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DIRECTED *ortho* METALATION OF N,N-DIETHYL BENZAMIDES. METHODOLOGY AND REGIOSPECIFIC SYNTHESIS OF USEFUL CONTIGUOUSLY TRI- AND TETRA-SUBSTITUTED OXYGENATED AROMATICS, PHTHALIDES AND PHTHALIC ANHYDRIDES†

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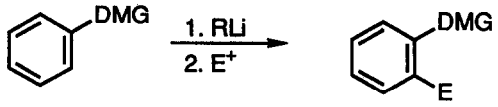
Abstract: *Full experimental details for the directed ortho metalation approach to a variety of simple ortho-substituted N,N-diethyl benzamides (**Table 1**) and contiguously 1,2,3- and 1,2,3,4-substituted benzamides (**Table 2**) are given. The efficient conversion of these benzamides (**6, 10, 12, 13, 18, 19**) into phthalides (**9a-b, 16b-c, 17**) and phthalic anhydrides (**8, 16a**), compounds previously available by demanding, classical methods, is detailed. A short synthesis of iso-ochracinic acid (**27**) is described.*

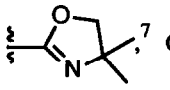
In the past decade, the directed *ortho* metalation (DoM) reaction[1] has deeply permeated the synthetic methodology repetoire used for fundamental, routinely encountered, problems in the construction of polysubstituted aromatics.[2] Among carbon-based directed metalation groups (DMGs) (**Scheme 1**), the pioneering work of Hauser[3] and synthetic explorations by Narasimhan[4] on the secondary amide ($CON^{-}R$) DMG was followed by the original disclosures by Beak[5] on the tertiary amide ($CONR_2$) and by Gschwend[6] and Meyers[7] on the 2-oxazolino group which provided strong impetus for elaboration and application of this methodology in synthetic aromatic[2,8] and, to a less meteoric extent, heteroaromatic chemistry.[9] In the interim, a number of other carbon-based DMGs at the carboxylic acid ($CSN^{-}R$[10], "TMEDA"-tertiary amide,[11] CON(R)CH(Z)TMS, Z = H, TMS,[12] CN[13] but also at other ($CH{=}NR$[14], $CH(O^{-})NR_2$[15], $CH(OR)_2$[16], CH_2O^{-}[17]) oxidation states have been developed to various extents and advantages/disadvantages. Based on the current survey[2], the $CONR_2$ and 2-oxazolino groups have evolved as powerful, conveniently applied, carbon-based metalation directors for a variety of methodological and total synthesis endeavors.

†To Gabor Fodor who, through the literature, first taught me anchimeric assistance, with respect and in recognition of his many fine contributions to natural product and synthetic chemistry.

Scheme 1



DMG (Directed Metalation Group) = $CON^{-}R$,[3,4], $CONR_2$,[2,11] CONRCHZ(TMS), Z = H, TMS,[12]

$CSN^{-}R$,[10]  ,[7] CN,[13] CH=NR,[14] $CH(NR_2)O^{-}$,[15] $CH(OR)_2$,[16] CH_2O^{-} [17]

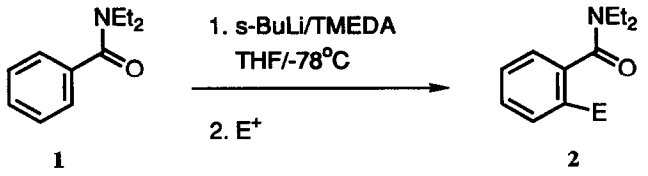
Herein we record details of our investigations on the directed *ortho* metalation chemistry of N,N-diethyl benzamides[18] and describe in order a) comprehensive methodological aspects related to the preparation of simple ortho-substituted systems, b) convenient procedures for contiguously tri- and tetra-substituted benzamides, and c) short and efficient routes to a variety of oxygenated aromatic synthons including phthalides and phthalic anhydrides of value in natural product construction. Point b) is, as recognized early,[5a,18] of major synthetic utility for the elaboration of valuable 1,2,3- and 1,2,3,4-substituted systems by alternative, regioselective introduction of carbon electrophiles into readily available oxygenated o-lithio benzamides (**Scheme 2**). Since such patterns have, in the past, been attained by demanding, invariable classical electrophilic susbtitution chemistry, the tertiary benzamide DoM tactic has seen wide utility[2] following the preliminary report.[5a,18] In this report, wherever complete experimental details of specific products are already recorded in the literature, we shall defer to other investigations and mention only briefly our additional or different observations. We shall end by a brief and critical comparison of available methods, including the DoM benzamide protocol, for the synthesis of phthalide and phthalic anhydride derivatives.

Methodological Studies

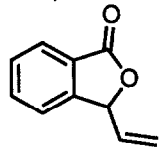
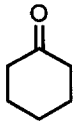
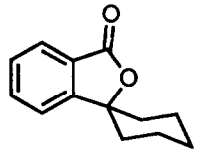
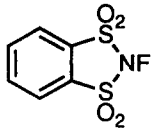
Table 1 summarizes the results of reactions of lithiated species of N,N-diethyl benzamide **1** with a variety of electrophiles to give products **2a-p**.[19] The original conditions (s-BuLi/TMEDA/THF/-78 °C/0.5-1 h) of Beak and Brown[5] have been standardized and are considered to be optimum for metalation of N,N-diethyl benzamide derivatives. Normally, the yellow to golden solution of the metalated species is quenched with the appropriate electrophile (in excess) at -78 °C and the solution is allowed to warm to room temperature overnight. Introduction of an ortho-carboxylic acid (entry 1), ester (entry 2), or aldehyde (entry 4)[19] proceeds in poor yield and contrasts with the good to excellent results in using the CO_2 and DMF electrophiles for substituted lithio benzamides (*vide infra*). In contrast, smooth reaction occurs with $ClCONEt_2$ (entry 3) which represents the introduction of another DMG, a concept whose synthetic value has been amply documented.[2] A variety of phthalides are conveniently obtained from reactions of benzamide derivatives with aldehydes followed by mild acid treatment;[2] two unreported reactions (entries 5, 6) extend this list, one of which (entry 5) is a prototype of a useful synthon.[20]

A spectrum of heteroatom electrophiles may also be introduced (**Table 1**, entries 7-16). The formation of salicylamide (entry 7) by the $B(OMe)_3/H_2O_2/HOAc$ procedure[5b] is more reproduceable and occurs in higher yields than the direct oxygenation of the o-lithiated benzamide followed by reductive workup.[19] This synthetically useful, regioselective OH^{+} synthon introduction into benzamides has been further studied[21] and applied in total synthesis.[2,22] Whereas I^{+} introduction using I_2 as the electrophile may be generally achieved in good yields, the corresponding reaction with Br^{+} reagents (Br_2, $BrCH_2CH_2Br$, $BrCH_2CH{=}CH_2$) leads, in general, to spurious results.[19] The use of $BrCF_2CF_2Br$ (entry 8) is therefore recommended and we have used this reagent[23] recently in several other DoM applications.[24] Alternative and competitive protocols for the synthesis of ortho-bromo benzamides involve *ipso* reactions of corresponding mercurial and trimethylsilyl

