SYNTHESIS OF 4-(CYANOMETHYLIDENE)- AND 4-(ETHOXYCARBONYLMETHYLIDENE)-4,5,6,7-TETRAHYDROINDOLES AND THEIR DEHYDROGENATION TO 4-(CYANOMETHYL)- AND 4-(ETHOXYCARBONYLMETHYL)INDOLES

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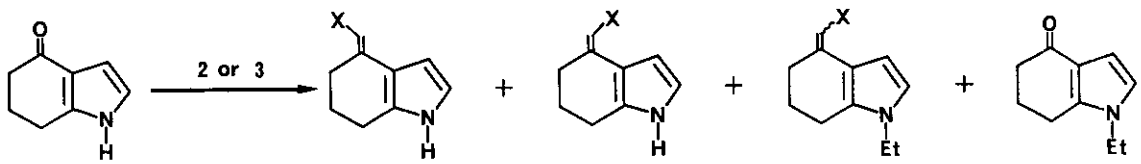
Abstract——The Horner-Wittig reaction of 4-oxo-4,5,6,7-tetrahydroindoles with $(EtO)_2P(O)CH_2CN$ and $(EtO)_2P(O)CH_2CO_2Et$ yielded respectively 4-(cyanomethylidene)- and 4-(ethoxycarbonylmethylidene)-4,5,6,7-tetrahydroindoles, which were catalytically dehydrogenated to 4-(cyanomethyl)- and 4-(ethoxycarbonylmethyl)indoles.

The synthesis of 4-alkylidene-4,5,6,7-tetrahydroindoles followed by oxidative aromatization is attractive as an entry to indoles bearing a carbon substituent at the 4-position.[1] We wish to report here an easy transformation of 4-oxo-4,5,6,7-tetrahydroindoles[2] to 4-(cyanomethylidene)- and 4-(ethoxycarbonylmethylidene)-4,5,6,7-tetrahydroindoles and their catalytic dehydrogenation to 4-(cyanomethyl)indoles and ethyl 4-indolylacetates.[3]

First, we examined the Horner-Wittig reaction of 4-oxo-4,5,6,7-tetrahydroindole (1-a) with diethyl cyanomethylphosphonate (2) and with triethyl phosphonoacetate (3). When the ketone 1-a was reacted with the sodium salt of 2 in tetrahydrofuran (THF) at refluxing temperature for 24 h, the desired 4-(cyanomethylidene)-4,5,6,7-tetrahydroindole (4-a) was obtained in a 73% yield



1-a (trans) (cis) 5: X=CN 6

2: $(EtO)_2P(O)CH_2CN$ 4-a: X=CN 8: $X=CO_2Et$

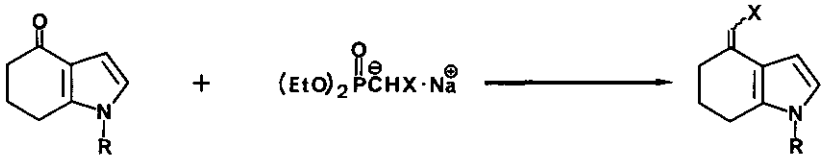
3: $(EtO)_2P(O)CH_2CO_2Et$ 7-a: $X=CO_2Et$

together with an N-ethyl derivative of 4-a, 5 (16.5% yield), and an N-ethylindole 6 (2.4% yield). The indole 4-a comprised of trans-isomer(77%) and cis-isomer(23%) whose stereochemistries were tentatively assigned by the NMR spectral analysis. Between the isomers, the major (anti) was able to be isolated in pure form.

Under the similar reaction conditions, the anion of the acetate 3 was far less reactive to the ketone 1-a than that of 2; after 72 h, only 2.7% of the desired 4-(ethoxycarbonylmethylidene)-4,5,6,7-tetrahydroindole (7-a) formed but a large amount of N-ethylated compounds 6 (50%) and 8 (2.1%) were produced.

