ChemPubSoc Europe

DOI: 10.1002/ejoc.201701142

EurJOC European Journal of Organic Chemistry

Full Paper

Directed *ortho*-Metalation

Directed *ortho*-Metalation of *O*-Aryl *N*,*N*-Dialkylcarbamates: Methodology, Anionic *ortho*-Fries Rearrangement, and Lateral Metalation

M. A. Jalil Miah*[a] Mukund P. Sibi,[b] S. Chattopadhyay,[c] Oluwole B. Familoni,[d] and Victor Snieckus*[e]

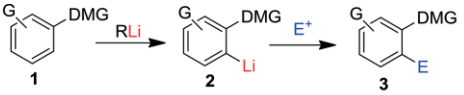
Dedicated to the Bangladesh nation with ardent hope for rising to the challenges of an improved state in the global village

Abstract: The directed *ortho*-lithiation reactions of *O*-aryl *N*,*N*-dialkylcarbamates as well as *O*-1-naphthyl and *O*-2-naphthyl *N*,*N*-dialkylcarbamates with *sec*-butyllithium/tetramethylethylenediamine (*s*BuLi/TMEDA) followed by quenching with various electrophiles afford a range of polysubstituted aromatic compounds. If the solutions of the *ortho*-lithiated carbamates are warmed to room temperature without the addition of external electrophiles, salicylamide and 1- and 2-hydroxynaphthamide derivatives are formed through anionic *ortho*-Fries rearrangements. The relative stabilities and reactivities of different *O*-aryl *N*,*N*-dialkylcarbamates were investigated. The lateral metalation of 2-tolyl carbamates with lithium diisopropylamide (LDA) provides a route to benzo[*b*]furan-2(3*H*)-ones. Previously reported results are used in a comparison of seven O-based directed metalation groups in reactions with several electrophiles. The described methodology is useful for the preparation of 1,2,3-substituted aromatic compounds.

Introduction

The directed *ortho*-metalation (DoM)[1–2] constitutes a synthetic strategy that has considerable utility for the efficient and regioselective construction of polysubstituted aromatic and heteroaromatic molecules of biological and agrochemical interest.[3,4] Among the considerable number of carbon- and heteroatom-based directed metalation groups (DMGs), oxygen-atom-based DMGs hold a prominent position owing to the original, almost concurrent, discovery of the *ortho*-metalation of anisole by Wittig[5] and Gilman.[6] Over the past 70 years, these original findings spawned numerous oxygen-based DMGs, the value of which is manifested particularly by their conversion into phenol derivatives (Table 1). The OMe and methoxymethoxy (OMOM) DMGs have been used extensively in synthesis, and $OCONR_2$[7–11] is now recognized as the most powerful DMG and has been challenged only recently by the $OP(O)(NR_2)_2$ group.[12] Since the discovery of the $OCONR_2$ DMG,[7] new preparation

Table 1. Oxygen-based directed metalation groups (DMGs).



DMG	Relative DMG power[a]	Discovery, year	Recent examples
OMe[b]	5	Wittig 1938, 1940[5] Gilman 1939, [6]	Smith 2009[13] Meskova 2013[14] Tietze 2014[15]
OMOM	2	Christensen 1975[16] Townsend 1981[17] Ronald 1982[18]	Snieckus 2007[19] Xiang 2007[20] Snider 2007[21]
OTHP	4	Parham 1948[22] Cassidy 1957[23]	Geneste 2001[24] Azzouz 2006[25]
$OCONR_2$	1	Snieckus 1983,[7]	Snieckus 1992[26] Snieckus 2008[27] Garg, Snieckus 2011[28]
OCH_2CH_2OMe[b]	3	Ellison 1973[29]	Wada 1985[30]
$OCH_2CH_2NMe_2$	Unknown	Wada 1985[30]	-
$OP(O)(NR_2)_2$	≥ $OCONR_2$	Nasman 1986[31]	Watanabe1989[32] Snieckus 2008 [12]
OSEM	Unknown	Snieckus 1990[33]	-
$OCON(Me)C\text{-}(Me)_2Ph$	Unknown	Snieckus 1999[34]	-
OSO_2NR_2	Unknown	Snieckus, 2005[35]	Garg, Snieckus 2011[28]
OCON(TMS)*i*Pr	Unknown	Hoppe 2001[36]	Snieckus 2005[37] Hoppe 2006[38]
$OP(O)(OR)_2$	Unknown	Melvin 1981[39] Cambie 1982[40]	Dhawan 1986[41] Watanabe 1989[32] Snieckus 2008 [12]

[a] Estimated from qualitative competitive experiments, see ref.[1b] [b] The ratio of (2-methoxyethoxy)benzene to anisole metalation ≈ 14:1 (deuteration experiment, see ref.[29]).