Table 1. Preparation of 2-Substituted N,N-Diethylbenzamides **2**



1 **2**

Entry	E^+	**2** (E)	Yield, %
1	CO_2	**2a** (CO_2H)	50
2	$NCCO_2Me$	**2b** (CO_2Me)	30
3	$ClCONEt_2$	**2c** ($CONEt_2$)	73
4	DMF	**2d** (CHO)	28
5		**2e** 	40
6		**2f** 	60
7	$B(OMe)_3/H_2O_2/HOAc$	**2g** (OH)	80
8	$BrCF_2CF_2Br$	**2h** (Br)	80
9		**2i** (F)	10
10	ClTMS	**2j** (TMS)	90
11	$ClPPh_2$	**2k** (PPh_2)	74
12	S_8	**2l** (SH)	40
13	$(PhS)_2$	**2m** (SPh)	73
14	Se/MeI	**2n** (SeMe)	21
15	$(PhSe)_2$	**2o** (SePh)	74
16	$ClSnMe_3$	**2p** ($SnMe_3$)	18

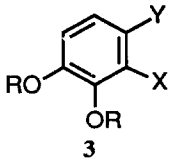
intermediates.[19] The introduction of the F^+ synthon into aromatic and heteroaromatic systems, a task of great value for pharmaceutical and agrochemical industries, has been vigorously pursued recently.[25] In our hands, a number of these reagents[25a-b] have failed to react with lithio benzamide under the standard conditions;[26] the use of the Davis reagent (entry 9)[25c] provided a low yield of product. On the other hand, the TMS group is introduced with ease (entry 10)[19] and finds further utility in regimens associated with protection of reactive metalation sites, "walk around the ring" metalation, and ipso halodesilylation.[27] The compatibility of TMSCl with lithium amide bases (e.g. LiTMP, LDA)[28] allows the *in situ* use of such combinations for the preparation of o-silylated benzamides with RLi-sensitive functionality.[27] Products of phosphorus (entry 11), sulfur (entries 12, 13), selenium (entries 14, 15), and tin (entry 16) electrophile introduction, obtained in variable yields, have not seen much synthetic application.[2]

A number of other electrophiles either failed to react with lithiated **1** or gave complex mixtures of products: CH_2O, $PhCO_2Me$, PhCOCl, $MeCO_2Et$, MeCOCl, Ac_2O, BrCN, $PhCH_2Br$, $CH_2{=}CHCH_2Br$ (may react as a Br^+ reagent, see above), aliphatic aldehydes, styrene oxide, and cyclohexene oxide. Here some differences in reactions using CON^-R^4 and 2-oxazolino[7b] DMGs is to be noted. In cases of $CH_2{=}CHCH_2Br$ and aliphatic aldehydes, an *ortho*-Li to *ortho*-MgX transmetalation protocol has overcome these reactivity problems.[29]

Synthesis of Contiguously Tri- and Tetra-Susbstituted Benzamides

1,2,3- and 1,2,3,4-substituted aromatics **3-5** (**Scheme 2**) and **8, 9a-b, 16a-c, 17** (**Scheme 3**) play important roles in the construction of diverse groups of natural products: anthraquinones (**3**[30a], **4**[30b], **5, 8**,[30c] **9**,[30d] **16**,[30e] **17**[30f]), anthracyclinones (**4**,[30g,30h], **5, 8, 9**[30i-l]), and protoberberine (**3**[30m-n], **5** [30o-q]), spirobenzylisoquinoline (**16, 17**[30r]), benzophenanthridine (**3**[30s-u]), and phthalideisoquinoline (**3**[30v]) classes of alkaloids. Prior to DoM conceptualization, these structural types were prepared, with two notable exceptions[30n,31] by tedious and largely inefficient classical sequences, e.g., **3**,[32a] **8**[32b-e], **9a-b**,[32f] **16b-c**,[32g-h] **17**.[32i]

