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Ortho Versus Adjacent-Benzylic Directed Lithiations of Substituted *N,N*-Diethylbenzamides

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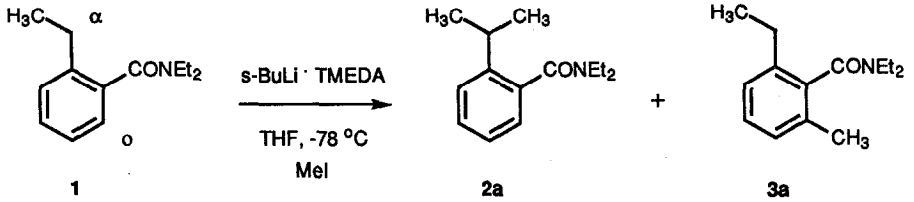
Abstract: Directed lithiation of substituted 2-*n*-alkyl *N,N*-diethylbenzamides gave mixtures of *ortho* and adjacent-benzylic alkylated products (2 and 3). The ratios of isolated products were dependent upon the substitution patterns of the benzene ring and on the reaction conditions. Substrates and reaction conditions that favor either *ortho* or adjacent-benzylic lithiation are presented.

The directed *ortho*-lithiation reaction of *N,N*-diethylbenzamides has found numerous synthetic uses. Benzamides with many different types of substitution patterns have been lithiated and the site of lithiation can usually be predicted.[2] In benzamides with a 2-methyl substituent, treatment with butyllithium is known to result in deprotonation at the more acidic, adjacent-benzylic (α) position and not at the *ortho*-proton at the 6-position. However, deprotonation is directed to the *ortho*-position when the 2-methyl group is first silyl protected (e.g., as 2-$CH(TMS)_2$). This strategy has been used in the synthesis of *peri*-methylanthraquinone natural products.[3] This result is consistent with earlier work which had shown that *N,N*-diethyl-2-isopropylbenzamide **2a** is lithiated exclusively at the *ortho*-proton.[4] The destabilizing steric interaction of the isopropyl methyl groups with the diethylamide in the formation of the benzylic anion transition state was proposed to favor *ortho*-lithiation over α-lithiation. These results showed that steric effects in the transition state of lithiated species can affect which site is lithiated. In this same report,[4] *N,N*-diethyl-2-isopropylbenzamide **2a** was prepared from *N,N*-diethyl-2-ethylbenzamide **1** in 55% yield. When **1** was treated with *s*-BuLi · TMEDA and quenched with MeOD, deuterium was reportedly incorporated only at the α-position, and none was detected at the *ortho*-position of the aromatic ring by ^{1}H-NMR.

This paper describes our study on the lithiation of **1** and other *N,N*-diethylbenzamides. We have shown that treatment of **1** with *s*-BuLi · TMEDA affords a mixture of *ortho*- and α-lithiated products where the α-substituted product predominates (e.g., **2a**). A rationale is discussed that accounts for the product ratios obtained in these systems.

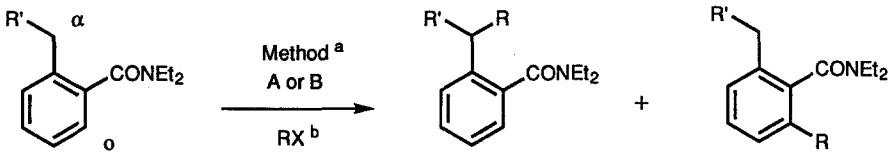


1 **2a** **3a**

We have used the *ortho*-lithiation reaction of *N,N*-diethylbenzamides as the key step in our novel method for the preparation of substituted benzisothiazolones.[5] During the course of this work, we found that the reaction of *N,N*-diethyl-2-ethylbenzamide **1**, under standard directed lithiation reaction conditions with *s*-BuLi ·

