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# Competitive Ortho Metalation Effects: The Kinetic and Thermodynamic Lithiation of 3-(*tert*-Butoxycarbonyl)amino-4-carbomethoxythiophene

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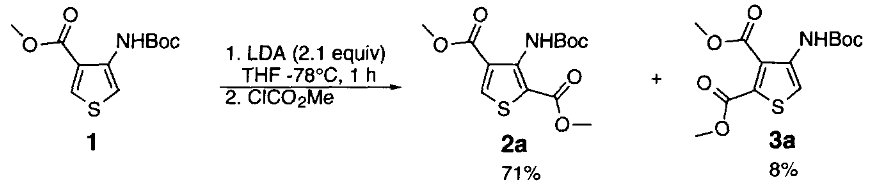
**Abstract:** Deprotonation of the thiophene **1** under kinetically controlled conditions with LDA takes place next to the NHBoc group and under thermodynamic conditions next to the methyl ester. N-Methylation leads to exclusive lithiation next to the ester. The methyl ester was found to be superior to the diethylamide in facilitating lithiation. © 1997 Elsevier Science Ltd.

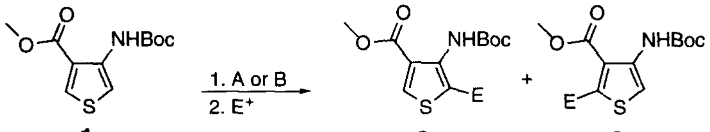
The propensity for the thiophene ring to undergo metalation α to sulfur with strong bases like n-BuLi or LDA is a well-known phenomenon.[1] The regioselectivity of this metalation on a 3-substituted thiophene has been shown to be dependent upon the nature of the 3-substituent.[1,2] As part of a synthetic program aimed at the preparation of substituted thiophenes, we recently had the opportunity to investigate the course of metalation of the thiophene **1**,[3,4] where deprotonation could in principle take place at either α position. Although the t-Boc-amino moiety is a well-known ortho-directing group,[5] the simple methyl ester has not been widely utilized due to its high reactivity toward the common metalating reagents. Under metalation conditions where the ester functionality is not subject to nucleophilic attack, however, it has proven to be an efficient ortho-directing group.[6]

Addition of thiophene **1** to a solution of LDA (2.1 equiv) at -78°C followed by stirring for 1 h, then addition of $ClCO_2Me$, reaction for 30 min and quenching at -78° with aqueous $NaHCO_3$ led to the formation of the adduct **2a** in 71% yield (eq 1). Also isolated in 8% yield was the minor isomer **3a**.[7] No products derived from attack of the methyl ester were isolated. In an effort to determine whether the preferential metalation next to the NHBoc was the result of kinetic or thermodynamic control, the dianion was allowed to warm to -30° for 20 min prior to treatment with $ClCO_2Me$ and quenching with $NaHCO_3$. Interestingly, under these conditions the mixture obtained in 26% yield now favored **3a** over **2a** by 4.5:1, indicating that the initial deprotonation next to the NHBoc group was indeed kinetically controlled.[8,9] Remarkably, increasing the reaction concentration from 0.12 M to 0.24 M followed by equilibration as above resulted in an improvement in the yield of **3a** to 74% with **2a** being formed to the extent of only 5%. Evidently the kinetic dianion is susceptible to a unimolecular decomposition in the absence of a sufficiently rapid equilibration to the thermodynamically more stable dianion. In order to ascertain if the ratio obtained in eq 1 reflected some level of concentration dependent equilibration at -78° this experiment was repeated at 0.06 M. No change in the ratio of **2a** to **3a** however was observed, suggesting that this is the intrinsic kinetic ratio of deprotonation with LDA.



eq 1

To demonstrate the synthetic utility of these regiocontrolled metalations in the preparation of substituted thiophenes, several additional electrophiles were reacted under kinetic and thermodynamic control (Table 1). In general, the yields and selectivities were comparable to those observed with $ClCO_2Me$. The best overall yields were realized when the reactions were quenched at -78° with aqueous $NaHCO_3$. For example, for entries 4, 6 and 7 yields of only 53%, 37% and 36% were obtained for the major product upon warming to RT prior to $NaHCO_3$ quench. In most cases the kinetic and thermodynamic products were readily separable by column chromatography.



