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CATALYSIS OF THE ARYLATION OF THE REFORMATSKY REAGENT BY PALLADIUM OR NICKEL COMPLEXES. SYNTHESIS OF ARYL ACID ESTERS *

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Summary

Arylation of $BrZnCH_2CO_2CH_2CH_3$ by aromatic halides proceeds smoothly and in fair yield in a mixture of dimethoxymethane and a dipolar aprotic solvent (HMPA, NMR (*N*-methylpyrrolidone), DMF, DMSO) when catalysed by soluble nickel or palladium complexes. The reaction can also be applied to functional aromatic halides.

Transition metals are now extensively used in synthetic reactions involving carbon—carbon bond formation [1,2,3] Very promising and intensively studied are the reactions of a "main group" organometallic compound (Grignard reagent [4,5], organolithium reagent [5], organozinc derivative [6], etc.) with an aromatic or a vinylic halide

We ourselves published some work on the reaction of Grignard reagents catalysed by palladium compounds [7] and we now wish to report our results on the reaction of the Reformatsky reagent $BrZnCH_2CO_2Et$ with aromatic halides [8] This reaction is one of the few examples of arylation of an enolate-like reagent under conditions which are neither radicalar nor benzynic [9,10].

Hexamethylphosphoramide (HMPA), a dipolar aprotic solvent, introduced to chemistry by H Normant [11] and which has been extensively used in organometallic laboratories, has been a key solvent giving good yields in our reactions

Vinylation of the Reformatsky reagent can also be performed under similar conditions Extensive results on vinylation will be published elsewhere.

Arylation and vinylation of $BrZnCH_2CO_2Et$

Arylation and vinylation of $BrZnCH_2CO_2Et$ prepared in methylal (dimethoxymethane) can be performed with simple aromatic and vinylic halides in the pres-

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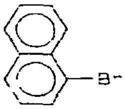
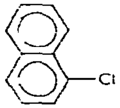
[*] Dedicated to Prof H Normant on the occasion of his 72nd birthday June 25th 1979

[**] Part of thesis of Doctorat d'Etat

TABLE 1

ARYLATION REACTIONS OF $BrZnCH_2CO_2Et$

Run	ArX	$ArCH_2CO_2Et$ (%)	Recovered ArX (%)
1	C_6H_5I	85[a]	12
2	C_6H_5Br	67[b]	14
3	C_6H_5Cl	65[b]	22
4	C_6H_5Cl	59[c]	28
5	C_6H_5F	0	100
6		69[b]	
7		24[b]	

[a] 1 hour at 45°C [b] 3 hours at 45°C [c] 15 hours at 20°C

ence of a transition metal catalyst (preferably $Ni(PPh_3)_4$) and HMPA as co-solvent (Table 1)

$$ArX + BrZnCH_2CO_2Et \xrightarrow[\text{HMPA/Methylal 1/1}]{Ni^0(PPh_3)_4,\ 10\%} ArCH_2CO_2Et + ZnBrX$$

We were unable to perform the reaction with aromatic fluorides, but inexpensive chlorides can be made to react with $BrZnCH_2CO_2Et$ without difficulty, although longer times are necessary as compared with bromides or iodides

Such a procedure can compete efficiently with other methods of synthesizing arylacetic derivatives (vegetal hormones and anti-inflamatories [12,13,14])

Vinylation can be readily performed, catalysed by $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$ With $Pd(PPh_3)_4$, the yield of the reaction is 54%, giving $CH_2{=}CHCH_2CO_2Et$ (63%) which is partly isomerized to ethyl crotonate $CH_3CH{=}CHCO_2Et$ (*cis* 12% + *trans* 25%). As in the case of vinylation of alkynylzinc derivatives [6a], palladium appears to be a better catalyst than nickel

Choice of the co-solvent

HMPA is necessary to achieve the catalytic coupling of the Reformatsky reagent with aromatic halides. Nickel complexes, otherwise insoluble in our reactions, are solubilised by HMPA and the reaction occurs under homogeneous conditions As some people think HMPA is carcinogenic[*], we use other dipolar aprotic solvents (dimethyl sulfoxide, dimethyl formamide, *N*-methylpyrrolidone)

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[*] In the conditions of the experiments described in ref 15, HMPA is devoid of acute toxicity and the observed carcinogenity can probably be related not to HMPA itself but to products resulting from the prolonged action of moist air

TABLE 2

RESULTS OF THE REACTION OF $PhCH_2CO_2Et$ WITH PhI OR PhCl IN APROTIC DIPOLAR SOLVENTS (3 h AT 45°C)

Solvent	$PhCH_2CO_2Et$ (%)	
	from PhI	from PhCl
HMPA	85	65
DMSO	88	19
DMF	72	23
NMP	86	86

The Reformatsky reagent was always prepared in methylal [16], and the aprotic dipolar solvent used in equal volume.

$$PhX + BrZnCH_2CO_2Et \xrightarrow{Ni(PPh_3)_4,\ 10\%} PhCH_2CO_2Et$$

All these reactions were performed under the same experimental conditions 3 h at 45°C (Table 2). HMPA and *N*-methylpyrrolidone are the best solvents for these reactions as they allow the use of chlorobenzene with good yields.

