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The reaction of sydnones with bromine in acetic anhydride revisited: a new route to 5-substituted-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones from *N*-aryl-*N*-bromocarbonylhydrazines

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Dedicated to Prof. Gordon Gribble upon the occasion of his retirement from Dartmouth College

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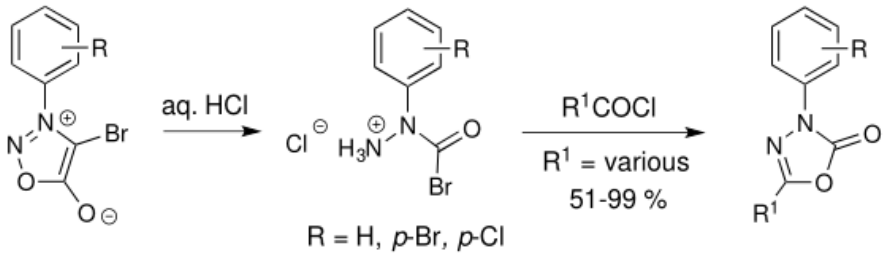
Abstract

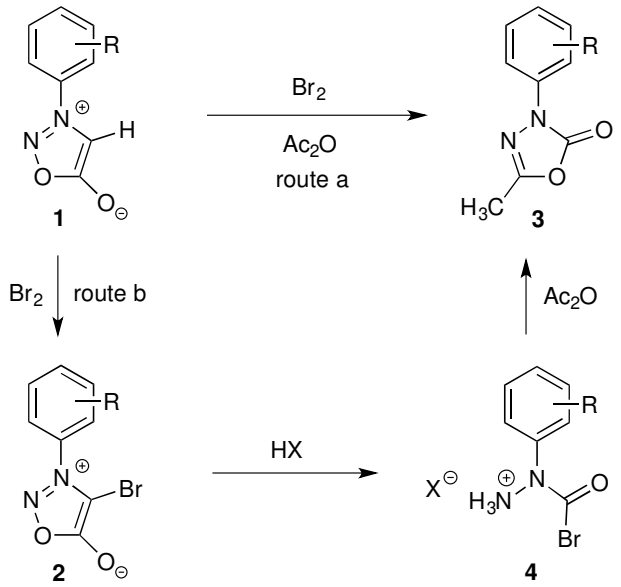
The reaction of 3-phenylsydnone with bromine in acetic anhydride to form 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one has been reexamined and improved. A new mechanism involving a bromocarbonylhydrazine species is proposed and its intermediacy is supported by the observation that it reacts with acetic anhydride to yield the corresponding 1,3,4-oxadiazol-2(*3H*)-one. The process has been expanded to the use of acid chlorides and a novel synthesis of 5-substituted-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones has been developed.



Keywords: 1,3,4-Oxadiazol-2(*3H*)-ones, sydnones, *N*-aryl-*N*-bromocarbonylhydrazines, bromine

Introduction

Sydnones (*c.f.* **1**) are members of the class of compounds known as mesoionic and have been studied extensively.[1] In 1946, Kenner and Mackay prepared 4-bromo-3-phenylsydnone (**2**, R = H) from the reaction of 3-phenylsydnone (**1**, R = H) with bromine in acetic acid.[2] Later, Baker, Ollis and Poole modified the process to use acetic anhydride as solvent.[3] However, when Stansfield[4] utilized the latter protocol he observed a vigorous evolution of gas at 30-40 ^{o}C and he isolated 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3a**) instead of the bromosydnone **2** (R = H) [Scheme 1, route a]. Over 40 years later, Badami *et al*. extended the process to the synthesis of a variety of 5-methyl-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones (**3**, R = various)[5] and they proposed a mechanism involving a 1,3-dipolar cycloaddition between **2** and the carbonyl group of the anhydride. They later concluded that HBr, which is formed *in situ*, is important for the process, but only as a catalyst for the 1,3-dipolar cycloaddition mechanism.[6] These mechanistic suggestions are surprising, especially since Yeh *et al*.[7] showed in 1994 that treatment of 4-bromo-3-phenylsydnone (**2**, R = H) with HX (X = Cl, Br) cleaves the ring to form an isolable bromocarbonyl hydrazine derivative (**4**, R = H). Given Yeh's results, it seemed likely to us that, rather than an unprecedented 1,3-dipolar cycloaddition process, the formation of the 1,3,4-oxadiazol-2(*3H*)-ones **3** (from **1**) instead involves the intermediacy of the corresponding bromocarbonyl hydrazine species **4** (*via* reaction of **2** with HBr formed *in situ*) and subsequent reaction of the latter with acetic anhydride (Scheme 1, route b).



