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# AROMATIC HETEROANNULATION VIA *ORTHO* LITHIATION-CYCLIZATION OF N-ACYL-2-BROMOBENZAMIDES

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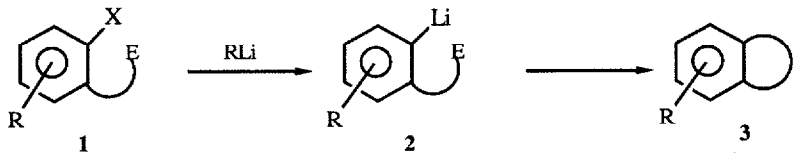
**Summary**: N-acyl-2-bromobenzamides participate in metal-halogen exchange with *n*-BuLi to form N-acyl-2-lithiobenzamides, which undergo cyclization to afford 3-alkylidenephthalimidines.

The pioneering work of Parham[1] first demonstrated that certain *ortho*- substituted aryllithuim reagents **2** can undergo cyclization to afford products **3** in what may be viewed as an anionic equivalent of the more common Lewis acid-catalyzed protocol for aromatic annulation. Such cyclizations can have a decided advantage over their



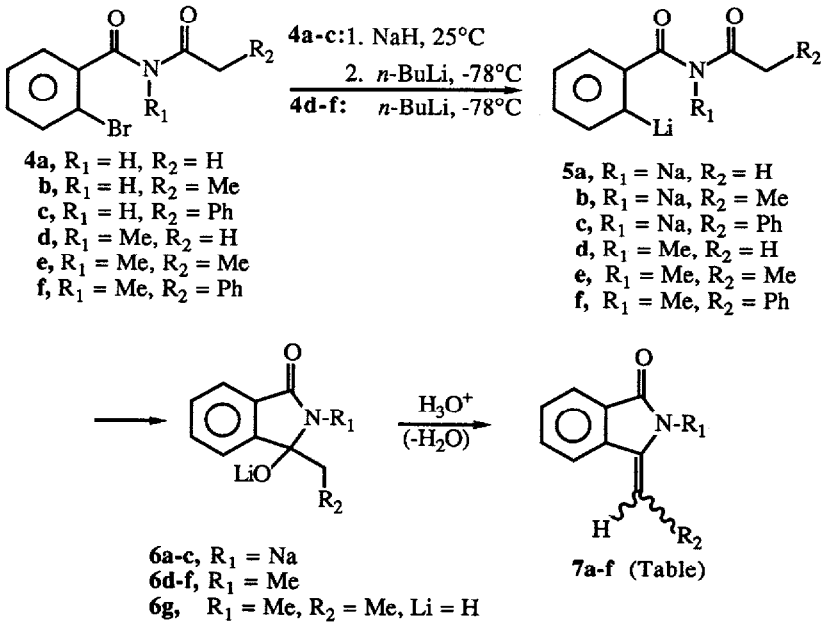

**1** **2** **3**

acid-catalyzed counterparts in that they afford products resulting from regiospecific reaction of the side chain electrophilic function E at the position originally occupied by halogen (X) in precursors **1**. In order for these reactions to be synthetically useful, E must remain passive during formation of lithio intermediates **2**, but eventually exhibit sufficient reactivity to participate in the annulation process. To date, bromo,[2] carboxyl,[3] N,N-dialkylcarboxamide,[3a] epoxide,[4] and aldimino[5] groups have been found to satisfy these criteria.

We now wish to report a new example of a Parham-type cyclization in which the N-acyl groups of N-acyl-2-bromobenzamides **4a-f** tolerate metal-halogen exchange when the imide nitrogen is either deprotonated by NaH or carries an alkyl substituent. The resulting *ortho*- lithio intermediates **5a-f** then undergo cyclization to yield 3-alkylidenephthalimidines **7a-f**. These reactions represent novel examples of the use of such cylizations for the syntheses of benzo-fused nitrogen heterocycles[5,6] and provide a convenient new method for the preparation of the phthalimidine ring system.[5,6a,7]

When N-acyl-2-bromobenzamides **4a-c**[8] were treated with *n*-BuLi (2.2-3.0 equiv) at -78°C for 2h, phthalimidines **7a-b** were obtained in low (<10%) yields, and **7c** could not be detected in the crude product mixture derived from **4c**. All of these reactions resulted in formation of 2-bromobenzamide as the major product. However, when the acidic imide hydrogen of **4a-c** was removed by prior treatment of these substrates (2 mmol) with NaH (2 mmol) in THF (40 ml) at 25°C, followed by addition of *n*-BuLi (2.1 mmol) at -78°C, 3-alkylidenephthalimidines **7a-c** were isolated in good yields upon quenching the reaction mixtures with 10% aqueous HCl after 2h at -78°C (Table). These reactions apparently proceed by formation and cyclization of dianions

