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Four Mechanisms in the Reactions of 3-Aminopyrrole with 1,3,5-Triazines: Inverse Electron Demand Diels–Alder Cycloadditions vs S_NAr Reactions via Uncatalyzed and Acid-Catalyzed Pathways

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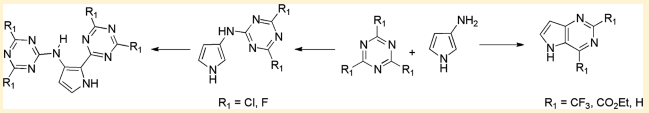
Supporting Information

ABSTRACT: Reaction of 3-aminopyrrole with seven 1,3,5-triazines was studied in a one-step reaction (in situ formation of 3-aminopyrrole) and a two-step reaction (using the tetraphenylborate salt and an amine base). An inverse-electron demand Diels–Alder reaction (IEDDA) was observed with R_1 = CF_3, CO_2Et, and H with the formation of 5*H*-pyrrolo[3,2-*d*]pyrimidine derivatives. S_NAr was observed when 2,4,6-trifluoro- or 2,4,6-trichloro-1,3,5-triazine were used—1,3,5-triazines that had leaving groups. If excess 1,3,5-triazine was present the initial S_NAr product reacted further, in the presence of acid and water, with another equivalent of 1,3,5-triazine to give compounds containing three linked heterocyclic rings. No reaction was observed with R_1 = C_6H_5 and OCH_3. Four mechanisms are proposed to explain the experimental results: uncatalyzed and acid catalyzed inverse electron demand Diels–Alder cascades leading to cycloaddition, and uncatalyzed and acid-catalyzed S_NAr reactions leading, respectively, to single and double substitution products. Acid catalysis was a factor when there was reduced reactivity in either reactant.



INTRODUCTION

Recently the first synthesis of 3-aminopyrrole was reported.[1] Prior to this, the only simple 3-aminopyrroles reported, without further substitution on the pyrrole ring, were 3-amino-1-tritylpyrrole as the imino tautomer,[2] and the picrate[3] of 1-phenyl-3-aminopyrrole. With the 3-aminopyrrole in hand, reactions not possible with the polyfunctional 3-aminopyrroles in the literature can now be studied.[4] We report on the reaction of 3-aminopyrrole with a series of 1,3,5-triazines. Inverse electron demand Diels–Alder (IEDDA) cycloaddition[5] competed with a S_NAr reaction[6] when the 1,3,5-triazine had a leaving group. The IEDDA reaction gave the 5*H*-pyrrolo[3,2-*d*]pyrimidine scaffold—privileged chemical structures[7] of interest because of their pharmacological properties. To the best of our knowledge, this is the first report of the synthesis of the 5*H*-pyrrolo[3,2-*d*]pyrimidine ring system using an IEDDA reaction.[8] Previously two general cyclization routes have been reported for the synthesis of the 5*H*-pyrrolo[3,2-*d*]pyrimidine ring system:[8] starting either from a pyrimidine or from a polyfunctional 3-aminopyrrole. In the case of the reactions of 1,3,5-triazines with leaving groups, the initially formed S_NAr product could react further with a second equivalent of 1,3,5-triazine. Heteroaryl-heteroaryl compounds were obtained from the observed S_NAr reactions: compounds that are of increasing interest in biological compounds, liquid crystals, and optoelectronic compounds.[9] Four mechanisms were needed to explain the results detailed below.

RESULTS

The reaction of 3-aminopyrrole (**1**) with seven symmetrical 1,3,5-triazines[10] **4** was carried out by generating the 3-aminopyrrole (**1**) in situ in two ways: a one-step reaction in which the reduction of 3-nitropyrrole (**2**) to 3-aminopyrrole (**1**), with Sn/acetic acid[11] in CH_2Cl_2, was carried out in the presence of the 1,3,5-triazine **4**; whereas, in the two-step procedure the 3-aminopyrrole (**1**) was generated in the presence of the 1,3,5-triazine **4** by treating the tetraphenylborate salt[1] of 3-aminopyrrole (**3**) with an amine base in THF or the salt in CH_2Cl_2/AcOH.

It was found that IEDDA cycloaddition reactions took place between 3-aminopyrrole and 1,3,5-triazines containing poor leaving groups **4a**, **4b**, and **4c** (R_1 = CF_3, CO_2Et, and H). It should be noted that the parent 5*H*-pyrrolo[3,2-*d*]pyrimidine (**5c**) has been previously prepared in a multistep sequence.[12] Water formed during reduction of 3-nitropyrrole hydrolyzed either **4b** or **5b** (R_1 = CO_2Et) and 4 Å molecular sieves were added to the reaction mixture to optimize the product yield of **5b**. Interestingly it was found that the best conditions for the IEDDA cycloaddition of the tetraphenylborate salt of 3-aminopyrrole (**3**) with **4a** and **4b** were under weakly acidic reaction conditions: direct mixture of salt **3** with the 1,3,5-triazine in the absence of an amine base. Reaction of salt **3** with **4c** (R_1 = H) to give 5*H*-pyrrolo[3,2-*d*]pyrimidine (**5c**) only occurred in the presence of a large excess of AcOH. Based on this, and as discussed below, it is proposed that **5c** was the product of a separate acid-catalyzed reaction.

The reaction of 3-aminopyrrole with electron deficient 1,3,5-triazines, containing leaving groups **4d** (R_1 = Cl) and **4e** (R_1 = F), proceeded via a S_NAr reaction generating heteroaryl-heteroaryl compounds **6d** and **6e**. Optimal conditions for these

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Scheme 1. Optimized Reactions of 3-Aminopyrrole with 1,3,5-Triazines

