-5-oxo-2*H*-pyrrol-2-ylphosphonates and Their Coupling with Aldehydes. Application to the Synthesis of C/D-Rings Component of Phycocyanobilin

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Diethyl 3,4-disubstituted 1,5-dihydro-5-oxo-2*H*-pyrrol-2-ylphosphonates were regioselectively prepared by acidic hydrolysis of diethyl 3,4-disubstituted 5-bromo-2-pyrrolylphosphonates. The resulting 1,5-dihydro-2*H*-pyrrol-2-ones readily underwent the coupling reaction with various aldehydes to afford the corresponding 1,5-dihydro-5-methylene-2*H*-pyrrol-2-ones including pyrromethenone derivatives in good yields. A series of these reactions was successfully applied to the synthesis of C/D-rings component of phycocyanobilin.

3,4-Disubstituted 1,5-dihydro-5-methylene-2*H*-pyrrol-2-one derivatives are useful building blocks for the synthesis of biologically important tetrapyrrole pigments such as bilirubin, the prosthetic groups of biliproteins such as phytochrome, and heme.[1] Several methods have been so far reported for the synthesis of such 3,4-disubstituted 1,5-dihydro-5-methylene-2*H*-pyrrol-2-one derivatives.[2—4] In the previous paper,[5] we have reported the Wittig-type coupling reaction of 3-methyl-4-(*p*-tolyl)-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one[4] (**1**) with various aldehydes by the use of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and two molar amounts of tributylphosphine to give the corresponding 5-methylene derivatives **2** including a pyrromethenone derivative as illustrated in Scheme 1. But in some cases, especially with aliphatic aldehydes, the yield of the expected 5-methylene compounds were poor probably due to the competitive aldol condensation of the aldehydes. This result prompted us to develop an alternative method for the synthesis of the 5-methylene derivatives.

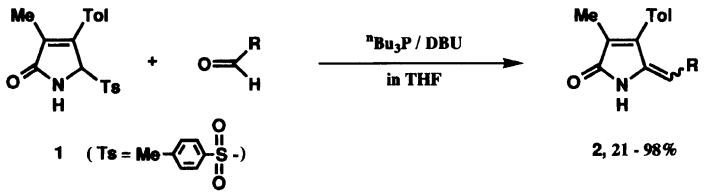
We wish to report here the alternative method involving Horner–Emmons-type coupling reaction of diethyl 1,5-dihydro-4-methyl-5-oxo-3-(*p*-tolyl)-2*H*-pyrrol-2-ylphosphonate (**3a**) with various aldehydes to afford the corresponding 5-methylene derivatives **2** and an application to the synthesis of pyrromethenone derivatives **11** and **12**.

Result and Discussion

Preparation of the diethyl 3,4-disubstituted 1,5-dihydro-5-oxo-2*H*-pyrrol-2-ylphosphonate (**3**) was first attempted starting from **1** and triethyl phosphite as shown in Scheme 2, however, the yield of **3** was not satisfactory in spite of many attempts under various conditions. Therefore, it was examined to prepare **3** by acidic hydrolysis of diethyl 3,4-disubstituted 2-pyrrolylphosphonate (**6**) in a similar way to the one developed by us for the synthesis of **1**.[4]

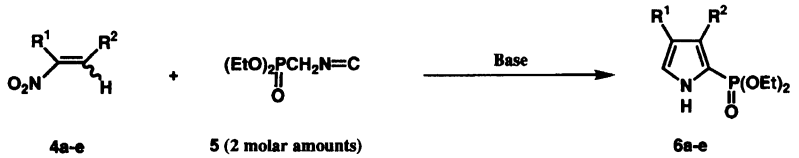
Recently, Yuan and Huang reported the preparation of the 2-pyrrolylphosphonates **6** from nitroolefins **4** and diethyl isocyanomethylphosphonate (**5**) by the use of lithium diisopropylamide (LDA) as a base according to Barton's method.[6,7] Although they described that the condensation of **4** and **5** in the presence of an organic base was unsuccessful,[7] we found that nitroolefin **4a** reacted with **5** in the presence of DBU giving the pyrrole derivative **6a** in 62% yield (Entry 1 in Table 1). Nevertheless, in the case of an isomerizable aliphatic nitroolefin **4b**, no cyclization took place in the presence of a base like DBU, ^{t}BuOK, ^{n}BuLi, NaOEt, and K_2CO_3 under various conditions. Such an unsuccessful result, in contrast to the case where isocyanoacetic acid ester[6] or tosylmethyl isocyanide (TosMIC)[4] was used instead of **5**, seemed to be due to the relatively weak acidity of methylene protons of **5** as expected from the values of the chemical shift of methylene protons of them [^{1}H NMR (δ in $CDCl_3$): $CNC\underline{H}_2P(O)(OEt)_2$ (**5**), 3.74 ppm; $CNC\underline{H}_2CO_2Et$, 4.23 ppm; $CNC\underline{H}_2Ts$ (TosMIC), 4.58 ppm]. Thus, the free base isomerizes aliphatic nitroolefin **4b** into useless allylic nitro-compound prior to the reaction with **5**, followed by polymerization. Accordingly, we examined the pyrrole formation from the nitroolefin **4b** by means of two phase system in order to keep the amount of the base in the organic phase small throughout the reaction. When an equimolar amount of the compounds **4b** and **5** were reacted using 0.1 molar amount of tetrabutylammonium bromide as a phase-transfer catalyst in 40% aqueous NaOH and CH_2Cl_2, the corresponding pyrrole **6b** was obtained in 39% yield. The yield of the pyrrole could be improved by using two molar amounts of diethyl isocyanomethylphosphonate (**5**) under the same reaction conditions, up to 67% (Entry 2 in Table 1). In a similar manner, the pyrrole derivatives **6c—e** were also prepared in reasonable yields as shown in Table 1. It is now revealed that the present two phase system provides a new methodology for the preparation of pyrrole derivatives from nitroolefins.

