Stereospecific 1,4-Addition of Organolithium Reagents to *Unprotected* 1- and 2-Naphthalenecarboxylic Acids. A Facile Route to 1,1,2- and -1,2,2-Trisubstituted 1,2-Dihydronaphthalenes

Barbara Plunian, Jacques Mortier,* and Michel Vaultier*

Université Rennes-I, Groupe de recherches de physicochimie structurale, unité associée au CNRS no. 704, avenue du Général Leclerc, 35042 Rennes Cedex, France

Loïc Toupet

Université Rennes-I, Groupe de physique cristalline, unité associée au CNRS no. 15, avenue du Général Leclerc, 35042 Rennes Cedex, France

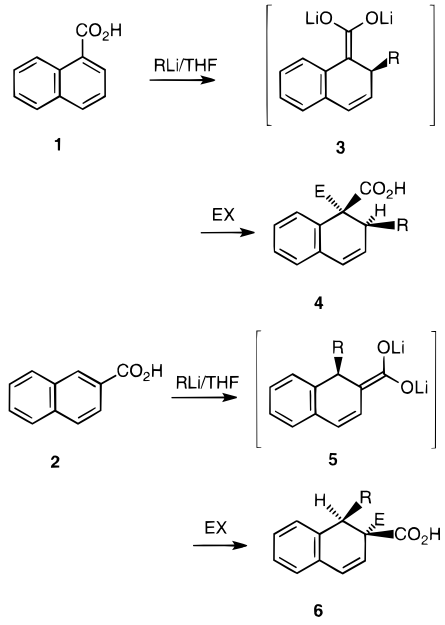
Received May 21, 1996

The reaction of strong nucleophiles with α,β-unsaturated carbonyl compounds usually leads to products resulting from carbonyl addition.[1] Products resulting from the alternate 1,4 or conjugate addition mode generally require the use of organocopper reagents derived from reactive nucleophiles.[2] While a plethora of methods have been developed and widely utilized addressing this type of transformation, one area that has slowly developed and only recently shown promise is the conjugate addition of organolithium reagents to Michael acceptors.[3]

The conjugate addition reactions of α,β-unsaturated carboxylic acid derivatives can be promoted by steric interference with the 1,2-addition process. Organolithium reagents undergo predominantly 1,4-addition reactions with unsaturated trityl ketones[4,5] as well as amide acceptors derived from highly hindered amines.[6] Unsaturated esters of 2,6-di-*tert*-butyl-4-methoxyphenol derivatives (BHA esters) undergo conjugate addition reactions with a range of organolithium reagents.[7]

The conjugate addition to α,β-unsaturated carboxylic acids has scarcely been achieved by using Grignard and alkylcopper reagents.[8] However, the conjugate addition to α,β-ethylenic carboxylic acids has never been performed by using any organolithium reagents. We have recently demonstrated that the directed ortho-metalation of *unprotected* benzoic acid can be achieved by treatment with 2.2 equiv of *s*-BuLi/TMEDA in THF at low temperature (−90 °C).[9] We now describe a stereospecific route to 1,1,2- and 1,2,2-trisubstituted 1,2-dihydronaphthalenes **4** and **6** that involves the nucleophilic conjugate addition of organolithium reagents to *unprotected* 1- and 2-naphthalenecarboxylic acids (**1**, **2**) followed by trapping of the intermediate carboxylic acid dilithium enolates **3** and **5** with several electrophiles (Scheme 1).[10,11]

Scheme 1



Treatment of a 0.1 M THF solution of naphthalenecarboxylic acids **1** or **2** with organolithium reagents (2.2 equiv) under the conditions depicted in Table 1, followed by addition of an electrophile (4.0 equiv), produced the adducts **4** and **6** in generally good yields.[12] The addition of *s*-butyllithium to **1** and **2** (−78 °C) followed by quenching with methyl iodide (−78 °C) gave the adducts **4a,a′** (80%) and **6a,a′** (90%) as 90:10 and 70:30 mixtures of diastereoisomers (entries 1 and 6, Table 1, and Scheme 2). The trans addition was verified in each system by single-crystal X-ray determination of the crystalline major isomers.[13,14] Presumably, in either case the carboxylic acid dilithium enolates **3** and **5** are the initial products formed, and entry of the electrophile (MeI) proceeds from the more accessible opposite face to that carrying the alkyl group. Furthermore, the X-ray struc-

