LETTER

Practical and innate carbon–hydrogen functionalization of heterocycles

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Nitrogen-rich heterocyclic compounds have had a profound effect on human health because these chemical motifs are found in a large number of drugs used to combat a broad range of diseases and pathophysiological conditions. Advances in transition-metal-mediated cross-coupling have simplified the synthesis of such molecules; however, C–H functionalization of medicinally important heterocycles that does not rely on pre-functionalized starting materials is an underdeveloped area1–9. Unfortunately, the innate properties of heterocycles that make them so desirable for biological applications—such as aqueous solubility and their ability to act as ligands—render them challenging substrates for direct chemical functionalization. Here we report that zinc sulphinate salts can be used to transfer alkyl radicals to heterocycles, allowing for the mild (moderate temperature, 50 °C or less), direct and operationally simple formation of medicinally relevant C–C bonds while reacting in a complementary fashion to other innate C–H functionalization methods2–5 (Minisci, borono-Minisci, electrophilic aromatic substitution, transition-metal-mediated C–H insertion and C–H deprotonation). We prepared a toolkit of these reagents and studied their reactivity across a wide range of heterocycles (natural products, drugs and building blocks) without recourse to protecting-group chemistry. The reagents can even be used in tandem fashion in a single pot in the presence of water and air.

The strategy that we describe here was conceived with a strong desire to make use of the native chemical reactivity9 of nitrogen-rich heterocycles rather than attempting to override it with pre-functionalization (Fig. 1a). Minisci’s pioneering work demonstrated the ability of heterocycles to react with certain alkyl and acyl radicals2 (derived from carboxylic acids and halides (Fig. 1b)). This form of innate C–H functionalization, however, is limited to a subset of alkyl and acyl donors, and often requires higher temperatures (for example, greater than 70 °C), transition-metal additives and strongly oxidizing conditions5. In 2010, it was reported that aryl boronic acids can be used as aryl radical precursors for heterocycle functionalization4. Later, it was shown that alkyl boronic acids and trifluoroborate salts can serve as radical precursors5–8. In 2011, it was demonstrated that sodium trifluoromethanesulphonate, a reagent extensively studied by Langlois8, was used to transfer alkyl radicals to heterocycles, allowing for the mild (moderate temperature, >50 °C) functionalization of various heterocycles, all of which result in products that cannot be efficiently generated by standard Minisci protocols and would otherwise require programmed, multistep processes. These salts represent examples of what we anticipate to be a general
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Figure 1 | Development of a reagent toolkit for an innate C–H functionalization of heterocycles. a, Comparison of different methods of heterocycle functionalization. b, Evolution of the radical precursor. c, Invention of new reagents for heterocycle functionalization.

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reagent class that will permit the rapid diversification of heterocycles using an operationally simple protocol\(^1\). Functionalization using zinc bis(alkanesulphonate) salts affords a marked improvement over functionalization with sodium-based sulphonate salts\(^*\) and is a generalization of the zinc difluoromethanesulphonate chemistry developed previously\(^6\).

We identified a modular set of zinc sulphonate salts as being highly desirable for the installation of medicinally relevant moieties (Fig. 1c): zinc trifluoromethanesulphonate (TFMS; A), zinc difluoromethanesulphonate (DFMS; B), zinc trifluoroethanesulphonate (TFES; C), zinc monofluoromethanesulphonate (MFMS; D), zinc isopropylsulphonate (IPS; E), and zinc triethylenglycolysulphonate (TEGS; F). The fluoralkyl and alkyl groups that we wish to introduce hold privileged positions in drug discovery and are described in detail below.

The CF\(_2\) group is an excellent bioisostere of a methyl group because the former is similar in size to the latter but does not suffer metabolic oxidation\(^1\). It can also be used to tune the steric and electronic properties of a known scaffold, and to grant favourable physicochemical attributes to a lead target\(^12\). For these reasons, trifluoromethylation methodology has received much attention, with nucleophilic CF\(_3\) reagents\(^9\) (for example carbonyl functionalization), electrophilic CF\(_3\) reagents\(^9\) (for example enolate functionalization) and cross-coupling procedures dominating arenne functionalization\(^13\). (Metal-catalysed C–H activation for trifluoromethylation is also known\(^17\).) However, the trifluoromethylation of heterocycles is less common owing to substrate-mediated reagent or catalyst deactivation in these strongly basic, acidic or transition-metal-catalysed reactions.