The unexpected N-ethylated products might be derived from the reaction of the pyrrole anion of 1-a, 4-a, or 7-a with the esters of phosphonic acid 2 or 3, or diethyl phosphate produced in the Horner-Wittig reaction. The idea that ethyl esters of phosphoric acid or of phosphonic acid could act as an alkylating reagent was confirmed by the following experiment; when the pyrrole 1-a was reacted with sodium hydride and triethyl phosphate in THF under refluxing, the N-ethylpyrrole 6 was produced in a 56% yield. Conclusively, the desired Wittig reaction competed with the N-alkylation. These phenomena might be mainly due to

Table I. Synthesis of 4-alkylidene-4,5,6,7-tetrahydroindoles 4 and 7.



1 R		2 or 3 X		yield (%)	trans:cis[a]	mp of trans-isomer (°C)
(1-a)	H	CN	(4-a)	73	77:23	158-160
(1-b)	Ts	CN	(4-b)	96	69:31	147-152
(1-c)	Me	CN	(4-c)	86	77:23	108-110
(1-d)	CH_2Ph	CN	(4-d)	80	75:25	71-72
(1-a)	H	CO_2Et	(7-a)	3	-----[b]	114-116
(1-b)	Ts	CO_2Et	(7-b)	86	87:13	135-136.5
(1-c)	Me	CO_2Et	(7-c)	9	-----[b]	58-59
(1-d)	CH_2Ph	CO_2Et	(7-d)	18	-----[b]	66-67

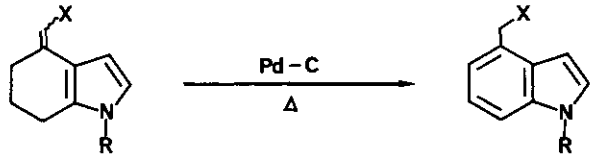
a) determined by NMR spectral analysis. b) only trans-isomer was observed.

the enaminone structure of the ketone 1-a, in which the 4-carbonyl is deactivated toward nucleophilic attack and the NH function become acidic enough to react easily with an electrophile under the basic conditions.

Introduction of an electron-withdrawing substituent at the nitrogen of 1-a improved remarkably the desired olefination. The Horner-Wittig reaction of 1-(p-toluenesulfonyl)indole 1-b with 2 proceeded smoothly at room temperature to yield 96% of the corresponding olefin 4-b. The reaction of the ketone 1-b with the ester 3 was also successful to afford an adduct 7-b in a 86% yield. N-Methyl-, 1-c, and N-benzylketone 1-d gave a little improved results comparing with the N-free ketone 1-a. These results were summarized in the Table I.

The oxidative aromatization of the methylidenetetrahydroindoles 4 and 7 into 4-substituted indoles has been reported to be unsuccessful.[5] On the other hand, Pd-catalyzed dehydrogenation of the ketone 1-a has recently been reported to be successfully attained to yield 4-hydroxyindole by devising the reaction conditions.[6] The facts encouraged us to examine the catalytic dehydrogenation of the alkylideneindoles 4 and 7 obtained here into 4-(cyanomethyl)indoles and 4-indolylacetates.

When the olefin 4-a was heated with Pd(5%) on carbon in diethyleneglycol diethyl ether under bubbling of an argon at 200°C for 3 h, 4-(cyanomethyl)indole (9-a) was obtained in a 69% yield. Similarly, the other

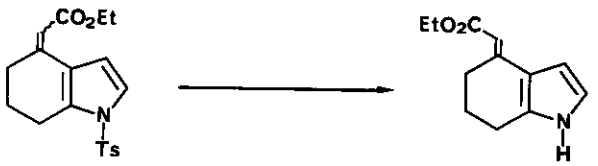


4:X=CN, 7:X=CO_2Et 9:X=CN, 10:X=CO_2Et

Table II. Pd-catalyzed aromatization of 4-alkylidene-4,5,6,7-tetrahydroindoles 4 and 7 to 4-alkylindoles 9 and 10.

