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Carbolithiation of ene-carbamates. Application to the synthesis of 2,3-disubstituted ene-carbamates

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Abstract—A simple and efficient protocol for the synthesis of 2,3-disubstituted seven-membered ring ene-carbamates has been developed, based on the first reported carbolithiation of ene-carbamates.

The synthesis of *N*-heterocycles of various sizes constitutes a very important theme within organic chemistry owing to their presence in a wide range of natural and synthetic products. Recently, we used vinylphosphates for the synthesis of substituted benzoxazines, pyridoxazines and benzothiazines.[1] These heterocyclic systems were prepared via the first reported extension of the Suzuki reaction involving palladium-catalyzed coupling of vinylphosphates with aryl or heteroaryl boronic acids. In this way, we also prepared in high yields several 6-, 7- and 13-membered ring ene-carbamates substituted on position C-2 with aryl or heteroaryl groups.[2] We then focused our interest on the study of the reactivity of these ene-carbamates for the construction of more complex heterocyclic systems. Since the first carbometallation discovered by Ziegler[3] an ever-increasing number of these reactions have been reported[4,5] although the addition of organometallic derivatives to carbon–carbon multiple bonds is not always synthetically useful in terms of chemo-, regio- and stereoselectivity. Only a limited number of functional groups can be present in unsaturated derivatives submitted for a carbometallation reaction. In fact, most organometallics may react with several functional groups (even of relatively low reactivity) before adding to a carbon–carbon multiple bond. Furthermore, organometallics can also act as bases, abstracting allylic or propargylic protons.

To the best of our knowledge, the addition of an organometallic reagent to the double bond of an ene-carbamate has not yet been described. We decided to investigate the behaviour of organometallic derivatives towards compound **1**, an easily accessible seven-membered ring ene-carbamate,[2] which we chose as a model substrate. Carbolithiation was first considered and compound **1** was submitted to a small range of commercially available organolithium reagents. Treatment of **1** in THF at −78 °C with an excess of RLi in solution (see Table 1), then warming to 0 °C led to the formation of anionic species, which were quenched with H_2O after stirring for 30 min.

Under these conditions, allylic protons were not affected and we were pleased to observe the expected regioselective addition of RLi to the C-3 position of compound **1**; compounds **3a**–**e** were obtained in high yields, after hydrolysis, as mixtures of stereoisomers (Scheme 1 and Table 1).[6]

These preliminary results were very encouraging and, therefore, we planned to quench the anionic species **2**

Table 1. Formation of derivatives **3** by carbolithiation of **1**

RLi (solvent)	Equivalent	Compound	Yield (%)[a]
MeLi (diethyl ether)	1.2	**3a**	87
n-BuLi (hexane)	1.2	**3b**	83
s-BuLi (cyclohexane)	1.2	**3c**	88
t-BuLi (pentane)	4.0	**3d**	84
PhLi (cyclohexane/ether)	2.0	**3e**	95

[a] Isolated yield.

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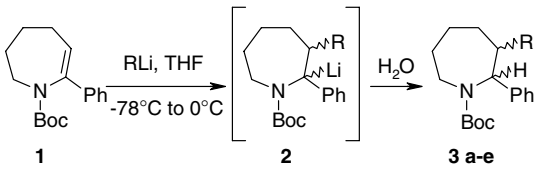
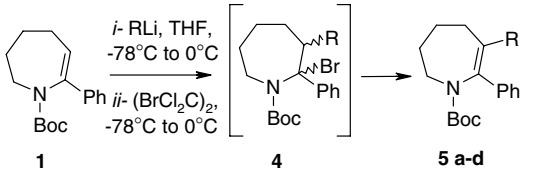


Scheme 1.



Scheme 2.

Table 2. 'One-pot' synthesis of disubstituted ene-carbamates **5**

RLi (solvent)	RLi (equiv)	$(BrCl_2C)_2$ (equiv)	Compound	Yield (%)[a]
MeLi (diethyl ether)	2.1	3.2	**5a**	79
n-BuLi (hexane)	2.1	3.2	**5b**	83
t-BuLi (pentane)	4	5.1	**5c**	67
PhLi (cyclohexane/ether)	2	3.1	**5d**	56

[a] Isolated yield.

with other electrophilic agents in view of obtaining various substituted azepino-derivatives. We first turned our attention to the synthesis of disubstituted ene-carbamates expecting the feasibility of a 'one-pot' reaction sequence: carbolithiation, bromination of **2** and then dehydrobromination (Scheme 2).

