A NEW EFFICIENT DECARBOXYLATIVE REDUCTION OF
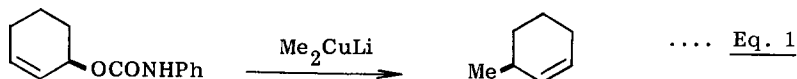## γ-CARBAMOYLOXY-α,β-UNSATURATED ESTERS WITH LITHIUM DIALKYLCUPRATE

Toshiro Ibuka,* G.-Namg Chu, and Fumio Yoneda

Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida-shimoadachi-cho,
Sakyo-ku, Kyoto 606, Japan

Abstract: A new synthetically useful decarboxylative reduction of γ-carbamoyloxy-α, β-
unsaturated esters with lithium dialkylcuprate under mild condition was described.

Carbamates are usually well crystalline compounds suitable for characterization and isolation of synthesized and natural compounds except for derivatives of lower alcohols.[1] Furthermore, because primary and secondary amines are very susceptible to oxidation and to substitution reactions involving the N-H bonds, protecting groups are indispensible device to prevent reactivity at the N-H group during the synthetic operations.[2] In the synthesis of biologically active natural products, N-H groups are often protected as their carbamates.[3]

Gallina[4] and Goering[5] recently reported that treatment of allylic N-arylcarbamates with lithium dialkylcuprate gave exclusive or predominant γ-alkylation in both cyclic and acyclic systems. (Eq. 1)

$$\text{(cyclohexenyl-OCONHPh)} \xrightarrow{\text{Me}_2\text{CuLi}} \text{(Me-cyclohexenyl)} \quad \cdots \cdots \text{Eq. 1}$$

During the course of our synthetic study on a toxic alkaloid of poison dart frog,[6] we had a occasion to explore a new decarboxylative reduction of γ-carbamoyloxy-α,β-unsaturated esters with lithium dialkylcuprates as shown in Eq. 2 and 3. Scanning the literatures revealed that a method for the decarboxylative reduction of γ-carbamoyloxy-α,β-enoate with zinc-acetic acid reported by Overman was available.[7] Although organocopper(I) reagents are useful for carbon-carbon bond formation,[8] decarboxylative reduction of γ-carbamoyloxy-α,β-enoates with the Gilman reagent has no precedent in the literature. The unfortunate lack of reports on the synthetically useful decarboxylative reduction with lithium dialkylcuprates prompted us to describe our result.[9]
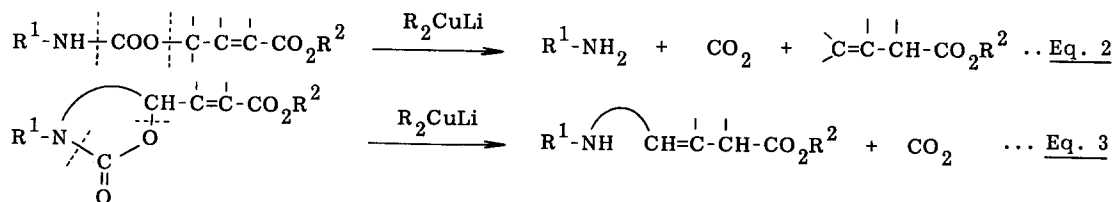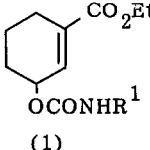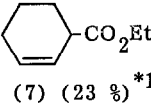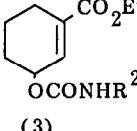
$$R^1\text{-NH}\!\!-\!\!\text{COO}\!\!-\!\!\overset{|}{\underset{|}{C}}\text{-C=C-CO}_2R^2 \xrightarrow{R_2\text{CuLi}} R^1\text{-NH}_2 + CO_2 + \overset{|}{\underset{}{C}}\text{=C-CH-CO}_2R^2 \quad \cdots \text{Eq. 2}$$

$$R^1\text{-N}\underset{\underset{O}{\overset{\|}{C}}}{\overset{O}{\diagdown}}\!\!\text{CH-C=C-CO}_2R^2 \xrightarrow{R_2\text{CuLi}} R^1\text{-NH} \quad \text{CH=C-CH-CO}_2R^2 + CO_2 \quad \cdots \text{Eq. 3}$$
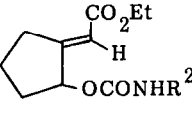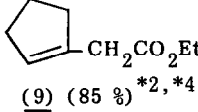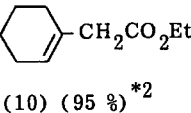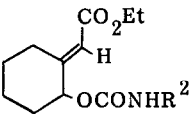
Chart 1