Next, we attempted to convert the diethyl 3,4-disubstituted 2-pyrrolylphosphonate (**6**) to the corresponding diethyl 3,4-disubstituted 1,5-dihydro-5-oxo-2*H*-pyrrol-2-ylphosphonate (**3**) (Scheme 3). The bromination[4] at



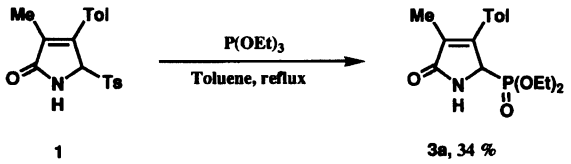
Scheme 1.

Table 1.



Entry	4a—e	R^1	R^2	Base (molar amounts)	Conditions	Yields of 6a—e/%
1	4a[b]	CH_3	*p*-$CH_3C_6H_4$	DBU (1.2)	CH_3CN, r.t., on[a]	**6a**, 62
2	**4b**	CH_3	CH_3CH_2	40% aq NaOH (5)	CH_2Cl_2, 0 °C→r.t., 7 h Bu_4NBr (0.1 molar amount)	**6b**, 67
3	**4c**	CH_3	$C_6H_5CH_2CH_2$	40% aq NaOH (5)	CH_2Cl_2, 0 °C→r.t., on[a] Bu_4NBr (0.1 molar amount)	**6c**, 43
4	**4d**	CH_3	*p*-$CH_3OC_6H_4$	40% aq NaOH (5)	CH_2Cl_2, 0 °C→r.t., on[a] Bu_4NBr (0.1 molar amount)	**6d**, 53
5	**4e**	CH_3CH_2	CH_3	40% aq NaOH (5)	CH_2Cl_2, 0 °C→r.t., on[a] Bu_4NBr (0.1 molar amount)	**6e**, 56

a) on: overnight. b) Equimolar amount of **5** was used.



Scheme 2.

α-position of the pyrrole derivatives **6** with two molar amounts of trimethylphenylammonium tribromide was found to give the corresponding brominated compounds **7** in quantitative yields, which were subsequently subjected to acidic hydrolysis without further purification. The hydrolysis[4] of **7** with aqueous trifluoroacetic acid (TFA : H_2O=5 : 1) did not take place at room temperature in contrast to the case of the previous 2-tosylpyrroles, but proceeded at 45 °C to give the corresponding pyrrolinone derivatives **3** in moderate yields.

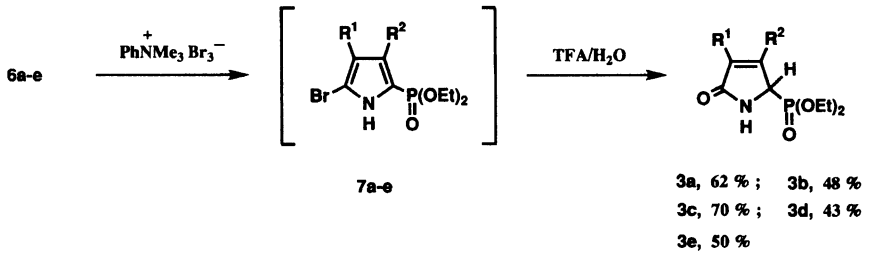
Finally, the coupling reaction of the compound **3a** was examined with two molar amounts of *p*-tolualdehyde in the presence of 1.4 molar amounts of ^{t}BuOK in CH_2Cl_2 at −72 °C and then at room temperature to afford the corresponding 5-methylene derivative **2a** in 69% yield, as an isolable mixture of (*Z*)-(55%) and (*E*)-(14%) isomers. When two molar amounts of ^{t}BuOK were used, the yield of **2a** was improved up to 79% (*Z*/*E*=78/22). Similarly, other 5-methylene derivatives **2b**—**i** were also obtained in good yields with various aldehydes including aliphatic aldehydes (Entries 8 and 9, see also Experimental section in order to compare with the preparation of **2i** (33% yield) by a conventional method) as shown in Table 2. A plausible reaction pathway is depicted in Scheme 4. From the fact that the use of ^{t}BuOK more than equimolar to **3a** gave higher yield of **2** (Entries 1—3), the dianion intermediate (**9a**,**b**) seems to be partially formed by stabilization of its 6π-electrons aromaticity as illustrated.

In addition, the present method mentioned above was employed for the condensation of the pyrrolinones **3a**,**e** with a formyl pyrrole **10**[8] to afford the corresponding pyrromethenone derivatives **11** and **12** in 80 and 85% yields, respectively, as a mixture of (*Z*)- and (*E*)-isomers (Scheme 5). The (*E*)-isomers could be converted to thermodynamically favored (*Z*)-isomers in quantitative yields by treatment with I_2 at room temperature.[5] The pyrromethenone **12** thus obtained is a C/D-rings component of phycocyanobilin dimethyl ester.[9] While a reported base-catalyzed Knoevenagel-type condensation to the pyrromethenone **12** required a subsequent reesterification with diazomethane, the present method does not require such a tedious procedure.[3]

Thus, a series of present preparation and reaction of diethyl 3,4-disubstituted 1,5-dihydro-5-oxo-2*H*-pyrrol-2-ylphosphonates (**3**) provides a new useful method for the synthesis of the tetrapyrrole pigments.

