

**DILITHIATED SYNTHONS OF TERTIARY BENZAMIDES,
PHTHALAMIDES, AND O,O'-ARYL DICARBAMATES**

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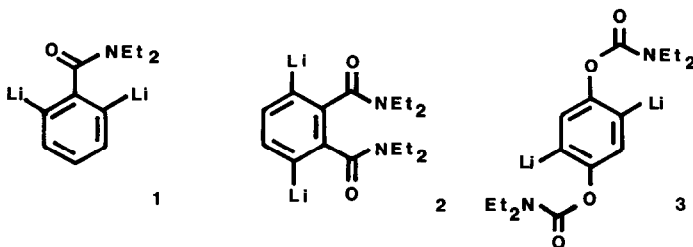
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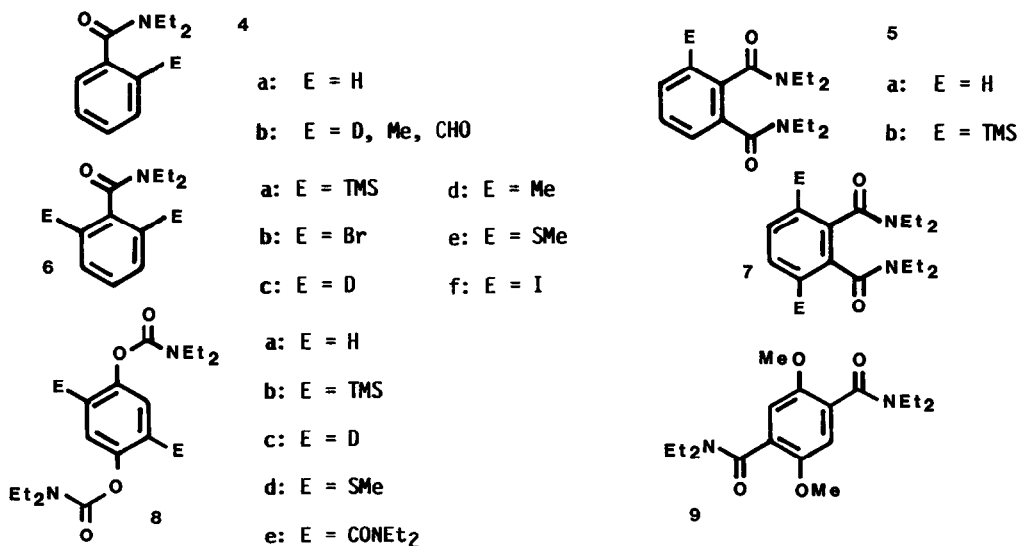
Abstract: Dilithiated species **1**, **2**, and **3**, generated by metal-halogen exchange and directed ortho metalation, undergo reaction with electrophiles to afford, in high yield, polysubstituted aromatics **6**, **7**, and **8** respectively; **9** is formed via a bis anionic Fries rearrangement of **3**.

The accelerating utility of organolithium intermediates in synthesis has given momentum to structural and theoretical studies¹ in order to provide much needed insight into the nature and reactivity of these species. Among these, dilithiated aromatics, invariably generated by metal-halogen exchange,² constitute relatively unknown,³ synthetically underdeveloped⁴ intermediates. In the context of our methodological work on the directed ortho metalation reaction,⁵ we have studied the generation of dilithiated tertiary benzamides **1**, phthalamides **2** by metal-halogen exchange, and O,O'-aryl dicarbamates **3** by directed metalation processes.⁶ Herein we demonstrate that these dimetalated species⁷ offer new approaches for the preparation of highly carbon- and heteroatom-substituted benzene derivatives.

Treatment of N,N-diethyl benzamide **4a** with up to 3 equiv of *s*-BuLi (3 equiv TMEDA/THF/-78°C) followed by quenching with excess of various electrophiles (MeOD, MeI, DMF) afforded monosubstituted products **4b** (40-60% yields) with no evidence (NMR, GLC) of 2,6-disubstitu-



tion. However, when **4a** was metalated with 2.2 equiv of \underline{s} -BuLi/2.2 equiv TMEDA/THF/-78°C and then treated with an excess of TMSCl, the 2,6-disilylated benzamide **6a** was obtained in 90% yield. In light of recent observations concerning the compatibility of TMSCl with LiTMP in aromatic metalation⁸ and the slow rate of reaction between TMSCl and \underline{s} -BuLi,⁹ the formation of **6a** may be rationalized by a stepwise lithiation mechanism.¹⁰ The successful mono metal-halogen exchange on an \underline{o} -bromobenzamide¹¹ and the availability of **6b** by bis ipso bromodesilylation¹² of **6a** prompted bis metal-halogen exchange experiments on **6b**. In the event, metalation of **6b** under optimized conditions (4.4 equiv \underline{t} -BuLi/THF/-78°C/30 min)¹³ followed by quenching with selected electrophiles led to 2,6-disubstituted benzamides **6c-f** (Table). The results of clean 2,6-disubstitution with electrophiles which are expected to react rapidly with the alkyl lithium reagent strongly support the intermediacy of the dilithiated species **1**.¹⁴