To fill this gap in methodology, we have begun to study a radical-based approach to trifluoromethylation\(^7\). Although the introduction of the CF\(_3\) group by a radical pathway is known, reagents that achieve this radical transformation are difficult to handle and are toxic (CF\(_3\)I (ref. 18), a gas), ozone-depleting (CF\(_3\)Br (ref. 19), a gas) or corrosive (CF\(_3\)SO\(_2\)Cl (refs 20, 21), a low-boiling liquid). Furthermore, CF\(_3\)CO\(_2\)H does not generate radicals under Minisci conditions, and CF\(_3\)B(OH)\(_2\), as an analogy to borono-Minisci chemistry, is an unknown chemical species (other CF\(_3\-)boron sources such as CF\(_3\)-B(OMe)\(_3\)) and CF\(_3\)-BF\(_3\) (K are not viable radical precursors\(^7\)). Although sodium trifluoromethanesulphonate (CF\(_3\)-SO\(_2\)Na), a stable solid addressed many of the above difficulties for heterocycle trifluoromethylation, TFMS (A) was found to be superior in terms of both stability and reactivity (47% yield was obtained for a reaction of pentoxifylline (2) with CF\(_3\)-SO\(_2\)Na in 2.5:1 CH\(_2\)Cl\(_2\):H\(_2\)O at room temperature for 3 h (Table 1) and 99% yield was obtained for a reaction of 2 with TFMS in 2.5:1 CH\(_2\)Cl\(_2\):H\(_2\)O at room temperature for 3 h (Table 1)).

The CF\(_2\)H group can act as a lipophilic hydrogen-bond donor and has been used in bioisostere design variously to mimic a thiol, a hydroxyl and an amide\(^11\). Although the CF\(_3\)H group can be formed using (diethylamino)sulphur trifluoride on an aldehyde and can be introduced using (trimethylsilyl)difluoromethane\(^22\) or other difluoromethyl precursors\(^22\), direct difluoromethylation strategies on heterocycles had not been explored before the invention of DFMS\(^*\) (B).

The CH\(_2\)CF\(_3\) group is an excellent bioisostere of an ethyl group and acts as a mild electron-withdrawing group (trifluoroethanol is about 3.5 orders of magnitude more acidic than ethanol). Appendage of the CH\(_2\)CF\(_3\) group is typically achieved by multistep strategies (such as nucleophilic addition of CF\(_3\) into an aldehyde followed by deoxygenation), and a catalytic cross-coupling method for this purpose was reported only recently\(^24\). A direct, free-radical-based approach for the introduction of the CH\(_2\)CF\(_3\) group was unknown, and therefore TFES (C) was developed to fill this gap in methodology.

Much like the CF\(_3\) group, the CH\(_2\)F group can act as a useful bioisostere of a methyl group because the fluorne atom can also prevent metabolic oxidation owing to its electron-withdrawing effect. Furthermore, the CH\(_2\)F group has also been considered bioisosteric with hydroxymethyl (CH\(_2\)OH) and methoxymethyl (CH\(_2\)-OCH\(_3\)) groups\(^23\). However, monofluoromethylation methods are limited and less well studied compared with trifluoromethylation and are typically introduced using ‘auxiliary’ approaches\(^23\), for example appending a fluoro(phenylsulphonyl)methyl group and then removing the phenylsulphonyl group\(^26\). The generation of a monofluoromethyl radical is almost unknown, with only one report made on its characterization by a matrix reaction of bromofluoromethane with alkali metals, without demonstration of synthetic applicability\(^27\). As fluoroacetic acid (CH\(_2\)F-CO\(_2\)H) cannot generate radicals under standard Minisci conditions, a practical CH\(_2\)F radical precursor and its application to synthetic chemistry is required; MFMS (D) is a new reagent devised for this purpose.

The ability to add steric bulk and lipophilicity where needed may prove valuable when probing for structure–activity relationships or when blocking metabolically labile positions. Methods for the direct introduction of this hindered group include the use of toxic isopropymercuric reagent ((CH\(_3\))\(_2\)CH-HgCl (ref. 28)) or the use of air- and water-sensitive isopropylithium or isopropymagnesium chloride. Furthermore, the use of (CH\(_3\))\(_2\)CH-CO\(_2\)H or (CH\(_3\))\(_2\)CH-I with the Minisci protocol on caffeine (1) did not afford the desired product at room temperature or higher temperatures. A ‘programmed’ approach to installing an isopropyl group is often low-yielding and problematic using Suzuki- or Negishi-type couplings (with a few notable exceptions\(^29\)) and we therefore designed an ‘innate’ approach using IPS (E).