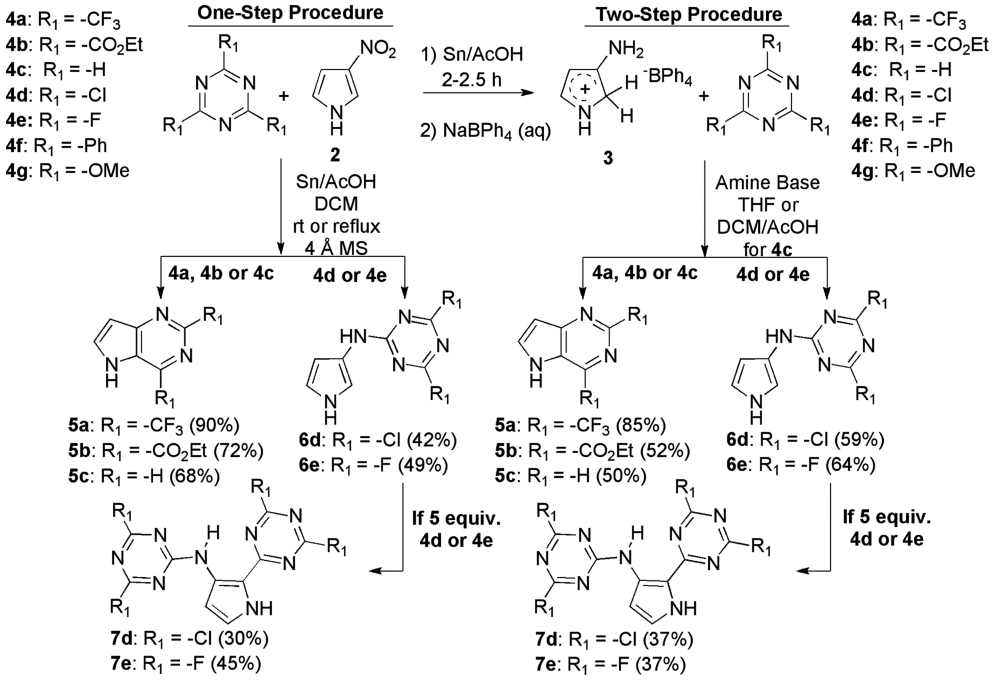

Table 1. Yields of 5*H*-Pyrrolo[2,3-*d*]pyrimidines

entry	R_1	method[a,b]	equiv (4)	solvent	additive	temp	time (h)	5[d]
1	CF_3	Two-Step	1	THF	X	room temp	2	85%
2	CF_3	One-Step	1	3:2 DCM:AcOH	X	reflux	1	75%
3	CF_3	One-Step	1	3:2 DCM:AcOH	X	room temp	1	90%
4	CO_2Et	Two-Step	1	THF	X	room temp	2.5	52%
5	CO_2Et	Two-Step	1	THF	50% Et_3N	room temp	2.5	49%
6	CO_2Et	One-Step	1	3:2 DCM:AcOH	X	reflux	1	trace
7	CO_2Et	One-Step	1	3:2 DCM:AcOH	4 Å MS	room temp	2	54%
8	CO_2Et	One-Step	1	3:2 DCM:AcOH[c]	4 Å MS	room temp	2	72%
9	H	Two-Step	1	THF	X	room temp	1	0%
10	H	Two-Step	1	THF	X	reflux	0.5	0%
11	H	Two-Step	1	THF	100% Et_3N	room temp	0.25	trace
12	H	Two-Step	2	THF	X	room temp	1	0%
13	H	Two-Step	1	THF	$NaHCO_3$	room temp	18	0%
14	H	Two-Step	1	THF	500% AcOH	room temp	23	trace
15	H	Two-Step	1	3:2 DCM:AcOH	X	room temp	4	44%
16	H	Two-Step	2	3:2 DCM:AcOH	X	room temp	4	50%
17	H	Two-Step	2	3:2 DCM:AcOH[c]	4 Å MS	room temp	22	38%
18	H	One-Step	1	3:2 DCM:AcOH	X	room temp	1.5	45%
19	H	One-Step	1	3:2 DCM:AcOH	X	reflux	0.5	44%
20	H	One-Step	1	3:2 DCM:AcOH	4 Å MS	room temp	2.5	41%
21	H	One-Step	2	3:2 DCM:AcOH	X	room temp	2	68%
22	Ph	Two-Step	1	THF	X	reflux	2	NR
23	Ph	One-Step	1	3:2 DCM:AcOH	X	reflux	5	NR
24	Ph	One-Step	1	3:2 ACN:AcOH	X	reflux	20	NR
25	OMe	Two-Step	1	THF	X	room temp	72	NR
26	OMe	One-Step	1	3:2 DCM:AcOH	X	reflux	2	NR

[a]Two-Step Method/**3**. [b]One-Step Method/**2**/Sn (5 equiv). [c]Solvent mixture dried over 4 Å MS prior to reaction. [d]Isolated yield of purified products.

reactions were found to be the more basic two-step procedure conditions with the reaction of salt **3** with **4d** in the presence of 2 equiv DIPEA[13] and reaction of salt **3** with **4e** in the presence of 0.5 equiv Et_3N. Surprisingly the reaction of 3-aminopyrrole with 5 equiv of **4d** or **4e** (in an attempt to increase the yield of **6**) produced the double substitution products **7d** and **7e** as the major reaction products, but only under acidic conditions; results that suggested that formation of **7** was acid catalyzed.[14] The reaction of 3-aminopyrrole with electron rich 1,3,5-triazines **4f** ($R_1 = C_6H_5$) and **4g** ($R_1 = OCH_3$) failed under all

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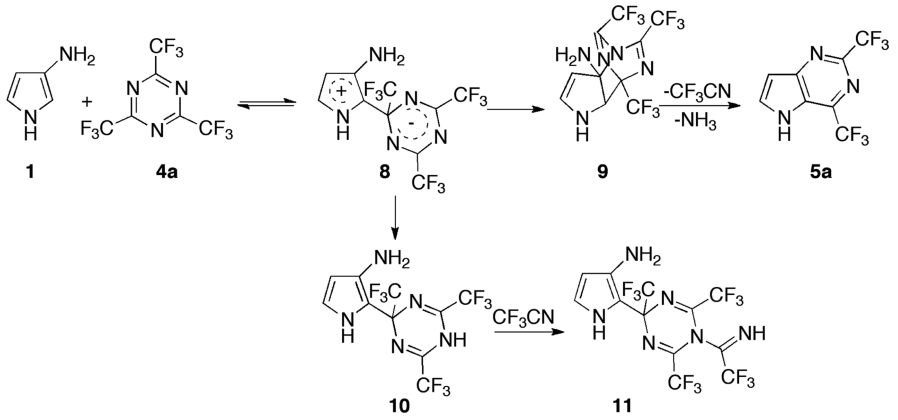
Scheme 2. Cascade Mechanism for the Reaction of 3-Aminopyrrole with a 1,3,5-Triazine



the conditions explored. X-ray crystallography was used to confirm the structures of **5a** (R_1 = CF_3) and **7e** (R_1 = F).[15]

During the course of the reaction of 2,4,6-tris-(trifluoromethyl)-1,3,5-triazine (**4a**) with 3-aminopyrrole (two-step) an unstable intermediate **11** was isolated. Based on its H-1 (three different NH protons), F-19 (four CF_3 groups in a ratio of 2:1:1) NMR spectra and HRMS, structure **11** was proposed (Scheme 2). When this reaction was carried out with the one-step method this intermediate was not observed by TLC. Its formation and subsequent reaction will be discussed below.

Based on the results summarized in Scheme 1 and Table 1 it is proposed that there are four possible mechanisms: they are determined by the nature of the substituent present on the 1,3,5-triazine or the 3-aminopyrrole, and if an acid is added or generated in situ. The four possible mechanisms are an inverse electron demand Diels–Alder cascade leading to cycloaddition products **5a** (R_1 = CF_3) and **5b** (R_1 = CO_2Et), acid catalyzed cycloaddition that gives product **5c** (R_1 = H), a neutral S_NAr reaction that gives products **6d** (R_1 = Cl) and **6e** (R_1 = F), and an acid catalyzed S_NAr reaction that gives the double substitution products **7d** and **7e**. Each of these mechanisms will be discussed in a separate section below.

DISCUSSION

1. Cycloaddition via an Inverse Electron Demand Diels–Alder (IEDDA) Cascade. The inverse electron demand Diels–Alder reactions of 2-aminopyrroles,[16] 1-substituted-5-amino-1*H*-imidazoles,[17] 5-amino-1*H*-pyrazoles,[18] and aminothiophenes[19] with azadienes have been reported. These studies have proposed that the IEDDA reactions of electron-rich aminoheterocycles with azadienes were stepwise in nature and the first step was the formation of a zwitterion. Reaction of 1-*tert*-butyl-2-aminopyrrole[16d] with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine has been shown, by multinuclear NMR, to involve at least five intermediates, one of them a zwitterion analogous to **8**. Scheme 2 (with R_1 = CF_3) illustrates the proposed cascade mechanism.

