

Facilitation of addition–elimination reactions in pyrimidines and purines using trifluoroacetic acid in trifluoroethanol

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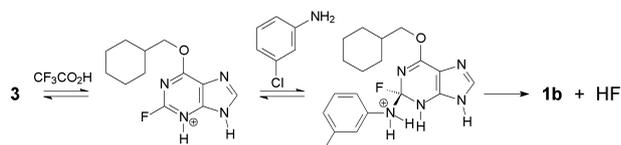
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S_NAr displacement reactions of 6-cyclohexylmethoxy-2-fluoropurine, 6-amino-2-butylsulfonyl-4-cyclohexylmethoxypyrimidine and 2-amino-6-chloropurine with substituted anilines (e.g. the weakly nucleophilic 4-aminobenzenesulfonamide) are dramatically accelerated in the presence of trifluoroacetic acid and occur especially efficiently in 2,2,2-trifluoroethanol solvent.

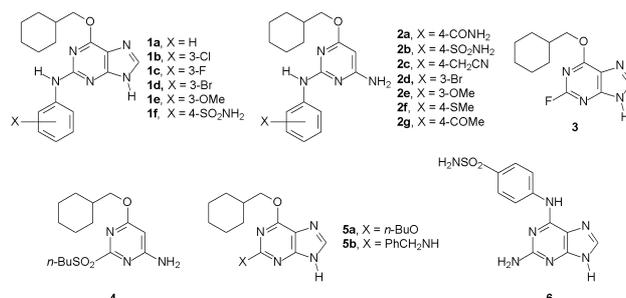
The classical method for introducing amino-substituents at the 2/4-positions of pyrimidines and the 2/6-positions of purines is to react a precursor heterocycle containing a suitable leaving group with an amine.^{1,2} This type of reaction occurs by an addition–elimination (S_NAr) mechanism, *i.e.* formation of a tetrahedral intermediate that eliminates the leaving group (Scheme 1).^{3,4} Although this method has been partly superseded by the use of palladium-mediated substitutions,^{5,6} the direct substitution method is still the mainstay of many syntheses of substituted heterocycles. However, the reaction often fails with poorly nucleophilic amines, *e.g.* anilines bearing electron-withdrawing groups. In a programme seeking potent inhibitors of cyclin-dependent kinases,⁷ we required purines **1** and pyrimidines **2** substituted at C-2 with anilino groups.⁸ Of particular interest were anilines with electron-withdrawing substituents at C-4 (e.g. SO_2NHR and $CONHR$) as these are associated with high potency against CDK1 and CDK2.⁹ To access the purines, the fluoro-substituted precursor **3** was chosen, whereas for the pyrimidines the *n*-butylsulfonyl precursor **4** was selected. We have found that the combination of trifluoroacetic acid (TFA) as catalyst and 2,2,2-trifluoroethanol (TFE) as solvent provides a remarkably effective way to achieve nucleophilic substitutions in the substrates described, even with anilines of low nucleophilicity.

In initial studies with 6-cyclohexylmethoxy-2-fluoro-9H-purine **3**, prepared by a Balz–Schiemann reaction on 2-amino-6-cyclohexylmethoxy-9H-purine, reactions were performed with a substituted aniline (e.g. 3-chloroaniline) in refluxing butan-1-ol as solvent. In addition to product **1b**, a significant by-product from this reaction was 2-butoxy-6-cyclohexylmethoxypurine **5a**. It was observed that the desired substitution reaction appeared to accelerate at longer reaction times, and this was ascribed to a catalytic effect of the hydrogen fluoride formed. Substitution reactions of halopyrimidines with amines are known to be accelerated by acidic catalysts [e.g. copper(II) sulfate].^{1a,2} A systematic study was therefore undertaken in which different acids were added to the reaction mixture. It was found that for



Scheme 1 Reaction of fluoropurine **3** with 3-chloroaniline catalysed by TFA [*n.b.* **3** protonated at N-1 and N-9 will also be present, with $3-H^+$ (N-1) also able to react with 3-chloroaniline].

† This paper is dedicated to the memory of Hayley Whitfield (1977–2001).



a 0.2 M solution of substrate **3** in butan-1-ol at 120 °C containing an excess of an aniline or a substituted aniline (e.g. 3-F, 3-Cl, 3-Br or 3-MeO; up to 7 mole equiv.), with and without TFA, the formation of the product (**1a–e**) was substantially accelerated in the presence of acid (0.4, 5 or 10 mole equiv. TFA). The results described were rationalised by postulating that the presence of TFA generates both mono-protonated **3** and protonated aniline at equilibrium with their non-protonated precursors. Reaction of *protonated 3* with *non-protonated* aniline leads to a tetrahedral intermediate that loses first a proton and then fluoride to give product **1b** (Scheme 1). The loss of fluoride requires that this anion is solvated, and this can be achieved either by the use of a protic solvent or by an added acid. In support of the proposed mechanism, increasing the amount of aniline initially increased but eventually decreased (at 7 mole equiv.) product yields, presumably by buffering the acid. Weaker acids (e.g. acetic acid) were ineffective as a catalyst.

