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Mild Synthesis of Substituted 1,2,5-Oxadiazoles Using 1,1′-Carbonyldiimidazole as a Dehydrating Agent

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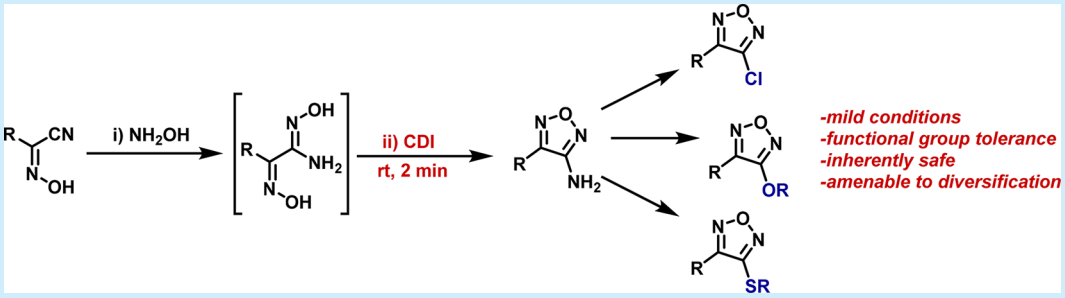
Supporting Information



ABSTRACT: 1,1′-Carbonyldiimidazole was found to induce the formation of a variety of 3,4-disubstituted 1,2,5-oxadiazoles (furazans) from the corresponding bisoximes at ambient temperature. This method enables these inherently energetic compounds to be prepared at temperatures well below their decomposition points and with improved functional group compatibility relative to prior methods. Conditions were developed that allowed for the first high-yielding synthesis of chlorofurazans from their amino counterparts, enabling the mild synthetic manipulation of these heterocycles.

Furazans (1,2,5-oxadiazoles, **B**, Figure 1) constitute an important class of heterocycles that have found a myriad of applications in organic chemistry,[1] in areas as disparate as the production of biologically active molecules[2] and energetic materials.[3] Although numerous methods for the preparation of furazans have been disclosed, the most straightforward approach involves the dehydrative cyclization of vicinal bisoximes (**A**, Figure 1). To this end, a typical reaction entails refluxing the precursor in a high-boiling solvent (100−150 °C) in the presence of a strong base, such as NaOH or KOH, followed by direct precipitation of the product or extractive workup. Various activating reagents, including Ac_2O,[4] $SOCl_2$,[5] succinic anhydride,[2j,5f,6] and others,[2c,7] have been reported to facilitate this cyclization, but temperatures greater than 100 °C are typically required.

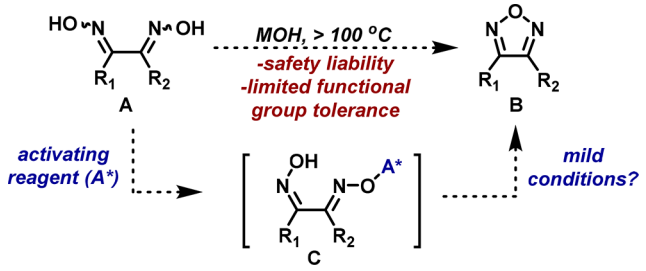


Figure 1. Cyclodehydration approach to furazan synthesis.

Although this method has been the standard in furazan synthesis for over a century,[1] it possesses inherent liabilities. The harsh conditions required preclude the presence of sensitive functional groups, such as esters or base-sensitive stereocenters, elsewhere in the molecule. Perhaps more importantly, the presence of two nitrogen−oxygen bonds contained within a cyclic array confers considerable energetic properties to furazans, such that they are being actively investigated as next-generation explosives. Furthermore, the bisoxime precursors, which also contain multiple nitrogen−oxygen bonds, are expected to be similarly energetic (vide infra). These features represent significant drawbacks to the preparation of furazan-containing molecules on both laboratory and production scales with respect to manufacturing, handling, and shipping.

