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Catalysis of Heterocyclic Azadiene Cycloaddition Reactions by Solvent Hydrogen Bonding: Concise Total Synthesis of Methoxatin

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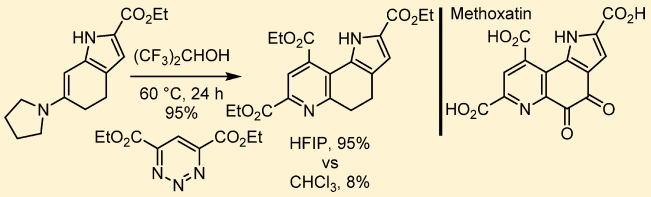
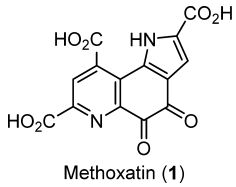
Supporting Information

ABSTRACT: Although it has been examined for decades, no general approach to catalysis of the inverse electron demand Diels–Alder reactions of heterocyclic azadienes has been introduced. Typically, additives such as Lewis acids lead to nonproductive consumption of the electron-rich dienophiles without productive activation of the electron-deficient heterocyclic azadienes. Herein, we report the first general method for catalysis of such cycloaddition reactions by using solvent hydrogen bonding of non-nucleophilic perfluoroalcohols, including hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE), to activate the electron-deficient heterocyclic azadienes. Its use in promoting the cycloaddition of 1,2,3-triazine **4** with enamine **3** as the key step of a concise total synthesis of methoxatin is described.



INTRODUCTION

In 1964, Hauge isolated a redox active compound from the denatured glucose dehydrogenase of *Bacterium anitratum* (*Acinetobacter caloaceticus*).[1] Shortly thereafter, the identical molecule was isolated from the denatured alcohol dehydrogenase of *Pseudomonas* sp. M27.[2] It was not until 1979 that Salisbury (X-ray) elucidated the structure of the enzyme cofactor, which was named methoxatin (Figure 1).[3]



Methoxatin (**1**)

Figure 1. Structure of methoxatin.

Methoxatin (**1**), also known as pyrroloquinoline quinone (PQQ), has now been isolated from a range of methylotrophic bacteria.[4] This densely functionalized heterocyclic quinone serves as a cofactor for methanol dehydrogenase, which catalyzes the conversion of methanol to formaldehyde and allows bacteria to survive on a diet of single carbon units.[4] The discovery of this new cofactor in bacteria stimulated investigations aimed at identification of methoxatin-dependent mammalian enzymes.[5] Because these efforts have not yet detected such an enzyme even though candidates periodically emerge,[5] it remains controversial whether **1** may be a cofactor for a mammalian enzyme and constitutes a required dietary vitamin.[5] Methoxatin has been shown to play a productive role in a variety of mammalian processes, including mitochondrial biogenesis[6] and the attenuation of neurodegenerative diseases,[7] albeit without a defined biological target that accounts for the functional activity.[8] Most significant of these functional activities is its ability to reduce damage in ischemia reperfusion injury of a heart attack or stroke.[9] As a result and although not presently classified as a vitamin, it is offered as a dietary supplement.[10] This interest and its unusual structure have resulted in the disclosure of a series of methoxatin total syntheses that have become increasingly concise in the intervening years since its discovery.[11] Herein, we report a remarkably concise total synthesis of methoxatin that emerged as a consequence of our development of the inverse electron demand Diels–Alder reactions of 1,2,3-triazines.[12] Its development permits the use of a series of complementary heterocyclic azadiene cycloaddition reactions[13] for the late-stage divergent[14] synthesis of analogues containing replacements for the fused pyridine or its substituents. Its success rested on the discovery of a powerful hydrogen bonding activation of the heterocyclic azadiene cycloaddition, and its completion resulted in the discovery of a solution to the previously unsuccessful direct single-step pyrroloquinoline oxidation to an *o*-quinone.[11e]