Ethylene glycol units are excellent solubilizing units, and the utility of poly(ethylene glycol) chains in drug delivery has been extensively investigated\(^30\). As a proof of concept for the appendage of poly(ethylene glycol) units onto heterocycles, we planned to introduce a shorter, tri(ethylene glycol), chain that might retain the ability to increase the hydrophilicity of a lead target. Methods to directly append an oligo (ethylene glycol) unit onto heterocyclic frameworks are unknown, and TEGS (F) was therefore devised.

The ability to incorporate fluoroalkyl, alkyl and alkoxyalkyl groups into heterocyclic frameworks is highly desirable; however, until now the chemistry to access substituted heterocycles rapidly has been underdeveloped and of limited scope. The power of the zinc sulphinate tool kit is demonstrated here with a synthesis of an exemplary set of medicinally relevant heterocycles (>50 examples), most of which represent new chemical entities.

As shown in Table 1, we used an operationally simple procedure to functionalize xanthines (1 and 2), pyridines (3 and 4), quinoxalines (5), pyrimidines (6), pyridazines (7) and pyrroles (8): the heterocycle substrate and the zinc sulphinate salt were combined with a mixture of organic solvent and water and cooled in an ice-water bath, tert-butyl hydroperoxide (TBHP) was added and this mixture was warmed to room temperature or 50°C. Exclusion of air or purification of solvents is unnecessary, and the reaction flask is sealed only with a plastic cap to prevent solvent evaporation. Fluoroalkylated zinc sulphinate reagents (A–D) performed best in halogenated solvents such as CH\(_2\)Cl\(_2\), CICH\(_2\)CH\(_2\)Cl, perfluorotoluene and perfluorohexane, whereas alkylated zinc salts (E and F) reacted more favourably in DMSO or in an electron-rich aromatic solvent such as anisole. For substrates that showed low conversion, addition of one or more of the following was performed: zinc sulphinate salt, TBHP or trifluoroacetic acid.

Perhaps the most notable aspect of C–C bond formation using zinc sulphinate chemistry is the mildness of the reaction conditions. As shown in Table 1, reactive groups such as nitriles, ketones and esters are tolerated. The level of functional group compatibility can be extended even to reactive heteroaryl halides, free carboxylic acids and boronate esters, three groups of particular utility in pharmaceutical chemistry owing to the ease of further functionalization via cross-coupling methods or amide bond formation (Fig. 2a). These groups are typically incompatible with most organic reactions, much less C–H functionalization strategies; however, under our reaction conditions, simple pyridine building blocks bearing a reactive chloro (9), pinacolato-boron (10) or carboxylic acid (11) moiety can be functionalized with
CF₃ or CF₂H groups. In particular, carboxylic acid 11 is a quintessential example of the unique chemoselectivity and mildness of the reaction conditions, because Minisci or borono-Minisci conditions would not leave the carboxylic acid unit intact. It is of note that the modest yields observed in these reactions are due to difficulties in product isolation, for example the high volatility of difluoromethylated compounds in this table are new.

Isolated yields are shown. Percentage conversions by gas chromatography (GC) mass spectrometry are indicated in parentheses, and regioisomeric ratios are shown in square brackets. Compounds have been previously synthesized with Langlois reagent (ref. 7), and compounds have been previously prepared using DFMS (ref. 9) and are included for completeness; all other compounds in this table are new.

* Standard conditions involve heterocycle (1.0 equiv.), zinc salt (2.0–3.0 equiv.), TBHP (3.0–5.0 equiv.) and solvent:water (2.5:1) at a specified temperature for a period of 3–12 h. Solvent and temperature: THF, RT; DMSO, CHCl₃, 50 °C; perfluorohexane, CH₂Cl₂, RT; trifluoroacetic acid; TFA, trifluoroacetic acid.

** When the GC percentage conversion is lower than the isolated yield, it signifies that only one addition of Zn salt was made for the 'GC yield reaction', but that a second addition of Zn salt and TBHP was performed after 12 h for the 'isolated yield reaction'.

