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DIRECTED LITHIATION OF N,N-DIETHYLBENZAMIDES. REGIOSPECIFIC SYNTHESIS OF CONTIGUOUSLY TRI- AND TETRA-SUBSTITUTED ALKOXYBENZENES

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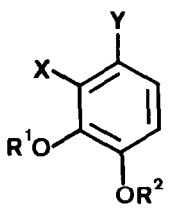
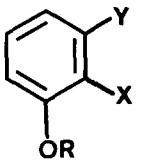
We report a general protocol for the regiospecific construction of alkoxybenzene derivatives bearing three (2) and four (1) contiguous ring substituents via the ortho lithiation reaction[1] of N,N-diethylbenzamides. In the accompanying Letters,[2,3] we demonstrate the utility of this methodology for the synthesis of naturally occurring anthraquinones and phthalideisoquinoline alkaloids.



1 (X = CHO, CO_2R; Y = CHO, CH_2Cl, CH_2CO_2R)



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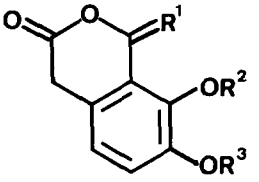
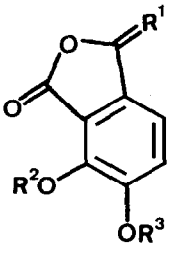
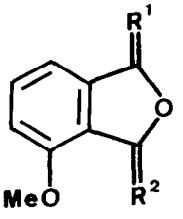


3 (R^1 = H_2, O)



	R^1	R^2	R^3
4a:	H_2	Me	Me
4b:	H,CO_2H	Me	Me
4c:	H,CO_2H	-CH_2-	
4d:	O	Me	Me

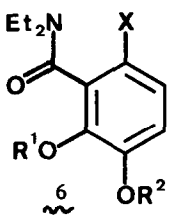


	R^1	R^2
5a:	O	H_2
5b:	H_2	O
5c:	O	O

1,2,3,4-Tetrasubstituted aromatic synthons (1) have played important roles in the developed routes to several classes of benzylisoquinoline alkaloids[4] (protoberberines: 1[5a,b], 3[5a,c-e]; spirobenzylisoquinolines: 4[6], benzophenanthridines: 1[7a-c], 4[7a], phthalideisoquinolines: 4[8]) and anthraquinone natural products[9] (1[10a], 4[10b,c]). Furthermore, 1,2,3-trisubstituted aromatics (2) are widely used starting materials for the elaboration of anthraquinones (2[11a], 5[11b,c]) and the anthracycline antitumor antibiotics (2[12a,b], 5[12a,c-f]). With two notable exceptions,[5b,8c] these types of compounds have been prepared by lengthy and/or

inefficient classical sequences. Our work was triggered by the discovery of Beak and Brown[13] that tertiary anisamides undergo exclusive lithiation ortho to the amide function (p-anisamide) and between the two ring substituents (m-anisamide). We have explored the implications of these results and now show that the directed lithiation reaction provides ready access to a variety of highly substituted benzenes (TABLE) from a few common amide precursors (6-9, X = H). Potential alternate procedures to type-1 and -2 systems via ortho-lithiated aryl oxazolines,[14,15] cyclohexylimines,[8c,16] secondary amides[1c,14c,17] and thioamides,[18] and tertiary amides[19] have not been adequately evaluated.

Ortho lithiation[13] (1 equiv. sec-BuLi/1 equiv. TMEDA/THF/-78°/1 h) of 6, X = H, $R^1 = R^2$ = Me resulted in the formation of a yellow solution which upon methylation (5 equiv. MeI/-78° → rt/2 h) gave 6a. Similarly, dimethoxylated aromatics 6b-h were obtained (TABLE). Products of electrophilic attack ortho to the methoxy group were not detected. The formylated product 6c was converted by successive reduction ($NaBH_4$/EtOH/rt/24 h) and cyclization (TsOH/PhMe/Δ/24 h) into meconine (4a) (90%)[20] and by hydrolysis (10% aq. $HClO_4$/Δ/48 h) into opianic acid 1, X = CO_2H, Y = CHO, $R^1 = R^2$ = Me (50%).[21] The carboxylated amide 6b was likewise hydrolyzed and cyclized (MeCOCl/Δ/2 h) to hemipinic anhydride (4d) (70%)[22] while the glyoxalate 6d was hydrolyzed (5% NaOH/100°/2 h), reduced ($NaBH_4$), and cyclized (conc. HCl/100°/3 h) in one pot to meconine-α-carboxylic acid (4b) (72%).[23] These results provide chemical proof for the site of substitution.[24]



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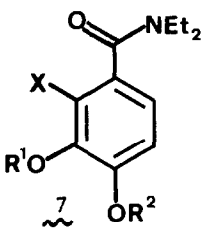

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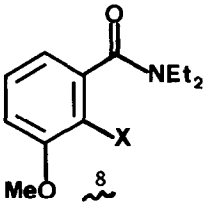