Choice of the catalyst

The yield and the ease of the reaction depend considerably on the catalyst used. Catalysts have been tested under the same conditions.

$$PhI + BrZnCH_2CO_2Et \xrightarrow[\substack{\text{HMPA, methylal} \\ \text{3 h at 45°C}}]{\text{[cat] 10\%}} PhCH_2CO_2Et + BrZnI$$

To be active the catalyst must be reducible, for example Ni^{II} to Ni^0, Pd^{II} to Pd^0. $PdCl_2L_2$ and $NiCl_2L_2$ are inactive alone, since the Reformatsky reagent is unable to reduce these complexes to their zerovalent analogues. Contact with air inhibits a reaction catalysed by Ni^0L_4 by oxidizing Ni^0 to Ni^{II}. The catalyst must be stable. Nickel complexes need four ligands attached to nickel in the solution to prevent decomposition. $NiCl_2L_2$ + 2 EtMgBr gives an inactive catalyst resembling a metallic catalyst. $PhNiBrL_2$ is more efficient in the presence of excess L. $Ni(COD)_2$ is inactive under our reaction conditions.

The catalyst must react with ArX. $Ni(diphos)L_2$ * or $Ni(diphos)_2$ do not undergo oxidative addition with ArX [17,18] and are therefore inactive. PdL_4 is inactive with PhBr under 60°C and totally inactive with ArCl [19,20].

Ni^0L_4 appears to be the best tested Ni^0 derivative and can be conveniently prepared by mixing $NiCl_2(PPh_3)_2$ + 2 PPh_3 + 2 EtMgBr/ether in the reaction vessel. To the same vessel ArX, $BrZnCH_2CO_2Et$ in methylal and lastly HMPA are added.

Pd^0L_4 appears to be the best Pd^0 catalyst, better than $Pd(o\text{-tolyl}_3P)_4$, but in

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* diphos = $Ph_2PCH_2CH_2PPh_2$

TABLE 3

YIELDS OF CATALYSED REACTIONS OF $BrZnCH_2CO_2Et$ WITH PhI

Run	Catalyst L = PPh_3	$PhCH_2CO_2Et$ (%) (GLC)	Recovered PhI (%) (GLC)
1	$NiCl_2L_2$ + 2 L + 2 EtMgBr	85	10
2	NiI_2L_2 + 2 L + 2 EtMgBr	81	9
3	$PhNiBrL_2$	53	32
4	$PhNiBrL_2$ + 2 L	88	14
5	NiI_2L_2 + 2 L	1	98
6	NiL_2 + COD [a] + 2 EtMgBr	45	38
7	$NiCl_2L_2$ + 2 SPh_2 + 2 EtMgBr	26	48

[a] COD = cyclooctadiene

the case of palladium, 2L attached to the metal may suffice since $PhPdIL_2$ is an excellent catalyst

We were unable to relate catalytic activity to the geometry of the complexes

Mechanism

Three different mechanisms are commonly used to explain the catalysis of nucleophilic substitution on RX by transition metal complexes.

(1) Oxidative addition of the nucleophilic reagent to the low valency transition metal complex (Felkin) [3].

Example: $[Ni^0L_2] + R'MgX \rightarrow R'NiMgXL_2$

$R'NiMgXL_2 + RX \rightarrow RR' + MgX_2 + [Ni^0L_2]$

(2) Oxidative addition of RX (Parshall) [21]

Example: $Ni^0L_4 + ArX \rightarrow ArNiXL_2 + 2L$

followed by ligand substitution and reductive elimination

$ArNiXL_2 + RMgX \rightarrow ArNiRL_2 + MgX_2$

$ArNiRL_2 + 2L \rightarrow Ni^0L_4 + ArR$

(3) Reductive elimination caused by single electron transfer to the electrophilic substrate (Kochi) [18].

