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Chlorination of 3-Arylsydnones with Iodine Monochloride

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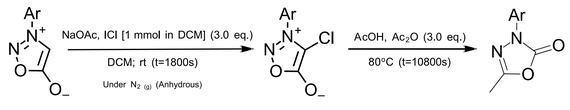
Abstract

An improved method for the chlorination at the 4-position of 3-arylsydnones **1** was developed, using iodine monochloride (ICl) dissolved in DCM. 1,3,4-Oxadiazol-2(3H)-ones **3** were then synthesized from the resultant 4-chloro-3-arylsydnones **2**. The scope and limitations will be presented.

Scheme 1: Overall scheme for chlorination of sydnones and subsequent transformation into 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones



1 a-j **2 a-j** **3 a-j**

a, Ar = H; b, Ar = p-Cl; c, Ar = p-Br; d, Ar = p-CH_3; e, Ar = p-$COCH_3$; f, p-OCH_3; g, m-OCH_3; h, 3,4-$DiCH_3$; i, 2,3-$DiCH_3$; j, 2,4-$DiCH_3$;

Introduction to Sydnones

Sydnones are unique, dipolar heterocycles, which are archetypal members of the class of compounds known as mesoionic.[1,2]

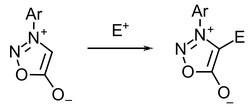
Synthesis of Sydnones

N-arylglycines can be converted to the corresponding 3-arylsydnones by transformation into the N-nitroso compounds followed by cyclization with acetic anhydride.[1,2,3]

Reactions of Sydnones

The process of electrophilic aromatic substitution is an integral part of sydnone research. When the sydnone ring is unsubstituted at the 4-position it becomes very susceptible to electrophilic attack and this allows for a variety of different substitutions of the sydnone-H.[3]

Scheme 2: Electrophilic Aromatic Substitution (EAS)



The most common example of EAS is halogenation.[3,4,5] While bromination[6] has been the most studied, several methods have been developed for chlorination at the sydnone 4-position. These methods include the use of Cl_2[7], NCS/DMF[8], $KClO_3$/HCl[9], $PhICl_2$[10] and a variety of electrochemical methods.[11]

Spectroscopic Properties of Sydnones

IR Spectrum
Sydnone C=O stretch: ~1744 cm^{-1}
Sydnone C-H stretch: ~3150 cm^{-1}
^1H NMR Spectrum
Sydnone CH: ~6.8 - 7.0 ppm
^{13}C NMR Spectrum
Sydnone C-4: ~95 ppm
Sydnone C-5: ~165 ppm

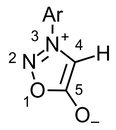
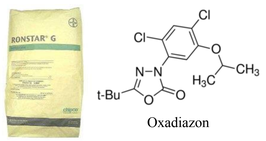


Figure 1. 3-Arylsydnone IUPAC numbering

Introduction of 1,3,4-oxadiazol-2(3H)-ones

Biological and Structure-Activity Relationship (SAR) studies have been performed on 1,3,4-oxadiazol-2(3H)-ones. It was observed that these chemical species could be utilized as herbicidal, anti-tumoral, anti-bacterial and anti-fungal agents.[12,13,15] Ronstar (Oxadiazon) an herbicide, is an example of a commercially available 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-one.

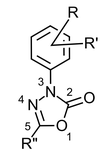


Oxadiazon

Figure 2. Common commercially available 1,3,4-oxadiazol-2(3H)-one

Synthesis of 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones

Many 5-R"-3-aryl-1,3,4-oxadiazol-2(3H)-ones have been prepared previously from 3-arylsydnones,[12,14,] hydrazides[16], carbamates[17] and phosgene.[18]



5-substituted-3-aryl-1,3,4-oxadiazol-2(3H)-one

Figure 3. 5-Substituted-3-aryl-1,3,4-oxadiazol-2(3H)-one IUPAC numbering

Reactivity 1,3,4-oxadiazol-2(3H)-ones

Previous work from our lab has shown that 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones are susceptible to electrophilic aromatic substitutions (EAS). Common examples include halogenation and nitration.

