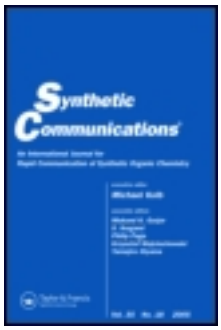

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An Improved Method for the Iodination of Sydnones

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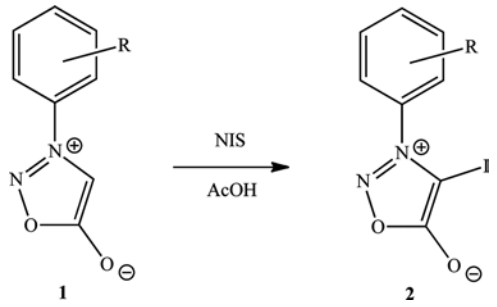
Abstract

Iodination at the sydnone C-4 position has been achieved in high yields for a series of 3-arylsydnones using N-iodosuccinimide in acetic acid.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



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KEYWORDS: iodination; mesoionic compounds; sydnones

INTRODUCTION

Sydnones are the most studied members of the class of heterocyclic compounds known as mesoionic.[1] They undergo a wide range of transformations including electrophilic aromatic substitution,[2] metalation,[3] 1,3-dipolar cycloaddition,[4] and cleavage with

aqueous acids to afford hydrazines[5] or heterocycles.[6] Halogenation of the sydnone ring at the C4 position has been achieved by a number of methods, however, of those reported, iodination remains the most problematic. For the latter, indirect routes involving 4-chloromercuri[7] and Grignard intermediates[8] have been described, however, such avenues suffer from toxicity or stability issues. One report of the use of N-iodosuccinimide (NIS) for the iodination of 3-(3-pyridyl)sydnone has been forthcoming,[9] however, the yield of the 4-iodo product was low and the generality of the process was unclear. To date, the most effective route to the preparation of 4-iodo sydnones **2** from the unsubstituted precursors **1** has been with iodine monochloride in acetic acid and, in general, very good yields of the iodinated products result.[2b,e] However, for another study, we required 4-iodosydnones and, while the ICl approach did provide the desired compounds, we had issues with the instability of the reagent. Accordingly, we elected to explore further the NIS methodology first reported by Greco in 1979 for the preparation of a single compound,[9] since NIS is a stable, crystalline compound.

RESULTS & DISCUSSION

For our initial test, we treated 3-phenylsydnone (**1**) with NIS (1.1 equivalents) in methanol at room temperature and, even after 36 hours of stirring, no reaction was observed and the starting material was recovered unchanged. Gratifyingly, changing the solvent to acetic acid resulted in an 89% yield of the corresponding 4-iodo species **2** after 4 hours at room temperature and we now report that this method is a general process for the iodination of 3-arylsydnones (Scheme 1).

In general, the yields are very good for a range of aryl substituents [Table 1, entries 1-9], though for **1g** the reaction required heating at 50°C for 5 hours for completion and a lower than expected yield of **2i** was obtained from **1i**. In these cases it is likely that the resonance withdrawing effect of the nitro group (in **1g**) and the steric encumbrance afforded by the 2-iodo substituent (in **1i**) are controlling factors. However, given the limited number of such examples available, further study will be necessary to determine any such trends. The 4-iodo products **2a-i** were identified by comparison with authentic samples (for **2a**,**c**,**d** and **i**) or from their infrared, proton and carbon nmr spectra. For the latter, attachment of an iodine atom at the sydnone C-4 position shifted the signal from ~95 ppm to ~55 ppm, allowing ready assessment of product identity.

In conclusion, we have developed an effective iodination methodology for 3-arylsydnones using 1.1 equivalents of N-iodosuccinimide in acetic acid at room temperature. In general, the product yields are high and work-up is straightforward, though strongly electron-withdrawing or sterically hindering groups may hamper the process. The further scope and limitations of this approach will be reported in due course.

EXPERIMENTAL

General Notes

3-Phenylsydnone (**1a**) and its substituted analogs **1b-1i** were synthesized according to reported procedures.[4a,10,11] All other starting reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired on a Mattson Genesis II FTIR. NMR spectra were acquired on a Bruker 300MHz NMR

spectrometer and are reported relative to tetramethylsilane as an internal standard. Combustion analyses were performed by Midwest Microlab, Indianapolis.

General Procedure For The Synthesis Of 4-Iodo-3-Aryl Sydnones 2 From 3-Arylsydnones 1 With N-Iodosuccinimide In Acetic Acid.

N-iodosuccinimide (NIS) (1.1 equiv) was added to a stirred solution of the 3-arylsydnone **1** (0.200 g) in acetic acid (3 mL). The mixture was allowed to stir at room temperature for 4 hours after which time water (10 mL) was added. The resultant precipitate was isolated by filtration and the filtrate was extracted with dichloromethane (3x 3 mL). The combined extracts were washed with aqueous NaOH (10%), separated then dried with magnesium sulfate, filtered and evaporated. The combined solids were then recrystallized from dichloromethane / hexanes.

Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found *via* the "Supplementary Content" section of this article's webpage.

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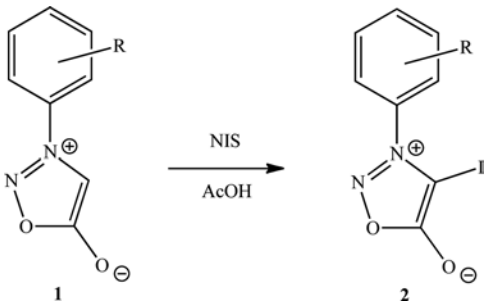
Table 1. Reaction of 3-arylsydnones 1a-i with N-iodosuccinimide / acetic acid to afford the corresponding 4-iodo congeners 2a-i

Entry	R in **1** & **2**	Yield of **2** (%)	mp °C	Lit. mp °C
1	a, H	89	163-5	164-5[2e]
2	b, 4-Me	77	168-9	---
3	c, 4-MeO	76	158-60	160-2[4b]
4	d, 4-Br	84	159-61	160-2[4a]
5	e, 4-Cl	87	161-3	---
6	f, 4-I	79	203-5	---
7	g, 4-NO_2	73	208-10	205-8[4b]
8	h, 3-CF_3	76	103-4	---
9	i, 2-I	64	183-5	190-1[3d]

Scheme I. Iodination of 3-arylsydnones **1**



1 **2**