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INTRODUCTION OF FURAN RING BY A NOVEL REAGENT, LITHIUM DI(3-FURYL)CUPRATE·2FURYLLITHIUM, INTO LESS REACTIVE OXIRANES

Yasuhiro Kojima and Natsuki Kato*

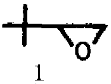
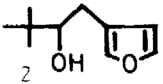
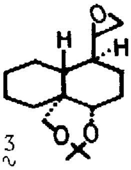
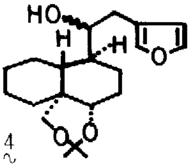
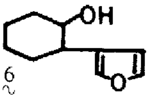
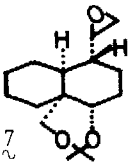
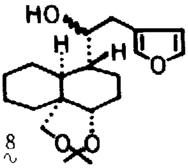
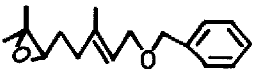
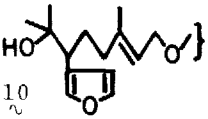
Department of Agricultural Chemistry,
Nagoya University, Chikusa, Nagoya 464, Japan

Summary: A new reagent, lithium di(3-furyl)cuprate·2furyllithium, which is distinct from lithium di(3-furyl)cuprate, possesses an excellent nucleophilicity and gives 3-substituted furans in good yields by the reactions with less reactive oxiranes.

Lithium organocuprates (R_2CuLi) are widely used as excellent reagents for synthetic reactions, and it is assumed that they exist as a dimeric tetrahedral structure in solution1). Now, in the course of the synthesis of the model compounds2) for investigating the structure-activity relationships about antifeeding substances3) such as clerodin4a), clerodendrin A4a), and caryoptin4c), we developed a new reagent, lithium di(3-furyl)cuprate (A)5), for one step synthesis of 3-substituted furans. For example, 3,3-dimethyl-1,2-epoxybutane 1 was converted into the corresponding furan-alcohol 2 by the reaction with the cuprate (A) in good yield (Entry 1).

On the other hand, reaction of the cuprate (A) and (B) with a key intermediate 36) for synthesis of a clerodin analog (-20 ∿ 0°C) gave the desired product 4 in only 5 ∿ 20% yield (Entry 2). In spite of the use of a large excess of the cuprate (A) (20 equiv.), no further increase of the yield of 4 was recognized. This may be due to steric hindrance of a C^1 equatorial proton of A ring in 3, or deactivation of the remained cuprate by furyl copper generating from the reagent. We supposed that, if the latter would be responsible for the low yields, the effect of the furyl copper might be mitigated by reproduction of the furyl cuprate with addition of further furyllithium. When additional furyllithium was poured into the above reaction mixture, the furan derivative 4 was given in surprisingly high yield of 72% (Entry 2). Even when the substrate was added to the solution of the cuprate (A) prepared with 2 equiv. excess of furyllithium, the epoxide 3 was also converted into the furan-alcohol 4 in

Table 1

Entry	Substrate	Product a)	Reagent b)	Reaction temperature (°C)	Reaction time (hr)	yield c) (%)
1	 1	 2	A	-20	10	75
2	 3	 4	A & B	-20 ∿ 0	60	5 ∿ 20
			C	0	40	72
			D	0	20	100 d)
3	 5	 6	A	0	24	28
			C	0	47	89
			D	0	24	90
4	 7	 8	A	0	24	20
			C	0	47	67
			D	0	24	77
5	 9	 10	C	rt	24	0
			D	rt	36	15

a) Satisfactory spectroscopic data (NMR, MS, IR) were obtained for these substances.

b) A: lithium di(3-furyl)cuprate. B: reagent A + Me$_2$S. C: lithium di(3-furyl)cuprate - 2furyllithium. D: reagent C + Me$_2$S. All reactions were carried out with three equiv. moles of the cuprate.

c) Isolated yield.