Table 1. Reaction of γ-Carbamoyloxy-α,β-enoates with some Reagents

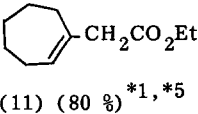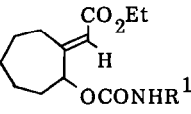| Substrate	Entry	Reagent (equiv.)	Solvent	Reaction Condition	Product(s) (Yield)
(1) cyclohexene with CO$_2$Et and OCONHR^1	1	Zn (200)	AcOH	Reflux 18 hr	cyclohexene-CO$_2$Et **(7)** (23 %)[*1]
	2	CrCl$_2$ (5)	Me$_2$CO-H$_2$O (10 : 1)	R. T. 5 hr	No reaction occurred.
	3	Bu$_2$CuLi (10)	Et$_2$O-HMPT (10 : 0.5)	-50~-20° 2 hr	**(7)** (97 %)[*1]
(2) ^{n}BuCHCH=CHCO$_2$Et, OCONHR^2	4	Bu$_2$CuLi (10)	Et$_2$O-HMPT (10 : 1)	-35~-30° 2 hr	^{n}BuCH=CHCH$_2$CO$_2$Et **(8)** (76 %)[*2,*3]
(3) cyclohexene with CO$_2$Et and OCONHR^2	5	Bu$_2$CuLi (5)	Et$_2$O-HMPT (10 : 1)	-70~-20° 2 hr	**(7)** (67 %)[*2]
	6	Bu$_2$CuLi (10)	Et$_2$O-HMPT (10 : 1)	-70~-20° 2 hr	**(7)** (97 %)[*2]
(4) cyclopentane with =CO$_2$Et, H, OCONHR^2	7	MeCu(CN)Li (10)	Et$_2$O-HMPT (10 : 1)	-30~0° 1.5 hr	No reaction occurred.
	8	Me$_2$CuLi (10)	Et$_2$O-HMPT (10 : 1)	-30~0° 1 hr	cyclopentene-CH$_2$CO$_2$Et **(9)** (85 %)[*2,*4]
(5) cyclohexane with =CO$_2$Et, H, OCONHR^2	9	Bu$_2$CuLi (10)	Et$_2$O-HMPT (10 : 1)	-35~-30° 2 hr	cyclohexene-CH$_2$CO$_2$Et **(10)** (95 %)[*2]
(6) cycloheptane with CO$_2$Et, H, OCONHR^1	10	Me$_2$CuLi (10)	Et$_2$O-HMPT (10 : 1)	-40~0° 2 hr	cycloheptene-CH$_2$CO$_2$Et **(11)** (80 %)[*1,*5]

R^1= α-Naphthyl; R^2= Phenyl.

*1 α-Naphthylamine was also isolated and characterzed.   *2 Aniline was also isolated.

*3 About 1:1 mixture of <u>cis</u> and <u>trans</u> stereoisomers.

*4 α,β-Enoate **(12)** was also isolated (11 % yield).

*5 α,β-Enoate **(13)** was also isolated (12 % yield).
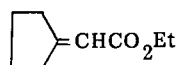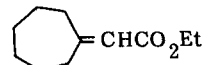
 =CHCO$_2$Et **(12)**   =CHCO$_2$Et **(13)**

Reaction of the carbamate (1) with excess zinc in acetic acid[7] under reflux gave the β,γ-unsaturated ester (7) in 23 % yield along with a mixture of substantial amount of reddish by-products. (Table 1, Entry 1). In the attempted decarboxylative reduction with chromous chloride[10] (Entry 2) or lithium cyanomethylcuprate[11] (Entry 7), neither reduction product nor arylamine was present in any more than trace amount.