Reaction at C2 of 3-aminopyrrole (**1**) gave zwitterion **8**. This type of zwitterion, formed when the nucleophile/electrophile pair are aromatic and/or heteroaromatic, has been termed a Wheland-Meisenheimer complex;[20−22] recently, the X-ray structure of such a complex was reported.[23] Formation of Wheland-Meisenheimer complexes has also been reported to be reversible.[23] Other examples of zwitterions have been proposed as intermediates in IEDDA reactions with 2-aminopyrroles,[16d] S_NAr reactions of 1-alkyl-substituted-2-aminopyrroles with 2,4,5,6-tetrachloropyrimidine,[24] and in other systems[16f,17b,25−27] that, in retrospect, are Wheland-Meisenheimer complexes. It is also possible that the initially formed zwitterion ion (Wheland-Meisenheimer complex **8**) was present as, or in equilibrium with, its ammonium tautomer as has been observed for the conjugate acids of 3-aminopyrrole (**1**).[1] Once formed, **8** (or a tautomer) can then cyclize to tricyclic adduct **9**, that in turn could undergo a retro-Diels–Alder reaction, followed by loss of ammonia to give **5a**. It is also possible that loss of ammonia occurred first,[6d] followed by the retro-Diels–Alder reaction.[28]

When the reaction was carried out by the two-step method with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**5a**), unstable **11** was isolated. It is the product of the reaction of intermediate **10** with trifluoroacetonitrile (formed in the cascade leading to **5a**). Reactions of amines with trifluoroacetonitrile under mild conditions have been reported.[29] A similar derivative was reported in a previous study of the reaction of 1-*tert*-butyl-2-aminopyrrole with **5a**.[16d] Intermediate **10** is a tautomer of Wheland-Meisenheimer **8**; its isolation, as **11**, is additional evidence for the formation of **8**.[30] Over a period of 2-weeks isolated intermediate **11** converted to the cycloadduct **5a**. Intermediate **11** was not detected in the one-step process possibly because its conversion to product was acid catalyzed or it was not formed in the presence of acid.

2. Cycloaddition via an Acid Catalyzed Inverse Electron Demand Diels–Alder (IEDDA) Cascade. As noted above and in Table 1, the reaction of 1,3,5-triazine (**4c**) and 3-aminopyrrole (**1**) only occurred under acidic conditions (acetic acid). Boger has reported acid-catalyzed IEDDA reactions of 1,3,5-triazines and enamines.[31,32] It has been reported that the IEDDA reaction of 1,3,5-triazine (**2c**) with enaminones was acid-catalyzed.[33] Protonation of **4c** lowered the LUMO–HOMO interaction and made cycloaddition easier.[33] This calculation was carried out using AM1.[33] The reaction of 1,3,5-triazine (**2c**) with naphthalene and 2-napthyl ethers was facilitated by polyphosphoric acid (PPA).[34,35] The IEDDA reaction of 1-substituted-5-amino-1*H*-imidazoles with 1,3,5-triazines[17b,25] has been reported to be catalyzed by TMSO-triflate, a strong Lewis acid.[36] Lewis acid catalysis of other IEDDA reactions have been reported.[37] Interestingly the IEDDA reactions of 2-amino-4-cyanopyrroles with 1,3,5-triazines were carried out using the HCl salts of the 2-aminopyrroles studied.[16a,38] Literature precedent, and the results in Table 1, suggested that the reaction leading to **5c** was

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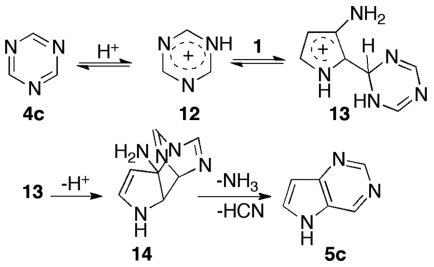
acid-catalyzed as shown below in Scheme 3. Yields of **5a** and **5b** were slightly higher under acidic conditions (Table 1). It is possible that both the neutral and acid catalyzed cycloadditions were occurring under these conditions.

Scheme 3. Suggested Mechanism for Reaction of 1,3,5-Triazine and 3-Aminopyrrole



3. Nucleophilic Aromatic Substitution (S_NAr). Formation of **6** took place via a conventional S_NAr mechanism.[6] Reaction of 3-aminopyrrole (**1**) with a 1,3,5-triazine **4** at the 3-amino group would give zwitterion **15**. When a leaving group (F or Cl) was present, a S_NAr reaction took place and **6** was formed (Scheme 4 with R_1 = F). Reaction at the 3-amino group would also be expected when the 1,3,5-triazine had a poor leaving group. Zwitterions **8** (Scheme 2) and **15** were likely in equilibrium, with the formation of **5** (IEDDA) or **6** (S_NAr) determined by the nature of the leaving group present in the 1,3,5-triazine.

An analogous S_NAr reaction was observed in the reaction of 1-substituted-2-aminopyrroles with 2,4,5,6-tetrachloropyrimidine; reactions took place at the 3-amino group or at C_2 or C_5 of the pyrrole ring depending on the size of the 1-substituent.[24] In the reaction of pyrrole and 1-methylpyrrole with 4,5-dicyanopyridiazine a S_NAr reaction competed with cycloaddition—here the leaving group was cyanide ion.[39] Reactions of 1 equiv of 2,4,6-trifluoro- or 2,4,6-trichloro-1,3,5-triazine with 3-aminopyrrole (**1**) to give **6**, took about the same time (60−90 min) using either method (Table 1). There did not appear to be an element effect. This implied that the formation of zwitterion **15** was the rate-determining step in the formation of **6**, and not the breaking of the C-X bond.[6] These results are typical for conventional S_NAr reactions. It is proposed that the formation of the zwitterion **15** was reversible as is generally found in S_NAr reactions.[6] No evidence was found for a S_NAr reaction at C_2 or C_5 of the pyrrole ring of 3-aminopyrrole (**1**), as was found in the reaction 1-alkyl-2-aminopyrroles with 2,4,5,6-tetrachloropyrimidine.[24] There was also no evidence of the tautomerism of **6** as was observed in the analogous chloropyrimidyl derivatives.[40] Table 2 summarizes the data for the S_NAr reactions.

4. Acid Catalyzed Nucleophilic Aromatic Substitution (S_NAr). Formation of the disubstituted product **7** was unexpected. It might have been expected that in **6**, an electron-withdrawing difluoro- or dichloro-1,3,5-triazine group bonded to the 3-amino group would have reduced its nucleophilic character such that it would not have been very reactive toward electrophiles. As noted above **7** was obtained when, in order to increase its yield, excess 1,3,5-triazine (5 equiv) was used, but only under specific conditions did **6** react further to give **7**. Studies, with 2,4,6-trifluoro-1,3,5-triazine (**4e**) and its derivatives, are summarized in Scheme 5.

Both acid and water (from the reduction of the nitro group) were needed for the formation of disubstituted **7e**. This can be seen from the following (Scheme 5 and Table 2): (1) reaction of **6e** with 2,4,6-trifluoro-1,3,5-triazine (**4e**) to give **7e**, under neutral conditions, was slow and the yield was very low (3%); and (2) no **7e** was formed in the presence of molecular sieve, even when excess 2,4,6-trifluoro-1,3,5-triazine (**4e**) was present. Analogous aminations of chloropyrimidines[41] and halopurines[41e,42] have been reported to be acid-catalyzed;[43] in some cases they were carried out in aqueous acid, or needed water.[41a,b,g,h] Given the role that water played in this reaction, specific-acid catalysis is proposed in which the catalytic species was the hydronium ion: formation of **16** occurred in a rapid pre-equilibrium followed by a subsequent rate-determining step (Scheme 6). This appears to the first time that specific-acid catalysis has been identified as the catalytic mechanism in these types of aminations.

