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Journal of Organometallic Chemistry 531 (1997) 101–105

Journal of Organometallic Chemistry

A facile one-pot synthesis of alkylarylcarbinols from α,α-dichloroarylmethanes and trialkylboranes in the presence of magnesium or lithium

Nan-Sheng Li, Su Yu, George W. Kabalka *

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

Received 12 June 1996; revised 5 August 1996

Abstract

α-Chlorobenzylmagnesium chloride or α-chlorobenzyllithium generated from α,α-dichloroarylmethane and magnesium or lithium, reacts in situ with trialkylboranes in THF at room temperature to produce the corresponding alkylarylcarbinols in good yields after oxidation with sodium perborate.

Keywords: Alkylarylcarbinols; α,α-Dichloroarylmethane; Trialkylboranes; α-Chlorobenzylic anion; Boron; Magnesium; Lithium

1. Introduction

The alkylation of carbonyl compounds by organometallic reagents is one of the most useful reactions in synthetic organic chemistry [1]. However, trialkylboranes, generally do not alkylate carbonyl compounds, although a few exceptions are known [2]. Hence, indirect routes which are equivalent to the 1,2-addition of a trialkylborane to a carbonyl group have been developed. For example, Knochel and coworkers reported that trialkylboranes could first be converted to dialkylzinc reagents via a boron–zinc transmetallation and then the dialkylzinc reagents reacted with carbonyl compounds to generate the 1,2-addition products [3]. We reported that aryl aldehyde tosylhydrazones reacted with trialkylboranes under basic conditions to generate new trialkylboranes that could be oxidized to produce alkylarylcarbinols [4].

Carbonyl compounds are readily transformed into geminal dichloro compounds by reaction with phosphorus pentachloride or thionyl chloride [5]. In addition, α-chloro anions are important reaction intermediates that can be prepared from geminal dihalocompounds and alkyllithium reagents via a halogen–lithium interconversion. Brown et al. [6] and Sadhu and Matteson [7] each reported that α-chloromethyllithium can be generated in situ from chloroiodomethane and *n*-butyllithium via an iodine–lithium interconversion and reacted with boron substrates at −78 °C to give homologated products. Recently, we reported that α-chloroarylmethyllithium could be generated in situ from α,α-dichloroarylmethane and t-butyllithium at −78 °C via a chlorine–lithium exchange; the α-chloro anion was then trapped by trialkylboranes to afford alkylarylcarbinols after oxidation [8].

We now wish to report a more convenient and efficient reaction of α-chloro anions, generated in situ from α,α-dichloroarylmethanes and magnesium (or lithium), at room temperature with trialkylboranes. The new reaction is equivalent to the 1,2-addition of trialkylboranes to carbonyl compounds and is an alternative to the alkylation of carbonyl compounds with organomagnesium or organolithium reagents.

α-Haloorganomagnesium compounds have previously been postulated as intermediates in carbonyl addition and trimethylsilylation reactions, but low yields of desired products were obtained [9–11]. It is thus interesting to note that the reaction of dichloroarylmethane

* Corresponding author.

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PII S0022-328X(96)06722-8

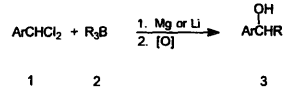
with magnesium in the presence of trialkylboranes affords alkylarylcarbinols in high yields after oxidation.

2. Results and discussion

The reaction procedure is straightforward: a mixture of dichloroarylmethane, trialkylborane and magnesium (or lithium) in dry THF is stirred at room temperature under an argon atmosphere. (The reaction rate can be enhanced by the addition of a small crystal of iodine.) The reaction mixture is stirred at room temperature until the disappearance of most of the metal. The mixture is then oxidized with sodium perborate [12] to give alkylarylcarbinols as shown in Scheme 1.

The reactions of various α,α-dichloroarylmethanes with trialkylboranes in the presence of magnesium or lithium have been examined and the results are summarized in Table 1. The reactions presumably occur via the formation of α-chlorobenzylmagnesium chloride, or α-chlorobenzyllithium; [1] the α-chloroanion then reacts with trialkylborane to form a borate complex that produces a new trialkylborane via a 1,2-migration process as outlined in Scheme 2. The reaction mechanism is reminiscent of the Matteson alkylation reaction involving α-haloboronates [14,15].