RESULTS AND DISCUSSION

Thus, methoxatin (**1**) was envisioned to arise from a late-stage oxidation of **5** to its corresponding *o*-quinone and subsequent saponification of the resulting triester (Figure 2). The central feature of the approach is the synthesis of dihydropyrroloquinoline **5**, which was envisioned to arise from the regioselective intermolecular inverse electron demand Diels–Alder reaction between the enamine derived from the known ketone **2** and 1,2,3-triazine **4**. This strategy would permit a rapid synthesis of

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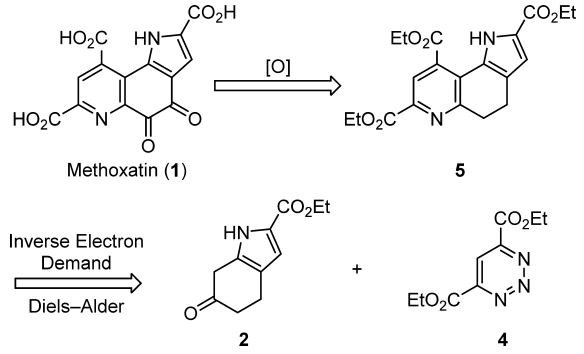
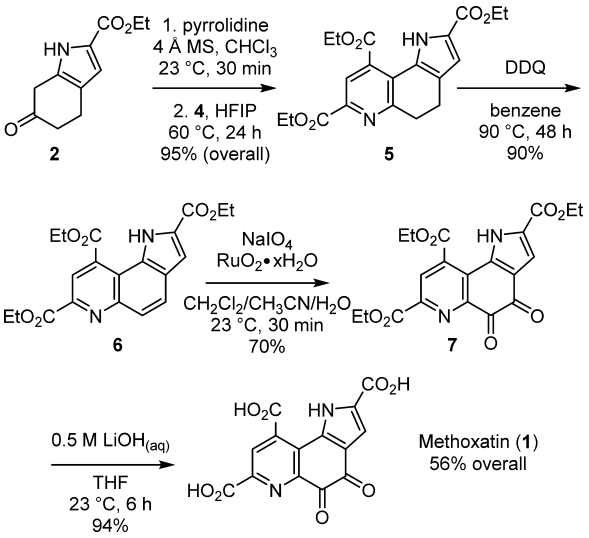


Figure 2. Retrosynthetic analysis.

methoxatin (**1**) amenable to the divergent synthesis of analogues as well as provide a formidable test of the 1,2,3-triazine inverse electron demand Diels–Alder methodology.

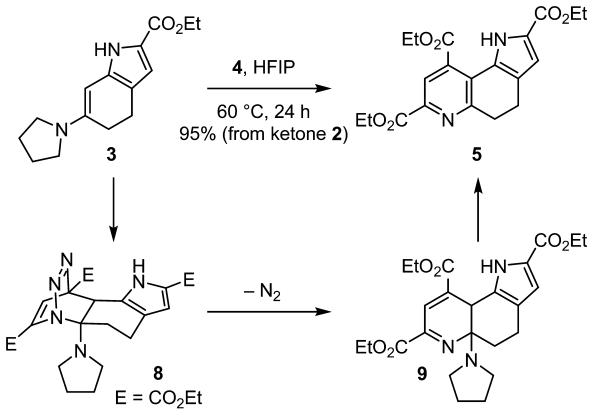
Treatment of ketone **2**[15] with pyrrolidine (5.0 equiv, 4 Å MS, 0.01 M $CHCl_3$, 23 °C, 30 min) provided enamine **3**, which was dried *in vacuo* to ensure complete removal of excess pyrrolidine, and was carried forward without purification (Scheme 1).[16]