* To whom correspondence should be addressed. Phone: (33) 99 28 16 91. Fax: (33) 99 28 69 55. E-mail: jacques.mortier@univ-rennes1.fr.

(1) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: New York, 1974.

(2) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1992; Vol. 9. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(3) Review: Hunt, D. A. *Org. Prep. Proced. Int.* **1989**, *21*, 705.

(4) Seebach, D.; Ertas, M.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264.

(5) Occasional reports of conjugate addition reactions of organolithium reagents to unsaturated *sec*-butyl and *tert*-butyl esters have also appeared: (a) Munch-Peterson, J. *J. Org. Chem.* **1957**, *22*, 170. (b) Munch-Peterson, J. *Org. Synth.* **1961**, *41*, 60. (c) Cooke, M. P., Jr. *Org. Synth.* **1984**, *49*, 1144.

(6) First report on the Michael-type reactivity of α,β-unsaturated amides: (a) Gilbert, G.; Aycock, B. F. *J. Org. Chem.* **1957**, *22*, 1013. Conjugate addition of organolithium reagents to unsaturated secondary and tertiary thioamides: (b) Tamaru, Y.; Kagotani, M.; Furukawa, Y.; Amino, Y.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 3413.

(7) Cooke, M. P., Jr. *J. Org. Chem.* **1986**, *51*, 1637.

(8) (a) Klein, J.; Turkel, R. M. *J. Am. Chem. Soc.* **1969**, *91*, 6186. (b) Klein, J.; Zitrin, S. *J. Org. Chem.* **1970**, *35*, 666. (c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

(9) (a) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042. (b) Moyroud, J.; Guesnet, J. L.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881. (c) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265. (d) Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 133. (e) Moyroud, J.; Chêne, A.; Guesnet, J.-L.; Mortier, J. *Heterocycles* **1996**, *43*, 221.

(10) The functionalization of chiral 1- and 2-naphthyloxazolines has become a prominent route by which many important chiral organic compounds are accessed: Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107 and references cited therein.

(11) For addition of organolithium to naphthalene and Grignard addition to acylnaphthalenes, ate complexes of boranes, arene−Cr-(CO)3 complexes, 2,6-di-*tert*-butyl-4-(methoxyphenyl)-1- and -2-naphthalenecarboxylates (BHA esters), see: (a) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681. (b) Kündig, E. P.; Ripa, A.; Liu, R.; Bernardinelli, G. *J. Org. Chem.* **1994**, *59*, 4773 and references cited therein. (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429. Ortho-metalation appears to be the major reaction pathway in the carboxamides when they are in the 1- and the 2-positions of the naphthalene: (d) Mpango, G. B.; Mahalanabis, K. K.; Madhavi, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823.

(12) All new compounds show ^{1}H and ^{13}C NMR and combustion analysis in full agreement with the proposed structures. See the supporting information.

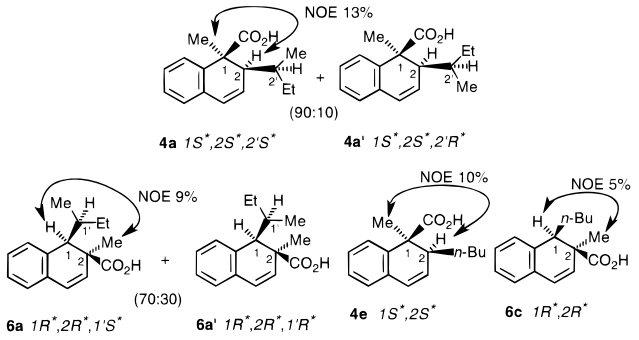
S0022-3263(96)00934-6 CCC: $12.00

Table 1. Tandem Additions to Unprotected 1- and 2-Naphthoic Acids (1 and 2)[a]

