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Recent advances in the trifluoromethylation methodology and new CF_3-containing drugs

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ABSTRACT

This review provides a brief assessment of the methodological field of trifluoromethylation and its possible impact on the development of new CF_3-containing pharmaceuticals. Structural aspects of five new drug-candidates, [tafenoquine (aromatic CF_3), roniciclib (heteroaromatic CF_3), BAY-38-7271 (aliphatic CF_3), sonidegib ($O–CF_3$) and navitoclax ($S-CF_3$)] currently under the development in phase II and III clinical studies, and their biological properties, therapeutic area and synthesis are critically discussed.

1. Introduction

Fluorine chemistry has quite a few success stories of truly historic proportion in shaping up the modern-day science and technology [1]. The most recent one is the impact that fluorine is currently making on the development of contemporary pharmaceutical industry [2]. Considering the fact that fluorine, among light elements, is the most xenobiotic, its rise to the prominence as key designer component in the structure of modern biologically active compounds is rather incredible and fascinating scientific progress. It is generally known that introducing fluorine atoms and/or fluorine-containing groups into bioactive molecules can have a range of overall positive effects, such as rendering them more selective, potent, increasing efficacy, or making them easier to administer [3]. Some of the fluorine effects on the molecules' properties are well understood [4], however, in most of the cases the development of a fluorine containing drug is a tedious trial-and-error process. As one can assume, the fluorine-scan approach, placing fluorine in various structural positions, is strictly limited by the availability of the corresponding synthetic methodology allowing preparation of the fluorinated target molecules. Thus, it is obviously clear that the emergence of certain fluorinated drugs on the pharmaceutical market [2] comes after the development of the suitable methodology allowing a desired particular type of fluorination on a commercial scale. Connecting this trend with the recent methodological "revolution" in the area of trifluoromethylation [5], it seems apparent that future generations of pharmaceuticals will have increasing number of CF_3-bearing molecules. Drawing inspiration from this prospect, we have designed the present review article providing a brief outline of the recent advances in the trifluoromethylation methodology in connection with some CF_3-containing drug candidates currently under the development by the pharmaceutical industries. We believe this innovative treatment of synthetic and medicinal chemistry literature will be of general interest to all practitioners working in this most exciting multidisciplinary area.

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2. Brief appraisal of the current trifluoromethylation methodology

In the last several years the trifluoromethylation methodology has been extensively and comprehensively reviewed [6], focusing on a particular source of CF_3 group, mechanistic or structural considerations. To avoid any overlap with these excellent reviews, we present herein a brief outline of the most recent literature highlighting advances in preparation of trifluoromethyl-containing compounds based on a structural type of C–CF_3 or heteroatom–CF_3 bond, which can be found in the drug-candidates profiled in this article.

2.1. Trifluoromethylation of aromatic compounds

Trifluoromethyl arenes have been traditionally prepared using the procedure developed by Swarts at the end of 19th century [7]. However, this involves very harsh reaction conditions in order to transform toluene to (trichloromethyl)benzene and then to (trifluoromethyl)benzene, and therefore it is obvious that new synthetic protocols are in great demand, especially for late stage introduction of CF_3 groups into already functionalized aromatic rings. In addition, special attention has been recently dedicated to the discovery of catalytic processes [6b].

In principle, replacement of a halide atom by a CF_3 group is the most reliable method in terms of selectivity [6a,6d]. For many years, the reaction of aryl iodides with a stoichiometric amount of $CuCF_3$ species has been the method of choice, most of the times using CuI and the Ruppert–Prakash reagent (CF_3SiMe_3) or its analogs as the Cu(I) and trifluoromethyl sources, respectively [8] (Scheme 1, path a). As a consequence, a substantial amount of metal waste was always produced. Furthermore, relatively high temperatures and long reaction times were usually required. These shortcomings led to the development of room temperature protocols employing isolable Cu–CF_3 complexes, either preformed or used *in situ*. These reagents also display a broader substrate scope and higher compatibility with other functional groups, especially carbonyl moieties [9].