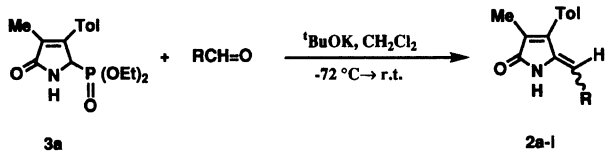
Experimental

All the melting points were determined with a micro melting apparatus (Yanagimoto Seisakusho) and were uncorrected. The ^{1}H NMR, IR, and MS spectra were recorded



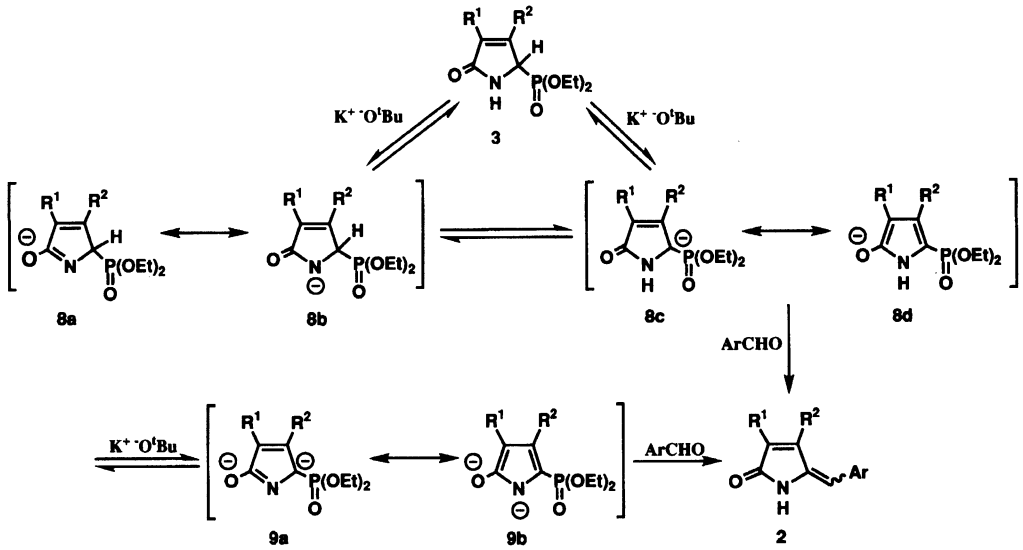
Scheme 3.

Table 2.



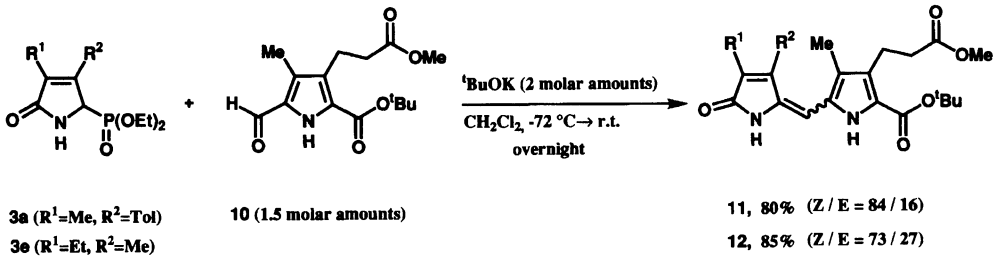
Entry	RCHO (molar amounts)	^{t}BuOK molar amounts	Time	Yield of **2a**—**i**/%	Ratio[a] of Z/E
1	*p*-$CH_3C_6H_4CHO$ (2)	1.4	Overnight	**2a**, 69	80/20
	p-$CH_3C_6H_4CHO$ (2)	2.0	Overnight	79	78/22
2	*p*-$O_2NC_6H_4CHO$ (2)	1.4	Overnight	**2b**, 69	85/15
	p-$O_2NC_6H_4CHO$ (2)	2.0	Overnight	71	85/15
3	*p*-BrC_6H_4CHO (2)	1.4	Overnight	**2c**, 29	100/0
	p-BrC_6H_4CHO (2)	2.0	Overnight	66	100/0
4	*o*-BrC_6H_4CHO (3)	1.4	Overnight	**2d**, 86	73/27
5	2-Furaldehyde (2.4)	2.0	5 h	**2e**, 90	88/12
6	C_6H_5CH=$CHCHO$ (2) (*E*)	2.0	Overnight	**2f**, 80	75/25
7	EtO_2CCHO (2)	2.0	Overnight	**2g**, 88	75/25
8	CH_3CHO (10)	3.0	Overnight	**2h**, 81	53/47
9	$C_6H_5CH_2CH_2CHO$ (1)	1.0	Overinght	**2i**, 67	85/15
	$C_6H_5CH_2CH_2CHO$ (2)	2.0	Overinght	80	96/4

a) Determined by NMR spectra.



