Tetrahedron Letters, Vol.22, No.43, pp 4259 - 4262, 1981
Printed in Great Britain

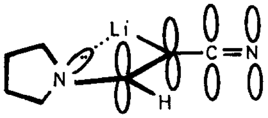
0040-4039/81/434259-04$02.00/0

INFLUENCE OF SUBSTITUENTS ON REGIOSELECTIVITY OF VINYLLITHIUM FORMATION WITH ACRYLIC ACID DERIVATIVES [1)]

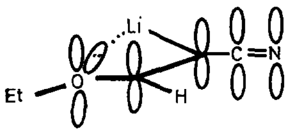
Richard R. Schmidt* and Heike Speer
Fakultät Chemie, Universität Konstanz
Postfach 5560, D-7750 Konstanz, Germany

Abstract: *ß-Alkoxy, ß-dialkylamino, and ß-N-alkylacylamino substituents determine the regioselectivity of the vinylic deprotonation of acrylic ester and nitrile derivatives: either α- or ß-vinyllithium species may be generated. The corresponding acrylamides or systems with additional α-alkyl or α-methylmercapto substituents are lithiated at ß-position.*

Direct lithiation of ß-aminoacrylonitrile 1a led to preferential kinetic ß-metalation and to thermodynamic α-metalation [2,3)] (table 1); either α- or ß-substituted products were obtained with different electrophiles. These results were discussed in terms of inductive (I) and mesomeric (M) effects and different intramolecular complexation and solvation [3)]. Surprisingly, with ß-ethoxyacrylonitrile 2a only α-lithiation was observed under similar reaction conditions (table 1), even though the C_{β}H-acidity should be relatively higher because of the stronger -I- effect of the ethoxy group. Two factors may be responsible for this result: (i) The increase of the C_{β}H-acidity by the -I- effect of the ß-ethoxy group in 2a is not as pronounced as the decrease of the C_{α}H-acidity by the mesomeric effect of the ß-amino group in 1a, thus contributing to kinetic ß-deprotonation in 1a. This argument is supported by calculations and spectroscopic evidence [3,4)]. (ii) Intramolecular complexation in 1a-α contributes strongly to the thermodynamic α-deprotonation in 1a according to theoretical calculations [3)], even though there is no conjugation between the amino group and the π-system. However, intramolecular complexation of the lithium atom by the ethoxy oxygen atom in 2a-α is possible without loss of π-conjugation because of the geometry of the second pair of free electrons, thus favoring general α-deprotonation in 2a.

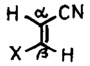
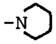
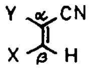
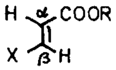
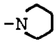
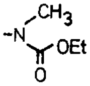
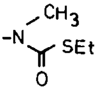
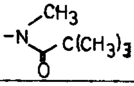
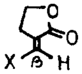
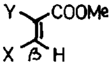
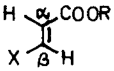
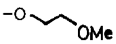
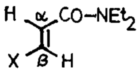
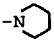


1a – α



2a-α

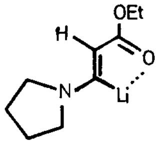
Table 1: Deprotonation of ß-Substituted Acrylic Acid Derivatives 1-6.

		Compound			Reaction Conditions [a]				Deuteration [b]	
		X	Y	R	Base	Base-equ.	[°C]	[min]	Yield[%][c]	α/ß
	1a		-	-	LDA	1.2	-113	40	95	2/98[d]
					LDA	1.2	- 76	60	82	α[d]
	2a	-OEt	-	-	LDA	1.5	-100	2	45	α
					n-BuLi	1.5	-100	30	71	α
					n-BuLi	1.5	- 50	2	40	α
	1b	$-N(CH_3)_2$	SCH_3	-	n-BuLi	1.5	-110	45	48	ß
	2b	-OEt	CH_3	-	LDA	1.6	-100	2	98	ß
	3a		-	Et	t-BuLi	1.4	-113	15	70	ß[d]
					t-BuLi	1.4	- 65	0.5	90	ß[d]
	3b		-	Me	LDA	1.5	-120	10	58	90/10
					LDA	1.5	-100	2	62	80/20
					LDA	1.5	- 80	10	45	60/40
					LDA	1.5	- 80	60	38	30/70
	3c		-	Me	LDA	1.5	-100	2	62	α
					LDA	1.5	-100	25	64	α
					LDA	1.5	- 80	2	50	α
	3d		-	Me	LDA	1.5	-100		47	α
	3e	$-N(CH_3)_2$	-	-	n-BuLi	1.6	-100	15	71	ß
	3f	$-N(CH_3)_2$	$-SCH_3$	-	LDA	1.6	- 80	25	72	ß
	4a	-OEt	-	Et	LDA	1.6	- 90	2	87	5/95[d]
					LDA	1.6	- 90	300	95	43/57[d]
	4b		-	Et	LDA	1.6	-100	2	62	10/90
					LDA	1.6	-100	10	65	ß
					LDA	1.6	-100	120	58	ß
					LDA	1.6	- 70	10	41	ß
	5a		-	-	t-BuLi	1.4	-113	30	95	ß[d]
	6a	-OMe	-	-	LDA	1.6	-100	30	87	ß
					LDA	1.6	- 60	10	71	ß

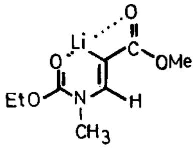
[a] Solvent: THF; [b] with CH_3OD; [c] isolated yield of deuterated material; [d] see ref. 2.

