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The Sydnone Ring as an *ortho*-Director of Lithiation. Dilithiation of 3-Phenylsydnone and Trapping by Electrophiles

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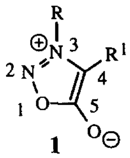
Abstract: Readily available 3-phenylsydnone (**3**) reacts with *n*-butyllithium / TMEDA to form the dilithio species **4** which can be trapped with suitable electrophiles. This represents the first use of a mesoionic ring system for directed lithiation. © 1997, Elsevier Science Ltd. All rights reserved.

Sydnones (*cf.* **1**) are unique, dipolar, heteroaromatic members of the general class of mesoionic compounds.[1] They undergo a variety of reactions including electrophilic aromatic substitution[2] (if $R^1 = H$), 1,3-dipolar cycloaddition (with, *e.g.* alkynes[3]), acid induced cleavage to hydrazines[4] (or products therefrom[5]) and metallation at the 4-position (if $R^1 = H$) and subsequent reaction with electrophiles.[6] Among the latter, lithiation (usually with n-butyllithium[7]) has been the most studied case and the pK_a of the sydnone ring proton has been estimated to be ~18-20.[8]

Our interest in sydnones stems from a desire to prepare fused ring congeners (*cf.* **2**) by modification of appropriately substituted *ortho*-substituted aryl precursors and this has proven to be a fertile area for study.[9] Unfortunately, the majority of suitable *ortho*-substituted arylsydnones are not readily available, requiring 4 step (or often more) syntheses from the appropriate aniline precursors.[10] Clearly, synthetic advantages would accrue from the availability of a *single* precursor to a variety of *ortho*-substituted arylsydnones and we now report that 3-phenylsydnone (**3**), readily prepared in two high yield steps from commercially available N-phenylglycine, fulfills this role. The success of this approach is predicated on two well known features of lithiation chemistry, *viz.* the *ortho* directing effect of groups capable of coordination to the lithium metal[11] and the base strengthening effect of tetramethylethylenediamine (TMEDA).[12] While these strategies have been applied successfully to the selective substitution of numerous aryl containing systems using a variety of directing groups,[13] no sydnone (or other mesoionic system) has been functionalized similarly.



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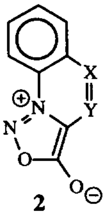
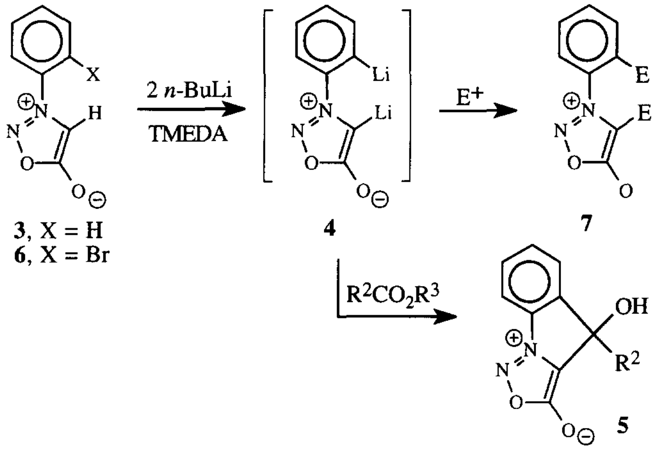


2

We believed that the sydnone moiety could act as a director of lithiation either by metal coordination to the electron-rich N-2 position or, subsequent to abstraction of the proton at C-4, to the lithium cluster then present.[14] Apparently, this premise is correct and we now report the *first* utilization of the sydnone ring as a director of *ortho*-lithiation using *n*-butyllithium / TMEDA (Scheme 1). Thus, we exposed 3-phenylsydnone (**3**) to 2.2 equivalents of *n*-BuLi in the presence of TMEDA in dry THF at -78°C. Subsequent treatment with methyl 2-methylpropanoate gave the sydnoindole **5** ($R^2 = {}^iPr$) in 96% yield, confirming that *ortho*-lithiation had taken place. The identity of **5** ($R^2 = {}^iPr$) was confirmed by comparison with an authentic sample prepared previously by generation of the presumed dilithio intermediate **4** from 3-(2-bromophenyl)sydnone (**6**).[15]

Scheme 1



Bolstered by this finding, we examined the reactions of the dilithio species **4** with a variety of electrophiles (Table 1). In all cases, disubstitution occurred to form the corresponding sydnones **7** in 85 - 93 % yield after 1h at -78°C followed by warming to 0°C. For the reactions with DMF and MeI, complete disubstitution (to form **7b** and **7f**, respectively) required longer periods at 0°C, presumably due to the relative unreactivity of the electrophiles. For the former, this is in line with recent results regarding the formylation of 4-lithiosydnones,[16] whereas, for the latter, to the best of our knowledge no successful alkylation of a 4-lithiosydnone has been reported. The identities of the products were confirmed by comparison with authentic materials (for **7g**),[15] or satisfactory combustion analyses, the presence of the sydnone C=O stretching vibration at ~1750 cm^{-1} (and the absence of the singular sydnone ring C-H stretching vibration at ~3150 cm^{-1}) in their infrared spectra and the expected chemical shifts and splitting patterns in their proton and carbon NMR spectra.

Overall, we have developed a useful preparation of 4-substituted *ortho*-substituted aryl sydnones which, due to the utility of the latter as precursors for hydrazines[4] and pyrazoles,[3] may find considerable application. We intend to explore further the directing abilities of other mesoionic systems as well as delineate the scope and limitations of the present discovery.

Table 1. Reactions of 3-Phenylsydnone **3** with BuLi / TMEDA then Electrophiles (E^+)

	E^+	E (in **7**)	Yield (%) of **7**[a]	mp(°C)
a	TMSCl	TMS	93	72-4
b	$HCONMe_2$	CHO	89	109-11
c	PhCHO	CH(OH)Ph	86	164-7
d	I_2	I	92	190-1
e	PhSSPh	SPh	88	113-15
f	CH_3I	CH_3	85	64-6
g	Br_2	Br	91	94-6

[a] All compounds were fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and combustion analysis

Representative Procedure

To a stirred solution of 3-phenylsydnone **3** (0.25g, 1.54mmol) in dry tetrahydrofuran (100mL) at -78°C under an atmosphere of dry nitrogen gas was added N,N,N',N'-tetramethylethylenediamine (0.29mL, 1.93mmol) then *n*-butyllithium (2.31mL, 3.47mmol, 1.5M in pentane) dropwise. After 0.5h, the appropriate electrophile (3.85mmol) was added to the golden yellow solution and, after an additional 1h, the mixture was allowed to warm to 0°C until reaction was complete (TLC evidence), whereupon it was quenched with saturated brine (100mL) and extracted with dichloromethane (3 x 100mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the corresponding disubstituted sydnone **7** as an oil which was purified by column chromatography (silica gel, dichloromethane as eluant) folowed by recrystallization from dichloromethane / hexane.

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