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Preparation of *o*-bromobenzophenone derivatives from lithium diarylcuprate(I) reagents

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The reaction of lithium diarylcuprate(I) reagents with *o*-bromobenzoyl chloride has been investigated. In general, the reaction proceeds well to give synthetically useful *o*-bromobenzophenone derivatives as the major product. It is suggested that a minor substituent effect, whereby diarylcuprate reagents containing an *ortho* or *meta* substituent react more favourably, may be attributed to small changes in the structure of the organometallic reagent. Copyright © 2000 John Wiley & Sons, Ltd.

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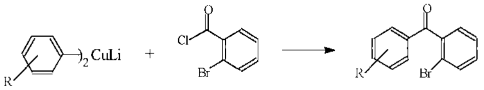
INTRODUCTION

As part of an ongoing study into the transition-metal-mediated preparation of novel heterocyclic compounds, it has became desirable for us to prepare a series of 2-bromobenzophenone derivatives.[1] A currently popular method for the synthesis of such unsymmetrical ketones, which avoids the formation of isomers, is the reaction of organometallic reagents with acid chlorides.[2] Recently Palladium(0) catalysts[3] and some elaborately prepared organocopper[4] or copper–zinc[5] reagents have been employed for this purpose. However, due to their familiarity and relative ease of preparation, we initially considered the reaction of lithium diarylcuprate(I) reagents with *ortho* bromo-substituted aromatic acid chlorides as a possible means of synthesis of these derivatives. (Eqn [1]).



[1]

In contrast to the extensive use which has been made of organocuprates for coupling reactions with R—X[6,7] and for conjugate addition to (α,β)-unsaturated carbonyl compounds,[7,8] relatively little attention has been paid to their application in the reaction with acid chlorides;[9] in those studies that have been carried out, concentration has generally focused on the reaction of methyl or n-alkyl cuprates with unsubstituted acid chlorides.[10] However, there has been one example reported concerning the reaction of a cuprate (lithium dimethylcuprate) with a substituted aromatic acid chloride (*p*-iodobenzoyl chloride).[11] This reaction occurs cleanly at the low temperature of −78 °C. However, above this temperature side reactions are expected to occur, as are seen in the reaction of $(nBu)_2CuLi$ with iodobenzene at 0 °C, which affords both metal–halogen exchange and alkylation products.[12]

These types of competing side reactions may also be expected to occur at the bromide position of 2-bromoaroyl chlorides.[13] Indeed, in reactions closely related to this work, alkylation is the major process in the copper-assisted reaction of active methylene carbanions with *ortho*-substituted bromobenzenes such as *o*-bromobenzoic acid[14] and *o*-bromophenol.[15] In comparison, metal–halogen exchange occurs at the alkyl bromide site in α-bromoketones to afford enolates.[16] For these reasons, we decided it would be beneficial to carry out an investigation into the reactivity of lithium diarylcuprate(I) reagents with *o*-bromobenzoyl chloride. We report here our results that in this reaction C–C bond formation proceeds readily at convenient temperatures to afford the desired diaryl ketones, and that other expected side reactions do not occur to more than a small extent.

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Table 1 Yields and primary analytical data for the product benzophenone derivatives

Entry	Ar in Ar_2CuLi	Ar in ArC(O)Cl	Product	Yield[a] (%)	M.p. (lit)[b] (°C)	IR: ν_{co} (cm^{-1})	UV: λ_{max} (nm) (ε)
1	Ph	Ph	**1**	68	48 (48.1)	1652	245 (8 010)
2	2-$CH_3C_6H_4$	Ph	**2**	96	—[c] (<-18)	1670	237 (17 600)
3	2-$CH_3OC_6H_4$	Ph	**3**	88	40 (41)	1665	240 (16 900)
4	Ph	2-BrC_6H_4	**4**	48	41 (42)	1665	250 (9 900)
5	2-$CH_3C_6H_4$	2-BrC_6H_4	**5**	60	49	1650	248 (5 500)
6	2-$CH_3OC_6H_4$	2-BrC_6H_4	**6**	70	64	1638	250 (4 926)
7	3-$CH_3C_6H_4$	2-BrC_6H_4	**7**	91	57	1672	230 (15 100)
8	4-$CH_3C_6H_4$	2-BrC_6H_4	**8**	42	89	1665	250 (3 582)

[a] Yields are of crystallised materials.
[b] From Ref. 17.
[c] Characterized as oxime; m.p. 105 °C.