TMEDA (Method A), followed by methyl iodide results in an inseparable mixture of the isopropyl derivative **2a** and the 2,6-dialkyl derivative **3a** in contrast to the literature report (see Table 1, entry 1).[4] When the anion of **1** was quenched with trimethylsilyl chloride, the isomers **2c** and **3c** were obtained and separated by flash chromatography (entry 3). When substrate **4**, where the R' substituent is ethyl rather than methyl, was subjected to the same reaction conditions, the *ortho*-lithiated product **3d** predominated (entry 7). This change from methyl to the ethyl substituent lowered the α/o ratio *11 fold* (compare entries 5 and 7). These mixtures of **2** and **3** are formed under kinetic conditions and it is known that *ortho*-lithio benzamides do not equilibrate significantly under these conditions.[6]

Table 1. Ratio of α- to *ortho*-Lithiation Products (2/3).



1 R' = CH_3
4 R' = CH_2CH_3

2 **3**

entry	start. mat.	method	R' =	R =	% yield of 2	% yield of 3	α/o ratio
1	**1**	A	CH_3	CH_3	**2a** (69)[c]	**3a** (12)[c]	5.8
2	**1**	B	CH_3	CH_3	**2a** (50)[d]	**3a** (<5)[e]	>10
3	**1**	A	CH_3	TMS	**2c** (68)	**3c** (16)	4.3
4	**1**	B	CH_3	TMS	**2c** (80)	**3c** (<5)[e]	>16
5	**1**	A	CH_3	CH_2CH_3	**2b** (70)[c]	**3b** (11)[c]	6.4
6	**1**	B	CH_3	CH_2CH_3	**2b** (74)	**3b** (<5)[e]	>15
7	**4**	A	CH_2CH_3	CH_2CH_3	**2d** (31)	**3d** (55)	0.56
8	**4**	B	CH_2CH_3	CH_2CH_3	**2d** (76)	**3d** (<5)[e]	>15

[a] Method A: *s*-BuLi, TMEDA, THF, -78 °C, RX. Method B: LDA, THF,-78 °C, RX. [b] RX = MeI, EtI, or TMSCl. [c] Inseparable mixtures. Yields extrapolated from chromatographed yield of the mixture and ^{1}H-NMR. [d] The yield of **2a** was extrapolated from the yield of the inseparable mixture of **2a** (50%) and **1** (35%) using ^{1}H-NMR. [e] **3a-3d** were not detected by TLC or NMR. At worst there could be 5% of **3a-3d** present.

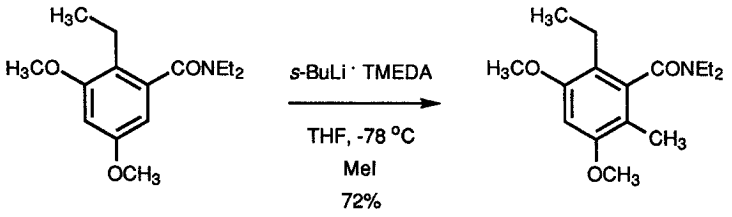
Both **1** and **4** have similar barriers to rotation around the carbonyl-aryl bond,[7] therefore, the results in entries 5 and 7 can not be explained based on the accessible conformations of the diethylamide group in **1** and **4**. We suggest that the terminal CH_3 of **4**, since **4** has an additional degree of freedom about the $ArCH_2$-CH_2 bond, causes an unfavorable steric interaction with *s*-BuLi, enough to slow the rate of α-lithiation. Also, A(1,3) type strain between the 3-H and R', may cause R' to lie out of plan.[8] This is supported by studies which show that the stable conformation of an ethyl or *n*-propyl group has the $ArCH_2$-CH_2 bond positioned orthogonal to the phenyl ring.[9] Since the barrier for $ArCH_2$-CH_2 bond rotation is probably low, then the terminal methyl group of **4** could cause a steric interaction with the amide, destabilizing the transition-state for α-lithiation. This would slow the rate of α-lithiation such that *ortho*-lithiation is competitive with α-lithiation in benzamide **4**.

