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Synthesis of oxadiazole-2-oxide analogues as potential antischistosomal agents

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ABSTRACT

The synthesis of several 1,2,5-oxadiazole-2-oxide (Furoxan) analogues is described herein. These compounds were prepared in an effort to probe the SAR around the phenyl substituent and oxadiazole core for our studies toward thioredoxin-glutathione reductase (TGR) inhibition and antischistosomal activity.
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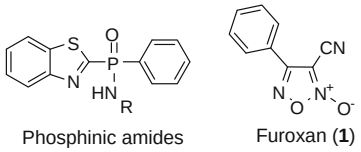
As part of our ongoing interest in neglected diseases of third world countries, we recently reported the identification of several novel chemotypes[1,2] (Fig. 1) for the treatment of schistosomiasis.[3,4] Schistosomiasis is caused by five species of the trematode flatworm, two of which are *Schistosoma mansoni* (*S. mansoni*) and *Schistosoma haetobium*. It has been estimated that more than 200 million people are infected worldwide with an estimated 200,000–280,000 deaths occurring annually in sub-saharan Africa alone as a result of this disease.[5] Current treatment of schistosomiasis relies primarily on the use of praziquantel (PZQ) because of its low cost and effectiveness against all schistosome species. However, given its widespread use, drug-resistant parasites may become more prevalent and PZQ-resistant isolates have already been identified.[6,7]

The majority of eukaryotes contain two native mechanisms by which they detoxify reactive oxygen species, the tripeptide glutathione (GSH) and the 12 kDa protein thioredoxin (Trx).[8,9] These systems also play a critical role in several other cellular functions including cell proliferation, redox regulation of gene expression, and xenobiotic metabolism to name a few.[10] Interestingly, Williams and co-workers found that in *S. mansoni* both TrxR and GR pathways are absent, and instead rely on a single multifunctional selenocysteine-containing flavoenzyme, thioredoxin-glutathione reductase (TGR).[11] As a result, one may expect that inhibition of TGR would present a viable target for the treatment of *S. mansoni* parasites. Accordingly, we sought out and discovered numerous small molecules with potent in vitro inhibition of TGR, including the oxadiazole-2-oxide chemotype (Furoxan) (**1**).

Our initial interest was to explore modification of the phenyl moiety of furoxan (**1**). Ideally, we hoped to develop a convergent synthesis which would allow for late-stage installation of differentially substituted phenyl groups providing rapid access to a library of compounds. Unfortunately, as shown in Scheme 1, these attempts were met with limited success. Synthesis of amidoxime **3** did proceed as planned to haloglyoxime **4** using HBr and $NaNO_2$,[12] however this product proved unstable and thus could not be cyclized to halo-furoxan **5**. Additionally, direct conversion of 4-amino-3-cyano furoxan (**2**) using various conditions to compound **5** also failed. Alternatively, in a one-pot procedure, amidoxime **3** was treated with $BF_3{\cdot}OEt_2$ to form the diazonium ion **6** in situ which was then subjected to palladium-imidazolium carbene catalyzed Suzuki–Miyaura coupling conditions.[13] As shown in Scheme 1, this too failed to produce the desired product **7**. In light of these findings, we chose to focus our efforts on more conventional approaches to furoxan analogues.

Gasco and co-workers have studied furoxan and related analogues for many years and have published pioneering work toward their syntheses.[14–21] The key step typically involves treatment of the requisite cinnamyl alcohol **10** with sodium nitrate and acetic acid at room temperature to form the corresponding 4-phenyl-3-furoxanmethanol derivative **11** (Scheme 2). While Gasco and co-workers often report the use of aqueous sodium nitrate in acetic acid, we found that the use of glacial acetic acid with anhydrous sodium nitrate worked best for the analogues reported herein. The required cinnamyl alcohols were obtained either through esterification of commercially available cinnamic acid derivatives **8** or via Heck coupling of the corresponding aryl bromides with ethyl acrylate to give **9**. Subsequent hydride reduction with DIBAL-H gave alcohols of type **10**. Of note, the sodium nitrate-mediated cyclization often gave a mixture of two products **11a** and **11b**, always favoring the desired regioisomer **11a**. The structural assignments were based on known differences in ^1H and ^{13}C NMR reso-



Phosphinic amides Furoxan (**1**)

Figure 1. Quantitative high-throughput screen (qHTS) hits.[1]