HF was formed as a byproduct of the second S_NAr reaction (Scheme 6), and possibly by the hydrolysis 2,4,6-trifluoro-1,3,5-triazine (**4e**); as an acid, stronger than acetic acid, it would increase the stoichiometric concentration of hydronium ion present in the reaction mixture. Since HF was formed as the reactions progressed, its effect was likely autocatalytic; autocatalysis of aminations of halopyrimidines and halopurines have also been reported.[41d,e,42b] Studies with 2,4,6-trichloro-1,3,5-triazine (**4d**) were not as clear; this was most likely a consequence of the much greater reactivity[44,45] of this 1,3,5-triazine with the resulting formation of HCl and the likely autocatalytic nature of the reaction. Scheme 6 illustrates the proposed acid-catalyzed S_NAr mechanism.

CONCLUSIONS

Aminopyrroles are highly electron-rich and unstable compounds. Only when one or more electron-withdrawing groups are present[2b] can aminopyrroles be isolated—but the same groups that stabilize the aminopyrroles also diminish the scope of their possible reactions. This can be seen in the synthetic and mechanistic results presented in this work on 3-aminopyrrole without further substitution on the ring.

Synthetically the first example of the inverse electron demand Diels−Alder reaction of 3-aminopyrrole, or of any 3-aminopyrrole, has been reported. Starting with 3-nitropyrrole the 5*H*-pyrrolo[3,2-*d*]pyrimidine ring system can be obtained in one

Scheme 4. Nucleophilic Aromatic Substitution (S_NAr) Mechanism

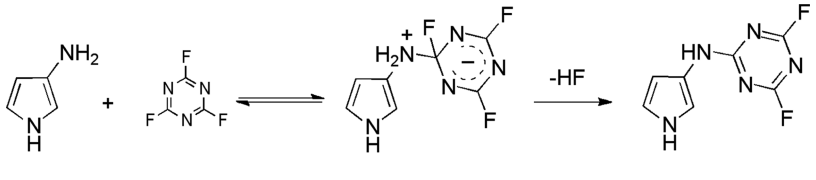


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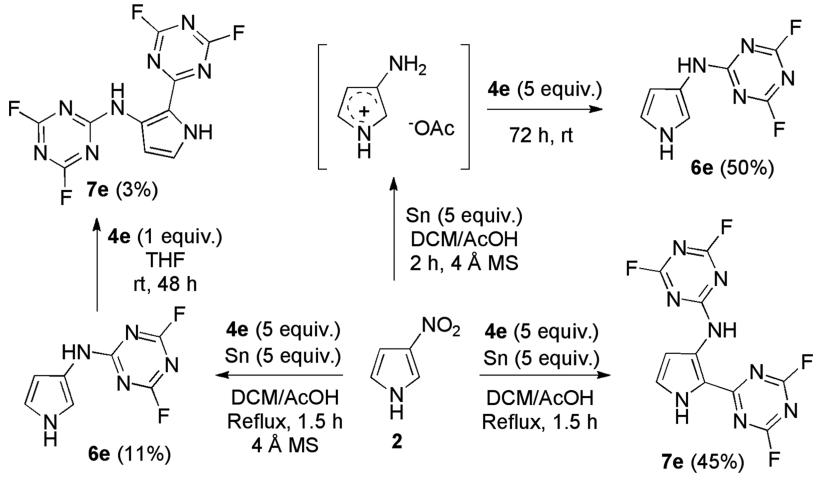
Table 2. S_NAr Reactions of 3-Aminopyrrole with 2,4,6-Trifluoro- or 2,4,6-Trichloro-1,3,5-triazine

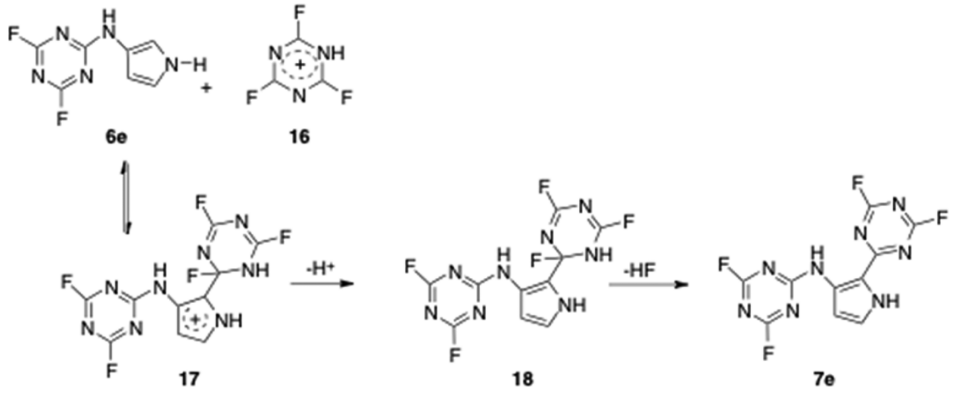
entry	R_1	method[a,b]	equiv (4)	solvent	additive	temp	time (h)	6[h]	7[h]
1	F	Two-Step	1	THF	X	room temp	1	46%	X
2	F	Two-Step[c]	1	THF	50% Et_3N	room temp	1	64%	X
3	F	Two-Step	1	THF	200% Et_3N	room temp	1	54%	X
4	F	Two-Step	1	THF	200% Et_3N	0 °C to rt	1.5	29%	X
5	F	Two-Step	1	THF	200% DIPEA	room temp	1	34%	X
6	F	Two-Step	1	THF	200% base[f]	room temp	1.5	33%	X
7	F	Two-Step	5	THF	X	room temp	23	X	37%
8	F	Two-Step	5	THF	100% Et_3N	room temp	20	X	20%
9	F	One-Step[d]	1	3:2 DCM:AcOH[e]	4 Å MS	room temp	1.5	49%	X
10	F	One-Step	2	3:2 DCM:AcOH	X	reflux	2	26%	X
11	F	One-Step	5	3:2 DCM:AcOH	X	reflux	1.5	X	45%
12	F	One-Step[d]	5	3:2 DCM:AcOH[e]	4 Å MS	room temp	72	50%	trace
13	F	One-Step[d]	5	3:2 DCM:AcOH[e]	4 Å MS	reflux	20	dec	dec
14	F	One-Step	5	3:2 DCM:AcOH[e]	4 Å MS	reflux	1.5	11%	trace
15	Cl	Two-Step[c]	1	THF	50% Et_3N	room temp	1	38%[g]	X
16	Cl	Two-Step	1	THF	200% base[f]	room temp	1	37%	X
17	Cl	Two-Step	1	THF	200% DIPEA	room temp	1	59%	X
18	Cl	Two-Step	1.5	DCM	4 Å MS[e]	room temp	20	33%	X
19	Cl	Two-Step	5	THF	100% base[f]	room temp	26	X	37%
20	Cl	One-Step	1	3:2 DCM:AcOH	4 Å MS	room temp	1.5	7%[g]	45%[g]
21	Cl	One-Step[d]	1	3:2 DCM:AcOH	4 Å MS	room temp	1.5	42%	trace
22	Cl	One-Step	5	3:2 DCM:AcOH	X	reflux	2.5	X	30%

[a]Two-Step Method/**3**. [b]One-Step Method/**2**/Sn (5 equiv). [c]Triazine and salt premixed before the addition of base. [d]3-Aminopyrrole formed prior to addition of the triazine. [e]Solvent mixture dried over 4 Å MS prior to reaction. [f]Base = 2,6-di-*tert*-butylpyridine. [g]80−90% pure after chromatography. [h]Isolated yield of purified products.