For these reasons, we sought to develop a method for the synthesis of furazans from the corresponding bisoximes that would proceed under mild conditions, minimizing the aforementioned safety and functional group compatibility concerns. Specifically, we hypothesized that a systematic survey might identify a dehydrating reagent capable of significantly lowering the barrier to cyclization upon adduct formation with a bisoxime (**C**, Figure 1). Table 1 shows the results of a series of experiments, in which bisoxime **1a** was subjected to various potential dehydrating reagents at 25 °C for 2 h. Although **1a** was consumed to some extent in all cases, the corresponding yields of furazan **2a** were typically poor, presumably due to stalling at the stage of adduct formation. Strikingly, however, 1,1′-carbonyldiimidazole (CDI) was found to effect the desired transformation in nearly quantitative yield (Table 1, entry 6). Subsequent experimentation demonstrated that this reactivity was general across a range of non-nucleophilic (and thus unreactive

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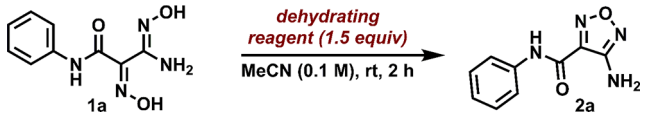
Table 1. Survey of Potential Dehydrating Reagents

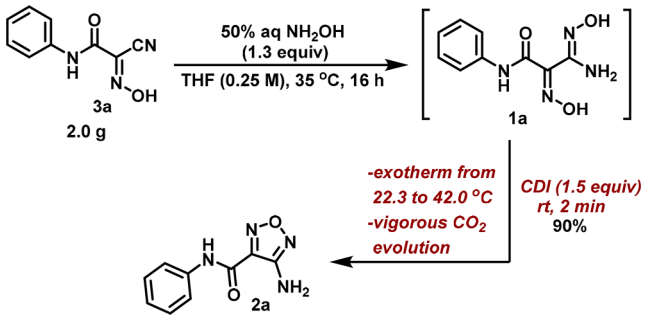


entry[a]	reagent	conversion (%)[b]	yield (%)[b]
1	Ac_2O	100	0
2	$SOCl_2$	36	2
3	$POCl_3$	74	34
4	BzCl	71	12
5	TFAA	65	38
6	CDI	100	93
7	Tf_2O	18	0
8	KOH	94	3
9	HATU	60	17
10	T3P	64	47
11	Burgess reagent	18	13
12[c]	*CDI*	*100*	*>99*

[a]Reactions conducted using 0.1 mmol **1a**. [b]Determined via UPLC using area percent vs concentration calibration curves. [c]Reaction conducted in THF (0.25 M) with a 2 min reaction time.

with CDI) solvents, and that the reaction was complete instantaneously upon mixing of **1a** and CDI (Table 1, entry 12). Furthermore, it was found that furazan **2a** could be formed without any loss in yield from bisoxime **1a** generated in situ by the addition of hydroxylamine to cyano-oxime **3a**, precluding the requirement for isolation of this potentially hazardous intermediate (vide infra). Notably, a reaction conducted on preparative scale (Scheme 1) was accompanied by a 19.7 °C increase in

Scheme 1. Synthesis of Furazan 2a without Isolation of Intermediate Bisoxime



temperature that was concomitant with evolution of CO_2. This latter feature is believed to provide the driving force for the otherwise recalcitrant cyclization.

Figure 2 depicts a collection of additional substrates that underwent CDI-induced furazan formation. To avoid isolation of the intermediate bisoximes (**1**), we elected to generate them in situ from the corresponding cyano-oximes **3**, resulting in a series of substituted aminofurazans (**2**). Substrates containing both tertiary (**3b–d**) and secondary (**3e–i**) amides bearing both alkyl (**3i**) and electronically diverse aryl (**3a,e–h**) substituents underwent smooth cyclization via the action of CDI at room temperature. In all cases, the reactions were judged to be complete as quickly as they could be assayed. A ketone-bearing cyano-oxime (**3n**) underwent the desired reaction, albeit with a diminished yield (55%) due to the competitive condensation with hydroxylamine prior to the addition of CDI. Additionally, furazans containing both aryl (**2j–l**) and heteroaryl (**2m**)

