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Synthetic Methods

Trifluoroacetic Acid in 2,2,2-Trifluoroethanol Facilitates S_NAr Reactions of Heterocycles with Arylamines**

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Abstract: Small-molecule drug discovery requires reliable synthetic methods for attaching amino compounds to heterocyclic scaffolds. Trifluoroacetic acid-2,2,2-trifluoroethanol (TFA-TFE) is as an effective combination for achieving S_NAr reactions between anilines and heterocycles (e.g., purines and pyrimidines) substituted with a leaving group (fluoro-, chloro-, bromo- or alkylsulfonyl). This method provides a variety of compounds containing a "kinase-privileged fragment" associated with potent inhibition of kinases. TFE is an advantageous solvent because of its low nucleophilicity, ease of removal and ability to solubilise polar substrates. Furthermore, TFE may assist the breakdown of the Meisenheimer–Jackson intermediate by solvating the leaving group. TFA is a necessary and effective acidic catalyst, which activates the heterocycle by N-protonation without deactivating the aniline by conversion into an anilinium species. The TFA-TFE methodology is compatible with a variety of functional groups and complements organometallic alternatives, which are often disadvantageous because of the expense of reagents, the frequent need to explore diverse sets of reaction conditions, and problems with product purification. In contrast, product isolation from TFA-TFE reactions is straightforward: evaporation of the reaction mixture, basification and chromatography affords analytically pure material. A total of 45 examples are described with seven discrete heterocyclic scaffolds and 2-, 3- and 4-substituted anilines giving product yields that are normally in the range 50–90%. Reactions can be performed with either conventional heating or microwave irradiation, with the latter often giving improved yields.

Introduction

The bis-arylaniline unit has been termed a "kinase-privileged fragment" owing to its frequent appearance as a structural motif in kinase inhibitors, as exemplified by imatinib (Figure 1).[1] Given the importance of kinases in current drug discovery programs,[1] it is vital that efficient synthetic methods are available to access bis-arylanilines. In this context, one of the most important reaction classes aiding the synthesis of bis-arylanilines is the attachment of an aniline to a heterocyclic scaffold.[2] Numerous examples of this class have been described whereby an amine is coupled to a heteroaryl halide catalysed by a metallo-phosphine species (e.g., Buchwald–Hartwig methodology).[3] An alternative approach achieves such couplings by direct reaction (S_NAr) of a suitably activated heteroaryl halide with an amine (e.g.,[4]). In projects seeking to identify potent lead inhibitors of kinases, for example, cyclin-dependent kinases,[5,6] we required series of arylamino-heterocycles for the development of structure–activity relationships (SAR). Initially, we employed classical S_NAr conditions whereby a 2-fluoropurine was heated with an aniline in 2-butanol.[7,8] Whereas this procedure was satisfactory with relatively basic/nucleophilic anilines, it failed with weakly nucleophilic anilines, such as 4-nitroaniline. Although the desired products might have been accessible by treating the aniline with a 2-iodopurine in the presence of a palladium/phosphine catalyst, we explored alternative S_NAr conditions, resulting in the discovery of the versatile and reliable protocol described herein. In earlier studies we found that the treatment of 2-fluoro-6-cyclohexyl-

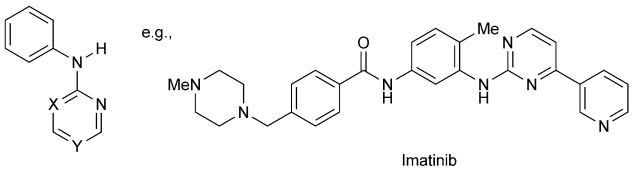

Figure 1. Example of a kinase-privileged fragment (e.g., X = N, Y = H) and a drug (imatinib) containing this fragment.