Scheme 1. The reaction of sydnones with Br_2 in Ac_2O.

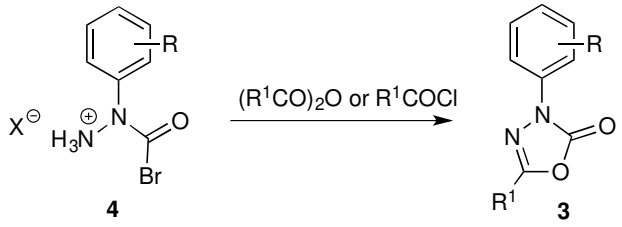
The present work was undertaken to reinvestigate this transformation, initially, by preparing the bromocarbonylhydrazine salt (**4**, R = H, X = Cl) from 4-bromo-3-phenylsydnone (**2**, R = H) and allowing it to react with acetic anhydride in the expectation that 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3a**) would result. If so, this avenue would be extended to the formation of different 5-substituted-3-phenyl-1,3,4-oxadiazol-2(*3H*)-ones (**3**, R = various) by the use of a variety of acid chlorides. The 1,3,4-oxadiazol-2(*3H*)-one core is found in a diverse array of bioactive species and 3,5-disubstituted examples have attracted considerable attention. *Inter alia*, such species exhibit protoporphyrinogen oxidase inhibition,[8] especially for herbicidal activity [*e.g.* oxadiazon[9] and oxadiargyl[10]], monoamine oxidase B inhibition,[11] fungicidal activity,[12]

hormone-sensitive lipase inhibition,[13] Ca^{2+}-activated potassium channel opening (BMS-191011),[14] antimycobacterial activity (NCS 130852)[15] and ABHD6 inhibition (3-substituted 5-alkoxy derivatives).[16] 3,5-Disubstituted 1,3,4-oxadiazol-2(*3H*)-ones have been prepared by a variety of methods, many of which involve the reaction of hydrazide derivatives with phosgene[16-18] or involved procedures.[19,20] More recently, 3,5-disubstituted oxadiazolinones have been prepared *via* alkylation of 2-ethoxy-1,3,4-oxadiazoles,[21] Pd-catalyzed carbonylation of hydrazides[22,23] and 1,3-dipolar cycloaddition of nitrile imines with carbon dioxide.[9]

Results and Discussion

First, it was important to reproduce the reported synthesis of **3a** [Scheme 1, route a], to provide an authentic sample of the product and to act as a benchmark for the process. Using the reported conditions (bromine in acetic anhydride added to **1** (R = H) at 0 °C, warming to 60 °C, then addition to water and standing overnight) afforded **3a** in low yield and purity and two recrystallizations were required to afford pure product. The structure of the isolated product was confirmed as **3a** from its ^{1}H-NMR and ^{13}C-NMR spectra, however, extra peaks, most noticeably a singlet at δ 4.27 in the ^{1}H-NMR spectrum, were present in the crude material and, after analysis by GC-MS, it was concluded that these were due to the presence of 5-bromomethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3b**). Indeed, separation by column chromatography allowed for complete analysis of the by-product (^{1}H-NMR, ^{13}C-NMR, GC-MS) and its identity as **3b** was confirmed by its independent synthesis from the reaction of the hydrazine salt **4** (R = H, X = Cl) with bromoacetyl chloride (*vide infra*, Scheme 2, R^1 = $BrCH_2$; Table 1, Entry 2). Modifications to the initial procedure demonstrated that the amount of by-product could be reduced drastically and that **3a** could be obtained with <2% impurity before recrystallization (<0.5% after recrystallization; GC/MS analysis). It is probable that **3b** arises from α-bromination of the acetic anhydride to form both mono- and di-bromoacetic anhydrides, which then react competitively with the bromocarbonylhydrazine intermediate **4** (R = H).

