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Uncatalysed coupling of an activated aryl chloride with aryllithium and aryl Grignard reagents

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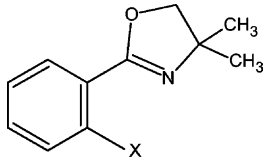
Abstract—Substitution of the chloro group in 2-(2-chlorophenyl)-4,4-dimethyl-2-oxazoline to afford biaryls occurs upon reaction with either aryllithium reagents or aryl Grignard reagents. The reactions with Grignard reagents occur under similar conditions to a previously reported manganese-catalysed procedure. The reactions with lithium reagents, whilst not always affording greater yields of product than the Grignard reagents, involve much shorter reaction times and afford yields, which are comparable with those obtained from the corresponding fluoro derivative.

1. Introduction

In general, coupling reactions between organometallic reagents and aryl halides are most frequently carried out using transition metal catalysts or reagents and aryl bromides or iodides. The direct coupling of Grignard or lithium reagents with aryl halides is rarely successful although exceptions are known with certain aryl fluorides. Thus, hexafluorobenzene gives pentafluorophenylalkanes on reaction with organolithium compounds.[1] This can be contrasted with the behaviour of hexachlorobenzene, which affords pentachlorophenyllithium by metal–halogen exchange.[2] Another example of an organic fluoride, which undergoes successful coupling with lithium reagents is the aryloxazoline **1a**, which has been found to undergo several useful coupling reactions by the group of Meyers.[3] However, for this particular compound, the number of applications has been restricted because the methoxy derivative **1b** also shows a similar reactivity[4] and is preferable due to reasons of cost and availability. Thus, the reaction of **1b** and related compounds with Grignard reagents has been used for the synthesis of a variety of natural products[5–7] and in some cases, this direct approach has proved superior to transition metal catalysed approaches.[8]



1a (X=F)
1b (X=OMe)
1c (X=Cl)
1d (X=Br)

Again primarily due to reasons involving cost and availability, there has been considerable interest recently in the development of cross-coupling reactions of aryl chlorides. These efforts have focussed, in particular, on palladium-catalysed cross-coupling processes such as the Suzuki[9,10] and Kumada[11] reactions for the preparation of biaryls, and related processes such as the Heck[10] or Negishi[12] reactions for the preparation of substituted arenes. However, in work related to that described above, Cahiez et al. have shown that the reaction of **1a** and the related chloro and bromo derivatives **1c** and **1d** undergo manganese-catalysed substitution of the halogen upon reaction with a variety of Grignard reagents in THF.[13] We report here that the chloro-oxazoline derivative **1c** does in fact also undergo substitution reactions in the absence of a catalyst with both aryllithium reagents and aryl Grignard reagents and that these reactions are comparable in conditions and yields with the catalysed method.

Keywords: Nucleophilic aromatic substitution; Aryl chloride; Aryllithium; Aryl Grignard reagent; Coupling.
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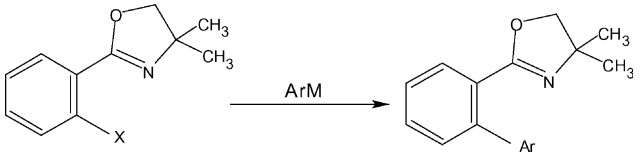
2. Results and discussion

The reactions of the aryl chloride **1c** with lithium reagents and Grignard reagents were carried out in refluxing diethyl ether using an excess of the organometallic reagent (Eq. 1). Conditions and yields are given in Table 1.



(1)

In all cases the coupled products were obtained in fair to reasonable yields, although the reactions with the Grignard reagents required a larger excess of reagent and longer reaction times. No evidence was obtained for either metal–halogen exchange or orthometallation processes. If metal–halogen exchange had occurred, one would have expected the unsubstituted derivative, 2-phenyl-4,4-dimethyl-2-oxazoline, to have formed upon aqueous work up by overall displacement of Cl from **1c** with H. However, it was determined by TLC monitoring of experiments that none of this unsubstituted product was formed. This is in contrast with the chemistry of the bromo derivative (**1d**) and the iodo analogue, which have recently been observed to undergo metal–halogen exchange with Ph_2CuLi.[14] In experiments, which were carried out to determine whether orthometallation had occurred, benzoyl chloride was added to the reaction mixture, subsequent to the addition of the phenyllithium reagent. In all experiments, substitution of Cl with Ph was determined to be the primary product. The only other product formed to a significant extent was benzophenone, which arised from coupling of benzoyl chloride with excess phenyllithium. This presents an interesting contrast to the observed reactivity of **1c** with butyllithium, which has been reported to afford 2,6-disubstituted aryloxazolines after orthometallation and combination with an electrophile.[15]

