A Facile Preparation of 3-Alkylindoles via Wittig Reaction of 1-Acetylindol-3(2*H*)-ones with Stabilized Phosphonium Ylides

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3-Alkylindoles can be conveniently prepared by the Wittig reaction of 1-acetyl-indol-3(2*H*)-ones with the stabilized phosphonium ylides.

Although the reaction of the 3-oxo function of 1-acetylindol-3(2*H*)-ones **1** with nucleophiles seems to be the useful method for the preparation of 3-substituted indoles, this reaction is limited due to the propensity of **1** to enolize in the presence of nucleophiles. For example, the Wadsworth-Emmons modification of the Wittig reaction of **1** with the anion of diethyl cyanomethanephosphonate is used in the synthesis of indomethacin[1] and tryptamines.[2,3] However, the reaction of **1** with the anions of other phosphonates to afford 3-alkylindoles failed.[1,2] This paper describes a facile preparation of 3-alkylindoles **4** by the Wittig reaction of 1-acetylindol-3(2*H*)-ones **1**[4] with the stabilized ylides **2**.

1-Acetylindol-3(2*H*)-one (**1a**) was treated with methoxycarbonylmethylenetriphenylphosphorane (**2a**) in refluxing toluene for 4 hours to give methyl indole-3-acetate (**4a**) in 86% yield. The structure of **4a** was confirmed by the spectral data and the alternative preparation of **4a** from the 2-methoxy-2,3-dihydroindole derivative **6**,[5] which excluded the isomeric structure **3a**.

In a similar manner, 3-alkylindoles **4b–g** were obtained in good yields. In the case of **4g**, however, its deacetylated product **5** was also obtained (Table). The reaction proceeds via the isomerization of the intermediate Wittig reaction product **3**, and is sensitive to the reactivity of the ylide **2**[6] and to the bulkiness of the substituents in **1** and **2**.

In conclusion, the facile Wittig reaction described here provides a general method for the preparation of 3-alkylindoles in good yields.

All melting and boiling points are uncorrected. Melting points were measured on a Yanagimoto micromelting point apparatus. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra and mass spectra were recorded on JEOL JNM-PMX 60 and JMS-DX 302 spectrometers, respectively.

3-Alkylindoles 4a–g and 5; General Procedure:

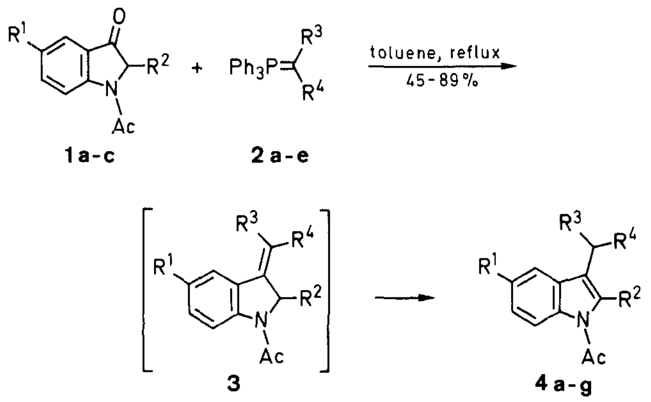
A solution of indol-3(2H)-ones **1a–c** (1 mmol) and ylides **2a–e** (3 mmol) in toluene (3 mL) is refluxed for 4–80 h (Table). The mixture is evaporated under reduced pressure to give an oily residue. The residue is chromatographed on silica gel using an appropriate solvent [**4a**, EtOAc/hexane (1:1); **4b** and **4d**, CH_2Cl_2/hexane (3:1); **4c**, EtOAc/hexane (4:5); **4f**, CH_2Cl_2/hexane (3:2); **4g**, CH_2Cl_2/hexane (2:1)] as an eluent to give **4a–g** and **5**.

