A FACILE SYNTHESIS OF 4-(CYANOMETHYL)INDOLES AND 4-(ETHOXYCARBONYLMETHYL)INDOLES FROM 5-HALO-4-OXO-4,5,6,7-TETRAHYDROINDOLES

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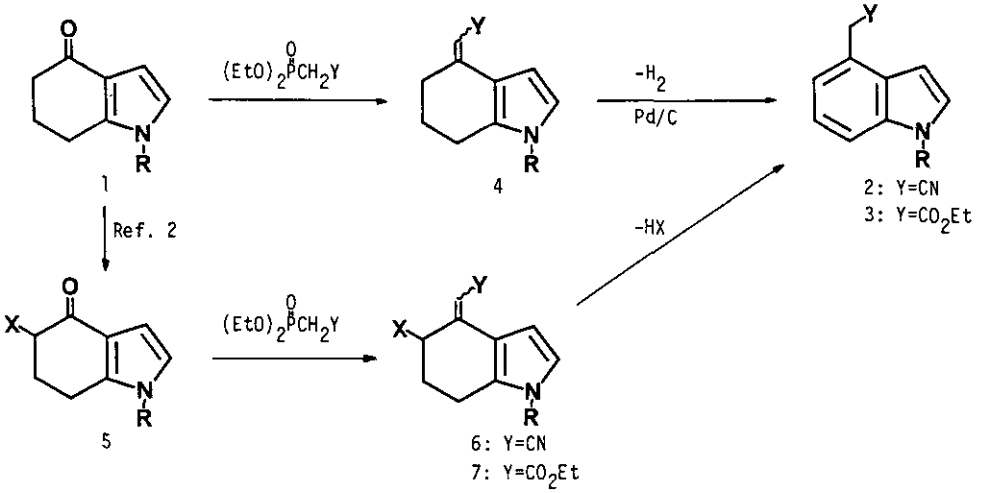
Abstract—— 4-(Cyanomethyl)indoles and 4-(ethoxycarbonylmethyl)-indoles were synthesized from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles by means of Horner-Wittig reaction and successive dehydrohalogenation.

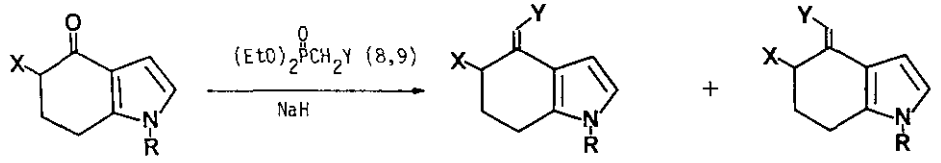
The Wittig olefination of 4-oxo-4,5,6,7-tetrahydroindoles 1 followed by the Pd-catalyzed oxidative aromatization has recently been shown to provide a simple route to 4-substituted indoles such as 4-(cyanomethyl)indoles 2 and 4-indolylacetates 3.[1] The oxidative aromatization of the intermediary 4-alkylidene-4,5,6,7-tetrahydroindoles 4 has, however, required high reaction temperature and has been still limited to use. We report here that 5-halo-4-oxo-4,5,6,7-tetrahydroindoles 5[2], which are the beforehand oxidized form of the ketones 1, lead easily to 4-substituted indoles 2 and 3 through 5-halo-4-alkylidenetetrahydroindoles 6 and 7 under the mild conditions.

When 5-chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (5a) was



treated with the sodium salt of diethyl cyanomethylphosphonate (8) in tetrahydrofuran (THF) at room temperature, the expected olefin 6a (R=Ts, X=Cl, Y=CN) was produced in a yield of 98%. The olefin 6a comprised of cis- and trans-isomers (cis/trans=4/3) and only cis-isomer was isolated as crystals.[3] Similar reaction was applied to ketone 5b (R=SO_2Ph, X=Cl) and bromoketone 5c (R=Ts, X=Br) to yield the corresponding olefin 6b and 6c. The chloroketone 5a and 5b underwent smoothly the Horner-Wittig reaction with triethyl phosphonoacetate (9) to give the desired olefin 7a and 7b. On the other hand, the reaction of the bromoketone 5c with the acetate 9 was sluggish to afford only 22% of olefin 7c. These results were summarized in the Table I.

Table I. Synthesis of 5-halo-4-methylidene-4,5,6,7-tetrahydroindoles.

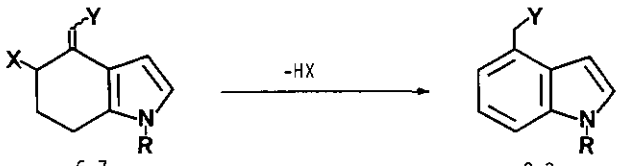


substrate		temp. (°C)	time (h)	product	X	R	Y	yield(%)	cis/trans*
5a	8	r.t.	0.5	6a	Cl	Ts	CN	98	57/43
5b	8	r.t.	3.0	6b	Cl	SO_2Ph	CN	97	67/33
5c	8	r.t.	1.5	6c	Br	Ts	CN	92	67/33
5a	9	r.t.	6.0	7a	Cl	Ts	CO_2Et	72	63/37
5b	9	r.t.	6.0	7b	Cl	SO_2Ph	CO_2Et	92	83/17
5c	9	40	2.7	7c	Br	Ts	CO_2Et	22	**

* The ratio was determined by the NMR spectral analysis. ** Only cis-isomer was obtained.