$ArNiRL_2 + ArX \rightarrow [ArNi^{III}RL_2]^+ + ArX^-$

$[ArNi^{III}RL_2]^+ \rightarrow [Ni^IL_2]^+ + ArR$

$ArX^- + [Ni^IL_2]^+ \rightarrow ArNiXL_2$

As we have shown, the Reformatsky reagent reacts easily with $PhPdXL_2$

TABLE 4

YIELDS OF CATALYST REACTIONS OF $BrZnCH_2CO_2Et$ WITH PhI

Run	Catalyst L = PPh_3	$PhCH_2CO_2Et$ (%) (GLC)	Recovered PhI (%) (GLC)
8	PdL_4	45	54
9	$PhPdIL_2$	90	8
10	$PhPdIL_2$ + 2 L	54	34
11	$PdL_2(SPh_2)_2$	37	62
12	$PdCl_2(o\text{-tolyl})_3P_2$ + 2(o-tolyl)$_3$P + 2 EtMgBr	21	65

(X = Cl Br I) or PhNiIL$_2$ to give PhCH$_2$CO$_2$Et and Pd^0 or Ni^0 [8] PhMXL$_2$ (M = Ni, Pd) catalyses the reaction of BrZnCH$_2$CO$_2$Et with ArX (Tables 3 and 4)

We have demonstrated therefore that ArMXL$_2$ can be an intermediate in our catalytic cycle

When ArX is unable to undergo oxidative addition with M^0 (e g PhCl + PdL$_4$) no reaction occurs, although PhPdClL$_2$, independently prepared, reacts cleanly with BrZnCH$_2$CO$_2$Et

At 45°C, PhBr does not give oxidative addition with Pd^{0}L$_4$ and does not couple with BrZnCH$_2$CO$_2$Et in presence of Pd^{0}L$_4$ At 80°C in benzene PhBr undergoes slow oxidative addition with Pd^{0}L$_4$ and slowly couples with BrZnCH$_2$CO$_2$Et

We think therefore, that the first step of our reaction is the oxidative addition of ArX to a Pd^0 or Ni^0 complex

We cannot exclude the possibility that the second step proceeds via single electron transfer, but in THF, at a platinum electrode or at a mercury electrode, neither PhCl nor PhBr are easily reduced Also ArNiXL$_2$ is oxidized at +0 2 V and reduced at −2 2 V (vs Ag/AgClO$_4$ 0 1 *M*), i e reduction to Ni^0 occurs before PhCl, PhBr and even PhI can be reduced to ArX$^-$ [22]

Therefore, we think that the mechanism proposed by Parshall [21] is the best simple mechanism which accomodates our results

Synthetic applications

Our reaction could be useful in synthesis if it were applicable to aromatic halides bearing functional groups

Organozinc derivatives are sufficiently mild to allow the inclusion of many functional groups without reacting with them [6b]

We therefore tried our reactions with different functional aromatic halides (Table 5)

With p-CH$_3$COC$_6$H$_4$X, the addition to the carbonyl group competes favorably with the coupling

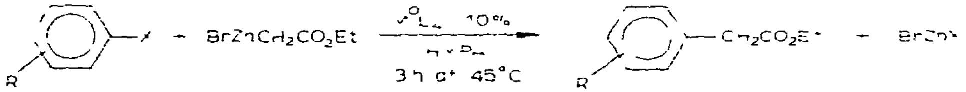
Yields are generally better with electron withdrawing rather than electron-donating substituents, but NO$_2$ deactivates M^{0}L$_4$ by oxidation [17]

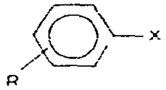
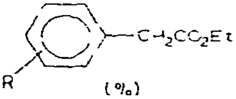
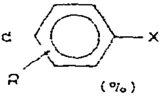
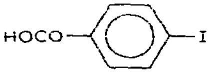
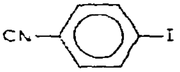
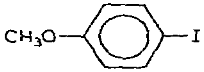
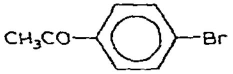
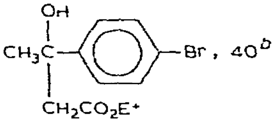
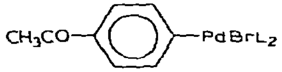
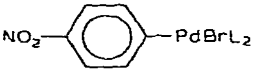
When the catalytic reaction fails, it is also possible to prepare ArMXL$_2$ independently and treat this with BrZnCH$_2$CO$_2$Et (examples p-CH$_3$COC$_6$H$_4$-PdBrL$_2$ and p-NO$_2$C$_6$H$_4$PdBrL$_2$ (Table 5).