[a] *Department of Chemistry, Rajshahi University, Rajshahi 6205, Bangladesh*
E-mail: jalilmiah@gmail.com
http://www.ru.ac.bd/chemistry
[b] *Department of Chemistry, North Dakota State University, Fargo, ND 58105-5516, USA*
[c] *Department of Chemistry, Jadavpur University, Kolkata 700032, India*
[d] *Department of Chemistry, University of Lagos, Akoba-Yaba, Lagos, Nigeria*
[e] *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada*
E-mail: snieckus@chem.queensu.ca
http://faculty.chem.queensu.ca/people/faculty/snieckus/index.html
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701142.

and deprotection methods have been developed[38,42,43] and it has been used extensively in synthesis.[44] Recently, Sanz and co-workers[44a] reported a thorough study of the DoM and AoF rearrangement of dichloro, dibromo, and difluoro *O*-carbamates, and their results nicely extend those reported herein. The $OCONR_2$ group also participates in directed remote metalation reactions[45] and Ni-catalyzed Suzuki–Miyaura[46] and Kumada–Corriu[47] cross-coupling reactions and has been the subject of mechanistic studies.[48]

Herein, we report (1) an extensive methodological investigation of the DoM reactions of *O*-aryl and *O*-naphthyl carbamates, (2) the anionic *ortho*-Fries (AoF) rearrangement in both series, (3) the effect of the variation of the carbamate *N*-alkyl group on the efficiency of the DoM and the AoF, and (4) the competitive DoM and lateral metalation of *ortho*-tolyl *O*-carbamates, including conversion to benzofuranones for the latter. In an accompanying paper, we present intramolecular competition studies of the *O*-carbamate with several other prominent DMGs and illustrative iterative DoM chemistry.[49] These combined studies extend the preliminary results[7] substantially in all aspects above and provide new avenues for the diverse utility of the $OCONR_2$ DMG in DoM reactions of potential synthetic value.

Results and Discussion

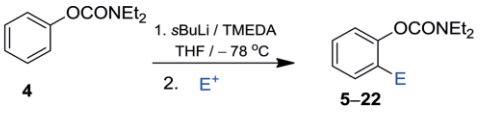
Methodological Studies

O-Phenyl *N*,*N*-diethylcarbamate (**4**), which can be obtained readily through the treatment of phenol with *N*,*N*-diethylcarbamoyl chloride in pyridine (see Supporting Information), was subjected to metalation under the originally established optimized conditions [*s*BuLi, tetramethylethylenediamine (TMEDA), and tetrahydrofuran (THF) at –78 °C][7] followed by deuteration (MeOD) to afford the deuterated product **5** in almost quantitative yield (95 %) and with high D incorporation (96 % D_1, Table 2).

From the synthetic perspective, the quantitative D incorporation indicates the formation of a high anion concentration under the given conditions. On the basis of this result and the relative reactivity, a variety of electrophiles were introduced to give products **6**–**22** in good-to-excellent yields; the exceptions were **12** and **15**, possibly because of the presence of acidic C–H bonds in the electrophile and single electron transfer (SET) reactions, respectively. Thus, in addition to alkylation and allylation (**6** and **7**) products, diverse carbon electrophiles at carboxaldehyde (**8**), carboxylic acid (**9**–**11**), and carbinol (**13**–**15**) oxidation states were obtained. Products with *ortho*-sulfur (**17** and **18**), -halo (**19**–**21**), and -hydroxy (**22**) substituents were also obtained cleanly, and the latter result shows the differentiation of catechol hydroxy groups. Compounds **10** and **11** are poised for further DoM reactions,[49] whereas products **16**, **17**, **19**–**21**, and **22** are basic substrates for further modern synthetic manipulations.

In view of the ready availability of *O*-phenyl *N*,*N*-dimethylcarbamate (**23**) and to make a parallel comparison and contrast with the *N*,*N*-diethyl- versus *N*,*N*-dimethylbenzamide DoM reactivity,[50] we tested **23** in electrophile quench experiments

Table 2. Synthesis of 2-substituted *O*-aryl *N*,*N*-diethylcarbamates.