Scheme 5. Reactions of 2,4,6-Trifluoro-1,3,5-triazine



Scheme 6. Suggested Mechanism for the Acid-Catalyzed S_NAr Reaction



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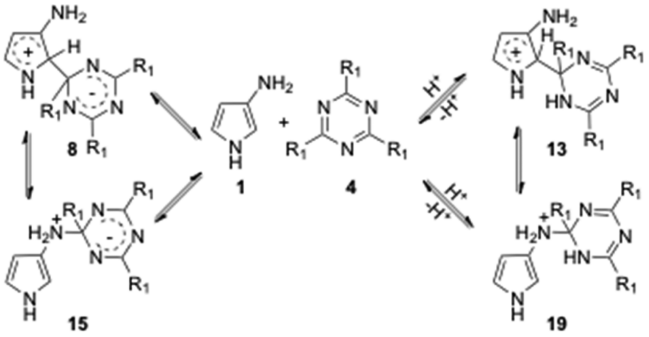
step or two. When a leaving group was present (F or Cl) S_NAr reaction took place leading to the reaction of 3-aminopyrrole with 1 or 2 equiv of the 1,3,5-triazine; the latter resulted in novel compounds with three-linked heterocyclic rings.

Mechanistically evidence that 3-aminopyrrole could react with 1,3,5-triazines via four reaction pathways was uncovered. Aminopyrroles are ambident nucleophiles that can react at either the 3-amino group or at a pyrrole-ring carbon; the attacking electrophile can be either the 1,3,5-triazine or its conjugate acid. These possibilities are illustrated in Scheme 7.

Scheme 7. Ambident Reactivity of 3-Aminopyrrole



Interestingly, it can be seen that if equilbria exist between intermediates **8**, **13**, **15**, and **19**, respectively, with starting compounds, then the equilibria between **8** and **15**, and **13** and **19**, are tautomeric, in which the mobile group is a 1,3,5-triazine moiety.[46,47]

Formation of the initial intermediates is reversible. If the initial reactions were not reversible it might be expected that some cycloaddition would be observed under all reaction conditions. Only one type of reaction is observed under a given set of conditions: determined by the substituent present on the 1,3,5-triazine and the reactivity of the reactants. Acid-catalyzed pathways became important when the 1,3,5-triazine did not contain an electron-withdrawing activating group or the 3-amino group had an electron-withdrawing group attached to it. Protonation increased the electrophilicty of the resulting conjugate acid of the 1,3,5-triazine and made reaction possible. No direct evidence for intermediate **19** was obtained. Evidence for the analogous intermediate **17**, leading to the double substitution product, was presented above (Scheme 6). Scheme 7 indicates that stoichiometric concentrations of all four intermediates might be expected when acid is present. If the same product is formed under both acidic and neutral conditions (one-step and two-step reactions respectively in this study) the possibility that both the catalyzed and uncatalyzed reactions were taking place, under acidic conditions, cannot be explicitly ruled out, e.g., the formation of **5** and **6**. As noted above the yields of **5a** (R_1 = CF_3) and **5b** (R_1 = CO_2Et) were slightly higher under acidic conditions (Table 1) suggesting that both the neutral and acid catalyzed cycloadditions were occurring under these conditions. It can be seen that when studying reactions of aminoazoles with azadienes it is necessary to rule out the possibility that the reaction under study is not acid catalyzed, even when acid has not been added, given that acid could be formed as a by-product or be adventitious.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed under an atmosphere of either argon or nitrogen gas. Reactions were monitored by TLC analysis and visualization was accomplished with a 254 nm UV light. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, acetone-d_6, or THF-d_8 unless otherwise specified. Chemical shifts were reported in parts per million with the residual solvent peak or TMS used as an internal standard. ^{1}H NMR spectra were recorded at either 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constants. ^{13}C NMR were recorded at either 75 or 100 MHz using a proton-decoupled pulse sequence with a d_1 of 5 s, and are tabulated by observed peak. All of the triazines used in this work were commercially available except for 2,4,6-tricarbethoxy-1,3,5-triazine which was synthesized according to a literature procedure.[10] The 3-nitropyrrole (**2**) used in this work was commercially available and the 1*H*-pyrrol-3(2*H*)-iminium tetraphenylborate (**3**) was synthesized according to a newly published procedure.[1]

Two-Step IEDDA Cascade Reaction Procedures: 2,4-Bis(trifluoromethyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (5a, Table 1: Entry 1). To a black solution of **3** (78.4 mg, 0.195 mmol) in THF (1.0 mL) was added **4a** (52.7 μL, 0.186 mmol). The reaction mixture was stirred at room temperature for 2 h and was then concentrated under reduced pressure (50 °C) in the presence of SiO_2 (1.0 g). The dry SiO_2 was then added to the top of a preconditioned column for chromatography (SiO_2; 2:1 petroleum ether/EtOAc). The product fractions were concentrated under reduced pressure (30−50 °C), transferred to a preweighed vial with DCM (2.5 mL), and reconcentrated by a stream of N_2 (g). The resulting solids were then redissolved in DCM (1.0 mL) and reconcentrated by a stream of N_2 (g) 3× to remove traces of EtOAc. The product was dried in vacuo over P_2O_5 to afford **5a** as a pale yellow crystalline solid (40.1 mg, 85%): R_f = 0.50 (SiO_2; 1:1 hexane/EtOAc); Mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (br-s, 1H), 8.05 (app. t, 1H, J = 3.0 Hz), 7.03 (dd, 1H, J = 3.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (d, J_{C-F} = 1.0 Hz), 148.4 (q, J_{C-F} = 37 Hz), 137.7 (q, J_{C-F} = 38 Hz), 137.0, 122.5, 121.1 (q, J_{C-F} = 273 Hz), 120.1 (q, J_{C-F} = 273 Hz), 104.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.23 (3F), −68.87 (3F); HRMS (TOF MS ES+) m/z calcd for $C_8H_4N_3F_6$ 256.0309, found 256.0302.