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methoxypurine with aniline appeared to accelerate at later reaction times.[7] This was ascribed to the formation of hydrofluoric acid, which autocatalysed the reaction, presumably by activation of the purine by N-protonation. An investigation, in which various acid catalysts and solvents were explored, led to the identification of trifluoroacetic acid-2,2,2-trifluoroethanol (TFA-TFE) as a convenient and efficacious combination for effecting S_NAr reactions with purines and pyrimidines.[5,7,9] The benefit of acidic catalysis for S_NAr reactions of appropriate heterocycles had already been recognised long ago by Banks[10,11] and Chapman,[12,13] and subsequent to our initial studies, further quantified by Liu and Robins.[14] The use of acidic catalysis in S_NAr reactions employed for the scale-up synthesis of drugs is increasingly commonplace.[4,15]

In this study, we describe the application of TFA-TFE to facilitate S_NAr reactions of arylamines with a variety of heterocyclic templates and leaving groups, which can be selected from fluoro-, chloro-, bromo- and alkylsulfonyl. The roles of both TFA and TFE in facilitating S_NAr reactions are discussed and partly validated experimentally. The methodology is generally applicable to diverse heterocyclic substrates. It complements organometallic methodology and is even preferable in many cases because of the seldom need to explore varied sets of conditions. Furthermore, the TFA-TFE methodology is compatible with a variety of functional groups, some of which (e.g., alkynyl, thioamido, 1,3-dithian-2-yl) may be unsuitable for metal-assisted couplings. In addition, the use of certain protected heteroaryl substrates and anilines (e.g., N^9-tetrahydropyranyl-purines, *N*-butyloxycarbonyl-anilines) can reduce the number of steps in a synthetic sequence by in situ deprotection during the TFA-TFE reaction.

Results

Synthesis of substrates

The syntheses of heterocyclic substrates used in this study, when not commercially available, have either been described[5,7–9] or utilised standard methods (see the Experimental Section and the Supporting Information).

Scope of the reaction

Table 1 and Table 2 summarise the panel of heterocycles and anilines that have been examined (further examples are given in the Supporting Information, Table S1). The methodology therefore embraces a wide selection (45 examples) of halogenated (hetero)aryl substrates (purine, pyrimidine, pyrazolo[3,4-*d*]pyrimidine, [1,2,3]triazolo [3,4-*d*]pyrimidine, imidazo[1,2-*a*]pyrimidine, pyrazolo[1,5-*a*]pyrimidine, quinoline, dinitrobenzene) and a range of substituted anilines. Instead of a halide, the leaving group can also be an alkylsulfonyl group. Yields are generally good to excellent, although modest yields may be obtained with less reactive systems, for which microwave heating is invariably beneficial. The most reactive anilines are those with substituents at the 3- and/or 4-positions, including electron-withdrawing groups (NO_2, SO_2NH_2, CO_2H, CF_3 and CN). With 2-substituted anilines the reaction is only effective when the 2-substituent is electron-releasing (e.g., OMe). Although most of the entries in the tables are for heterocycles, we have also studied 2,4-dinitrofluorobenzene. In this case, and of mechanistic significance (see below), is the observation that whereas TFE is a beneficial solvent with respect to reaction rate, addition of TFA has no accelerating effect because substrate reactivity cannot be enhanced by protonation.

Mechanistic studies

Reactions of anilines with 4,7-dichloroquinoline at 25 °C were studied by varying the concentration of TFA in TFE from 0.5 up to 10 equivalents (Table 3). The optimal consumption of 4,7-dichloroquinoline with aniline occurred with approximately 1 equiv TFA. This gave good conversion of substrate into product with the reaction being essentially complete after 512 min. Further experiments were conducted with 4-substituted anilines (4-methoxy, 4-chloro, 4-trifluoromethyl and 4-cyano) of different basicity/nucleophilicity (Table 3; see also Supporting Information). Optimal conversions were in the range 0.5–2.5 equiv TFA, although only the reactions of 4-methoxy and 4-chloro-aniline were complete after 512 min (4-trifluoromethyl, 88% complete; 4-cyano, 36% complete with 1 equiv TFA; see Tables S5 and S6 in the Supporting Information). For the heteroaryl substrates in Tables 1 and 2, the preferred amount of added TFA was found to be in the range 2.5–5 equivalents, compared to 2-amino-6-chloropurine with aniline (Table 3).

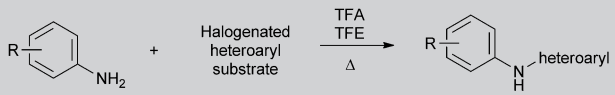
Comparative S_NAr reactions of 1-fluoro-2,4-dinitrobenzene (Sanger's reagent) were performed with 4-methoxyaniline in TFE alone and in TFA-TFE at 22 °C. In TFE alone, the reaction was complete within 5 min, whereas in the presence of TFA (4 equivalents) the reaction was only complete after at least 6 h (Table S7 in the Supporting Information).

