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## Selective preparation of (Z)- and (E)-prop-1-enylamides from N-allylbenzamides

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Abstract—A series of *para*-substituted *N*-allylbenzamides was submitted to isomerization under basic conditions. With LDA at  $-78^{\circ}$ C, the corresponding (*E*)-*N*-(prop-1-enyl)benzamide was the major product. With *n*-butyllithium and the mixture warmed to 0°C, the (*Z*)-isomer was essentially furnished. © 2001 Elsevier Science Ltd. All rights reserved.

The directed *ortho*-metallation of arenes is a powerful method for the elaboration of complex aromatic compounds.<sup>1</sup> Although deprotonation of aromatic amides by alkyllithium and electrophilic capture of lithiated species is of particular interest for preparing *ortho*-substituted derivatives,<sup>2</sup> the major problems associated with the use of these *ortho*-directing groups are their great resistance to hydrolysis and the difficulty of their transformation to other useful functionalities.<sup>3</sup> Tischler reported base-induced isomerization of *N*-allylbenzamide **1a** to enamides that were easily hydrolyzed (Scheme 1).<sup>4</sup> Starting from benzamides **1** (R=H, OCH<sub>3</sub>), Fisher and co-workers used 1:1 mixtures of (*Z*)- and (*E*)-*N*-(prop-1-enyl)benzamides to prepare isoquino-1(2*H*)-ones.<sup>5</sup>

During the study of the preparation substituted isoquinolones, we observed that isomerization of *para*substituted benzamides **1b**-e under basic conditions gave mixtures of enamides **2** and **3** with ratios varying from about 3:2 to 1:9 (Scheme 1).<sup>6</sup> Herein, we report the results obtained for optimizing the stereoselectivity and yield of reaction.

Benzamide 1a was used in a preliminary study and the results are summarized in Table 1. The lithiated derivatives were prepared by addition of a solution of 1a in THF into a solution of LDA (2.2 equiv.) in THF at -78°C. After 5 min, the reaction mixture was allowed to warm (entries 1-3). At  $0^{\circ}$ C the mixture rapidly turned from a deep purple to a dark yellow color. <sup>1</sup>H NMR analysis of the mixture obtained after work-up indicates a quantitative isomerization of the allylamide to a 2:3 mixture of (E)- and (Z)-N-(prop-1-enyl)benzamides (2a and 3a).7 When the reaction mixture was maintained at -78°C and quenched at this temperature with methanol (entries 4–7), the E/Z ratio remained essentially the same, with 2a as the major product. Consequently, the isomerization was supposed to be the result of a relatively slow metallation reaction at -78°C.

Some experiments were conducted with *n*-butyllithium instead of LDA. A solution of *n*-butyllithium in hexane (2.2 equiv.) was added to a solution of benzamide **1a** in THF at  $-78^{\circ}$ C; an intense color developed upon the addition of the second equivalent of base. When the



Scheme 1. Base: *n*-BuLi, *i*-Pr<sub>2</sub>Li; R:  $\mathbf{a} = H$ ,  $\mathbf{b} = CH_3$ ,  $\mathbf{c} = CH(OMe)_2$ ,  $\mathbf{d} = C(OMe)_2CH_3$ ,  $\mathbf{e} = C(OMe)_2Ph$ .

Keywords: lithiation; isomerization; allylbenzamides; enamides.

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propylamine to provide the (*E*)-enamide **2a** after hydrolysis (Scheme 2). At higher temperatures, an equilibrium was reached; the intermediate **3-Li** becomes predominant and finally gave (*Z*)-enamide **3a** after work-up. Semi-empirical calculations, using the PM3 method,<sup>8,9</sup> indicated that the more stable dilithiated species was the (*Z*)-isomer **3-Li**, as a result of an internal chelation involving the lithium atom and the oxygen and/or nitrogen atoms.<sup>10,11</sup> With *n*-butyllithium, because there was no reprotonating agent present, the more stable lithiated intermediate **3-Li** was favored.

Assuming that acceleration of trapping of dithiated intermediate 2-Li enhanced the yield of isomer 2a, treatment with LDA was carried out at  $-78^{\circ}$ C in the presence of 20 equiv. of diisopropylamine and there was a small increase of the yield of (*E*)-enamine 2a of about 10% (entries 12–14).

Finally, the results obtained with a series of *para*-substituted *N*-allylbenzamides are reported in Table 2. In summary, when the reaction proceeds under kinetic control, with LDA at  $-78^{\circ}$ C, the corresponding (*E*)-*N*-(prop-1-enyl)benzamides **2b**-e are the major products. With *n*-butyllithium, the mixture prepared at  $-78^{\circ}$ C and allowed to warm to  $0^{\circ}$ C, provides essentially the (*Z*)-isomers **3b**-e.

