Tetrahedron Letters,Vol.23,No.44,pp 4629-4632,1982 0040-4039/82/444629-04$03.00/0
Printed in Great Britain

SELECTIVE MONO-ARYLATION AND -ALKYLATION OF CHLOROPHENYL ALKYL SULFIDES BY NICKEL CATALYSED CROSS-COUPLING WITH GRIGNARD REAGENTS

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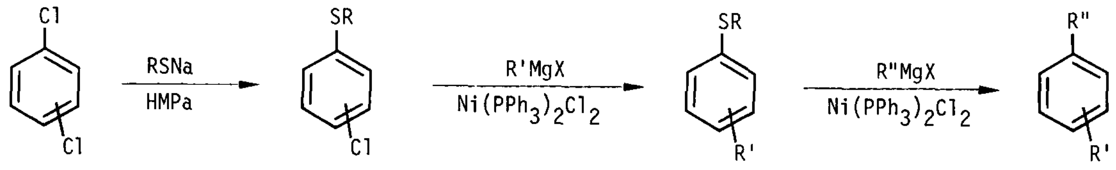
SUMMARY: Chlorophenyl alkyl sulfides are mono-arylated and -alkylated selectively with Grignard reagents, in the presence of $Ni(PPh_3)_2Cl_2$, to give aryl- and alkyl-phenyl alkyl sulfides.

The recent report by Naso and coworkers[1] on the selective coupling reactions of Grignard reagents with 1-bromo-2-phenylthioethene in the presence of nickel or palladium catalysts prompts us to report the results of closely related investigations in the aromatic series. We have shown recently[2] that selective arylations and alkylations can be effected on bis(alkylthio)benzenes, because their reactions with Grignard reagents, catalysed by low-valent nickel species, are very sensitive to steric effects. Thus, (methylthio)phenyl *i*-propyl sulfides reacted with RMgX to give products in which the Grignard residue has substituted the less sterically hindered carbon-sulfur bond, i.e. $C_6H_4(R)SCHMe_2$. We now report the attainment of the same goal by the use of benzene derivatives substituted by two totally different leaving groups whose displacement by Grignard reagents depends on electronic, rather than steric factors[3].

It is known that chlorobenzenes[4] and alkylthiobenzenes[2,5] undergo the cross-coupling reaction with Grignard reagents and that PhCl is slightly more reactive than PhSMe in the reaction with BuMgBr, catalysed by $Ni(dppp)Cl_2$[6]. It now can be shown that the reactions of several Grignard reagents with chlorophenyl alkyl sulfides ($\underset{\sim}{2}$) and ($\underset{\sim}{3}$), in the presence of $Ni(PPh_3)_2Cl_2$, occur selectively at the carbon-chlorine bond, giving the substituted phenyl alkyl sulfides ($\underset{\sim}{4}$) and ($\underset{\sim}{5}$) in moderate to good yields. The products then can be made to react with a different Grignard reagent, yielding disubstituted benzenes ($\underset{\sim}{6}$)[2]. The starting materials ($\underset{\sim}{2}$) and ($\underset{\sim}{3}$) are easily available from dichlorobenzenes ($\underset{\sim}{1}$)[7]. Scheme 1 exemplifies the reaction sequence and the results are summarised in Table I.

SCHEME 1



(1)

(2) R = CHMe$_2$
(3) R = Me

(4) R = CHMe$_2$
(5) R = Me

(6)

TABLE I. The Reactions of Chlorophenyl Alkyl Sulfides (2) and (3) (5 mmol) with 1.3 eqv of Grignard Reagents in Benzene, in the Presence of 0.1 eqv of Ni(PPh$_3$)$_2$Cl$_2$.

Run	Starting Materials (2) or (3)	R' in R'MgX	Temp. °C	Time hr[a]	Products[b,c] (4) or (5)	Yields %[d]
1	*o*-ClC$_6$H$_4$SCHMe$_2$	Ph	50	1	*o*-PhC$_6$H$_4$SCHMe$_2$	83.5[e]
2	*m*-ClC$_6$H$_4$SCHMe$_2$	Ph	0	10	*m*-PhC$_6$H$_4$SCHMe$_2$	65.2[e]
3	*p*-ClC$_6$H$_4$SCHMe$_2$	Ph	0	5	*p*-PhC$_6$H$_4$SCHMe$_2$	73.5[e,f]
4	*p*-ClC$_6$H$_4$SCHMe$_2$	*n*-Bu	50	1	*p*-BuC$_6$H$_4$SCHMe$_2$	56[g]
5	*o*-ClC$_6$H$_4$SCHMe$_2$	Me	25	2	*o*-MeC$_6$H$_4$SCHMe$_2$	63
6	*m*-ClC$_6$H$_4$SCHMe$_2$	Me	25	2	*m*-MeC$_6$H$_4$SCHMe$_2$	50
7	*p*-ClC$_6$H$_4$SCHMe$_2$	Me	25	2	*p*-MeC$_6$H$_4$SCHMe$_2$	60
8	*m*-ClC$_6$H$_4$SCHMe$_2$	(Me)C=CH$_2$	40	2	*m*-CH$_2$=C(Me)C$_6$H$_4$SCHMe$_2$	61.7[h]
9	*p*-ClC$_6$H$_4$SCHMe$_2$	(Me)C=CH$_2$	40	2	*p*-CH$_2$=C(Me)C$_6$H$_4$SCHMe$_2$	70[h]
10	*m*-ClC$_6$H$_4$SCHMe$_2$	CH$_2$CH=CH$_2$	25	6	*m*-CH$_2$=CHCH$_2$C$_6$H$_4$SCHMe$_2$	38[h]
11	*p*-ClC$_6$H$_4$SCHMe$_2$	CH$_2$CH=CH$_2$	25	6	*p*-CH$_2$=CHCH$_2$C$_6$H$_4$SCHMe$_2$	67.3[h]
12	*p*-ClC$_6$H$_4$SMe	Ph	25	2.5	*p*-PhC$_6$H$_4$SMe	45[i]
13	*p*-ClC$_6$H$_4$SMe	Me	25	0.5	*p*-MeC$_6$H$_4$SMe	50[j]
14	*p*-ClC$_6$H$_4$SMe	(Me)C=CH$_2$	25	5	*p*-CH$_2$=C(Me)C$_6$H$_4$SMe	50[k,l]
15	*p*-ClC$_6$H$_4$SMe	CH$_2$CH=CH$_2$	25	6	*p*-CH$_2$=CHCH$_2$C$_6$H$_4$SMe	35[k]