The product ratios were independent of the alkylation agent since alkylation of the anion of **1** with either methyl iodide, ethyl iodide, or trimethylsilyl chloride gave similar α/o ratios (entries 1, 3, and 5). Switching to the thermodynamic and weaker base, LDA (Method B), resulted in exclusive α-deprotonation, and subsequent alkylation with methyl iodide, gave **2a** and no **3a** (entry 2). Quenching the anion of **1** that was formed with

LDA with trimethylsilyl chloride or ethyl iodide under the same conditions resulted in exclusive formation of **2c** or **2b** in high yield (entries 4 and 6). Under the same LDA conditions, alkylation of the anion of **4** with ethyl iodide gave only **2d** (entry 8). Therefore, LDA (Method B) gave only α-alkylated materials and provided a better route into the 2-branched-alkyl *N,N*-diethylbenzamides **2b-d**. The diisopropyl amide derivative of **1**, *N,N*-diisopropyl-2-ethylbenzamide, on treatment with *s*-BuLi in the absence of TMEDA has recently been reported to give products resulting in exclusive lithiation at the α-position.[10] This method could not be used with our diethylamides due to the competitive addition of *s*-BuLi to the amide.

The benzamide **1** on treatment with LDA followed by the addition of either trimethylsilyl chloride or ethyl iodide (entries 4 and 6) gave products resulting from exclusive α-deprotonation, while the use of methyl iodide always gave mixtures of starting material **1** and product **2a**[11] (entry 2). This result was obtained in repeated experiments. We propose that the deprotonation of **1** with LDA may not be complete and may be at equilibrium when the alkylating agent is added to the reaction. With trimethylsilyl chloride and ethyl iodide these alkylating agents are stable to LDA and only react with the anion of **1** as it is formed during the course of the reaction. LDA is known undergo only minimal reaction with trimethylsilyl chloride and has been used in the in situ quenching method for the controlled formation of silyl enol ethers.[12] We suggest that methyl iodide competitively reacts with the anion of **1** and with LDA leading to a mixture of **1** and **2a**.

The lithiation of 2-isopropyl-*N,N*-diethylbenzamide **2a** with *s*-BuLi · TMEDA gives only the *ortho*-substituted product in good yield.[4,13] In this case, the sterically hindered 2-isopropyl group of **2a** has an increased barrier of rotation compared to the 2-ethyl group of **1**[7] which suggests that steric congestion between the 2-isopropyl group and the amide group precludes the formation of the transition-state leading to α-lithiation, and therefore exclusive *ortho*-lithiation results.



5 **6**

Substituents at the 3- and 5-position of the phenyl ring showed a striking affect on the resulting product distribution. Although small changes in the location of the amide oxygen may effect the rate of the directed lithiation, steric effects of the group directly attached to the benzylic carbon also play an important role. In comparison to compound **1**, some α-lithiation for compound **5** could have been expected, however, when **5** was subjected to method A only the *ortho*-alkylated product **6** was obtained and none of the α-lithiation product was detected. When compound **5** was subjected to method B, no deprotonation occurred, and only starting material was recovered. The inaccessibility of the α-proton could be explained by steric hindrance due to a buttressing effect and the high energy barrier for amide bond rotation.[7] The buttressing effect of the 3-methoxy group on the 2-ethyl may destabilize the conformations where the C-H bonds are orthogonal to the phenyl ring. Also, the high energy barrier for amide bond rotation precludes the conformation of the amide that is necessary for complexation with *s*-BuLi to deprotonate the α-position, thus only *ortho*-lithiation occurs.

