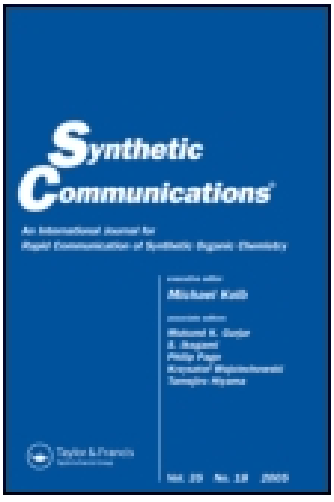

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Microwave-Assisted Generation and Reactions of Nitrile Sulfides

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Microwave-Assisted Generation and Reactions of Nitrile Sulfides

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Abstract: An improved practical method is described for the generation of benzonitrile sulfide based on microwave-assisted decarboxylation of 5-phenyl-1,3,4-oxathiazol-2-one. Reaction times for the preparation of cycloadducts (e.g. isothiazoles and 1,2,4-thiadiazoles) derived from the nitrile sulphide are reduced from typically 15–30 h to approximately 15 min.

Keywords: Microwave-assisted cycloadditions, nitrile sulfides, 1,3,4-oxathiazol-2-ones

INTRODUCTION

The chemistry of nitrile sulfides ($R-C{\equiv}N^{+}-S^{-}$) has received much less attention[1] than that of the other nitrilium betaines:[2] the nitrile ylides ($R-C{\equiv}N^{+}-CR_2^{-}$), nitrile imines ($R-C{\equiv}N^{+}-NR^{-}$), and nitrile oxides ($R-C{\equiv}N^{+}-O^{-}$). And yet nitrile sulfides are uniquely well suited for the synthesis of five-membered heterocycles incorporating the $C=N-S$ unit *via* their 1,3-dipolar cycloaddition reactions with double- and triple-bonded dipolarophiles (Scheme 1). Examples of such heterocycles accessible by

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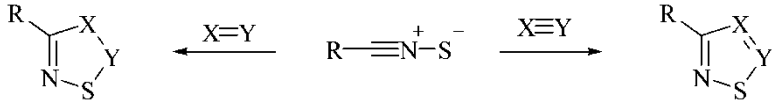


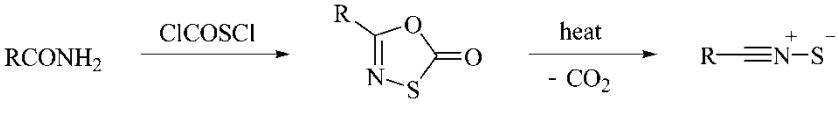
Scheme 1.

this means include isothiazoles,[3–6] 2-isothiazolines,[7] 1,2,4-thiadiazoles,[8–12] 1,3,4-oxathiazoles,[13] and 1,4,2-dithiazoles.[14]

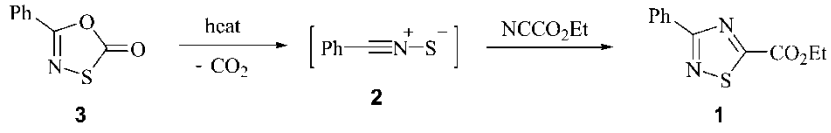
As nitrile sulfides are short-lived intermediates that are prone to decompose to sulphur and the corresponding nitrile, for preparative purposes they are always generated in the presence of the dipolarophile. The most widely used precursors are 1,3,4-oxathiazol-2-ones,[3] which undergo decarboxylation to the nitrile sulphide on heating (Scheme 2). The oxathiazolones usually have a good shelf life and can readily be prepared by treatment of the corresponding carboxamide with chlorocarbonylsulfenyl chloride.[3,15] Their utility as a source of nitrile sulfides is, however, restricted by the forcing conditions required to accomplish the decarboxylation. For example, typical experimental procedures involve heating at reflux in chlorobenzene or *p*-xylene (130–135°C)[3,13] for prolonged periods (5–170 h). Such lengthy reaction times and the need for high boiling solvents are not ideal for rapid throughput synthesis. To reduce the reaction times and extend the range of solvents, we have investigated the feasibility of using microwave irradiation to accelerate the rate-determining decarboxylation. This technique is now finding widespread application[16] in organic synthesis and has been used to promote various cycloaddition reactions including those involving nitrile oxides[17,18] and nitrile imines,[18,19] but not nitrile sulfides.