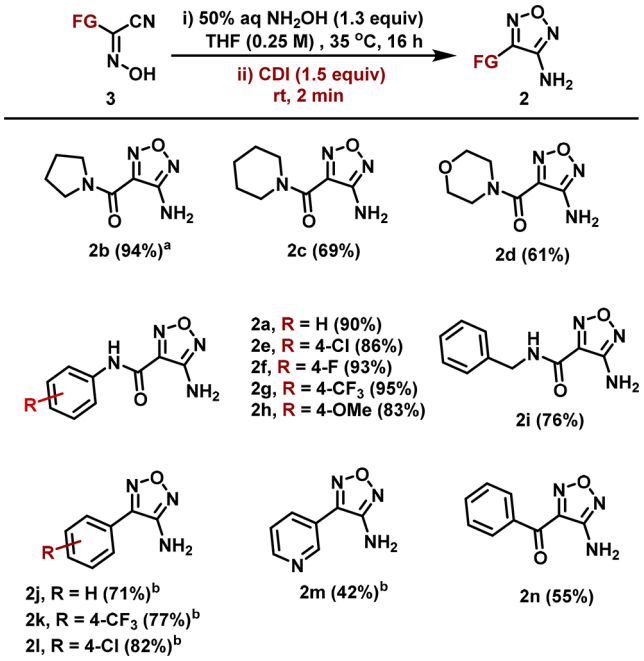
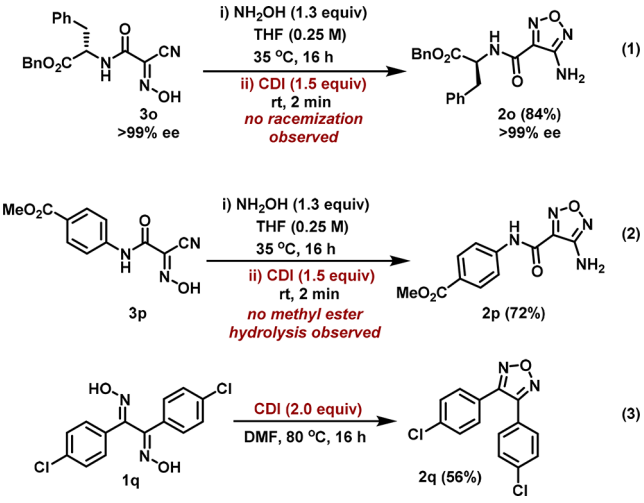


Figure 2. Scope of tandem hydroxylamine addition/CDI-induced cyclodehydration. [a]Isolated yields for reactions conducted on 1.0–1.5 mmol scale. [b]Hydroxylamine addition conducted in MeOH.

substituents could be formed from the analogous cyano-oxime precursors.

To highlight the functional group compatibility of this technique, cyano-oxime **3o** containing both a benzyl ester and a labile stereogenic center (>99% ee) underwent hydroxylamine addition and subsequent CDI-induced cyclization in 84% yield without any detectable loss in enantiopurity (eq 1). Furthermore, methyl-ester-containing furazan **3p** was formed in 72% yield (eq 2). Neither of these results would be expected under the standard furazan-forming conditions requiring hydroxide at



increased temperature. Finally, bisaryl furazan **2q** was formed in 56% yield upon heating with CDI in DMF at 80 °C (eq 3). Previous syntheses of related compounds have required heating of the bisoxime precursor in neat succinic anhydride at 180 °C.[2j]

To demonstrate the advantage of this method over the alternative thermal cyclodehydration from a safety perspective, the energetic content of selected cyano-oximes (**3a,j**), bisoximes

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(**1a,q**), and furazans (**2a,j,q**) was characterized via differential scanning calorimetry (DSC). As shown in Table 2, six of the

Table 2. DSC Data for Selected Compounds

compound	type	exotherm (J/g)[a]	t_{init} (°C)
3a	cyano-oxime	1470	166
3j	cyano-oxime	1448	151
1a	bisoxime	1596	129
1q	bisoxime	1414	209
2a	furazan	1624	248
2j	furazan	1679	234
2q	furazan	705	243

[a]Standard run parameters for DSC: 5 °C/min up to 350 °C.

seven compounds tested displayed exothermic events of greater than 1000 J/g, including the cyano-oxime precursors and bisoxime intermediates. Merck internal process safety guidelines[8] indicate that any compound displaying an exotherm greater than 400 J/g upon DSC testing should be considered potentially hazardous, not only from the standpoint of processing (e.g., isolation, drying and handling) but also for transportation. As all compounds listed in Table 2 fit this criterion, the ability to conduct all manipulations more than 100 °C below their decomposition points offers a clear advantage.