TFA was used as an additive.

When the GC percentage conversion is lower than the isolated yield, it signifies that only one addition of Zn salt was made for the 'GC yield reaction', but that a second addition of Zn salt and TBHP was performed after 12 h for the 'isolated yield reaction'.

Et, ethyl; Me, methyl; NR, no reaction; RT, room temperature (25 °C); TBHP, tert-butyl hydroperoxide; TFA, trifluoroacetic acid.

Table 1 | Substrate scope of the zinc sulphinate salt toolkit

| Heterocycle | CF₃ (A) | CF₂H (B) | CH₂CF₂ (C) | CH₂F (D) | CH₂O₂ (E) | (CH₂CH₂)₂CH₂ (F) |
|-------------|--------|----------|------------|----------|-----------|-----------------|
| 1           | 89 (100)† | 73 (57)†⩾ | 51# | 80# | 41** | 40‡† |
| 2           | 79 (100)† | 72 (41)†⩾ | 44# | 75# | 37** | 49‡† |
| 3           | 35 (77)† | 66 (100)† | 18 (85)# | 73*‡‡ | 47‡ | 41†† |
| 4           | 66 (65)†⩾ | 60 (96)† | 33# | NR | 41†† | NR |
| 5           | 75 (100)† | 50 (67)† | 31 (77)‡ | 56# | 43** | 32** |
| 6           | 42 (44)‡ | 21 (44)‡ | 21** | NR | 46** | 16‡† |
| 7           | 45 (90)‡ | 57 (71)‡ | NR | NR | 49** | 32 (38)‡† |
| 8           | 76 (91)† | 65 (100)† | 58** | 40‡ | 17** | 10 (43)‡† |

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performed a one-pot sequential C–H functionalization of the antimalarial drug dihydroquinine (15; Fig. 2b). Because our previous studies suggested that electrophilic radicals add to the C7 position of 15 (ref. 7) and that nucleophilic radicals add to the C2 position of 15 (ref. 9), we expected 15 to react sequentially when an electrophilic and a nucleophilic radical were added in one pot. To test this, we added TFMS (A) and then IPS (E) to a reaction vessel containing 15, after which difunctionalized dihydroquinine derivative 16 was isolated in 30% yield. The scope of this sequential functionalization was further extended to examples including pyridines (17 and 18) and purines (19). This strategy is particularly useful for the construction of lipophilic derivatives of hydrophilic molecules such as dihydroquinine and 6-chloropurine, because the isolation of water-soluble intermediates can be avoided and only the lipophilic bis-substituted product is isolated.

Finally, the versatile nature of this transformation is demonstrated by the ability to carry out difluoromethylation and triluoromethylation in unconventional media (conversion to product confirmed by high-performance liquid chromatography), including cell lysate (Fig. 2c, i), tea (Fig. 2c, ii) and a Tris buffer solution in the presence of a serine-based β-lactamase (Fig. 2c, iii), which retained its functional activity after resolation. These findings may have important implications in the area of bioconjugation.

Although zinc sulphinate chemistry can provide a great number of new chemical entities that are difficult or impossible to access in other ways, and yet have high levels of chemoselectivity, this procedure, much like other methods, is not without limitations. For instance, some nucleophilic radicals gave markedly lower yields when reacting with certain electron-rich substrates, for example a 17% yield in the reaction of IPS (E) with pyrrole 8 (Table 1). We found that many solvents sometimes had to be screened to achieve the desired reaction (for example for MFMS (D)). Nevertheless, we believe that the practicality, versatility and functional group tolerance of this innate functionalization of heterocycles makes it a valuable addition to the range of C–H functionalization methods that can be used to construct pharmaceutically important targets. In addition, comparison of traditional programmed approaches (of which none exist for the three of the six salts described in Table 1) with the synthesis of compounds in Table 1 and, especially, those in Fig. 2 shows that it would be extremely difficult to devise a faster, simpler or cheaper way to make such molecules.