Scheme 1. Total Synthesis of Methoxatin



With enamine **3** in hand, the key intermolecular cycloaddition reaction was initially examined under conditions reported for the use of **4**[15] (2 equiv, 0.1 M $CHCl_3$, 60 °C, 5 h).[12c] These conditions afforded a complex mixture of products, containing a disappointing 8% yield of the desired cycloadduct **5**. We initiated optimization studies, examining the reaction solvent, temperature, stoichiometry, additives, and concentration (see Supporting Information). These initial efforts established that addition of 1.5 equiv of trifluoroacetic acid (TFA, 2 equiv **4**, 0.1 M $CHCl_3$, 23 °C, 5 h) improved the reaction, resulting in a 34% yield of the desired cycloadduct **5** and a simplified product mixture. The success of TFA and, to a lesser extent, other haloacetic acid additives suggested that the enhanced reactivity observed may arise from aiding aromatization of intermediate **9** by protonation of the pyrrolidine in **9** or may arise from a hydrogen bonding interaction between the haloacetic acids and 1,2,3-triazine **4**. Unaromatized cycloadduct was not detected in the reactions and did not constitute a stalled intermediate in the route to product, accounting for the low conversions. Rather, it is the [4 + 2] cycloaddition that was not progressing in the instances of low conversion. Thus, the additives were not simply serving as a catalyst for the final aromatization step, but were found to be accelerating the cycloaddition itself.

In order to probe the role of hydrogen bonding,[17] further optimization of the reaction conditions was undertaken, exploring hydrogen bonding additives and solvents from which hexafluoroisoproanol (HFIP) emerged as a remarkable solvent for the [4 + 2] cycloaddition reaction (Figure 3). Under



entry	additive	solvent	temp (°C)	time (h)	yield
1	none	$CHCl_3$	60	24	8%
2	none	CH_3CN	60	24	7%
3	none	dioxane	60	24	8%
4	none	toluene	60	24	7%
5	TFA (1.5 equiv)	$CHCl_3$	23	5	34%
6	none	TFE	23	24	36%
7	none	HFIP	23	24	41%
8	none	HFIP	60	24	95%
9	none	EtOH	60	24	0%
10	none	^{i}PrOH	60	24	0%

Figure 3. Optimization of cycloaddition reaction of enamine **3** with **4**, with selected results.

these newly found conditions, the cycloaddition of enamine **3** and 1,2,3-triazine **4** (2 equiv, 0.1 M HFIP, 60 °C, 24 h) proceeded cleanly to provide the desired cycloadduct **5** in a stunning 95% yield (from ketone **2**). The solvents HFIP and trifluoroethanol (TFE) were uniquely successful among all solvents examined, which spanned a range of polarity, dielectric constant, and hydrogen bonding capability. This behavior arises from not only the ability of HFIP to hydrogen bond to the 1,2,3-triazine, thereby activating it for the subsequent cycloaddition, but also from its inability to serve as a nucleophile nonproductively consuming the starting 1,2,3-triazine.

To confirm hydrogen bonding of HFIP with **4**, serial addition of 1,2,3-triazine **4** (0–1.5 equiv) to HFIP ($CDCl_3$) was examined and led to diagnostic progressive and pronounced downfield chemical shifts of the HFIP alcohol proton (Δ1.36 ppm) and smaller shifts in the HFIP methine proton (Δ0.19 ppm), accompanied by small shifts in the 1,2,3-triazine aryl hydrogen (Δ 0.03 ppm) in the ^{1}H NMR (see Supporting Information). ^{19}F NMR analysis of the titration was also conducted and revealed no appreciable change in the chemical shifts of the HFIP fluorine signal (Δ0.09 ppm, see Supporting Information). Potentially further contributing to the overall success of the reaction, HFIP may also serve as a mild acid catalyst for promoting the final aromatization reaction involving the loss of pyrrolidine.[18] Finally, the cycloaddition of **3** with 1,2,3-triazine **4** proceeds exclusively through a single mode of cycloaddition (C4/N1 vs C5/N2 1,2,3-triazine

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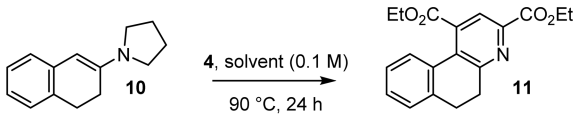
cycloaddition) and with complete regioselectivity (enamine nucleophilic carbon attached to C4). Although this is in line with expectations based on our studies with **4**,[12c] it is notable that **4** bears two electron-withdrawing groups (−CO_2Et) placed at noncomplementary sites that enhance the intrinsic reactivity of the 1,2,3-triazine without altering its mode of enamine cycloaddition.[12,19]

