Review

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Synthesis of quinolines and acridines by the reaction of 2-(perfluoroalkyl)anilines with lithium and Grignard reagents

DOI 10.1515/hc-2015-0074
Received April 10, 2015; accepted April 11, 2015; previously published online May 23, 2015

Abstract: This review summarizes the synthesis of quinolines and acridines by the reactions of anionically activated 2-(perfluoroalkyl)anilines. Mechanistic studies including isolation of the intermediate aza-*ortho*-xylylene are discussed.

Keywords: acridines; anilines; Grignard reagent; lithium reagent; perfuoroalkyl; quinolines.

Introduction

An unconventional synthetic route to quinolines and acridines involves ionization of 2-(perfluoroalkyl)aniline or an analogue followed by elimination of fluoride from the resultant anion and then intramolecular or intermolecular cyclization of thus generated non-aromatic intermediate product. Large series of new quinolines and acridines have been synthesized by using this methodology and tested for diverse biological activity. Studies have shown that substituted quinolines, acridines, and analogues are anti-HIV-1 agents [1–3]. Since a statistically significant correlation between binding of these compounds to double-helical regions of RNA and biological activity was found, it was suggested that the mechanism of action of the active agents involves intercalation with RNA [2]. This subject has been reviewed [4]. Subsequently, it has been found that 2-arylquinolin-4-amines can intercalate with double- and triple-helical DNA. Importantly, it has been demonstrated that compounds can be designed for selective stabilization of triplex DNA in the presence of duplex DNA [5–13]. Additional studies have shown that certain quinolines and acridines are antagonists of immunostimulatory bacterial DNA [14–17] and, as such, can induce remissions of the rheumatoid arthritis and systemic lupus erythematosus. These most recent biological studies have been mentioned in the particular synthetic papers and complete reviews will be published in due course.

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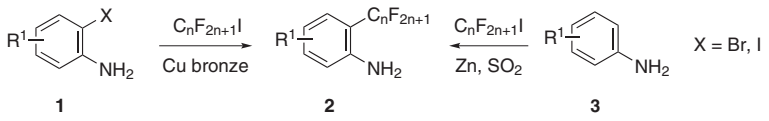
2-(Perfluoroalkyl)anilines

These starting materials 2 (Scheme 1) are inexpensive commercial products or can easily be prepared by perfluoroalkylation of 2-haloanilines 1 or anilines 3 [18–21]. Interestingly, the trifluoromethylation of 3 is *ortho*-regioselective [21]. Common substituents R^1 are well tolerated in the preparation of 2. The perfluoroalkyl group can be introduced at position 2 of heteroaromatic amines by using an analogous approach [21]. A different preparation of 3-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine [22, 23] involves reductive cyclization of 2-fluoro-3-(trifluoroacetyl) pyridine by treatment with hydrazine (not shown). The heteroaromatic analogues of **2** can undergo transformations that are similar to the syntheses of quinolines and acridines discussed below. The recently developed oxidative trifluoromethylation of aryl boronic acids by the reaction with (trifluoromethyl)trimethylsilane in the presence of a copper catalyst has yet to be adapted to the synthesis of substrates **2** [24–27].

Synthesis of quinolines

This section pertains to synthesis of 2-arylquinolines that are substituted at position 4 with a functionalized amino