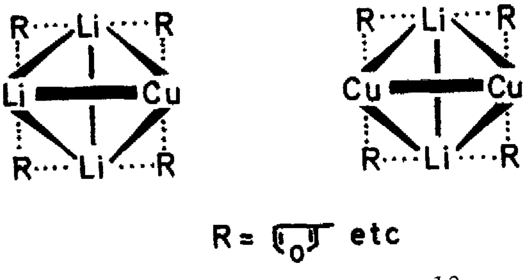
d) Five equiv. moles of the cuprate for the substrate were used.

high yield. It was determined by the reaction with cyclohexene oxide 5 that a quantity of furyllithium for adding to the cuprate (A) required two equivalents, as follows (Entry 3): the cuprate (A) containing furyllithium of additional two or more equivalents gave a furan derivative 6 in 89% yield, whereas the reagent (A) which was added one equivalent furyllithium yielded 6 in 40% only7). These results show that furyllithium for adding to the cuprate (A) is necessary at least the two equivalent moles in order to obtain substituted 3-furyl derivatives in a good yield, and suggest strongly that the reagent is made of a novel cuprate species, $Li_3Cu(3\text{-furyl})_4$ [reagent (C)]8). This reagent (C) is a white suspension in ether, and is stable at room temperature for more than two days even under light although reagent (A) is very unstable at this temperature and for light and degradates completely at room temperature whithin several hours becoming a dark brown suspension5a).

Reaction of the reagent (C) with several oxiranes which were less reactive for the cuprate (A) is summarized in Table 1. An epoxide 7, a diastereomer of 3, was also converted into a furan derivative 8 in 67% yield (Entry 4). However, the reaction of the reagent (C) with a trisubstituted epoxide 9 gave no desired product 10. This will be possibly attributed to the increased softness of an electrophilic carbon (*tert*-carbon atom) in 9. So, we carried out the reaction of 9 and lithium di(3-furyl)cuprate·2furyllithium-dimethyl sulfide complex (D), which was anticipated to be a softer nucleophile4a) than the cuprate (C), and obtained the desired product 10 in 15% yield (Entry 5). The most striking characteristic of this reagent (D) is increase of a reaction rate. That is to say, the treatment of the substrates 5 and 7 by the complex (D) gave the furan derivatives 6 and 8, respectively, with the reaction rate of two times or above as fast as before (Entry 3 and 4). Moreover, the use of 5 equiv. moles of the complex (D) converted the epoxide 3 into the furan alcohol 4 in quantitative yield.

As mentioned so far, lithium di(3-furyl)cuprate·2furyllithium is a further

$R_2CuLi \cdot 2RLi$ $(R_2CuLi)_2$



11 12

excellent reagent than lithium di(3-furyl)cuprate for synthesizing 3-substituted furan derivatives in a single step. And we assumed that the increased nucleophilicity of the cuprate reagent was attributed to formation of a monomeric tetrahedral cuprate rather than dimeric tetrahedral structure[1]. In view of the facts that both RCu compounds and many RLi compounds have tetrameric clusters[1], we tend to adopt cluster structure 11 with C_3 symmetry for the cuprate (C) as a working hypothesis compared with dimeric structure 12 with S_4 symmetry for the cuprate (A).

References and Footnotes

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6. Y. Kojima and N. Kato, Symposium paper, 22st Symposium on the Chemistry of Natural Products, Fukuoka, Japan, 1979, p.102.
7. The reaction by cuprate (A) alone for 5 and 6 in 28% yield (see Table 1).
8. Mcdonald and Clark Still reported that the reagent prepared by mixing lithium dimethylcuprate with methyllithium (2 : 3) reacted with cyclohexanones to produce axial alcohols with high stereoselectivity and in high yield. And Ashby and Lin clarified that Me_3CuLi_2 was superior to Me_3Cu_2Li, $Me_5Cu_3Li_2$, and Me_2CuLi for the substitution reactions with alkyl, cycloalkyl, and aryl halides. Both groups assumed that the most reasonable explanation was that lithium dimethylcuprate and methyllithium react to form highly reactive cuprate having Me_4CuLi_3, however they had not proved the formation of the species with stoichiometric experiments.

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