

SYNTHESES OF 3-SUBSTITUTED FURANS VIA LITHIUM DI(3-FURYL)CUPRATE

---THE APPLICATION OF LITHIUM DI(3-FURYL)CUPRATE TO THE TOTAL SYNTHESIS OF DENDROLASIN

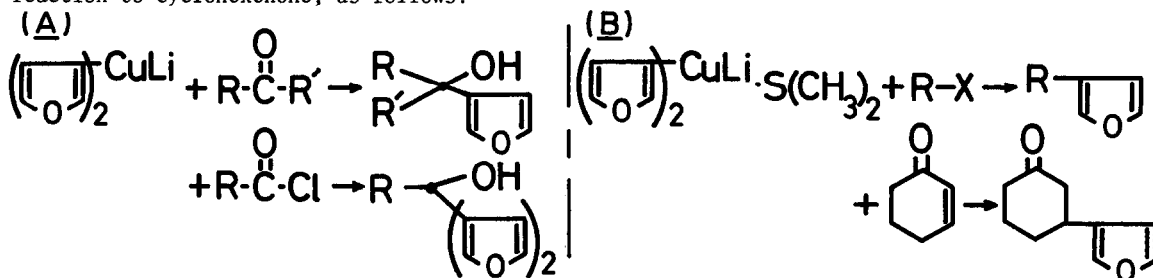
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Summary: One step syntheses of 3-substituted furans by the reactions of a new reagent, lithium di(3-furyl)cuprate λ , with various substrates and the application of λ to a total synthesis of dendrolasin are described.


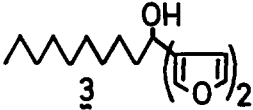
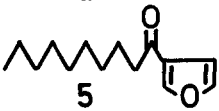
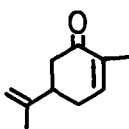
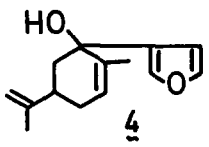
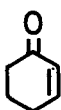
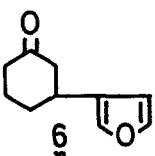
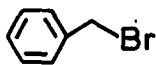
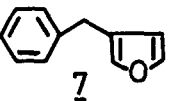

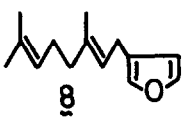

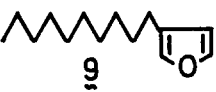
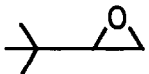
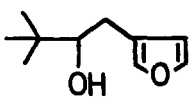
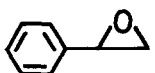
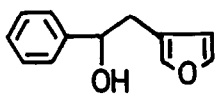
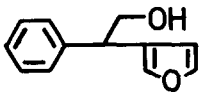
Naturally occurring compounds having a 3-substituted furan ring are widespread in nature as sesquiterpene and diterpene compounds¹⁾. From the synthetic point of view, the development of a simple synthetic method for 3-substituted furans is of important significance, not only in order to synthesize natural products, but to utilize them as synthetic intermediates. In spite of considerable effort, relatively few simple methods have been only available for the syntheses of 3-substituted furans²⁾. Now we found that the 3-substituted furans were synthesized in one step by the reactions of a new reagent, lithium di(3-furyl)cuprate λ . In this letter, we wish to report the reactions of λ with a variety of substrates and the application of our synthetic method to a total synthesis of dendrolasin³⁾.

Lithium di(3-furyl)cuprate λ was generated from 3-bromofuran⁴⁾ in the following ways; method A (A): preparation by adding the preformed 3-furyllithium⁵⁾ to the purified cuprous iodide⁶⁾ in ether at -78°; method B (B): generation in tetrahydrofuran by adding 3-furyllithium, prepared by the metalation of 3-bromofuran (1 equiv.) with t-BuLi (2 equiv.), to the mixture of purified cuprous iodide and dimethyl sulfide at -50v-40°. The results of the reactions of the cuprate λ with a variety of substrates are shown in Table I. We inferred that, generally, the former cuprate λ (A) is a hard nucleophile and gives 3-substituted furan derivatives by a 1,2-addition reaction to carbonyl group, whereas the latter cuprate λ (B) is a soft nucleophile and affords the furan compounds by substitution for organohalides and 1,4-addition reaction to cyclohexenone, as follows:



