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Chlorination of 3-Arylsydones with Iodine Monochloride

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

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

Introduction to Sydones
Sydones are unique, dipolar heterocycles, which are archetypal members of the class of compounds known as mesoionic.1,2

Synthesis of Sydones
N-arylcyanoacetic acids can be converted to the corresponding 3-arylsydones by transformation into the N-nitroso compounds followed by cyclization with acetic anhydride.1,3,4

Reactions of Sydones
The process of electrophilic aromatic substitution is an integral part of sydnone research. When the N-aryl 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-H3

Spectroscopic Properties of Sydones
IR Spectrum
Sydnone C=O stretch: ~1744 cm⁻¹
Sydnone C-H stretch: ~3150 cm⁻¹
1H NMR Spectrum
Sydnone C2: ~8.6 - 7.0 ppm
13C NMR Spectrum
Sydnone C-4: ~95 ppm
Sydnone C-6: ~165 ppm

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-tumor, anti-bacterial and anti-fungal agents.5,6,7 Remstar (Oxadiazon) an herbicide, is an example of a commercially available 5-aryl-1,3,4-oxadiazol-2(3H)-one.

Synthesis of 5-aryl-1,3,4-oxadiazol-2(3H)-ones
Many 5-aryl-1,3,4-oxadiazol-2(3H)-ones have been synthesized previously from 3-arylsydones,12,14 hydrazides,15 carboxamides16 and phosphines.17

Reactivity 1,3,4-Oxadiazol-2(3H)-ones
Previous work from our lab has shown that 5-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-aryl-1,3,4-oxadiazol-2(3H)-ones have also been shown to react at the carbon of the C3 with “hard” nucleophiles such as methoxide and ethoxide ions, resulting in a ring-opening reaction.

Spectroscopic Properties of 5-Alkyls-1,3,4-oxadiazol-2(3H)-ones
IR Spectrum
C=O stretch: ~1780 cm⁻¹
C3-H stretch: ~2930 cm⁻¹
C=C stretch: ~1490 cm⁻¹
1H NMR Spectrum
Aliphatic CH3: ~2.4 ppm
13C NMR Spectrum
C-2: ~135.79 ppm
C-5: ~151.09 ppm

Background to Aims (sydnone)
In 1997, Dimitracis observed iodination of 3-phenylsydnone with ICl in acetic acid18

Scheme 3: Reaction of 3-arylsydones with “soft” ICl to give AC

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

Scheme 4: Iodination reaction in DCM with ICl

Background to Aims (1,3,4-Oxadiazol-2(3H)-ones)
Staudinger in 1938, reported the first synthesis of 5-aryl-1,3,4-oxadiazol-2(3H)-ones from a variety of acid anhydrides (scheme 5).

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

Table 1: Oxidation parameters for IC50 (5-HT2A) assay

Results (1,3,4-Oxadiazol-2(3H)-ones)
The 4-chlorinated sydnone was synthesized via IC50 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 test results of 5-aryl-1,3,4-oxadiazol-2(3H)-ones 3.
Nonetheless, both 4-bromo and 4-chloro sydnone were examined for this synthetic work, 3 being an active 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

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

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

Conclusion
4-Chloro-3-arylsydones were synthesized in high yields and purity via the optimized procedure. 5-Methyl-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-1,3,4-oxadiazol-2(3H)-ones were improved by this process, which is now the most efficient avenue to such species

Reference

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