Scheme 4.

on a JEOL JNM-GX 400 (400 MHz) FT-NMR spectrometer, a JASCO IRA-1 diffraction grating infrared spectrometer, and a Hitachi M-80 mass spectrometer, respectively. The chemical shifts of NMR are reported in the δ-scale rel-



Scheme 5.

ative to TMS as an internal standard. All the solvents were distilled and stored over a drying agent. Thin layer chromatography (TLC) and flash-column chromatography were performed by the use of Merck's silica gel 60 PF_{254} (Art. 7749) and Wakogel C-300, respectively.

Preparation of Diethyl 4-Methyl-3-(*p*-tolyl)-2-pyrrolylphosphonate (6a): A solution of DBU (332 mg, 2.19 mmol) in 2 ml of dry CH_3CN was added dropwise to a mixed solution of diethyl isocyanomethylphosphonate[10] (318 mg, 1.80 mmol) and 1-(*p*-tolyl)-2-nitropropene (318 mg, 1.80 mmol) in 2 ml of dry CH_3CN at 0 °C under N_2 atmosphere with stirring, and the reaction mixture was allowed to stand overnight. After removal of the solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the resulting residue was separated by a preparative TLC (SiO_2, AcOEt) to give **6a** in 62% yield (343 mg) as a colorless solid; Mp 153 °C (from AcOEt–hexane, lit,[7] 158—160 °C); IR (KBr) 3180, 2980, 2900, 1520, 1460, 1440, 1380, 1340, 1250, 1190, 1150, 1020, 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 (6H, t, J=7.02 Hz), 2.04 (3H, s), 2.37 (3H, s), 3.80—4.00 (4H, m), 6.83—6.85 (1H, m), 7.18 (2H, d, J=7.94 Hz), 7.27 (2H, d, J=7.94 Hz), 9.17 (1H, br). Found: C, 62.50; H, 7.22; N, 4.40%. Calcd for $C_{16}H_{22}NO_3P$: C, 62.54; H, 7.17; N, 4.56%.

Preparation of Diethyl 3-Ethyl-4-methyl-2-pyrrolylphosphonate (6b): To a mixed solution of diethyl isocyanomethylphosphonate (354 mg, 2.0 mmol) and 2-nitro-2-pentene (115 mg, 1.0 mmol) in 3 ml of dry CH_2Cl_2 was added a solution of Bu_4NBr (32 mg, 0.1 mmol) in 1 ml of dry CH_2Cl_2 at 0 °C under N_2 atmosphere with stirring. Then, 40% aqueous NaOH (2.5 ml) was added dropwise and the reaction mixture was allowed to stand overnight at room temperature with stirring. After neutralization with 6 mol dm^{-3} HCl, the organic layer was separated and subsequently washed with aqueous $NaHCO_3$ and brine followed by drying over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was separated by a preparative TLC (SiO_2, benzene/AcOEt=1/1, v/v) to obtain **6b**[7] as a colorless oil in 67% yield (164 mg): MS m/z 245 (M^+, 100%), 230 (12.38), 217 (18.48), 216 (66.81), 188 (62.21), 174 (14.62), 170 (12.28), 158 (14.97), 136 (11.24), 109 (16.73), 108 (23.62); IR (neat) 3200, 2960, 2920, 2850, 1470, 1440, 1380, 1300, 1240, 1150, 1040, 1020, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 (3H, t, J=7.63 Hz), 1.31 (6H, t, J=7.02 Hz), 2.03 (3H, s), 2.57 (2H, q, J=7.63 Hz), 3.92—4.14 (4H, m), 6.69—6.71 (1H, m), 9.42 (1H, br).

In a similar way, the pyrrole derivatives **6c**—**e** were prepared from the corresponding nitro olefins and diethyl isocyanomethylphosphonate. Their physical and spectral data are shown in the following.

Diethyl 4-Methyl-3-phenethyl-2-pyrrolylphosphonate (6c): An oil; MS m/z 321 (M^+, 30.29%), 231 (12.06), 230 (100), 186 (26.13), 174 (20.61), 158 (49.51), 156 (19.36), 91 (17.88); IR (neat) 3220, 3020, 2980, 2920, 2860, 1570, 1440, 1380, 1240, 1160, 1020, 780, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32 (6H, t, J=7.02 Hz), 1.97 (3H, s), 2.75—2.86 (4H, m), 3.95—4.20 (4H, m), 6.71—6.73 (1H, m), 7.16—7.29 (5H, m), 9.5 (1H, br).

Diethyl 3-(*p*-Methoxyphenyl)-4-methyl-2-pyrrolylphosphonate (6d): A colorless solid; mp 153 °C (from AcOEt/hexane, lit,[7] 148—150 °C); IR (KBr) 3160, 2960, 2880, 1590, 1510, 1430, 1350, 1230, 1160, 1020, 820, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (6H, t, J=7.02 Hz), 2.03 (3H, s), 3.83 (3H, s), 3.80—4.01 (4H, m), 6.79—6.81 (1H, m), 6.87 (2H, d, J=8.24 Hz), 7.26 (2H, d, J=8.24 Hz), 9.29 (1H, br). Found: C, 59.40; H, 6.87; N, 4.28%. Calcd for $C_{16}H_{22}NO_4P$: C, 59.44; H, 6.86; N, 4.33%.