As noted in Table 1, the magnesium reactions are generally slower than the reactions using lithium. However, the yields of the reactions using magnesium are generally better than that of the corresponding reactions using lithium. This might be due to the slower formation and higher stability of α-chloroarylmethylmagnesium chloride compared with the corresponding lithium reagent. It is surprising that no reaction occurs even when the mixture is stirred at room temperature for 48 h in the case of p-$CH_3OC_6H_4CHCl_2$; the reaction must be heated under reflux for 10 h (Table 1, entry 13). Side reactions include dimerizations caused by S_N2 reactions of the anion intermediates [9,10] and protonolysis [4] of the newly formed trialkylborane; protonation products are detectable in all experiments using either the perborate or the standard hydrogen peroxide procedure. However, the modified hydrogen peroxide procedure which was developed by Brown and Jayaraman [13] can be used to increase the yield of the desired alcohols in difficult cases (Table 1, entries 18 and 20).



Scheme 1.

n-Butyldiisopropoxyborane and n-octylcatecholborane were also utilized in this reaction. The results are shown in Table 2, the modest yields of alkylarylcarbinols might be due to the decreased electrophilicity of boronic esters when compared with trialkylboranes; hence, the 'self-consumption' side reaction of α-chloro anion becomes more serious [9,10].

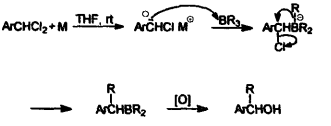
3. Conclusion

The reaction described in this paper provides a useful, one-pot synthesis of alkyarylcarbinols and is the first high yield trapping reaction of an α-chloro Grignard reagent or an α-chlorolithium reagent prepared directly from geminal dihalo compounds with magnesium or lithium.

4. Experimental section

All reagents and solvents were transferred using techniques designed to eliminate contact with air. All glassware and syringes were oven-dried for 24 h prior to use. THF was distilled from sodium benzophenone ketyl. The aryl aldehydes, n-butyldiisopropoxyborane, borane–THF complex (1.0 M solution in THF), catecholborane, tributylborane (1.0 M solution in THF), magnesium (turnings), and lithium shot (−4 + 16 mesh, dry) were purchased from Aldrich Chemical Company and used as received. Alkenes, Aldrich Chemical Company, were purified by distillation over calcium hydride. α,α-Dichlorotoluene, Aldrich Chemical Company, was dried and purified by distillation from phosphorus pentoxide. Other α,α-dichloroarylmethanes were prepared from phosphorus pentachloride and the corresponding aryl aldehydes according to literature procedures [5]. ^{1}H NMR and ^{13}C NMR were obtained using a Bruker AC-250 (250 MHz) NMR spectrometer.

[1] Ashby reported that the reaction of α,α-dichlorotoluene with magnesium in the presence of benzophenone produced triphenylethylene in 44% yield. In addition, we found that the reaction of α,α-dichlorotoluene with magnesium in the presence of cyclohexene gave mainly stilbene in 75% yield accompanied by the formation of the cyclopropyl derivative in 3% yield based on the GC-MS analysis. These results support the suggestion that the reaction intermediate is the α-chloro anion, and not the arylcarbene. See Ref. [9].



Scheme 2.

Table 1
Alkylarylcarbinols prepared

Entry	Product [a]	Ar	R	M	Time (h)	Isolated yield (%)
1	3a	Ph	*n*-Bu	Mg	24	75
2	3a	Ph	*n*-Bu	Li	3.5	61
3	3b	Ph	n-C_6H_{13}	Mg	21	82
4	3b	Ph	n-C_6H_{13}	Li	10	62
5	3c	Ph	n-C_7H_{15}	Mg	20	80
6	3c	Ph	n-C_7H_{15}	Li	14	70
7	3d	Ph	n-C_8H_{17}	Mg	20	76
8	3d	Ph	n-C_8H_{17}	Li	11	60
9	3e	p-ClC_6H_4	*n*-Bu	Mg	24	61
10	3e	p-ClC_6H_4	*n*-Bu	Li	2	58
11	3f	p-$CH_3C_6H_4$	*n*-Bu	Mg	26	65
12	3f	p-$CH_3C_6H_4$	*n*-Bu	Li	6	64
13 [b]	3g	p-$CH_3OC_6H_4$	*n*-Bu	Mg	10	67
14	3g	p-$CH_3OC_6H_4$	*n*-Bu	Li	3.5	41
15	3h	m-$CH_3OC_6H_4$	*n*-Bu	Mg	36	65
16	3h	m-$CH_3OC_6H_4$	*n*-Bu	Li	4	62
17	3i	α-naphthyl	*n*-Bu	Mg	50	38 (38) [c]
18 [d]	3i	α-naphthyl	*n*-Bu	Mg	50	58 (11) [c]
19	3i	α-naphthyl	*n*-Bu	Li	6	0 (40) [c]
20 [d]	3i	α-naphthyl	*n*-Bu	Li	5	15 (40) [c]

[a] All reaction products exhibited physical and spectral characteristics in accord with literature values.
[b] Experiment carried out at reflux in THF for 10 h.
[c] Yield in parentheses is the yield of 1-pentylnaphthalene.
[d] Oxidation is achieved using the modified hydrogen peroxide procedure [13].