Diethyl 5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-dicarboxylate (5b, Table 1: Entry 4). To a mixture of **3** (210 mg, 0.523 mmol) and **4b** (148 mg, 0.498 mmol) was added THF (2.0 mL). The resulting black reaction mixture was stirred at room temperature for 2.5 h and was concentrated under reduced pressure (55−60 °C) in the presence of SiO_2 (1.0 g). The dry light green SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; EtOAc). The mixture was chromatographed 2× under identical conditions. The product fractions were concentrated under reduced pressure (55−60 °C). The resulting light brown solids were found to be contaminated with a mixture of unknown tetraphenylborate salts by TLC and ^{1}H NMR (60 MHz, $CDCl_3$). The solids were dissolved in EtOAc (1.0 mL) and hexane (2.0 mL) was added at room temperature. A dark brown oil precipitated which was removed from the mother liquor by decantation and was triturated 5× with a 2:1 hexane/EtOAc mixture (3.0 mL). The EtOAc/hexane washings were combined, brought to a boil, diluted with hexane (5.0 mL), and concentrated to 10 mL. The resulting turbid solution was cooled to room temperature for 1 h and a solid precipitated which was isolated by vacuum filtration, washed with hexane (10 mL), and dried in vacuo over P_2O_5 to afford **5b** as a light yellow crystalline solid (57.9 mg, 44%). The mother liquor containing the hexane wash was concentrated to 10 mL by boiling and was cooled to −20 °C for 4 d to afford an additional batch of **5b** as a yellow crystalline solid (10.1 mg, 8.0%). Combined yield (68.0 mg, 52%): R_f = 0.42 (SiO_2; EtOAc); Mp 141.9−142.8 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 11.42 (br-s, 1H), 8.15 (d, 1H, J = 3.0 Hz), 6.87 (d, 1H, J = 3.2 Hz), 4.52 (q, 2H, J = 7.1 Hz), 4.43 (q, 2H, J = 7.1 Hz), 1.41 (dt, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.4, 164.9,

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155.1, 149.9, 137.7, 137.2, 126.5, 103.8, 62.8, 62.0, 14.6, 14.5; HRMS (TOF MS ES+) m/z calcd for $C_{12}H_{14}N_3O_4$ 264.0984, found 264.0972.

5*H*-Pyrrolo[3,2-*d*]pyrimidine (5c, Table 1: Entry 16). A yellow suspension of **3** (78.4 mg, 0.195 mmol) and **4c** (31.6 mg, 0.390 mmol, 2 equiv) was stirred in a 3:2 DCM/glacial AcOH mixture (2.5 mL) at room temperature for 4 h. The resulting black reaction mixture was concentrated under reduced pressure (55−60 °C) in the presence of SiO_2 (1.0 g). The dry light brown SiO_2 was then added to the top of a preconditioned column for chromatography (SiO_2; DCM (10% MeOH)). Two fractions A and B were isolated, combined separately, concentrated under reduced pressure (50−55 °C), transferred to preweighed vials with DCM (2.0 mL, fraction A) or EtOAc (2.0 mL, fraction B), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5. Fraction A (TLC: SiO_2; DCM (10% MeOH); R_f = 0.88) was isolated as a pale orange solid and was found to be an unknown tetraphenylborate salt by ^{1}H NMR (60 MHz, $CDCl_3$, 30.9 mg). Fraction B was isolated crude as an orange/pink solid which was dissolved in boiling EtOAc (3.0 mL), filtered through a plug of cotton (to remove a black solid), and washed through with boiling EtOAc (1.0 mL). The EtOAc solution was concentrated to 1.0 mL by boiling and then hexane (2.0 mL) was added slowly to the boiling mixture. A solid precipitated upon cooling to room temperature and then to −20 °C for 1 h. The resulting solid was isolated by vacuum filtration, washed with hexanes (10 mL), and dried in vacuo over P_2O_5 to afford **5c** as a pale orange solid (11.7 mg, 50%): R_f = 0.29 (SiO_2, DCM (10% MeOH)); Mp 168.8−170.0 °C; Lit mp[12] 172−174 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 11.0 (br-s, 1H), 8.92 (s, 1H), 8.85 (s, 1H), 7.87 (s, 1H), 6.63 (d, 1H, J = 3.2 Hz).

One-Step IEDDA Cascade Reaction Procedures: 2,4-Bis-(trifluoromethyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (5a, Table 1: Entry 3). To a gray suspension of **2** (50.0 mg, 0.446 mmol) and tin powder (265 mg, 2.23 mmol, 5 equiv) in a 3:2 DCM/glacial AcOH (5.0 mL) mixture was added **4a** (126 μL, 0.446 mmol). The light yellow/green heterogeneous reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure (50−55 °C, vacuum pump) in the presence of SiO_2 (1.0 g). The dry SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; DCM). The product fractions (TLC: SiO_2; DCM; R_f = 0.20) were concentrated under reduced pressure (50 °C), transferred to a preweighed vial with DCM (2.0 mL) and reconcentrated by a stream of N_2 (g). The product was dried in vacuo over P_2O_5 to afford **5a** as a white solid (102 mg, 90%).

Diethyl 5*H*-Pyrrolo[3,2-*d*]pyrimidine-2,4-dicarboxylate (5b, Table 1: Entry 8). A 3:2 DCM/glacial AcOH (5.0 mL) solution was dried over powdered 4 Å molecular sieves (500 mg) for 3.5 h prior to reaction. To this suspension was added **2** (50.0 mg, 0.446 mmol) and tin powder (265 mg, 2.23 mmol, 5 equiv) followed by **4b** (133 mg, 0.446 mmol). The dark brown heterogeneous reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure (65−70 °C, vacuum pump) in the presence of SiO_2 (1.0 g). The dry light brown SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; EtOAc). The product fractions were concentrated under reduced pressure (50 °C), transferred to a preweighed vial with DCM (2.0 mL), and reconcentrated by a stream of N_2 (g). The product was dried in vacuo over P_2O_5 to afford **5b** as a pale yellow solid (84.5 mg, 72%).

5*H*-Pyrrolo[3,2-*d*]pyrimidine (5c, Table 1: Entry 21). A gray suspension of **2** (50.0 mg, 0.446 mmol), tin powder (265 mg, 2.23 mmol, 5 equiv), and **4c** (72.4 mg, 0.892 mmol, 2 equiv) in a 3:2 DCM/glacial AcOH (5.0 mL) mixture was stirred at room temperature for 2 h. The resulting brown reaction mixture was concentrated under reduced pressure (50−60 °C, vacuum pump) in the presence of SiO_2 (1.0 g). The dry light brown SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; DCM (10% MeOH)). The product fractions were concentrated under reduced pressure (45−50 °C). The isolated product was dissolved in boiling EtOAc (4.0 mL), filtered through a plug of cotton, and washed through with boiling EtOAc (1.0 mL). The EtOAc solution was concentrated to 1.0 mL by boiling and then hexane (5.0 mL) was added slowly to the boiling mixture. A solid precipitated upon cooling to room temperature and was isolated by vacuum filtration, washed with hexanes (5.0 mL), and dried in vacuo over P_2O_5 to afford **5c** as a pale yellow solid (36.0 mg, 68%).

Two-Step S_NAr Reaction Procedures (Mono-Addition Product): 4,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (6d, Table 2: Entry 17). To a brown solution of **3** (78.4 mg, 0.195 mmol) in THF (1.0 mL) was added DIPEA (66.4 μL, 0.381 mmol, 2 equiv) at room temperature. After 5 min, the reaction mixture turned dark green and **4d** (34.3 mg, 0.186 mmol) was added. After 1 h, the reaction mixture was concentrated under reduced pressure (55−60 °C) and the resulting black oil was added in EtOAc (2.0 mL) to the top of a preconditioned column chromatography (SiO_2, 3:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (55−60 °C). The resulting product was found to be ∼90% pure by ^{1}H NMR (60 MHz, acetone-d_6) and was recrystallized from boiling DCM (2.5 mL) followed by cooling to room temperature and then to −20 °C for 1 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (15 mL), and dried in vacuo over P_2O_5 to afford **6d** as a light green solid (22.4 mg, 52%). An additional 2.7 mg of **6d** precipitated from the mother liquor upon the addition of hexane (15 mL) and was isolated to afford additional **6d** (25.1 mg total, 59%): R_f = 0.18 (SiO_2; 3:1 hexane/EtOAc); Mp >260 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.10 (br-s, 1H), 9.89 (br-s, 1H), 7.27−7.26 (m, 1H), 6.77−6.75 (m, 1H), 6.33−6.31 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6, mixture of 2 rotamers) δ 171.4, 169.7, 163.7, 163.6, 122.3, 122.2, 117.6, 117.4, 110.5, 110.3, 102.6, 102.5; HRMS (TOF MS ES+) m/z calcd for $C_7H_6N_5Cl_2$ 230.0000, found 229.9994.