Diethyl 4-Ethyl-3-methyl-2-pyrrolylphosphonate (6e): A colorless solid; mp 55.5—56.0 °C (from hexane); IR (KBr) 3250, 2980, 2920, 1560, 1440, 1380, 1240, 1210, 1040, 800, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.17 (3H, t, J=7.63 Hz), 1.30 (6H, t, J=7.02 Hz), 2.13 (3H, s), 2.40 (2H, q, J=7.63 Hz), 3.94—4.11 (4H, m), 6.70 (1H, m), 10.10 (1H, br). Found: C, 53.95; H, 8.20; N, 5.71%. Calcd for $C_{11}H_{20}NO_3P$: C, 53.87; H, 8.22; N, 5.71%.

Diethyl 1,5-Dihydro-4-methyl-5-oxo-3-(*p*-tolyl)-2*H*-pyrrol-2-ylphosphonate (3a): A solution of $PhNMe_3Br_3$ (150 mg, 0.4 mmol) in 3 ml of dry CH_2Cl_2 was added to a solution of **6a** (62 mg, 0.2 mmol) in 3 ml of dry CH_2Cl_2 at 0 °C. After stirring for 10 min, the solvent was removed in vacuo and the residue was partitioned between AcOEt and water. The organic layer was separated and washed successively with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. The crude brominated compound **7a** obtained by evaporation of the solvent was treated with TFA/H_2O (5/1) under N_2 atmosphere at 45 °C for 5 h. After concentration, the residue was partitioned between AcOEt and water. The organic layer was successively washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was seperated by a preparative TLC (SiO_2, AcOEt/EtOH=10/1, v/v) to give the corresponding desired compound **3a** as a colorless solid in 62% yield (40 mg): Mp 185 °C (from AcOEt/hexane); IR (KBr) 3180, 3040, 2900, 2860, 1660, 1500, 1430, 1250, 1160, 1020, 810, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.09 (3H, t, J=7.01 Hz), 1.18 (3H, t, J=7.02 Hz), 2.01 (3H, dd, J=1.83, 4.27 Hz), 2.40 (3H, s), 3.85—4.02 (4H, m), 4.87

(1H, d, J=17.09 Hz), 6.87 (1H, br), 7.23 (2H, d, J=7.94 Hz), 7.27 (2H, d, J=7.94 Hz). Found: C, 59.16; H, 6.82; N, 4.39%. Calcd for $C_{16}H_{22}NO_4P$: C, 59.44; H, 6.86; N, 4.33%.

In a similar manner, the 3-pyrrolin-2-ones **3b**—**e** were prepared and their physical and spectral data are shown in the following.

Diethyl 3-Ethyl-1,5-dihydro-4-methyl-5-oxo-2*H*-pyrrol-2-ylphosphonate (3b): A colorless oil; MS m/z 261 (M^+, 56.41%), 246 (12.17), 205 (29.94), 190 (11.69), 125 (28.28), 124 (100), 123 (46.78), 109 (10.58), 91 (29.48); IR (neat) 3200, 2980, 2920, 2840, 1670, 1440, 1360, 1240, 1150, 1020, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15 (3H, t, J=7.33 Hz), 1.27 (3H, t, J=7.02 Hz), 1.33 (3H, t, J=7.02 Hz), 1.84 (3H, d, J=4.27 Hz), 2.49—2.63 (2H, m), 4.06—4.19 (4H, m), 4.39 (1H, d, J=17.70 Hz), 7.01 (1H, br).

Diethyl 1,5-Dihydro-4-methyl-5-oxo-3-phenethyl-2*H*-pyrrol-2-ylphosphonate (3c): A colorless oil; MS m/z 337 (M^+, 100%), 246 (95.34), 200 (81.62), 199 (80.25), 198 (62.23), 183 (15.49), 156 (10.80), 91 (90.33); IR (neat) 3220, 3020, 2980, 2920, 2860, 1570, 1440, 1380, 1240, 1160, 1020, 780, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (3H, t, J=7.02 Hz), 1.32 (3H, t, J=7.02 Hz), 1.73 (3H, dd, J=1.84, 4.28 Hz), 2.76—2.92 (4H, m), 4.07—4.18 (4H, m), 4.23 (1H, d, J=17.09 Hz), 6.08 (1H, br), 7.15–7.29 (5H, m).

Diethyl 1,5-Dihydro-3-(*p*-methoxyphenyl)-4-methyl-5-oxo-2*H*-pyrrol-2-ylphosphonate (3d): A colorless solid; mp 163 °C (from AcOEt/hexane); IR (KBr) 3200, 3040, 2980, 2900, 2840, 1670, 1590, 1500, 1350, 1240, 1160, 1020, 770, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10 (3H, t, J=7.02 Hz), 1.20 (3H, t, J=7.02 Hz), 1.99 (3H, dd, J=1.84, 4.27 Hz), 3.84 (3H, s), 3.85—4.02 (4H, m), 4.84 (1H, d, J=17.09 Hz), 6.92 (2H, d, J=8.44 Hz), 7.27 (1H, br), 7.32 (2H, d, J=8.44 Hz). Found: C, 56.51; H, 6.41; N, 4.22%. Calcd for $C_{16}H_{22}NO_5P$: C, 56.63; H, 6.53; N, 4.13%.

Diethyl 4-Ethyl-1,5-dihydro-3-methyl-5-oxo-2*H*-pyrrol-2-ylphosphonate (3e): A yellow oil; MS m/z 261 (M^+, 29.80%), 190 (11.81), 125 (14.38), 124 (100), 109 (14.86), 107 (20.50), 96 (22.63), 81 (16.59), 80 (13.30), 53 (10.90), 41 (19.73), 29 (22.37); IR (neat) 3200, 2980, 2920, 2880, 1680, 1440, 1380, 1240, 1040, 960, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (3H, t, J=7.33 Hz), 1.30 (3H, t, J=7.02 Hz), 1.32 (3H, t, J=7.02 Hz), 2.11 (3H, d, J=2.44 Hz), 2.27—2.32 (2H, m), 4.04—4.19 (4H, m), 4.28 (1H, d, J=17.70 Hz), 7.19 (1H, br).

