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Tandem Carbolithiation/Cyclization of 2-(3-Phenyl-2-Propen-1-yl) Oxazolines. A Novel Route to Cyclobutane Derivatives

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Abstract: Reaction of the 2-(3-phenyl-2-propen-1-yl) oxazolines **1** and **3** with organolithium reagents leads to cyclobutane ring formation by a novel tandem carbolithiation/cyclization sequence. The products (e.g., **2a** and **4a**) may be hydrolyzed to the corresponding substituted cyclobutanones (e.g., **7** and **8**). © 1997 Elsevier Science Ltd.

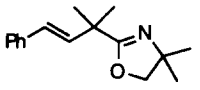
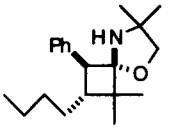
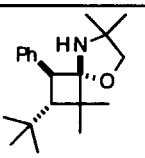
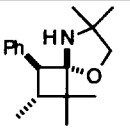
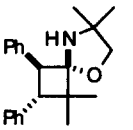
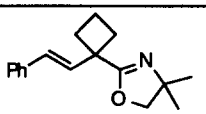
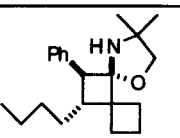
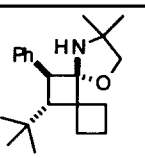
Carbolithiation of styrene derivatives is an established C-C bond-forming process.[1] However, the potential of the intermediate α-aryl carbanions to undergo cyclization via intramolecular attack at a remote electrophilic site has been little explored.[2] During efforts to define the scope of oxazoline-directed olefin CH metalation,[3,4] we examined several 2-(1,1-dialkyl-2-propen-1-yl) oxazolines, including the styryl oxazoline **1**,[5] as potential metalation substrates. Whereas oxazoline-directed lithiation of **1** did not take place, efficient formation of substituted cyclobutane derivatives (**2**) was observed. Details of this reaction, an example of a sequential styrene carbolithiation/α-aryl carbanion cyclization, are provided in this Communication.

1 **2**

Treatment of **1** in Et_2O at 0°C with a 2-fold excess of *n*-BuLi in hexane led to rapid formation of a yellow species which was quenched with D_2O after stirring in an ice bath for an additional 1.5 h. Thin layer chromatography indicated the dominant outcome of the reaction to be formation of a more polar product; starting material incorporating deuterium at either olefinic position was not detected by NMR. Flash chromatography on silica gel allowed isolation of the diastereomerically pure cyclobutane derivative **2a** in 76% yield (Table). Similar results were obtained following exposure of **1** to *t*-BuLi, MeLi and PhLi leading to isolation of cyclobutanes **2b-d** in yields of 90%, 47% and 37% respectively.[6,7,8] The lower isolated yields of **2c** and **2d** are attributed to the production of side products arising under the more forcing conditions required for reaction (RT/overnight). For example, the reaction to give **2d** was accompanied by the formation of *trans*-stilbene, the product of PhLi addition and elimination of the anion of 2-isopropyl-4,4-dimethyloxazoline.

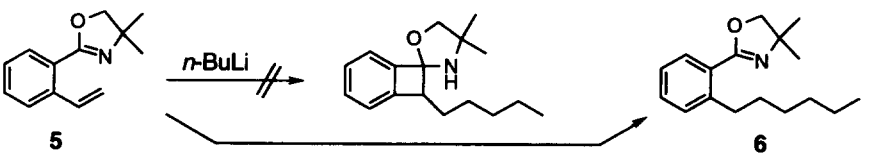
A limited number of experiments were carried out to further define the generality of the carbometalation-cyclization. Organomagnesium reagents do not appear to be sufficiently reactive to take part in the reaction based on the lack of reaction of EtMgBr (-78° to 20°C/THF) with **1**. The capacity of the reaction to produce more strained spirocycloalkyl systems was demonstrated by the reactions of **3**[9] with *n*-BuLi and *t*-BuLi to

TABLE

Substrate	RLi Solution[a]	Conditions[b]	Product	Yield (%)
1 	*n*-BuLi/hexane	0°C 1 h	**2a** 	76
1	*t*-BuLi/pentane	-78°C to -20°C 1.5 h	**2b** 	90
1	MeLi/Et_2O	0°C to RT overnight	**2c** 	47
1	PhLi/cyclohexane	-78°C to RT overnight	**2d** 	37
3 	*n*-BuLi/hexane	0°C 1 h	**4a** 	55
3	*t*-BuLi/pentane	-78°C to -40°C 0.75 h	**4b** 	63

a: In all cases, 2.4 to 2.5 equivalents of organolithium were used. b: All reactions were performed in Et_2O.