Metalation of the N,N-diethyl phthalamide **5a** using 2.2 equiv of \underline{s} -BuLi/2.2 equiv TMEDA/THF/-78°C followed by TMSCl quench resulted in the isolation of monosilylated (**5b**, 52%) and disilylated (**7a**, 20%) products.¹⁵ However, sequential treatment of **5a** with 3 equiv \underline{s} -BuLi/3 equiv TMEDA/THF/-78°C followed by quenching with an excess of TMSCl under the conditions used for the formation of **6a** furnished the disilylated phthalamide **7a** in 64% yield. Bis ipso bromodesilylation (Br₂/CH₂Cl₂/40°C/4h) afforded the corresponding

dibromo derivative **7b** (89% yield). Metal-halogen exchange on **7b** (4.4 equiv *t*-BuLi/THF/-78°C/30 min)¹³ resulted in the formation of **2** which upon quenching with excess electrophile gave the 3,6-disubstituted phthalamides **7c-f** (Table).¹⁶

Table Reaction of Dianions **1**, **2**, and **3** with Electrophiles

Substrate	Electrophile	Product	Yield, % ^a	Mp (bp)°C
6b	MeOD	6c	97 ^b	82-85/0.01 mm ^e
6b	MeI	6d	84	106-108/0.02 mm ^e
6b	(MeS) ₂	6e	65	89-90 ^f
6b	I ₂	6f	59	112-114 ^f
7b	MeOD	7c	56 ^c	120-128/0.10 mm ^e
7b	MeI	7d	69	64-67 ^g
7b	(MeS) ₂	7e	65	94.5-95.5 ^g
7b	I ₂	7f	74	128.5-129.5 ^f
8a	TMSCl	8b	67	175-176 ^h
8a	MeOD	8c	83 ^d	101-102 ^h
8a	(MeS) ₂	8d	71	202-204 ^h
8a	ClCONEt ₂	8e	63	151-152 ^h

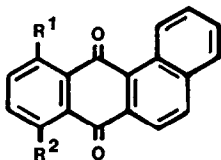
^a Yields correspond to purified (chromatographed and/or distilled and recrystallized) materials. ^b d₂ = 95% by MS. ^c d₂ = 92% by MS. ^d d₂ = 85% by MS. ^e Temperature of Kugelrohr oven bulb-to-bulb distillation. ^f Recrystallized from Et₂O/hexane. ^g Recrystallized from hexane. ^h Recrystallized from CH₂Cl₂/hexane.

In contrast to the above unsuccessful attempts to form dilithiated species **1** and **2** based on the powerful ortho metalation ability of the tertiary amide function,⁵ direct generation of the dilithiated species **3** was achieved by subjecting the O,O'-aryl dicarbamate **8a**¹⁷ to standard metalation conditions (2.2 equiv *s*-BuLi/2.2 equiv TMEDA/THF/-78°C). Subsequent treatment with electrophiles led smoothly to 2,5-disubstitued products **8b-e** (Table). Furthermore, warming a solution of the dianion **3** to room temperature resulted in a bis anionic Fries rearrangement¹⁷ to give, after methylation (MeI/K₂CO₃/Acetone), the terephthalamide **9** in 25% overall yield.

These readily generated, reactive dilithiated benzamide, phthalamide, and aryl dicarbamate synthons may find utility in the regiospecific construction of polysubstituted arenes.^{18,19,20}

References and Footnotes

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10. We have also shown that $(\text{MeS})_2$ but not Me_2SO_4 is compatible with *s*-BuLi/TMEDA. (Mills, R.J.; Snieckus, V. unpublished results). Recently Nwokogu and Hart have demonstrated the compatibility of Me_2SO_4 with *n*-BuLi.⁴
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13. See Corey, E.J.; Beames, D.J. J. Am. Chem. Soc. **1972**, *94*, 7210; Seebach, D.; Neumann, H. Chem. Ber. **1974**, *107*, 847; Saulnier, M.G.; Gribble, G.W. J. Org. Chem. **1982**, *47*, 757 and reference cited therein.
14. Mono metal-halogen exchange (2.2 equiv *t*-BuLi/THF/ -78°C) on **6b** is also synthetically useful and provides, by condensation with aromatic aldehydes via previously delineated sequences (ref. 11), regiospecific routes to bromo PAH quinones, e.g. i ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Br}$) and ii ($\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{H}$) (Mills, R.J.; Snieckus, V. unpublished results).



i: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Br}$
 ii: $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{H}$

15. The formation of **5b** as the major product suggests that one equiv of RLi strongly coordinates with the two amide functions, see Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D.J.; Mills, S.; Smith, S.G. J. Am. Chem. Soc. **1983**, *105*, 2080. This is supported by the result of recovery of starting material using 1 equiv *s*-BuLi/TMSCl quench.
16. To date, *N,N*-diethyl isophthalamide has not been converted into a disilylated derivative under the conditions employed for **5a**. *N,N*-diethyl terephthalamide has been transformed (2.2 equiv *t*-BuLi) into the corresponding 2,5-disilylated product (77% yield) but the ipso bromodesilylation, even under vigorous conditions, gave only complex mixtures of products.
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18. All new compounds show analytical and spectral (IR, ^1H and ^{13}C NMR and MS) data in complete accord with the assigned structures.
19. For synthetic use of dilithiated thiophene 2-carboxamides, see Doadt, E.G.; Snieckus, V. Tetrahedron Lett. following Letter in this issue.
20. We are grateful to NSERC of Canada for financial support and Professor P. von R. Schleyer for a stimulating lecture in organolithium chemistry.

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