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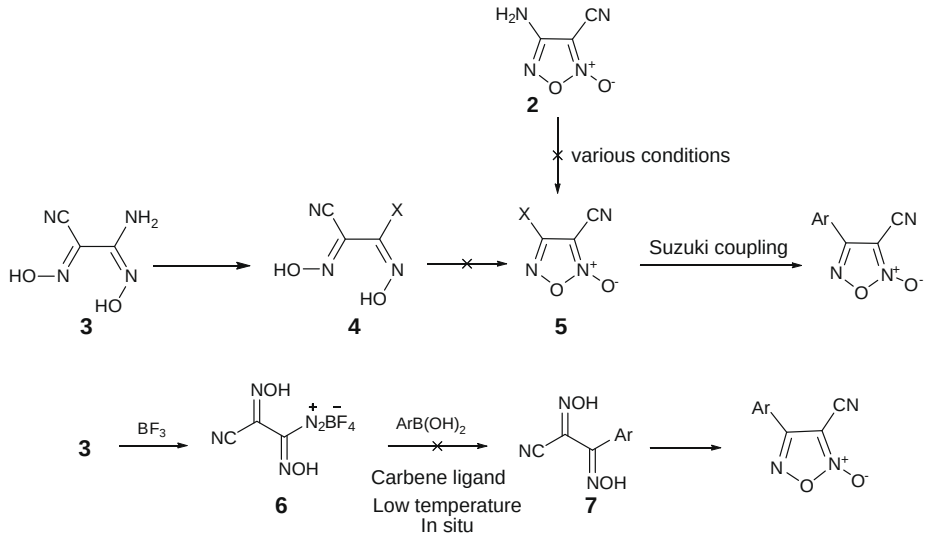
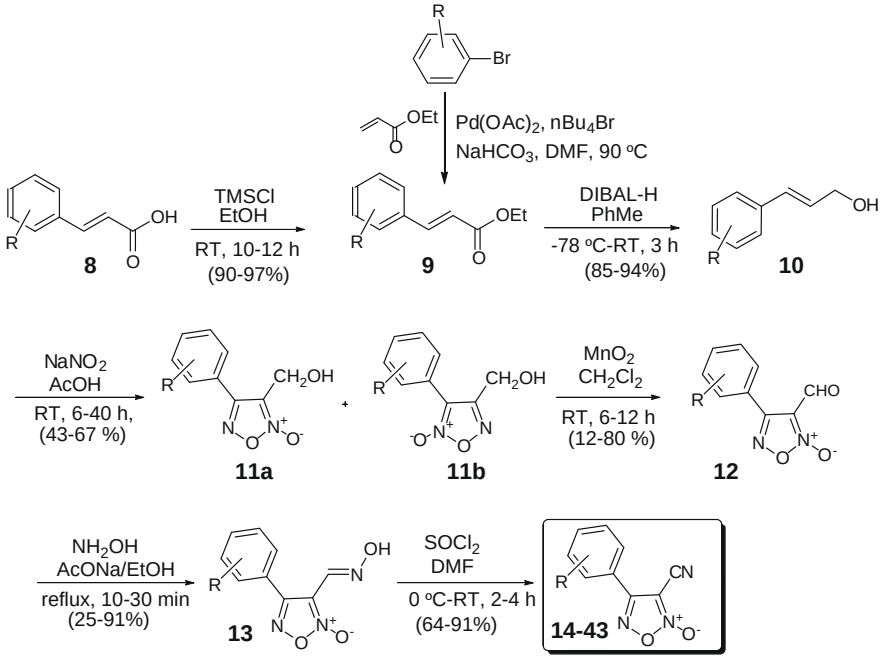


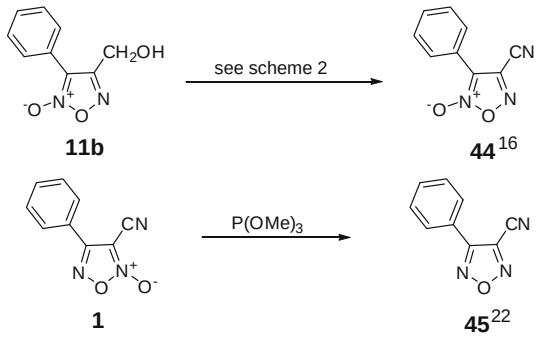
Scheme 1. Unsuccessful attempts at a convergent synthesis of furoxan analogues.



Scheme 2. General Scheme for the synthesis of furoxan analogues **14**–**43**.