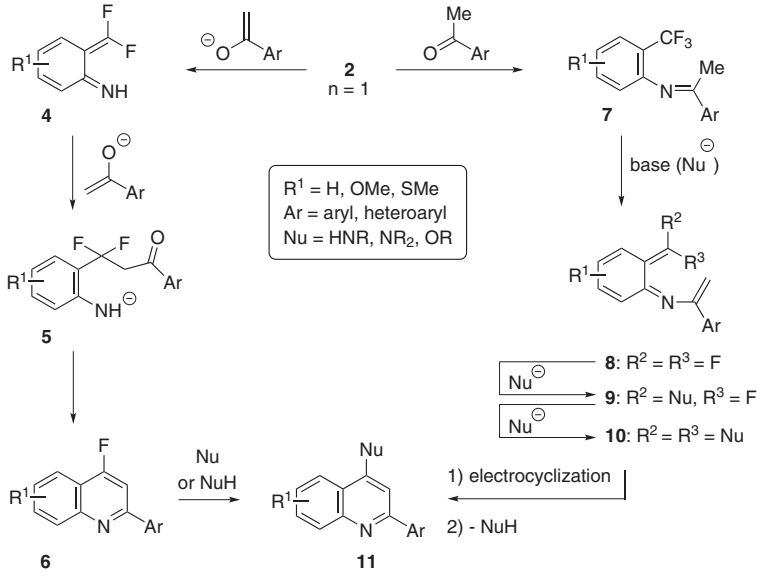


Scheme 1

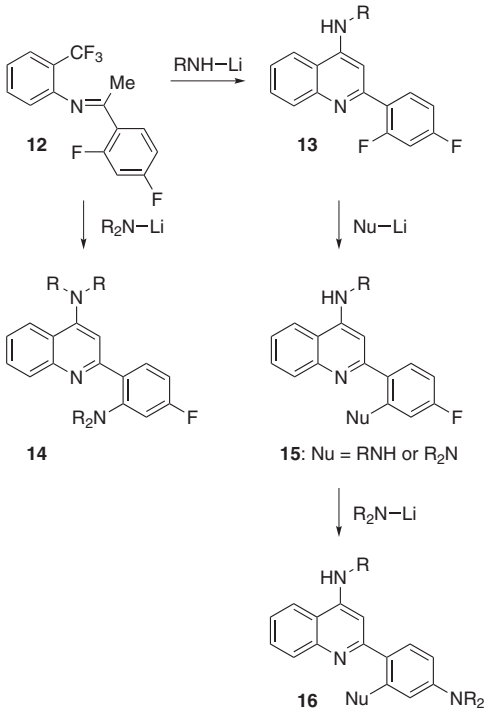
or alkoxy group. The classical synthetic routes to these relatively simple compounds are cumbersome, especially at the workup step, and are limited to the preparation of a small number of derivatives. By contrast, the synthetic routes to 2-arylquinolines, which are based on the chemistry of the anionically activated 2-(trifluoromethyl)anilines **2** or their ketimines, are experimentally simple, efficient, and allow for the introduction of a variety of functionalities at the 2-arylquinoline system (Scheme 2). There are two approaches to the construction of the quinoline ring system with **2** as the substrate. The first methodology is illustrated by the synthesis of 2-aryl-4-fluoroquinoline **6** by the reaction of **2** with lithium enolate of aryl methyl ketone [28, 29]. Briefly, the anion derived from **2** undergoes elimination of fluoride, and then the resultant non-aromatic intermediate product **4** is aromatized by the addition reaction with enolate anion to generate **5**. Quinoline **6** is produced by intramolecular cyclization of **5** followed by aromatization of the cyclized intermediate product. Nucleophilic displacement of fluoride in **6** provides an easy access to 4-substituted quinolines **11**.

Alternatively, quinolines **11** can be efficiently synthesized by base-mediated cyclization of ketimines **7** that are obtained by condensation reaction of **2** with aryl methyl ketones [30, 31]. The resulting quinolines **11** derived from **7** contain either an amino or an oxygen function in position 4, depending on the nature of the strong base utilized for cyclization (lithium alkylamide, lithium dialkylamide, or potassium alkoxide). The mechanistic pathway involves a series of internal nucleophilic processes that generate intermediate products **8**–**10**. It is the adduct **10** that undergoes intramolecular 6π-electron cyclization, as evidenced by the isolation and characterization of intermediate 4,4-disubstituted-3,4-dihydroquinoline [30]. The two methodologies discussed above are quite general in scope, and a large array of other substituted quinolines [29, 32–38] and fused quinolines including acridines [39, 40] can easily be prepared by the reaction of **2** or **7** with various basic/nucleophilic reagents [41–45].