entry	RLi[b]	1 or **2** (addn *T*, °C)[c]	EX (addn *T*, °C)[c]	1,4-add product % yield, diast ratio[d,e]	1,2-add product % yield[d]
1	*s*-BuLi	**1** (−78)	MeI (−78)	**4a,a′** (80, 90:10)	**7** (8)
2	*s*-BuLi	**1** (−78)	EtI (−78)	**4b,b′** (44, 75:25)	**7** (12)
3	*s*-BuLi	**1** (−78)	Me_2S_2 (−78)	**4c,c′** (82, 65:35)	**7** (10)
4	*s*-BuLi	**1** (−78)	C_2Cl_6 (−78)	**11** (70)[f]	**7** (5)
5	*n*-BuLi	**1** (−78)	MeI (−78)	**4e** (36)	**8** (8)
6	*s*-BuLi	**2** (−78)	MeI (−78)	**6a,a′** (90, 70:30)	**9** (7)
7	*s*-BuLi	**2** (−90)	MeI (−90)	**6a,a′** (60, 75:25)	**9** (10)
8	*s*-BuLi	**2** (−45)	MeI (−45)	**6a,a′** (50, 69:31)	**9** (35)
9	*s*-BuLi	**2** (−78)	C_2Cl_6 (−78)	**12** (78)[f]	**9** (11)
10	*n*-BuLi	**2** (−78)	MeI (−78)	**6c** (38)	**10** (5)

[a] The following procedure for the synthesis of **4a,a′** is representative. In a 250-mL flask, equipped with a magnetic stirrer and maintained under Ar, was placed 40 mL of dry THF. *s*-Butyllithium in hexane (25.4 mL, 1.3 M, 33 mmol) was slowly added at −30 to −40 °C. The mixture was then cooled to −78 °C, and 1-naphthalenecarboxylic acid (**1**) (2.58 g, 15 mmol) in THF (150 mL) was slowly added. After the mixture was stirred for 1 h at −78 °C, a THF solution (20 mL) of methyl iodide (8.52 g, 60 mmol) was added. The solution was allowed to warm slowly to room temperature with stirring and then treated with water, washed with diethyl ether, and shaken. Concentration of the organic layer in vacuo and chromatography gave **7** (purified yield 0.25 g, 8%). The aqueous layer was acidified with 2 N HCl and diluted with diethyl ether, and the organic layer was separated, washed with $NaHCO_3$ and water, and dried with $MgSO_4$. Filtration, concentration in vacuo, and recrystallization (heptane/ethyl acetate) gave **4a,a′** (purified yield 2.93 g, 80%). [b] *n*-BuLi in hexane; *s*-BuLi in cyclohexane−hexane; 2.2 equiv of RLi was used. [c] Reaction was carried out at the reported temperature, 1 h. [d] Yields refer to purified isolated compounds. [e] Diastereoisomeric ratio was determined by ^{1}H NMR. [f] 1,4-Addition products **4d,d′** and **6b,b′** not isolated.