With a quantity of the desired oxadiazolone **3a** in hand, we turned now to the mechanism of the transformation shown in Scheme 1, path a. Since we conjectured that the key intermediate, *N*-phenyl-*N*-bromocarbonylhydrazine salt **4** (R = H), was formed from 4-bromo-3-phenylsydnone (**2**, R = H) [also formed *in situ*], we prepared the latter from 3-phenylsydnone (**1**, R = H) by bromination with Br_2 / $NaHCO_3$[24] and converted it into the salt **4** (R = H, X = Cl) using the method reported by Yeh *et al*.[7] Treatment of the salt **4** with acetic anhydride gave the expected oxadiazolone **3a** in reasonable yield (Scheme 2), a result which suggests strongly that the mechanism of the overall 3-phenylsydnone (**1**, R = H) to **3a** transformation involves a bromocarbonylhydrazine salt intermediate rather than the 1,3-dipolar cycloaddition mechanism proposed by Badami *et al*. Further support for this avenue is provided by Badami's observation that treatment of the 4-bromosydnone **2** (R = H) in acetic anhydride with HBr also yields the oxadiazolone product **3a**. These results give a high degree of certainty to our mechanistic proposal delineated in Scheme 1 (path b).



Scheme 2. Formation of 3,5-disubstituted-1,3,4-oxadiazol-2(*3H*)-ones.

While we had been able to prepare oxadiazolinone **3a** from the bromocarbonyl hydrazine salt **4** (R = H, X = Cl) as a test of our mechanistic proposal, as a practical synthetic avenue to oxadiazolinones, the method suffered from the same major deficiency inherent in the original sydnone **1** to oxadiazolinone **3a** conversion (Scheme 1, path a), *viz*. the use of the anhydride as both reactant and solvent. Accordingly, we explored the transformation of **4** (R = H, X = Cl) into **3a** using a variety of solvents and reduced amounts of acetic anhydride. From these studies, it was determined that the use of 1,2-dimethoxyethane (DME) as solvent gave the best results and the optimal protocol was with 2 eq. of acetic anhydride at 65 °C for 2 h. Extension to acid chlorides, including acetyl chloride, (Table 1, Entries 1-12) yielded the corresponding oxadiazolinones **3a-l** in good yields and the overall method provides a novel approach to the latter. The present findings exhibit further the utility of 3-arylsydnones as precursors to useful heterocycles and, accordingly, given the rather efficient avenues to sydnones,[25] including direct, one-pot avenues from *N*-substituted glycines,[26] the process may find considerable utility.

Table 1. Preparation of 5-substituted-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones **3** in DME

Entry	R in **1**-**4**	R^1 in **3**	Eq. R^1COCl	Time (h)	Product	Yield (%) of **3**
1	H	CH_3	2	3.5	**3a**	75
2	H	$BrCH_2$	2	3.5	**3b**	76[a]
3	H	CH_3CH_2	2	3.5	**3c**	83
4	H	$CH_3CH_2CH_2$	2	3.5	**3d**	51
5	H	C_6H_5	3.5	3.5	**3e**	83
6	H	4-$CH_3C_6H_4$	1.75	1.5	**3f**	95
7	H	4-$CH_3OC_6H_4$	1.75	1.5	**3g**	97
8	H	4-ClC_6H_4	1.75	1.5	**3h**	98
9	H	4-BrC_6H_4	2	3.5	**3i**	99
10	H	2-ClC_6H_4	1.75	1.5	**3j**	74
11	4-Br	CH_3	1.75	1.5	**3k**	81
12	4-Cl	CH_3	1.75	1.5	**3l**	81

[a] 1-2% of **3**, R = Ph, R^1 = $ClCH_2$ and ICH_2 also present (GC/MS).

Conclusions

The conversion of 3-phenylsydnone (**1**, R = H) into 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**3a**) has been reinvestigated, the major impurity (**3b**) identified and the protocol improved to minimize the amount of the latter. A new mechanism *via* a bromocarbonylhydrazine salt intermediate **4** (R = H) is proposed for the procedure and is supported by the observation that **4** reacts with acetic anhydride to yield **3a**. The procedure has been extended to the use of acid chlorides and a novel synthesis of 5-substituted-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones **3** from *N*-aryl-*N*-bromocarbonylhydrazine salts **4** (X = Cl) has been developed. Most of the products (**3a-j**) are derived from 3-phenylsydnone (**1**, R = H) and, accordingly, the substituent at the 3-position in the

products is consistently a phenyl group. However, as a proof of concept, two other sydnones (**1**, R = 4-Br and 4-Cl) were converted into the corresponding bromocarbonylhydrazines **4** (R = 4-Br and 4-Cl, X = Cl), and the latter reacted with acetic anhydride in DME to form the corresponding oxadiazol-2(*3H*)-ones **3l** and **3m**, respectively. It is planned to extend this protocol to the use of other sydnone-derived bromocarbonylhydrazine salts and acid chlorides in order to better delineate the scope and limitations.