In contrast, treatment of the carbamates (Entries 3, 4, 6, 8, 9, and 10) with ten molar equivalents of lithium dialkylcuprate in a mixture of Et_2O and hexamethylphosphoric triamide (HMPT) gave the respective decarboxylative reduction product in high yield under mild reaction condition. In these reactions, presence of HMPT was essential for the successful decarboxylative reduction and the usage of ten molar equivalents of lithium dialkylcuprate was necessary for the high yield of reduction (compare Entry 5 with 6). Furthermore, neither conjugate adduct nor substitution product was detected in the present study.

The method described above was also applicable to the cyclic carbamates and the reduction product was successfully used for the synthesis of gephyran (perhydropyrrolo[1,2-a]quinoline) derivative of the alkaloids of poison dart frog.[12]
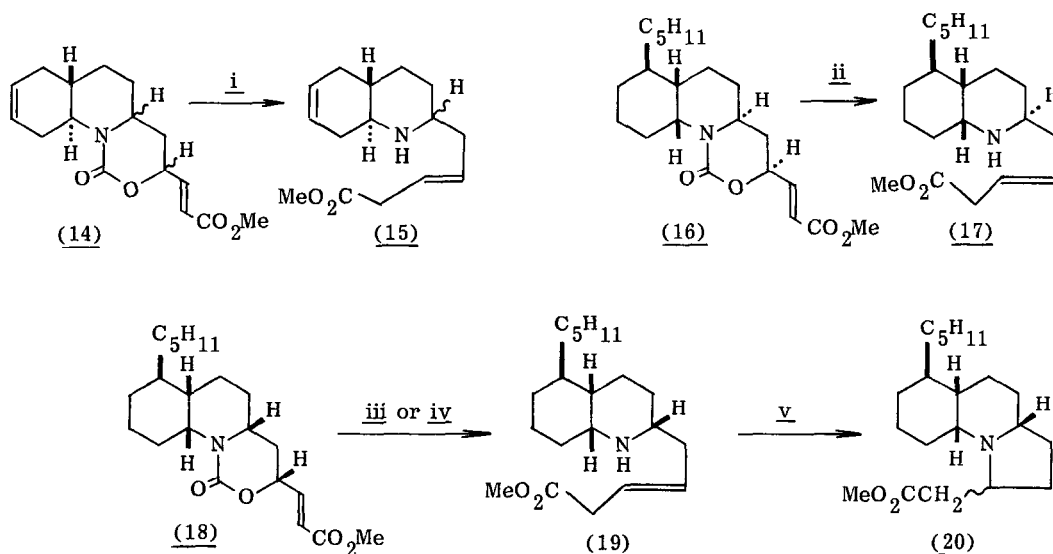
Reagents and Reaction Conditions: i, Me_2CuLi (20 equiv.), Et_2O, -73°, 5 min., 100 %; ii, Me_2CuLi (20 equiv.), Et_2O, -73°, 5 min., 97 % ; iii, Bu_2CuLi (10 equiv.), Et_2O, -73°, 5 min., 97 %; iv, Me_2CuLi (20 equiv.), Et_2O, -73°, 5 min., 99 %; v, 1 % NaOMe in MeOH, reflux, 3 hr., 50 %.

Chart 2

Thus, treatment of the carbamates (14) and (16) with Me_2CuLi gave the decarboxylative reduction products (15) and (17), respectively, in high yields. The compound (17) has recently been transformed into (+)-perhydrogephyrotoxin.[6,7] In these decarboxylative reduction, HMPT is not required and the reactions were completed at -73° within 5 min. In a similar manner, carbamate (18) was converted into the enoate (19) in high yield by treatment with Me_2CuLi or Bu_2CuLi. Although we can not conclusively rule out the contamination by a small amount of cis-isomer with respect to the double bond, the trans-stereochemistry in (15),

(17), or (19) was inferred from the fact that the same product (17) was obtained from the carbamate (16) by treatment with zinc in acetic acid at 90° for 12 hr in 34 % yield. Treatment of the enoate (19) with 1 % NaOMe in dry MeOH gave the gephyran derivative (20) in 50 % yield.