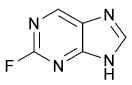
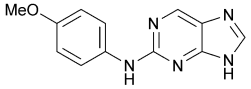
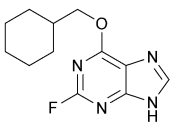
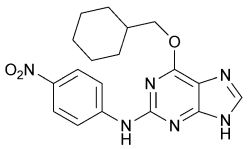
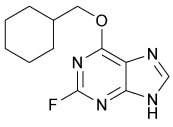
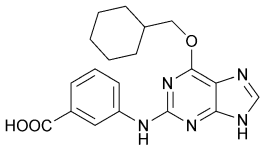
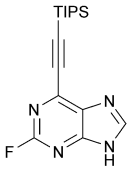
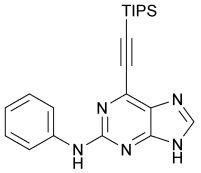
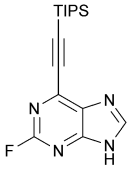
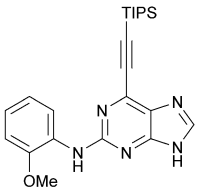
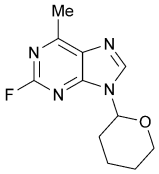
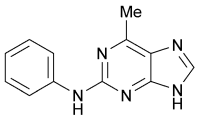
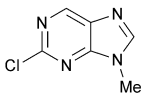
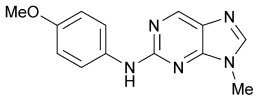
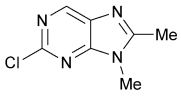
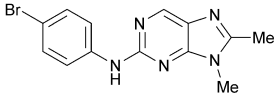
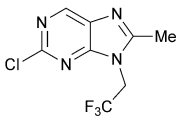
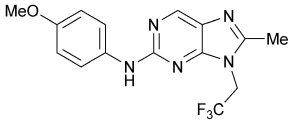
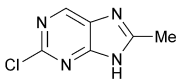
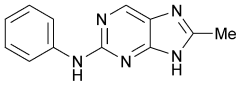
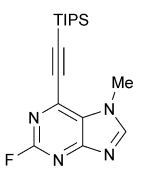
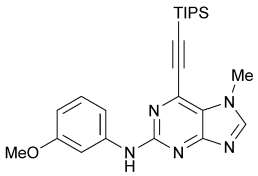
Discussion

General comments on the methodology

The S_NAr reaction is a classical method for the introduction of functional groups into aromatic and heteroaromatic systems,[16] and can be traced back at least to 1854 when Pisani[17] treated 2,4,6-trinitrochlorobenzene with ammonia to give picramide. The epithet S_NAr came much later and is attributed to A. J. Parker (1961)[18] after Bunnett and Zahler[19–21] had defined the mechanism of such reactions as an addition-elimination process via a Meisenheimer–Jackson[22,23] intermediate. Today the S_NAr reaction is still much used, but is frequently replaced by metal-mediated cross-coupling between an aryl halide or triflate and an amine (e.g., Buchwald–Hartwig reactions[24–28]). Although many powerful protocols have been described for such reactions, especially utilising palladium or copper catalysts, the cocktail of reagents required and myriad of published catalysts employed often demands time-consuming optimisation with new targets. For this reason and also considering reagent costs, the S_NAr reaction is still a mainstay whenever an

Table 1. Purine derivatives for S_NAr reactions with anilines facilitated by TFA-TFE.



Substrate	Product		TFA [equiv]	Heat at reflux		μW	
				t [h]	Yield [%]	*t* [h]	Yield [%]
		**1**	5	–	–	1.5[a]	82
		**2**	5	48	74	–	–
		**3**	5	24	71	–	–
		**4**	5	24	70	0.5[a]	89
		**5**	2.5	–	–	2[a]	43
		**6**	2.5	–	–	1[a]	90
		**7**	2.5	–	–	1[a]	90
		**8**	5	–	–	1[b]	71
		**9**	2.5	–	–	1[b]	68
		**10**	5	–	–	1[b]	83
		**11**	5	–	–	0.5[a]	66

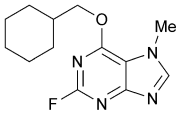
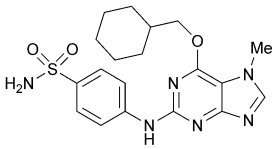
arylamino group requires attachment to a heterocyclic template.[2,8,29]

In earlier studies we focused on the use of TFA-TFE with conventional heating.[7] We have now found that the more difficult substitutions can be facilitated by microwave heating.[15,30] Furthermore, it is sometimes convenient to use an aniline hydrochloride as reactant, with the hydrogen chloride liberated providing acidic catalysis. Most reactions proceed with minimal by-product formation, although trifluoroethanol may occasionally compete with anilines of low nucleophilicity and yield a trifluoroethoxy-substituted by-product. Product isolation is straightforward: evaporation of the reaction mixture, basification to neutralise trifluoroacetate salts and finally chromatography gives analytically pure material.

