Preparation and Reactions of Polyfunctional Magnesium Arylcuprates Obtained by an Iodine–Copper Exchange

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Received 6 October 2003

Abstract: The preparation of polyfunctional magnesium cuprates of type **1** can be achieved via an iodine–copper exchange reaction using the cyclic magnesium cuprate **3**. A range of functional groups like an ester, halide (F, Br), nitrile or even a ketone can be tolerated. The new cuprates can be acylated and allylated in good yields leading to a range of polyfunctional products.

Key words: functionalized organometallics, cuprates, acylation, magnesium, iodine–copper exchange

The preparation of polyfunctional organometallics is an important research field since these versatile nucleophiles can react with a range of organic electrophiles with excellent yields.¹ The performance of an I/Mg- or a Br/Mg-exchange has been proved to be especially useful and provided an efficient preparation of a broad range of arylor heteroaryl- magnesium reagents,² which displayed high reactivity toward several important classes of electrophiles.³ A keto group was found to be compatible with the I/Mg-exchange reaction, but in some cases, low temperature and long reaction time had to be used for these exchanges due to the high reactivity of the Grignard reagent toward the keto group present in the substrate.⁴ To overcome these problems, we have developed a halide-copper exchange reaction, which allows a practical preparation of functionalized lithium cuprates compatible with the presence of a keto group.^{5,6} Herein we wish to report a related iodine-copper exchange, which provides functionalized magnesium cuprate reagents of type FG-ArCu(CN)MgBr (1). To perform the exchange reaction, we have used 1,5*bis*(bromomagnesium)pentane,⁷ which was readily prepared from 1,5-dibromopentane **2** and magnesium.^{7a} Its reaction with the THF-soluble copper salt CuCN·2LiCl⁸ provided a magnesium cuprate reagent tentatively formulated as **3**^{7c,d,9} (Scheme 1).

The ate-nature of the copper reagent **3** due to a possible coordination of the cyanide anion makes it potentially more reactive and useful for an iodine–copper exchange.^{10,11} Also the nature of the cation (MgBr instead of the previously used Li) allows the exchange to be performed very conveniently at room temperature. Especially interesting is that the cyclopentane should be the only side-product formed if reagent **3** is used for a halogencopper exchange (see below).

We found that a wide range of aromatic iodides undergo an I/Cu-exchange with reagent **3** (0.5 equiv) within 1-2hours at 25 °C in THF providing the cyanocuprates of type **1** (Scheme 1). Interestingly, this method allows the copper compounds to be prepared free of organic iodide. Thus, the cuprate resulting from the I/Cu-exchange was anticipated to undergo a rapid elimination reaction providing cyclopentane, and the cyanocopper reagent **1**. As the detection of cyclopentane in the crude reaction mixture was difficult, we have prepared the cuprate **5** of 3phenyl substituted 1,5-*bis*(bromomagnesium)pentane and performed the reaction with ethyl 4-iodobenzoate under





Scheme 1

SYNLETT 2004, No. 1, pp 0081–0084 Advanced online publication: 26.11.2003 DOI: 10.1055/s-2003-43358; Art ID: G26503ST © Georg Thieme Verlag Stuttgart · New York our standard reaction conditions to prove the formation of a cyclopentane as reaction product. We have observed a rapid exchange and detected the formation of phenylcyclopentane **6** (94%) and the expected cuprate **1a** as the sole reaction product. Cyclopentane derivative **6** was formed via a fast intramolecular substitution of the intermediate **7** generated during the iodine-copper exchange reaction (Scheme 2).

The newly prepared cyanocuprates of type **1** were quenched with allyl bromide and various acid chlorides providing the expected products of type **8** in 70–95% yields (Table 1). Thus, ethyl 4-iodobenzoate (**4a**) reacts with magnesium cuprate **3** (0.5 equiv) within 1 hour at room temperature and provides the corresponding copper reagent **1a** (entries 1–5, Table 1).

