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Articles

Scale-Up of an Intermolecular Barbier Reaction

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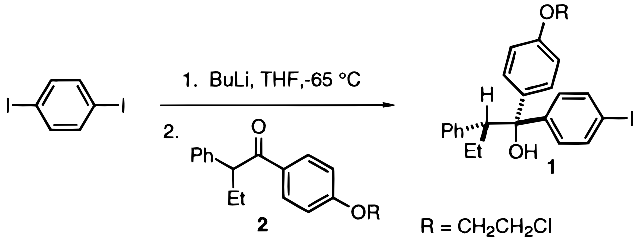
Abstract:

Addition of *n*-BuLi to a mixture of ketone (2) and 1,4-diiodobenzene provides access to alcohol (1) in high yield. This procedure has successfully been used on molar scale.

As part of a development programme, we sought an efficient preparation of alcohol (**1**).[2] This was initially achieved by a low-temperature halogen−metal exchange: 1,4-diiodobenzene was treated with *n*-BuLi at −65 °C in THF and the resulting lithio species was quenched with ketone (**2**) to form **1** as a single diastereoisomer[3] in 80% yield (Scheme 1).

Scheme 1



Although an efficient transformation on small scale (<1.6 M), the exothermic nature of both the iodine−lithium exchange (thermodynamic heat of reaction = −53 kJ mol^{-1})[4] and the carbon−carbon bond formation (thermodynamic heat of reaction = −126 kJ mol^{-1})[4] precluded effective temperature control at larger scale; for reaction in a 25 gallon hastelloy reactor, it was calculated that, given the available cooling capacity at −60 °C, *n*-BuLi would have to be added over 50 min in order to maintain the temperature below −50 °C. For the subsequent reaction with ketone (**2**) a minimum addition time of 110 minutes would be required! At temperatures above −50 °C and addition times in excess of 1 h, it was, however, found that yields of **1** dropped significantly due to the competing formation of 1-butyl-4-iodobenzene.[5] This procedure could, therefore, not be run efficiently at scales >16 molar.

In a variation of this process, we considered an intermolecular Barbier-type reaction (Table 1). Precedent for such a transformation comes from work of Kihara[6] and Dowd[7] (Scheme 2) who have effected intramolecular Barbier reactions with *n*-BuLi (as opposed to metals such as Li and Mg), the halogen−metal exchange taking place more rapidly than addition of *n*-BuLi to the reactive carbonyl centre.

We found that addition of *n*-BuLi to a mixture of 1,4-diiodobenzene and ketone (**2**) in THF led to high yields of alcohol (**1**) (entry 1, Table 1). More importantly, at temperatures up to −45 °C (entry 2, Table 1), and over prolonged addition of *n*-BuLi (entry 3, Table 1), yields remained high. Even interruption of the reaction[8] was not detrimental to the product yield. One limitation of the modified process was, however, the formation of the dimeric impurity (**3**). Azeotropic removal of THF with heptane caused precipitation of **3** from solution. Filtration, followed by dilution of the filtrate with toluene (heptane:toluene, 14:1) led to crystallisation of **1** containing acceptable levels (1−2%) of impurity (**3**). This procedure was used to prepare 13 kg of **1** to fund a toxicology study.

To optimise the process further and remove the need for the filtration step described above, we looked for conditions that would minimise the formation of **3**. Use of additives such as *N,N,N,N,*-tetramethyl-1,2-ethylenediamine (entry 4, Table 1) and KO-*t*-Bu (entry 5, Table 1) were detrimental to the yield of **1**. A similar result was observed using DME as the solvent (entry 6, Table 1).

s-BuLi failed to effect complete reaction (entry 7, Table 1). With *t*-BuLi (2 equiv), the halogen−metal exchange was efficient, but dimer (**3**) was still detected. However, carrying the reaction out in a nonpolar solvent such as toluene had a dramatic effect. The results are shown in Table 1.

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(2) McCague, R.; Potter, G. A.; Jarman, M. *Org. Prep. Proc. Int.* **1994**, *26*, 343.

(3) Determined by X-ray crystallography.

(4) As measured by reaction calorimetry.

(5) Butyl iodide, the byproduct of iodine−lithium exchange, reacts with 4-iodophenyllithium.

(6) Kihara, M.; Kashimoto, M.; Kobayashi, Y.; Kobayashi, S. *Tetrahedron Lett.* **1990**, *31*, 5347−5348.

