

Tetrahedron Letters 41 (2000) 1589-1592

TETRAHEDRON LETTERS

Copper(I) or (II)-mediated conjugate addition or dimerisation of functionalised organolithium compounds[†]

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Received 4 October 1999; accepted 16 December 1999

Abstract

The reaction of different functionalised organolithium intermediates 1–3 with several electrophilic olefins 6 (2-cyclopentenone, 2-cyclohexenone, methyl vinyl ketone, benzylideneacetone, benzylideneacetophenone and ethyl acrylate) in the presence of copper(I) salts (bromide and iodide) in THF at -78° C gives, after hydrolysis with ammonium chloride, the expected products resulting from a conjugate addition. In the presence of copper(II) chloride intermediates 1–5 undergo dimerisation to yield the expected dimers. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: copper reagents; conjugate addition; dimerisation; functionalised organolithiums.

Organocopper reagents are important intermediates in synthetic organic chemistry not only from an academic point of view, but also in industrial processes.¹ The most important reactions of these reagents are: (a) conjugate addition, (b) acylation, (c) alkylation/arylation, and (d) alkyne carbocupration. In general, organocopper reagents are prepared by transmetallation from the corresponding magnesium or, mainly, organolithium compounds. However, this approach is not generally applicable for functionalised organocopper reagents² due to the difficulty in obtaining stable functionalised organomagnesium or organolithium compounds. Examples of functionalised organocopper reagents prepared by tin/copper transmetallation,³ direct reaction of halogenated compounds with activated Rieke copper,⁴ or via organozinc⁵ or organozirconium⁶ reagents using copper cyanide or high order cyanocuprates, respectively, can be found in the literature. In the last decade, we have been developing a new methodology to prepare very reactive functionalised organolithium intermediates⁷ from halogenated⁸ or non-halogenated materials⁹ and performing lithiation with lithium powder and a catalytic amount of an arene: naphthalene and 4,4'-di-tert-butylbiphenyl (DTBB) being the most commonly used.¹⁰⁻¹² In this paper we describe the reaction of functionalised organolithium derivatives with copper(I) or (II) salts in order to obtain polyfunctionalised molecules through a conjugate addition to electrophilic olefins, or the corresponding dimerisation, respectively.

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[†] This paper is dedicated to the memory of Professor Raymond N. Castle.

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Fig. 1. Intermediates 1-5, olefins 6 and products 7-20

Intermediate **1** was prepared in THF by DTBB-catalysed lithiation of phthalan,^{7c,13} and was treated with a copper(I) salt at -78° C and the corresponding electrophilic olefin **6** to give, after hydrolysis with a saturated solution of ammonium chloride, the expected compounds **7–12**, resulting from a conjugate addition¹⁴ (Fig. 1 and Table 1, entries 1–12). Copper(I) bromide–dimethyl sulfide complex or copper(I)

Table 1
Preparation of compounds 7-15

		1-3	+ CuX <u>i. 6, THF, -78°C</u> ii. NH ₄ Cl-H ₂ O				7-15			
	Organolithi	um Copper(I)	Product					a		
Entry	intermedia	tte salt (eq)	Additive	6	No.	n	m	R	Z	Yield (%) ^b
1	1	$C_{\rm eff}(2)$		60	-	1	1	(CU		70
1	1	$\operatorname{Cul}\left(2\right)$	НМРА	oa Ch	0	1	1	$(CH_2)_2 CO$		27
2	1	$CuBr \cdot SMe_2(1)$	-	00	0	T	1	СП	2)300	61
1		$CuBr(SMe_2(2))$	ΗΜΡΔ							56
5		$\operatorname{Cull}(2)$	НМРА							50 74
6		$\operatorname{Cul}(2)$	DMPU							62
7	1	$\operatorname{Cul}(2)$	HMPA	6c	9	1	1	Н	COMe	51
8	1	$CuBr \cdot SMe_2(2)$	-	6d	10	1	1	Ph	COMe	50
9		CuI (2)	HMPA							64
10	1	CuI (2)	HMPA	6 e	11	1	1	Ph	COPh	62
11	1	CuI (2)	HMPA	6 f	12	1	1	Н	CO_2Et	12
12		$CuBr \cdot SMe_2(2)$	LiBrc							38
13	2	CuI (2)	HMPA	6 b	13	0	2	(CH	I ₂) ₃ CO	31
14	3	CuI (2)	HMPA	6 b	14	2	1	(CH	I ₂) ₃ CO	69
15	3	CuI (2)	HMPA	6d	15	2	1	Ph	COMe	58