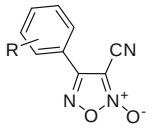
nances of the methylene group in the 3-position which results from shielding by the N-oxide moiety.[14,18] The chromatographic separation of these isomers was typically complex and thus the mixture was carried through and subsequently oxidized using MnO_2 to give the corresponding aldehydes **12** in yields ranging from 12% to 80%. At this stage, the mixture of regioisomers was easily separated using flash chromatography. Formation of oxime **13** was achieved using hydroxylamine hydrochloride in the presence of sodium acetate in ethanol. Dehydration was carried out using $SOCl_2$ in DMF to provide the requisite 4-phenyl-3-cyano derivatives **14**–**43**. Using this approach, 28 novel furoxan analogues were synthesized in an effort to define SAR around the phenyl moiety with respect to TGR inhibitory activity (Table 1).

Another primary interest was the importance of the N-oxide moiety. As such, we sought to synthesize both 3-phenyl-4-cyano



Scheme 3. Synthesis of furoxan analogues **44** and **45**.

Table 1
Phenyl ring analogues synthesized as depicted in Scheme 1



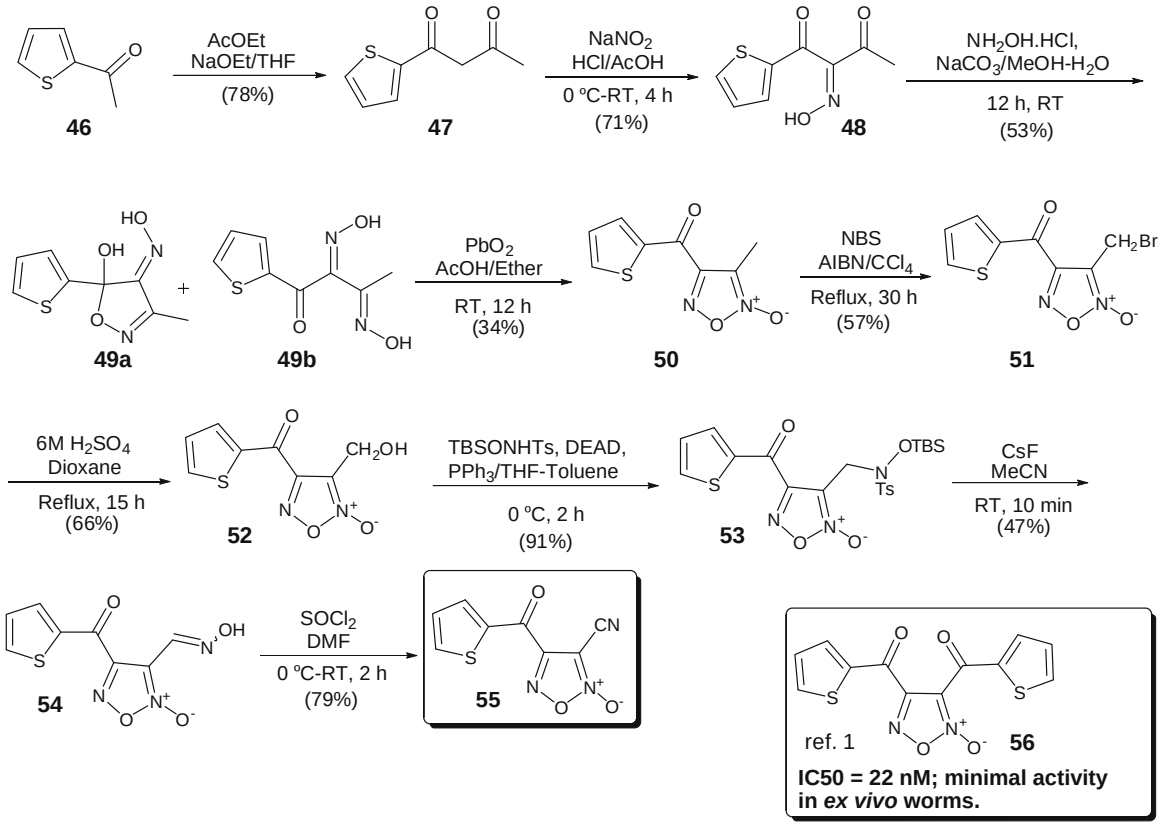
R = 4-F (**14**)	R = 3-OMe (28)
4-Cl (**15**)	3-OH (**29**)[c]
4-Br (**16**)	2-OMe (**30**)
4-CF_3 (**17**)	4-F, 3-Br (**31**)
4-NO_2 (**18**)	4-Cl, 3-NO_2 (**32**)
4-OMe (**19**)	3-CF_3, 5-CF_3 (**33**)
4-OH[21] (**20**)[a]	3,4,5-OMe (**34**)
4-Me (**21**)	3,4-OCH_2O (**35**)
4-Phe (**22**)	Naphthyl (**36**)
4-OCH_2CCH[b] (23)	Furan (**37**)
3-NO_2 (**24**)	Thiophene (**38**)
3-Cl (**25**)	2-NO_2-Furan (**39**)
3-Br (**26**)	3-Furoxan (i.e., *m*-bis-furoxan) (**40**)
3-CF3 (**27**)	4-Furoxan (i.e., *p*-bis-furoxan) (**41**)
	1,4-Thiophene-bis-furoxan (**42**)
	3-F,5-Furoxan (i.e., *m*-F, *m*-bis-furoxan) (**43**)