Mechanisms of S_NAr reactions facilitated by TFA-TFE

The rates of S_NAr reactions of aromatic compounds are governed by numerous factors, but amongst these, the benefit of electron-withdrawing substituents is well-known.[20,31] For heteroaromatic systems, the location of a nitrogen atom in an α or γ position to a leaving group is advantageous.[20] Furthermore, protonation of a nitrogen atom of a heteroaromatic ring can enhance the rate of a S_NAr reaction.[10–13] However, addition of an acid may deactivate the nucleophilic component of the reaction. The aniline needs to be in its non-protonated form, and thus increasing the amount of TFA will augment the population of unreactive protonated aniline. On the other hand, reducing the concentration of TFA will compromise the activation of a nitrogenous heterocycle and the rate of reaction will be reduced (Table 3). The pro-

Table 1. (Continued)

Substrate	Product		TFA [equiv]	Heat at reflux		μW	
				t [h]	Yield [%]	*t* [h]	Yield [%]
		**12**	5	24	61	–	–

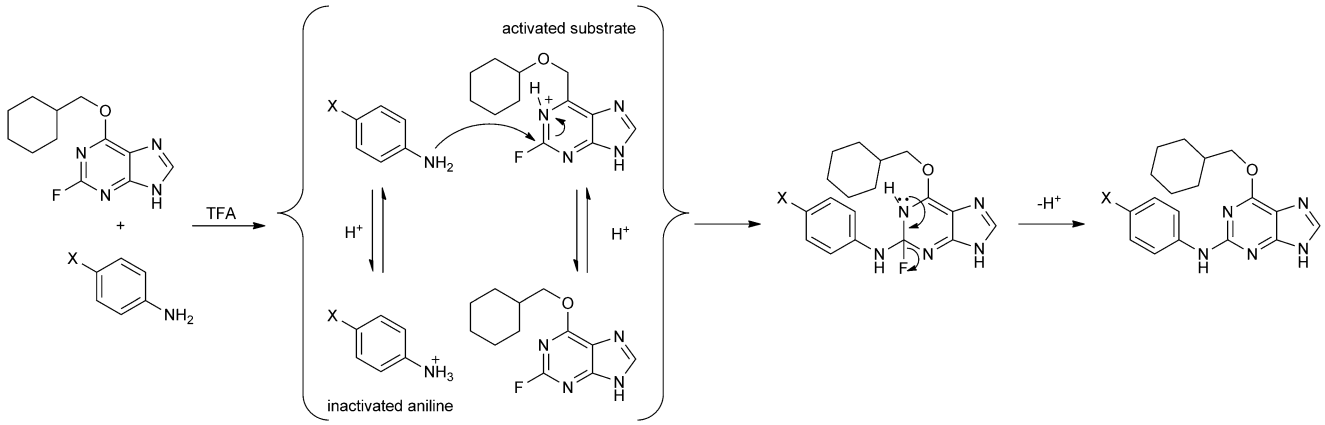
[a] μW (microwave irradiation) at 140 °C; [b] μW at 160 °C.

posed effect of changing acid concentration on reaction rate with one reactant protonated (e.g., purine in the present study) and the other not (aniline) is well established for a number of cases, for example, oxime formation.[32] The results in Table 3 imply that although the pK_a determines the concentration of free aniline, it is the pK_a of the nitrogenous heteroaryl substrate that is the key parameter dictating the optimal quantity of TFA. On account of the similarity of TFE and water with respect to polarity (E^N_T for TFE: 0.90; for water: 1.00),[33] pK_a values of anilines in TFE are likely to be similar to those measured in water (compare pK_a values of anilines in methanol and ethanol, which correlate closely with the polarities of these solvents relative to water).[34] It should be noted that at 25 °C, with or without TFA, no reaction was observed for 4,7-dichloroquinoline and benzylamine (pK_a 9.34) during 8.5 h in TFE. In this case, benzylamine is deactivated by TFA protonation, whereas in TFE alone the lack of activation of the quinoline by protonation also precludes any reaction.