A facile amination of fluorophenyl-substituted quinolines provides an important means for the synthesis of aminophenyl-substituted quinolines. For example, the *ortho*-fluorine atom in a 2,4-difluorophenyl derivative **13**, obtained by treatment of ketimine **12** with a lithium alkylamide, is displaced by the reaction with a lithium alkylamide or lithium dialkylamide to give **15** (Scheme 3).



Scheme 2

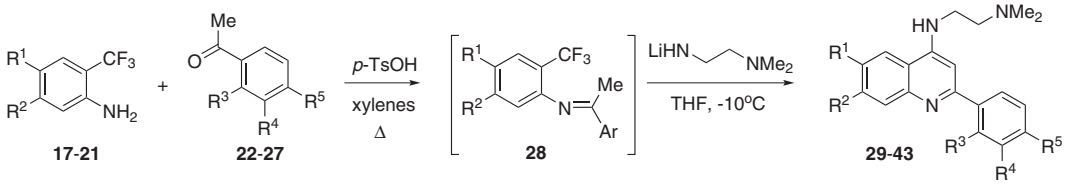


Scheme 3

This nucleophilic displacement proceeds with absolute regioselectivity. A subsequent *ipso* displacement of the remaining fluorine atom in **15**, upon treatment for an extended period with a dialkylamide reagent, produces **16**. The facility of the amination is in the order 2-F>4-F, and it is additionally exemplified by a direct preparation of a 2-(2-aminophenyl)quinoline derivative **14** upon treatment of ketimine **12** with a lithium dialkylamide reagent. The facile regioselective displacement of the *ortho*-fluorine atom in the presence of other fluorine atoms at the phenyl group is explained in terms of a complex induced proximity effect process [46, 47].

A greatly improved preparation of quinolines is illustrated in Scheme 4 [17]. The desired compounds **29–43** were synthesized by condensation of 2-(trifluoromethyl) anilines **17–21** with aryl methyl ketones **22–27** followed by cyclization of the resultant ketimines **28** by treatment with a lithium derivative of 2-(dimethylamino)ethylamine. Previously, this general methodology called for the use of analytically pure intermediate ketimines **28.** It was found that prepurification by a simple bulb-to-bulb distillation, giving **28** of about 90% purity, was adequate for the subsequent cyclization. In addition, tetrahydrofuran was used instead of diethyl ether as solvent in the cyclization reactions of **28**, which resulted in slightly increased yields of the quinoline products. As can be seen from Scheme 4, many substituents at substrates **17–27** are tolerated to give the corresponding substituted quinolines **29–43**.

Synthesis of quinolines described above is based on the chemistry of anionically activated trifluoromethyl group (n=1 in 2, Scheme 1). As shown in Scheme 2, the quinoline system construction is achieved by an



17: $R^1 = R^2 = H$
18: $R^1 = F$; $R^2 = H$
19: $R^1 = Cl$; $R^2 = H$
20: $R^1 = Br$; $R^2 = H$
21: $R^1 = H$; $R^2 = CF_3$

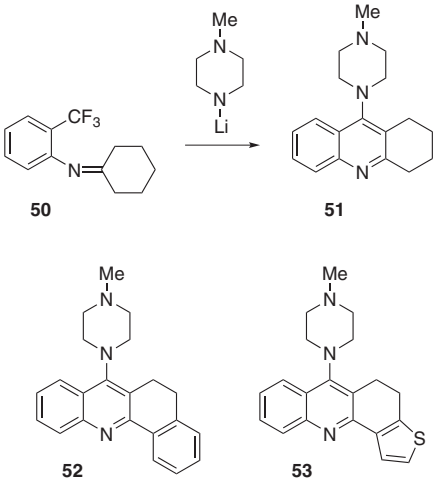
22: $R^3 = Cl$; $R^4 = R^5 = H$
23: $R^3 = F$; $R^4 = H$; $R^5 = OMe$
24: $R^3 = H$; $R^4 = F$; $R^5 = H$
25: $R^3 = H$; $R^4 = F$; $R^5 = OMe$
26: $R^3 = R^4 = H$; $R^5 = F$
27: $R^3 = R^4 = H$; $R^5 = CF_3$