[a] The progress of the reaction was monitored by tlc and glc. Quenching with a saturated solution of NH$_4$Cl was effected, when all the starting material had been consumed. [b] Reaction products were identified by comparison of their physical and spectral properties with those of authentic samples and by ^{1}H NMR spectroscopy. All new compounds gave satisfactory elemental analyses. [c] Biphenyl was present in all the reactions run with PhMgBr. [d] Yields based on isolated products after column chromatography. [e] A 10% yield of terphenyl also was obtained. [f] With Ni(dppe)Cl$_2$ as the catalyst the reaction was not selective[2]. [g] Minor amounts of unidentified products were present. [h] Some reduction product, C$_6$H$_4$SCHMe$_2$, also was isolated. [i] *p*-Terphenyl was isolated in 32% yield. [j] *p*-Xylene was present in about 20% yield (by glc). [k] Some reduction product, C$_6$H$_4$SMe, was isolated. [l] A 25% yield of the disubstituted product, (6), R' = R" = (Me)C=CH$_2$, was obtained also.

The transformations of compounds (2) and (3) into (4) and (5), respectively, were found to be very selective, only minute amounts of the products derived from the displacement of the SR groups (i.e. C_6H_4ClR') being detected by glc in every case. This great difference in reactivity between the carbon-chlorine and the carbon-sulfur bonds could not be anticipated from the results of the competitive experiments carried out by Takei and coworkers[6]. This discrepancy may be attributed to the presence of different catalysts in the two cases. In this regard it is worth noting the observation of the lack of selectivity in reactions of bis(alkylthio)benzenes with Grignard reagents, when $Ni(PPh_3)_2Cl_2$ had been replaced by $Ni(dppe)Cl_2$[2]. This dependence of selectivity on the catalyst ligands has been ovserved also in the reaction of *p*-chlorophenyl *i*-propyl sulfide with PhMgBr (run 3). It can be assumed that the behavior of $Ni(dppp)Cl_2$, used by Takei, is more like that of the $Ni(dppe)Cl_2$ than that of $Ni(PPh_3)_2Cl_2$. It also can be anticipated that, in view of the results obtained in the olefinic series[1], even better results may be obtainable by the use of palladium catalysts.

From the results of Table I there emerges a greater selectivity in the reactions of R'MgX with compounds (2) than with compounds (3). In the latter case, in fact, the amount of disubstituted products (6: R' = R") is considerably higher (*cf.* runs 3, 7 and 9 with 12, 13 and 14, respectively). This result is consistent with our previous findings[2], the reaction occurring much more easily at the Ar-SMe than at the $Ar\text{-}SCHMe_2$ bond. Good results were obtained also with the *o*-chlorophenyl *i*-propyl sulfide (runs 1 and 5). This is a particularly interesting result, since compounds *o*-(4) could not be obtained from the reactions of *o*-(methylthio)phenyl *i*-propyl sulfide with several Grignard reagents[2]. As has been observed previously[2], the use of $CH_2{=}C(Me)MgBr$ and $CH_2{=}CHCH_2MgBr$ lead to the formation of considerable amounts of the reduction products (C_6H_4SMe or $C_6H_4SCHMe_2$).

Other reactions of compounds (4) and (5) with appropriate Grignard reagents (R"MgX) led to the following products: *p*-(6) (R' = $(Me)C{=}CH_2$, R" = $CH_2CH{=}CH_2$) (58%) from *p*-(5) (R' = $(Me)C{=}CH_2$), *p*-(6) (R' = Ph, R" = $CH_2CH{=}CH_2$) (51%) from *p*-(5) (R' = Ph), and *p*-(6) (R' = Ph, R" = *p*-Tol) (65%) from *p*-(4) (R' = Ph)[8].

The procedure described in this paper thus allows the introduction of two different aryl or alkyl groups into the benzene nucleus by the sequential substitution of chloro and alkylthio groups of the easily available chlorophenyl alkyl sulfides.

Acknowledgements. We thank the C.N.R., Rome, and NATO (R.G. 094.81) for financial support.

References and Notes

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8. These reactions can be effected in one pot by the addition of the second Grignard reagent to the reaction mixtures containing the mono-substitution products.

(Received in UK 27 August 1982)