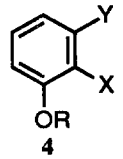
Scheme 2



3

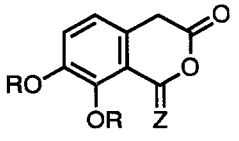
X = CHO, CO_2R

Y = CHO, CH_2Cl, CH_2CO_2R



4

X = Y = CO_2R

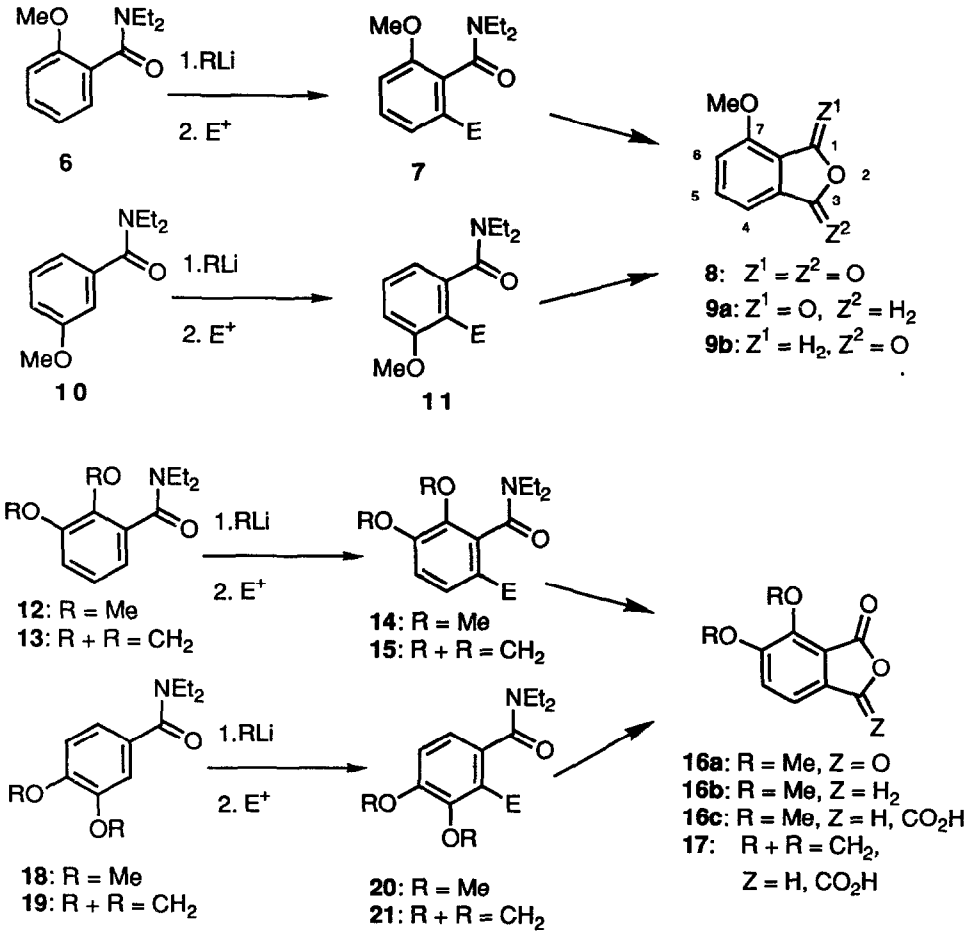


5

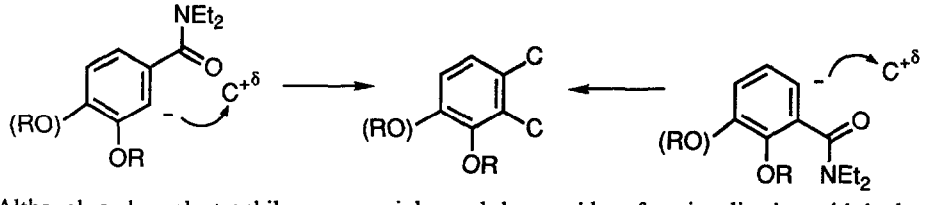
Z = H_2, O

The now well-recognized[2] implications of the DoM strategy depicted in **Scheme 4**, i.e., the stronger DMG power of $CONEt_2$ over OMe and the synergistic action of two DMGs in deprotonating the common site to both, were exploited for the preparation of some of the target substances **3-5, 8, 9a-b, 16a-c**, and **17** (**Scheme 3**). Starting with readily available benzamides **6, 10, 12, 13, 18**, and **19**, metalation - electrophile quench sequences were carried out to give corresponding products **7, 11, 14, 15, 20**, and **21** in good to excellent yields (**Table 2**). The synthesis of the isomeric pairs of o-aldehydes and -acids **7a, 7b** and **11a, 11b** respectively demonstrates the ability to manipulate carbon substituent oxidation states as a function of starting benzamide (**6** or **10**). Similar potential exists for the benzamide pairs **12, 13** and **18, 19** but with the additional consideration of the significantly more expensive benzoic acids corresponding to the pair **12, 13**. The formation of α-keto esters **14g** and **15c** using the diethyl oxalate electrophile constitutes rare examples of direct two-carbon, functionalized chain extensions of synthetic value (*vide infra*). Similarly, the uncomplicated results observed in DoM reactions of the benzamides **13** and **19** should be viewed in light of the knowledge that the methylenedioxy moiety is labile to strongly basic conditions.[31]

Scheme 3



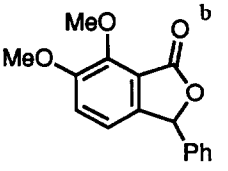
Scheme 4



Although carbon electrophiles were mainly used, benzamide o-functionalization with hydroxy (**7c**, **11c**) TMS (**14h**), and iodo (**14i**) groups was also effected. The formal introduction of OH^+ by the borate-hydrogen peroxide method may be of synthetic value in that the *ortho,ortho'*-dioxygen substitution is thereby

differentiated (e.g. **7c**, **11c**) leading to the potential, not yet explored, for regiospecific O-heteroring annelation to an aromatic nucleus.

Table 2. Synthesis of Alkoxybenzamides **7, 11, 14, 15, 20, 21**

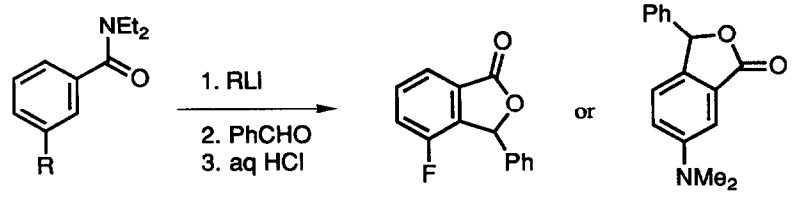
Entry	Benzamide	E+	Product (E)	Yield, %
1	**6**	DMF	**7a** (CHO)	75
2	**6**	CO_2	**7b** (CO_2H)	70
3	**6**	$B(OMe)_3/H_2O_2$/HOAc	**7c** (OH)	73
4	**10**	DMF	**11a** (CHO)	49
5	**10**	CO_2	**11b** (CO_2H)	18[a]
6	**10**	$B(OMe)_3/H_2O_2$/HOAc	**11c** (OH)	50
7	**12**	MeI	**14a** (Me)	97
8	**12**	DMF	**14b** (CHO)	88
9	**12**	CO_2	**14c** (CO_2H)	77
10	**12**	PhCHO	**14d** 	50
11	**12**	3,4-OCH_2O-C_6H_3CHO	**14e** 3,4-$OCH_2OC_6H_3CH(OH)$	76
12	**12**	PhNCO	**14f** (CONHPh)	71
13	**12**	$(CO_2Et)_2$	**14g** ($COCO_2Et$)	88
14	**12**	TMSCl	**14h** (TMS)	65
15	**12**	I_2	**14i** (I)	70
16	**13**	MeI	**15a** (Me)	97
17	**13**	CO_2	**15b** (CO_2H)	50
18	**13**	$(CO_2Et)_2$	**15c** ($COCO_2Et$)	80
19	**18**	MeI	**20a** (Me)	72
20	**18**	CO_2	**20b** (CO_2H)	71
21	**19**	MeI	**21a** (Me)	64
22	**19**	CO_2	**21b** (CO_2H)	89

[a] 3-Methoxyphthalic anhydride (30%) was also isolated. [b] The initial condensation product was not isolated but directly converted into 3-phenyl-6,7-dimethoxyphthalide (see Experimental Section).

The synthetic significance of regiospecific "in-between" metalation of 3-methoxy and 3-chloro benzamides,[5] prompted a brief investigation of the 3-fluoro and 3-dimethylamino systems, **22** and **23** (**Scheme 5**).[33] The regioselectivity was ascertained by reaction with benzaldehyde followed by acidic cyclization to respective phthalides. Based on NMR analysis, **22** and **23** afforded phthalides **24** and **25** respectively, in both cases to the exclusion (< 5%) of the other possible isomer. The suspected synergistic effect of the F DMG is therefore confirmed while a potential steric factor may be invoked to explain the

regiospecific C-6 metalation of **23**. The N,N-diethyl O-carbamate corresponding to **23** also undergoes C-6 metalation.[34]

Scheme 5



22: R = F
23: R = NMe_2

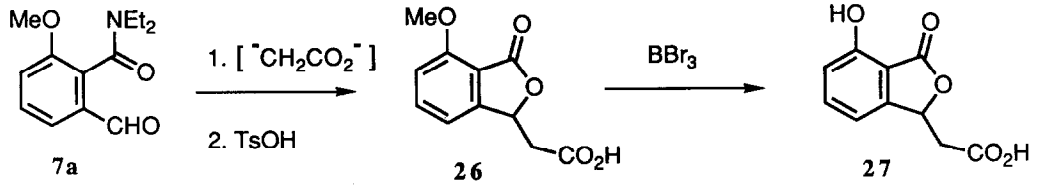
24 **25**

Synthesis of Oxygenated Phthalides 9a, 9b, 16b, 16c, 17 and Phthalic Anhydrides 8, 16a including Iso-ochracinic Acid (27)

The utility of the alkoxy benzamides (**Table 2**) as intermediates for difficult to access phthalides and phthalic anhydrides was demonstrated through a number of standard conversions (**Scheme 3**). The isomeric carboxy anisamides **7b** and **11b** both gave, upon hydrolysis (10% aq $HClO_4$) and cyclization (MeCOCl), 3-methoxyphthalic anhydride (**8**) in 70-80% yields. Reduction ($NaBH_4$)) and cyclization (TsOH/PhMe/reflux) of the corresponding aldehydes **7a** (prone to cyclize upon workup from the DoM reaction) and **11a** smoothly afforded the isomeric phthalides **9a** and **9b** in 95-97% yields.[35] Similarly, the formylated benzamide **14b** was hydrolyzed to give opianic acid (**3**, X = CO_2H, Y = CHO, R = Me) (50% yield) and reduced and cyclized to furnish meconine (**16b**) (> 95% yield) while both the carboxy benzamides **14c** and **20b** were transformed into hemipinic anhydride (**16a**) (65-70%) with some heed to procedural advice.[36] The glyoxalate benzamides **14g** and **15c** were hydrolyzed (aq NaOH), reduced ($NaBH_4$), and cyclized (HCl) in a one-pot operation to give meconine-α-carboxylic acid (**16c**) (72%) and the valuable[32i] corresponding methylenedioxy analogue **17** (37% yield) respectively.