In summary, clearly the described decarboxylative reduction methodology involving lithium dialkylcuprate has several advantages in terms of mildness, efficiency, and convenience. Application of this method for the synthesis of biologically active alkaloids such as gephyrotoxin 223 is under intense investigation.

REFERENCES

1) S. W. Ayer, J. Hellow, M. Tischler, and R. J. Andersen, Tetrahedron Lett., 25, 141, (1984); H. W. Johnson, Jr., R. J. Day, and D. S. Tinti, J. Org. Chem., 28, 1416 (1963).

2) T. W. Greene, "Protective Groups in Organic Synthesis", 218 (1981), John Wiley & Sons; J. B. Barton, in "Protective Groups in Organic Chemistry", J. F. W. McOmie, ed., 43 (1973), Plenum Press; R. G. Hiskey and J. B. Adams, Jr., J. Am. Chem. Soc., 87, 3969 (1965).

3) E. J. Corey, Y. Ueda, and R. A. Ruden, Tetrahedron Lett., 4347 (1975); R. Fujimoto and Y. Kishi, Tetrahedron Lett., 22, 4197 (1981); L. E. Overman, D. Lesuisse, and M. Hashimoto, J. Am. Chem. Soc., 105, 5373 (1983); L. E. Overman and K. L. Bell, J. Am. Chem. Soc., 103, 1851 (1981); L. E. Overman and R. J. McCready, Tetrahedron Lett., 23, 4887 (1982); H. W. Pauls and B. F.-Reid, J. Am. Chem. Soc., 102, 3956 (1980); P. A. Bartlett, D. J. Tanzella, and J. F. Barstow, Tetrahedron Lett., 23, 619 (1982).

4) C. Gallina and P. G. Ciattini, J. Am. Chem. Soc., 101, 1035 (1979).

5) H. L. Goering, S. S. Kantner, and C. C. Tseng, J. Org. Chem., 48, 715 (1983).

6) T. Ibuka, G.-N. Chu, and F. Yoneda, J. Chem. Soc. Chem. Commun., in press.

7) L. E. Overman and C. Fukaya, J. Am. Chem. Soc., 102, 1454 (1980).

8) G. H. Posner, "An Introduction to Synthesis using Organocopper Reagents", John Wiley & Sons, (1980); G. H. Posner, in "Organic Reactions", W. G. Dauben, ed., John Wiley & Sons, Vol. 19, p. 1 (1972); J. P. Collman and L. S. Hegedus, "Principles and Applications of Organotransition Metal Chemistry", University Science Books, p. 544 (1980); M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, Tetrahedron Lett., 21, 1311 (1980); Y. Yamamoto, S. Yamamoto, and K. Maruyama, J. Am. Chem. Soc., 102, 2318 (1980).

9) For reactions of γ-oxygenated-α,β-unsaturated carbonyl compounds with organocopper(I) reagents, see: T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita, and Y. Kawami, J. Chem. Soc. Chem. Commun., 1193 (1980); T. Ibuka and H. Minakata, Synthetic Commun., 10, 119 (1980); T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita, and N. Kimura, Tetrahedron Lett., 21, 4073 (1980); Y. Yamamoto, S. Yamamoto, H. Yatagi, Y. Ishihara, and K. Maruyama, J. Org. Chem., 47, 119 (1982); R. A. Ruden and W. E. Litterer, Tetrahedron Lett., 2043 (1975).

10) H. O. House and R. G. Carlson, J. Org. Chem., 29, 74 (1964).

11) P. Four, H. Riviere, and P. W. Tang, Tetrahedron Lett., 3879 (1977).

12) G. Habermehl and O. Thurau, Naturwissenschften, 67, 193 (1980); B. Witkop and E. Gössinger, in "The Alkaloids", A. Brossi, ed., Vol. 21, p. 139 (1983), Academic Press.