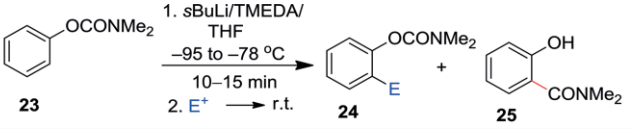
4 5–22

E^+	Product	E	Yield [%][a]
MeOD	**5**	D	95[b]
MeI	**6**	Me	80
	**7**		75
DMF	**8**[c]	CHO	73
CO_2	**9**	CO_2H	73
$ClCONEt_2$	**10**[d]	$CONEt_2$	86
PhNCO	**11**	CONHPh	80
Ac_2O	**12**	COMe	22
n-PrCHO	**13**	CH(OH)Pr-*n*	86
PhCHO	**14**	CH(OH)Ph	90
Ph_2CO	**15**	$C(OH)Ph_2$	22
TMSCl	**16**	TMS	79
$(MeS)_2$	**17**	SMe	79
$(PhS)_2$	**18**	SPh	87
Cl_3CCCl_3	**19**	Cl	86
$BrCH_2CH_2Br$	**20**	Br	86
I_2	**21**	I	78
$B(OMe)_3/H_2O_2$, HOAc	**22**	OH	98[e]

[a] Yields of purified (crystallized or distilled) materials. [b] 96 % D_1 (determined by MS). [c] 42 % of the product was isolated as salicylaldehyde. [d] Identical to the product prepared through the treatment of *N*,*N*-diethyl-2-hydroxybenzamide with $ClCONEt_2$. [e] Isolated as the product of hydrolysis (see Supporting Information).

under several different conditions (Table 3). Thus, **23** was subjected to lithiation under the standard conditions (*s*BuLi/TMEDA/THF at –78 °C) for 45 min and then quenched with MeI, and the salicylamide derivative **25**, resulting from an anionic *ortho*-Fries rearrangement (see below), was obtained exclusively in 75 % yield after the reaction mixture was warmed to room temperature rather than the *ortho*-methylated carbamate **24a** (Table 3, Entry 1). This result indicates that the rate of the anionic *ortho*-Fries rearrangement for **23** is very fast compared with that for the corresponding reaction of the *N*,*N*-diethyl analogue **4**. However, under these conditions but with a short lithiation time (10 min), the *ortho*-methyl derivative **24a** was

Table 3. Metalation studies of **23**.



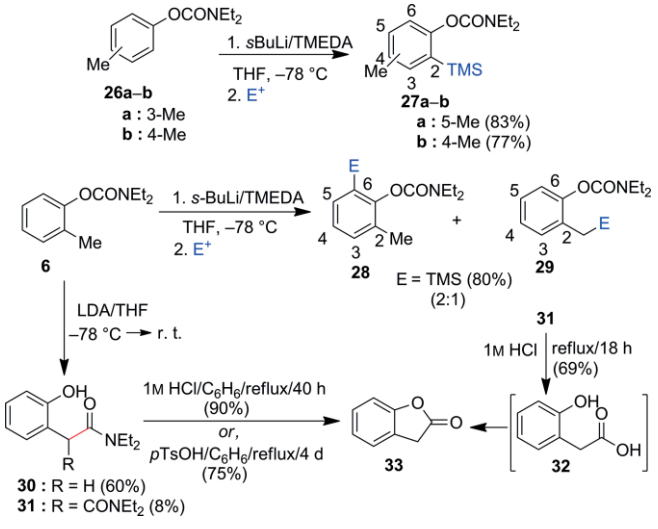
23 24 25

Entry	Temp [°C]	Time [min]	E^+	Product, yield [%][a] 24 (E)	25
1	–78	45	MeI	–	75
2	–78	10	MeI	**24a:** 60 (Me)	20
3	–95	10	MeI	**24a:** 90 (Me)	–
4	–95	10	Et_2NCOCl	**24b:** 70 ($CONEt_2$)	–
5	–95	10	TMSCl	**24c:** 88 (TMS)	–

[a] Yields of isolated products.

obtained as the major product (60 % yield) with minor amounts of the rearrangement product **25** (20 % yield; Table 3, Entry 2). At –95 °C and with a lithiation time of 10 min, only **24a** was isolated in high yield (90 %) with no detectable amount of **25** (Table 3, Entry 3). These conditions were adopted with two other electrophiles to furnish products **24b** and **24c** in good yields (Table 3, Entries 4 and 5).