The convenient ß-lithiations of 1b and 2b demonstrate, that direct ß-metalation of these acrylonitrile derivatives is possible when α-substituents are present; deprotonation at the allylic methyl group was not observed with 2b [5]. This clearly indicates an activating effect of the cyano group at the α- and at the ß-position [3]. Therefore, like 1a, 2a may possess comparable acidities at α- and ß-position even though ß-deprotonation was not observed.

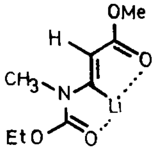
The weaker -I- effect of the ester group compared with the cyano group [6] and the more favorable intramolecular complexation in 3a-ß support the exclusive ß-lithiation of 3a [7]. A decrease of the + M-effect and an increase of the -I- effect of the ß-aminosubstituent change the situation completely: under kinetic control 3b is mainly and 3c and 3d exclusively lithiated at the α-position. Investigations with 3b at different temperatures demonstrated, that ß-deprotonation is thermodynamically favored. Because of the strong influence of intramolecular complexation on the regioselectivity of these vinylic lithiations, it is assumed, that the chelates 3b-α and 3b-ß contribute strongly to this behavior.



3a-ß



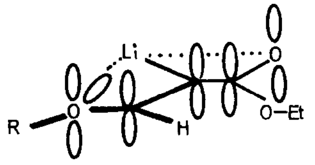
3b-α



3b-ß

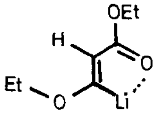
ß-Lithiation was obtained without any difficulty with the α-substituted ß-aminoacrylic acid derivatives 3e and 3f. Again, the allylic methylene group of 3f is less acidic than the vinylic C_{β}H-group under the applied reaction conditions.

Considering the results of 1a, 2a and 3a-d and the inductive and mesomeric effects in the ß-ethoxy acrylic ester 4a, deprotonation of 4a could lead to a result observed for 3b. However, the very different intramolecular stabilisations of the lithiated species 4a-α and 4a-ß are in favor of 4a-α to be the thermodynamically more stable vinyllithium derivative. This interpretation is supported by the behavior of 4b: the better intramolecular stabilisation of the ß-lithiated species 4b-ß compared with the α-lithiated species 4b-α_1 or 4b-α_2 results in a complete transformation of the initially formed α/ß-mixture into the ß-lithiated species 4b-ß.

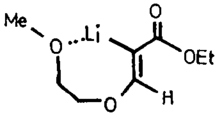


4a-α : R = Et

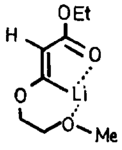
4b-α1 : R = $(CH_2)_2$ OMe



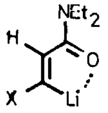
4a-β



4b α2



4b-β



5a – β : X=N

6a – β : X=OMe

The lower inductive effect of the carboxamide group together with a better intramolecular stabilisation in the β-lithiated species 5a-β and 6a-β leads to complete β-lithiation of 5a and 6a under very different reaction conditions. The observed lower reactivity of the vinyllithium species 5a-β, 6a-β, 3b-α, 4b-β towards electrophiles 8) supports the strong intramolecular complexation discussed above.

The investigations demonstrate, that β-alkoxy and β-amino acrylonitrile and acrylic ester derivatives may be lithiated at α- or β-position, thus being versatile intermediates for further syntheses 8).

---

1) Vinyl Carbanions, Part 11. - For part 10 see: B.A. Feit, U. Melamed, R.R. Schmidt, and H. Speer, Tetrahedron, in press.

2) R.R. Schmidt and J. Talbiersky, Angew.Chem. 89, 891 (1977); Angew.Chem.Int.Ed.Engl. 16, 851 (1977).

3) R.R. Schmidt, J. Talbiersky, and P. Russegger, Tetrahedron Lett. 1979, 4273.

4) E. Arguedas Chaverri, Dissertation, University Louvain La Neuve, 1981.

5) J. Hartmann, M. Stähle, and M. Schlosser, Synthesis 1974, 888.

6) R.W. Taft, jr. J.Am.Chem.Soc. 74, 2729 (1952); R.W. Taft, in "Steric Effects in Organic Chemistry", M.S. Newman, Ed., Wiley, New York 1956, Chapter 13.

7) R.R. Schmidt and J. Talbiersky, Angew.Chem. 90, 220 (1978); Angew.Chem.Int.Ed.Engl. 17, 204 (1978).

8) R.R. Schmidt and H. Speer, to be published; the reactivity is susceptible to the addition of complexing agents.

(Received in Germany 20 June 1981)