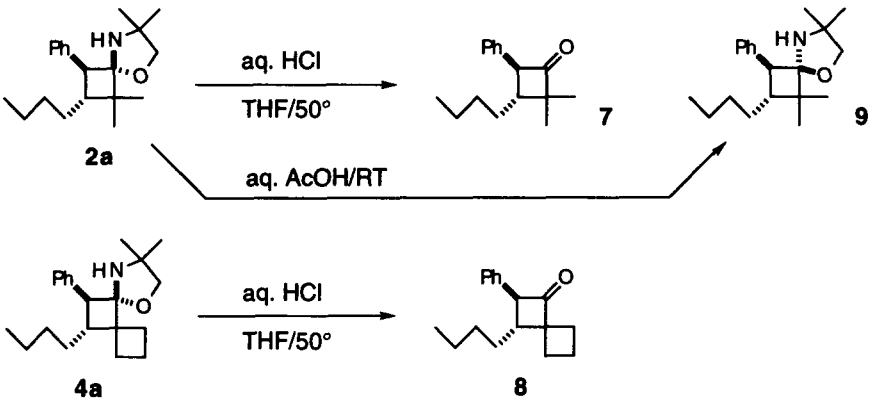
afford the spiro[3.3]cycloheptane derivatives **4a** and **4b** in yields of 55% and 63% respectively.[6,7,10] The possibility that substrates such as **5** could give rise to benzocyclobutane derivatives was also considered. However, following reaction of **5** with *n*-BuLi (0°C/Et_2O/10 min), the only product identified was the simple alkyllithium adduct **6**.[11] Presumably, in this case, the α-aryl carbanion, which is conjugated with the oxazoline C=N bond, is too stable to undergo cyclization.



5 **6**

The structures for **2a-d**, **4a** and **4b** were determined predominantly by ^{1}H NMR methods. Stereochemical assignments are based on nOe's observed in the ^{1}H NMR spectrum of **2b**. A *trans* relationship between the *t*-butyl and phenyl groups of **2b** is indicated by the observance of significant nOe's between the *t*-butyl signal and *both* cyclobutane methine absorbances and nOe's between each cyclobutyl methyl signal and only *one* of the cyclobutane methine absorbances. The *syn* relationship of the oxazolidine NH and the phenyl group is supported by an nOe between the phenyl and NH signals as well as the marked upfield absorbance of one of the oxazolidine methyl groups (ascribed to shielding by the *syn* phenyl group). That **2a**, **2c**, **2d**, **4a** and **4b** are stereochemically identical to **2b** is supported by the observance of nearly the same coupling constant (11-12 Hz) between the cyclobutane methine hydrogens in each case and a characteristic upfield shift of one oxazolidine methyl group in the cases of **2a**, **2c**, and **2d**.

Lending chemical support to the assigned structures, exposure of **2a** and **4a** to conditions for hydrolysis of the oxazolidine ring (1N HCl/THF/50°C) led to clean formation of the corresponding cyclobutanone derivatives **7** (IR ν_{max} = 1769 cm^{-1}) and **8** respectively.[7,12] Interestingly, attempted hydrolysis of **2a** using aqueous AcOH at RT brought about complete isomerization to **9**. Thus, while being kinetically favored in the carbolithiation/cyclization reaction, **2a** appears to be less thermodynamically stable than **9**. With a ^{1}H NMR spectrum of **9** in hand, it was possible to determine that a small amount of this isomer (approx. 1:10 **9** to **2a**) was present in the crude sample of **2a** indicating that the reaction of *n*-BuLi with **1** is not completely diastereoselective.[13]



Besides their novelty and diastereoselectivity (only one of four possible diastereomeric products predominates), the tandem carbolithiation/cyclizations of **1** and **3** are remarkable in that the conditions for organolithium addition to the styryl exocyclic C=C bond are very mild. Additives such as TMEDA, used in certain instances to promote carbolithiations of styryl derivatives,[1b,d] are not required. The fact that reaction is seen at all using MeLi is noteworthy considering reported failed attempts at styrene carbolithiation using this reagent.[1b,14] We attribute the facility with which **1** and **3** undergo reaction with organolithium reagents to precoordination by the oxazoline group.