This reagent was allylated with allyl bromide affording the desired product (**8a**) in 91% yield (entry 1). This test reaction indicated that the preparation of the cuprate was complete and that the functionalized magnesium cyanocuprates had reacted as expected. Then, we focused our attention on the preparation of polyfunctional ketones and performed the acylation reaction of **1a** with a range of acid chlorides¹² (Table 1). We found that the reaction of the magnesium cuprate with benzoyl chloride was completed within 15 minutes at room temperature leading to the ketone 8b in 94% yield (entry 2). Similarly, aliphatic acid chlorides like c-HexCOCl and t-BuCH₂COCl provide the corresponding products in 92-93% yields (entries 3 and 4). The acylation of **1a** with an unsaturated acid chloride like cinnamyl chloride led to the (E)-ketoester 8e in 85% yield (entry 5). Ethyl 3-iodobenzoate 4b was treated with the cuprate 3 (0.5 equiv, 25 °C, 2 h) leading to the cyanocuprate 1b and reacted with typical acid chlorides in 84-91% yields (entries 6-8). A cyano group is also well tolerated in the starting aryl iodide 4c and the I/Cu-exchange is completed within 40 minutes at 25 °C furnishing the magnesium cyanocuprate 1c. Its reaction with PhCOCl and *i*-PrCOCl gave the cyanoketones **8i** and **8j** in 90–92% yields (entries 9 and 10). Aromatic iodoketone was also submitted with success to the I/Cu-exchange. Thus, 4-iodophenyl tert-butyl ketone (4d) and 2-iodophenyl 4methoxylphenyl ketone (4e) are converted to the corresponding cuprates 1d and 1e by reaction with 3. In these cases, the iodoketones were added at -78 °C and the reaction mixtures were allowed to warm slowly to room temperature over 2 hours. Quenching with acid chlorides like PhCOCl and *i*-PrCOCl furnished the expected diketones 8k and 8l in 70-85% yields. The resulting ketone 8l can be readily converted to the heterocycle 9 by treatment with hydrazine monohydrate (EtOH, reflux, 30 min, 91% yield; see Scheme 3).¹³



Scheme 3

Synlett 2004, No. 1, 81–84 © Thieme Stuttgart · New York

Entry	Functionalized cuprate	Electrophile	Product of type 8	Yield (%) ^a
	EtOOC		EtOOC	
1	1a	Allyl bromide	8a : R = Allyl	91
2		PhCOC1	8b : R = COPh	94
3		c-HexCOCl	8c : R = CO <i>c</i> -Hex	93
4		t-BuCH ₂ COCl	8d : $\mathbf{R} = \text{COCH}_2 t$ -Bu	92
5		(E)-ClCOCH=CHPh	8e : R = COCH=CHPh	85
	EtOOC Cu(CN)MgBr		EtOOC R	
6	1b	c-PentCOCl	8f : $\mathbf{R} = c$ -Pent	91
7		4-FC ₆ H ₄ COCl	8g : $R = 4-FC_6H_4$	84
8		2-FurylCOCl	8h : R = 2-Furyl	85
	NCCu(CN)MgBr		NC	
9	1c	PhCOC1	8i : R = Ph	90
10		<i>i</i> -PrCOCl	8h : R = <i>i</i> -Pr	92
11	<i>t</i> -Bu	PhCOCl	t-Bu	70 ^b
12	MeO le	i-PrCOCl		85 ^b
	Br-Cu(CN)MgBr			
13	1f	PhCOC1	$\mathbf{8m}: \mathbf{R} = \mathbf{Ph}$	95
14		c-HexCOCl	$8\mathbf{n}: \mathbf{R} = c\text{-Hex}$	92

Table 1	Reactions of Cyanocuprates of Type 1 Generated from the Corresponding Functionalized Aryl Iodides of Type 4 with Allyl Bromide
and Acid	Chlorides to Form 8

^a Yield of analytically pure products.

^b In this case, the aryl iodide was added at –78 °C and the resulting mixture was then warmed slowly to r.t. over 2 h.

Finally, we have examined the reaction of a polyhalogenated aromatic substrate like 1-iodo-2-fluoro-4-bromobenzene (**4f**). Only the I/Cu-exchange was observed and no Br/Cu-exchange could be detected. After the reaction with acid chlorides like PhCOCl and *c*-HexCOCl, the expected halogenated ketones **8m** and **8n** were obtained in 92–95% yields (entries 13, 14). In summary, we have shown that the magnesium cuprate **3** is an excellent reagent for performing an iodine–copper exchange reaction, providing for the first time a range of new polyfunctional cyanocuprates, which react with acid chlorides leading to highly functionalized ketones in high yields.¹⁴

Acknowledgment

We thank the Fonds der Chemischen Industrie and the Ludwig-Maximilians-University (Munich) for the financial support. We thank the BASF AG (Ludwigshafen), Degussa (Hanau) and Chemetall GmbH (Frankfurt) for the generous gift of chemicals.