29-43	R^1	R^2	R^3	R^4	R^5
29	H	H	Cl	H	H
30	H	H	F	H	OMe
31	H	H	H	F	OMe
32	H	H	H	H	F
33	H	H	H	H	CF_3
34	F	H	F	H	OMe
35	F	H	H	F	H
36	F	H	H	F	OMe
37	F	H	H	H	CF_3
38	Cl	H	Cl	H	H
39	Cl	H	H	H	F
40	H	CF_3	F	H	OMe
41	H	CF_3	H	F	H
42	H	CF_3	H	F	OMe
43	H	CF_3	H	H	F

Scheme 4

intermolecular cyclization of aniline 2 with lithium enolate or by base-mediated intramolecular cyclization of the corresponding ketimine (Schemes 2 and 4).

Similar transformations of higher 2-(perfluoroalkyl) aniline 2 (n>1) furnish 4-(perfluoroalkyl)quinolines in which the perfluoroalkyl group ($C_{n-1}F_{2n-1}$) is shorter by one carbon atom than that in the starting aniline (C_nF_{2n+1}). These reactions are exemplified in Scheme 5 by the synthesis of 4-(perfluoropropyl)quinolines **44**–**47** by treatment of 2-(perfluorobutyl)aniline (2, n=4, R^1 = H) with various lithium enolates of ketones and by LDA-mediated electrocyclization of the corresponding ketimines **48** and **49** [32].

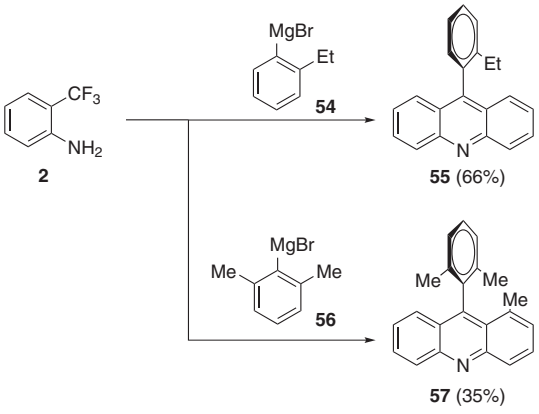


Scheme 6

Synthesis of acridines

Base-mediated cyclization of a ketimine derived from 2-(trifluoromethyl)aniline (**2**, n=1) and an acyclic ketone furnishes a quinoline, as discussed above, but a 1,2,3,4-tetrahydroacridine **51** [31] is produced in a similar transformation of a cyclohexanone derivative **50** (Scheme 6). Tetrahydroacridines **52** [39] and **53** [2] are obtained in a similar manner using the corresponding cyclic ketones. These products are formed in the presence of a lithium alkylamide used as a base and a nucleophile.

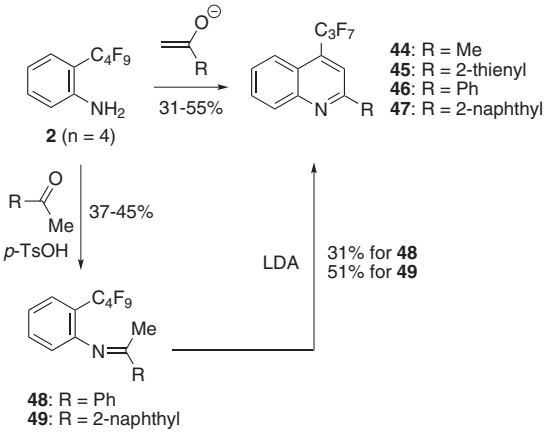
An entirely different reaction is observed upon treatment of the same substrate **2** with phenyl magnesium bromide or chloride that is substituted at position 2 with a methyl or ethyl group or at positions 2 and 6 with the methyl groups [48]. As exemplified in Scheme 7, the reaction of one molecule of **2** with two molecules of 2-ethylphenylmagnesium bromide (**54**) yields a substituted acridine **55** that is devoid of the ethyl group from one of