To further demonstrate the DoM regimen, we were attracted by the structure of iso-ochracinic acid (**27**, **Scheme 6**), a member of a small group of naturally occurring phthalides and a product of the parasitic fungus *Alternaria kukuchiana* which is responsible for the black spot disease on Japanese pears.[37] Two syntheses of **27** are available: an early, low yield route involving a non-regioselective Wittig reaction on 3-methoxyphthalic anhydride[38a] and a more recent, short sequence (44% overall yield) via carboxylation of dimetalated 3-methoxybenzyl alcohol.[38b] Two-carbon homologation of the formyl benzamide **7a** using Danishefsky's acetic acid dianion[39] followed by TsOH-catalyzed cyclization gave phthalide **26** which, upon BBr_3 demethylation afforded iso-ochracinic acid (**27**) in 40% overall yield.

Scheme 6

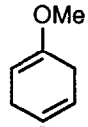
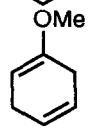
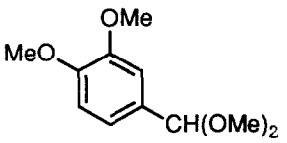
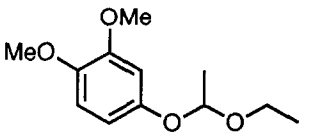


7a **26** **27**

Comparison of Methods for the Preparation of Phthalides and Phthalic Anhydrides

Table 3 compares classical and more recent, frequently used, procedures with the directed metalation methods for the preparation of oxygenated phthalide and phthalic anhydride synthons **8**, **9a-b**, **16a-c**, **17**. Several alternative DMGs to the tertiary amide have been used to prepare some of these materials (**9b**, **16b**, **3**

Table 3. Comparison of Methods for Synthons **8, 9a-b, 3** (X = CO_2H, Y = CHO, R = Me), **16a-c, 17**

Starting Material	Phthalide or Phthalic Anhydride	Overall yield Lit	(Number of steps) this work[a]
3-Nitrophthalic acid	**8**	9%(6)[b]	32%(5)
2,3-dimethylphenol	**8**	45%(3)[c]	32%(5)
	**8**	68%(3)[d]	32%(5)
	**9a**	31-44%(2)[e]	49%(4)
3-methoxybenzoic acid	**9b**	77%(3)[f]	43%(4)
2,3-dimethoxybenzoic acid	**3** (X = CO_2H, Y = CHO, R = Me)	13%(2)[g]	44%(3)
	**3** (X = CO_2H, Y = CHO, R = Me)	95%(2)[h]	44%(3)
2,3-dimethoxybenzoic acid	**16a**	25%(3)[i]	54%(4)
2,3-dimethoxybenzoic acid	**16b**	28%(1)[i]	79%(4)
	**16b**	91%(2)[h]	79%(4)
Opianic acid	**16c**	79%(2)[j]	63%(5)
Piperonal	**17**	34 %(3)[k]	30%(5)

[a] Based on the respective benzoic acid derivatives. [b] Horii, Z.I.; Hakusi, H.; Momose, T.; Yoshino, E. *Chem. Pharm. Bull. Jpn.* **1968**, *16*, 1251. [c] ref 30a, p 377, 388, 410, 413, 447. [d] Newman, M.S.; Kanakarajan, K. *J. Org. Chem.* **1980**, *45*, 3523. [e] Harland, P.A.; Hodge, P. *Synthesis*, **1983**, 419; regioselective reduction of **8**, prepared as in ref d, is an alternate route (49%): Makhlouf, M.A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 4810. [f] Meyers, A.I.; Avila, W.B. *J. Org. Chem.* **1981**, *46*, 3881. [g] ref 32a. [h] Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653. [i] ref 32g. [j] ref 32h. [k] ref 32i.

(X = CO_2H, Y = CHO, R = Me)). In noting the higher yields obtained via directed metalation, the usually lower reagent costs and technically easier scale up for the classical methods must, in several cases, be conceded. However, several older methods use the expensive 2,3-dimethoxybenzoic acid as starting material, an aspect which can be avoided in the benzamide metalation route as indicated for the preparation of **16a** and **16b**. Finally, it is important to recognize that hydrolysis of the highly recalcitrant amide is greatly facilitated by the anchimeric assistance offered by the ortho heteroatom substituents[40] which are introduced via the electrophile. To overcome this problem, a three-step transformation of $CONEt_2 \rightarrow CHO$ has been devised.[41] The oxazolino DMG offers an alternative solution and Meyers has devised several mild methods for its conversion to other useful functionality.[7b] Notwithstanding, in the context of preparing phthalides and phthalic anhydrides and related oxygenated N- and O-heterocycles, alkoxybenzamides serve as readily available and proximate precursors.

We conclude, on the basis of these and a growing body of results,[2] that reactions of *ortho*-lithiated benzamides with electrophiles is a versatile, short-range methodology for highly substituted aromatics. It continues to be a method with high evolutionary potential for incorporation into strategies of regiospecific carbon attachment, chain extension, and ring annelation of both simple and complex synthetic targets.

Experimental

General Methods

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points were determined on a Buchi model SMP-20 and are uncorrected. Infrared spectra were determined with a Perkin-Elmer model 983 spectrophotometer. Nuclear magnetic resonance specura were recorded in $CDCl_3$ containing 0.5% TMS as internal standard for ^1H NMR with either Brucker WP-80, AM-250 or WH-200 spectrometers. Mass spectra and HRMS were determined at McMaster University, Hamilton, Ontario, Canada, using VG 7070F spectrometers in EI mode. THF and Et_2O were distilled from benzophenone ketyl under nitrogen prior to use. s-BuLi, 1.3 M in cyclohexane, purchased from Aldrich Chemical Co., was titrated periodically against 2,5-dimethoxybenzyl alochol. N,N,N,N-Tetramethylethylene diamine (TMEDA) was distilled from CaH_2 before use. All other commercial materials were purchased from Aldrich Chemical Co. and Lancaster Co. Ltd. The phrase "standard workup" refers to the following procedure: the reaction mixture is treated with saturated aq NH_4Cl solution followed by extraction with CH_2Cl_2. The organic extract is dried (Na_2SO_4) and the solvent is removed under reduced pressure to afford the crude product. Subsequent flash chromatography of the crude material followed by distillation or recrystallization affords the pure product.

