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Arylation of 3-Oxo-2,3-Dihydroindoles with Aryllead Triacetates

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Key Words : C-arylation ; substitutedphenyllead triacetates ; ketones ; β-ketoesters ; 2-arylindoles .

***Abstract** : Arylation of 2-alkoxycarbonyl-3-oxo-2,3-dihydroindoles with aryllead (IV) triacetates leads selectively to 2-alkoxycarbonyl-2-aryl-3-oxo-2,3-dihydroindoles. Direct selective C-arylation of 1-substituted-3-oxo-2,3-dihydroindoles with aryllead (IV) triacetates affords the corresponding 1-substituted-2-aryl-3-oxo-2,3-dihydroindoles.*

2-Aryl-(2H)-indoles possess interesting antiinflammatory activity[1] or estrogen antagonist activity[2] . The chemistry of 2-aryl-(2H)-indoles is well documented[3] but with no or few functionnalities in the 3-position. 3-Oxo-2,3-dihydroindoles are key intermediates in the synthesis of biologically active compounds such as indomethacine[4] or ellipticine[5]. The selective indirect mono C-2 alkylation[6] and benzylation[7] of 1-acetyl-3-oxo-2,3-dihydroindole were recently described. But introduction of an aryl substituent at the C-2 position is only possible by multistep indirect procedures, leading *inter alia* to compounds such as the stable free radicals, the 2,2-disubstituted-3-oxoindolin-1-oxyls[8].

The efficiency of aryllead (IV) triacetates as regioselective arylating agents was discovered by Pinhey[9]. The regioselective arylation of heterocyclic systems[10,11], among them the C-2 arylation of 3-(2H)-benzofuranones[11], has recently been reported. Althought direct α-arylation of ketones with lead derivatives has been reported in a limited number of cases[9,11], it generally requires activation of the ketone[12-14] . Up to now, the only reported result on the arylation of indolic compounds with aryllead reagents was the failure of indole to react with or without copper catalysis[15]. We now want to report our preliminary results on the arylation of 3-oxoindole derivatives.

The nitrogen-protected β-ketoesters **1a** (R^1=H) , **1b** (R^1=Ac) and **1c** (R^1=Me) were smoothly C-arylated by 4-methoxyphenyllead triacetate **3**[16] or 2,4-dimethoxyphenyllead triacetate **4**[16] ($CHCl_3$, pyridine, reflux, 5 hours) to the corresponding 2-aryl-2-alkoxycarbonyl-3-oxo-2,3-dihydroindoles **2**.

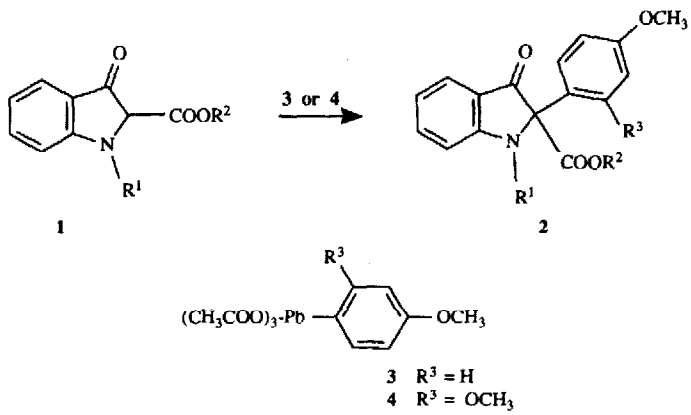


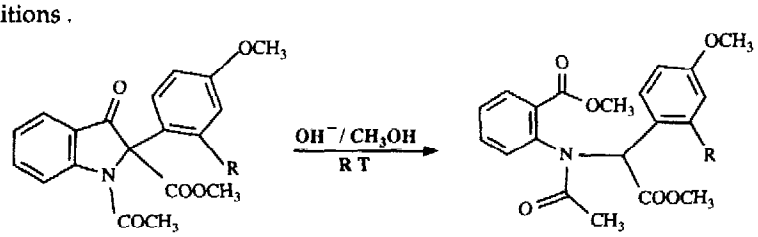
Table 1 : Arylation of 2-Alkoxycarbonyl-3-oxo-2,3-dihydroindoles **1** with Aryllead Triacetates **3** and **4** [a]

R^1	R^2	1	R^3	Aryl lead	2[17]	Yield %[b]	mp°C
H	CH_3	a	OCH_3	**4**	a	68	184
$COCH_3$	CH_3	b	OCH_3	**4**	b	62	135
CH_3	C_2H_5	c	OCH_3	**4**	c	67	60
CH_3	C_2H_5	c	H	**3**	d	98	oil
H	CH_3	a	H	**3**	e	95	141
$COCH_3$	CH_3	b	H	**3**	f	84	oil

[a] Reactions were carried out in anhydrous chloroform at reflux; the molar ratio of 1 : 3 or 4 : **pyridine** was in all cases 1 : 1.1 : 3.3.