Conclusion

Much more work will be necessary to define the scope and limitations of our reaction. However, aromatic nucleophilic substitution of a halogen by the enolate-like reagent BrZnCH$_2$CO$_2$Et, can be catalysed by a transition metal complex This reaction proceeds smoothly even with aromatic chlorides The catalytic arylation of the Reformatsky reagent is compatible with many functional groups and when the reaction cannot be conducted catalytically it can be conducted stoichiometrically with pre-formed ArMX complexes. Work on vinylic halide substitution is in progress and will be published later.

TABLE 5



	Catalys L = PPh3	 (%)	Recovered  (%)
	PdL4	85^a	0
	NiL4	60^a	0
	NiL4	25^b	70^b
	NiL4	56^a	0
	NiL4	, 40^b	60^b
	none	29^a	
	none	26^a	

[a] Isolated product [b] GLC

Experimental

All experiments were carried out under a dry argon atmosphere.

Products of the reaction were analysed by GLC using a Varian gas chromatograph fitted with a 3 m long, 30% SE 30 column, followed by a coupled GLC-mass spectrograph (on a 2.50 m, OV 17 4% column, Varian mat III mass spectrometer). The GLC yields were determined using suitable internal standards.

The isolated products were identified by their mass spectra, their infrared spectra (recorded on a Perkin—Elmer 580 spectrometer) and their ^{1}H-NMR spectra (recorded on a Jeol 60 MHz spectrometer).

The Reformatsky reagent was prepared in methylal, according to the procedure reported by Gaudemar [16].

The palladium complexes, $Pd(PPh_3)_4$, $PhPdX(PPh_3)_2$, p-$NO_2C_6H_4PdBr(PPh_3)_2$, and p-$CH_3COC_6H_4PdBr(PPh_3)_2$ were prepared according to the procedures reported by Coulson [19,23] and Fitton [20,24].

$NiCl_2(PPh_3)_2$ was prepared by the method of Venanzi [25] $PhNiXL_2$ by the method of Hidai [17]

Zerovalent nickel complexes $NiL_2L'_2$ were prepared in situ according to the followed procedure

Preparation of $Ni^0(PPh_3)_4$

To a suspension of 0 32 g (0 5 mmol) of $NiCl_2(PPh_3)_2$ and 0 26 g (1 mmol) of triphenylphosphine in 5 ml of anhydrous diethyl ether at 0°C was added 1 mmol of magnesium ethylbromide (4 ml of 0 25 *N* solution in ether) Effervescence occurred and a red-dark precipitate of $Ni(PPh_3)_4$ appeared The mixture was stirred for 15 min at 0°C

General procedure for the catalytical arylation of the Reformatsky reagent

To 0 5 mmole of $Pd(PPh_3)_4$ or $Ni(PPh_3)_4$ prepared as mentioned above, were added (at 0°C), 5 mmoles of aromatic halide 10 mmol of the Reformatsky reagent (10 ml of a 1 *N* solution in methylal) were then added, followed by at least 10 ml of HMPA or other dipolar aprotic solvent The mixture was stirred for 3 h at 45°C

The progress of the reaction was followed by a potentiometric titration (using aqueous $AgNO_3$ solution) of the solubilized halides taking a 1 ml aliquot The reaction mixture was then quenched with 50 ml of a saturated aqueous NH_4Cl solution The internal standard (generally bibenzyl) was then added to allow GLC titration The solution was extracted with diethyl ether and the organic layers dried with Na_2SO_4 The solvents were distilled off and the product analysed by GLC, by comparison with commercial material If no commercial material was available the products were isolated and characterized

General procedure for the stoichiometrical arylation of the Reformatsky reagent

To a suspension of 5 mmol of $ArPdXL_2$ in 5 ml of anhydrous diethyl ether were added 10 mmol of the Reformatsky reagent (5 mmol only in the case of p-$CH_3COC_6H_4PdBrL_2$) followed by 10 ml of HMPA The solution was stirred at 45°C for 3 h and extracted as mentioned above

Synthesis of $PhCH_2CO_2Et$ from PhI, PhBr, PhCl, $PhPdXL_2$ (X = I, Br, Cl, L = PPh_3), $PhNiI(PPh_3)_2$

In all cases this product was analysed by GLC by comparison with commercial material, and dosed by the internal standard method A coupled GLC-mass spectrograph gave peaks at 164, 119, 105, 91, 77 as in the mass spectrum of the commercial product