[a] Was obtained via deprotection of **19** with $AlCl_3$.
[b] Was obtained from reaction of **20** with propargyl bromide (see Supplementary data for details).
[c] Was obtained via deprotection of **28**.

furoxan **44**[16] and the 1,2,5-oxadiazole derivative **45** [22] (Scheme 3). As mentioned previously, cyclization of **10**–**11** gives a mixture of isomers, with the minor being 3-phenyl-4-cyano-furoxan **11b** (see Scheme 2). However, Gasco showed that heating **11a** in refluxing toluene leads to partial isomerization to **11b**,[14] allowing access to ample material of the minor isomer to be collected. Carrying through the remaining steps as shown in Scheme 2 gave 3-phenyl-4-cyano-furoxan **44**. Compound **45** was prepared by treatment of furoxan **1** with neat $P(OMe)_3$ as previously reported for a similar system.[22] The removal of the N-oxide moiety was confirmed by IR in which the common absorbance for the N-oxide at 1590–1620 cm^{-1} is absent.

Finally, we set out to synthesize the 4-(2-thienoyl)-3-cyano furoxan derivative **55** (Scheme 4). We reported previously that the bis-thienoyl furoxan **56** exhibits potent in vitro TGR inhibitory activity as compared to **1** (20 nM and 8 μM, respectively) yet lacked appreciable activity against ex vivo worms.[1] Structurally similar dibenzoyl furoxans have recently been shown by Nirode and co-workers to be effective NO-donors through nucleophilic attack of thiols.[23] Thus, we reasoned **55** may retain some of the desirable potency while the presence of the nitrile may provide the structural requirements necessary for *ex vivo* worm killing activity.

The synthesis commenced with condensation of commercially available 2-acetylthiophene (**46**) with ethyl acetate in the presence of sodium ethoxide to give 1,3-diketone **47** in 78% yield. Treatment with sodium nitrate in HCl/AcOH provided **48** in 71% yield. Oxime formation was achieved with hydroxyl amine hydrochloride to give the desired bisoxime **49b** in 53% yield along with a minor amount of undesired **49a**. Cyclization was accomplished with lead dioxide to give the requisite 4-ketothiophene-3-methyl furoxan **50** in 34% yield. Allylic bromination followed by hydrolysis gave 4-ketothiophene-3-furoxanmethanol **52** in 38% yield over two steps. Interestingly, typical oxidation conditions that were utilized in previous analogues (i.e., MnO_2) failed to give the desired product. Recently, Fukuyama and co-workers reported a mild two-step synthesis of oximes from alcohols via Mitsunobu reaction with *N*-(*tert*-butyldimethylsilyloxy)benzenesulfonamide followed by treatment with Cesium fluoride.[24] Gratifyingly, the reaction worked well on our system providing oxime **54** in 42% yield over two steps. Subse-



Scheme 4. Synthesis of 4-thienoyl-3-cyano furoxan (**55**).

quent treatment with $SOCl_2$ in DMF gave the target compound **55** in 79% yield.

In summary, the preparation of numerous novel furoxan analogues is described. While the convergent strategy was not successful, a combination of new and established chemistry provided access to the desired analogues for biological testing against a medicinally relevant target. Detailed evaluation of the activity against both the TGR enzyme in vitro and ex vivo worms (*S. mansoni*) is ongoing and will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures and NMR data for all final compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.120.

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