4,6-Difluoro-*N*-(1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (6e, Table 2: Entry 2). To a solution of **3** (75.0 mg, 0.186 mmol) in THF (1.0 mL) was added **4e** (15.2 μL, 0.186 mmol) followed by Et_3N (13.0 μL, 0.093 mmol, 0.50 equiv) at room temperature. The resulting black reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure (35 °C) in the presence of SiO_2 (1.0 g). The dry SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; 3:1 hexane/EtOAc). Two fractions A and B were isolated, concentrated under reduced pressure (50 °C), transferred to preweighed vials with EtOAc (3.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5. Fraction A (TLC: SiO_2; 3:1 hexanes/EtOAc; R_f = 0.47) was isolated as a clear crystalline solid and was found to be an unknown tetraphenylborate salt by ^{1}H NMR (60 MHz, $CDCl_3$, 13.9 mg). Fraction B was isolated as an off white solid affording **6e** (23.4 mg, 64%): R_f = 0.19 (SiO_2; 3:1 hexane/EtOAc); Mp 230.9 to >260 °C (dec.); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.07 (br-s, 1H), 9.97 (br-s, 1H), 7.25−7.24 (m, 1H), 6.77−6.75 (m, 1H), 6.32−6.30 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6, mixture of 2 rotamers) δ 173.2 (d, J_{C-F} = 123 Hz), 173.0 (d, J_{C-F} = 123 Hz), 171.0 (d, J_{C-F} = 123 Hz), 170.8 (d, J_{C-F} = 123 Hz), 167.4 (t, J_{C-F} = 17.5 Hz), 122.4, 122.3, 117.5, 117.4, 110.6, 110.4, 102.7, 102.6; ^{19}F NMR (282 MHz, DMSO-d_6) δ −39.5 (d, 1F, J = 14.79 Hz), −42.5 (d, 1F, J = 14.9 Hz); HRMS (TOF MS ES+) m/z calcd for $C_7H_6N_5F_2$ 198.0591, found 198.0580.

One-Step S_NAr Reaction Procedures (Mono-Addition Product): 4,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (6d, Table 2: Entry 21). A gray suspension of powdered 4 Å molecular sieves (500 mg), **2** (50.0 mg, 0.446 mmol), and tin powder (265 mg, 2.23 mmol) in a 3:2 DCM/AcOH (5.0 mL) mixture was stirred at room temperature for 2 h when **2** was found to be consumed by TLC (1:1 hexane/EtOAc). At this time, **4d** (82.2 mg, 0.446 mmol) was added and the resulting heterogeneous yellow reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure (50−60 °C) and dried in vacuo over P_2O_5. The dry solids were suspended in acetone (25 mL) and vacuum filtered through a plug of Celite which was flushed with additional acetone (40 mL). The filtrate was concentrated under reduced pressure (45−50 °C) and the residue was dissolved in EtOAc (2.0 mL). The EtOAc solution was added to the top of a preconditioned column for chromatography (SiO_2; 3:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (50−55 °C), transferred to a preweighed vial with EtOAc (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo

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over P_2O_5 to afford **6d** as a yellow solid (61.6 mg, 60%, ~90−95% pure). The product was then dissolved in boiling EtOAc (7.0 mL) and hexane (14 mL) was slowly added when the solution became turbid. After cooling to room temperature, a solid crystallized which was isolated by vacuum filtration, washed with hexane (15 mL), and dried in vacuo over P_2O_5 affording **6d** as yellow/orange crystals (43.5 mg, 42%).

4,6-Difluoro-*N*-(1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (6e, Table 2: Entry 9). To a predried 3:2 mixture of DCM/AcOH (5.0 mL) containing powdered 4 Å molecular sieves (500 mg) was added **2** (50.0 mg, 0.446 mmol) and tin powder (265 mg, 2.23 mmol) at room temperature. After 2 h, **2** was consumed by TLC (SiO_2; 1:1 hexane/EtOAc; R_f = 0.49) and **4e** (38.3 μL, 0.446 mmol) was added to the greenish/brown 3-aminopyrrole solution. After 1.5 h, the reaction mixture was concentrated under reduced pressure (55−60 °C, vacuum pump) in the presence of SiO_2 (1.0 g). The resulting light brown SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; 3:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (55−60 °C), transferred to a preweighed vial with EtOAc (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5 to afford **6e** as a white solid (42.8 mg, 49%).

Two-Step S_NAr Reaction Procedures (Double-Addition Product): 4,6-Dichloro-*N*-(2-(4,6-dichloro-1,3,5-triazin-2-yl)-1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (7d, Table 2: Entry 19). To a black solution of **3** (100 mg, 0.249 mmol) in THF (1.0 mL) was added 2,6-di-*tert*-butylpyridine (55.0 μL, 0.249 mmol, 1 equiv) at room temperature. After 5 min, **4d** (230 mg, 1.25 mmol, 5 equiv) was added and the resulting light brown suspension was stirred at room temperature for 26 h. The reaction mixture was then added directly to the top of a preconditioned column for chromatography (SiO_2; 3:1 hexane/EtOAc). The resulting impure product fractions were concentrated under reduced pressure (50 °C) in the presence of SiO_2 (1.0 g). The resulting solids were added to the top of a preconditioned column for a second chromatography (SiO_2; 4:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (50 °C), transferred to a preweighed vial with DCM (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5 to afford **7d** as a light yellow solid (35.1 mg, 37%): R_f = 0.43 (SiO_2; 3:1 hexane/EtOAc); Mp >260 °C; ^{1}H NMR (400 MHz, THF-d_8) δ 11.83 (br-s, 1H), 10.42 (br-s, 1H), 7.28 (app. t, 1H, J = 3.2 Hz), 7.18 (app. t, 1H, J = 2.6 Hz); ^{13}C NMR (100 MHz, THF-d_8, mixture of 2 rotamers) δ 171.9, 171.1, 166.2, 164.6, 134.2, 134.0, 129.3, 129.2, 114.7, 105.6 (2C); HRMS (TOF MS ES+) m/z calcd for $C_{10}H_5N_8Cl_4$ 376.9391, found 376.9406. An unidentified tetraphenylborate salt was also isolated (31.5 mg; yellow oil; TLC; SiO_2; 3:1 hexane/EtOAc; R_f = 0.62).

