

Improved synthesis and characterisation of 1,3,4-oxadiazole

Kati M. Aitken and R. Alan Aitken*

*EaStCHEM School of Chemistry, University of St Andrews, North Haugh,
St Andrews, Fife, KY16 9ST, United Kingdom
E-mail: raa@st-and.ac.uk*

Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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Abstract

Synthetic approaches to 1,3,4-oxadiazole have been investigated and an improved method involving dehydration of *N,N'*-diformylhydrazine with P₂O₅ in polyphosphoric acid is described. The ¹³C NMR spectrum of this compound is reported for the first time including determination of ¹J_{C-H} and ³J_{C-H}.

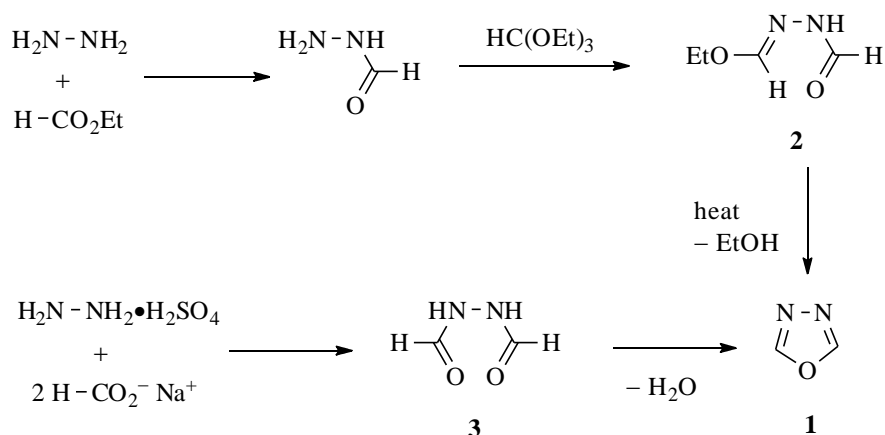
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Introduction

In the context of recent experimental and computational studies on the high resolution vibrational spectra of some fundamental heterocyclic compounds,¹⁻⁶ we needed to prepare 1,3,4-oxadiazole **1**.⁷ Although this simple compound was first reported in 1965,⁸ only one method has ever been described for its preparation,⁹ and this involves thermal elimination of ethanol from compound **2**, itself formed by reaction of *N*-formylhydrazine with triethyl orthoformate (Scheme 1). We have found this method to be unsatisfactory in various ways. The preparation of **2** must be carefully controlled to avoid formation of a 1,2,4-triazole byproduct,⁹ it exists as a mixture of different *E/Z* isomers leading to complex, and as yet unexplained, NMR spectra and problems in obtaining it in pure crystalline form, and the final thermolysis reaction, reported to proceed in “about 50% yield”,⁹ was found to be unpredictable and to give yields in our hands ranging from 0–10%. We therefore set out to develop a more convenient synthesis and describe here the results.

Results and Discussion

We first re-examined the literature method in an attempt to overcome the problems encountered. In our hands, heating the solid compound **2** above its melting point under atmospheric pressure and collecting the liquids which distilled off afforded mainly ethanol and ethyl formate with <1% yield of **1**. The use of various methods that would favour the intramolecular cyclisation with loss of EtOH as opposed to intermolecular reactions leading to polymerisation was attempted. Moving to vacuum distillation and mixing the compound **2** with an inert solid such as SiO₂ was of little benefit. Flash Vacuum Pyrolysis (FVP), which involves passing the substrate through a furnace in a flow system under high vacuum, is well known as a method for clean and efficient extrusion reactions where polymerisation is to be avoided. This did result in a significant improvement with **1** being obtained in a reproducible 10% yield upon FVP at 600–700 °C, but the yield was still disappointing so attention was turned to alternative methods avoiding **2**.



Scheme 1

An attractive alternative approach involves the cyclodehydration of the readily available *N,N'*-diformylhydrazine **3** but, although this is a well known route to oxadiazoles in general,¹⁰ it does not seem to have been reported for the parent heterocycle. Exposure of compound **3**,¹¹ to a variety of standard dehydration reagents and conditions showed that the desired transformation was not easily achieved (Table 1, entries 1–12). Part of the problem was that the methods tried for dehydrative cyclisation frequently involved acidic conditions under which the target product would be protonated. A basic work up followed by extraction was therefore used but this sometimes resulted in hydrolysis of the compound. The first sign of success came from treatment with P₂O₅ in toluene (entry 13). By moving to polyphosphoric acid, a much better result was achieved (entry 14), but we were concerned to find that repeating this reaction with newly purchased polyphosphoric acid gave no product (entry 15). The problem was eventually traced to the fact that the original polyphosphoric acid was dehydrated with a crust of solid around the bottle and this effect could be duplicated by addition of 10% w/w of P₂O₅ to new polyphosphoric

acid (entry 16). Even with this reagent, the reaction time proved to be critical with too long a reaction time again leading to no product (entry 17). The other important aspect was found to be the work-up. Initially we neutralised the reaction mixture with aqueous NaOH before extracting with CH₂Cl₂ but it was later found to be better to use the milder base NaHCO₃ to minimise losses through hydrolytic breakdown of product **1**.