[b] Yield data is for isolated homogeneous material.

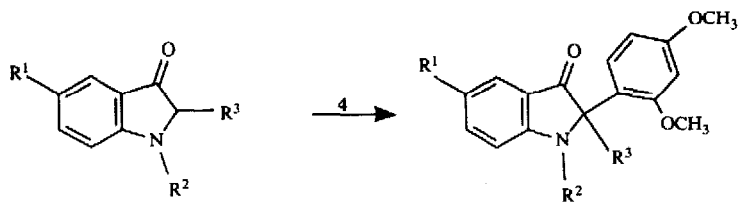
Although the cleavage of the amide bond in the series of 1-acetyl-3-oxo-2,3-dihydroindoles is known to be easy [4], base-catalysed hydrolysis of the compound **2b** and **2f** did not lead to the expected **2a** and **2e**. Instead, compounds **5b** and **5f** were obtained, resulting from the five-membered ring opening by a retro-Dieckmann reaction on the sterically hindered β-keto-esters **2b** and **2f**, under very mild conditions .



2 b
2 f

5 b R = OCH_3
5 f R = H

In our studies on the arylation of benzofuranones, we have found that arylation of the unactivated ketone could be performed, albeit in poor yield and only with the very electron-rich 2,4,6-trimethoxyphenyllead triacetate[11]. By contrast, the N-substituted-3-oxo-2,3-dihydroindoles **6** were easily arylated by less reactive reagents such as 2,4-dimethoxyphenyllead triacetate **4** . Indeed, a selective reaction was observed with monoarylation leading either to 2-monosubstituted 3-oxo-2,3-dihydroindoles (by arylation of 2-unsubstituted-3-oxo-2,3-dihydroindole) or to unsymetrically 2,2-disubstituted-3-oxo-2,3-dihydroindole (by arylation of 2-monosubstituted 3-oxo-2,3-dihydroindole). Apart from the 5-methyl derivative **7f**, good yields were obtained in most cases and even a moderately good one was obtained for the synthesis of the bulky 2-phenyl-2-(2',4'-dimethoxyphenyl)-3-oxo-2,3-dihydroindole **7d**.



6 **7**

Table 2 : Arylation of 3-oxo-2,3-dihydroindoles **6** with 2,4-Dimethoxyphenyllead Triacetate **4** [a]:

R^1	R^2	R^3	**6**	**7**[17]	Yield %[b]	mp°C
H	$COCH_3$	H	a	a	70	143
H	$SO_2C_6H_5$	H	b	b	60	132
H	$COCH_3$	CH_3	c	c	72	147
H	$COCH_3$	C_6H_5	d	d	42	234
CH_3O	$COCH_3$	H	e	e	81	188
CH_3	$COCH_3$	H	f	f	26	134

[a, b] see Table 1.

Whereas in the corresponding oxygen-heterocycle benzofuranone the 2-aryl derivatives were only isolated from the palladium acetate-catalysed decarboxylation of the 2-allyloxycarbonyl derivatives, no such activation is required in the indole analogues as the unactivated ketone is directly and efficiently arylated. This might relate to a much higher percentage of enolic form in the 3-oxo-2,3-dihydroindole compared to the 3-oxo-2,3-dihydrobenzofuran series, enabling a facile formation of a covalent indole-3-oxylead intermediate.