Applying the principles developed with the anilines described above to less nucleophilic anilines gave relatively poor product yields, *e.g.* 27% of 6-cyclohexylmethoxy-2-(4-sulfamoylanilino)-9H-purine **1f** from a reaction in which compound **3** (1 M in a 1 : 1 ethanol–glycerol mixture containing 1 mole equiv. TFA) and 7 mole equiv. 4-aminobenzenesulfonamide (sulfanilamide) was heated at reflux for 7 days. It was surmised that performing the reaction in the more polar protic solvent 2,2,2-trifluoroethanol (TFE) would favour formation of the charged tetrahedral intermediate (Scheme 1) and facilitate loss of fluoride from this intermediate. Also, the formation of the by-product 2-alkoxy-6-cyclohexylmethoxypurine should be suppressed by the use of an alcohol of lower nucleophilicity. Gratifyingly, the use of TFE with TFA provided optimum conditions for achieving reactions of anilines with **3**, even for very weakly nucleophilic anilines. A further advantage of the use of TFE was that all reactions were homogeneous in this solvent. A series of experiments were performed for the reaction of **3** with sulfanilamide in which the solvent and concentration of TFA were varied. For a 0.1 M solution of **3** in TFE for 6 hours at reflux, yields of **1f** were 17 (0), 74 (0.5), 79 (1), 83 (2), 89 (3) and 91% (5) [the numbers in brackets are mole equiv. TFA]. These data confirmed that TFE–TFA is the medium/acid of choice and provided a reliable and efficient experimental procedure.‡ Under these conditions, no product from displacement of fluoride from **3** by TFE was detected, and we did not observe *N*-trifluoroacetylation of the aniline, which was another significant side-reaction for reactions performed in butan-1-ol. Other solvents explored were propan-2-ol and pentan-2-ol,

which reduced the yield of by-product 2-alkoxy-6-cyclohexylmethoxypurine, but only gave *ca.* 60% **1f** under conditions where the use of TFE gave > 90% yield. Aprotic solvents and mixtures of aprotic and protic solvents generally gave significantly reduced yields of **1f**, with the exception of acetonitrile which gave comparable yields but with by-products.

We also found that Amberlyst 15 (polymer-supported sulfonic acid), camphorsulfonic, hydrochloric, chloroacetic and formic acid were not useful catalysts at comparable concentrations to TFA. This suggests that for optimal catalysis the acid strength should be sufficient to generate a viable concentration of protonated **3** (Scheme 1), but not so strong that the amine reaction partner is almost completely protonated. When benzylamine was used as nucleophile with **3** in trifluoroethanol or dimethyl sulfoxide, the formation of product **5b** occurred readily in the *absence* of TFA. However, addition of 5 mole equiv. TFA to this reaction dramatically suppressed the formation of **5b** (none detectable after heating at reflux for 1 hour, under which conditions formation of **5b** was nearly quantitative in the absence of the acid). In this case, addition of TFA clearly completely protonates and deactivates the more basic benzylamine.

Similar results were obtained for the substrate 6-amino-2-*n*-butylsulfonyl-4-cyclohexylmethoxypyrimidine **4**¹⁰ and 2-amino-6-chloropurine, showing that the leaving groups *n*-butylsulfonyl and chloride are also compatible with the TFE-TFA milieu. Thus, heating compound **4** (0.15 M in TFE) at reflux for 2 hours with 2 mole equiv. 4-aminobenzamide in the presence of 5 mole equiv. TFA gave 4-(6-amino-4-cyclohexylmethoxypyrimidin-2-ylamino)benzamide **2a** (62% isolated yield of recrystallised, analytically pure material). In a similar manner, **4** with the appropriate aniline gave the corresponding adduct **2b-g** (yields of analytically pure product in the range 45–71%). 2-Amino-6-chloropurine in TFE did not react with sulfanilamide in the absence of TFA, but on addition of 5 mole equiv. of the acid, 77% of 2-amino-6-(4-sulfamoylanilino)-9H-purine **6** was obtained after heating at reflux for 3 hours.