RESULTS AND DISCUSSION

For initial experiments we selected as a representative example the synthesis of ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**1**) from benzonitrile sulfide (**2**), generated from 5-phenyl-1,3,4-oxathiazol-2-one (**3**),[3,15] and ethyl cyanoformate as the dipolarophile[8] (Scheme 3). For comparison, an authentic sample of the thiadiazole **1** was prepared by the conventional thermolysis method. A solution of the phenyloxathiazolone **3** and ethyl cyanoformate



Scheme 2.



Scheme 3.

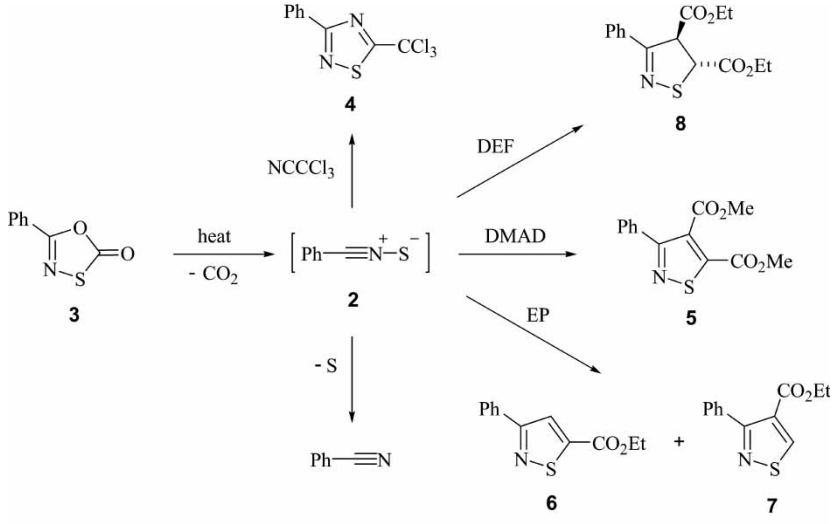
(~1:10 reactant ratio) in *p*-xylene was heated under reflux for 18 h. Removal of the solvent and excess dipolarophile afforded an oily solid from which the target compound was isolated in 62% yield by crystallization and recrystallization from hexane. A repeat experiment was then carried out with the same solvent and reactant ratio, but using microwave irradiation (200 W, 10 min, 160°C) instead of conventional heating. The ^{13}C NMR spectrum of the crude product obtained after removal of the solvent and excess ethyl cyanoformate indicated that the thiadiazole **1** had been formed in near quantitative yield. It showed characteristic signals for the thiadiazole ring at 178.8 (C-5) and 174.4 ppm (C-3) in addition to those of the ethoxycarbonyl and phenyl substituents, and was indistinguishable from that of the authentic sample. Significantly, neither the oxathiazolone precursor nor the expected by-product, benzonitrile, was detectable. A series of experiments was then carried out under various reaction conditions. The isolated yield remained high (89%) at a lower temperature (140°C) and also for a smaller excess of dipolarophile (3:1) (82%). In both cases NMR spectroscopy gave no indication of by-product formation. One of the advantages of the microwave technique is the ability to routinely use lower boiling solvents and thus facilitate workup of the reaction mixture. In the present case, replacing the *p*-xylene with THF and with chloroform resulted in yields of 72% and 76% respectively. Ethyl acetate proved to be particularly useful, affording the target thiadiazole in a 94% isolated yield.

Cycloaddition of nitrile sulfides, generated by conventional thermolysis of oxathiazolones, to trichloroacetonitrile afforded 5-trichloromethyl-1,2,4-thiadiazoles in moderate to good yields (45–65%),[10,20] although the reaction times are reported to be long (3–4 days). A typical reaction was therefore carried out under microwave conditions. Irradiation (300 W) of oxathiazolone **3** and trichloroacetonitrile (molar ratio 1:10) in acetonitrile at 160°C for 10 min, followed by workup, afforded the target 1,2,4-thiadiazole **4** in 61% yield. It is noteworthy that the nitrile sulphide reacts with the cyano group of the trichloroacetonitile rather than the acetonitrile solvent. This observation is consistent with previous reports[8–12] that electron-withdrawing substituents increase the dipolarophilic activity of nitriles in their cycloaddition reactions with nitrile sulfides.