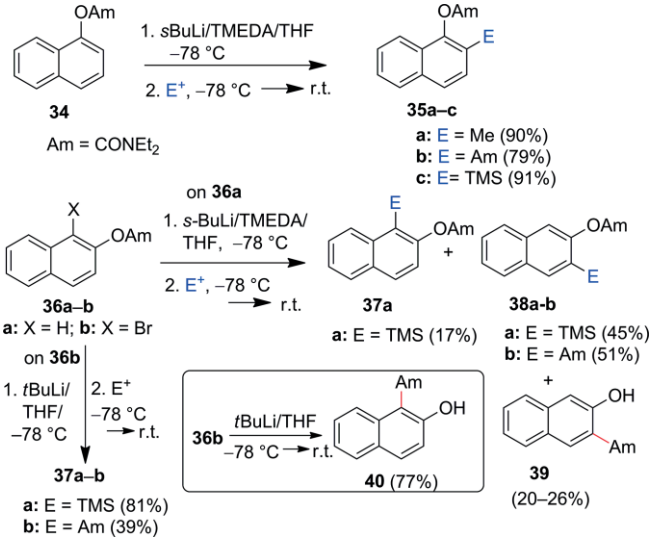
To define further the scope of the DoM chemistry of aryl *O*-carbamates, systems bearing additional DMGs were investigated, and the results are reported separately,[49] whereas the metalations of the three isomeric *ortho*-tolyl carbamates **26a**, **26b**, and **6** are presented in Scheme 1. The 3-methyl isomer **26a** led to the formation of silylated product **27a**, and this result matches the behavior of the corresponding benzamide,[50] which also undergoes reaction at the less hindered C-2 site. The 4-methyl derivative **26b** underwent clean metalation and silylation to give **27b** as the only detected (NMR spectroscopy) and isolated product; thus, the expected inconsequential and relatively weak acidity of the 4-methyl hydrogen atoms under these conditions was confirmed.[50]



Scheme 1. DoM and lateral metalation reactions of 2-methyl *O*-carbamates. Synthesis of benzofuranone.

The 2-methyl *O*-carbamate **6** behaved uniquely to give a mixture of DoM (**28**) and lateral metalation (**29**)[7,51] products in a trimethylsilyl chloride (TMSCl) quench experiment (**28**/**29** = 2:1 from integration of the Me and CH_2 signals in the ^1H NMR spectrum; Scheme 1). On the other hand, metalation with lithium diisopropyl amide (LDA) resulted in the formation of products **30** (60 % yield) and **31** (8 % yield), which indicate that metalation occurs exclusively at the benzylic position. In the context of the complex-induced proximity effect (CIPE),[45] the strongly basic *s*BuLi/TMEDA conditions are responsible for the predominant formation of the *ortho*-metalation product **28** over the lateral metalation product **29**, whereas the use of LDA without an electrophile quench allows the formation of an equilibrium concentration of the *ortho*-tolyl anion, which is driven to carbamoyl migration to form **30** by the substantial effect of the phenolate leaving group. The formation of **31** may be rationalized by intermolecular carbamoyl migration from **6** facilitated by the higher acidity of the resulting α-acetamide anion in spite of its phenolate deactivation. The treatment of **30** under acid-catalyzed conditions (1 M HCl or *p*TsOH/C_6H_6; *p*TsOH = *p*-toluenesulfonic acid) led to 2(3*H*)-benzofuranone (**33**, 72–94 % yield), whereas **31** underwent facile hydrolysis and decarboxylation (1 M HCl) to give 2-hydroxyphenylacetic acid (**32**, 69 % yield), which, without isolation, also underwent cyclization to afford **33**. This methodology has found use for the synthesis of benzofuranone derivatives with substituent patterns that are difficult to obtain by other means. For instance, 7-chloro-, 7-methoxy-, and 6-methyl-2(3*H*)-benzofuranones as well as an unnamed metabolite from a *Helenium* species bearing the 2(3*H*)-benzofuranone system were prepared by this sequence.[44g]

The DoM reaction was then extended to *O*-naphthyl carbamates. *O*-1-Naphthyl *N*,*N*-diethylcarbamate (**34**) underwent smooth lithiation under the standard conditions (*s*BuLi/TMEDA/THF at –78 °C) and the resulting lithiated species was subsequently quenched with MeI, Et_2NCOCl, and TMSCl to afford products **35a**, **35b**, and **35c**, respectively, in high yields (Scheme 2).[52]