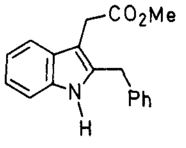
Table. 3-Alkylindoles **4a–g** and **5** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/Torr[b]	Molecular Formula[c] or Lit. mp (°C) or bp (°C)/Torr	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
4a	4	86	160–165/0.3	150/0.5[7]	1740, 1707	2.58 (s, 3H), 3.68 (s, 5H), 7.05–7.7 (m, 4H), 8.33 (d, 1H, J = 8)	231 (M^+, 25), 189 (28), 130 (100)
4b	2	89	122–124 (Et_2O)	$C_{13}H_{12}BrNO_3$ (310.1)	1742, 1717	2.60 (s, 3H), 3.68 (s, 2H), 3.75 (s, 3H), 7.1–7.85 (m, 2H), 8.32 (d, 1H, J = 8)	311 (42), 309 (M^+, 45), 269 (57), 267 (57), 210 (96), 208 (100), 129 (18)
4c	5	81	114–116.5 (AcOH/hexane)	118[2]	2260, 1716	2.63 (s, 3H), 3.78 (s, 2H), 7.15–7.75 (m, 4H), 8.3–8.65 (m, 1H)	198 (M^+, 56), 156 (100), 130 (34)
4d	18	59	150–155/0.2	120	1709	2.10 (s, 3H), 2.32 (s, 3H), 3.67 (s, 2H), 7.2–7.85 (m, 4H), 8.15–8.5 (m, 1H)	215 (M^+, 29), 172 (16), 130 (100)
4e	39	65	158–160 (EtOAc)	$C_{18}H_{15}NO_2$ (277.3)	1723, 1684	2.58 (s, 3H), 4.37 (s, 2H), 7.15–7.75 (m, 7H), 7.8–8.2 (m, 2H), 8.25–8.6 (m, 1H)	277 (M^+, 54), 172 (19), 130 (100)
4f	16	54	134–139/0.2	$C_{15}H_{17}NO_3$ (259.3)	1731, 1713	1.23 (t, 3H, J = 7), 1.61 (d, 3H, J = 7), 2.62 (s, 3H), 3.93 (q, 1H, J = 7), 4.18 (q, 2H, J = 7), 7.2–7.9 (m, 4H), 8.3–8.7 (m, 1H)	259 (M^+, 34), 217 (10), 186 (19), 144 (100)
4g	80	45	205–210/0.2	$C_{20}H_{19}NO_3$ (321.4)	1731, 1713	3.23 (t, 3H, J = 7), 3.62 (s, 3H), 3.75 (s, 2H), 4.52 (s, 2H), 6.8–8.0 (m, 9H)	321 (M^+, 50), 279 (63), 220 (100), 206 (19)
5		41	99–102 (Et_2O/hexane)	$C_{18}H_{17}NO_2$ (279.3)	3488, 1736	3.62 (s, 3H), 3.75 (s, 2H), 4.10 (s, 2H), 7.0–7.95 (m, 10H)	279 (M^+, 36), 220 (100), 206 (19)

[a] Yield of isolated pure product.

[b] Bath temperature of a Buchi GKP-50 distillation apparatus. Products **4b** and **4e** gave satisfactory microanalyses: C ±0.08, H ±0.23, N ±0.03. Products **4f**, **4g**, and **5** gave satisfactory HRMS (±0.0003 amu).





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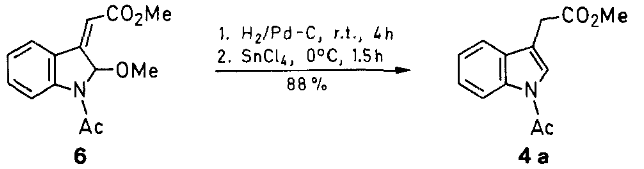

1	R^1	R^2	**2**	R^3	R^4	**2**	R^3	R^4
a	H	H	**a**	H	CO_2Me	**d**	H	COPh
b	Br	H	**b**	H	CN	**e**	Me	CO_2Me
c	H	CH_2Ph	**c**	H	COMe			

4	R^1	R^2	R^3	R^4	**4**	R^1	R^2	R^3	R^4
a	H	H	H	CO_2Me	**e**	H	H	H	COPh
b	Br	H	H	CO_2Me	**f**	H	H	Me	CO_2Me
c	H	H	H	CN	**g**	H	CH_2Ph	H	CO_2Me
d	H	H	H	COMe					

1-Acetyl-3-methoxycarbonylmethylindole (4a) from (*Z*)-1-Acetyl-2-methoxy-3-methoxycarbonylmethylene-2,3-dihydroindole (6):
A mixture of **6**[5] (1 g, 3.8 mmol) and 10% Pd-C (0.1 g) in MeOH (25 mL) is vigorously stirred under H_2 atmosphere at r.t. for 4 h. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure to give a colorless oil (0.94 g). To the solution of the oily product in CH_2Cl_2 (50 mL), $SnCl_4$ (1.04 g, 4 mmol) is gradually added under ice cooling. After 1.5 h, the mixture is extracted with CH_2Cl_2 (500 mL) and the extract is washed with H_2O, dried ($MgSO_4$), and evaporated under reduced pressure to give an oily residue. The residue is chromatographed on silica gel (CH_2Cl_2) to give **4a** yield: 0.78 g (88%); bp 170–175 °C/1 Torr (bath temp.) (Lit.[7] bp 150/0.5 Torr).

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