^a All compounds **7-15** were \geq 95% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and MS). ^b Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the heterocyclic precursor of the organolithium intermediates **1-3** (see text). ^c Two equivalents were used.

		R ^{FG} Li 1-5	i. CuCl ₂ , ii. NH ₄ Cl	THF, -78° -H ₂ O	C → 1/:	2 R ^{FG} - R ^{FG} 16-20				
	Organolithium	CuCl2	Producta							
Entry	intermediate	eq	No.	n	m	Х	Y	Yield (%)b		
1 2 2	1	1 1.5	16	1	1	-	-	63 37 20		
3 4 5 6 7	2 3 4 5	1 1 1 1	17 18 19 20	0 2 -	2 1 -	- - OEt H	- OEt OH	20 53 59 72 33		

Table 2 Preparation of compounds **16–20**

^a All compounds **16-20** were \geq 93% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and MS). ^b Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting precursor of the organolithium intermediates **1-5** (see text) and corresponding to the reaction shown above. ^c DMF was used as cosolvent in the reaction.

iodide were used either with or without an additive such as hexamethylphosphoramide (HMPA) or N,N'-dimethylpropyleneurea (DMPU), as well as lithium bromide in the case of using ethyl acrylate as the olefinic component. In general, the combination of copper(I) iodide and HMPA gave the best results. The use of intermediate **2** (prepared by DTBB-catalysed lithiation of 2,3-dihydrobenzofuran¹⁵) and **3** (derived from isochroman by DTBB-catalysed lithiation^{7c,16}) gave, under the same reaction conditions, the expected products **13–15** (Fig. 1 and Table 1, entries 13–15).

In the second part of this study we considered the dimerisation of intermediates 1, 2, 3 and 4 (prepared by reaction of the corresponding chloroacetal with lithium naphthalene¹⁷) and 5 [prepared from the corresponding alcohol by reaction with (1) ^{*n*}BuLi, THF, -78° C, and (2) lithium naphthalenide, -78° C¹⁸] by means of copper(II) chloride in equimolar amounts at -78° C using THF as the solvent. Thus, the expected dimers **16–20** were the only reaction products isolated after hydrolysis with saturated ammonium chloride (Fig. 1 and Table 2, entries 1–7).

From a mechanistic point of view, in both processes mentioned above using copper(I) or copper(II) salts, intermediates of the type $R^{FG}Cu$ or $(R^{FG})_2Cu$ can be involved.¹ However, radical-type reactions, especially in the second case, cannot be ruled out.

General procedure for compounds 7–15: To a solution of anhydrous copper(I) iodide (2 mmol) and the corresponding olefin 6 (1.1 mmol) in THF (4 ml) and HMPA (2 ml) was added a THF solution (6 ml) of the corresponding organolithium compound 1–3 (1 mmol) at -78° C. After 25 min stirring at the same temperature the resulting mixture was hydrolysed with saturated NH₄Cl (10 ml). After warming to room temperature it was extracted with ether (5×8 ml), the organic layer dried over anhydrous MgSO₄ and evaporated (15 Torr) giving a residue which was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield the title compounds.

General procedure for compounds **16–20**: To a solution of copper(II) chloride (2 mmol) in THF (5 ml) was added a solution of the corresponding organolithium compound 1-5 (2 mmol) in THF (6 ml)

at -78° C and the mixture was stirred for 45 min at the same temperature. Then it was hydrolysed and worked up as described above for compounds 7–15.

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the Spanish Ministerio de Educación y Cultura (MEC) through the grant no. PB97-0133. I.M.P. thanks the Generalitat Valenciana for a predoctoral fellowship.

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