RESULTS AND DISCUSSION

As shown in Table 1, reactions were carried out between a variety of metallated arenes and benzoyl chloride or 2-bromobenzoyl chloride. The aroyl chloride was added to the cuprate at 0 °C and quenching was carried out after the reaction mixture had been allowed to warm to room temperature. Products were initially identified by comparison of their melting points with literature data and by the observation of characteristic peaks in their IR and UV spectra (Table 1). ^1H NMR spectroscopic and analytical results of the unsymmetrically substituted benzophenone derivatives **5–8** are given in Table 2. The yields of the reactions were generally good and introduction of the bromo group into the aroyl chloride seemed to have little effect on the yield of the reaction. It is worth pointing out, however, that when the Ar group of the metallated arene was unsubstituted or contained a 4-methyl substituent, the yield was less satisfactory than when there was a substituent in the *ortho* or *meta* position. In these cases, column chromatography of the crude products indicated the presence of several minor products. However, these minor products were either obtained as mixtures or in insufficient quantities to allow full characterization. In the case of the reaction between the unsubstituted reagent lithium diphenylcuprate(I) and 2-bromobenzoyl chloride (entry 4), we decided to investigate whether the relatively low yield of product may have arisen from a reaction at the aryl bromide group of the product with unreacted copper–lithium reagent. Thus, a reaction between the product, **4**, and lithium diphenylcuprate(I) was carried out and monitored by HPLC. However, in this reaction, no consumption of **4** was observed. This result indicates that the overall yield of the reaction may be determined at an early stage in the reaction pathway, perhaps during initial interaction of the organometallic reagent with the electrophilic aroyl chloride. Therefore, it seems reasonable to suggest that different substitution patterns in the aryl group of the organometallic reagent afford subtle changes in the structure of the cuprate and that these changes can affect the initial nucleo-

Table 2 ^1H NMR and analytical data for the unsymmetrical disubstituted benzophenone derivatives **5–8**

Product	^1H NMR	Elemental analysis (%)
5	2.62 (s, 3H), 7.21 (m, 1H) 7.28 –7.46 (m, 6H), 7.65 (m, 1H)	C: 61.014 (61.11)[a] H: 3.791 (4.03)
6	3.73 (s, 3H), 6.91 (m, 1H), 7.04 (m, 1H), 7.27 –7.40 (m, 3H), 7.53 (m, 1H), 7.60 (d, 1H, $J = 7.6$ Hz) 7.68 (m, 1H)	C: 57.743 (57.75) H: 3.680 (3.81)
7	2.41 (s, 3H), 7.31–7.45 (m, 5H), 7.56 (d, 1H, $J = 7.7$ Hz), 7.63 –7.68 (m, 2H)	C: 61.006 (61.11) H: 3.976 (4.03)
8	2.45 (s, 3H), 7.21 –7.49 (m, 5H), 7.64 (m, 1H), 7.71 (m, 2H)	C: 61.470 (61.11) H: 3.959 (4.03)

[a] Calculated values are given in parentheses.

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phile–electrophile interaction and therefore affect the overall amenability towards side reactions. This suggestion is consistent with the generally accepted idea that the solution structure of cuprates (which may be dimeric[18] or an equilibrium mixture of several discrete identities[19] is highly dependent upon a number of factors, including solvent, temperature and counter-ion.[20]

CONCLUSION

This work has demonstrated that the reaction of lithium diarylcuprate(I) reagents with bromo-substituted aroyl chlorides is a highly convenient method for the preparation of synthetically useful bromobenzophenones. As such, this work is complementary to the research of other groups who are investigating the preparation of synthetically useful products via the use of copper reagents which contain functional groups.[4,5]

EXPERIMENTAL

All experiments were carried out under an atmosphere of dry nitrogen. Diethyl ether was dried and distilled prior to use. Bromobenzene, 2-bromoanisole, 3-bromotoluene and 4-bromotoluene were purchased from Aldrich and used as received. 2-Bromotoluene was purchased from Fluka and used as received. Elemental analyses were carried out at Tübitak Instrumental Analysis Laboratory, Ankara. 1H NMR spectra were recorded on a Bruker 300 MHz FT-NMR spectrometer at the Department of Chemistry, University of Alberta, Canada. Aryllithium reagents were prepared in diethyl ether from the corresponding bromoarene and lithium metal by the standard procedure,[21] and their concentrations were determined by titration against standardized 0.1 M HCl. The diarylcopper–lithium reagents were prepared by addition of 2 equiv. of aryl-lithium solution to 1 equiv. of CuCN in ether at 0 °C. The reagents were allowed to warm to room temperature with stirring for 10 min before recooling in an ice-bath. To the solution, was added the neat aroyl chloride (1 equiv.) dropwise. The resultant mixture was allowed to warm to room temperature with stirring for 1 h before quenching with dilute HCl and work-up. Crude products were obtained after extraction into diethyl ether and were subjected to column chromatography (silica gel, 40:1 hexane/ethyl acetate) and crystallization. HPLC experiments were carried out using a JASCO PU-180/UV-970 modular HPLC system, and a HICHROM 25 cm × 0.2 cm C_{18} column. The solvent system was 60% MeOH/40% acetate buffer (pH 5).

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