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

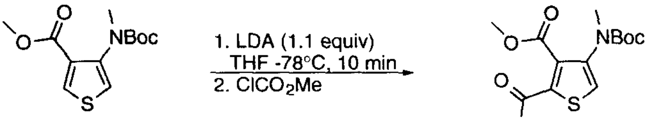
A: *kinetic lithiation*; 2.1 equiv LDA, -78°, 1 h, 0.12 M in THF
B: *thermodynamic lithiation*; 2.1 equiv LDA, -30°, 20 min, 0.24 M in THF

**Table 1**

| Entry | Method | $E^{+a}$ | Time | E | $2^b$ | $3^b$ |
|---|---|---|---|---|---|---|
| 1 | A | $ClCO_2Me$ | 30 min | $CO_2Me$ | 71 | 8 |
| 2 | B | $ClCO_2Me$ | 30 min[c] | $CO_2Me$ | 5 | 74 |
| 3 | A | MeI | 2 h | Me | 71[d] | 7[d] |
| 4 | B | MeI | 2 h | Me | 11[d] | 70[d] |
| 5 | A | TMSCl[e] | 30 min[c] | TMS | 64 | 10 |
| 6 | B | TMSCl | 5 min | TMS | 0 | 46(56) |
| 7 | A | $HCO_2Me$ | 1 h | CHO | 60 | 0 |
| 8 | B | $HCO_2Me$ | 30 min | CHO | 0 | 24[f] |
| 9 | B | DMF | 90 min | CHO | 10(14) | 43(61) |

a. 1.1 Equiv electrophile added at -78°, reaction allowed to proceed for the indicated time and quenched at -78° with aqueous $NaHCO_3$ unless otherwise indicated. b. Percent yield after flash chromatogaphy given; numbers in parentheses based upon recovered starting material. c. Reaction allowed to warm to rt before $NaHCO_3$ quench. d. Ratio by $^1H$ NMR of mixture after chromatography. e. 2.1 equiv TMSCl. f. The formyl group of the product reacted with the dianion to give 35% dimer.

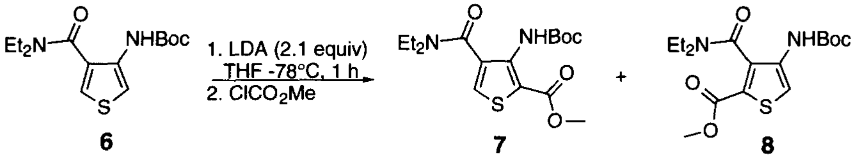
Intrigued by the kinetic preference for deprotonation adjacent to the NHBoc, we decided to probe the importance of the initially formed monoanion in directing the ring metalation. To this end **1** was N-methylated with NaH/MeI.[10] The N-Me compound **4** was added to LDA (1.1 equiv) in THF at 0.12 M for 10 min at -78°C, then reacted



**4** **5** eq 2

with $ClCO_2Me$ as before to provide in 38% yield[11] as the sole product **5**, resulting from metalation next to the methyl ester. Although the formation of this product does not rule out the possilbility of a kinetic deprotonation next to the NMeBoc followed by a rapid equilibration, it does at least point out the importance of the NHBoc in directing metalation with LDA and stabilizing the adjacent anion.

In order to compare the regioselectivity of deprotonation using LDA versus an alkyllithium, the ester **2** was converted to the diethylamide **6**.[12,13] Subjection of **6** to metalation with LDA according to the conditions of eq 1 gave a



eq 3

59% yield of **7** and **8** in a 20:1 ratio (eq 3) by $^1$H NMR, indicating that once again preferential metalation had taken place adjacent to the NHBoc. Interestingly, warming the reaction to -30°C for 20 min prior to quenching with $ClCO_2Me$ failed to isomerize the dianion as in the case of the ester **1** but rather resulted in only a small erosion in the ratio of **7**:**8** to 10:1. The failure of the amide to facilitate isomerization as seen with the ester may be attributable to an unfavorable steric interaction of the bulkier amide with the lithiated NBoc group, preventing the amide from adopting the proper orientation to stabilize the ortho-anion. By contrast, addition of s-BuLi (2.1 equiv) to a solution of **6** in THF at -78°C, followed by reaction with $ClCO_2Me$ after 5 min and quenching as before gave a nearly statistical mixture of products consisting of 18% each of **7** and **8** plus 19% recovered **6** and 16% dicarbomethoxylated product. The different ratios of products obtained with LDA versus s-BuLi illustrate how the pK of and nature of the base may greatly influence the regioselectivity of the directed metalation reaction.