4.1. 1-Phenyl-1-octanol (3c)

The synthesis is representative: a mixture of α,α-dichlorotoluene (2.5 mmol, 0.40 g), tri-*n*-heptylborane [2] (2.5 mmol in THF), magnesium (2.8 mmol, 0.067 g), THF (10 ml), and a small crystal of iodine were stirred under an argon atmosphere at room temperature for 20 h. The reaction mixture was oxidized by adding $NaBO_3 \cdot 4H_2O$ (7.5 mmol, 1.2 g) and water (2.5 ml), stirring the reaction mixture at room temperature for 2 h, and then heating to reflux for 30 min to ensure completion of the reaction. The mixture was extracted with ether (3 × 10 ml), the solvent removed, and the product isolated by flash chromatography (eluent: hexane–ethyl acetate 9/1 (v/v)). 1-Phenyl-1-octanol (3c) [17] was obtained in 80% yield (0.41 g). A 70% yield (0.36 g) was obtained when the reaction mixture was stirred at room temperature for 14 h using lithium shot (Table 1, entry 6). ^{1}H NMR ($CDCl_3$/TMS): δ 7.30 (m, 5H), 4.60 (t, 1H, J = 6.6), 2.21 (br s, 1H), 1.80–1.61 (m, 2H), 1.25 (br s, 10H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 144.9, 128.3, 127.3, 125.9, 74.6, 39.0, 31.8, 29.4, 29.2, 25.8, 22.6, 14.0 ppm.

All other alkylarylcarbinols were prepared via the procedure outlined for 3c. Changes in reaction times and yields are indicated in Table 1. The spectral characteristics of these compounds are as follows.

[2] Tri-*n*-heptylborane (2.5 mmol) was prepared via the hydroboration of 1-heptene (7.5 mmol) with borane–THF (2.5 mmol, 2.5 ml of a 1 M solution in THF). See Ref. [16].

4.2. 1-Phenyl-1-pentanol (3a) [8]

^{1}H NMR ($CDCl_3$/TMS): δ 7.29 (m, 5H), 4.60 (t, 1H, J = 6.7), 2.19 (br s, 1H), 1.88–1.56 (m, 2H), 1.45–1.12 (m, 4H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 144.9, 128.3, 127.4, 125.9, 74.6, 38.8, 27.9, 22.6, 13.9 ppm. Additional reactions were carried out utilizing α,α-dichlorotoluene (2.5 mmol, 0.40 g) and *n*-butyldiisopropoxyborane (2.5 mmol, 0.47 g) in THF (10 ml) in the presence of both Mg and Li. The reaction conditions and isolated yields are summarized in Table 2.

4.3. 1-Phenyl-1-heptanol (3b) [18]

^{1}H NMR ($CDCl_3$/TMS): δ 7.28 (m, 5H), 4.56 (t, 1H, J = 6.6), 2.47 (br s, 1H), 1.84–1.56 (m, 2H), 1.49–1.14 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 145.0, 128.2, 127.2, 125.8, 74.5, 39.0, 31.7, 29.1, 25.7, 22.5, 14.0 ppm.

4.4. 1-Phenyl-1-nonanol (3d) [19]

^{1}H NMR ($CDCl_3$/TMS): δ 7.28, (m, 5H), 4.57 (t, 1H, J = 6.6), 2.45 (br s, 1H), 1.87–1.55 (m, 2H), 1.48–1.22 (m, 12H), 0.87 (t, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 145.0, 128.2, 127.2, 125.8, 74.5, 39.0, 31.8,

Table 2
Preparation of alkylarylcarbinols via the reaction of α,α-dichlorotoluene with boronate esters in the presence of magnesium or lithium

Entry	Product [a]	Boric ester	Metal	Conditions	Isolated yield (%)
1	**3a**	*n*-BuB $(OCH(CH_3)_2)_2$	Mg	rt, 57 h, THF	21
2	**3d**	*n*-Octyl–B(O)(O)C$_6$H$_4$	Mg	rt, 27 h, THF	42
3	**3a**	*n*-BuB $(OCH(CH_3)_2)_2$	Li	rt, 4 h, THF	23

[a] All reaction products exhibited physical and spectral characteristics in accord with literature values.