(7) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1993**, *34*, 2095−2098. For a review, see: Blomberg, C. *The Barbier Reaction and Related One-step Process*; Springer-Verlag: Berlin, 1993.

(8) Addition of *n*-BuLi was stopped after 50% of the required charge had been added. The reaction mixture was maintained at −65 °C. After 2 h, the remaining *n*-BuLi was added as normal.

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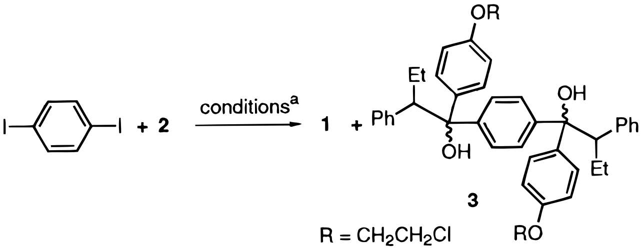
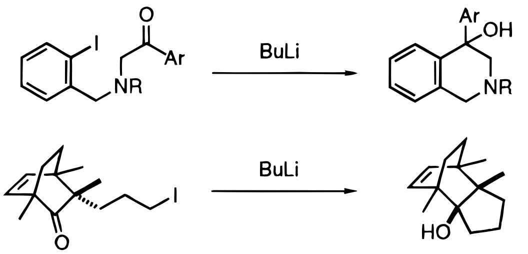
Table 1. **Preparation of Alcohol (1)**



entry	reactant	solvent^b	temp. (°C)	addn time	yield **1**^{c} (%)	yield **3**^{c} (%)
1	*n*-BuLi	A	−65	1	75^d	8^d
2	*n*-BuLi	A	−45	1	73	7
3	*n*-BuLi	A	−65	12	71	8
4	*n*-BuLi/TMEDA	A	−65	1	58^e	13
5	*n*-BuLi/KO-*t*-Bu	A	−65	1	5^e	0
6	*n*-BuLi	B	−65	1	26^e	8
7	*s*-BuLi	A	−65	1	56^e	6
8	*t*-BuLi	A	−65	1	76	8
9	*n*-BuLi	C	−65	1	83^d	0
10	*n*-BuLi	C	−40	1	76	0
11	*n*-BuLi	C	−20	1	77	0
12	*n*-BuLi	C	−10	1	77	0
13	*n*-BuLi	C	20	1	71	1
14	*n*-BuLi	C	−65	3	80	0

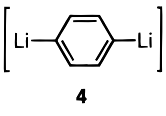
[a] General method: Ketone (**2**) (2.0 g, 6.6 mmol) and 1,4-diiodobenzene (2.43 g, 7.3 mmol) in the appropriate solvent (26 mL) and at the appropriate temperature were treated with the required organolithium reagent (1.2 equiv, with the exception of *t*-BuLi when 2.2 equiv was used) over the required addition time. [b] A = THF (300−500 ppm H_2O), B = DME (200 ppm H_2O), C = toluene (100−200 ppm H_2O). [c] HPLC solution yields. [d] Isolated yields. [e] Starting ketone (**2**) constitutes the balance to 100% (HPLC).

Scheme 2



At −65 °C (entry 9, Table 1), **1** was obtained in 83% yield and no impurity (**3**) was detected. At elevated temperatures ranging from −40 to −10 °C (entries 10−12, Table 1), reproducibly good yields of high purity **1** were obtained. Even at 20 °C (entry 13, Table 1), the amount of **3** detected was only 1% (HPLC) and the yield of **1** remained high. In analogy to the Barbier reaction performed in THF, similar boundary conditions were investigated; addition of *n*-BuLi over a 3−12 h period and interuption of the reaction were tolerated.

We believe that, in THF, the dianion species **4**[9] is formed, subsequent quench with **2** leading to the observed dimer (**3**). This dianion formation is suppressed in toluene.



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We have subsequently employed this robust, efficient, and highly controlled “one-pot” Barbier-type reaction in toluene at −65 °C to prepare 43 kg batches of alcohol (**1**).

Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H NMR were recorded on a JEOL 270 MHz instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield (δ) relative to TMS as an internal standard in $CDCl_3$. MS were recorded on a Perkin-Elmer Sciex API-III instrument. IR are reported in wavenumbers (cm^{-1}).