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- 7. Synthesis of (E)-N-(prop-1-enyl)benzamide (2a): To a solution of diisopropylamine (30.8 mL, 22 mmol) in tetrahydrofuran (55 mL) under nitrogen at -78°C was added n-butyllithium (8.8 mL, 22 mmol) 2.5 M in hexanes. The solution was stirred for 15 min at 0°C, cooled to -78°C and then treated with a solution of N-allylbenzamide (1.61 g, 10 mmol) in tetrahydrofuran (15 mL). The solution was stirred 6 h at -78°C, warmed to 0°C and treated with methanol (1 mL), ether (30 mL) and an aqueous solution of ammonium chloride. The organic solution was washed with aqueous ammonium chloride (4×25 mL) and brine (2×25 mL). The extract was dried over MgSO<sub>4</sub> and concentrated in vacuo. Column chromatography on silica gel using 20% EtOAc in petroleum ether afforded 1.237 g (77%) of 2a: R<sub>f</sub> 0.37 (EtOAc/ petroleum ether 1:3); FTIR: 3296, 1640, 1529, 1316, 954, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.29 (s, 1H), 7.79 (dd, J=2.2 and 8.3 Hz, 2H), 7.49-7.44 (m, 1H), 7.39–7.34 (m, 2H), 6.92 (ddq, J = 1.6, 10.3 and 14.1 Hz, 1H), 5.37 (dq, J=6.7 and 14.1 Hz, 1H), 1.69 (dd, J=1.6and 6.7 Hz) ppm; <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  164.9, 134.2, 132.1, 128.9, 127.5, 124.1, 109.6, 15.4 ppm.
  - Synthesis of (Z)-N-(prop-1-enyl)benzamide (3a): To a solution of N-allylbenzamide (1.61 g, 10 mmol) in tetrahydrofuran (55 mL) under nitrogen at -78°C was added n-butyllithium (8.8 mL, 22 mmol) 2.5 M in hexanes. The solution was stirred for 15 min at -78°C and then for a further 90 min at 0°C. The solution was cooled to -78°C and treated with methanol (1 mL), ether (30 mL) and an aqueous solution of ammonium chloride. The organic solution was washed with aqueous ammonium chloride (25 mL) and brine (2×25 mL). The extract was dried over MgSO<sub>4</sub> and concentrated in vacuo. Column chromatography on silica gel using 20% EtOAc in petroleum ether afforded 1.205 g (75%) of 3a: R<sub>f</sub> 0.44 (EtOAc/petroleum ether 1:3); FTIR: 3260, 1637, 1518, 1292, 704 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.82–7.78 (m, 2H), 7.73 (m, 1H), 7.54–7.40 (m, 3H), 7.92 (ddq, J = 1.7, 8.8 and 10.7 Hz, 1H), 4.93 (dq, J=8.8 and 7.0 Hz, 1H), 1.70 (dd, J=1.7 and 7.0) ppm; <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$ 164.9, 134.4, 132.3, 129.1, 127.5, 122.7, 106.7, 11.4 ppm.
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Entry	Base	Additive	Conditions	Conversion <sup>a</sup>	<i>E</i> / <i>Z</i> ratio <sup>a</sup> 2a:3a	
		(equiv.)	°C (min)	(%)		
1	LDA		-78 (5), 0 (5)	100	40:60	
2	LDA		-78(5), -25(90)	100	50:50	
3	LDA		-78 (5), $-40$ (120)	100	60:40	
4	LDA		- 78 (5) <sup>b</sup>	26	76:24	
5	LDA		-78 (45) <sup>b</sup>	69	74:26	
6	LDA		-78 (120) <sup>b</sup>	85	80:20	
7	LDA		-78 (240) <sup>b</sup>	97	78:22	
8	n-BuLi		$-78(5)^{b}$	0	_	
9	n-BuLi		-78 (120) <sup>b</sup>	25	10:90	
10	n-BuLi		-78 (15), 0 (90), $-78$ (15) <sup>b</sup>	96 (75)°	7:93	
11	n-BuLi		-78 (15), 0 (1) <sup>b</sup>	92	5:95	
12	LDA	HDA <sup>d</sup> (20)	-78 (120) <sup>b</sup>	81	87:13	
13	LDA	HDA <sup>d</sup> (20)	-78 (210) <sup>b</sup>	89	85:15	
14	LDA	HDA <sup>d</sup> (20)	- 78 (360) <sup>b</sup>	99 (77) <sup>c</sup>	87:13	

Table	1.	Isomerization	of	N-all	ylbenzamide	1a	to	enamides	2a	and	3a
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<sup>a</sup> Conversion and ratio were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

<sup>b</sup> Quenched with methanol instead of water.

<sup>c</sup> Isolated yield of pure product for a 10 mmol scale reaction.

<sup>d</sup> HDA:diisopropylamine.

mixture was quenched after 5 min with methanol (entry 8), methanol-d or DCl in  $D_2O$ , the starting material was recovered practically unchanged. These results show that the intense color developed does not prove the formation of a great quantity of metallated product. When the contact of the reagents was maintained at a higher temperature, the major product, (Z)-N-(prop-1-enyl)benzamide **3a**, was obtained in good yields (entries 9–11). Quenching the reaction mixture at 0°C with methanol-d provided essentially the (Z)-N-(3-deutero-

prop-1-enyl) derivative, as shown by analysis of the <sup>1</sup>H NMR spectrum of the crude product.

These results indicate that compound 3a was obtained from the more stable intermediate. Therefore, compound 2a should be the result of a kinetically controlled isomerization reaction.

When the reaction was performed with LDA at  $-78^{\circ}$ C, the initially predominant 2-Li was trapped by diiso-



Scheme 2.

Table 2. Isomerization of p-substituted N-allylbenzamides 1b-e

R (para substituent)	Conditions <sup>a</sup>	Time (min)	Conversion (%) <sup>b</sup>	<i>E/Z</i> ratio <sup>b</sup> 85:15	
Ib CH <sub>3</sub>	Α	240	92		
5	В	90	87	5:95	
1c CH(OMe) <sub>2</sub>	Α	300	97	83:17	
× /2	В	90	30°	50:50	
1d C(OMe) <sub>2</sub> CH <sub>3</sub>	Α	300	98	82:18	
( 72 5	В	90	61	11:89	
le C(OMe) <sub>2</sub> Ph	А	180	98	78:22	
× 72	В	90	84	0:100	

<sup>a</sup> A: LDA, THF-diisopropylamine (20 equiv.), -78°C; B: n-BuLi, THF, -78 to 0°C, then MeOH.

<sup>b</sup> Conversion and ratio were determined by <sup>1</sup>H NMR analysis of the crude mixture.

<sup>c</sup> Partial decomposition.