Reaction of cuprate λ (A) with decanoyl chloride gave furan-alcohol ξ in a nearly quantitative yield (entry 1)⁷⁾, and L-(-)-carvone also was quantitatively converted into 1,2-addition product ζ (entry 2). It has been known that organocuprates generally give no alcohols by 1,2-addition reactions to carbonyl groups⁸⁾, but several papers have recently reported on the 1,2-

Table I

Entry	Substrate	Product ^{a)}	Method ^{b)}	Reaction conditions	Yield ^{c)} (%)
1			A	-78°, 15 min	95.7
			B	-40°, 7 hrs	55.0
2			A	-78°, 15 min	95.6
			B	-20°, overnight	0
3			B	-20°, overnight	40.0
			B	-20°, in the dark, 5 hrs	54.0
4			B	r.t., overnight	45.0
			B	r.t., in the dark, overnight	100.0
5			B	r.t., in the dark, overnight	80.0
6			B	r.t., in the dark, overnight	60.5
7			A	-20°, 10 hrs	75.0
8			1	A	-50~-40°, 10 hrs
			2		

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

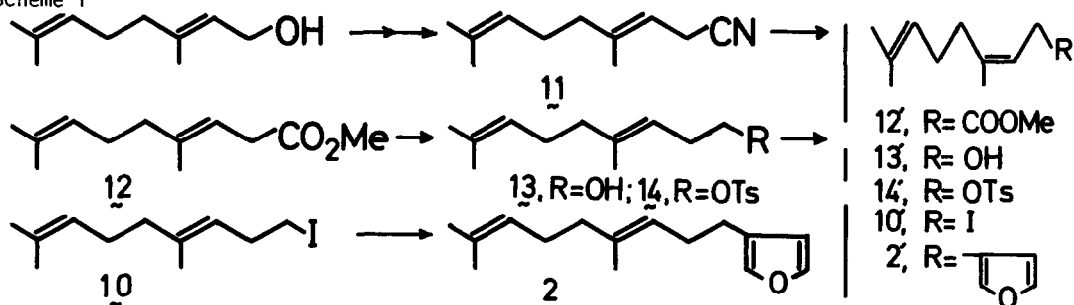
b) All reactions were carried out with 3 equiv. moles of the cuprate $\frac{1}{\nu}$.

c) Isolated yield.

addition reactions of some kinds of organocuprates to carbonyl groups⁹). Addition of the cuprate $\overset{\sim}{\text{C}}(\text{A})$ to carbonyl groups was regulated by use of the cuprate $\overset{\sim}{\text{C}}(\text{B})$ prepared by the same procedures that of lithium di(α -methoxyvinyl)cuprate^{9b}). When *n*-decanoyl chloride was treated with the cuprate $\overset{\sim}{\text{C}}(\text{B})$ at -40° , the expected product $\overset{\sim}{\text{C}}(\text{B})$ was obtained in 55.0% yield (entry 1). This fact accords with a conception that soft nucleophiles do not attack the hard acceptor of the carbonyl carbon atom, therefore, the cuprate $\overset{\sim}{\text{C}}(\text{B})$ complexed with the sulfide is definitely more soft nucleophile than the cuprate $\overset{\sim}{\text{C}}(\text{A})$. On the other hand, neither 1,2-addition nor 1,4-addition products were obtained by the reaction of the cuprate $\overset{\sim}{\text{C}}(\text{B})$ with *L*-(-)-carvone (entry 2). This result might be explained on the ground that the cuprate $\overset{\sim}{\text{C}}(\text{B})$ compared with the vinyl cuprate is more sensitive to the steric environment at a C-5 isopropenyl group of *L*-(-)-carvone^{9b}), since cyclohexenone without any substituent at C-5 was converted into 3-(3'-furyl)-cyclohexenone of the 1,4-addition product in 40.0% yield (entry 3).