In order to establish the generality of the observations, the cycloaddition of the pyrrolidine enamine derived from *β*-tetralone (**10**) with the 1,2,3-triazine **4** was studied in a more systematic manner, examining a larger range of apolar and polar aprotic solvents as well as a systematic series of protic solvents capable of varying propensities for hydrogen bonding (Figure 4). Only the cycloaddition conducted in HFIP provided the



Non-Hydrogen Bonding Solvents

entry	solvent	dielectric constant*	yield
1	CCl_4	2.24	10%
2	C_6H_6	2.28	27%
3	Et_2O	4.27	10%
4	CH_2Cl_2	8.93	11%
5	THF	7.52	0%
6	CH_3CN	36.6	0%
7	DMSO	47.2	4%

Hydrogen Bonding Solvents

entry	solvent	dielectric constant*	yield
8	$CHCl_3$	4.81	17%
9	EtOH	25.3	0%
10	^{i}PrOH	20.2	0%
11	^{n}BuOH	17.8	0%
12	TFE	27.7	34%
13	HFIP	16.7	86%

*from: *CRC Handbook of Chemistry and Physics*, 91st ed. Haynes, W. M., Ed.; CRC Press: Boca Raton, FL, 2010

HFIP as an Additive to $CHCl_3$

entry	equiv HFIP	yield
14	1.0	9%
15	5.0	8%
16	7.5	39%
17	10	55%
18	25	80%
19	50	82%
20	100	86%

Figure 4. Effect of solvent on cycloaddition.

cycloadduct **11** effectively, and it did so with excellent conversion (86%). Similarly, the use of HFIP as an additive to the cycloaddition reaction of **4** with **10** conducted in $CHCl_3$ progressively improved the conversion to **11** as the amount of HFIP additive was increased (Figure 4).

Additionally and just as significantly, the observations were not limited to the enamine substrates **3** and **10**. The enamines **12** and **14**, which react with **4** poorly, participate in much more productive cycloaddition reactions when they are conducted in TFE (Figure 5). With such nonconjugated enamines, TFE often proved to be a more effective activating solvent than HFIP since the acidity of the latter (pK_a 9.3 vs 12.4) can lead to competitive nonproductive consumption of the starting enamine.

Finally, a series of heterocyclic azadienes that exhibit a wide range of intrinsic reactivities were examined, comparing their behavior toward **10** under standard conditions to the use of HFIP as solvent (Figure 6). This included not only a series of 1,2,3-triazines **4**, **16**−**21** that we recently introduced,[12] but also

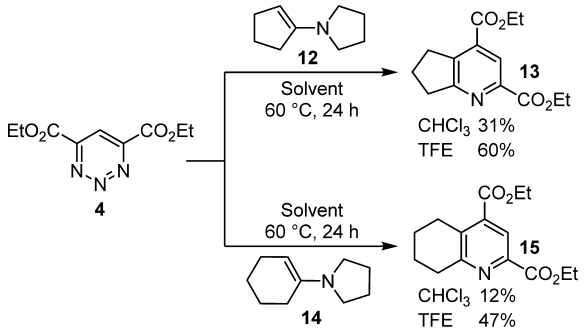


Figure 5. Additional representative enamines.