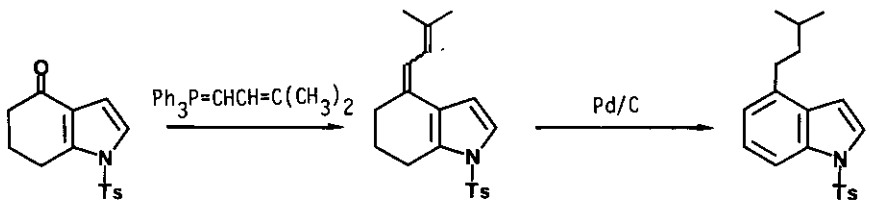
substrate	R	X	indole yield(%)	substrate	R	X	indole yield(%)
(4-a)	H	CN	(9-a) 69	(7-a)	H	CO_2Et	(10-a) 80
(4-b)	Ts	CN	(9-b) 29	(7-b)	Ts	CO_2Et	(10-b) 62
(4-c)	Me	CN	(9-c) 61	(7-c)	Me	CO_2Et	(10-c) 67
(4-d)	CH_2Ph	CN	(9-d) 63	(7-d)	CH_2Ph	CO_2Et	(10-d) 97

methylidenetetrahydroindoles 4-b,c,d and 5-a,b,c,d were oxidatively aromatized into the corresponding cyanomethylindoles 9-b,c,d and 4-(ethoxycarbonylmethyl)indoles 10-a,b,c,d. The results in the Table II showed that, in the Pd-catalyzed aromatization, (i) the esters 7 tended to give more favorable results than the cyanides 4, and (ii) the olefins with the N-tosyl group 4-b and 7-b were somewhat difficult to be oxidized. Thus, for the N-tosyl derivatives 4-b and 7-b, deprotection was required prior to the aromatization, and was attained by the use of K_2CO_3 in refluxing ethanol; a stereoisomeric mixture of 7-b was converted into trans-isomer of 7-a in a 91% yield without hydrolysis of the ester function.



7-b 7-a

The ketone 1-b also underwent the Wittig reaction with a non-activated phosphorane. The ylide prerpared from prenyltriphenylphosphonium chloride reacted smoothly with the ketone 1-b to afford a diene 11 in an 82% yield. Under the aromatization conditions with Pd catalyst, the diene 11 gave, however, 4-(3-methylbut-1-yl)indole (12) in place of 4-prenylindole 13 in a 91% yield. The case was formally a double bond isomerization but not the oxidative aromatization.



1-b 11 12

The combination of the Wittig olefinations of 4-oxo-4,5,6,7-tetrahydroindoles and the successive Pd-catalyzed aromatizations were shown to be useful as a facile method to prepare 4-substituted indoles, especially 4-(cyanomethyl)indoles and 4-indolylacetates. The typical procedures were described in the following experimental section.

EXPERIMENTAL

4-(Cyanomethylidene)-4,5,6,7-tetrahydroindole (4-a). 4-Oxo-4,5,6,7-tetrahydroindole (1-a)(1.35g, 10mmol) was added to a solution of sodium salt of diethyl cyanomethylphosphonate [prepared from 2.6g (14.7mmol) of 2 and 0.53g (50%, 11mmol) of NaH] in THF (20 ml) and stirred under an argon atmosphere at refluxing temperature for 24h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and then concentrated. The residue was chromatographed on silica gel. Elution with dichloromethane gave a stereoisomeric mixture (75:25) of 1-ethyl-4-(cyanomethylidene)-4,5,6,7-tetrahydroindole (5) as a viscous oil in a yield of 16.5% (0.31g) and 4-(cyanomethylidene)-4,5,6,7-tetrahydroindole (4-a) as a viscous oil in a yield of 73.0% (1.15g). Further elution with dichloromthane-ethyl acetate (4:1) gave 1-ethyl-4,5,6,7-tetrahydroindole (6) (2.4%) and the starting material 1-a (3.4%).

When the oily stereoisomeric mixture of 4-a was treated with hexane-ethyl acetate, the major isomer was crystallized as a pure form, which was tentatively assigned as an trans-isomer.