Experimental Section

General. 3-Phenylsydnone (**1**, R = H),[27] 3-(4-bromophenyl)sydnone (**1**, R = 4-Br),[28] 3-(4-chlorophenyl)sydnone (**1**, R = 4-Cl),[29] 4-bromo-3-phenylsydnone (**2**, R = H)[2] and the *N*-phenyl-*N*-bromocarbonylhydrazine salts (**4**, R = H, 4-Cl and 4-Br)[7] were prepared as reported previously. Melting points were determined on a Mel-Temp melting point device and remain uncorrected. Infrared spectra were performed on a KBr salt plate and were taken on a Nicolet 6700 FTIR. NMR spectra were obtained on a Bruker Advance 300 MHz NMR in $CDCl_3$ and are reported relative to tetramethylsilane as an internal standard. Column chromatography was accomplished either manually or on an Isco CombiFlash Separator System Sg100c. Thin layer chromatographic assessments were performed on silica gel. Elemental analyses were determined by Midwest Microlab LLC, Indianapolis, Indiana, U.S.A.

Improved procedure for the conversion of 3-phenylsydnone (1, R = H) into 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (3a) using bromine in acetic anhydride. 3-Phenylsydnone (5.002 g, 0.031 mol) was dissolved in Ac_2O (25 mL) and Br_2 (5.271 g, 0.033 mol) was added dropwise at rt with stirring. After 15 min the mixture was heated to 60 ^oC and, after a further 30 min, cooled to rt and poured carefully over ice. The resultant precipitate was collected by filtration *in vacuo*, washed with water and dried to afford **3a** as a light yellow solid, 4.917 g, 90.5%. Recrystallization from 95% EtOH gave the title compound as pale yellow crystals, 3.95 g, 73%, identical (IR, NMR) to an authentic sample.[4]

General procedure for the synthesis of 5-substituted-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones 3a-m from the corresponding bromocarbonylhydrazines 4 (**R = H, 4-Br, 4-Cl, X = Cl**). To the bromocarbonylhydrazine salt **4** (*ca.* 0.15 g) in DME (8 mL) was added the appropriate acid chloride (1.75-4 equivalents) dropwise with stirring. After heating at 65 ^oC for 1.5-4 h, the reaction mixture was allowed to cool to rt and then was poured carefully into saturated, aq $NaHCO_3$ (30 mL). The quenched mixture was warmed to 50 ^oC to reduce the volume of DME and then cooled to ice bath temperature. The resultant precipitate was filtered off, rinsed with ice-cold water, dried overnight *in vacuo* and recrystallized from 95% EtOH to afford **3a-l** in 51-99% yield.

5-Methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3a**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.150 g, 0.560 mmol] with AcCl (0.080 mL, 1.12 mmol) in the general procedure for 3.5 h gave after work-up, colorless crystals, 0.075 g. 75%, mp 90-91 ^oC, lit.[4] mp 92-3 ^oC, identical (IR, NMR) to an authentic sample.

5-Bromomethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3b**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.159 g, 0.570 mmol] with bromoacetyl chloride (0.096 mL, 1.14 mmol) in the general procedure for 3.5 h gave after work-up, light tan crystals, 0.116 g, 76%, mp 80-81 °C; IR (KBr): 3042, 2982, 1778, 1492, 960 cm^{-1}; ^1H NMR ($CDCl_3$): 7.81-7.83 (d, 2H), 7.42-7.47 (t, 2H), 7.26-7.30 (t, 1H), 4.28 (s, 2H); ^{13}C-NMR ($CDCl_3$): 152.0, 150.3, 135.6, 129.3, 126.5, 118.3, 17.6 ppm. Elemental analysis: calc. for $C_9H_7BrN_2O_2$ (256.07) C: 42.38, H: 2.77, N: 10.98. Found C: 42.67, H: 2.74, N: 10.96%.