The finding that 1-fluoro-2,4-dinitrobenzene reacts much faster with 4-methoxyaniline in TFE compared to TFA-TFE, is consistent with the premise that in this case there is no activation of the fluoro substrate by protonation. The presence of TFA merely serves to reduce the concentration of free 4-methoxyaniline. It has been proposed that fluoride loss from the reversibly generated Meisenheimer–Jackson intermediate is rate limiting when weakly nucleophilic anilines react with 1-fluoro-2,4-dinitrobenzene.[35,36]

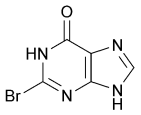
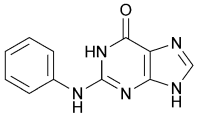
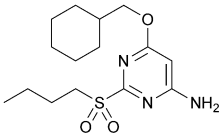
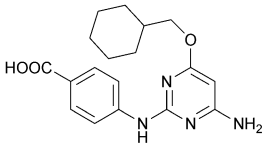
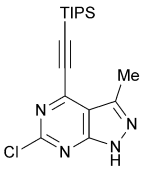
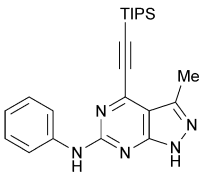
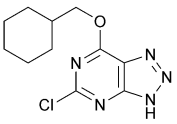
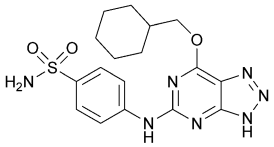
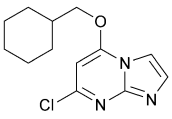
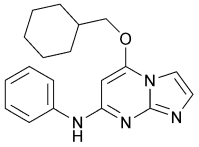
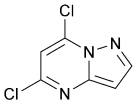
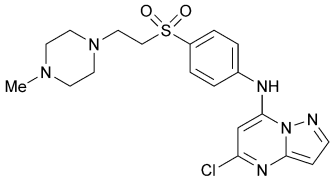
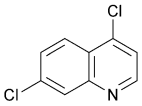
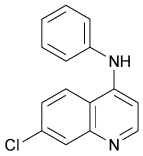
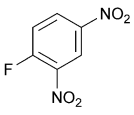
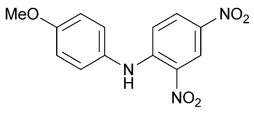
For the heterocycles described herein there are no reliable pK_a data available, and it is therefore difficult to quantify the degree of protonation because there are several basic sites. By analogy with adenine derivatives, the primary sites of protonation of the purines are expected to be N-1 and N-7, and possibly N-3.[14,37,38] Protonation of a purine at N-1 (or N-3) followed by attack of an aniline leads to the Meisenheimer–Jackson intermediate. The basic mechanistic scheme is illustrated in Scheme 1 for the S_NAr reaction of anilines with 6-cyclohexylmethoxy-2-fluoropurine. The beneficial role of TFE may reside in its ability to solvate the leaving group by hydrogen bonding during the breakdown of the Meisenheimer–Jackson intermediate. This suggestion requires that decomposition of the intermediate is rate limiting[20,23,39] and is most likely when fluoride is the leaving group. A study of TFA-catalysed reactions of 6-halopurines (halo = F, Cl, Br and I) with aniline in acetonitrile concluded that loss of halide from the Meisenheimer–Jackson intermediate was indeed rate limiting.[14] The importance of fluoride solvation in solvolysis of alkyl fluorides (e.g., 4-methoxybenzyl fluoride in water) is well-known.[33] A marked effect of TFE relative to ethanol in solvolysis of glycosyl fluorides was ascribed to better solvation of fluoride by TFE.[40] In another recent study, it was shown that for reaction of 2,5,6-trifluoronicotinenitrile with the amino group of 3-isopropoxy-1*H*-pyrazol-5-amine in tetrahydrofuran, monoprotonated 1,4-diaza [2,2,2]-bicyclooctane assisted the loss of the 6-fluoro group from the intermediate.[41] In this case, formation of the Meisenheimer–Jackson intermediate was rate limiting, with fluoride loss being a fast process.