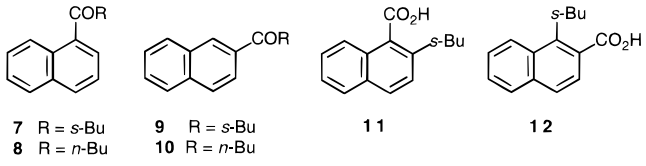
Scheme 2



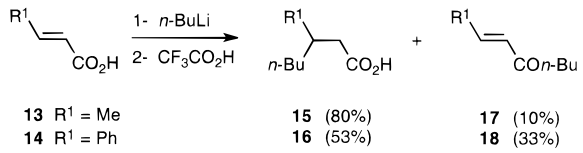
tures also establish the relative stereochemistry of the tertiary carbon of the *sec*-butyl chain. Further proof was gathered for the stereochemistry at C1 and C2 by qualitative homonuclear NOE difference spectroscopy. Thus, individual irradiations of H-2 in **4a** and H-1 in **6a** showed a large enhancement of the neighboring methyl group (13%, 9%). Since the reaction of *n*-BuLi with **1** and **2** afforded **4e** and **6c** as a single isomer (36 and 38% yields, respectively, Table 1, entries 5 and 10),[15] it may be assumed that the minor isomers **4a′** and **6a′** differ from **4a** and **6a** by the configuration of the tertiary carbon of the alkyl side chain.

From Table 1, it can be seen that the addition temperature of the electrophile to the dilithium enolate **5** has a minimal effect upon the degree of diastereoselectivity. Thus, methyl iodide added at −90 or −45 °C resulted in a loss of diastereoselectivity of only 5−10% (Table 1, entries 7 and 8). However, the rate of 1,4-addition began to slow considerably as the temperature was lowered. The 1,2-addition products **7**−**10** (Chart 1) were obtained as byproducts in 5−12% yields at −78 °C. At −45 °C, the 1,2-addition rate of the organolithium to the carboxylate was comparatively higher (Table 1, entry 8). Furthermore, addition of HMPA or TMEDA at −78 or −90 °C was virtually without effect. The carboxylate is apparently a much better ligand for *s*-BuLi than HMPA and TMEDA. This result also suggests that the organolithium is reacting as a monomer since it is unlikely it could aggregate in the presence of HMPA or TMEDA.

Chart 1



Scheme 3



Commercial methyllithium and phenyllithium did not add to **1** and **2**. At the present time we are comparing the addition behavior of various organolithium reagents generated from different sources.[16] Treatment of naphthalenecarboxylic acid **1** or **2** with *s*-butyllithium at −78 °C, followed by addition of hexachloroethane, resulted mainly in the aromatization of **4d,d′** and **6b,b′** and afforded **11** and **12** in moderate yields (Table 1, entries 4 and 9).[17]

Additionally, acyclic α,β-unsaturated crotonic and cinnamic acids (**13**, **14**) were treated with 2 equiv of *n*-butyllithium (THF, −78 °C) (Scheme 3), and the resulting enolates were quenched with trifluoroacetic acid to give the 1,4-adducts **15** (80%) and **16** (53%) as major products along with the 1,2-adducts **17** (10%) and **18** (33%).

In conclusion, we have developed for the first time a methodology for generation and subsequent alkylation of carboxylic acid dilithium enolates by organolithium reagents. The versatility of the dialkylation is thereby demonstrated to possess the potential for reaching a variety of diastereoisomeric products. Since the present process to 1,1,2- and 1,2,2-trisubstituted dihydronaphthalenes is an alternative to the elegant reaction scheme developed by Meyers based on the oxazoline and imine chemistry,[10] our next goal is the development of an enantioselective procedure based on a strategy of using a chiral diether or diamine as a stereocontrol catalyst.[11a]

Supporting Information Available: Spectral and analytical data for **4a**−**c,e**, **6a,c**, **7**−**12**, and **15**−**18** (6 pages).

JO960934Z

(13) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) The major isomers **4a**−**c** and **6a** were obtained pure by fractional recrystallization (heptane/EtOAc).

(15) The stereochemical assigment of **4e** and **6c** was also found to be cis at C1 and C2 *via* NOE (10%, 5%) while the relative configuration may be assumed to be as drawn (1*S**,2*S** and 1*R**,2*R**).

(16) Facile additions to naphthalene oxazolines of organolithium reagents derived from LiDBB (lithium 4,4′-di-*tert*-butylphenyl) have been reported: Rawson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **1991**, *32*, 2095 and references cited therein.

(17) Traces of **4d,d′** and **6b,b′** could be detected by NMR analysis of the crude reaction mixture.