Having established that 1,2,4-thiadiazoles could readily be prepared from activated nitriles and nitrile sulfides generated by this approach, attention was

turned to other classes of dipolarophiles (Scheme 4). Dimethyl acetylenedicarboxylate (DMAD) was the dipolarophile originally employed by Franz and Black to trap benzonitrile sulfide[21] and has subsequently been widely used for the preparation of isothiazole-4,5-dicarboxylates.[1a,3] Under forcing conditions, however, the product is sometimes contaminated by DMAD-derived by-products, and it was anticipated that this could be avoided using the microwave technique. Irradiation (200 W) of oxathiazolone **3** and DMAD (molar ratio 1:3) in chloroform at 160°C for 10 min afforded, after workup, the isothiazoledicarboxylate **5** in 56% yield. Under similar conditions the reaction of oxathiazolone **3** with ethyl propiolate (EP) (molar ratio 1:10) yielded a regioisomeric mixture of ethyl 3-phenylisothiazole-5- and 4-carboxylates **6** and **7**. The isomer ratio (**6**:**7**) was measured as 13:14 from the ^{1}H NMR spectrum of the mixture by comparison of the 4-H peak of the 5-carboxylate at 8.04 ppm with that of the 5-H peak of the 5-carboxylate at 9.26 ppm. This approximately 1:1 ratio is similar to that reported for the corresponding conventional thermolysis reaction.[3] The corresponding reaction with the activated alkene dimethyl fumarate afforded the expected cycloadduct **8**; the *trans* configuration of the product was evident from the ^{1}H NMR spectrum in which there was a ^3J coupling for 4-H/5-H of 3.4 Hz.

In conclusion, these results demonstrate that using microwave irradiation reduces the reaction times for the generation of nitrile sulfides from hours/days to 10–15 minutes. Furthermore, the workup of the reaction mixtures is facilitated by the use of low boiling-point solvents and the yields of



[DMAD = $MeO_2CC \equiv CCO_2Me$; EP = $HC \equiv CCO_2Et$; DEF = *E*-$EtO_2CCH \equiv CHCO_2Et$]

Scheme 4.

cycloadducts are comparable to or greater than those observed under traditional thermal conditions.

EXPERIMENTAL

Microwave experiments were conducted in a CEM Discoverer microwave with a 5-min ramp time and 20 min cooling. ^{1}H and ^{13}C NMR spectra were recorded with Brucker WP200SY or AX250 spectrometers on solutions in $CDCl_3$ with Me_4Si as internal standard. Positive-ion FAB and high-resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC; detection was by UV or sulfuric acid charring. Preparative chromatography was carried out, either using Kieselgel GF_{254} and eluted under water pump vacuum or using Strata Si-1 silica (55 μm, 70A) columns with 10 g/60 ml tubes. 5-Phenyl-1,3,4-oxathiazol-2-one was prepared as previously reported.[3] Typical procedures for the nitrile sulfide cycloaddition reactions are given below.

Typical Procedures

Ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate **1**

Conventional thermolysis. A solution of oxathiazolone **3** (193 mg, 1.08 mmol) and ethyl cyanoformate (ECF) (1.0 ml, ~10.1 mmol) in *p*-xylene (6 ml) was heated at reflux for 16 h. After removal of the excess ECF and the solvent under reduced pressure, the residue was recrystallized from hexane to afford the compound **1** as white crystals (156 mg, 62%); mp 67°C (lit.[8] 70–71°C); ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 8.30 (2H, m, PhH), 7.35–7.45 (3H, m, PhH), 4.46 (2H, q, $J = 7.1$ Hz, OCH_2), 1.41 ppm (3H, t, $J = 7.1$ Hz, CH_3); ^{13}C NMR δ_C (40 MHz, $CDCl_3$) 178.8 (C-5), 174.4 (C-3), 158.3 (C═O), 131.8 (PhC), 130.7, 128.6, 128.3 (5 PhC), 63.1 (CH_2), 14.0 (CH_3); HRMS (FAB) Found: $M^+ + 1$, 235.0547. $C_{11}H_{10}NO_2S$ requires $M^+ + H$ 235.054413.

Microwave irradiation. A solution of oxathiazolone **3** (100 mg, 0.56 mmol) and ethyl cyanoformate (ECF) (0.5 ml, ~5.0 mmol) in *p*-xylene (3 ml) was heated in the microwave at 160°C and with a 200-W power input for 10 min. After cooling, the excess ECF and the solvent were removed under reduced pressure and the residue examined by ^{1}H and ^{13}C NMR spectroscopy. The resulting spectra were almost indistinguishable from those of the authentic sample of compound **1**, indicating that it had been formed in near quantitative yield. The reaction was repeated at 140°C (89% isolated yield), and using a three-fold excess of ECF at 160°C (82%).

Reactions were also carried out (160°C/1:10 reactant ratio) in THF (72%), chloroform (76%), and ethyl acetate (94%). Compounds **4**–**8** were prepared similarly.

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