Synthesis of p-$HOCOC_6H_4CH_2CO_2Et$ from commercial p-$HOCOC_6H_4I$

This product was isolated after treating the organic layer with an aqueous 2*N* NaOH solution The aqueous basic layers were made acid with a 2*N* HCl solution whence a white solid appeared After water recrystallisation, the product was characterised. M p 114°C, IR (KBr) $\nu(C{=}O)_{ester}$ 1730 cm^{-1}, $\nu(C{=}O)_{acid}$ 1675 cm^{-1}. ^1H NMR (CCl_4 + TMS) t, 3H, 1 2 ppm (OCH_2CH_3), s, 2H, 3 65 ppm ($ArCH_2CO$), q, 2H, 4 15 ppm (OCH_2CH_3), 2d, 4H, 7.35, 8 05 ppm (p-XC_6H_4Y), s, 1H, 10 2 ppm (OH). Mass spectrum· *m/e* 208, 163, 135, 121. Analysis, Found C, 62 45; H, 5 86, O, 30 88, $C_{11}H_{12}O_3$ Calcd.: C, 63 46, H, 5 81, O, 30.73.

Synthesis of p-$CH_3OC_6H_4CH_2CO_2Et$ from commercial p-$CH_3OC_6H_4I$

After distillation of the solvent, the mixture was filtered on a short alumina column. A colourless liquid was obtained which was then distilled B p 142—144°C/10 mmHg (Lit [26] b p 153 -154°C/17 mmHg) IR(CCl_4) $\nu(C=O)$ 1730 cm^{-1}, $\nu(C=C)$ 1610, 1510, 1470 cm^{-1} $\nu(=C—O)$ 1250 cm^{-1} ^1H NMR (CCl_4 + TMS) t, 3H, 1 2 ppm (OCH_2CH_3), s, 2H, 3 4 ppm ($ArCH_2CO$), s, 3H 3 6 ppm (CH_3O), q, 2H, 4 05 ppm (OCH_2CH_3), 2d, 4H, 6 7, 7 1 ppm (p-XC_6H_4Y) Mass spectrum m/e 194, 179, 149 135, 121, 91, 77

Synthesis of p-$CNC_6H_4CH_2CO_2Et$ from commercial p-CNC_6H_4I

After distillation of the solvent, the product was stirred with a water/cyclohexane mixture to remove HMPA A white precipitate was found, which was recrystallised from ethanol M p 88°C (Lit [29] m p 87—88°C) IR (KBr) $\nu(C\equiv N)$ 2230 cm^{-1}, $\nu(C=O)$ 1735 cm^{-1}, $\nu(C=C)$ 1610, 1510, 1470 cm^{-1} ^1H NMR (CD_3COCD_3 + TMS) t, 3H, 1 2 ppm (OCH_2CH_3), s, 2H, 3 75 ppm ($ArCH_2CO$), q, 2H, 4 1 ppm (OCH_2CH_3), 2d, 4H, 7 4, 7 8 ppm (p-XC_6H_4Y) Mass spectrum m/e 189, 160, 144, 116, 89

Synthesis of p-$CH_3COC_6H_4CH_2CO_2Et$ from p-$CH_3COC_6H_4PdBr(PPh_3)_2$

The product was obtained after filtration on an alumina column. The solid was recrystallized from ethanol. M p 60—61°C (Lit [28] m p 62—68°C) IR(KBr) $\nu(C=O)$ 1735 cm^{-1}, $\nu(C=O)$ 1680 cm^{-1}, $\nu(C=C)$ 1610, 1510, 1420 cm^{-1} ^1H NMR(CCl_4 + TMS): t, 3H, 1.2 ppm (OCH_2CH_3), s, 3H, 2.45 ppm ($COCH_3$), s, 2H, 3 55 ppm ($ArCH_2CO$), q, 2H, 4 1 ppm (OCH_2CH_3), 2d, 4H, 7 25, 7.75 ppm (p-XC_6H_4Y). Mass spectrum: m/e 206, 191, 163, 133, 118, 105, 90

Synthesis of p-$NO_2C_6H_4CH_2CO_2Et$ from p-$NO_2C_6H_4PdBr(PPh_3)_2$

The product was obtained after filtration on a alumina column The solid was recrystallized from ethanol. M.p. 63°C (Lit [27] m p 64°C) IR(KBr). $\nu(C=O)$ 1735 cm^{-1}, $\nu(N=O)$ 1520, 1350 cm^{-1}, $\nu(C=C)$ 1610, 1520, 1470 cm^{-1} ^1H NMR (CCl_4 + TMS): t, 3H, 1.2 ppm (OCH_2CH_3), s, 2H, 3 6 ppm ($ArCH_2CO$), q, 3H, 4.1 ppm (OCH_2CH_3), 2d, 4H, 7.35, 8.1 ppm (p-XC_6H_4Y) Mass spectrum: m/e 209, 193, 181, 164, 136, 137, 106

Acknowledgements

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