The reaction conditions described should be suitable for a variety of nucleophilic substitutions in heterocyclic systems, especially for weakly nucleophilic amines and for leaving groups that require effective solvation in order to decay to product from the tetrahedral intermediate. We have used this methodology to prepare numerous purines and pyrimidines related to structures **1** and **2** from a variety of mono- and di-substituted anilines (*cf.* ref. 10). With strongly nucleophilic amines (*e.g.* benzylamines), addition of TFA is detrimental because the amine is fully protonated and therefore deactivated.

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Notes and references

‡ Typical procedures:

To a suspension of 6-cyclohexylmethoxy-2-fluoro-9H-purine (0.41 g, 1.64 mmol) and sulfanilamide (0.55 g, 3.19 mmol) in trifluoroethanol (4 cm³) was added trifluoroacetic acid (0.61 cm³, 8 mmol). The resulting solution was boiled under reflux for 16 h, when LC-MS analysis showed complete conversion of 6-cyclohexylmethoxy-2-fluoro-9H-purine to **1f**. The solvent was removed and the residue was taken up in methanol. The methanolic solution was filtered through a bed of basic alumina. The filtrate was concentrated and the residual solid was recrystallised from propan-2-ol to afford compound **1f** as an analytically pure white solid (69%).

To a suspension of 6-amino-2-*n*-butylsulfonyl-4-cyclohexylmethoxypyrimidine **4** (0.20 g, 0.61 mmol) and 4-aminobenzamide (0.17 g, 1.22 mmol) in trifluoroethanol (4 cm³) was added trifluoroacetic acid (0.24 cm³, 3.05 mmol). The resulting solution was boiled under reflux for 2 h. The solvent was removed and the solid was extracted into ethyl acetate and washed with water. The organic layer was collected, dried (Na₂SO₄) and filtered. The solvent was removed to yield a white solid. Recrystallisation from MeOH yielded **2a** as a white solid (0.13 g, 0.38 mmol, 62%).

All new compounds gave spectroscopic data and elemental analyses in accord with their assigned structure.

- (a) B. C. Uff, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984, **vol. 2**, p. 360; (b) B. C. Uff, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984, **vol. 5**, p. 561.
- H. E. Mertel, in *The Chemistry of Heterocyclic Compounds*, ed. A. Weissburger, Interscience, New York, 1962, Pt. 2, p. 352.
- E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 1662.
- G. B. Barlin and N. B. Chapman, *J. Chem. Soc.*, 1965, 3017.
- C. Enguehard, H. Allouchi, A. Gueiffier and S. L. Buchwald, *J. Org. Chem.*, 2003, **68**, 4367 and references cited therein.
- S. Ding, N. S. Gray, X. Wu, Q. Ding and P. G. Schultz, *J. Am. Chem. Soc.*, 2002, **124**, 1594.
- M. Knockaert, P. Greengard and L. Meijer, *Trends Pharmacol. Sci.*, 2002, **23**, 417; Y.-T. Chang, N. S. Gray, G. R. Rosania, D. P. Sutherlin, S. Kwon, T. C. Norman, R. Sarohia, M. Leost, L. Meijer and P. G. Schultz, *Chem. Biol.*, 1999, **6**, 361.
- I. R. Hardcastle, R. J. Griffin and B. T. Golding, *Ann. Rev. Pharm. Toxicol.*, 2002, **42**, 325; C. Arris, F. T. Boyle, A. H. Calvert, N. J. Curtin, P. Jewsbury, J. A. Endicott, A. E. Gibson, B. T. Golding, R. J. Griffin, L. N. Johnson, A. Laurie, N. K. Lembicz, D. R. Newell, M. E. M. Noble, E. Sausville and R. Schultz, *J. Med. Chem.*, 2000, **43**, 2797–2804.
- T. G. Davies, J. Bentley, C. E. Arris, F. T. Boyle, N. J. Curtin, J. A. Endicott, A. E. Gibson, B. T. Golding, R. J. Griffin, I. R. Hardcastle, P. Jewsbury, L. N. Johnson, V. Mesguiche, D. R. Newell, M. E. M. Noble, J. A. Tucker, L. Wang and H. J. Whitfield, *Nat. Struct. Biol.*, 2002, **9**, 745.
- K. L. Sayle, J. Bentley, F. T. Boyle, A. H. Calvert, Y. Cheng, N. J. Curtin, J. A. Endicott, B. T. Golding, I. R. Hardcastle, P. Jewsbury, V. Mesguiche, D. R. Newell, M. E. M. Noble, R. J. Parsons, D. J. Pratt, L. Z. Wang and R. J. Griffin, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3079.