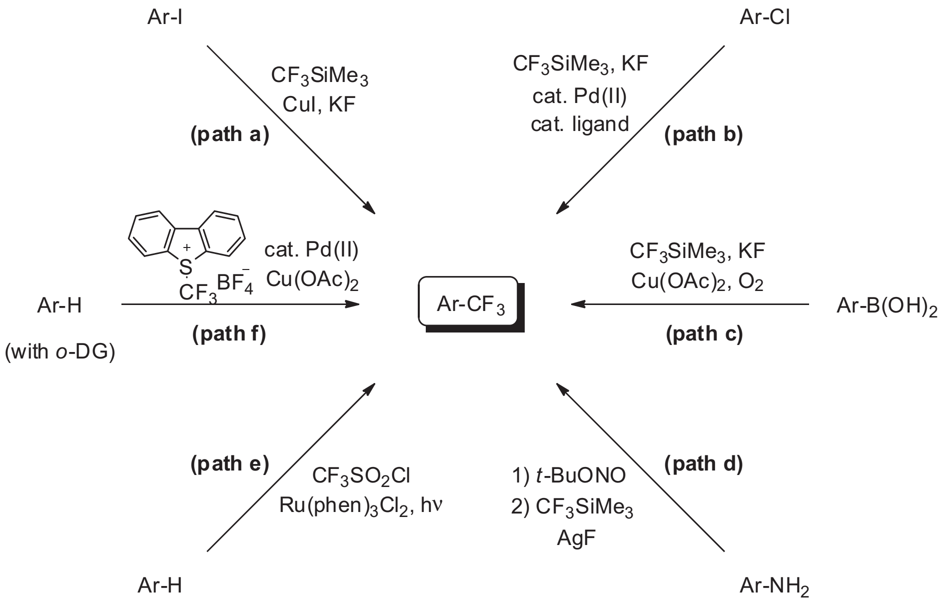
The development of a catalytic method in copper constituted a landmark in the trifluoromethylation of arenes. This involved the reaction of electron-deficient aryl iodides with CF_3SiEt_3 and a catalytic amount of CuI in the presence of a chelating diamine ligand, 1,10-phenanthroline (phen) [10]. Subsequently, other procedures have been reported based on more stable or cheaper sources of CF_3, such as potassium (trifluoromethyl)trialkoxyborates [11], trifluoroacetaldehyde (fluoral) [12] or environmentally friendly fluoroform [13].

Pd(II) and Pd(IV) complexes containing an aryl and CF_3 groups can act as intermediates in the trifluoromethylation of aryl iodides by a reductive elimination step leading to Ar–CF_3 bond formation [14]. These discoveries paved the way for a major advance in this area: the development of a Pd(II)-catalyzed trifluoromethylation method by way of the correct choice of ligands, that allowed using the much cheaper and available aryl chlorides as substrates with amounts as low as 3 mol% of palladium catalyst [15] (Scheme 1, path b).

Aryl boronic acids are a suitable alternative to aryl halides as substrates in trifluoromethylation processes, due to their higher reactivity and easy synthetic access. The first examples reported consisted in the copper-mediated reaction with CF_3SiMe_3, in the presence of oxidants such as Ag_2CO_3 [16] or oxygen [17] (Scheme 1, path c). Soon afterward, a plethora of related protocols have increased the potential of aryl boronic acids employing different sources of CF_3, which include other nucleophilic (potassium (trifluoromethyl)trialkoxyborates [18]), electrophilic (trifluoromethyl sulfonium salts [19]), or radical reagents ($NaSO_2CF_3$/TBHP [20]) as well as fluoroform [21]. From these findings, catalytic procedures have also been developed, by using CF_3SiMe_3 [22], Togni's reagent [23], Umemoto's reagent [24], CF_3I/visible light [25] or again $NaSO_2CF_3$/TBHP [26].

Anilines can be converted into trifluoromethyl arenes by means of a Sandmeyer-type process. Two synthetic protocols have been recently described to perform this transformation, consisting in the reaction of the derived diazonium salts with Umemoto's reagent and Cu metal [27], or with CF_3SiMe_3 and AgF [28] (Scheme 1, path d).

In the absence of a pre-positioned and replaceable functional group, trifluoromethylation of arenes can be achieved by C–H activation, although regioselectivity issues may then arise. This strategy has been pursued employing CF_3SiMe_3/AgOTf at 80 °C [29], or more efficiently at room temperature with CF_3SO_2Cl in the presence of visible light and $Ru(phen)_3Cl_2$ as photocatalyst [30]



Scheme 1. Selected methods for the synthesis of Ar–CF_3 compounds.