**5a-c** to form alkoxide intermediates **6a-c**, which undergo subsequent protonation and dehydration during acid workup. Initial removal of the imide proton of **4a-c** with NaH presumably reduces the acidity of the α hydrogens of the N-acyl moiety to the extent that metal-halogen exchange by means of *n*-BuLi competes effectively with α deprotonation and/or cleavage of the N-acyl group. However, the N-acyl carbonyl function of deprotonated imides **5a-c** is still sufficiently electrophilic to participate in cyclization.[9] Isolation of N-(phenylacetyl) benzamide (42%) along with phthalimidine **7c** (43%) from the reaction of **4c** with NaH/*n*-BuLi is indicative of initial conversion of **4c** to N, *ortho*-dialkali derivative **5c** followed by divergent reaction pathways involving cyclization and proton-metal exchange. This premise is supported by the observation that, when the reaction mixture was quenched with $DCl/D_2O$, the resulting N-(phenylacetyl)benzamide contained only benzylic deuterium with no deuterium at the *ortho* position.




**4a**, $R_1$ = H, $R_2$ = H
**b**, $R_1$ = H, $R_2$ = Me
**c**, $R_1$ = H, $R_2$ = Ph
**d**, $R_1$ = Me, $R_2$ = H
**e**, $R_1$ = Me, $R_2$ = Me
**f**, $R_1$ = Me, $R_2$ = Ph

**5a**, $R_1$ = Na, $R_2$ = H
**b**, $R_1$ = Na, $R_2$ = Me
**c**, $R_1$ = Na, $R_2$ = Ph
**d**, $R_1$ = Me, $R_2$ = H
**e**, $R_1$ = Me, $R_2$ = Me
**f**, $R_1$ = Me, $R_2$ = Ph

**6a-c**, $R_1$ = Na
**6d-f**, $R_1$ = Me
**6g**, $R_1$ = Me, $R_2$ = Me, Li = H

**7a-f** (Table)

Although it was necessary to deprotonate **4a-c** with NaH prior to treatment with *n*-BuLi, direct treatment of N-methyl imides **4d-f**[10] (2 mmol) with 2 mmol of *n*-BuLi in 40 ml of THF for 2h at -78°C gave, after quenching with HCl, N-methyl-3-alkylidenephthalimidines **7d-f** in good yields (Table). We also discovered that when the reaction mixture obtained from treatment of N-methyl-N-propionyl-2-bromobenzamide (**4e**) with *n*-BuLi was quenched with saturated aqueous $NH_4Cl$ rather than HCl, 3-ethyl-3-hydroxy-2-methylphthalimidine (**6g**)[11,7c] was isolated in 62% yield. This observation implicates **6a-f** as intermediates in the overall cyclization process.

Table. 3-Alkylidenephthalimidines from **4a-f**

| Starting Material | Product No. | $R_1$ | $R_2$ | Yield, % | E/Z | mp,°C | Ref. |
|---|---|---|---|---|---|---|---|
| **4a** | **7a** | H | H | 80 | -- | -- | 12 |
| **4b** | **7b** | H | Me | 89 | Z | 209-210 | 7c,13 |
| **4c** | **7c** | H | Ph | 43 | Z | 178-181 | 7d,13 |
| **4d** | **7d** | Me | H | 91 | -- | -- | 14,17 |
| **4e** | **7e** | Me | Me | 93 | E | 76-78 | 7c,13,15,17 |
| **4f** | **7f** | Me | Ph | 65 | E | 126-128 | 7d,13,16,17 |

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**SUPPLEMENTARY MATERIALS AVAILABLE**: Detailed experimental procedures for the preparation of compounds **4a-f**, **6g**, and **7a-f**, as well as spectral and analytical data for these compounds may be obtained from the authors.