In most contexts of discovery chemistry, reactions that can be conducted open to the air on unprotected, late-stage molecules in 10–50% yield are preferable to time-intensive, multistep routes, especially when the overall yield of such routes (for instance a typical sequence of protection, lithiation, iodination, cross-coupling and deprotection) is comparable to this direct approach. It is of note that 50 of the 52 compounds reported here have not been prepared before (or have only previously been described by our laboratory7,9; several other methods are listed in compound databases but no preparations are reported). Zinc sulphinate chemistry is not limited to the six salts presented above. Salts have also been prepared for the transfer of CH2Cl, CH3CO2Me, cyclohexyl (for example, see 18 in Fig. 2b) and perfluoroalkyl (for example C8F13) groups, and the extent of their scope is currently being examined (Supplementary Information).

We have described the invention of a zinc sulphinate toolkit containing ten different groups (CF3, CF2H, CH2CF3, CH3F, CH(CH3)2, (CH3)2CH, CH3Cl, CH3CO2CH3, cyclohexyl and C8F13) for the simple and rapid diversification of heterocycles. Four of these reagents are currently commercially available from Sigma-Aldrich (TFMS, catalogue no. L510106; DFMS, catalogue no. L510084; TFES, catalogue no. L511234; IPS, catalogue no. L511161). Particular advantages of this chemistry include (1) the superiority of zinc over sodium alkylsulphinates, which led to the identification of a highly active counter-cation and allowed for an efficient radical generation from alkylsulphinates; (2) the mildness of the reaction conditions, which tolerated highly sensitive functional groups such as chloro and boryl groups; (3) a different, transition-metal-free mode of radical generation compared with Minisci chemistry, as benzylic carboxylic acids were tolerated; (4) the feasibility of a sequential, one-pot operation that allowed for a site-selective bis-alkylation of heterocycles using two different alkylating agents; and (5) the ability to conduct these reactions under open air, without organic co-solvent and in the presence of extensive impurities in the reaction medium, which may have potential applications in bioconjugation.

This chemistry has already been ‘field-tested’ and is now widely used for medicinal chemistry at Pfizer; several of the building blocks reported in this work are currently in use there (3–5, 7, 13 and 14).
In many cases, building blocks that would be regarded as ‘low priority’ at Pfizer owing to prohibitively high cost or lengthy synthetic routes are now easily accessible. The extreme operational ease, functional group tolerance and ability to run reactions in unconventional media open to air bode well for the widespread application of zinc sulphinate in chemical synthesis. As a further outlook for the utility of innate heterocycle functionalization, zinc sulphinate reagents could potentially be used to cap metabolically susceptible positions in bioactive molecules and to identify the most reactive sites of a given heteroarene.

The development of such a ‘profiling system’, providing a set of empirically determined reactivity rules to organic chemists, is a topic of ongoing research in our laboratory.

METHODS SUMMARY

All reactions were carried out under an atmosphere of air. Reagents were of the highest commercial quality and were used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica plates (60F-254), using ultraviolet light as the visualizing agent and KMMoO₄ as a developing agent. For full experimental details and procedures for all reactions performed and any associated references are available in the online version of the paper.

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Supplementary Information is available in the online version of the paper.

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METHODS

Our standard procedure for the functionalization of heterocycles was as follows. A solution of heterocycle (0.125–0.250 mmol, 1.0 equiv.) and Zn salt (2.0–3.0 equiv.) in an organic solvent was cooled in an ice-water bath, and this was followed by the slow addition of TBHP (70% solution in water, 54–179 μl, 3.0–5.0 equiv.) using an Eppendorf pipette (metal needles should not be used as they decompose the reagent) with vigorous stirring. The reaction mixture was warmed to room temperature or 50 °C and monitored by thin-layer chromatography until reaction completion. For substrates that do not achieve reaction completion in 12–24 h, a second addition of Zn salt (2.0–3.0 equiv.) and TBHP (3.0–5.0 equiv.) may be added to drive the reaction further. On consumption of the starting material, the reaction was partitioned between EtOAc (5.0 ml) and saturated NaHCO₃ (5.0 ml) or CH₂Cl₂ (5.0 ml) and saturated NaHCO₃ (5.0 ml). The organic layer was separated, and the aqueous layer was extracted with EtOAc or CH₂Cl₂ (3 × 5.0 ml). The organic layers were dried with Na₂SO₄, concentrated and purified by column chromatography on silica gel. We note that if the TBHP is added too rapidly, the resulting exotherm can result in reduced yield and selectivity. This is especially important on larger scales, where a syringe pump may be used to add the TBHP.