Substitution reaction with benzyl bromide by the cuprate $\overset{\sim}{\text{C}}(\text{B})$ (rt, overnight) yielded benzyl furan $\overset{\sim}{\text{C}}(\text{B})$ in 45.0% yield (entry 4), whereas it remained to recover the starting material at -20° . The reagent $\overset{\sim}{\text{C}}(\text{B})$ itself had degraded gradually at room temperature and its degradation rate had exceeded the rate of the reaction with the substrate at this condition. This would suggest that an order of the degradation rate raised to the higher one than that at low temperature. Thus, at room temperature, the degradation will become to pass through other pathways or certain causes will lead to accelerate the decomposition rate of the cuprate¹⁰). As one of the causes, we assumed at first the effect of room-light. Therefore, after addition of benzyl bromide to the reagent at -40° , in the dark, the reaction temperature was gradually raised to room temperature, followed by stirring overnight. From the clear red-brown solution not accompanying degradation products of the cuprate, benzyl furan $\overset{\sim}{\text{C}}(\text{B})$ was quantitatively isolated as the result (entry 4). Additionally, cyclohexenone was converted into the keto-furan $\overset{\sim}{\text{C}}(\text{B})$ in better yield than the case exposed to room-light (entry 3). It is noticeable that the results suggest an anionic mechanism for the substitution and addition reaction of the cuprate $\overset{\sim}{\text{C}}(\text{B})$ ¹¹) and make it possible to raise the reaction temperature up to room temperature or above. By the same procedure, geranyl bromide and decyl bromide were also converted into geranyl furan $\overset{\sim}{\text{C}}(\text{B})$ and decyl furan $\overset{\sim}{\text{C}}(\text{B})$, respectively, in good yield (entry 5 and 6). And epoxide derivatives were also converted into the corresponding furan alcohols in good yield (entry 7 and 8). In *t*-butyl substituted epoxide, the nucleophile $\overset{\sim}{\text{C}}(\text{A})$ attacked to the less hindered carbon atom, whereas addition of the nucleophile to styrene oxide occurred preferentially at the more electrophilic

Scheme 1



position. As mentioned so far, lithium di(3-furyl)cuprate $\underline{1}$ is evidently a good reagent for synthesizing a variety of 3-substituted furans in a single step, which are also potential precursors of 1,4-dialdehydes.

In this paper, furthermore, we describe the application of the reagent $\underline{1}$ to the total synthesis of dendrolasin $\underline{2}$ (Scheme 1). Our synthetic route is based on the substitution reaction of homogeranyl iodide $\underline{10}$ with the cuprate $\underline{1}$ (B). Geranyl cyanide $\underline{11}$ was prepared from geraniol in two steps¹²⁾. Hydrolysis of the cyanide $\underline{11}$ with aq.KOH (reflux, 20hrs) followed by esterification with diazomethane yielded a methyl ester $\underline{12}^{13}$ in 65.0% yield with the geometric isomer $\underline{12}'$ (ratio 71.4 : 28.6)¹⁴⁾. The methyl ester $\underline{12}$ and $\underline{12}'$ were converted into alcohols $\underline{13}$ and $\underline{13}'^{13}$ by reduction with LAH (Et₂O, 1hr, 95.0%), and treatment of the alcohols with tosyl chloride gave tosylates $\underline{14}$ and $\underline{14}'^{13}$ in a quantitative yield. Tosylates were converted into homogeranyl iodides $\underline{10}$ and $\underline{10}'^{13}$ by substitution reaction with NaI (An-DMF, rt, overnight, 85.0%). Reaction of lithium di(3-furyl)cuprate $\underline{1}$ (B) with the iodides gave dendrolasin $\underline{2}$ accompanied by the geometrical isomer $\underline{2}'$ in 78.0% yield (ratio $\underline{2} : \underline{2}' = 66.1 : 33.9$)^{13,14)}.

The example of homogeranyl iodide is given here as a typical experiment: to a solution of 500 mg(3.4 mmoles) of 3-bromofuran in 4 ml of THF at -78° was added dropwise, 3.4 ml(6.8 mmoles) of 2M t-BuLi (pentane). After stirring for 1hr at -78°, this solution was added to a suspension of 297 mg(1.6 mmoles) of purified cuprous iodide and 0.23 ml(3.2 mmoles) of dimethyl sulfide in 2 ml of THF at -40° over 5 min. After stirring for 15 min at -40°, 148 mg(0.53 mmoles) of the iodides $\underline{10}$ and $\underline{10}'$ in 2 ml of THF was added over 5 min. The mixture was then warmed to room temperature in the dark and stirred for 6 hrs. Work-up was accomplished by quenching with saturated ammonium chloride at -78°, followed by ether extraction. Purification on silica gel TLC then gave 90.5 mg of a mixture of $\underline{2}$ and $\underline{2}'$ in 78.0% yield.

References and footnotes

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7. When 1 equiv. mole of the cuprate $\underline{1}$ (A) was used to this reaction, a mixture of $\underline{3}$ and keto-furan $\underline{5}$ was obtained in the ratio ca. 1 : 1.
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13. Satisfactory spectroscopic data (NMR, mass spectrum, IR) were obtained for this substance.
14. This ratio was determined by GLC.

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