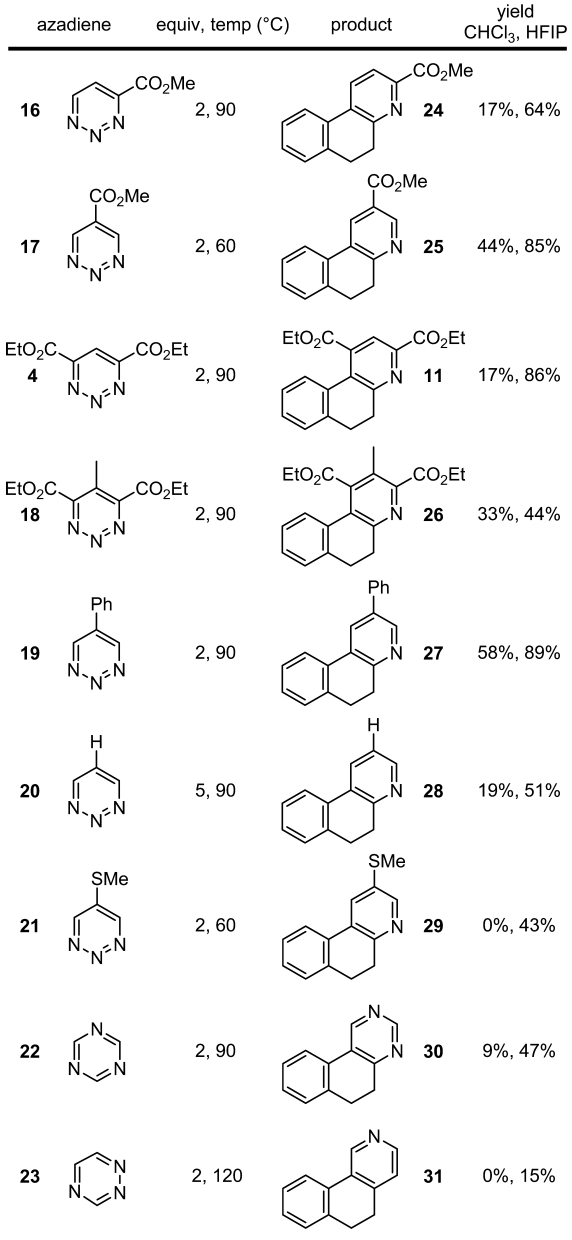


Figure 6. Scope of heterocyclic azadienes, upon reaction with enamine **10** (24 h).

the isomeric 1,3,5-triazine (**22**)[20] and 1,2,4-triazine (**23**).[21] In each case and without deliberate optimization efforts (run at 60, 90, or 120 °C, 24 h), the cycloadditions were more effective in HFIP, including many (e.g., **4**, **20**−**23**) that ordinarily do not

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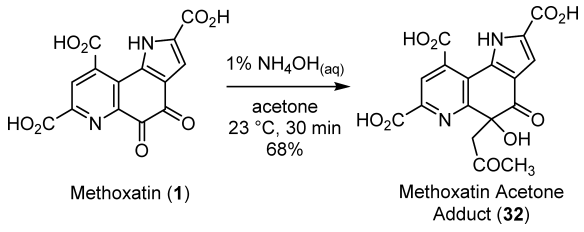
productively react with **10** because of their modest intrinsic reactivity. Just as significantly, the regioselectivity and mode of cycloaddition were unaltered in each case examined. Thus, the use of HFIP as reaction solvent and its hydrogen bond activation extend to the larger family of heterocyclic azadienes, providing a general solution to catalyzing their inverse electron demand [4 + 2] cycloaddition reactions. Not surprisingly, the less reactive heterocycles 1,2-diazine (pyridazine), 1,3-diazine (pyrimidine), and 1,4-diazine (pyrazine) are unreactive toward enamine **10** with or without use of HFIP as solvent.

With cycloadduct **5** in hand, our focus returned to its conversion to methoxatin (**1**). While ostensibly straightforward on the basis of phenanthrene oxidation precedent,[22] extensive efforts by Hendrickson and co-workers to affect a similar oxidation to the *o*-quinone in route to methoxatin were not successful.[11e] We began with treatment of cycloadduct **5** with DDQ (4.0 equiv, 0.004 M C_6H_6, 90 °C, 48 h) to afford pyrroloquinoline **6** in 90% yield (Scheme 1). At this stage, efforts were undertaken to identify conditions capable of delivering *o*-quinone **7**. As reported by Hendrickson, most common oxidation methods were ineffective, either returning starting material or affecting its nonproductive consumption.[11e] Although OsO_4 failed to react with **6** under a variety of conditions, we found that its more reactive congener RuO_4 successfully provided **7**.[23] Although initial efforts with RuO_4 provided only small amounts of product, systematic optimization identified conditions that were substoichiometric in Ru (0.4 equiv RuO_2, 5.0 equiv $NaIO_4$, 0.004 M $H_2O/CH_2Cl_2/CH_3CN$ 1:1:1, 23 °C, 30 min), capable of generating RuO_4 *in situ* that provided the desired *o*-quinone **7** cleanly in 70% yield.[24]