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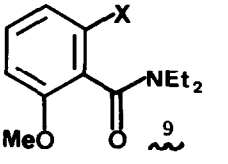

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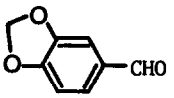
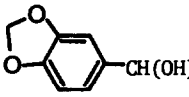
Methylation and carboxylation of the lithiated veratramide 7, X = H, $R^1 = R^2$ = Me, also proceeded regiospecifically to give 7a and 7b respectively.[25] Thus the oxidation state of the carbon substituents can be manipulated as a function of the starting amide (6 or 7, X = H). These results also recommend the use of 7, X = H rather than the considerably more expensive 6, X = H for the preparation of certain type-1 systems, e.g., 4d.

Using similar conditions, the 2,3-methylenedioxybenzamide 6, X = H, $R^1 + R^2 = CH_2$ gave compounds 6i-k without complications.[26] The glyoxalate 6k was subjected to the one-pot sequence used to obtain 4b to give the valuable[8c] phthalide-α-carboxylic acid 4c (37%). In

TABLE

Electrophile	Product	X	R^1	R^2	Yield %	Mp(bp)[a] °C
MeI	6a	Me	Me	Me	97	(130/0.1 mm)
CO_2	6b	CO_2H	Me	Me	77	133-135(Et_2O)
DMF	6c	CHO	Me	Me	88	(170/0.35mm)
$(CO_2Et)_2$	6d	$COCO_2Et$	Me	Me	88	118(PhH-pet. ether)
	6e		Me	Me	76	117.5-118.5(PhH-pet. ether)
PhNCO	6f	PhNHCO	Me	Me	71	178(PhH-pet.ether)
Me_3SiCl	6g	$SiMe_3$	Me	Me	65	(120-123/0.1 mm)
I_2	6h	I	Me	Me	70	(130-135/0.1 mm)
MeI	6i	Me	$-CH_2-$		47	(115-118/0.1 mm)
CO_2	6j	CO_2H	$-CH_2-$		50	173-175 (PhH)
$(CO_2Et)_2$	6k	$COCO_2Et$	$-CH_2-$		80	b
MeI	7a	Me	Me	Me	72	(135-138/0.1 mm)
CO_2	7b	CO_2H	Me	Me	71	b
MeI	7c	Me	$-CH_2-$		64	(127-130/0.1 mm)
CO_2	7d	CO_2H	$-CH_2-$		89	139-140(PhH-pet. ether)
CO_2	8a	CO_2H			54	147-149($CHCl_3$)
DMF	8b	CHO			49[c]	(140-145/0.1 mm)
CO_2	9a	CO_2H			70	138-139(Et_2O)
DMF	9b	CHO			75	(125-130/0.08 mm)

[a] Molecular still bath temp. [b] Semisolid, decomposes upon attempted distillation. [c] Based on recovered starting material.

the interest of synthetic economy, compounds 7c and 7d were also prepared via lithiation of the piperonylamide 7, X = H, $R^1 + R^2 = CH_2$.

In order to apply the ortho lithiation method to the preparation of useful anthraquinone[10] and anthracycline[11] precursors and as a prelude to our study,[2] the anisamides 8 and 9 (X = H) were converted into compounds 8a, 8b and 9a, 9b respectively. Upon hydrolysis and cyclization as for 6b, both 8a and 9a gave 3-methoxyphthalic anhydride (5c)[27] (70-80%) while reduction ($NaBH_4$) and cyclization (TsOH/PhMe/Δ/4 h) of 8b and 9b afforded the isomeric phthalides 5a (95%) and 5b (97%) respectively.[12a]

We conclude that ortho lithiation of tertiary benzamides is a useful strategy for the synthesis of highly substituted oxygenated aromatics. The versatile 1,2-carbon functionality in 6-9 provides potential handles for chain extension and ring annelation.[28,29]

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20. Compare with a 28% overall yield: E.H. White and M.M. Bursey, J. Org. Chem. 31, 1912 (1966).
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24. The position of substitution in 6 and 7 is strongly suggested by the nmr spectra which shows the doubling of the diethylamide signals (hindered rotation) and the well-defined AB pattern of the aromatic hydrogens.
25. Hydrolysis and cyclization of 7b as for 6b also yielded hemipinic anhydride (4d) (65%).
26. The methylenedioxy group is known to be labile to strongly basic conditions: B. Nalliah, Q.A. Ahmed, R.H.F. Manske, and R. Rodrigo, Can. J. Chem. 50, 1819 (1972).
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28. All new compounds show spectral data consistent with their assigned structures. Yields are based on isolated material (crystallized or chromatographed) and have not been optimized. Mp's are uncorrected. Known compounds show mp's, and mixture mp's and ir/nmr spectra (where available), in agreement with those reported in the literature. Starting benzamides were prepared by standard methods and distilled under high vacuum.

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