5-Ethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3c**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.150 g, 0.560 mmol] with propionyl chloride (0.097 mL, 1.120 mmol) in the general procedure for 3.5 h gave after work-up, colorless crystals, 0.089 g, 83%, mp 58-60 ^{o}C, lit.[4] mp 60-61.5 ^{o}C, identical (IR, NMR) to an authentic sample.

3-Phenyl-5-propyl-1,3,4-oxadiazol-2(*3H*)-one (**3d**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.150 g, 0.560 mmol] with butyryl chloride (0.115 mL, 1.120 mmol) in the general procedure for 3.5 h gave after work-up colorless crystals, 0.059 g, 51%, mp 56-57 ^{o}C, lit.[4] mp 57.5-58.5 ^{o}C, identical (IR, NMR) to an authentic sample.

5-Phenyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3e**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.156 g, 0.600 mmol] with PhCOCl (0.249 mL, 2.160 mmol) in the general procedure for 3.5 hours gave after work-up colorless crystals, 0.113 g, 83%, mp 108-109 ^{o}C, lit.[9] mp 109-110 ^{o}C, identical (IR, NMR) to an authentic sample.

5-(4-Methylphenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3f**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.151 g, 0.601 mmol] with *p*-toluoyl chloride (0.138 mL, 1.052 mmol) in the general procedure for 1.5 h gave after work-up, light tan crystals, 0.144 g, 95%, mp 148-149 ^{o}C, lit.[9] mp 155-156 ^{o}C, identical (IR, NMR) to an authentic sample.

5-(4-Methoxyphenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3g**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.176 g, 0.698 mmol] with anisoyl chloride (0.167 mL, 1.222 mmol) in the general procedure for 1.5 h gave after work-up colorless crystals, 0.182 g, 97%, mp 140-141 ^{o}C, lit.[23] mp 137-138 ^{o}C, identical (IR, NMR) to an authentic sample.

5-(4-Chlorophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3h**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.159 g, 0.633 mmol] with anisoyl chloride (0.139 mL, 1.107 mmol) in the general procedure for 1.5 h gave after work-up, light tan crystals, 0.169 g, 98%, mp 125-126 ^{o}C, lit.[9] mp 118-119 ^{o}C, identical (IR, NMR) to an authentic sample.

5-(4-Bromophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3i**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.153 g, 0.600 mmol] with 4-bromobenzoyl chloride (0.263 g, 1.200 mmol) in the general procedure for 3.5 h gave after work-up colorless crystals, 0.188 g, 99%, mp 128-130 ^{o}C, lit.[9] mp 123-124 ^{o}C, identical (IR, NMR) to an authentic sample.

5-(2-Chlorophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**3j**). Reaction of *N*-phenyl-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.128 g, 0.51 mmol] with 2-chlorobenzoyl chloride (0.111 mL, 0.89 mmol) in the general procedure for 1.5 h gave after work-up, light tan crystals, 0.103 g, 74%, mp 114-115 ^{o}C, lit.[23] mp 145-146 ^{o}C; IR (KBr): 1785, 1480, 1029, 973, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$): □ 8.0 (d, 1H), 7.91(d, 2H), 7.58 (m, 2H), 7.54 (t, 1H), 7.46 (t, 1H) 7.42 (d, 1H), 7.31(t, 1H); ^{13}C-NMR ($CDCl_3$): 151.7, 150.3, 136.0, 132.9, 132.4, 131.6, 130.1, 129.5, 127.1, 126.3, 122.3, 118.4 ppm.

3-(4-Bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**3k**). Reaction of *N*-(4-bromophenyl)-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = 4-Br, X = Cl) [0.200 g, 0.605 mmol] with AcCl (0.076 mL, 1.059 mmol) in the general procedure for 1.5 h gave after work-up, colorless crystals, 0.125 g, 81%, mp 123-124 ^{o}C, lit.[5] mp 124-125 ^{o}C, identical (IR, NMR) to an authentic sample.

3-(4-Chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**3l**). Reaction of *N*-(4-chlorophenyl)-*N*-bromocarbonylhydrazine hydrochloride (**4**, R = H, X = Cl) [0.160 g, 0.560 mmol] with AcCl (0.070 mL, 0.979 mmol) in the general procedure for 1.5 h gave, after work-up, colorless crystals, 0.951 g, 81%, mp 122-123 ^{o}C, lit.[5] mp 121-122 ^{o}C, identical (IR, NMR) to an authentic sample.

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