References and Notes

1. Recent papers: (a) Muck-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025. (b) Wei, X.; Taylor, R. J. K. *J. Chem. Soc. Chem. Commun.* **1996**, 187. (c) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (d) Klein, S.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1994**, *59*, 2925.
2. To our knowledge such a process was unknown until very recently: Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **1997**, *62*, 4898.
3. Mander, L.N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 5718.
4. For a recent review on the chemistry of oxazolines see: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
5. Prepared from 2,2-dimethyl-4-phenyl-3-butenoic acid (Stratford, E. S. *J. Med. Chem.* **1975**, *18*, 242) by conversion to the acid chloride ($COCl_2$/benzene), amide formation (2-amino-2-methyl-1-propanol/CH_2Cl_2) and cyclization (CCl_4/PPh_3/MeCN/pyridine) according to Vorbrüggen, H., Krolikiewicz, K. *Tetrahedron Lett.* **1981**, 22, 4471.
6. Yields are unoptimized. Significant amounts of starting material remained after using only 1 equiv. RLi.
7. Characterized by ^1H NMR, ^{13}C NMR and MS. All compounds were oils except **2b**, a white solid (mp 72-74°C) which gave a satisfactory elemental analysis.
8. ^1H NMR data ($CDCl_3$) for **2a**: δ 7.35-7.18 (m, 5 H), 3.42 (d, J = 11.1 Hz, 1 H), 3.40 (d, J = 7.4 Hz, 1 H), 3.23 (d, J = 7.4 Hz, 1 H), 1.96-1.86 (m, 1 H), 1.5-1.1 (m, 7 H), 1.17 (s, 3 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 0.83 (t, J = 6.7 Hz, 3 H), 0.78 (s, 3 H). **2b**: δ 7.3-7.15 (m, 5 H), 3.64 (d, J = 12.5 Hz, 1 H), 3.31 (d, J = 7.5 Hz, 1 H), 3.12 (d, J = 7.5 Hz, 1 H), 1.91 (d, J = 12.5 Hz, 1 H), 1.6 (br s, 1 H), 1.29 (s, 3 H), 1.17 (s, 3 H), 1.05 (s, 3 H), 0.87 (s, 9 H), 0.62 (s, 3 H). **2c**: δ 7.36-7.17 (m, 5 H), 3.44 (d, J = 11 Hz, 1 H), 3.43 (d, J = 7.4 Hz, 1 H), 3.27 (d, J = 7.4 Hz, 1 H), 2.03-1.90 (m, 1 H), 1.46 (br s, 1 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.83 (s, 3 H). **2d**: δ 7.33-7.19 (m, 10 H), 4.27 (d, J = 11.8 Hz, 1 H), 3.53 (d, J = 7.6 Hz, 1 H), 3.42 (d, J = 7.6 Hz, 1 H), 3.25 (d, J = 11.8 Hz, 1 H), 1.67 (br s, 1 H), 1.31 (s, 3 H), 1.16 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).
9. Prepared from 1-styrylcyclobutanecarboxylic acid (Treves, G. R.; Stange, H.; Olofson, R. A. *J.Am. Chem. Soc.* **1967**, *89*, 6257) as in Ref. 5.
10. ^1H NMR data ($CDCl_3$) for **4a**: δ 7.30-7.26 (m, 2 H), 7.21-7.17 (m, 3 H), 3.49 (d, J = 7.5 Hz, 1 H), 3.28 (d, J = 7.5 Hz, 1 H), 3.09 (d, J = 11.0 Hz, 1 H), 2.33-2.31 (m, 1 H), 2.18-2.11 (m, 2 H), 2.00-1.98 (m, 1 H), 1.90-1.79 (m, 3 H), 1.65-1.56 (m, 2 H), 1.44-1.38 (m, 1 H), 1.30-1.20 (m, 4 H), 1.18 (s, 3 H), 0.83 (t, J = 7.0 Hz, 3 H), 0.69 (s, 3 H). **4b**: δ 7.29-7.15 (m, 5 H), 3.46 (d, J = 7.7 Hz, 1 H), 3.41 (d, J = 12.0 Hz, 1 H), 3.23 (d, J = 7.7 Hz, 1 H), 2.56-2.48 (m, 1 H), 2.46-2.40 (m, 1 H), 2.21-2.15 (m, 1 H), 2.09-2.01 (m, 1 H), 1.86-1.74 (m, 4 H), 1.17 (s, 3 H), 0.92 (s, 9 H), 0.61 (s, 3 H).
11. Additions of organolithium reagents to *o*-styryl oxazolines (e.g., **5**) are known: Seijas, J. O.; Vazquez-Tato, M. P.; Castedo, L.; Estevez, R. J.; Ruiz, M. *J. Org. Chem.* **1992**, *57*, 5283.
12. ^1H NMR data ($CDCl_3$) for **7**: δ 7.36-7.18 (m, 5 H), 4.13 (d, J = 9.3 Hz, 1 H), 2.29-2.19 (m, 1 H), 1.85-1.65 (m, 2 H), 1.4-1.25 (m, 4 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 0.90 (t, J = 6.8 Hz, 3 H). **8**: δ 7.32-7.15 (m, 5 H), 3.86 (d, J = 8.5 Hz, 1 H), 2.38-2.26 (m, 3 H), 2.17-2.00 (m, 3 H), 1.90-1.75 (m, 2 H), 1.65-1.58 (m, 1 H), 1.43-1.36 (m, 4 H), 0.91 (t, J = 7.2 Hz, 3 H).
13. Based on the ^1H NMR spectra of the crude product mixtures yielding **2b-d**, **4a** and **4b**, it appears that minor amounts of the diastereomers corresponding to **9** were formed. However, these products were not isolated or characterized.
14. Richey, H. G.; Heyn, A. S.; Erickson, W. F. *J. Org. Chem.* **1983**, *48*, 3821.

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