In summary, conditions have been identified that permit the regioselective lithiation of **1** at either the 2 or 5 position. Reaction of the dianions with electrophiles leads to the selective formation of various substituted thiophenes. The successful metalation adjacent to the ester is of significant interest given the versatility of this functionality in subsequent transformations relative to typical directing groups. It is presently unknown if the mechanism of isomerization from the kinetic to the thermodynamic dianion of **1** is a simple bimolecular process or whether the presence of diisopropylamine or the slight excess of LDA play a role in mediating the equilibration.

## Experimental

*Method A. Standard conditions for kinetic dianion formation.* To a solution of LDA (2.1 equiv) in THF (1 mL) at -78°C under $N_2$ was added dropwise a solution of **1** (58.0 mg, 0.226 mmol) in THF (1 mL). After 1 h at -78°, $ClCO_2Me$ (20 μL, 1.1 equiv) was added to the bright yellow reaction mixture, stirred 30 min and quenched with saturated $NaHCO_3$ solution. After warming to room temperature, the reaction was poured into aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3x). The organics were dried ($Na_2SO_4$), filtered, solvent evaporated, and flash chromatographed (5:1 hexane/ethyl acetate) to give 50.6 mg (71%) **2a** and 6.0 mg (8%) **3a**.

*Method B. Standard conditions for thermodynamic dianion formation.* To a solution of LDA (2.1 equiv) in THF (1 mL) at -78°C under $N_2$ was added slowly a solution of **1** (124.4 mg, 0.484 mmol) in THF (1 mL). The reaction was warmed to -30°C for 20 min, during which time the reaction color changed from yellow to amber. The mixture was cooled back to -78°C, treated with $ClCO_2Me$, stirred 30 min, allowed to warm to room temperature, quenched in saturated $NaHCO_3$ and extracted with $CH_2Cl_2$ (3x). The organics were dried ($Na_2SO_4$), filtered, solvent evaporated and flash chromatographed (4:1 hexane/ethyl acetate) to provide 112.4 mg (74%) **3a** and 7.9 mg (5%) **2a**.

## Acknowledgements

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3. The thiophene **1**[4] was obtained from 3-amino-4-carbomethoxythiophene[14] by formylation with acetic formic anhydride, reaction with $Boc_2O$ (2 equiv)/DMAP (0.1 equiv) in $CH_3CN$,[15] followed by cleavage of the formyl group with NaOMe/MeOH.[16]
4. $^1H$ NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 3.89 (s, 3H), 7.60 (br s, 1H, $C_2$-H), 8.01 (d, J=3.7 Hz, 1H, $C_5$-H), 9.11 (br s, 1H, NH). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.3, 51.8, 80.4, 107.3 ($C_2$), 121.2 ($C_4$), 132.4 ($C_5$), 137.2 ($C_3$), 152.9, 164.2.
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7. The structures for **2a** and **3a** were assigned by ROESY experiments that showed an NOE between the lone aromatic proton and the NH for **3a** but not for **2a**. In agreement was the observation of a strong 3-bond C-H coupling (PFG-HMBC) between the aromatic proton and an ester carbonyl for **2a** but not for **3a** where much weaker 4-bond w-couplings were observed between the proton and the ester carbonyls. Also, quenching the dianion formed under the conditions of eq. 1 with excess MeOD led to 60% deuterium incorporation at the 2 position. Incomplete deuterium incorporation with the use of LDA has been reported previously: Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.
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10. Compound **4** was obtained in only 15% yield due to an apparent competing methylation of the sulfur of the thiophene.
11. Since unreacted **4** was not recovered from this reaction, the low yield of **5** appears to be due to decomposition.
12. Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
13. The diethylamide **6** was obtained from **1** via hydrolysis with LiOH (2 equiv) in 2:1 THF/$H_2O$ followed by an EDCI/HOBt mediated coupling of the acid with $Et_2NH$.
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