References

- (a) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. Org. React. 2001, 58, 417. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. Synthesis 2002, 265.
- (2) For some recent examples of polyfunctional magnesium reagents, see: (a) Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* 2003, 233. (b) Bonnet, V.; Mongin, F.; Trecount, F.; Breton, G.; Marsais, F.; Knochel, P.; Queguiner, G. *Synlett* 2002, 1008. (c) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* 2001, 477. (d) Vardui, G.; Kofink, C.; Lindsay, D. M.; Ricci, A.; Knochel, P. *Chem. Commun.* 2003, 396. (e) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* 2002, 41, 1610.
- (3) (a) Kopp, F.; Sapountzis, I.; Knochel, P. Synlett 2003, 885.
 (b) Gommermann, N.; Koradin, C.; Knochel, P. Synthesis 2002, 2143. (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. Synlett 2001, 1901.
- (4) Kneisel, F. F.; Knochel, P. Synlett 2002, 1799.
- (5) (a) Piazza, C.; Knochel, P. Angew. Chem. Int. Ed. 2002, 41, 3263. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. Org. Lett. 2003, 5, 1229.
- (6) For alternative preparations of functionalized copper reagents, see: (a) Ebert, G. W.; Rieke, R. D. J. Org. Chem. **1988**, *53*, 4482. (b) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. (c) Wu, T.-C.; Wehmeyer, R. M.; Rieke, R. D. J. Org. Chem. **1987**, *52*, 5057. (d) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513.
- (7) (a) Whitesides, G. M.; Gutowski, F. D. *J. Org. Chem.* 1976, *41*, 2882. (b) Bickelhaupt, F. *Pure Appl. Chem.* 1986, *58*, 537. (c) Spek, A. L.; Schat, G.; Holtkamp, H. C.; Blomberg, C.; Bickelhaupt, F. *J. Organomet. Chem.* 1977, *131*, 331. (d) Bickelhaupt, F. *Grignard Reagents*; John Wiley and Sons Ltd: Chichester, 2000, 367–393.
- (8) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. Org. Chem. 1988, 53, 2390.

- (10) Jastrzebski, J.; Johann, T. B. H.; van Koten, G. Modern Organocopper Chemistry; Wiley-VCH: Weinheim, 2002, 1–44.
- (11) (a) Hamon, L.; Levisalles, J. J. Organomet. Chem. 1983, 251, 133. (b) Huang, H.; Alvarez, K.; James, P.; Penner-Hahn, J. E. J. Am. Chem. Soc. 1996, 118, 8808.
- (12) (a) Dieter, R. K. Modern Organocopper Chemistry; Wiley-VCH: Weinheim, 2002, 79–144. (b) Rieke, R. D.; Wehmeyer, R. M.; Tse, C.; Ebert, G. W. Tetrahedron 1989, 45, 443.
- (13) Haddadin, M. J.; Agha, B. J.; Tabri, R. F. J. Org. Chem. 1979, 44, 494.
- (14) Typical Procedure: A dry and argon filled 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 1,5-bis(bromomagnesium)pentane (0.46 M/THF, 4.4 mL, 2.0 mmol) in THF (8 mL). The solution of CuCN·2LiCl in THF (1.0 M/THF, 2.0 mL, 2.0 mmol) was added dropwise at -78 °C. The resulting mixture was stirred for 30 min and ethyl 4-iodobenzoate 4a (552 mg, 2.0 mmol) was added at -78 °C. The resulting mixture was warmed to r.t. for 1 h and then benzoyl chloride (421 mg, 3.0 mmol) was added. After 30 min, the solution was quenched with sat. aq NH₄Cl solution and poured into H₂O (20 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic fractions were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (SiO₂, *n*-pentane/ $Et_2O = 50:1$) yielded 478 mg (94% yield) of **8b** as a colorless oil. IR (film): 3402 (m, br), 2982 (m), 1720(vs), 1661 (vs), 1597 (m), 1579 (w), 1448 (m), 1405 (s), 1356 (s), 1369 (s), 1317 (s), 1275(vs), 1105(vs), 1020 (m), 939 (m), 927 (m), 851 (w), 769 (w), 715 (s), 698 (m), 657 (m)cm⁻¹. ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3)$: $\delta = 8.07 \text{ (dd}, J = 8.4 \text{ and } 1.8 \text{ Hz}, 2 \text{ H}),$ 7.73 (m, 4 H), 7.53 (m, 1 H), 7.40 (t, J = 8.0 Hz, 2 H), 4.34 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.1 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 195.0, 164.8, 140.2, 136.0, 132.6, 131.9, 129.1, 128.7, 128.4, 127.4, 126.2, 60.4, 13.3. MS (EI, 70 eV): m/z (%) = 254 (48) [M⁺], 226 (14), 209 (45), 181 (18), 177 (57), 152 (10), 149 (14), 130 (20), 118 (17), 104 (100). HRMS (EI): calcd for C₁₆H₁₄O₃ [M⁺]: 527.7580. Found: 527.7579.