A stereoisomeric mixture (75:25) of 5. NMR($CDCl_3$)δ1.34(t,J=7Hz,3H), 1.74-2.10(m,2H), 2.30-2.76(m,4H), 3.79(q,J=7Hz,2H), 4.57 and 4.97[two br s,(0.25+0.75)H], 6.08(d,J=3Hz,0.75H), 6.40-6.54(two d,1H),and 6.90(d,J=3Hz,0.25H)ppm. IR(liquid film) 2200, 1595, and 1503 cm^{-1}. MS(m/z,%) 186(M^+,100) and 185(73).

A stereoisomeric mixture (77:23) of 4-a. NMR($CDCl_3$)δ1.76-2.16(m,6H), 4.75 and 5.16[two br s, (0.23+0.77)H], 6.25(dd,0.77H), 6.58-6.70(m.1H), 7.04(dd,0.23H), and 8.32-8.90(m,1H)ppm.

Trans-isomer of 4-a. Colorless plates melted at 158-160°C. NMR($CDCl_3$)δ 1.95(q,J=6.2Hz,2H), 2.70(t,J=6.2Hz,4H), 5.16(br s,1H), 6.25(m,1H), 6.63(m,1H), and 8.08-8.80(m,1H)ppm. IR(KBr) 3280, 2200, and 1590 cm^{-1}. MS(m/z,%) 158(M^+,100), 157(86), and 130(37). Anal. Calcd.($C_{10}H_{10}N_2$,%): C,75.92; H,6.37; N,17.71. Found: C,75.90; H,6.23; N,17.73.

4-(Ethoxycarbonylmethylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (7-b). 4-Oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1-b) (1.45g, 5mmol) was added to a solution of sodium salt of triethyl phosphonoacetate (3)

[prepared from 1.6g(7.1mmol) of 3 and NaH(50%,0.27g,5.5mmol) in THF (20ml) and stirred under an argon atmosphere at refluxing temperature for 18h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and then concentrated. The residue was chromatographed on silica gel. Elution with dichloromethane gave a stereoisomeric mixture (13:87) of 7-b as a viscous oil in a yield of 85.6%(1.54g). Treatment of the mixture with hexane-ethyl acetate gave a pure major isomer (trans-form) as colorless granules melted at 135-136.5°C. NMR($CDCl_3$)δ1.25(t,J=7Hz,3H), 1.64-1.98(m,2H), 2.37(s,3H), 2.68-3.10(m,4H), 4.13(q,J=7Hz,2H), 5.88(br s,1H), 6.39(d,J=3.5Hz,1H), 7.14-7.38(m,3H), and 7.60-7.76(m,2H)ppm. IR(KBr) 1700, 1620, 1600, and 1500cm^{-1}. MS(m/z) 359(M^+,47), 204(33), 176(35), 158(46), 132(30), 131(37), 130(100), and 91(87). Anal. Calcd.($C_{19}H_{21}NO_4S$,%) C,63.48; H,5.89; N,3.90; S,8.93. Found: C,63.43; H,5.81; N,3.77; S,8.84.

4-(Cyanomethyl)indole (9-a). A solution of 4-(cyanomethylidene)-4,5,6,7-tetrahydroindole (4-a)(0.50g, 3.2mmol) in diethyleneglycol diethyl ether (3.5ml) was stirred together with Pd on carbon (5%, 0.25g) under bubbling Ar gas at 200 °C for 3h. The mixture was diluted with dichloromethane and filtered. From the filtrate dichloromethane was removed, the residue was diluted with hexane (ca. 30ml) and was allowed to stand until the indole 9-a were precipitated as white crystals (0.34g, 68.7% yield).

Colorless needles (from ethyl acetate) melted at 114-115 °C. NMR($CDCl_3$)δ3.92(s,2H), 6.46-6.58(m,1H), 7.02-7.42(m,4H), and 8.10-8.64(m,1H)ppm. IR(KBr) 3380, 2237, 1495, and 1405 cm^{-1}. MS(m/z,%) 156(M^+,100), 155(79), and 130(18). Anal. Calcd.($C_{10}H_8N_2$,%) C,76.90; H,5.16; N,17.94. Found: C,76.90; H,4.98; N,17.93.