Table 1. Conversion of **3** into **1**

Entry	Reagents	Conditions	Yield of 1 (%)
1	—	FVP, 500–800 °C	1–2
2	4Å Molecular sieves	toluene, reflux 4 h	0
3	4Å molecular sieves, Amberlite R-120	toluene, reflux 12 h	0
4	(CF ₃ CO) ₂ O, CF ₃ CO ₂ H	reflux, 4 h	0
5	Ac ₂ O, AcOH	reflux 4 h	0
6	10 equiv. SOCl ₂ , hexane	reflux, 3 h	0
7	ClCOCOCl, CH ₂ Cl ₂	reflux, 8 h	0
8	6 equiv. conc. H ₂ SO ₄	0 °C, 2 h then RT, 2 h	0
9	DCCI, CH ₂ Cl ₂	RT, 40 h	0
10	DCCI, MeCN	reflux, 7 h	0
11	DEAD, Ph ₃ P, THF	reflux, 8 h	0
12	5 equiv. P ₂ O ₅ , THF	reflux, 48 h	0 (THF reacts)
13	P ₂ O ₅ , toluene	reflux, 4 h	<5
14	polyphosphoric acid (old)	100 °C, 8 h	30
15	polyphosphoric acid (new)	100 °C, 8 h	0
16	polyphosphoric acid (new) + 10% P ₂ O ₅	100 °C, 4 h	30
17	polyphosphoric acid (new) + 10% P ₂ O ₅	100 °C, 18 h	0

By using these conditions we have been able to prepare multi-gram quantities of 1,3,4-oxadiazole as required for spectroscopic investigation, and the high-resolution vibrational spectra have already been published.⁷ Compound **1** is a colourless liquid with bp 150 °C and shows a ¹H NMR signal in CDCl₃ at δ_H 8.52 (Lit.,⁸ 8.73). We were surprised to discover that, despite detailed studies of the ¹⁵N and ¹⁴N NMR spectra having been reported some time ago,^{12,13} the ¹³C NMR spectrum of this fundamental heterocyclic compound has apparently remained unreported until now. The observed chemical shift of δ_C 152.7 is in good agreement with values reported for similar compounds such as C-2 of oxazole (δ_C 151.2)¹⁴ and thiazole (δ_C 152.8).¹⁴ By recording the uncoupled ¹³C NMR spectrum, the C–H coupling constants were determined as ¹J_{C–H} = 234 Hz and ³J_{C–H} = 5 Hz.

Finally, we were attracted by the recent reports of Ramazani and Souldozi,^{15,16} that aromatic carboxylic acids may be converted directly into 2-aryl-1,3,4-oxadiazoles under mild conditions by treatment with isocyanoiminotriphenylphosphorane, Ph₃P=N–N=C:. This phosphinimine was

readily prepared,¹⁷ but unfortunately attempts to react it with formic acid under a wide variety of conditions gave no trace of 1,3,4-oxadiazole **1**.

Experimental Section

General. NMR spectra were obtained for ¹H at 300 MHz and for ¹³C at 75 MHz using a Bruker AM300 instrument. All spectra were run on solutions in CDCl₃ with internal Me₄Si as reference. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants *J* are in Hz. *N*-Formylhydrazine was prepared from ethyl formate and hydrazine hydrate using the reported method¹⁸ and converted into compound **2** as described.⁹ *N,N'*-Diformylhydrazine **3** was prepared from hydrazine sulfate and sodium formate using the literature method.¹¹

1,3,4-Oxadiazole (1). Polyphosphoric acid (18.0 g) was stirred at 80–100 °C while P₂O₅ (2.0 g) was added, followed after 15 min by *N,N'*-diformylhydrazine **3** (2.0 g, 35.7 mmol). The mixture was stirred at 100 °C for 4 h and then added to ice (100 g). The resulting mixture was neutralised by addition of NaHCO₃ (13.8 g) and then extracted with CH₂Cl₂ (3 × 50 cm³). Drying and evaporation of the extract gave the product (0.42 g, 30%) as a colourless liquid, bp ~150 °C; δ_H 8.52 (2 H, s); δ_C 152.7; δ_C (undecoupled) 152.7 (dd, *J* 234, 5); HRMS (CI) Calcd. for C₂H₃N₂O (*M*+*H*): 71.0245. Found: 71.0247.

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