In further work from our lab, 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones have also been shown to react at the carbon of the C=O with "hard" nucleophiles such as methoxide and ethoxide ions; resulting in a ring-opening reaction.

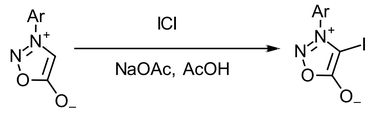
Spectroscopic Properties of 5-Alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones

IR Spectrum
C=O stretch: ~ 1780 cm^{-1}
C-H stretch: ~ 2930 cm^{-1}
C=N stretch: ~1490 cm^{-1}
^1H NMR Spectrum
Aliphatic CH_3: ~2.4 ppm
^{13}C NMR Spectrum
C-2: ~153.79 ppm
C-5: ~151.09 ppm

Background to Aims (sydnones)

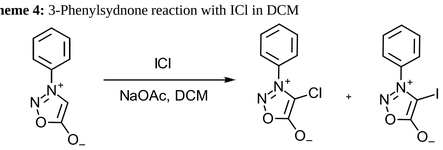
- In 1997, Dumitrascu observed iodination of 3-phenylsydnone with ICl in acetic acid[19]

Scheme 3: Reaction of 3-arylsydnones with "neat" ICl in AcOH



- In 2001, Imad Nashashibi from our lab observed the formation of two products, 4-chloro-3-phenylsydnone and 4-iodo-3-phenyl sydnone,[20] from the reaction of 3-phenylsydnone with ICl in DCM (see scheme 4).

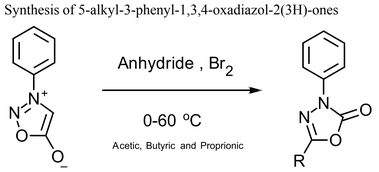
Scheme 4: 3-Phenylsydnone reaction with ICl in DCM



Background to Aims (1,3,4-oxadiazol-2(3H)-ones)

- Stansfield, in 1958, reported the first synthesis of 5-alkyl-3-phenyl-1,3,4-oxadiazol-2(3H)-ones from 3-phenylsydnone with a variety of acid anhydrides (scheme 5).[14]

Scheme 5: Synthesis of 5-alkyl-3-phenyl-1,3,4-oxadiazol-2(3H)-ones



Background to Aims (1,3,4-oxadiazol-2(3H)-ones) Cont'd.

- Badami et al. in 2000 synthesized a series of 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones from substituted 3-arylsydnones[12]
- Badami et al. suggested a 1,3-dipolar cycloaddition mechanism for the transformation to the 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones.[12] However, Yeh in 1994 reported that 4-halogenated-3-arylsydnones react with HX to form halocarbonyl arylhydrazine salts.[21]
- We believe that HX formed in the initial reaction with HCl or HBr cleaves the sydnone ring to the halocarbonyl arylhydrazine which then reacts with anhydride. Madaram in our lab (2015) proved this premise by reaction of the hydrazine salt with acid chlorides and anhydrides to prepare the 1,3,4-oxadiazol-2(3H)-ones.[22]

Specific Aims

- Selectively chlorinate 3-arylsydnones with ICl in DCM
- Assess the best avenue to 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones from halocarbonyl arylhydrazine salt intermediates using different HX and 4-halogenated-3-arylsydnones
- Synthesize 5-alkyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones from 4-chlorinated-3-arylsydnones, in one-pot, while minimizing the amount of anhydride used

Results (Chlorination with ICl in DCM)

- Using ICl dissolved in DCM, as opposed to "neat" ICl, the concentration of ICl was varied in an attempt to maximize 4-chloro-3-phenylsydnone yield (scheme 6, Ar = Ph).