The higher C-C rotation barrier of **2a** and **5** compared to **1** and **4**, shows that a significant steric interaction occurs between the 2-alkyl substituent and the carbonyl group. This steric interaction in **2a** and **5** must prevent the 2-alkyl from adopting the conformation necessary for α-deprotonation, therefore, the reaction occurs with *ortho*-deprotonation.[4] A subtle steric effect by the 2-*n*-propyl substituent in **4** accounts for the kinetic formation

of the *ortho*-lithiated product **3d**, while the 2-ethyl benzamide **1** lithiates at the α-position to give **2a** as the major product. This steric effect is less in magnitude compared to the steric effect in **2a** and **5**, since treatment of **4** with LDA at -78 °C gives α-lithiation, while **5** does not react with LDA even at room temperature.

***Method A*: Preparation of 2d and 3d.** To a solution of *sec*-butyllithium (4.2 mL, 5.5 mmol of a 1.3 M solution in cyclohexane) and *N,N,N',N'*-tetramethylethylenediamine (0.85 mL, 5.6 mmol) in 35 mL of tetrahydrofuran at -78 °C and under nitrogen was added dropwise over 15 min a solution of 2-*n*-propyl-*N,N*-diethylbenzamide **4** (1.10 g, 5.0 mmol) in 15 mL of tetrahydrofuran. After stirring for 20 min at -78 °C, a solution of ethyl iodide (0.80 mL, 10 mmol) in 5 mL of tetrahydrofuran was added dropwise over 5 min and stirred at -78 °C for 50 min. The reaction was quenched at -78 °C by adding 15 mL of saturated ammonium chloride, allowed to come to room temperature, and extracted with diethyl ether, and purified by flash chromatography (SiO_2, 10% ethyl acetate-hexanes) to give 0.38 g (31%) of **2d**[15] and 0.68 g (55%) of **3d**[16] as colorless oils. ***Method B*. Preparation of 2d.** To a solution of *N,N*-diisopropylamine (0.83 mL, 6.25 mmol) in 20 mL of tetrahydrofuran at -78 °C and under nitrogen as added *n*-butyllithium (2.6 mL, 6.0 mmol of a 2.3 M solution in cyclohexane). After stirring for 30 min at -78 °C, a solution of 2-*n*-propyl-*N,N*-diethylbenzamide **4** (1.10 g, 5.0 mmol) in 5 mL of tetrahydrofuran was added dropwise over 5 min, then the reaction mixture was allowed to come to room temperature over 60 min. After cooling to 0 °C, ethyl iodide (0.80 mL, 10 mmol) was added quickly, then was allowed to come to room temperature over 1 h. The reaction was quenched by adding 15 mL of saturated ammonium chloride, extracted with diethyl ether, and purified by flash chromatography (SiO_2, 20% ethyl acetate-hexanes) to give 0.94 g (76%) of **2d**[15] as a colorless oil.

References and Notes

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7. Activation Energies for Bond Rotation Determined by NMR Methods.[14] Compound, α/o ratio, $\Delta E^{\dagger}_{C\text{-}C}$: **1**, 5.8, 14.4 kcal/mol; **4**, 0.56, 14.3 kcal/mol; **2a**, < 0.05, 15.6 kcal/mol; **5**, < 0.07, 15.6 kcal/mol.
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14. Unpublished results. Private communicaton from P. Mark Henrichs, Laszlo L. Musza, and Charles A. Rodger of Sterling Winthrop Inc.
15. **2d** : ^{1}H NMR ($CDCl_3$) δ 0.70 (overlapping t, 6H), 1.05 (t, 3H), 1.22 (t, 3H), 1.61 (m, 4H), 2.49 (m, 1H), 3.14 (cm, 3H), 3.87 (m, 1H), 7.24 (cm, 4H). Anal. calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.69; H, 10.27; N, 5.64.
16. **3d** : ^{1}H NMR ($CDCl_3$) δ 0.96 (t) and 1.01 (t)(6H), 1.21 (t) and 1.26 (t)(6H), 1.64 (cm, 2H), 2.50 (cm, 4H), 3.08 (q, 2H), 3.62 (m, 2H), 7.08 (m, 2H), 7.22 (m, 1H). Anal. calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.71; H, 10.26; N, 5.61.

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