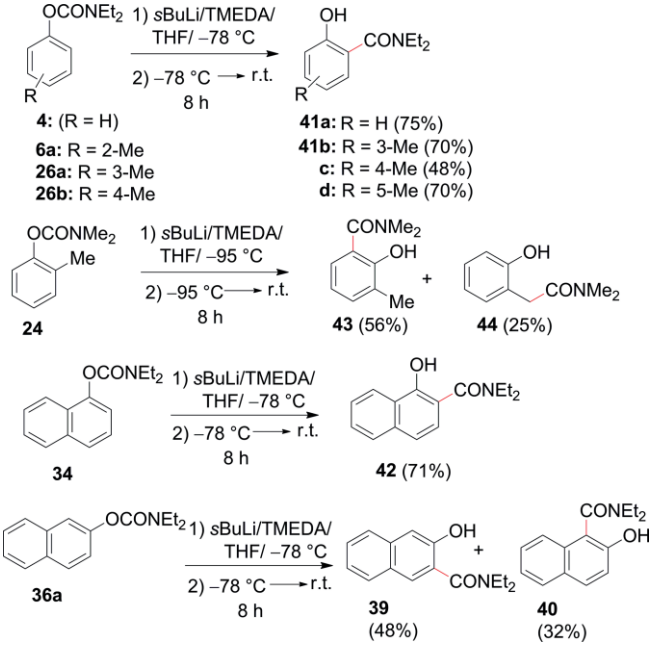
Scheme 2. DoM reactions of 1- and 2-naphthyl *O*-carbamates.

On the other hand, *O*-2-naphthyl *N*,*N*-diethylcarbamate (**36a**) afforded isomeric 1- and 3-substituted naphthyl carbamates **37a** (17 % yield) and **38a** (45 % yield) for TMSCl and **38b** (51 % yield) for Et_2NCOCl quenching experiments, respectively (Scheme 2). In addition, the AoF rearrangement product, 3-hydroxy-2-naphthamide (**39**), was obtained in 20–26 % yields in both series. Although the purification of **37a** was difficult (see Supporting Information), it was obtained cleanly in 81 % yield by the metal–halogen exchange/TMSCl quench procedure of 1-bromo-2-naphthyl carbamate (**36b**) under the preferred metal–halogen exchange conditions.[53] This result and the analogous quench experiment with Et_2NCOCl to give **37b** (39 % yield) shows unambiguously that C-1-regioselective metalation had occurred. It also allows the conclusion that the 1-lithiated 2-carbamoyloxy species is stable under these conditions with respect to equilibration to the corresponding 3-lithiated spe-

cies. The stability of the 1-lithio intermediate was established for an extended time (6 h) at –78 °C before treatment with TMSCl to furnish only **37a** (85 % yield) and no other identifiable products (see Supporting Information). Furthermore, 2-hydroxy-1-naphthamide (**40**, 77 % yield) was obtained cleanly from **36b** under metal–halogen exchange conditions through the AoF rearrangement. The conditions for greater C-1 over C-3 regioselectivity in the context of the synthesis of multisubstituted naphthalene derivatives with lithium tetramethylpiperidide (LiTMP) and LDA bases have been studied recently in our laboratories.[2d] We have also previously reported that the 2-(trimethylsilyl)ethoxymethoxy (OSEM) derivative of 2-naphthol shows a preference for C-3 DoM chemistry.[33]

The Anionic *ortho*-Fries Rearrangement

As observed previously,[7] in the absence of an external electrophile, the intermediate lithiated species formed under the standard conditions (*s*BuLi/TMEDA/THF at –78 °C) from **4** undergoes rearrangement upon slow warming to room temperature to give the salicylamide derivative **41a** (Scheme 3) by a process that is the equivalent of the well-known Lewis acid-catalyzed transformation[54] and may be formally termed the anionic *ortho*-Fries (AoF) rearrangement. In the AoF rearrangement, the *O*-carbamate effectively serves as a "carrier" of the amide group, which is a powerful DMG,[1b] into the *ortho* position to entice further DoM chemistry.



Scheme 3. Anionic *ortho*-fries rearrangement to salicylamide and naphthamide derivatives.