All reactions were run under a nitrogen atmosphere. Water content of solvents was determined by Karl Fischer analysis: THF contained 300−500 ppm of H_2O; toluene contained 200 ppm of H_2O. Reactions were monitored by HPLC analysis: Nova-Pak C_{18} column, 1:1 THF:H_2O mobile phase at 1 mL/min; UV detection at 254 nm. Solution yields of **1** and **3** were obtained against standards of 0.15 mg/mL.

1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butanone (2). Ketone (**2**) was prepared according to the procedure of McCague and co-workers.[2]

1-[4-(2-Chloroethoxy)phenyl]-1-(4-iodophenyl)-2-phenyl-1-butanol (1). *Original Barbier Conditions.* To a solution of 1,4-diiodobenzene (6.06 kg, 18.3 mol) and ketone (**2**) (5.0 kg, 16.5 mol) in THF (65 L) was added *n*-BuLi (11.45 L, 18.3 mol, 1.6 M in hexane) over 40 min, maintaining the reaction temperature between −65 and −55 °C. The mixture was stirred at between −65 and −55 °C for a further 0.5 h, and the reaction was then quenched by pouring it into a solution of ammonium chloride (6.0 kg in 20 L of H_2O). The product was extracted into EtOAc (50 L), the aqueous layer was separated, and the organic layer was concentrated to low volume (approximately 20 L) and replaced with heptane (125 L) by a series of put and take distillations. The hot solution was then filtered [to remove dimeric impurity (**3**)] into a vessel containing toluene (10 L). A heptane wash (13 L) gave a heptane-to-toluene ratio of 14:1. Cooling of the solution led to crystallisation. After 1 h at 20−25 °C, the suspension was filtered (hastelloy plate filter) and washed with heptane (22 L), and the product was dried *in vacuo* (45−50 °C) to give alcohol (**1**) (6.24 kg, 75%) as a white solid: mp 95 °C; ^{1}H NMR δ 0.73 (t, 3H, $J = 7.6$ Hz), 1.74 (m, 2H), 3.54 (dd, 1H, $J = 7.6, 4.6$ Hz), 3.74 (t, 2H, $J = 6.8$ Hz), 4.11 (t, 2H, $J = 6.8$ Hz), 6.67 (d, 2H, $J = 8.4$ Hz), 7.04−7.17 (m, 7H), 7.28 (d, 2H, $J = 8.4$ Hz), 7.67 (d, 2H, $J = 8.4$ Hz); MS *m/z* 524 [$(MNH_4)^+$, 69%], 489 [$(MH - H_2O)^+$, 100%]; IR (neat) 3550, 1610, 1248; HPLC 97.5% peak area ratio (PAR), 95.8% assay.

Modified Barbier Conditions. (a) *16.5 mM Scale.* To a solution of **2** (5.0 g, 16.5 mmol) and 1,4-diiodobenzene (6.06 g, 18.3 mmol) in toluene (65 mL) was added *n*-BuLi (11.45 mL, 18.3 mmol, 1.6 M) at −65 °C over 40 min. After 15 min, saturated ammonium chloride (20 mL) was added to the reaction mixture. The organic layer was isolated, and the solvent was concentrated to low volume (10 mL).

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[9] Fossatelli, M.; den Besten, R.; Verkruijsse, H. D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 527−528.

Heptane (125 mL) was added to the concentrate, and the suspension was heated until dissolution had taken place and then cooled to 28 °C where crystallisation occurred. The solid was isolated by filtration, washed with heptane (22 mL), and dried *in vacuo* to give **1** (6.95 g, 83%) as a white solid.

(b) *99 Molar Scale.* *n*-BuLi in hexane (48.42 kg, 114 mol, 1.6 M) was added to a suspension of ketone (**2**) (30 kg, 99 mol) and 1,4-diiodobenzene (36.3 kg, 110 mol) in toluene (390 L) at −60 to −55 °C. The reaction mixture was stirred for an additional 0.5 h at −60 to −55 °C, and the reaction was then quenched by pouring it into a solution of ammonium chloride (50 kg, 150 L of H_2O). The aqueous layer was separated, and the organic layer was concentrated and replaced with EtOH by azeotropic distillation for further reaction. HPLC solution yield of **1** was 85% [equating to 43 kg of alcohol (**1**)].

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