Preparation of 1,5-Dihydro-3-methyl-4-(*p*-tolyl)-5-(*p*-tolylmethylene)-2*H*-pyrrol-2-one (2a): A solution of *p*-tolualdehyde (24 mg, 0.2 mmol) in 1 ml of dry CH_2Cl_2 was added to the suspension of ^{t}BuOK (22 mg, 0.2 mmol) in 1 ml of dry CH_2Cl_2 at −72 °C under N_2 atmosphere with stirring. Then, a solution of **3a** (64 mg, 0.2 mmol) in 1 ml of dry CH_2Cl_2 was added dropwise and the reaction mixture was allowed to stand overnight at room temperature. The product was extracted with ethyl acetate from the residue obtained by removal of the solvent and the extract was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to a preparative TLC (SiO_2, benzene/AcOEt=5/1, v/v) to afford (*Z*)- and (*E*)-**2a** as colorless solids in 55% (32 mg) and 14% (8 mg) yields, respectively. (*E*)-Isomer was readily converted to (*Z*)-isomer by treatment with a small amount of iodine in CH_2Cl_2 at room temperature in quantitative yield. (*Z*)-Isomer; A colorless solid; mp 256 °C (from AcOEt); IR (KBr) 3200, 3080, 2920, 1660, 1500, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.35 (3H, s), 2.44 (3H, s), 5.96 (1H, s), 7.18 (2H, d, J=8.24 Hz), 7.24 (2H, d, J=8.24 Hz), 7.31 (2H, d, J=8.24 Hz), 7.51 (2H, d, J=8.24 Hz), 7.86 (1H, br). Found: C, 83.27; H, 6.70; N, 4.86%. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84%. When an exoolefin proton was irradiated, 3.46 and 8.26% of NOE were observed for the ortho protons of both *p*-tolyl groups at 4- and *gem*-positions.

(*E*)-Isomer; A colorless solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.94 (3H, s), 2.18 (3H, s), 2.25 (3H, s), 6.54 (1H, s), 6.81 (2H, d, J=7.84 Hz), 6.87 (2H, d, J=7.84 Hz), 7.25 (2H, d, J=7.84 Hz), 7.71 (2H, d, J=7.84 Hz), 8.19 (1H, br).

In a similar manner, the compounds **2b**—***i*** were also prepared from **3a** and the corresponding aldehydes. Their physical and spectral data are shown in the following.

1,5-Dihydro-3-methyl-5-(*p*-nitrophenylmethylene)-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2b): (*Z*)-Isomer; A yellow solid; mp 293 °C (from AcOEt); IR (KBr) 3200, 3040, 2880, 1660, 1620, 1490, 1320, 1120, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.00 (3H, s), 2.45 (3H, s), 5.99 (1H, s), 7.32 (2H, d, J=7.84 Hz), 7.25 (2H, d, J=7.84 Hz), 7.52 (2H, d, J=7.84 Hz), 8.19 (1H, br), 8.24 (2H, d, J=7.84 Hz). Found: C, 71.34; H, 4.93; N, 8.69%. Calcd for $C_{19}H_{16}NO_3$: C, 71.24; H, 5.03; N, 8.74%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho protons of *p*-tolyl and *p*-nitrophenyl groups in 6.07 and 7.67%, respectively.

(*E*)-Isomer; A yellow solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.95 (3H, s), 2.23 (3H, s), 6.54 (1H, s), 6.81 (2H, d, J=7.93 Hz), 6.87 (2H, d, J=7.93 Hz), 6.94 (2H, d, J=7.93 Hz), 7.71 (2H, d, J=7.93 Hz), 7.93 (1H, br).

5-(*p*-Bromophenylmethylene)-1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2c): (*Z*)-Isomer; A colorless solid; mp 285 °C (from AcOEt); IR (KBr) 3200, 3040, 2880, 1640, 1610, 1480, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.24 (3H, s), 5.89 (1H, s), 7.20 (2H, d, J=8.24 Hz), 7.24 (2H, d, J=8.24 Hz), 7.30 (2H, d, J=8.24 Hz), 7.50 (2H, d, J=8.24 Hz), 7.63 (1H, br). Found: C, 64.64; H, 4.48; N, 3.88%. Calcd for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55; N, 3.95%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho protons of *p*-tolyl and *p*-bromophenyl groups in 7.02 and 7.34%, respectively.

5-(*o*-Bromophenylmethylene)-1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2d): (*Z*)-Isomer; A colorless solid; mp 198 °C (from ethanol); IR (KBr) 3160, 3040, 2920, 1680, 1640, 1500, 1420, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.02 (3H, s), 2.43 (3H, s), 6.17 (1H, s), 7.15 (1H, t, J=7.63 Hz), 7.28 (4H, s), 7.36 (1H, t, J=7.63 Hz), 7.49 (1H, d, J=7.63 Hz), 7.61 (1H, d, J=7.63 Hz), 7.76 (1H, br). Found: C, 64.59; H, 4.45; N, 3.94%. Calcd for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55; N, 3.95%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensity of the ortho protons of *p*-tolyl group in 7.69%.