Table 1. Product yields and conditions for the formation of biphenyl derivatives according to Eq. 1

Entry	Ar M	X	Ratio[a]	Condition[b]	Yield
1	PhLi	Cl	1:4	1 h	54
2	2-$CH_3C_6H_4Li$	Cl	1:4	1 h	56
3	3-$CH_3C_6H_4Li$	Cl	1:4	1 h	61
4	4-$CH_3C_6H_4Li$	Cl	1:4	1 h	40
5	PhMgBr	Cl	1:8	18 h	40
6[c]	PhMgBr	Cl	1:6	24 h[c]	63[c]
7	2-$CH_3C_6H_4MgBr$	Cl	1:8	18 h	64
8	3-$CH_3C_6H_4MgBr$	Cl	1:8	18 h	78
9	4-$CH_3C_6H_4MgBr$	Cl	1:8	18 h	37
10	PhLi	F	1:4	15 min	55
11	2-$CH_3C_6H_4Li$	F	1:4	15 min	86
12	3-$CH_3C_6H_4Li$	F	1:4	15 min	71
13	4-$CH_3C_6H_4Li$	F	1:4	15 min	59

[a] Ratio of **1c**:ArM.
[b] All reactions carried out in refluxing diethyl ether.
[c] Entry 6 represents results given in Ref. 13 using Mn catalysis.

A direct comparison of this uncatalysed approach with the Mn-catalysed method of Cahiez et al. can only be made for PhMgBr and the conditions for the two methods are given in entries 5 and 6. For this combination of aryl halide and Grignard reagent, a yield of 63% was reported using the catalytic method. This can be deemed more favourable than our yield of 40%, although both methods required a considerable excess of reagent and a lengthy reaction time. However, the conditions employed by us for the lithium reagents are superior to those used for the Grignard reagents with or without catalysis. As indicated above, extensive use has been made of compound **1b** and derivatives in synthesis.[5–7] Examples of relevance to this work include the reactions of tolyl[16] and anisyl[17,18] Grignard reagents with **1b** as key steps in the synthesis of aryl substituted tetrahydroisoquinoline derivatives, which were required for screening as dopamine antagonists[17] or angiotensin II receptor antagonists.[16,18] It is, therefore, extremely notable that **1c**, which is considerably more favourable than **1b** on availability and economic grounds, couples directly with lithium reagents under surprisingly convenient conditions.

A comparison of this work with the reported reactivity of the 3-chloro isomer of **1c**, is also warranted. This *meta* substituted aryl chloride reacts with PhLi to afford the corresponding *meta*-substituted biphenyloxazoline (by overall displacement of Cl with Ph) but also affords the isomeric *ortho*-substituted biphenyloxazoline that was formed in this study (Table 1, entry 1) in a reaction, which occurs via a benzyne intermediate.[19] By carrying out the reaction at −78 °C in pentane, product yields of 24% for the *meta*-substituted product and 48% for the *ortho*-substituted product were obtained as determined by gas chromatography.[20]

As seen in Table 1, for both lithium and Grignard reagents, slightly better yields were observed for the *ortho*- and *meta*-tolyl reagents than for the *para*-substituted and unsubstituted examples. The Grignard reagents seem to be more sensitive to this effect, with the best yield we obtained for coupling to the chloro compound **1c**, being for 3-$CH_3C_6H_4MgBr$ (78% entry 8). For comparative purposes, we also carried out the reactions of the fluoro compound **1a** with organolithium reagents under the same conditions. As expected, due to the greater reactivity of F^- as a leaving group in the SnAr reaction, it was observed that the fluoro derivative does generally give slightly better yields than were obtained for the chloro derivative. However, again it was noticed that under these conditions, better yields were observed with the 2-tolyl and 3-tolyl reagents. We suspect that the reasons for this preference are likely to be connected with the orientation of coordination that is expected to occur between the organometallic reagent and the oxazoline group prior to coupling.[4] Thus, it may be suggested that the different positions of the methyl group

in the different tolyllithium reagents cause a slight difference in the mode of pre-coordination and that a more favourable mode of pre-coordination for the coupling reaction occurs when the methyl group is in the *ortho* or *meta* position. No attempt was made to optimise reaction yields for the fluoro derivative. Under different conditions high yields may be obtainable for both phenyllithium and *p*-tolyllithium in addition to the *ortho* and *meta* derivatives. As an example, at −45 °C in THF, *n*-BuLi is known to couple to **1a** in 92% yield.[3]

Acknowledgements

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