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5. Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 327. The procedure described herein, which gives modest yields of 1-phenyl-1,2,3,4-tetrahydroisoquinolines, appears to be the only published report of the use of an intramolecular ("direct")[1] Parham-type cyclization for the syntheses of benzo-fused nitrogen heterocycles. The procedures reported in refs. 2 and 4a-c have been used to prepare benzofurans, benzopyrans and benzoxepins, respectively.
6. For examples of the use of intermediates of type **2** in intermolecular ("indirect")[1] syntheses of benzo-fused nitrogen heterocycles including phthalimidines see: refs. 3,5 and (a) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184; (b) Parham, W. E.; Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.*

**1978**, *43*, 1606; (c) Hergrueter, C. A.; Brewer, P.D.; Tagat, J.; Helquist, P. *Tetrahedron Lett.* **1977**, 4145 .

7. For traditional syntheses of phthalimidines, see: (a) White, J. D.; Mann, M. E. *Adv. Heterocycl. Chem.* **1969**, *10*, 113 and references cited therein. For specific preparations of 3-alkylidenephthalimidines, see: (b) Perjessy, A; Lacova, M; Hrnciar, P. *Coll. Czechoslov. Chem. Commun.* **1971**,*36*, 2775; (c) Ang, W. S.; Halton, B. *Aust. J. Chem.* **1971**,*24*, 851; (d) Marsili, A; Scartoni, V. *Gazz. Chim. Ital.* **1972**, *102*, 806.
8. Prepared by treatment of 2-bromobenzamide (50 mmol) with 0.11 mol of NaH in 250 ml of THF at 25°C for 1h followed by addition of 55 mmol of the appropriate acid chloride at -78°C and then allowing the reaction mixture to come to 25°C over a period of 4h. Compounds **4a** (mp 86-87° C), **4b** (mp 90-91°) and **4c** (mp 145-146°C) were crystallized from ether-hexane and had elemental analyses, mass spectra, and $^1$H NMR data consistent with the assigned structures.
9. In contrast to **5a-c**, the N,*ortho*-dilithio salt of phenylpropionamide fails to undergo cyclization.[3a] Recently it has been reported that dialkali derivatives analogous to **5a-c**, prepared from the Boc derivative of 2-bromodopamine dimethyl ether by successive treatment with KH and *n*-BuLi, do not undergo cyclization. See: Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.
10. These compounds, all of which were colorless oils, were prepared by methylation of **4a-c** according to the procedure of Pachter, I. J.; Kloetzel, M. C. *J.Am. Chem. Soc.* **1952**, *74*, 1321, and had elemental analyses, mass spectra and $^1$H NMR spectra consistent with the assigned structures.
11. 3-Ethyl-3-hydroxy-2-methylphthalimide (**6a**) was identical with an authentic sample prepared by the method of Ang and Halton[7c] and, although there was a discrepancy between our melting point (88-90°C) and that reported (141-142°),[7c] spectral data confirm its structure; $^1$H NMR (270 MHz, $CDCl_3$) δ0.35 (t, 3H, $CH_3$ of $C_2H_5$), 2.00 (m, 2H, $CH_2$), 2.60 (s, 3H, $NCH_3$), 4.69 (s, 1H, OH), 7.27-7.52 (m, 4H, Ar); MS, m/e (relative intensity) 173 ($M^+$ - 18, 100), 158 (40), 144 (70), 131 (35).
12. Compound **7a** was isolated as an unstable, colorless oil by flash chromatography; $^1$H NMR (90 $MH_z$, $CDCl_3$) δ 4.8 (d, 1H, =CH), 5.12 (d, 1H, =CH), 7.00-7.8 (m, 4H, Ar), 9.25 (br s, 1H, NH); MS, m/e (relative intensity) 145 ($M^+$, 100), 144 (5), 117 (22), 116 (17), 104 (40), 103 (16), 77 (17), 76 (22).
13. Stereochemical assignments are based on comparison of $^1$H NMR data with that reported in refs. 7c and 7d.
14. An earlier report [7c] of this compound gave only ir data. We were able to isolate **7d** as a colorless oil which was stable at ambient temperatures for several weeks when stored under a nitrogen atmosphere. Satisfactory combustion analysis, as well as $^1$H NMR and mass spectral data were obtained for **7d**.
15. Ang and Halton[7c] report mp 71-73°C for the E isomer of **7e**. The $^1$H NMR spectrum is consistent with that of the E isomer as assigned by these authors.
16. Marsili and Scartoni[7d] report mp 116-118°C for the E isomer of **7f**. The $^1$H NMR spectrum is consistent with that of the E isomer as assigned by these authors.
17. N-Methyl-2-bromobenzamide was obtained as a minor (ca 15%) product of the reaction indicating that, although metal-halogen exchange and subsequent cyclization predominate, some acyl cleavage does occur.

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