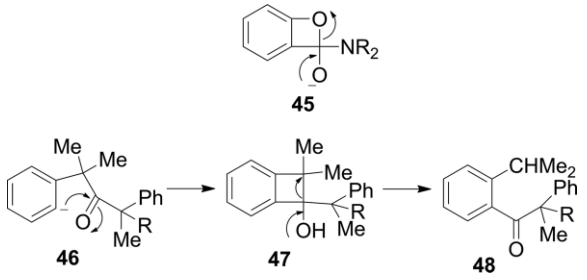
The AoF rearrangement reaction was extended to the synthesis of methyl-substituted salicylamide derivatives **41b**–**41d** from the readily available starting materials **6a**, **26a**, and **26b** (Scheme 3) and has been applied to systems bearing other DMGs in work described separately.[49] Not surprisingly, on the basis of the DoM chemistry of **26b**, for which the deprotonation of the methyl group is not observed (see Table 2), its anionic *ortho*-Fries rearrangement leads to 2-hydroxy-5-methylbenzamide (**41d**) in good yield. On the other hand, the 3-methyl and 2-methyl *O*-carbamates (**26a** and **6a**, respectively) lead solely to the 4-methyl (**41c**) and 3-methyl (**41b**) derivatives, respectively, and these regioselective processes differ from their behavior in the kinetic electrophile quench experiments (see Table 2). The thermodynamic control of the rearrangements may imply that the deprotonation of the methyl group occurs but the reactions are driven to their end products by the leaving-group stabilities of the respective phenolate anions. Interestingly, the metalation of the *N*,*N*-dimethylcarbamate **24**, which corresponds to **6a**, afforded a mixture of the rearrangement product **43** (56 % yield) and the lateral metalation carbamoyl migration product **44** (25 % yield, see Supporting Information). Furthermore, notable contrasting results were observed in reactions of **6a** and the corresponding dimethylamide of **24** mediated by excess LDA and *s*BuLi/TMEDA (see Supporting Information). Although further rationalization is presently inappropriate owing to the lack of structural and theoretical evidence, the synthetic value of the rapid access to salicylamides **41b**–**41d**, in particular the 1,2,3-contiguously substituted **41b**, may be appreciated, for example, in view of the recent establishment of mild conditions for the benzamide to benzaldehyde conversion with the Schwartz reagent.[43c]

In a comparative study, the metalation of *O*-phenyl *N*,*N*-dimethylcarbamate (**23**, Table 3) with *s*BuLi/TMEDA/THF at –95 °C for 5.5 h followed by quenching with NH_4Cl at this temperature and then warming to room temperature afforded the AoF rearrangement product **25** in 86 % yield, whereas the application of identical conditions for the *O*-phenyl *N*,*N*-diethylcarbamate (**4**) but with the metalation at –78 °C for 5.5 h and quenching at –78 °C followed by warming to room temperature over 8 h gave a mixture of **4** and **41a** in a 92.5:7.5 ratio in 90 % yield; these results indicate the relatively higher stability of the lithiated species of **4** over that of **23**.

In a concurrent study, the 1- and 2-naphthyl *O*-carbamates **34** and **36a** were subjected to the AoF rearrangement conditions to furnish amides **42** and a mixture of amides **39** and **40**, respectively, and these results match those from the electrophile quench experiments (Scheme 2). Compound **39** is known, and product **40** was identified by comparison of its spectral and physical properties with those of the material prepared from the bromo derivative **36b** through metal–halogen exchange followed by anionic rearrangement (see Supporting Information).

To distinguish between an intra- and intermolecular anionic 1,3-carbamoyl migration, a mixture of 1 equiv. each of **23** and **26b** was lithiated with 2 equiv. of base, (–95 °C, 8 h, warming to room temp.), and the corresponding salicylamide derivatives **25** (75 % yield) and **41d** (7 % yield) were obtained with no evidence for crossover products; thus, an intramolecular anionic O-to-C carbamoyl migration occurs (AoF rearrangement).

The high yields of the anionic *ortho*-Fries rearrangement products that are usually obtained (Scheme 3) also suggest that the reaction proceeds through an intramolecular mechanism with the formation of the tetrahedral intermediate **45**, analogous to the intermediate **47** formulated for the anionic rearrangement of ketone **46** to product **48** (Scheme 4).[55]

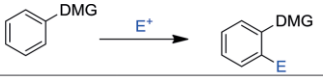


Scheme 4. Mechanisms of carbamoyl and carbonyl migrations.