All benzamides were prepared by standard procedures, distilled or recrystallized, and stored in a vacuum dessicator.

N,N-Diethylbenzamide (1): bp 90-95 °C (0.5 torr), lit[42] bp 150-151°C (15 torr).

N,N-Diethyl 2-methoxybenzamide (6): bp 105-106 °C (0.5 torr), lit[43] bp 100-104 °C (1 torr).

N,N-Diethyl 3-methoxybenzamide (10): bp 102-104 °C (0.03 torr), lit[44] bp 177 °C (14 torr).

N,N-Diethyl 2,3-dimethoxybenzamide (12): bp 110-120 °C (0.05 torr), lit[45] bp 130 °C (1 torr); IR (film) υ (max) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (m, 6H), 3.4 (m, 4H), 3.92 (s, 3H), 7.0 (m, 3H); MS m/e (rel intensity) 237 (M^+, 100), 135 (100).

N,N-Diethyl 2,3-methylenedioxybenzamide (13): bp 140-150 °C (1.1 torr), lit[45] bp 180 °C (1 torr); IR (film) υ (max) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (m, 6H), 3.45 (m, 4H), 6.0 (s, 2H), 6.82 (m, 3H); MS m/e (rel intensity) 221 (M^+, 47), 149 (100).

N,N-Diethyl 3,4-dimethoxybenzamide (18): bp 120-122 °C (0.01 torr), lit[46] bp 130-132 °C (0.03 torr).

N,N-Diethyl 3,4-methylenedioxybenzamide (19): bp 130-135 °C (0.5 torr), lit[45] bp 150 °C (1 torr); IR (film) υ (max) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (m, 6H), 3.45 (m, 4H), 6.1 (s, 2H), 6.92 (m, 3H); MS m/e (rel intensity) 221 (M^+, 47), 149 (100).

N,N-Diethyl 3-fluorobenzamide (22): bp 90-95 °C (0.05 torr), lit[46] bp 80-82 °C (0.03 torr).

N,N-Diethyl 3-dimethylaminobenzamide (23): bp 130-135 °C (0.05 torr); IR (film) υ (max) 1629, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, J =6.8. Hz, 6H), 2.96 (s, 6H), 3.35 (m, 4H), 6.66 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.72 (dd, J = 2.3, 8.5 Hz, 1H), 7.22 (dd, J = 7.5, 8.5 Hz, 1H); MS m/e (rel intensity) 220 (M^+, 77), 148 (87), 121 (100); HRMS calcd for $C_{13}H_{20}ON_2$ 220.1577, found 220.1574.

Synthesis of Substituted Benzamides (Table 1)

General Procedure: To a stirred solution of a N,N-diethylbenzamide (2.1 mmol) in THF (50 mL) under nitrogen at -78 °C (dry ice/acetone bath) was injected sequentially through a septum inlet TMEDA (2.2 mmol) and s-BuLi (2.2 mmol). The solution was stirred at -78 °C for 1 h. To this solution, the electrophile (2.2 mmol) was added and the solution was allowed to warm to room temperature over 8-12 h, at which time the reaction mixture was subjected to the standard workup.

Using the above procedure, the benzamides **2a-p** listed below were prepared.

N,N-Diethyl 2-carboxybenzamide (2a): 50% yield; mp 155-156 °C (EtOAc-hex), lit[47] mp 154-155 °C.

N,N-Diethylphthalamic acid (2b): 30% yield, oil.[48]

N,N-Diethyl 2-(N,N-diethylcarboxamido)benzamide (2c): 73% yield; bp 118-120 °C (0.01 torr); IR (neat) υ (max) 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99-1.29 (m, 12H), 3.12-3.62 (m, 8H), 7.20-7.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.0, 13.1, 38.4, 42.7, 125.2, 127.6, 134.4, 168.8; MS m/e (rel intensity) 276 (M^+, 19), 204 (100); Anal. calcd for $C_{16}H_{24}O_2N_2$ C, 69.53; H, 8.75; N, 10.14; found, C, 69.14; H, 8.96; N, 10.33.

N,N-Diethyl 2-formylbenzamide (2d): 28% yield, oil.[49]

Phthalide (2e): The crude product was treated with 6N HCl to afford **2e**, 40% yield; bp 80-85 °C (0.05 torr); IR (neat) υ (max) 1766 cm^{-1}; ^1H NMR δ 5.40 (m, 1H), 5.60 (m, 1H), 5.85 (m, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H); MS m/e (rel intensity) 160 (M^+, 100), 105 (70); HRMS calcd for $C_{10}H_8O_2$ 160.0524, found 160.0525.

Phthalide (2f): The crude product was treated with 6 N HCl to give **2f**, 60% yield, mp 75-76 °C (EtOAc-hex); IR (nujol) υ (max) 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70- 2.00 (m, 10H), 7.40 (d, J = 6.7 Hz, 1H), 7.50 (t, J = 6.7 Hz, 1H), 7.65 (t, J = 6.7 Hz, 1H), 7.88 (d, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 24.7, 36.4, 86.9, 120.9, 125.5, 125.7, 128.9, 133.8, 154.9, 170.0; MS m/e (rel intensity) 202 (M^+, 63), 159 (100); HRMS calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0999.

N,N-Diethyl 2-hydroxybenzamide (2g): 80% yield; mp 100- 101 °C (EtOAc-hex), lit[50] mp 101 °C.

N,N-Diethyl 2-bromobenzamide (2h): 80% yield; bp 110-115 °C (0.05 torr), lit[51] bp 186 °C (17 torr).

N,N-Diethyl 2-fluorobenzamide (2i): 10% yield; bp 95-97 °C (0.2 torr), lit[51] bp 154 °C (18 torr); ^{19}F NMR ($CDCl_3$) δ -155.3 (dt, J = 6.1, 9.4 Hz).

N,N-Diethyl 2-trimethylsilylbenzamide (2j): 90% yield; mp 53-54 °C (hex), lit[46] mp 53-54 °C.

N,N-Diethyl 2-diphenylphosphinobenzamide (2k): 74% yield; mp 150-151°C; IR (film) υ (max) 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.4 (m, 6H), 3.0 (q, J = 7.5 Hz, 2H), 3.5 (q, J = 7.5 Hz, 2H), 7.30 (m, 14H); MS m/e (rel intensity) 361 (M^+, 38), 261 (100); HRMS calcd for $C_{23}H_{24}NOP$ 361.1595, found 361.1598.

N,N-Diethyl 2-mercaptobenzamide (2l): 40% yield; mp 56-58 °C (EtOAc-hex); lit[52] mp 55-56 °C.

N,N-Diethyl 2-thiophenylbenzamide (2m): 73% yield; oil; IR (neat) υ (max) 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 3.13 (q, J = 7.1 Hz, 2H), 3.55 (q, J = 7.1 Hz, 2H), 7.15-7.45 (m, 9H); MS m/e (rel intensity) 285 (M^+, 18), 185 (100); HRMS calcd for $C_{17}H_{19}NOS$ 285.1187, found 285.1190.