Compared to, for example, ethanol, TFE is markedly more acidic (pK_a 12.4[30] vs. 16). This property of TFE may enhance the reactivity of a monoprotonated heterocycle by hydrogen bonding to a non-protonated heteroatom. Besides playing a key mechanistic role (see below) TFE is also an advantageous



Scheme 1. Proposed intermediates in the TFA-facilitated S_NAr reactions of anilines (X = H, MeO, NO_2, Br, SO_2NH_2, CO_2H, Cl, CF_3 and CN) exemplified with 6-cyclohexylmethoxy-2-fluoropurine.

Table 2. Further heterocyclic derivatives for S_NAr reactions with anilines facilitated by TFA-TFE.

Substrate	Product		TFA [equiv]	Heat at reflux	
				t [h]	Yield [%]
		**13**	5	24	73
		**14**	5	24	82
		**15**	2.5	18	73
		**16**	5	18	35
		**17**	5	24	34
		**18**	17.6	48	49
		**19**[a]	1	9	95
		**20**[a]	0	1	80

[a] At 20 °C.

solvent because of its low nucleophilicity, ease of removal (b.p. 78 °C) and hence suitability for recycling, as well as its ability to solubilise numerous polar substrates.

Conclusion

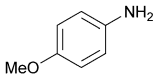
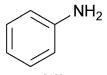
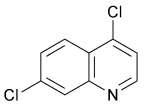
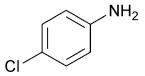
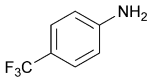
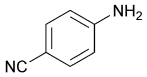
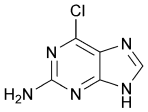
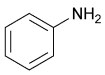
The use of trifluoroacetic acid in 2,2,2,-trifluoroethanol is an efficient, practical and reliable methodology for the acidic catalysis of S_NAr reactions of anilines with nitrogen-containing heteroaromatic substrates, exemplified by 45 distinct examples (Tables 1–3, and Table S1 in the Supporting Information). We anticipate the use of TFA in TFE to facilitate S_NAr reactions of numerous other heterocycles, with optimisation of reaction conditions following the principles outlined above. We have found TFA-TFE to be immensely useful for the synthesis of numerous heterocyclic derivatives required for SAR studies in medicinal chemistry research programs. For example, the methodology proved invaluable for the discovery of NU6102, one of the most potent and selective inhibitors of the cyclin-dependent kinase CDK2.[6] We have recently demonstrated the value of TFA-TFE in the synthesis of N^7-methyl- and N^7-ethyl-purines,[46] and also for facilitating the Paal–Knorr synthesis of pyrroles under microwave heating.[47] TFE alone has many benefits as a solvent[48] including facilitation of: imino-Diels–Alder reactions,[49] reductive aminations of aldehydes and ketones,[50] and nucleophilic ring openings of epoxides.[51] The "magical" solvent properties of TFE and other fluorinated solvents (e.g., 1,1,1,3,3,3-hexafluoro-2-propanol) have been denoted as a "booster effect" relative to non-fluorinated analogues and quantified by computational studies.[52]

Experimental Section

General information

For details concerning equipment and chemicals see the Supporting Information.

Table 3. Product [%] at 32 min for reactions of 4,7-dichloro-quinoline, 2-amino-6-chloropurine and 1-fluoro-2,4-dinitrobenzene with anilines, varying the concentration of TFA (0, 0.5, 1, 2.5, 5 and 10 equiv) in TFE at 25 °C.

Heteroaryl substrate	Aniline	TFA equivalents 0	0.5	1	2.5	5	10
	 pK_a 5.29[42]	0	37	51	53	0	0
	 pK_a 4.87[43]	0	48	60	60	6	0
	 pK_a 4.05[44]	3	35	53	51	3	0
	 pK_a 2.6[45]	0	17	22	19	0	0
	 pK_a 1.75[44]	0	8[a]	11[a]	11[a]	0	0
		0	0	9[a]	26[a]	73[a]	68[a]

[a] Yield [%] at 128 min.

Caution! TFA and TFE should be handled with care. TFA causes severe burns and TFE is irritating to the respiratory system and skin and can seriously damage the eyes.