29.5, 29.5, 29.2, 25.7, 22.6, 14.0 ppm. α,α-Dichlorotoluene (2.5 mmol, 0.40 g) was also reacted with *n*-octylcatecholborane (2.5 mmol) prepared via a literature procedure [20]. Using magnesium, a 42% yield (0.23 g) of **3d** was obtained (Table 2, entry 2).

4.5. 1-(p-Chlorophenyl)-1-pentanol (3e) [21]

^{1}H NMR ($CDCl_3$/TMS): δ 7.29 (d, 2H, J = 8.5), 7.23 (d, 2H, J = 8.5), 4.58 (t, 1H, J = 6.6), 2.41–2.10 (br s, 1H), 1.83–1.54 (m, 2H), 1.43–1.14 (m, 4H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 143.3, 133.0, 128.4, 127.2, 73.9, 38.8, 27.8, 22.5, 13.9 ppm.

4.6. 1-(p-Methylphenyl)-1-pentanol (3f) [22]

^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H, J = 8.1), 7.12 (d, 2H, J = 8.1), 4.56 (t, 1H, J = 6.7), 2.32 (s, 3H), 2.24 (br s, 1H), 1.85–1.57 (m, 2H), 1.42–1.23 (m, 4H), 0.86 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 141.8, 136.9, 128.9, 125.8, 74.4, 38.6, 27.9, 22.5, 21.0, 13.9 ppm.

4.7. 1-(p-Methoxylphenyl)-1-pentanol (3g) [23]

^{1}H NMR ($CDCl_3$/TMS): δ 7.24 (d, 2H, J = 8.6), 6.86 (d, 2H, J = 8.6), 4.57 (t, 1H, J = 6.7), 3.78 (s, 3H), 2.23–2.04 (br s, 1H), 1.88–1.56 (m, 2H), 1.48–1.13 (m, 4H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 158.8, 137.1, 127.0, 113.6, 74.1, 55.1, 38.6, 28.0, 22.5, 13.9 ppm.

4.8. 1-(m-Methoxylphenyl)-1-pentanol (3h) [24]

^{1}H NMR ($CDCl_3$/TMS): δ 7.18 (t, 1H, J = 8.0), 6.89–6.81 (m, 2H), 6.78–6.71 (m, 1H), 4.50 (t, 1H, J = 6.6), 3.72, (s, 3H), 3.00 (br s, 1H), 1.80–1.53 (m, 2H), 1.41–1.12 (m, 4H), 0.86 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 159.4, 146.7, 129.1, 118.1, 112.5, 111.2, 74.1, 54.8, 38.6, 27.8, 22.4, 13.8 ppm.

4.9. 1-(α-Naphthyl)-1-pentanol (3i) [21]

^{1}H NMR ($CDCl_3$/TMS): δ 8.04–7.95 (m, 1H), 7.84–7.74 (m, 1H), 7.69 (d, 1H, J = 8.1), 7.52 (d, 1H, J = 7.0), 7.48–7.31 (m, 3H), 5.29 (t, 1H, J = 6.3), 2.48 (br s, 1H), 1.93–1.68 (m, 2H), 1.50–1.16 (m, 4H), 0.84 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 140.6, 133.7, 130.3, 128.8, 127.6, 125.8, 125.6, 125.3, 123.1, 122.7, 71.0, 38.0, 28.3, 22.6, 14.0 ppm.

4.10. 1-Pentylnaphthalene [25]

^{1}H NMR ($CDCl_3$/TMS): δ 8.01 (d, 1H, J = 7.6), 7.84–7.74 (m, 1H), 7.65 (d, 1H, J = 8.0), 7.50–7.23 (m, 4H), 3.02 (t, 2H, J = 7.8), 1.80–1.63 (m, 2H), 1.46–1.27 (m, 4H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 139.0, 133.9, 131.9, 128.7, 126.4, 125.8, 125.6, 125.5, 125.3, 123.9, 33.1, 32.0, 30.5, 22.6, 14.1 ppm.

Acknowledgements

We wish to thank the Department of Energy and the Robert H. Cole Foundation for the support of this research.

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