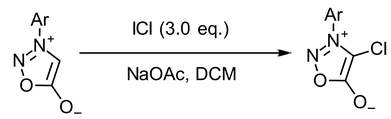
Table 1. Optimization parameters for ICl chlorination of sydnone

ICl eq.	Solvent	Reaction Time (Hr)	Product Composition (%)
1.1	DCM	0.5	4-Cl: ~60; 4-I: ~40*
1.1	DCM	6	4-Cl: ~60; 4-I: ~40*
1.5	DCM	0.5	4-Cl: 70; 4-I: 30
1.5	DCM	6	4-Cl: 70; 4-I:30
2	DCM	0.5	4-Cl: 80; 4-I: 20
2	DCM	6	4-Cl: 80; 4-I: 20
2.5	DCM	0.5	4-Cl: 90; 4-I:10
2.5	DCM	6	4-Cl: 90; 4-I:10
3	DCM	0.5	4-Cl: 100
3	DCM	6	4-Cl: 100

* Represents minimal presence of starting material

- Complete chlorination of 3-phenylsydnone occurred in 30 minutes using 3.0 equivalents of ICl (1 mmol in DCM).
- The procedure was extended to a variety of 3-arylsydnones on the basis of these results (scheme 6).

Scheme 6: 4-Chlorination of 3-arylsydnones utilizing ICl/NaOAC in DCM



Ar: 4-ClPh, 4-BrPh, 4-OMePh, 4-MePh, 3-OMePh, 4-$COCH_3$, 2,3-DiMe

Table 2. Products with melting points and yields from optimized ICl chlorination of 3-arylsydnones

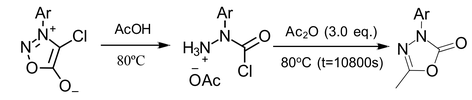
Products	Lit. MP (°C)	Expt. MP (°C)	Yield (%)	Pure Yield (%)
2a	127	116.5-117	87	72
2b	108	108-109	92.1	71
2c	110	111-112	108	71
2d	136-138	139	95	81
2e	N/A	138-139	84	46
2f	100	101-102	92.4	68
2g	95-96	93-94	92.4	74
2i	126-128	125-127	94	76.4

- ^1H, ^{13}C NMR, and IR were used to characterize the products from scheme 6

Results (1,3,4-oxadiazol-2(3H)-ones)

- The 4-chlorinated-3-arylsydnones **2** synthesized via ICl in DCM were subjected to a variety of tests prior to being converted to their corresponding 1,3,4-oxadiazol-2(3H)-ones **3.**
- The tests assessed stability based on the halogen attached at the sydnone 4 position (prior to ring cleavage) and if the acid used to form halocarbonyl arylhydrazine **4** effected reactivity with the anhydride (scheme 7)
- Nonetheless, both 4-bromo and 4-chloro sydnones were examined for this study using acetic anhydride 3.0 eq. in acetic acid
  - 4-Bromo analogs provided a complex mixture of products
  - 4-Chloro analogs, however, provided one spot by TLC and products could be precipitated by pouring over ice (scheme 7)

Scheme 7: Synthesis of 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones from 4-chloro-3-arylsydnones in acetic acid



2 a-j **4 a-j** **3 a-j**

a, Ar = H; b, Ar = p-Cl; c, Ar = p-Br; d, Ar = p-CH_3; e, Ar = p-$COCH_3$; f, p-OCH_3; g, m-OCH_3; h, 3,4-$DiCH_3$; i, 2,3-$DiCH_3$; j, 2,4-$DiCH_3$;

- Products were identified by ^1H, ^{13}C NMR, GC/MS, IR and melting point
- Crude material provided acceptable samples for all analyses

Table 3. Melting points and yields for products **3** synthesized via scheme 7

Products	Literature MP (°C)	Experimental MP (°C)	Crude Yield (%)
3a	91-92	90-91	78
3b	98-99	121-122	93
3c	129	124-125	98
3d	82-83	79-80	97
3e	138-139	168-170	64
3f	N/A	90-92	77
3g	N/A	75-76	88
3i	N/A	64-65	47

*3h and 3j not synthesized – not enough sample

Conclusion

- 4-Chloro-3-arylsydnones **2** were synthesized in high yields and purity using the optimized procedure
- 5-Methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones **3** were synthesized (from **2**) in high yields and purity, all in a novel one-pot synthetic procedure
- The quality and yields of 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones were improved by this process, which is now the most efficient avenue to such species

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Acknowledgements

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