Comparison of O-Based DMGs

We have demonstrated that *N*,*N*-diethyl *O*-carbamate is an excellent DMG for the regioselective construction of substituted aromatics by DoM chemistry; the reaction has generality for aryl (Table 2) and naphthyl (Scheme 2) *O*-carbamates, and methyl-substituted *O*-carbamates to afford highly substituted products and also has potential for the synthesis of benzofuranones (Scheme 1). Together with the facile and practical anionic *ortho*-Fries rearrangement, these protocols furnish products not readily available by other methodologies (Scheme 3). The hierarchical position of the *O*-carbamate (Table 1) and its conversion into phenol under mild reductive conditions[56] places it in a compelling position as the DMG of choice (Table 4) for synthetic aromatic chemistry. Bearing in mind the caveat for the required reproduction of synthetic experiments, several useful points may be perceived from the presented data: (1) for the seminal OMe DMG OMe (Table 4, Entry 1), the use of *t*BuLi appears to be commonly adopted (Table 4, Entries 2–5) but perhaps not required; (2) the OMOM DMG survives metalation at 0 °C and room temp. to provide reasonably efficient reactions (Table 4, Entries 6–11); (3) the acid-labile 2-methoxyethoxy (OMEM) DMG is an inadequately investigated DMG (Table 4, Entries 12–16); the use of *n*BuLi/THF/TMEDA at –20 → 10 °C provides high product yields for the underappreciated, mildly deprotectable OTHP (THP = tetrahydropyran) DMG (Table 4, Entries 17–19); (4) the OSO_2NR_2 and $OP(O)(NR_2)_2$ DMGs are perhaps uncompetitive for broad synthetic use in view of the low temperatures required for the deprotonation (Table 4, Entries 20–28); (5) the $OCONR_2$ DMG fares well in comparison with other O-based DMGs, for example, in *N*,*N*-dimethylformamide (DMF) and CO_2 quench experiments (Table 4, Entries 30 and 31). To conclude, for the requirements of mild acid-sensitive DMGs, OMOM is a primary choice with the proviso that OTHP deserves further investigation. For Lewis acid stability, the $OCONR_2$ DMG is a worthy choice. The fact that all comparisons were made for unsubstituted DMG systems is the final caveat for the application of these prototype reactions.

Table 4. Comparison of the reaction efficiencies of selected O-based DMGs.



DMG	Entry	Conditions	E^+	E	Yield [%]	Ref.
OMe	1	[a]	DMF	CHO	60	[57]
	2	[b]	PhCHO	Ph(CH)OH	75	[13]
	3	[c]	CO_2	COOH	54–60	[6]
	4	[b]	CO_2	CO_2H	80	[13]
	5	[d]	CO_2/CH_2N_2	CO_2Me	70	[18]
OMOM	6	[e]	MeI	Me	59	[59]
	7	[f]	DMF	CHO[c]	80–85	[16]
	8	[g]	DMF	CHO	89–95	[58]
	9	[h]	DMF	CHO	78	[60]
	10	[h]	CO_2	CO2H	76	[60]
	11	[h]	I_2	I	73	[60]
OMEM	12	[h]	MeI	Me	68	[30]
	13	[h]	DMF	CHO	62	[30]
	14	[h]	PhCHO	CH(OH)Ph	29	[30]
	15	[h]	CO_2	CO_2H	70	[30]
	16	[h]	TMSCl	TMS	43	[30]
OTHP	17	[i,j]	TMSCl	TMS	90	[22,24]
	18	[i]	$(PhS)_2$	PhS	83	[22]
	19	[i]	C_2Cl_6	Cl	89	[22]
$OSO.NR_2$	20	[k]	DMF	CHO	63	[35]
	21	[k]	PhCHO	CH(OH)Ph	80	[35]
	22	[k]	TMSCl	TMS	96	[35]
	23	[k]	$(MeS)_2$	MeS	88	[35]
	24	[k]	I_2	I	78	[35]
$OP(O)-(NR_2)_2$	25	[l]	MeI	Me	87	[12,32]
	26	[l]	PhCOMe	PhC(OH)Me	64	[32]
	27	[l]	TMSCl	TMS	79	[32]
	28	[l]	$(PhS)_2$	PhS	64	[32]
$OCO-NR_2$	29	[m]	MeI	Me	80	[7]
	30	[m]	DMF	CHO	73	[7]
	31	[m]	PhCHO	CH(OH)Ph	86	[7]
	32	[m]	CO_2	CO_2H	73	[7]
	33	[m]	TMSCl	TMS	79	[7]
	34	[m]	I_2	I	78	[7]

