Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7727-7730, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01661-5

Enolate Free α-Alkoxyvinyllithium Reagents: Improved Preparation and Reaction with N,N-Dialkylcarboxamides

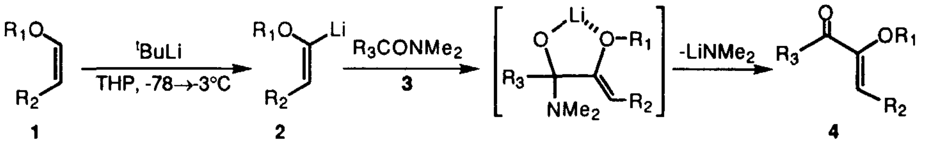
Masanao Shimano and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523 U.S.A.

Summary: *The titled lithium reagents add to a variety of N,N-dialkylcarboxamides furnishing the enol ethers of α-dicarbonyl compounds.*

α-Alkoxyvinyllithiums **2** derived from the corresponding alkyl vinyl ethers **1** (cyclic and acyclic) have been utilized as carbonyl anion equivalents. Due to their ease of preparation, there are many reports in which α-alkoxyvinyllithium reagents have been employed in 1,2-addition reactions,[1] 1,4-addition reactions,[2] and for natural product syntheses.[3] However, the addition of α-alkoxyvinyllithiums **2** to N,N-dialkylcarboxamides **3** has not been investigated despite the structurally attractive and functionalized products that might result as shown in Scheme I.[4] These same products, however, are also available by the reaction of α-alkoxyvinyllithiums and carboxylic acids,[5,6] although this reaction requires at least 2 equiv. of lithium reagent at room temperature, still affording modest yields.[7] Furthermore, the preparation of α-alkoxyvinyllithium reagents **2** from the corresponding alkyl vinyl ether **1** is generally accomplished with ${}^tBuLi$ in THF at 0°C. However, in many cases the *t*-BuLi deprotonation of THF competes with the desired metalation. In order to avoid this side reaction, Boeckman *et al.* employed excess ${}^tBuLi$ (1.5 ~ 3.0 equiv.) in a

Scheme I



R_1=alkyl, R_2=H or R_1=R_2=$(CH_2)_n$

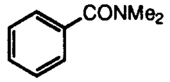
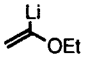
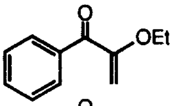
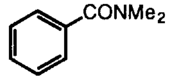
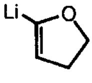
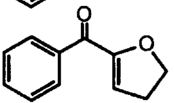
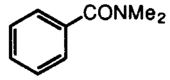
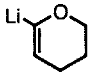
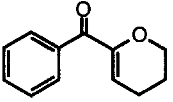
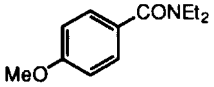
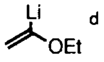
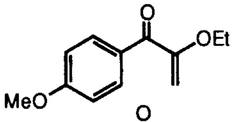
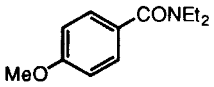
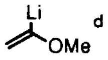
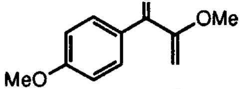
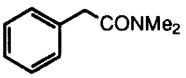
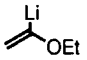
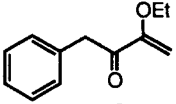
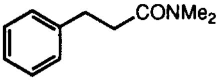
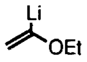
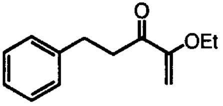
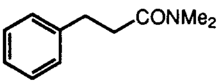
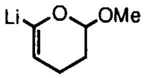
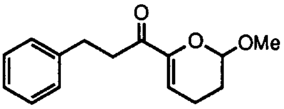
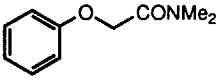
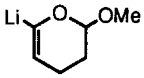
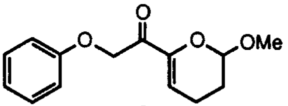
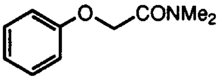
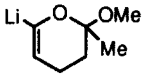
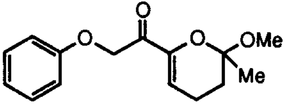
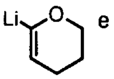
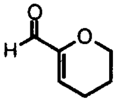
minimal amount of THF.[1d,1g] Sebastian *et al.* used this procedure with 1.5 equiv. of ^{t}BuLi to obtain α-ethoxyvinyllithium.[8] Although a good yield of α-alkoxyvinyllithium can be obtained by using excess ^{t}BuLi, these lithium reagents are always contaminated with acetaldehyde enolate anion and ethylene from the decomposition of THF by excess ^{t}BuLi.[1l] In this paper, we wish to describe the preparation of enolate-free α-alkoxyvinyllithiums **2** and their reactions with N,N-dialkylcarboxamides **3**.