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17 All new compounds gave spectroscopic data in agreement with the assigned structures; compound **2b**; IR($CHCl_3$): 1750, 1725, 1685 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS): δ=2.07(s, 3H, CH_3); 3.35(s, 3H, OCH_3); 3.81(s,3H, OCH_3); 3.85(s, 3H, OCH_3); 6.36(d, J=2.4, 1H, H'$_3$arom); 6.55(dd, J=2.4, 8.7, 1H, H'$_5$arom); 7.23(t, J=8.5, 1H, Harom); 7.51(fd, J=7.7, 1H, H'$_6$arom); 7.66(ftd, J=1.4, 7.4, 1H, Harom); 7.78(d, J=7.6, 1H, Harom); 8.4(br d, 1H, Harom); ^{13}C-NMR($CDCl_3$): 25.83(CH_3); 53.90, 55.41, 55.46(OCH_3); 77.99(CH); 99.50, 104.25, 116.54, 122.80, 123.91, 133.11, 136.91, 152.7, 158.30, 161.62(Carom); 165.96, 169.8(COO, NCO). 196.2(CO); MS(CI) m/e 370(MH^+); compound **5f**; yield 82%; mp 158°C; IR($CHCl_3$): 1735, 1710, 1650 cm^{-1}; ^{1}H-NMR($CDCl_3$): 1.82(s,3H, CH_3); 3.65(s, 3H, OCH_3); 3.71(s, 3H, OCH_3); 3.74(s, 3H, OCH_3); 6.00(s,1H, CH); 6.53(d, J=8.6, 2H, H'$_{3,5}$arom); 6.78(d, J=8.5, 2H, H'$_{2,6}$arom), 7.24(td, J=1.2, 6.8, H$_5$arom); 7.48(td, J=2, 8, 1H, H$_4$arom); 7.62(dd, J=1.8, 8, 1H, H$_3$arom); 7.76(dd, J=1.8, 8, 1H, H$_6$arom); ^{13}C-NMR($CDCl_3$): 23.19(CH_3); 52.24, 52.49, 55.19(OCH_3); 63.23 (CH); 113.56, 124.40, 128.51, 130.19, 131.21, 131.41, 131.65, 132.97, 133.03, 139.79, 159.63, 165.42(Carom); 170.97, 171.46, 172.01(COO, NCO); MS(CI) m/e 372(MH^+); compound **7a**; IR($CHCl_3$): 1720, 1670 cm^{-1}; ^{1}H-NMR($CDCl_3$): 2.05(s, 3H, CH_3); 3.79(s, 3H, OCH_3); 3.80(s, 3H, OCH_3); 5.59(s, 1H, CH); 6.42(dd, J=2.4, 8.7, 1H, H'$_5$arom); 6.51(d, J=2.4, 1H, H'$_3$arom); 6.88(d, J=8.7, 1H, H'$_6$arom); 7.25(fd, J=7.8, Harom); 7.69(ft, J=7.8, 1H, Harom); 7.75(fd, J=7.8, 1H, Harom); 8.6(fd large , 1H, Harom); MS(CI) m/e 312(MH^+).

Typical procedure: A mixture of 2-methoxycarbonyl-3-oxo-2,3-dihydroindole **1a** (0.535g, 2.8 mmol), (2,4-dimethoxyphenyl)lead triacetate **4**[16] (1.606g, 3.08mmol) and pyridine (0.728g) in anhydrous chloroform (30 ml) was refluxed for 5 hours; acidic treatment (HCl 1N)) , extraction with CH_2Cl_2 (2x20 ml), drying over $MgSO_4$ and evaporation in vacuo afforded a solid which was chromatographed over silica gel column; elution with CH_2Cl_2 gave **2a**; yield 0.671g(68%); mp 184°C; IR($CHCl_3$): 3360(NH), 1725($COOCH_3$), 1690(CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$/TMS): 3.71(s, 3H, OCH_3); 3.76(s, 3H, OCH_3); 3.79(s, 3H, OCH_3); 6.44(dd, J=2.4, 8.5, H$_{5'}$); 6.48(fd, J=2.4, 1H, H$_{3'}$); 6.83(t, J=7.1, Harom); 6.88(d, J=8.2, Harom); 7.24(d, J=8.5, 1H, H$_{6'}$); 7.45(t, J=7.7, Harom); 7.64(d, J=7.9, Harom); 5.80(s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 53.66, 55.54, 55.71 (OCH_3); 74.31(C_2); 99.5, 104.4, 113.06, 119.70, 125.27, 128.22, 138.02 (CH); 118.67, 119.79, 158.90, 161.06 (Cquat); 169.2($COOCH_3$); 194.65(CO); MS (CI) m/e 328(MH^+).

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