The 5-halo-4-methylidene-4,5,6,7-tetrahydroindoles 6 and 7 obtained here were, next, subjected to the dehydrohalogenation giving 4-substituted indoles 2 and 3. The dehydrohalogenation was attained by the use of lithium halide in dimethylformamide (DMF) or of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) as shown in the Table II. When one use DBU for the present dehydrohalogenation, one have no need to isolate the olefins 6 and 7. Thus, one can carry out in one-pot the reaction sequence, the Horner-Wittig reaction and the successive dehydrohalogenation (see experimental).

Table II. Synthesis of 4-substituted indoles.

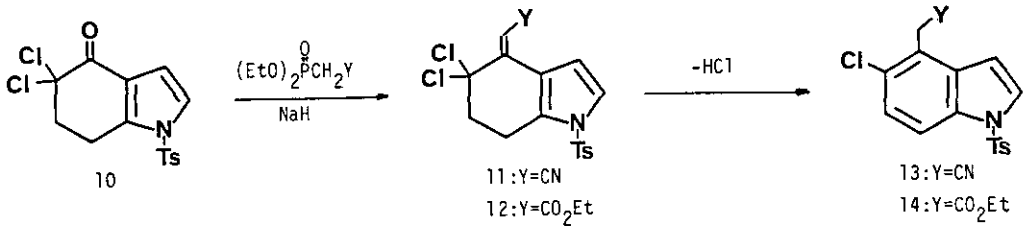


alkylidenetetrahydroindole				reagent	solvent*	temp.	time	indole	
	R	X	Y	(mol ratio)		(°C)	(h)		yield(%)
6a	Ts	Cl	CN	LiCl(1.7)	DMF	reflux	3.0	2a	94
6b	SO_2Ph	Cl	CN	LiCl(1.5)	DMF	reflux	3.0	2b	93
6c	Ts	Br	CN	LiBr(3.0)	DMF	110	3.7	2a	76
6c	Ts	Br	CN	DBU(3.0)	DME	r.t.	3.0	2a	94
7a	Ts	Cl	CO_2Et	LiCl(2.0)	DMF	reflux	1.5	3a	73
7a	Ts	Cl	CO_2Et	DBU(3.0)	THF	r.t.	4.0	3a	95
7b	SO_2Ph	Cl	CO_2Et	DBU(3.0)	THF	r.t.	15.0	3b	93
7c	Ts	Br	CO_2Et	DBU(3.0)	DME	r.t.	5.0	3a	65**

* DMF = dimethylformamide. DME = dimethoxyethane. THF = tetrahydrofuran.

** Conversion yield was 91%.

The Horner-Wittig reaction of 5,5-dichloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (10) was also successful. The dichloroketone 10 gave alkylidenetetrahydroindole 11 (75%) and 12 (56%), which were selectively converted into 5-chloro-4-(cyanomethyl)indole 13 and 5-chloro-4-indolylacetate 14.[4]



The work described here presents a convenient process from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles to 4-(cyanomethyl)indoles and 4-indolylacetates. The synthesis of alkaloids starting from these indoles will be reported in near future.

EXPERIMENTAL

5-Chloro-4-(cyanomethylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (6a). 5-Chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (5a) (3.24 g,10.0 mmol) was added to a solution of sodium salt of diethyl cyanomethylphosphonate [prepared from 2.60 g (14.7 mmol) of 8 and 0.53 g (50%, 11.0 mmol) of NaH] in THF (20 ml) and stirred under Ar atmosphere at room temperature for 30 min. The mixture was washed with water and extracted with ether. The ether layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-hexane to afford stereoisomeric mixture (cis/trans=57/43) of the olefin 6a as an oil in a 98% yield (3.41 g). The oil of 6a was treated with hexane-ether to yield pure cis-isomer as colorless needles melted at 129-130°C.

NMR($CDCl_3$) δ2.00-2.36(m,2H), 2.42(s,3H), 2.94-3.14(m,2H), 4.58-4.70(m,1H), 5.28(s,1H), 7.14-7.38(m,4H), 7.62-7.76(m,2H) ppm. IR(KBr) 2225, 1620, 1600, 1500, 1372, 1178 cm^{-1}. Mass(m/z,%) 348(M^+,16), 346(M^+,41), 191(33), 155(72), 91(100). Anal. Calcd. for $C_{17}H_{15}ClN_2O_2S$ (%): C,58.87; H,4.36; N,8.08; S,9.24; Cl,10.22. Found: C,58.87; H,4.45; N,7.98; S,9.17; Cl,10.30.