Once again, the carbolithiation was effective at 0 °C; after cooling to −78 °C a solution of 1,2-dibromotetrachloroethane in THF was added to obtain **4**. After warming to 0 °C, elimination occurred, the excess of organolithium reagent acting as a base. The desired disubstituted ene-carbamates **5** were obtained in fair to good yields after work-up and chromatographic purification on SiO_2 (Table 2).[7,8] These derivatives might be submitted to a new carbolithiation to form possibly tri or tetrasubstituted nitrogen-containing heterocycles.

In summary, we have realized the first reported carbolithiations of the double bond of an ene-carbamate. These reactions allow an easy access to saturated or unsaturated polysubstituted nitrogen-containing heterocycles. Experiments designed to explore the stereoselectivity of the process in the presence of a chiral ligand are in progress and will be described in due course.

References and Notes

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6. Synthesis of compounds **3a**–**e**, general procedure. To a solution of **1** in anhydrous THF (0.1 M) previously cooled to −78 °C, RLi (equiv: see Table 1) was added slowly at −78 °C. The resulting solution was stirred at 0 °C for 30 min. After hydrolysis, the aqueous layer was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The mixture of inseparable diastereoisomers **3** was purified by flash chromatography on silica gel (PE/EtOAc: 9/1). Compounds were obtained with an unoptimized diastereoisomeric excess near 10%.
7. Formation of compounds **5a**–**d**, general procedure. To a solution of **1** in anhydrous THF (0.1 M) previously cooled to −78 °C, RLi (equiv: see Table 2) was added slowly at −78 °C. The resulting solution was stirred at 0 °C for 30 min. The mixture was then cooled to −78 °C, and treated with 1,2-dibromotetrachloroethane (equiv: see Table 2). The solution was stirred at −78 °C for 15 min. After hydrolysis, the aqueous layer was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The product was purified by flash chromatography on silica gel (PE/EtOAc: 9/1).
8. Spectral data for compounds **5a**–**d**. **5a** oily solid, ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9H); 1.40–1.43 (m, 1H); 1.79 (m, 3H); 1.84 (s, 3H); 2.04–2.09 (m, 1H); 2.41–2.46 (m, 1H); 2.93 (m, 1H); 4.37–4.41 (m, 1H); 7.19–7.31 (m, 5H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.10, 23.05, 28.05, 29.40, 35.25, 48.80, 79.50, 126.75, 127.55, 128.45, 131.45, 137.30, 139.80, 154.50. **5b** oily solid, ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.83 (t, 3H, $J = 7$ Hz); 1.09 (s, 9H); 1.23–1.26 (m, 3H); 1.40–1.44 (m, 2H); 1.80 (m, 3H); 2.12–2.15 (m, 3H); 2.33 (m, 1H); 2.88–2.92 (m, 1H); 4.39 (m, 1H); 7.17–7.31 (m, 5H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.00, 22.80, 24.15, 28.10, 29.65, 30.60, 32.70, 33.85, 48.90, 79.50, 126.85, 127.55, 128.45, 135.95, 137.80, 139.85, 154.5. **5c** oily solid, ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.97 (s, 9H); 1.24 (s, 9H); 1.5 (m, 1H); 1.77–1.85 (m, 3H); 2.28–2.35 (m, 2H); 2.97 (m, 1H); 4.2–4.31 (m, 1H); 7.19–7.25 (m, 5H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.70, 28.35, 29.10, 30.85, 31.15, 36.26, 48.88, 79.60, 126.86, 127.12, 127.48, 128.19, 131.13, 141.74, 144.39. **5d** white solid, mp 117–118 °C, ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (s, 9H); 1.66–1.8 (m, 4H); 2.49 (m, 1H); 2.77 (m, 1H); 3.03 (m, 1H); 4.46 (m, 1H); 6.88–7.07 (m, 10H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.02, 27.96, 29.02, 36.54, 48.70, 74.76, 126.59, 122.34, 128.11, 129.03, 129.62, 136.07, 139.36, 142.48, 154.33.