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New reactions of hydrazides. Part 1: Directed *ortho-* and lateral metalation of aromatic carbocyclic and heterocyclic systems

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Abstract

Aromatic and heterocyclic 2,2-dialkylhydrazides undergo directed metalation with 2 equivalents of n-, s- or t-BuLi, and the resulting C,N-dilithio species react with a variety of electrophiles. The products may be readily converted to the corresponding carboxylic acids or esters by oxidation with manganese dioxide in water or methanol containing acetic acid. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The directed *ortho*-metalation (DoM) of carboxamides and carbamates¹ is a versatile method for appending a wide range of substituents onto the aromatic nucleus. When an aldehyde is used to quench an *ortho*-lithiated *sec*- or *tert*-amide, subsequent acid treatment results in intramolecular expulsion of the amine to generate a phthalide. However, if no participating group is available, conversion of the amide to the carboxylic acid is frequently very difficult. A recent case that we encountered exemplifies this problem: although 2-methoxy-N-methylbenzamide 1 was readily dilithiated² and converted to the 6-ethyl compound 2, base hydrolysis of this substance failed up to the point of corrosion of the glass vessel, and strong acid treatment gave demethylation to 3, followed by decomposition. Seeking a more easily cleaved amide, we noted a study by Barton and co-workers,³ which showed that a variety of acylhydrazines 4, where $R^1-R^3=H$ or primary or secondary alkyl, could be oxidized in a mildly acidic, aqueous medium to afford the acids, RCO₂H, with the concomitant conversion of the alkyl groups to the corresponding carbonyl compounds. These mild deprotection conditions suggested that we should examine the metalation of *N*-alkylated aryl hydrazides; no previous report describing the use of these compounds in DoM processes has appeared, although the related *N*-methoxyamide group (used as a CONH₂ equivalent) is known to direct lithiation processes.⁴



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Notes:

- a: After metalation, the electrophile was added, the mixture stirred without cooling for discharge of the yellow colour, and the reaction worked up in aq. sodium bicarbonate ethyl acetate.
- b: Isolated yield of chromatographically purified product from a 2-10 mmol scale run. All new
- compounds gave satisfactory elemental analyses and/or high-resolution mass spectra. c: >90% conversion to crude products. Pure 11 crystallized from dichloromethane.
- **d:** Only the cyclic carbinolamine form was present in solution.

In this paper, we report that the -CONHN(alkyl)₂ group is a highly effective director of *ortho*- and lateral metalation, and that the products resulting from subsequent addition of an electrophile may be readily converted to the corresponding acids and esters. We also note that the same group can direct *ortho*-diplacements.

When *sec*-butyllithium (2.1-2.2 equiv.) was added to a solution (0.15-0.2 M in anhydrous THF) of a dimethylhydrazide⁵ 5 or 6, a yellow C,N-dilithio species formed (10 min at -70°C for 5 and at 0-10°C for 6). Addition of a range of carbon- or heteroatom-centered electrophiles then afforded good to excellent yields of products, shown in Table 1.

Typical reactions of the introduced functional groups were not affected by the hydrazide moiety. For example, the boronic acid (11) was cleanly oxidized⁶ (H₂O₂, THF-H₂O, Na₂CO₃, 1 h at 10°C) to the salicyl hydrazide (14), and also participated in a Suzuki coupling⁷ (2 equiv. 4-FC₆H₄I, 0.07 equiv. Cl₂Pd(dppf), Na₂CO₃, THF-H₂O, reflux, 3 days) to afford 15 (42% overall without purifying the intermediate boronic acid).