Initially, we examined conventional metalation conditions (^{t}BuLi or ^{n}BuLi in hexane, pentane, hexane-ether, hexane-THF; 2 equiv, hexane-HMPA) in an attempt to prepare α-ethoxyvinyllithium but none of these methods were successful. However ethyl vinyl ether is deprotonated efficiently by ^{t}BuLi in tetrahydropyran (THP)[9,10] and this was confirmed by the reaction of piperonal with α-ethoxyvinyllithium.[11,12] Furthermore, this procedure could be applied to the preparation of other α-alkoxyvinyllithiums (See Table I). The reaction of several α-alkoxyvinyllithium reagents with N,N-dialkylcarboxamides are shown in Table I. Unless otherwise noted, 1.3 equiv. of ^{t}BuLi was employed to generate the α-alkoxyvinyllithium. In all cases, the amide addition afforded the desired α-alkoxy-α,β-unsaturated ketone in good to excellent yields.[13] Surprisingly, in entry 6, the very acidic protons present at the α-position of the carbonyl group did not deter the nucleophilic displacement of the amido group. In entries 8, 9 and 10, the methoxy-substituted and 6,6-disubstituted dihydropyran anions are shown. Although literature reports indicated that these two dihydropyrans required 2 equiv. and 3 equiv. of ^{t}BuLi in THF, respectively,[1d,1g] 1.3 equiv. of ^{t}BuLi was sufficient in THP solution. In an effort to change the course of addition we also performed the reaction in entry 1 in the presence of HMPA, and found that it had no effect on the results in the table. Finally, it should be noted that although there are extensive reports of ortho-metalation of N,N-dialkylbenzamides (*e.g.* entries 4 and 5, Table I) using lithium bases,[14] little or no such reaction was found to occur under these conditions.

Typical Procedure for 5-phenyl-2-ethoxy-1-penten-3-one (Table 1, entry 7): To a stirred, cooled (-78°C) solution of ethyl vinyl ether (138 mg, 1.92 mmol) in THP (Aldrich, used as received, 0.70 mL) was added ^{t}BuLi (1.66 M of pentane solution, 0.88 mL, 1.47 mmol) dropwise. After stirring at -78°C for 10 min, the mixture was warmed to -3~-5°C, stirred for 30 min, recooled to -78°C, diluted with THF (3.0 mL) and treated with N,N-dimethyl hydrocinnamic carboxamide (200 mg, 1.13 mmol) in THF (0.4 mL). After stirring for 12 h at -78°C, the mixture was poured into water, and extracted with ethyl acetate. The extract was washed once with water, brine, dried over $MgSO_4$ and concentrated. Flash chromatography[15] (10 % EtOAc/hexanes) gave 5-phenyl-2-ethoxy-1-penten-3-one (202 mg, 88 %) as a colorless oil.

Acknowledgement: Financial support for this program by the National Institutes of Health is gratefully acknowledged. A granted leave to MS by Kaken Pharmaceutical Co., Ltd. is gratefully acknowledged.

Table 1. Reaction of α-Alkoxyvinyllithiums with Dialkylcarboxamides.

	Amide **3**	α-Alkoxyvinyllithium **2**[a,b]	Product **4**	Yield (%)[c]
1.				90
2.				93
3.				88
4.				83
5.				83
6.				88
7.				88
8.				92
9.				95
10.				62
11.	DMF			70 (98)[f]

a) All reactions were carried out at -78°C and the reaction time was about 10 h. b) Unless otherwise noted, 1.3 equiv. of α-alkoxyvinyllithium was used. c) All yields are for isolated products. d) 1.5 equiv. of lithium reagent was used. e) 1.2 equiv. of lithium reagent was used. f) Crude yield. The purity was determined to be 91% by ^{1}H-NMR. The main impurity was Et_2O(6%).

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2. a) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822. b) Boeckman, R. K.; Jr.; Bruza, K. J.; Baldwin, J. E.; Lever, O. W., Jr. *J. Chem. Soc. Chem. Commun.* **1975**, 519. c) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 13.
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4. Reactions between N,N-dialkylcarboxamides and alkyllithiums or aryllithiums have been well studied. Cf.: Wakefield, B. J. *Organolithium Methods*, Academic Press, London, **1988**.
5. Reactions between carboxylic acids and alkyllithiums or aryllithiums have been well studied. Cf.: Jorgensen, M. J. *Org. React.* **1970**, *18*, 1. Also see ref.4.
6. The reaction between α-methoxyvinyllithium and benzoic acid has been reported. See ref.1b.
7. We checked the reaction of phenylacetic acid and hydrocinnamic acid with α-ethoxyvinyllithium (corresponding to entry 6 and 7 in Table I) and the crude yields were 32% and 66%, respectively. In both cases, the crude products were contaminated with about 10% of dialkenylated by-products.
8. Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959.
9. THP has been used previously for room temperature reactions with ^{t}BuLi: Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571.
10. ^{s}BuLi (1.5 equiv.) in tetrahydropyran (THP) could partially generate α-ethoxyvinyllithium from ethyl vinyl ether and the reaction with N,N-dimethylbenzamide (1.0 equiv.) gave the desired adduct **4** along with considerable recovery of starting amide (the ratio of product and the starting amide was 2.44 : 1.0).
11. α-Ethoxyvinyllithium prepared from ^{t}BuLi (1.1 equiv.) and ethyl vinyl ether (1.5 equiv.) in THP was treated with piperonal (1.0 equiv.) to give a good yield of the expected hydroxy adduct.
12. The stability of ^{t}BuLi in THP at -3°C was also checked and was stable for at least 30 minutes.
13. The dialkenylated by-product was found to be less than 2% in the crude NMR in every reaction in the table.
14. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
15. Silica gel was deactivated with Et_3N prior to use.

(*Received in USA* 19 *July* 1994; *revised* 23 *August* 1994; *accepted* 26 *August* 1994)