The three esters of *o*-quinone **7** were saponified according to previous reports (0.01 M THF/0.5 M LiOH(aq), 23 °C, 6 h) to provide methoxatin (**1**) in 94% yield as a bright red solid, which displayed spectral and physical properties in full agreement with an authentic sample.[11] Because **1** bears so few ^{1}H NMR signals, synthetic methoxatin (**1**) was further converted in 68% yield to its acetone adduct **33** (0.003 M acetone/1% NH_4OH(aq) 4:1, 23 °C, 30 min), which also displayed spectral and physical properties in full agreement with literature reports (Scheme 2).[11]

Scheme 2. Synthesis of Methoxatin Acetone Adduct

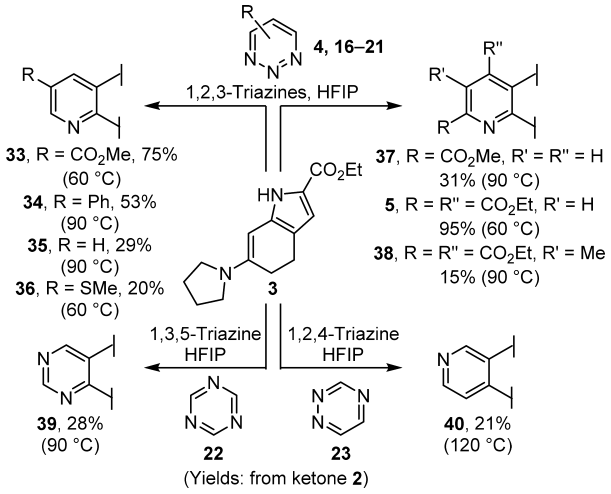


Methoxatin (**1**) — Methoxatin Acetone Adduct (**32**)

As highlighted earlier, the approach was purposefully chosen to permit the divergent synthesis of methoxatin analogues by altering the selection of heterocyclic azadiene cycloaddition partner. Thus, a series of representative heterocyclic azadienes were reacted with enamine **3** in HFIP (24 h) without optimization by simply adopting conditions identified with **10** (Figure 6) to afford the corresponding cycloadducts **33**–**40** (Scheme 3).

The use of Lewis acid catalysis along with other approaches has been examined extensively for years in efforts to accelerate

Scheme 3. Divergent Synthesis of Cycloadduct Analogues



(Yields: from ketone **2**)

or promote the inverse electron demand Diels–Alder reaction of heterocyclic azadienes.[17,25–28] Although there are notable successes, including Wegner's diboraanthracene[26] for use with phthalazines, Rawal's Ag(I)-promoted reactions of silyloxy alkynes with phthalazines,[27] and our own use of pressure-promoted reactions,[28] these efforts have been largely unsuccessful in providing a general solution. Typically, additives preferentially lead to consumption of the electron-rich dienophile without productive activation of the electron-deficient heterocyclic azadienes.

■ CONCLUSIONS

Herein, we report the first general method for catalyzing heterocyclic azadiene Diels–Alder reactions, enlisting the hydrogen bonding and non-nucleophilic character of perfluoroalcohols (HFIP and TFE) to selectively activate the electron-deficient heterocyclic azadienes. Its use in a concise synthesis of the bacterial enzyme cofactor methoxatin (**1**) from **2**[15] in 56% overall yield was disclosed. The route employed the key hydrogen bonding facilitated intermolecular inverse electron demand Diels–Alder reaction of the 1,2,3-triazine **4** for assembling the carbon skeleton of the natural product in a single step in superb yield (95%, from ketone **2**). The synthetic strategy outlined and the expanded heterocyclic azadiene cycloaddition scope derived from the HFIP-promoted reactions purposefully allowed for the divergent synthesis of cycloadduct analogues not easily accessible by other approaches.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05438.

Full experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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