N,N-Diethyl 2-methylselenobenzamide (2n): Powdered Se (1.5 equiv) was added followed, after 1 h at -78 °C, by MeI (3 equiv), 21% yield; bp 80-83 °C (0.03 torr); IR ($CHCl_3$) υ (max) 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90-1.15 (t, J = 7 Hz, 3H), 1.15-1.45 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 2.95-3.35 (q, J =7 Hz, 2H), 3.35-3.80 (q, J = 7 Hz, 2H), 7.1-7.5 (m, 4H); MS m/e (rel intensity) 271 (M^+, 20), 171 (100); HRMS calcd for $C_{12}H_{17}NOSe$ 271.0475, found: 271.0489.

N,N-Diethyl 2-phenylselenobenzamide (2o): 74% yield; bp 133-135 °C (0.03 torr) ; IR ($CHCl_3$) υ (max) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-1.5 (m, 6H), 3.0-3.4 (q, J = 7 Hz, 2H), 3.4-3.8 (q, J = 7 Hz, 2H), 7.15-7.45 (m, 4H); MS m/e (rel intensity) 333 (67), 332 (M^+, 28), 261 (100); HRMS cacld for $C_{17}H_{19}NOSe$ 333.0627, found: 333.0642.

N,N-Diethyl 2-trimethylstannylbenzamide (2p): 18% yield, oil; IR (neat) υ (max) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (s, 9H), 1.05-1.35 (m, 6H), 2.2-2.6 (m, 4H), 7.24-7.36 (m, 3H), 7.54-7.58 (m, 1H); Instability prevented the determination of MS and analytical data.

Preparation of Alkoxybenzamides 7, 11, 14, 15, 20, and 21. These compounds were prepared according to the **General Procedure** described above.

N,N-Diethyl 2-formyl-6-methoxybenzamide (7a): 75% yield; bp 125-130 °C (0.08 torr); IR ($CHCl_3$): υ (max) 1705, 1620 cm^{-1};^1H NMR ($CDCl_3$) δ 1.05 (m, 3H), 1.30 (m, 3H), 3.40 (m, 4H), 3.90 (s, 3H), 7.40 (m, 3H), 10.20 (s, 1H); MS m/e (rel intensity) 235 (M^+, 5), 206 (100), 163 (100), 135 (100); Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95, found: C, 66.44; H, 7.69; N, 5.75.

N,N-Diethyl 2-carboxy-6-methoxybenzamide (7b): 70% yield; IR ($CHCl_3$) υ (max), 3500, 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (m, 3H), 1.30 (m, 3H), 3.15-3.80 (m, 4H), 3.85 (s, 3H), 7.1-7.9 (m, 3H), 11.50 (s, 1H, exchangeable with D_2O); converted without purification into the phthalic anhydride **8**.

N,N-Diethyl 2-hydroxy-6-methoxybenzamide (7c): 73% yield; mp 139-140 °C (EtOAc-hex), lit[21] mp 139-140 °C.

N,N-Diethyl 2-formyl-3-methoxybenzamide (11a): 49% yield; bp 140-145 °C (0.1 torr); IR ($CHCl_3$) υ (max) 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 8 Hz, 3H), 1.30 (t, J = 8 Hz, 3H), 3.05 (q, J = 8 Hz, 2H), 3.58 (q, J = 8Hz, 2H), 3.90 (s, 3H), 6.70-7.80 (m, 3H), 10.13 (s, 1H); MS m/e (rel intensity) 235 (M^+, 8), 207 (67) 135 (100); Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95, found: C, 66.86; H, 7.26; N, 5.42.

N,N-Diethyl 2-carboxy-3-methoxybenzamide (11b): From **10** (828 mg, 4 mmol) there was obtained a solid which upon recrystallization from Et_2O gave 372 mg of material composed of 179 mg (18% yield based on **10**) of the acid **11b** and 193 mg (30% yield based on **10**) of 3-methoxy phthalic anhydride (**8**) (see below). ^1H NMR of **11b** in the mixture: ($CDCl_3$) δ 1.01 (t, J = 8 Hz, 3H), 1.25 (t, J = 8 Hz, 3H), 3.15 (q, J = 8 Hz, 2H), 3.52 (q, J =8 Hz, 2H), 3.85 (s, 3H), 7.0-8.0 (m, 3H), 8.75 (s, 1H, exchangeable with D_2O).

N,N-Diethyl 2-hydroxy-3-methoxybenzamide (11c): 50% yield; mp 81-82 °C (EtOAc-hex), lit[21] mp 82-83 °C.

N,N-Diethyl 2,3-dimethoxy-6-methylbenzamide (14a): 97% yield; oil; IR ($CHCl_3$) υ (max) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3H), 1.38 (t, J = 7 Hz, 3H), 2.30 (s, 3H), 3.20 (q, J = 7 Hz, 2H), 3.65 (q, J = 7 Hz, 2H), 3.90 (s, 6H), 6.90 (s, 2H); MS m/e (rel intensity) 351 (M^+, 22), 251 (100); HRMS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1525.

N,N-Diethyl 2-formyl-5,6-dimethoxybenzamide (14b): 88% yield; bp 170 °C (0.35 torr); IR ($CHCl_3$) υ (max) 1693, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 6 Hz, 3H), 1.30 (t, J = 6 Hz, 3H), 3.12 (q, J = 6 Hz, 2H), 3.62 (q, J = 6 Hz, 2H),

3.90 (s, 3H), 3.98 (s, 3H), 7.10 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 9.8 (s, 1H); MS m/e (rel intensity) 265 (M^+, 2), 237 (17), 236 (100); HRMS calcd for $C_{14}H_{19}NO_4$ 265.1314, found 265.1317.

N,N-Diethyl 2-carboxy-5,6-dimethoxybenzamide (14c): 77% yield; mp 133-135 °C (Et_2O); IR ($CHCl_3$) υ (max) 1700, 1625 cm $^{-1}$; ^{1}H NMR($CDCl_3$) δ 1.05 (t, J =7 Hz, 3H), 1.38 (t, J = 7 Hz, 3H), 3.20 (q, J = 7 Hz, 2H), 3.65 (q, J = 7 Hz, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 7.00 (d, J = 9 Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 12.00 (bs, 1H, exchangeable with D_2O); MS m/e (rel intensity) 282 (M^+, 17), 264 (14), 250 (14), 236(36), 209 (100); Anal. calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98, found: C, 59.11; H, 6.63; N, 4.40.

6,7-Dimethoxy-3-phenylphthalide (14d): The crude product from the quench with PhCHO was refluxed in PhMe containing a catalytic amount of p-TsOH for 48 h. Standard workup afforded **14**, 50% yield; mp 110-111 °C (Et_2O); IR ($CHCl_3$) υ (max) 1765 cm $^{-1}$; ^{1}H NMR($CDCl_3$) δ 3.90 (s, 3H), 4.15 (s, 3H), 6.30 (s, 1H), 6.95 (d, J = 9 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.35 (s, 5H); MS m/e (rel intensity) 270 (M^+, 56), 165 (100); Anal. calcd for $C_{14}H_{19}NO_5$: C, 71.10; H, 5.22, found: C, 71.56; H, 5.26.