4-(3-Methylbut-2-enylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (11). 1-(p-Toluenesulfonyl)-4-oxo-4,5,6,7-tetrahydroindole (1-b)(4.9g, 17mmol) was added to a solution of an ylide prepared from prenyltriphenylphosphnium chloride (6.34g, 17.3mmol) and butyllithium (15% hexane solution, 18mmol) in THF and was stirred under an argon atmosphere at room temperature for 17h. The reaction mixture was diluted with ether and filtered to remove the insoluble part. The ether solution was concentrated and the residue was chromatographed on silica

gel. Elution with dichloromethane gave a stereoisomeric mixture of the diene 11 as a pale yellow viscous oil in a yield of 82%(4.75g).

NMR($CDCl_3$)δ1.60-2.00(m,8H), 2.18-2.54(m,2H), 2.36(s,3H), 2.64-2.90(m,2H), 5.86-6.60(m,3H), 7.10-7.34(m,3H) and 7.52-7.74(m,2H)ppm. IR(liquid film) 1610, 1600, and 1495cm^{-1}. MS(m/z,%) 341(M^+,55), 326(27), 186(100), and 91(28). High Mass(m/z) 341.1446 (er= -0.1mmu)(M , $C_{20}H_{23}NSO_2$).

4-(3-Methyl-1-butyl)-(p-toluenesulfonyl)indole (12). A mixture of 4-(3-methylbut-2-ylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (11)(338mg) and Pd on carbon (5%, 170mg) in diethyleneglycol diethyl ether (1.5ml) was stirred under an argon atmosphere at 200°C for 3h. The mixture was diluted with dichloromethane and filtered to remove the Pd catalyst. the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel. Elution with dichloromethane afforded the indole 12 as a colorless viscous oil in a 91% yield.

NMR($CDCl_3$)δ0.94(d,J=5.6Hz,6H), 1.35-1.79(m,3H), 2.33(s,3H), 2.67-2.91(m,2H), 6.71(d,J=3.6Hz,1H), 6.97-7.40(m,4H), 7.57(d,J=3.6Hz,1H) and 7.69-7.93(m,3H)ppm. IR(liquid film) 1600 and 1490cm^{-1}. MS(m/z,%) 341(M^+,34), 285(29), 130(100), and 91(40). High Mass(m/z) 341.1432(er= -1.5mmu)(M^+, $C_{20}H_{23}NSO_2$).

REFERENCES AND NOTES

1) Recently, 4-(sulfonylmethyl)indoles have been synthesized by $CuCl_2$-oxidation of 4-sulfonylmethylidene-4,5,6,7-tetrahydroindoles. N. Hatanaka, O. Ozaki, and M. Matsumoto, Tetrahedron Lett., in press. See also ref. 5.

2) M. Matsumoto and N. Watanabe, Heterocycles, 1984, 22, 195. and ref. therein.

3) These 4-substituted indoles are important for the synthesis of biologically active indoles such as ergot alkaloids. H. Plieninger and K. Suhr, Ber., 1957, 90, 1980. H. Plieninger and W. Muller, Ber., 1960, 93, 2024. However, the synthesis of these indoles has been complicated and less practical. H. Plieninger and K. Suhr, Ber., 1956, 89, 270. G. S. Ponticello and J. J. Baldwin, J. Org. Chem., 1979, 44, 4003.

4) The NMR spectrum of trans-4-a showed a doublet due to the 3-H proton at δ6.25ppm and a multiplet due to the 5-H protons at 2.56-2.90, whereas that of cis-4-a showed a doublet of 3H proton at 7.04 and a multiplet of 5-H protons

at 2.38-2.56. Similar tendencies were observed for all the isomeric pairs of the alkylideneindoles 4 and 7 obtained here.

5) W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, J. Org. Chem., 1970, 36, 1232.

6) Japan Kokai Tokkyo Koho JP 81,103,160 (to Seitetsu Kagaku Co).

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