A New Method for Indole Functionalization. Nucleophilic Displacement Reactions of [η⁶-(4- or 5-Chloroindole)](η⁵-cyclopentadienyl)ruthenium(II) Hexafluorophosphates

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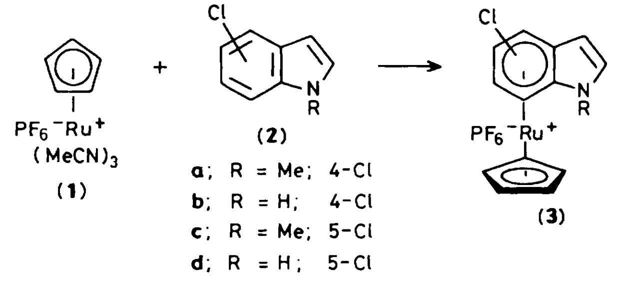
New cyclopentadienylruthenium complexes of 4- or 5-chloroindole prepared by a thermal substitution reaction of (cyclopentadienyltrisacetonitrile)ruthenium with 4- or 5-chloroindole undergo smooth nucleophilic aromatic substitution with various nucleophiles.

Indoles substituted at the positions 4—7 make up an important class of indole alkaloids.[1—3] Syntheses of 4-, 5-, 6-, or 7-substituted indole systems fall into three categories.[3] The first proceeds from an appropriately substituted *o*-nitrotoluene with subsequent construction of the fused pyrrole (Leimgruber–Batcho method).[3] Similarly the Fischer indolisation reaction, often coupled with the Japp–Klingemann reaction, places the substituents at the desired position on the indole by preselection in the benzene ring.[3] A second category starts with an intact pyrrole ring and builds up the benzene ring, *e.g. via* photo-oxygenation of the pyrrole, or a Diels–Alder reaction, or by more elaborate syntheses.[3] The third category proceeds from an intact indole ring and employs either intramolecular electrophilic or radical reaction.[3]

What is missing from this area of synthesis is a route involving direct nucleophilic displacement of a ring halogen by a carbanion or other desirable potential substituent. We now report such a method, based upon our work on nucleophilic displacement by enolate anions upon various (η^6-chloroarene)(η^5-cyclopentadienyl)iron(II) hexafluorophosphates.[4]

Arene halides can be activated toward nucleophilic displacement by complexation with [(η^5-C_5H_5)Ru]$^+$, [(η^5-



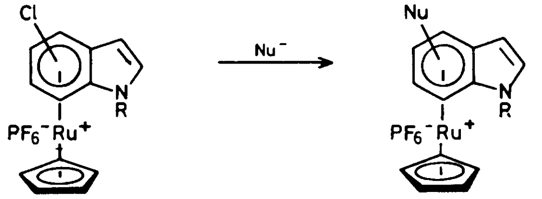
(1)

(2)

a; R = Me; 4-Cl
b; R = H; 4-Cl
c; R = Me; 5-Cl
d; R = H; 5-Cl

(3)

Scheme 1



(3) a; 4-Cl R = Me (4) 4-subst.
c; 5-Cl (5) 5-subst.

Nu = a; OMe
b; OCH_2Ph
c; SCH_2CO_2H
d; $CH(CO_2Me)_2$
e; $CH(CO_2Et)_2$
f; HNMe

Scheme 2

Table 1. Nucleophilic substitution reactions of [η^6-(4- or 5-chloroindole)](η^5-cyclopentadienyl)ruthenium hexafluorophosphates with nucleophiles.

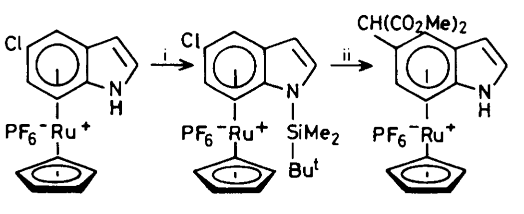
Nucleophile	Complex	Product	Yield (%)	M.p. (°C)
NaOMe	(**3c**)	(**5a**)	82	223—225
$NaOCH_2Ph$	(**3c**)	(**5b**)	80	162—164
$NaSCH_2CO_2Na$	(**3a**)	(**4c**)	72	185—187
$NaSCH_2CO_2Na$	(**3c**)	(**5c**)	70	186—188
$NaCH(CO_2Me)_2$	(**3a**)	(**4d**)	86	143—145
$NaCH(CO_2Me)_2$	(**3c**)	(**5d**)	88	215—217
$NaCH(CO_2Et)_2$	(**3a**)	(**4e**)	85	145—147
$NaCH(CO_2Et)_2$	(**3c**)	(**5e**)	86	166—168
H_2NMe	(**3c**)	(**5f**)	40	143—145

$C_5H_5)Fe]^+$, or other ligand-bound metals.[4—6] This methodology has not been extended to more complicated heteroaromatic systems such as halogenoindoles because of the drastic nature of reaction conditions required for attachment of the organometallic ligand [*e.g.* Cp_2M (M = Fe or Ru), $AlCl_3$, Al, halogenoindole, high temperature[5]].