Finally, we demonstrated that the aminofurazans produced by this method could be conveniently functionalized. The most common approach involves oxidation of the amine to the corresponding nitro group, followed by nucleophilic displacement (Figure 3a).[3i,9] Given the inherent safety concerns associated

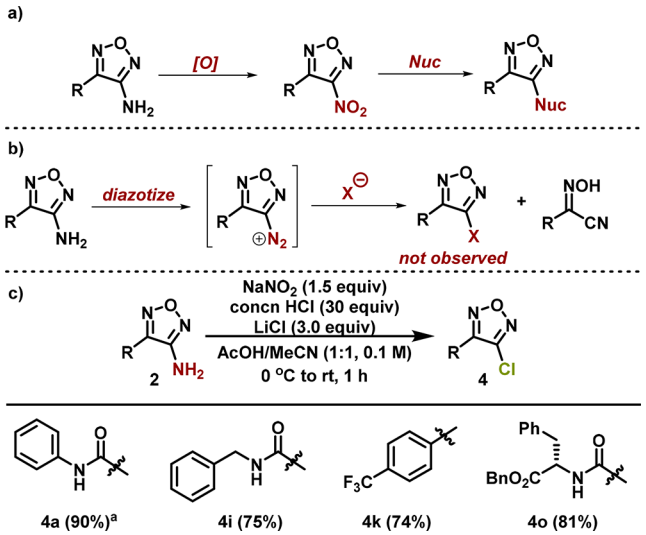
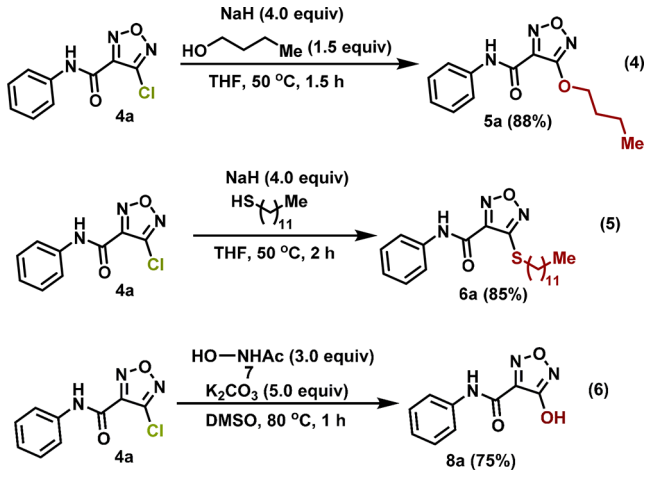


Figure 3. Aminofurazan derivatization: (a) derivatization via nitro intermediate; (b) competitive cyano-oxime formation upon attempted halogenation; (c) selected examples of aminofurazan chlorination. [a]Isolated yields for reactions conducted on 1.0 mmol scale.

with conversion of an energetic material to its nitro-containing analogue, we sought to develop an alternative. Although nucleophilic aromatic substitution on the corresponding halofurazan would be preferable, this strategy has found limited use, principally owing to the difficulty of forming the requisite halofurazans due to competitive ring opening to the parent cyano-oximes (Figure 3b).[1]

After considerable experimentation, we discovered that chlorofurazans (**4**) could be obtained in good yields by treatment of an acidic solution of the corresponding aminofurazans (**2**) with sodium nitrite in the presence of lithium chloride, with minimal formation of the ring-opened byproducts (Figure 3c). Key to the success of this reaction was minimization of water present during diazotization. Notably, previous reports detailing aminofurazan chlorination proceeded in less than 25% yield.[2b,10]

With these chlorofurazans (**4**) in hand, we demonstrated their utility as substrates for nucleophilic aromatic substitution. To this end, chlorofurazan **4a** underwent smooth reaction with both *n*-butanol (eq 4) and dodecanethiol (eq 5), affording good yields of the corresponding furazans (**5a** and **6a**) under mild conditions. Although hydroxide itself was not a competent nucleophile, it was found that hydroxide surrogate *N*-acetylhydroxamic acid (**7**)[11] afforded hydroxyfurazan **8a** in good yield (eq 6). This chlorination-displacement sequence represents the mildest functionalization of aminofurazans reported to date.



In conclusion, it has been demonstrated that CDI enables the cyclodehydration of bisoximes to the corresponding furazans at temperatures more than 100 °C lower than typically required. Based on this observation, a two-step protocol was developed involving (1) hydroxylamine addition to readily prepared cyano-oximes to afford the corresponding bisoximes in situ and (2) CDI- induced cyclodehydration to form furazans. This method was shown to be both more functional-group-tolerant and safer than its thermal alternatives. Conditions were developed that allowed the aminofurazan products to be further functionalized via a high-yielding chlorination-displacement sequence. Given the aforementioned advantages, we believe that this methodology will be rapidly adopted by the synthetic community for the synthesis of furazan-containing molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00568.

Full experimental details, characterization, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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