(*E*)-Isomer; A colorless solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.93 (3H, s), 2.18 (3H, s), 6.49 (1H, s), 6.54 (1H, m), 6.56 (1H, m), 6.80 (4H, s), 7.31 (1H, s), 7.37 (1H, d, J=8.24 Hz), 7.96 (1H,

br).

5-(2-Furylmethylene)-1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2e): (*Z*)-Isomer; A colorless solid; mp 186 °C (from AcOEt–hexane); IR (KBr) 3200, 3000, 2900, 1680, 1630, 1500, 1470, 1000, 810, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.42 (3H, s), 5.75 (1H, s), 6.33 (1H, d, J=2.35 Hz), 6.44 (1H, dd, J=1.83, 2.35 Hz), 7.21 (2H, d, J=7.94 Hz), 7.28 (2H, d, J=7.94 Hz), 7.49 (1H, d, J=1.83 Hz), 8.49 (1H, br). Found: C, 77.07; H, 5.68; N, 5.30%. Calcd for $C_{17}H_{15}NO_2$: C, 76.86; H, 5.70; N, 5.28%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho protons of *p*-tolyl group and the proton at 3-position of furyl group in 5.05 and 3.84%, respectively.

(*E*)-Isomer; A yellow solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.90 (3H, s), 2.38 (3H, s), 5.37 (1H, d, J=3.35 Hz), 6.05 (1H, dd, J=1.22, 3.35 Hz), 6.19 (1H, s), 6.95 (1H, d, J=1.22 Hz), 7.12 (2H, d, J=7.94 Hz), 7.27 (2H, d, J=7.94 Hz), 7.42 (1H, br).

1,5-Dihydro-3-methyl-5-(3-phenylallylidene)-4-(*p*-tolyl)-2*H*-pyrrrol-2-one (2f): (*Z*)-Isomer; A yellow solid; mp 239 °C (from cyclohexane); IR (KBr) 3120, 3000, 2900, 2840, 1660, 1600, 1480, 1430, 1360, 1140, 800, 740 cm^{-1}; ^1H NMR δ=2.20 (3H, s), 2.44 (3H, s), 5.91 (1H, d, J=11.9 Hz), 6.67 (1H, d, J=15.56 Hz), 7.24 (4H, m), 7.30 (2H, d, J=7.93 Hz), 7.34 (2H, d, J=7.93 Hz), 7.50 (2H, d, J=7.93 Hz), 8.97 (1H, br). Found: C, 83.87; H, 6.28; N, 4.57%. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho protons of *p*-tolyl group and two olefinic protons of styryl group in 9.34, 4.18, and 9.05%, respectively.

(*E*)-Isomer; A yellow solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.91 (3H, s), 2.50 (3H, s), 6.27 (1H, dd, J=3.96, 7.02 Hz), 6.46 (2H, m), 6.93 (2H, d, J=7.63 Hz), 7.16 (3H, m), 7.32 (2H, m), 7.34 (2H, d, J=7.63 Hz), 9.23 (1H, br).

Ethyl 2-[1,5-Dihydro-4-methyl-5-oxo-3-(*p*-tolyl)-2*H*-pyrrol-2-ylidene]acetate (2g): (*Z*)-Isomer; A colorless solid; mp 88 °C (from ethanol); IR (KBr) 3300, 3040, 2980, 2920, 1710, 1680, 1620, 1500, 1410, 1340, 1260, 1200, 1150, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.27 (3H, t, J=7.02 Hz), 1.99 (3H, s), 2.39 (3H, s), 4.21 (2H, q, J=7.02 Hz), 5.27 (1H, s), 7.17 (2H, d, J=7.93 Hz), 7.93 (2H, d, J=7.93 Hz), 9.23 (1H, br). Found: C, 70.89; H, 6.38; N, 5.12%. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensity of the ortho protons of *p*-tolyl group in 3.05%.

(*E*)-Isomer; A colorless solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=0.92 (3H, t, J=7.02 Hz), 1.91 (3H, s), 2.38 (3H, s), 3.52 (2H, q, J=7.02 Hz), 5.66 (1H, s), 7.04 (1H, br), 7.12 (2H, d, J=7.93 Hz), 7.24 (2H, d, J=7.93 Hz).

5-Ethylidene-1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2h): (*Z*)-Isomer; A colorless solid; mp 167 °C (from AcOEt–hexane); IR (KBr) 3160, 3080, 2920, 2860, 1670, 1510, 1440, 820, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.92 (3H, d, J=7.32 Hz), 1.93 (3H, s), 2.40 (3H, s), 5.17 (1H, q, J=7.32 Hz), 7.17 (2H, d, J=7.94 Hz), 7.24 (2H, d, J=7.94 Hz), 8.93 (1H, br). Found: C, 78.86; H, 7.00; N, 6.47%. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho and methyl protons of *p*-tolyl group, and geminal methyl protons in 5.18, 5.76, and 10.83%, respectively.

(*E*)-Isomer; A colorless solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.45 (3H, d, J=7.93 Hz), 1.81 (3H, s), 2.40 (3H, s), 5.54 (1H, q, J=7.93 Hz), 7.11—7.23 (4H, m), 8.39 (1H, br).