5-Chloro-4-(ethoxycarbonylmethylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (7a). 5-Chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (5a) (3.24 g, 10.0 mmol) was added to a solution of sodium salt of triethylphosphonoacetate [prepared from 9 (3.20 g, 14.2 mmol) and NaH (50%, 0.53 g, 11.0 mmol)] in THF (20 ml) and stirred under Ar atmosphere at room temperature for 6 h. The mixture was poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-hexane to give the olefin 7a (2.85 g, 72%) as a stereoisomeric mixture (cis/trans=63/37). The physical properties of the cis-isomer were as follows. Colorless needles (from hexane-ether) melted at 112-113 °C. NMR($CDCl_3$) δ1.28(t,J=7.2Hz,3H), 2.00-2.48(m,2H), 2.40(s,3H), 2.92-3.16(m,2H), 4.17(q,J=7.2Hz,2H), 4.58-4.70(m,1H), 5.80(s,1H), 7.10-7.38(m,4H), 7.58-7.80(m,2H) ppm. IR(KBr) 1715, 1620, 1605, 1500, 1375, 1170 cm^{-1}. Mass(m/z,%) 395(M^+,40), 393(M^+,100), 347(44), 130(51), 91(100). Anal. Calcd. for $C_{19}H_{20}ClNO_4S$(%): C,57.94; H,5.12; N,3.56; S,8.14;

Cl,9.00. Found: C,57.84; H,5.33; N,3.55; S,8.24; Cl,8.96.

4-(Cyanomethyl)-1-(p-toluenesulfonyl)indole (2a). Stereoisomeric mixture of the chloroolefin 6a (150 mg, 0.43 mmol) and LiCl (30 mg, 0.71 mmol) was stirred in DMF (15 ml) under Ar atmosphere at refluxing temperature for 3 h. The mixture was poured into water and extracted with dichloromethane. The dichloromethane solution was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel and eluted with ether to give the indole 2a in a 94% yield (125 mg). Colorless prisms (from ethyl acetate) melted at 150-151°C. NMR($CDCl_3$) δ 2.31(s,3H), 3.84(s,2H), 6.66(d,J=3.6Hz,1H), 7.10-7.37(m,4H), 7.56-8.02(m,4H) ppm. IR(KBr) 2265, 1595, 1365, 1175 cm^{-1}. Mass(m/z,%) 310(M^+,54), 155(85), 91(100). Anal. Calcd. for $C_{17}H_{14}N_2SO_2$(%):C,65.79; H,4.55; N,9.03; S,10.33. Found: C,65.74; H,4.54; N,9.03; S,10.18.

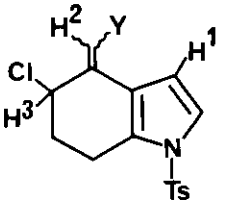
One-pot Synthesis of 4-(Cyanomethyl)-1-(p-toluenesulfonyl)indole (2a) from 5-Bromo-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (5c). 5-Bromo-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (5c) (3.01 g, 8.2 mmol) was added to a solution of sodium salt of diethyl cyanomethylphosphonate [prepared from 2.0 g (11.3 mmol) of 8 and 0.43 g (50%, 9.0 mmol) of NaH] in THF (25 ml) and stirred under Ar atmosphere at 0 °C for 20 min and then at room temperature for 40 min. To the solution, 1,8-diazabicyclo[5.4.0]-7-undecene (DBU, 1.87 g, 12.3 mmol) was added and stirred at room temperature for 3.7 h. The reaction mixture was poured into saturated NH_4Cl aq. solution and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane to give 2.21 g (87%) of 4-(cyanomethyl)-1-(p-toluenesulfonyl)indole (2a).

REFERENCES AND NOTES

1. M. Matsumoto and N. Watanabe, Heterocycles, in press.
2. M. Matsumoto, Y. Ishida, and N. Watanabe, Heterocycles, 1985, 23, 165.
3. The stereochemistries of trans- and cis-isomers of 6 and 7 were tentatively assigned by the NMR spectral analysis. Typical differences of the NMR spectra of isomers of 6a and 7a were shown in the Table III. Similar tendencies were observed for all the isomeric pairs of the alkylideneindoles 6 and 7 obtained here.

Table III. Typical proton chemical shifts of the alkylideneindoles 6a and 7a.*

		H^1	H^2	H^3
6a	cis	7.14-7.38#	5.28	4.58-4.70
	trans	6.34	5.31	5.14-5.24
7a	cis	7.10-7.38#	5.80	4.58-4.70
	trans	6.44	5.95	6.27-6.38



6a : Y = CN
7a : Y = CO_2Et

* δ ppm. # Peaks of other aromatic protons overlapped.

4. In the reaction of 10 with 8, the chloroindole 13 was produced as by-product in a yield of 24%. On the other hand, 5-chloro-4-hydroxy-1-(p-toluenesulfonyl)indole formed as by-product (44% yield) in the reaction of the ketone 10 with 9.

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