We have solved this problem of metal complexation by synthesizing the novel $[CpRu]^+$ complexes of 4- or 5-chloroindole under conditions compatible with the survival of the indole ring (Scheme 1).

The chloroindoles (**2a**—**d**) (1.5 mmol) and the salt (**1**) (1.0 mmol)[7] in 1,2-dichloroethane or dimethylformamide (20 ml) were heated overnight at 50—60 °C under nitrogen. The solvent was removed *in vacuo* and the residue was washed with ether; the remaining solid was crystallized (CH_2Cl_2/Et_2O) to give yellow compounds (**3a**—**d**) in 70—90% yields [based on the salt (**1**)].

The complexes (**3a** and **c**) were found to undergo clean S_NAr reactions[6] with a range of oxygen, nitrogen, sulphur, and carbon nucleophiles, to give the corresponding 4- or 5-substituted indole complexes (**4c**—**e**) and (**5a**—**f**) (Scheme 2 and Table 1). Typically, the complexes (**3a** and **c**) (1.0 mmol) were added as solids to a solution in tetrahydrofuran (THF) (20 ml) at room temperature of the carbanion (2.0 mmol) prepared from the corresponding conjugate acid (2.0 mmol) in THF with NaH (2.0 mmol). After heating at 50—60 °C for 10—12 h under nitrogen and work-up, the products were obtained in high yields.†



Scheme 3. *Reagents:* i, $NaH/THF/Bu^tSiMe_2Cl$; ii, $NaH/THF/CH_2(CO_2Me)_2$.

Other N-1 protecting groups such as t-butyldimethylsilyl have been successfully used as shown in (Scheme 3). The protecting group was removed during the aqueous HCl work-up. Ligand disengagement was accomplished by either photochemical arene displacement in MeCN or thermal sublimation under high vacuum to yield 80—90% of free 4- or 5-substituted indole. In conclusion, we have established that aromatic nucleophilic substitution in the indole series *via* temporary co-ordination to the cyclopentadienylruthenium unit is a valuable new method for selective functionalization of the indole nucleus.

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† All new compounds were characterized, *inter alia*, by ^1H n.m.r. and combustion analysis. Selected data are as follows: (**3a**): ^1H n.m.r. [200 MHz; $(CD_3)_2CO$] δ 8.02 (d, 1H), 7.20 (d, 1H), 6.79 (d, 1H), 6.52 (d, 1H), and 6.15 (t, 1H); ^{13}C n.m.r. [400 MHz; $(CD_3)_2CO$] δ 143.28, 110.10, 101.59, 98.50, 97.10, 83.36, 81.11, 80.94, 80.66, 70.37, and 33.83; (**4c**) ^1H n.m.r. [200 MHz; $(CD_3)_2CO$] δ 7.90 (d,1H), 7.13 (d, 1H), 6.73 (d, 1H), 6.30 (d, 1H), 6.11 (t, 1H), 5.09 (s, 5H), 4.07 (s, 2H), and 3.89 (s, 3H); ^{13}C n.m.r. [400 MHz; $(CD_3)_2CO$] δ 170.31, 142.42, 110.22, 102.33, 99.50, 95.24, 83.66, 81.22, 80.19, 69.85, 36.79, and 33.64; (**5d**) ^1H n.m.r. [200 MHz; $(CD_3)_2CO$] δ 7.83 (d, 1H), 7.24 (s, 1H), 7.22 (d, 1H), 6.60 (d, 1H), 6.20 (d, 1H), 5.05 (s, 5H), 4.90 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), and 3.82 (s, 3H); ^{13}C n.m.r. [400 MHz; $(CD_3)_2CO$] δ 167.91, 167.87, 142.81, 111.03, 103.47, 97.31, 93.15, 82.67, 80.02, 79.82, 70.22, 55.75, 53.68, 53.63, and 33.42.