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Novel ring transformation of quinolines to indole derivatives in two steps via 1,4-dihydroquinoline derivatives

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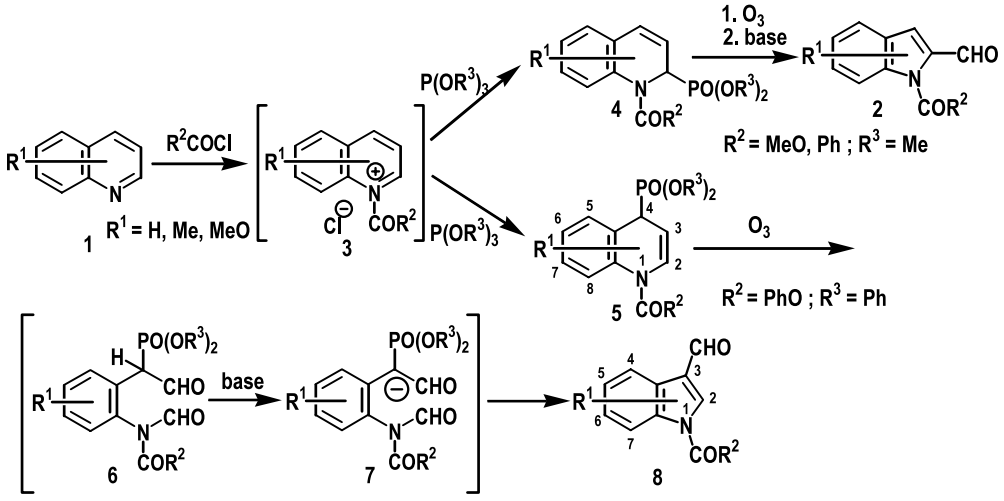
Abstract—Diphenyl 1-phenoxycarbonyl-1,4-dihydroquinoline-4-phosphonates **5c–g**, obtained from the reaction of corresponding quinoline derivatives **1** with phenyl chloroformate and triphenyl phosphite in one step, were ozonized in $CHCl_3$ and CH_3COOH. Treatment of the resulting mixture with $NaHCO_3$ produced the 3-formyl-1-phenoxycarbonylindole derivatives **8a–e** in high yields. The ring transformation of quinolines **1** to indoles **8** proceeds under mild conditions.

The Meisenheimer salts of diphenyl 1-phenoxycarbonyl-1,4-dihydroquinoline-4-phosphonates **5** were prepared by reaction of quinolines **1** with phenyl chloroformate and triphenyl phosphite. Ozonation of these salts followed by treatment with sodium hydrogen carbonate produced the 3-formyl-1-phenoxycarbonylindole derivatives **8** in high yield (Scheme 1).

Considerable efforts have been devoted to the construction of the indole ring system, which has been realized by Fisher,[1] Bischler–Mohlau,[2] Martinet,[3] Madelung,[4] Nenitzescu,[5] Reissert,[6] Sandmeyer,[7] Stolle,[8] and Fukuyama.[9] Recently we reported an indole synthesis that involves the ring transformation of quinolines **1** to 2-formylindoles **2** via 1-acyl-1,2-dihydroquinoline 2-phosphonates **4**.[10] The Meisenheimer salt **4** was synthesized by treatment of quinolines **1** with alkyl chloroformate and then trialkylphosphite. This report describes the formation of isomeric 1-acyl-4-phosphonate intermediates **5** and the conversion to 3-formylindoles **8**.



Scheme 1.

Keywords: pseudo base; phosphonate; dihydroquinoline; ozonation; formylindole.
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Table 1. Preparation of phosphonates **4**, **5** ($R^1 = H$)

Entry	COR^2	R^3	Total yield (%) of two isomers	Compd. No.		Ratio 1,2-dihydro der.:1,4-dihydro der.
				1,2-Dihydro der.	1,4-dihydro der.	
1	COOMe	*i*-Pr	70	**4a**	–	100:0
2	COOEt	*i*-Pr	94	**4b**	–	100:0
3	COOPh	*i*-Pr	99	**4c**	–	100:0
4	COOMe	Ph	70	**4d**	**5a**	10:90
5	COOEt	Ph	24	**4e**	**5b**	6:94
6	COOPh	Ph	74		**5c**	0:100

Table 2. Preparation of phosphonates **5** and formylindoles **8** ($R^2 = PhO$, $R^3 = Ph$)

5	R^1	Yield (%)	^1H NMR 3- and 4-H (δ)	**8**	R^1	Yield (%)	^1H NMR 3-CHO and 2-H (δ)
c	H	74	5.61, 4.36	**a**	H	32	10.16, 8.40
d	3-Me	37	–, 4.16	**b**	H[a]	93	2.56[b], 8.37
e	6-Me	67	5.60, 4.31	**c**	5-Me	24	10.12, 8.34
f	7-Me	68	5.62, 4.33	**d**	6-Me	51	10.13, 8.34
g	6-MeO	46	5.62, 4.33	**e**	5-MeO	54	10.13, 8.37

[a] 3-Acetyl-1-phenoxycarbonylindole.
[b] $COCH_3$.

The initial attempts to produce 1,4-dihydro Meisenheimer salts of quinolines using bulky trialkylphosphite failed and resulted in the formation of the 1,2-isomer, although 1,4-dihydropyridines were prepared under identical conditions.[11] Accordingly, reagents leading to the effective formation of the desired intermediates **5** were investigated. Treatment of **1a** ($R^1 = H$) with phenyl chloroformate and triisopropyl phosphite gave high yields of 1,2-dihydroquinolines **4** (Table 1, entries 1–3) whereas treatment with methyl chloroformate and triphenyl phosphite furnished 1,4-dihydroquinoline **5** and a small amount of the 1,2-isomer[12] **4** (entries 4–6) as contaminant. Consequently the regioselective formation of 1,4-dihydro Meisenheimer salts **5** was achieved by the use of phenyl chloroformate and triphenyl phosphite in 74% yield. This procedure was successfully applied to synthesis of commercially available quinoline derivatives **1b–e**, the results of which are summarized in Table 2.

The ring transformation of **5** to indoles **8** was effected according to our procedure,[10] i.e. the 2,3-double bond of **5** was oxidatively cleaved with ozone, and the resulting diformyl compound was again cyclized through a carbanion intermediate. Aromatization with loss of the diphenyl phosphite anion led to the formation of 3-formylindoles **8**. The structures of **5** and **8** were established by FAB-MS, IR and NMR analysis containing COSY, NOESY, CH-COSY and HMBC measurements.[13]

In conclusion, we report a novel synthetic method for the formation of indole derivatives, which is expected to be useful for the synthesis of indole-containing medicines and the synthesis of heat sensitive compounds, due to the mild reaction conditions. The preparation of derivatives from many known biologically active substances, for example quinine, is possible using this novel reaction, including transformation of a quinoline moiety into an indole adduct.

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13. For example **5c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (m, 3-H); 4.36 (dd, $J=6.4$, 26 Hz, 4-H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 105.02, 105.09 (3-C); 39.19, 40.15 (4-C); 156.54 (CO). IR (KBr) 1729 cm^{-1}. FAB-MS: m/z 484 [MH$^+$]. **8a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (s, 3-CHO); 8.40 (s, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.63 (3-CHO); 149.98 (CO); 135.86 (2-C); 126.20 (3-C). IR (KBr) 1760, 1677 cm^{-1}. FAB-MS: m/z 266 [MH$^+$].