The scope of the reaction was explored with other substrates, using chlorotrimethylsilane as the

standard electrophile after metalating with 2.2 equiv. of *sec*-butyllithium at -70° C. The 4-fluorobenzoyl compound 16 produced 82% of 17 with only 4% of 18, from metalation *ortho* to fluorine, and the *meta*-toluoyl hydrazide 19 yielded a readily separable 3:1 mixture of 20 and 21. This behavior is analogous to that reported for *meta*-toluamides.¹ Lateral metalation was also facilitated by the -CONHNMe₂ group: treatment of 22 with *n*-butyllithium (2.1 equiv. at 10°C) gave a deep red dilithio species, which afforded 23 as the sole product after reaction with iodomethane. For a heterocyclic example, we prepared the 2-furoic acid derivative 24 (the piperidine derivative was chosen to reduce water solubility) and found that some control of the site of metalation was possible. Reaction with 2.1 equiv. of *tert*-butyllithium at -70° C followed by quenching with chlorotrimethylsilane gave 63% of the 3-silylated compound 25 with smaller amounts of 26 and 27. With 2.1 equiv. of *n*-butyllithium at 10°C the 5-silyl compound 26 was obtained in high yield, as a consequence of the equilibration of intermediates to the thermodynamically more stable 5-lithio species. 2-Furoic acid and a derived oxazoline have been regioselectively metalated.⁸

We also noticed an interesting side-reaction during the metalation of the 2-methoxy compound 28. Under standard conditions (2.2 equiv. *sec*-BuLi, -70° C; C₂H₅I), 50–60% of the desired product 29 was obtained, plus starting material and 10% of a new product, which proved to be the 2-*sec*-butyl compound 30. This latter substance is presumably formed by a directed displacement⁹ of the methoxy group, in a manner reminiscent of oxazoline and aldimine chemistry.¹⁰ When excess *sec*-butyllithium was added to 28 at 20°C, followed by a water quench, 30 was obtained in a respectable 63% yield.



Model studies with moderately hindered 1-(2-methylbenzoyl)-2,2-dimethylhydazine established that the oxidative cleavage was most conveniently carried out with activated manganese dioxide (10–15 equiv.) over 1–2 h at 25°C in 60% aqueous acetic acid, producing 2-methylbenzoic acid in 85–90% yield. The more hindered compound **29** required 24 h at 25°C or 4–6 h at 50–60°C, and gave the corresponding acid **31** in 62% yield. On a small scale, it may sometimes be more convenient to proceed through the ester to facilitate purification, and we found that oxidation of **29** in 4:1 methanol:acetic acid (6 h at 50–60°C) gave 75% of the ester **32**. Oxidation with intramolecular trapping was also facile from appropriate substrates: benzaldehyde adduct **13**, upon treatment with manganese dioxide in CH₂Cl₂–HOAc at 25°C, afforded the phthalide **33** in quantitative yield.

In conclusion, we have shown that -CONHNR₂ groups are powerful directors of *ortho*- and lateral lithiation,¹¹ and that the products may be easily converted to the corresponding acids and esters. We continue to explore the utility of this and related groups in directed metalation and substitution processes, and also the extension of this chemistry to non-aromatic compounds and sulfonylhydrazines.

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Preliminary experiments indicate that N-methoxyamides can also induce ortho-methoxy displacement, and this and related reactions are currently being investigated in our laboratories.

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- 11. Representative experimental for 1-[2-(1-hydroxy-1-phenylmethyl)-4-(1,1-dimethylethyl)benzoyl]-2,2-dimethylhydrazine 13: A solution of 6 (6 mmol; 1.32 g) in dry tetrahydrofuran (30 mL) under nitrogen was cooled in ice, and *sec*-butyllithium (1.3 M in cyclohexanes; 11.0 mL) was added over 1 min. After stirring for a further 5 min, benzaldehyde (1.0 mL) was added, resulting in a discharge of a yellow color. The reaction was worked up in 10% aqueous sodium chloride, extracted twice with ethyl acetate, and the extracts dried over magnesium sulfate, evaporated and pumped under high vacuum for 20 h. The residue was crystallized from ether-hexanes to give a first crop weighing 1.49 g (76%). Mp: 139–141°C. Anal. found: C, 73.63; H, 8.09; N, 8.68%. C₂₀H₂₆N₂O₂ requires: C, 73.62; H, 7.98; N, 8.59%. By chromatographing the mother liquors, an additional 7% of pure product could be isolated.