1,5-Dihydro-3-methyl-5-(3-phenylpropylidene)-4-(*p*-tolyl)-2*H*-pyrrol-2-one (2i): (*Z*)-Isomer; A pale yellow solid; mp 145 °C (from AcOEt–hexane); IR (KBr) 3120, 3000, 2900, 2840, 1670, 1500, 1440, 1350, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.41 (3H, s), 2.59 (2H, t, J=7.32 Hz), 2.76 (2H, dt, J=7.32, 7.93 Hz), 5.15 (1H, t, J=7.93 Hz), 7.14—7.29 (9H, m), 8.63 (1H, br). Found: C, 82.92; H, 6.95; N, 4.56%. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of the ortho protons of *p*-tolyl group and geminal methylene protons in 6.69 and 6.98%, respectively.

(*E*)-Isomer; A pale yellow solid (contaminated by a small amount of (*Z*)-isomer); ^1H NMR ($CDCl_3$) δ=1.78 (3H, s), 2.12 (2H, dt, J=7.63, 8.24 Hz), 2.41 (3H, s), 2.49 (2H, t, J=7.63 Hz), 5.40 (1H, t, J=8.24 Hz), 6.87 (2H, d, J=7.93 Hz), 7.08 (2H, d, J=7.93 Hz), 7.12—7.28 (5H, m), 7.35 (1H, br).

Preparation of 2i by the Reaction of 1,5-Dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one with 3-Phenylpropanal According to a Conventional Method:[3,8] To a solution of 1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (20 mg, 0.11 mmol)[4] and 3-phenylpropanal (14 mg, 0.11 mmol) in 0.5 ml of abs MeOH was added 0.5 ml of 4 mol dm^{-3} aqueous KOH at 0° C under air. The reaction mixture was gradually warmed to room temperature and allowed to stand overnight with stirring. Insoluble substance precipitated out. Then the reaction mixture was diluted with a large amount of water and extracted with AcOEt. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to a preparative TLC (SiO_2, benzene/AcOEt=5/1, v/v) to afford only (*Z*)-isomer of **2i** in 33% yield. Mp 144.0 °C (from AcOEt–hexane). The ^1H NMR and IR spectra were identical with those described above.

5-[5-*t*-Butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolylmethylene]-1,5-dihydro-3-methyl-4-(*p*-tolyl)-2*H*-pyrrol-2-one (11): 1.5 molar amounts of **10** was used.

(*Z*)-Isomer; A yellow solid; mp 223.5—224 °C (from AcOEt); IR (KBr) 3360, 3000, 2980, 2920, 2880, 1720, 1680, 1650, 1440, 1260, 1120, 810, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.57 (9H, s), 1.96 (3H, s), 1.99 (3H, s), 2.43 (3H, s), 2.49 (2H, t, J=7.63 Hz), 2.97 (2H, t, J=7.63 Hz), 3.66 (3H, s), 5.84 (1H, s), 7.22 (2H, d, J=8.24 Hz), 7.28 (2H, d, J=8.24 Hz), 9.49 (1H, br), 9.52 (1H, br). Found: C, 69.53; H, 7.10; N, 6.02%. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.80; H, 6.94; N, 6.03%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of ortho protons of *p*-tolyl group, CH_3- and NH-protons of pyrrole ring in 5.22, 3.79, and 1.50%, respectively.

(*E*)-Isomer; A yellow solid (contaminated by a small amount of (*Z*)-isomer); ^{1}H NMR ($CDCl_3$) δ=1.47 (9H, s) 2.17 (3H, s), 2.19 (3H, s), 2.36 (3H, s), 2.39 (2H, t, J=7.63 Hz), 2.84 (2H, t, J=7.63 Hz), 3.66 (3H, s), 6.22 (1H, s), 7.05 (2H, d, J=7.94 Hz), 7.14 (2H, d, J=7.94 Hz), 7.45 (1H, br), 8.09 (1H, br).

5-[5-*t*-Butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolylmethylene]-3-ethyl-1,5-dihydro-4-methyl-2*H*-pyrrol-2-one (12): 1.5 molar amounts of **10** was used.

(*Z*)-Isomer; A yellow solid; mp 208—208.5 °C (from MeOH/ether) (lit,[3,8] Mp 205—207 °C, 206—208 °C); IR (KBr) 3370, 2980, 2970, 1730, 1690, 1650, 1440, 1270, 1240, 1130, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.09 (3H, t, J=7.63 Hz), 1.56 (9H, s), 2.09 (3H, s), 2.11 (3H, s), 2.44 (2H, q, J=7.63 Hz), 2.52 (2H, t, J=7.63 Hz), 3.00 (2H, t, J=7.63 Hz), 3.68 (3H, s), 5.94 (1H, s), 9.60 (1H, br), 9.65 (1H, br). Found: C, 65.70; H, 7.68; N, 6.85%. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96%. Stereochemistry was determined by NOE measurement. Irradiation of an exoolefin proton enhanced the signal intensities of 4-methyl and [3-methyl] protons in 9.53 (2.11 ppm) and 5.63% (2.09 ppm), respectively.

(*E*)-Isomer; A yellow solid; ^{1}H NMR ($CDCl_3$) δ=1.09 (3H, t, J=7.63 Hz), 1.57 (9H, s), 1.88 (3H, s), 1.99 (3H, s), 2.37 (2H, q, J=7.63 Hz), 2.53 (2H, t, J=7.63 Hz), 2.99 (2H, t, J=7.63 Hz), 3.67 (3H, s), 6.13 (1H, s), 8.21 (1H, br), 8.82 (1H, br).

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