N,N-Diethyl-2,3-dimethoxy-6-(3,4-methylenedioxyphenylhydroxymethyl)benzamide (14e): 76% yield; mp 117-118.5 °C (PhH-pet ether, 30-60 °C); IR ($CHCl_3$) υ (max) 3380, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1 (m, 6H), 2.9 (q, J = 6 Hz, 2H), 3.5 (q, J = 6 Hz, 2H), 3.9 (s, 3H), 3.95 (s, 3H), 5.95 (s, 2H), 4.70 (d, J = 8 Hz, 1/2 H), 5.05 (bd, J = 8 Hz, exchangeable with D_2O), 5.80 (d, J = 8 Hz, 1/2H), 7.0 (m, 5H); MS m/e (rel intensity) 387 (M^+, 8), 314 (100); HRMS calcd for $C_{21}H_{25}NO_6$ 387.1675, found 387.1690.

N,N-Diethyl-3,4-dimethoxy-6-(N-phenylcarbamoyl)benzamide (14f): 71% yield; mp 180-181°C (PhH-pet ether, 30-60 °C); IR ($CHCl_3$) υ (max) 1670, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (m, 6H), 3.0-3.8 (m, 4H), 3.98 (s, 6H), 7.4 (m, 7H), 9.15 (s, 1H); MS m/e (rel intensity) 356 (M^+, 4), 325 (12), 284 (67); Anal. calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86, found: C, 67.45; H, 6.94; N, 7.73.

Ethyl 3,4-dimethoxy-2-(N,N-diethylcarbamoyl)benzoylformate (14g): 88% yield; mp 118 °C (PhH-hex); IR (nujol) υ (max) 1775, 1730, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0-1.4 (m, 9H), 3.20 (q, J = 7 Hz, 2H), 3.56 (q, J =7 Hz, 2H), 3.85 (s, 3H), 3.90 (s, 3H), 4.25 (q, J = 7 Hz, 2H), 6.85 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H); MS m/e (rel intensity) 337 (M^+, 4), 237 (100); HRMS calcd for $C_{17}H_{23}NO_6$ 337.1519, found 337.1523.

N,N-Diethyl 2,3-dimethoxy-6-trimethylsilylbenzamide (14h): 65% yield; bp 120-123 °C (1 torr); IR (neat) υ (max) 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), 1.10 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 3.10 (q, J = 7 Hz, 2H), 3.58 (q, J = 7 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.90 (d, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 1H); MS m/e (rel intensity) 309 (M^+, 5), 294 (75), 237 (48), 165 (100); Anal. calcd for $C_{16}H_{27}NO_3Si$: C, 62.28; H, 8.79; N, 4.53, found: C, 62,19; H, 9.10; N, 4.43.

N,N-Diethyl 2-iodo-5,6-dimethoxybenzamide (14i): 70% yield; bp 115-125 °C (0.05 torr); IR (neat) υ (max) 1626 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 6H), 3.0 (q, J = 7 Hz, 2H), 3.25 (q, J = 7 Hz, 2H), 3.82 (s, 6H), 6.67 (d, J = 9 Hz, 1H), 7.42 (d, J = 9 Hz, 1H); MS m/e (rel intensity) 363 (M^+, 29), 332 (17), 291 (100); Anal. calcd for $C_{13}H_{18}INO_3$: C, 42.99; H, 5.00; N, 3.86, found: C, 43.87; H, 5.17; N, 3.80.

N,N-Diethyl 2-methyl-5,6-methylenedioxybenzamide (15a): 97% yield; bp 115-118 °C (0.1 torr); IR ($CHCl_3$) υ (max) 1620 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 8 Hz, 3H), 1.28 (t, J = 8 Hz, 3H), 2.30 (s, 3H), 3.25 (q, J = 8 Hz, 2H), 3.70 (q, J = 8 Hz, 2 H), 5.95 (s, 2H), 6.70 (m, 2H); MS m/e (rel intensity) 235 (M^+, 20), 220 (27), 206 (27), 163 (66), 135 (100), 83 (50); Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.38; N, 5.95, found: C, 66.86; H, 7.50; N, 5.56.

N,N-Diethyl 2-carboxy-5,6-methylenedioxybenzamide (15b): 50% yield; mp 173-175 °C (PhH); IR ($CHCl_3$) υ (max) 1700, 1620 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ 1.10 (m, 6H), 3.30 (m, 4H), 6.20 (s, 2H), 7.00 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H); Determination of MS was precluded due to sample polymerization in probe; Anal. calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.79; N, 5.28, found: C, 59.09; H, 5.76; N, 5.07.

Ethyl 5,6-methylenedioxy-2-(N,N-diethylcarbamoyl)benzoylformate (15c): 80% yield; bp unobtainable due to decomp; IR (neat) υ (max) 1780, 1730, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00-1.40 (m, 9H), 3.20 (q, J = 7 Hz, 2H), 3.50 (q, J =

7 Hz, 2H), 4.20 (q, J = 7 Hz, 2H), 6.10 (s, 2H), 6.90 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H); MS m/e (rel intensity) 321 (M^+, 3) 221 (100); HRMS calcd for $C_{16}H_{19}NO_6$ 321.1207, found 321.1211.

N,N-Diethyl 3,4-dimethoxy-2-methylbenzamide (20a): 72% yield; bp 135-138 °C (0.1 torr); IR (neat) υ (max) 1631 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 2.15 (s, 3H), 3.15 (q, J = 7 Hz, 2H), 3.40 (q, J = 7 Hz, 2H), 3.85 (s, 3H), 3.90 (s, 3H), 6.85 (d, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H); MS m/e (rel intensity) 251 (M^+, 7), 151 (100); HRMS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1530.

N,N-Diethyl 2-carboxy-3,4-dimethoxybenzamide (20b): 71% yield; semisolid, bp unobtainable due to decomp; IR (nujol) υ (max) 1701, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3H), 1.30 (t, J =7 Hz, 3H), 3.20 (q, J = 7 Hz, 2 Hz, 2H), 3.45 (q, J = 7 Hz, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 6.85 (d, J = 6 Hz, 1H), 7.00 (d, J = 6 Hz, 1H), 10.70 (bs, 1H, exchangeable with D_2O); MS m/e (rel intensity) 281 (M^+, 15), 181 (100); Anal. calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98, found: C, 59.21; H, 6.60; N, 4.45.

N,N-Diethyl 2-methyl-3,4-methylenedioxybenzamide (21a): 64% yield; bp 127-130 °C (0.1 torr); IR (neat) υ (max) 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0-1.4 (m, 6H), 2.20 (s, 3H), 3.20-3.60 (m, 4H), 6.20 (s, 2H), 6.90 (s, 2H); MS m/e (rel intensity) 235 (M^+, 40), 135 (100); HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1211.