[a] *n*BuLi/TMEDA/r.t. [b] *t*BuLi/THF/–78 °C. [c] *n*BuLi/Et_2O/reflux. [d] *t*BuLi/petroleum ether/0 °C. [e] *n*BuLi/hexane/r.t. [f] *n*BuLi/TMEDA/hexane/0 → 5 °C. [g] *n*BuLi/Et_2O/r.t. [h] *n*BuLi/Et_2O/r.t. [i] *n*BuLi/THF/TMEDA/–20 to –10 °C/E^+ → r.t. [j] *n*BuLi/THF/–70/E^+ → r.t. [k] *s*BuLi/TMEDA/THF/–93 °C → r.t. [l] *s*BuLi/THF/–105 → –78 → 0 °C to r.t. (R = Me, Et). [m] *s*BuLi/TMEDA/THF/–78 → 0 °C.

Conclusion

We have presented a comprehensive study of the directed *ortho*-lithiation reaction of *O*-aryl, *O*-1-naphthyl and *O*-2-naphthyl *N*,*N*-dialkylcarbamates. In addition, we have established and generalized the anionic *ortho*-Fries rearrangement reaction of the *ortho*-lithiated *O*-carbamates which leads to the synthesis of salicylamides and 1- and 2-hydroxynaphthamides. Both reactions provide new methodologies for the construction of highly substituted aromatics, in particular, difficult to access 1,2,3-substituted derivatives. To provide additional synthetic utility, the relative stability and reactivity of different *N*,*N*-dialkylcarbamates and lateral metalation of *O*-2-tolyl carbamate to afford benzo[*b*]furan-2(3*H*)-ones are reported. To indicate relative efficacy and convenience, a comparison of seven *O*-based directed metalation groups in reaction with several electrophiles with the *O*-carbamate group is tabulated. The utility of the presented methodology, already indicated by previous work from our laboratories and others,[44] in synthetic aromatic chemistry may be anticipated.

In the complementary study,[49] the comparative and synergistic effects of the *O*-carbamate with respect to several other DMGs in DoM reactivity are investigated.

Experimental Section

Procedure 1 – Lithiation of *O*-Aryl Carbamates with *s*BuLi/TMEDA: A solution of the carbamate in dry THF (5–10 mL) was added dropwise by syringe injection to a stirred solution of a 1:1 *s*BuLi/TMEDA complex in dry THF at –78 °C (or –90 °C as indicated) under nitrogen. After a reaction period (5 min to 1 h as indicated), the mixture was treated with an electrophile. The resulting solution was then warmed to room temp. over 8 h, after which an aqueous NH_4Cl solution (a few mL) was added, and the THF was removed in vacuo. Subsequent standard workup afford the crude product. The details of the lithiation procedures that follow this standard procedure are summarized as follows: name and number of molar equivalents of alkyllithium reagent used, reaction temperature, lithiation time, and name and number of molar equivalents of electrophile used.

Procedure 2 – Lithiation of *O*-Aryl Carbamates with LDA: To a THF solution of freshly distilled diisopropylamine (1.1 equiv.) was added *n*BuLi (1.1 equiv.) at 0 °C under nitrogen, and the solution was stirred for 30 min. The resulting LDA solution was cooled to –78 °C, and the required carbamate (1.0 equiv.) in THF (5 mL) was added by syringe injection. After 1 h, an electrophile was added, and the resulting solution was warmed to room temp. over 8 h and processed in the normal manner (as described for Procedure 1) to afford the crude product.

Procedure 3: The lithiation of the appropriate carbamate was performed with *s*BuLi/TMEDA (Procedure 1) or LDA (Procedure 2), and the resulting lithiated carbamate was warmed to room temp. over 8 h. Processing in the manner described for Procedure 1 afforded the crude product.

Acknowledgments

We are grateful to Natural Sciences and Engineering Research Council of Canada (NSERC) for Discovery Grants in support of our synthetic programs. M. A. J. M. is grateful to Rajshahi University, Bangladesh for sabbatical leave and Queen's University, Kingston, ON, Canada for a Visiting Professorship. Preliminary work was carried out by B. Beattie, B. Byron, and J. Lee, to whom we are grateful.

Keywords: Directed *ortho*-metalation · Anionic *ortho*-Fries rearrangement · *O*-Carbamates · Substituted aromatics · Benzofurans

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Received: August 15, 2017