General procedure A

Typically, to a stirred suspension of the appropriate heteroaryl substrate (1 equiv) and the aniline (2 equiv) in TFE ([heteroaryl substrate] = 0.1 M) was added TFA (2.5 equiv) dropwise. The resulting solution was heated at reflux for 24 h under a nitrogen atmosphere. The solvent was removed in vacuo and the residue was redissolved in EtOAc (10 mL). The solution was washed with saturated sodium bicarbonate solution (3×10 mL), and the aqueous extracts were combined and washed with EtOAc (10 mL). The combined organic layers were dried ($MgSO_4$ or Na_2SO_4) and the solvent was removed to give a residue that was purified as indicated for each product. Four representative examples of this procedure are given below with others to be found in Supporting Information.

6-(2-(Triisopropylsilyl)ethynyl)-*N*-phenyl-9*H*-purin-2-amine (4): The title compound was synthesised according to general procedure A using 2-fluoro-6-((triisopropylsilyl)ethynyl)-9*H*-purine (0.46 g, 1.43 mmol), aniline (260 μL, 2.86 mmol) and TFA (551 μL, 7.15 mmol) in TFE (7 mL). The crude material was purified by MPLC on silica (DCM/MeOH 19:1) to give the desired product as a yellow oil/gum (390 mg, 1.00 mmol, 70%). The title compound was also synthesised following general procedure B for 30 min using 2-fluoro-6-((triisopropylsilyl) ethynyl)-9*H*-purine (600 mg, 1.90 mmol), aniline (0.50 mL, 3.80 mmol) and TFA (0.7 mL) in TFE (19 mL). The crude product was purified by MPLC on amine silica (DCM/MeOH 95:5) to give the desired product as a pale yellow oil (660 mg, 89%). $R_f = 0.53$ (DCM/MeOH 9:1); UV λ_{max} (EtOH): 274 nm; IR (KBr): $\tilde{\nu} = 2940$, 2860, 2550, 1600, 1570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.14$–1.18 (21H, m, $CH(CH_3)_2$), 7.09 (1H, t, $J = 7.3$ Hz, Ar-H), 7.21 (1H, brs, NH), 7.32–7.35 (2H, m, Ar-H), 7.37 (1H, s, H-8), 7.53–7.57 (2H, m, Ar-H), 11.75 ppm (1H, brs, N^9-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.3$, 18.7, 100.8, 101.8, 120.7, 123.7, 129.3, 139.3, 140.9, 142.5, 153.2, 156.5, 184.8 ppm; HRMS calcd for $C_{22}H_{30}N_5Si$ $[M+H]^+$ 392.2270, found 392.2263.

6-Cyclohexylmethoxy-7-methyl-2-(4′-sulfamoylanilino)-7*H*-purine (12): The title compound was synthesised according to the general procedure A using 6-cyclohexylmethoxy-2-fluoro-7-methyl-7*H*-purine (50 mg, 0.19 mmol), sulfanilamide (65 mg, 0.38 mmol) and TFA (0.07 mL, 0.95 mmol) in TFE (4 mL). The crude product was purified by MPLC on silica (EtOAc/MeOH 9:1) to give a pale brown powder (48 mg, 61%). $R_f = 0.48$ (EtOAc/MeOH 9:1); m.p. 252–253 °C; UV λ_{max} (EtOH): 292 nm; IR (neat powder): $\nu_{max} = 3373$, 3313, 2922, 1569, 1504 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta = 0.95$–1.80 (11H, m, H-cyclo), 3.91 (3H, s, CH_3), 4.33 (2H, d, $J = 5.4$ Hz, OCH_2), 7.11 (2H, s, NH_2), 7.70 (2H, d, $J = 8.4$ Hz, Ar-H), 7.97 (2H, d, $J = 8.4$ Hz, Ar-H), 8.19 (1H, s, H-8), 9.65 ppm (1H, s, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO); $\delta = 25.6$, 26.3, 29.6, 33.9, 37.1, 71.7, 108.7, 117.5, 126.8, 135.8, 144.8, 147.0, 155.1, 157.4, 162.9 ppm; MS (ES^+) *m/z* 417 $[M+H]^+$; HRMS calcd for $C_{19}H_{25}N_6O_3S$ $[M+H]^+$ 417.1703, found 417.1704.