N,N-Diethyl 2-carboxy-3,4-methylenedioxybenzaimde (21b): 89% yield; mp 139-140 °C (PhH-hex); IR (nujol) υ (max) 1705, 1629 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 3H), 1.10 (t, J = 7 Hz, 3H), 3.2 (q, J = 7 Hz, 2H), 3.40 (q, J = 7 Hz, 2H), 6.20 (s, 2H), 6.90 (d, J = 6 Hz, 1H), 7.00 (d, J = 6 Hz, 1H). 10.5 (bs, 1H, exchangeable with D_2O); MS m/e (rel intensity) 265 (M^+, 10), 165 (100); Anal. calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.79; N, 5.28, found: C, 59.11; H, 5.66; N, 5.17.

Preparation of Phthalic Anhydrides 8 and 16a

3-Methoxyphthalic Anhydride (8): A solution of the isomeric phthalamide acid **11b** in 10% aq $HClO_4$ was refluxed for 24 h. The solution was extracted with CH_2Cl_2 and the organic extract was evaporated to dryness. The crude material was stirred with anhydrous AcCl for 6 h. Standard workup gave **8** (32% yield from **6**), mp 168-169 °C (pet ether-EtOAc), lit[53] mp 169-171°C.

3,4-Dimethoxyphthalic Anhydride (Hemipinic anhydride) (16a): Using the above procedure, the phthalamide acids **14c** and **20b** were converted into **16a** in 36% and 51% yields respectively, mp 176 °C ($CHCl_3$) lit[54] mp 177 °C, (undepressed mixture mp with an authentic sample).

Preparation of Phthalides 9a-b, 16b-c, and 17

7-Methoxyphthalide (9a):[35] To a solution of **7a** (1 equiv) in MeOH was added $NaBH_4$ (2 equiv). The solution was stirred for 3 h, and acidified with 2 N HCl and the whole was refluxed for 1 h. Standard workup afforded pure **9a** (49% yield from **6**), mp 105-106 °C ($CHCl_3$), lit[53] mp 107-109 °C.

4-Methoxyphthalide (9b): Using the above one-pot procedure, the phthalaldehydic amide **11a** was converted into **9b** (43% yield from **10**); mp 68-69 °C ($CHCl_3$), lit[55] mp 69-70 °C.

6,7-Dimethoxyphthalide (Meconine) (16b): Using the above one-pot procedure, the phthalaldehydic amide **14b** was converted into **16b** (79% yield from **12**), mp 101-102 °C ($CHCl_3$), lit[56] mp 102 °C, undepressed in mixture mp with an authentic sample.

3-Carboxy-6,7-dimethoxyphthalide (Meconine α-carboxylic Acid) (16c): To a stirred solution of crude **14g** (373 mg, 1.1 mmol) was added 5% NaOH and the solution was refluxed for 1.5 h and cooled. $NaBH_4$ (0.2 g) was added in portions and the solution was refluxed for 6 h. 12 N HCl (5 mL) was added and the solution was refluxed for 3 h. Standard workup afforded a solid which upon recrystallization from EtOAc/$CHCl_3$ (1:1) gave 261 mg (72%) of pure **16c** (72%), mp 91-92 °C ($CHCl_3$), lit[32h] mp 90 °C.

3-Carboxy-6,7-methylenedioxyphthalide (17): Using the above procedure, the glyoxylate amide **15c** was converted into **17** in 37% yield, mp 206-207 °C ($CHCl_3$), lit[32i] mp 210 °C.

3-Phenyl-4-fluorophthalide (24): The method for **14d** was followed to give **24**, 80% yield; mp 131-132 °C (EtOAc-hex); IR (nujol) υ (max) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) d 6.52 (s, 1H), 7.25-7.45 (m, 6H), 7.58 (dt, J = 4.5 Hz, 7.9 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 80.4, 121.4 (d, J = 19.0 Hz), 121.6 (J = 3.7 Hz), 126.9, 128.7 , 128.87, 129.4, 131.9 (d, J = 5.7 Hz), 134.8, 135.3 (d, J = 17.0 Hz), 156.9 (d, J = 254.0 Hz), 168.9; ^{19}F NMR ($CDCl_3$) δ -116.9 (dd, J = 4.4, 8.8 Hz); MS m/e (rel intensity) 228 (M^+, 100); HRMS calcd for $C_{14}H_9FO_2$ 228.0586, found 228.0589.

3-Phenyl-6-dimethylaminophthalide (25): The method for **14d** was followed to give **25**, 71% yield; mp 136-137 °C (EtOAc-hex); IR (nujol) υ (max) 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, 6H), 6.32 (s, 1H), 7.00 (dd, J =2.6, 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 7.23-7.30 (m, 2H), 7.30- 7.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 40.1, 82.1, 106.2, 118.9, 123.1, 126.5, 126.8, 128.6, 128.8, 137.1, 137.2, 151.2, 171.4; MS m/e (rel intensity) 253 (33), 129 (100); HRMS calcd for $C_{16}H_{15}NO_2$ 253.1102, found 253.1106.

7-Methoxyphthalide-3-acetic Acid (26): To a stirred solution of LDA (12.2 mmol) in THF (40 mL) at 0°C under nitrogen was added anhydrous HOAc (5 mmol, 0.29 mL). The mixture was stirred for 1.5 h at 0 °C and heated to 40 - 45 °C for 0.5 h. A solution of **7a** (637 mg, 2.7 mmol) in THF (5 mL) was injected by syringe. The solution was stirred for 12 h at 40 °C. Following sequential addition of H_2O (5 mL) and 2 N HCl (1 mL), the THF was removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and the resulting solution was extracted with a satd aq Na_2CO_3 solution (30 mL). The aqueous layer was acidified (6 N HCl), extracted with CH_2Cl_2 (3 x 40 mL) and the organic extract was evaporated to dryness to give a semi-crystalline material. A solution of this material and p-toluenesulfonic acid (100 mg) in toluene (10 mL) was refluxed for 12 h. The mixture was cooled and the toluene was removed in vacuo. The residue was redissolved in CH_2Cl_2 (20 mL) and the resulting solution was washed with satd Na_2CO_3 (20 mL). The aqueous phase was acidified with 6 N HCl and extracted with CH_2Cl_2 (4 x 30 mL). The CH_2Cl_2 extracted was dried over Na_2SO_4 and concentrated to give 391 mg of a colorless solid. Recrystallization ($CHCl_3$-hex-MeOH 5:4:1) afforded 336 mg (56%) of pure **26**, mp 201-202 °C, lit[38a] mp197-198 °C.

Iso-ochracinic Acid (27): A solution of **26** (94 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) at -78 °C under N_2 was treated with BBr_3 (4.3 mL, 4.3 mmol, 1 M solution in CH_2Cl_2) via a slow dropwise syringe addition. After stirring for 1 h, the cooling bath was removed and stirring was continued for 20 h. The excess BBr_3 was destroyed with aq MeOH and the solvent was evaporated in vacuo. The residue was dissolved in 10% Na_2CO_3 solution (10 mL) and the resulting solution was washed with CH_2Cl_2. The aqueous phase was acidified (6 N HCl) and extracted with EtOAc (4 x 30 mL). The EtOAc extract was dried (Na_2SO_4) and concentrated to give a semi-crystalline material. Continuous Soxhlet extraction with ether for 4 days gave 75 mg of crude material. Recrystallization (PhH-hex-MeOH 10:10:1) gave 47 mg (54%) of crystalline **2**, mp 160-161°C, lit[57] mp 162 °C.

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