***N*-(2-(4,6-Difluoro-1,3,5-triazin-2-yl)-1*H*-pyrrol-3-yl)-4,6-difluoro-1,3,5-triazin-2-amine (7e, Table 2: Entry 7).** To a black solution of **3** (78.4 mg, 0.195 mmol) in THF (1.0 mL) was added **4e** (83.6 μL, 0.975 mmol, 5 equiv) at room temperature. After 23 h, the thick green reaction mixture was concentrated under reduced pressure (50−55 °C) in the presence of SiO_2 (1.0 g). The resulting thick rubbery green solids were pulverized and added to the top of a preconditioned column for chromatography (SiO_2; 3:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (55 °C), transferred to a preweighed vial with EtOAc (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5 to afford **7e** as a white solid (22.7 mg, 37%): R_f = 0.43 (SiO_2; 3:1 hexane/EtOAc); Mp 228.0−229.5 °C; ^{1}H NMR (400 MHz, THF-d_8) δ 11.9 (br-s, 1H), 10.4 (br-s, 1H), 7.28 (app. t, 1H, J = 3.0 Hz), 7.17 (app. t, 1H, J = 2.8 Hz); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.5 (br-s, 1H), 10.39 (br-s, 1H), 7.41 (app. t, 1H, J = 3.1 Hz), 7.14 (app. t, 1H, J = 2.6 Hz); ^{13}C NMR (100 MHz, THF-d_8, mixture of 2 rotamers) δ 173.7 (d, J_{C-F} = 85 Hz), 173.5 (d, J_{C-F} = 85 Hz), 172.9 (br-m), 171.0 (d, J_{C-F} = 85 Hz), 171.3 (d, J_{C-F} = 85 Hz), 170.7 (br-m), 170.1 (t, J_{C-F} = 14 Hz), 168.5 (t, J_{C-F} = 18 Hz), 134.1, 134.0, 129.3, 129.2, 115.2, 105.7, 105.6; ^{19}F NMR (282 MHz, acetone-d_6) δ −38.75 (br-s, 3F), −39.03 (d, 3F, J = 13.5 Hz), −39.79 (br-s, 3F), −41.05 (d, 3F, J = 13.5 Hz).

One-Step S_NAr Reaction Procedures (Double-Addition Product): 4,6-Dichloro-*N*-(2-(4,6-dichloro-1,3,5-triazin-2-yl)-1*H*-pyrrol-3-yl)-1,3,5-triazin-2-amine (7d, Table 2: Entry 22). To a gray suspension of **2** (100 mg, 0.829 mmol) and tin powder (529 mg, 4.46 mmol, 5 equiv) in a 3:2 DCM/AcOH (10 mL) mixture was added **4d** (822 mg, 4.46 mmol, 5 equiv) at room temperature. The reaction mixture was heated to reflux for 2.5 h, cooled to room temperature, and the resulting suspension was vacuum filtered through a plug of Celite which was then flushed with EtOAc (50 mL). The yellow filtrate was concentrated under reduced pressure (55−60 °C) in the presence of SiO_2 (0.50 g). The yellow/orange SiO_2 mixture was added to the top of a preconditioned column for chromatography (SiO_2; gradient elution: 4:1 to 2:1 hexane/EtOAc). The product fractions were concentrated under reduced pressure (55 °C). The resulting yellow solids were recrystallized from a boiling 5:1 hexane/EtOAc mixture (25 mL) and after slowly cooling to room temperature, the precipitate was isolated by vacuum filtration, washed with hexane (20 mL), and dried in vacuo to afford **7d** as a light yellow solid (70.3 mg, 21%). The mother liquor was recrystallized a second time by the above method to afford an additional 30.8 mg of **7d** (101 mg total, 30%).

***N*-(2-(4,6-Difluoro-1,3,5-triazin-2-yl)-1*H*-pyrrol-3-yl)-4,6-difluoro-1,3,5-triazin-2-amine (7e, Table 2, Entry 11).** To a gray suspension of **2** (100 mg, 0.829 mmol) and tin powder (529 mg, 4.46 mmol) in a 3:2 DCM/AcOH (10 mL) mixture was added **4e** (383 μL, 4.46 mmol, 5 equiv) at room temperature. The reaction mixture was heated to reflux over 15 min and at reflux for 1.5 h. At this time, the reaction mixture was concentrated under reduced pressure (55−60 °C, vacuum pump) in the presence of SiO_2 (0.50 g). The dry solids were added to the top of a preconditioned column for chromatography (SiO_2; gradient elution: 3:1 → 1:1 hexane/EtOAc). The product (TLC: SiO_2; 1:1 hexane/EtOAc; R_f = 0.65) fractions were concentrated under reduced pressure (55 °C). The resulting pale yellow solid was recrystallized from a boiling 1:1 DCM/hexane (40 mL) mixture which was slowly cooled to room temperature and then to −20 °C for 15 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (10 mL), and dried in vacuo over P_2O_5 to afford **7e** as a pale yellow/green solid (124 mg, 45%).

2-(5-(2,2,2-Trifluoro-1-iminoethyl)-2,4,6-tris(trifluoromethyl)-2,5-dihydro-1,3,5-triazin-2-yl)-1*H*-pyrrol-3-amine (11). To a black solution of **3** (200 mg, 0.498 mmol) and **4a** (141 μL, 0.498 mmol) in THF (2.0 mL) was added Et_3N (34.7 μL, 0.249 mmol, 0.5 equiv), within one min of mixing, at room temperature. After 1 h, the reaction mixture was concentrated under reduced pressure (50−60 °C) in the presence of SiO_2 (0.50 g). The dry SiO_2 was added to the top of a preconditioned column for chromatography (SiO_2; 2:1 petroleum ether/EtOAc). Two products were isolated **5a** and **11**. The product fractions were combined separately and concentrated under reduced pressure (50−60 °C). Product **5a** was transferred to a preweighed vial with DCM (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5 to afford **5a** as white crystalline solid (36.6 mg, 29%). Product **11** was diluted with DCM (10 mL) and concentrated under reduced pressure (55 °C) in the presence of SiO_2 (0.50 g). The white SiO_2 was added to the top of a preconditioned column for a second chromatography (SiO_2; DCM). The product fractions were concentrated under reduced pressure (50 °C), transferred to a preweighed vial with DCM (2.0 mL), reconcentrated by a stream of N_2 (g), and dried in vacuo over P_2O_5 to afford **11** as a light green oil (50.6 mg) which was found to be contaminated with EtOAc by ^{1}H NMR (400 MHz, $CDCl_3$). The $CDCl_3$ was removed by a stream of N_2 (g) and the resulting light yellow/green oil solidified in vacuo to form **11** as a pale orange solid (46.3 mg, 20%): R_f = 0.63 (SiO_2; 2:1 petroleum ether/EtOAc); Mp 93.1−94.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (br-s, 1H), 6.95 (appt. t, 1H, J = 3.0 Hz), 6.23 (appt. t, 1H, J = 3.0 Hz), 5.46 (br-s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (br-m), 143.4 (q, J_{C-F} = 36 Hz), 136.1, 126.9, 122.7 (q, J_{C-F} = 288 Hz), 119.4, 118.2 (q, J_{C-F} = 275 Hz), 101.9, 74.0 (q, J_{C-F} = 34 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −76.77 (3F), −78.17 (6F), −89.64 (3F); HRMS (TOF MS ES+) m/z calcd for $C_{12}H_7N_6F_{12}$ 463.0514, found 463.0533.

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Conversion of 11 to 5a. A sample of **11** was dissolved in acetone-d_6 in an NMR tube. After 2 weeks at room temperature it was found that **11** had completely converted to **5a** by a ^{1}H NMR (60 MHz) comparison of the intermediate solution after 2 weeks vs a solution of **5a** in acetone-d_6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (H1, C13 and F19) of the products are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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