4-(6-Amino-4-cyclohexylmethoxy-5-pyrimidin-2-ylamino)benzoic acid (14): The title compound was prepared following general procedure A using 4-cyclohexylmethoxy-2-*n*-butylsulfonylpyrimidin-6-amine (0.30 g, 0.92 mmol), 4-aminobenzoic acid (0.25 g, 1.83 mmol) and TFA (0.36 mL, 4.59 mmol) in TFE (3 mL). The system was cooled to RT and concentrated under reduced pressure to yield an orange solid. An aqueous 2 M NaOH solution (20 mL) was added to the residue while stirring. After extraction with EtOAc (3×30 mL), the aqueous layer was acidified until pH < 2 with a 4 M HCl solution. A second extraction with EtOAc (4×30 mL) was performed on the aqueous acidic phase. The organic fractions were combined, washed with water (3×30 mL) and dried over Na_2SO_4. After the solvent was evaporated and the crude compound was recrystallized from MeOH, the title compound was recovered as an off-white solid (0.26 g, 82%). $R_f = 0.27$ (DCM/MeOH 95:5); m.p. 272–275 °C; UV λ_{max} (EtOH): 302 nm; IR (neat powder): $\nu_{max} = 3514$, 3404, 3105, 2932, 2847, 1673, 1567, 1510 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta =$ 0.95–1.29 (6H, m, H-cyclo), 1.68–1.79 (5H, m, H-cyclo), 4.01 (2H, d, $J = 5.9$ Hz, OCH_2), 5.28 (1H, s, H-5), 6.43 (2H, brs, NH_2), 7.78 (2H, d, $J = 8.7$ Hz, Ar-H), 7.88 (2H, d, $J = 8.7$ Hz, Ar-H), 9.35 (1H, brs, NH), 12.45 ppm (1H, brs, OH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 24.8$, 25.7, 28.9, 36.6, 70.0, 78.4, 117.0, 129.5, 139.1, 145.2, 155.0, 158.6, 166.7, 169.6 ppm; MS (ES^+) *m/z* 343.34 $[M+H]^+$; HRMS calcd for $C_{18}H_{23}N_4O_3$ $[M+H]^+$ 343.1765, found 343.1770.

8-Methyl-*N*-(4-phenoxyphenyl)-9*H*-purin-2-amine (28): The title compound was synthesised following general procedure A using 2-fluoropurine intermediate (70 mg, 0.46 mmol) and 4-phenoxyaniline (0.170 g, 0.92 mmol) were treated with TFA (177 μL, 2.30 mmol) in TFE (6 mL). The crude product was purified by MPLC on silica (DCM/MeOH 19:1) to afford a pale pink solid (0.101 g, 75%). $R_f =$ 0.39 (DCM/MeOH 19:1); m.p. 228–231 °C; UV λ_{max} (EtOH): 277 nm; IR (neat powder): $\nu_{max} = 3454$, 3253, 3194, 3044, 2924, 2161,

1617 cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 2.46$ (3H, s, CH_3), 6.95 (2H, dd, $J = 1.1$, 7.7 Hz, Ar-H), 7.00 (2H, d, $J = 9.0$ Hz, Ar-H), 7.07 (1H, dddd, $J = 1.1$, 1.1, 7.4, 7.4 Hz, Ar-H), 7.36 (2H, ddd, $J = 1.1$, 7.4, 7.7 Hz, Ar-H), 7.83 (2H, d, $J = 9.0$ Hz, Ar-H), 8.63 (1H, s, H-6), 9.45 (1H, s, NH), 12.68 ppm (1H, s, N9-H); ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 14.9$, 117.1, 119.7, 119.8, 122.4, 128.3, 129.8, 137.5, 146.4, 149.3, 151.4, 154.3, 155.9, 158.1 ppm; HRMS calcd for $C_{18}H_{16}N_5O$ $[M+H]^+$ 318.1349, found 318.1352.

General procedure B

As described in general procedure A, except that reagents were placed in a sealed microwave vial and the reactions were performed under microwave irradiation (140 °C for 90 min). A representative example of this procedure is given above with others to be found in Supporting Information.

Product formation as a function of TFA concentration

In a sealed tube equilibrated at 25 °C, containing a 0.25 M solution of the heteroaryl substrate (1 equiv) in TFE, was added the aniline (2 equiv). Timing started upon introduction of TFA and aliquots were taken at defined intervals (0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, 512 min) to follow the formation of the product and the disappearance of the heteroaryl substrate. All aliquots were quenched with a 1:1 (v/v) solution of saturated sodium bicarbonate and ethyl acetate. The organic extracts were analysed by LC-MS to monitor the percentage of product formed (equivalent to the percentage of reacted starting material) by integration of their respective peaks.

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Keywords: catalysis · heterocyclic drugs · S_NAr · synthetic methods · trifluoroethanol

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