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The Sydnone Ring as an *ortho*-Director of Lithiation. 2.[1] Dilithiation of 3-Phenylsydnone and Regiospecific o-Aryl Acylation Using N-methoxy-N-methylamides

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Abstract: Readily available 3-phenylsydnone (**1**) reacts with *n*-butyllithium / TMEDA to form the dilithio species **2** which can be regiospecifically acylated at the *ortho*-aryl position using N-methoxy-N-methylamides (Weinreb's amides).

Recently, we reported the *first* utilization of the sydnone ring as a director of *ortho*-lithiation using *n*-butyl lithium in conjunction with N,N,N',N'-tetramethylethylenediamine (TMEDA) [Scheme 1].[1] Therein, we exposed 3-phenylsydnone (**1**) to 2.2 equivalents of *n*-BuLi in the presence of TMEDA in dry THF. Subsequent treatment with a variety of electrophiles gave the corresponding disubstituted sydnones **3** in 85-93% yield after one hour at -78°C followed by warming to 0°C, presumably *via* the dilithio intermediate **2**. Having established that dilithiation was possible, it was of interest to see whether or not the site of electrophilic substitution could be controlled. The pK_a of the sydnone ring proton has been estimated to be approximately 18-20[2] and, accordingly, it appeared likely that, in **2**, the anion at the *ortho* position would be considerably more reactive than that on the sydnone ring. Selectivity for the *ortho*-position was of considerable interest to us since much of our previous work has utilized *ortho*-substituted arylsydnones as precursors to differently substituted sydnones,[3] to fused ring sydnones[4] or to various heterocycles.[5] Our first attempt to assess whether or not *ortho*-selectivity was possible was by the use of one equivalent of chlorotrimethylsilane. However, after reaction at -78°C with the presumed intermediate **2**, a mixture of 4 products was obtained which, by TLC comparison with authentic samples, were 3-phenylsydnone (**1**), 4-trimethylsilyl-3-(2-trimethylsilylphenyl)-sydnone (**3**, E = TMS), and the products of monosilylation on the sydnone ring and at the *ortho*-aryl position, *viz.* 4-trimethylsilyl-3-phenylsydnone and 3-(2-trimethylsilyl)phenylsydnone, respectively. It was apparent that the electrophile was too reactive to allow selectivity. Extension to other electrophiles gave varied results. Thus, with diphenyl disulfide a situation similar to that with chlorotrimethylsilane arose (*viz.* four products) except that

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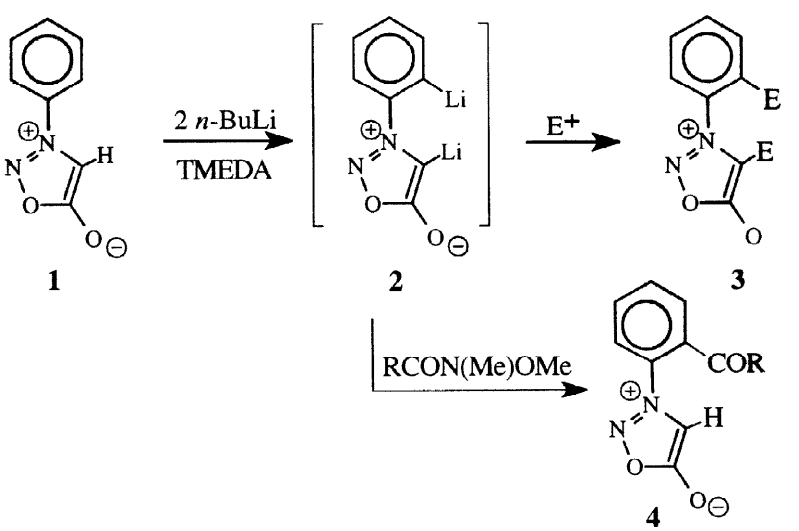
the product of sydnone ring substitution was absent. This result suggested that selectivity might be possible with the right electrophile and, indeed, somewhat surprisingly, reaction with iodine gave predominantly the *ortho*-iodo product, 3-(2-iodophenyl)sydnone. A similar result arose with benzophenone as electrophile, however, it proved impossible to effect complete conversion; 30-40% starting material remained. Complete selectivity for the *ortho*-aryl position was realized using methyl iodide as electrophile (3-(2-tolyl)sydnone resulted), however, extension to the preparation of other *ortho*-alkyl sydnones is problematic since ethyl iodide did not react under these conditions, presumably due to competitive elimination. The most consistent results were obtained using a weak electrophile such as an N-methoxy-N-methylamide (Weinreb's amide, prepared by reaction of the appropriate acid chloride with N,O-dimethylhydroxylamine in chloroform / pyridine)[6] and we now wish to report that use of these reagents allows regiospecific *ortho*-acylation in excellent yields. Thus, treatment of 3-phenylsydnone (**1**) with *n*-butyllithium / TMEDA at -78°C followed by the appropriate Weinreb's amide and an aqueous work-up affords the corresponding o-acyl arylsydnone **4** in 40-90% yield (Scheme 1). The success of this approach relies not only on the relatively greater nucleophilicity of the *ortho*-anion (in **2**) but also on the key characteristic of such reactions, *viz.* that, after initial attack of the *ortho*-anion upon the amide, in the resultant intermediate, effective complexation of the lithio intermediate prevents further reaction with excess organolithium reagent or the anion on the sydnone ring since the carbonyl group is not "revealed" until after work-up.

Scheme 1



Of the amides utilized (Table 1) only that derived from cyclohexanecarbonyl chloride (entry 9) failed to react and, as can be seen, alkyl (entry 1), haloalkyl (entry 2), arylalkyl (entry 4), phenyl (entry 3) and substituted aryl

(entries 5-8) ketones could be prepared using this method. It is unclear why no reaction occurred with N-methoxy-N-methylcyclohexanecarboxamide (entry 9) even under more vigorous conditions (48 hours at room temperature) or why the yield was so low (40%) with 2-phenyl-N-methoxy-N-methylacetamide (entry 4), although, for the latter, it is possible that the acidity of the methylenic protons in the reagent is a contributing factor.

The identities of the products were confirmed by comparison with authentic materials (for entries 1[7] and 3[8]), or satisfactory combustion analyses, the presence of the sydnone C=O stretching vibration at ~1750 cm^{-1} and 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 *ortho*-acyl arylsydnones which, due to the utility of the latter as precursors for 1-bromocarbonylindazoles,[5b] 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 **1** with BuLi / TMEDA then Weinreb's amides

Entry	R (in **4**)	Yield (%) of **4**[a]	mp(°C)
1	CH_3	84	112-14 [7]
2	CH_2Cl	86	164-6
3	Ph	90	113-14[8]
4	CH_2Ph	40	oil
5	4-BrC_6H_4	88	157-9
6	4-ClC_6H_4	88	137-9
7	4-$CH_3C_6H_4$	70	oil
8	4-$CH_3OC_6H_4$	75	107-9
9	C_6H_{11}	0	-

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

Representative Procedure

To a stirred solution of 3-phenylsydnone (**1**) [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 N-methoxy-N-methylamide (or other electrophile) [1.93mmol] was added to the golden yellow solution and,

after an additional 1h, the mixture was quenched with aqueous hydrochloric acid (100mL, 10% v/v) then extracted with dichloromethane (3 x 100mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the corresponding *o*-acylated sydnone **4** as an oil which was purified by column chromatography (silica gel, dichloromethane as eluant) followed by recrystallization from dichloromethane / hexane to afford colourless crystals (except for entries 4 and 7 which gave oils).

References and Notes

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