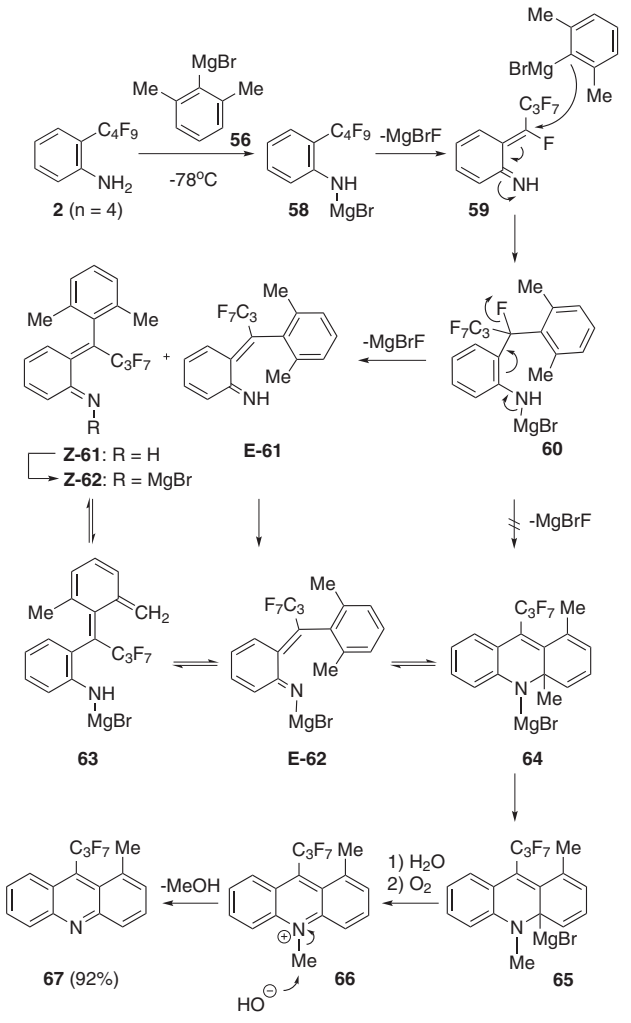
Scheme 7

the molecules of the Grignard reagent that reacted. In a similar way, the treatment of **2** with 2,6-dimethylphenylmagnesium bromide (**56**) furnishes an acridine **57**, the molecular formula of which is shorter by one carbon atom (methyl group) than that of the molecular combination of one molecule of **2** and two molecules of the starting Grignard reagent.

Treatment of a higher homologue **2** (n=4) with the same Grignard reagent **56** produces acridine **67** that is devoid of one of the methyl groups of the two molecules of the Grignard reagent required for this reaction (Scheme 8). The reaction is quite general, and a number of substituted 9-perfluoroalkylacridines have been obtained [49, 50]. The pattern is identical in all cases studied: one alkyl group of the two molecules of the *ortho*-substituted aromatic Grignard reagent is not present in the acridine product, and the 9-($C_{n-1}F_{2n-2}$)-substituted acridine is produced starting with 2-(C_nF_{2n+1})-substituted aniline.



Scheme 5



Scheme 8

Mechanism of this unusual acridine synthesis has been investigated in detail [50] and is shown in Scheme 8 for the particular synthesis of acridine **67** by the reaction of 2-(perfluorobutyl)aniline **2** (n=4) with Grignard reagent **56.** The first step is deprotonation of the aniline, which generates an anionic intermediate product **58.** Elimination of fluoride from the benzylic position of **58** is then followed by nucleophilic addition of the Grignard substrate to the resultant *o*-quinoid intermediate **59.** This reaction gives rise to the aromatic adduct **60**, which can undergo another elimination of fluoride in a way similar to the initial reaction mentioned above to give two *cis* and *trans* isomers **Z-61** and **E-61.** The aza-*ortho*-xylylene **E-61** (half-life of 6 h at 23°C) has been isolated and characterized by spectral methods [50]. It is suggested that these isomers can undergo equilibration under basic conditions by deprotonation of a methyl group and the intermediary of **63.** It is the intermediate product **E-62** (magnesium derivative of **E-61**) that undergoes electrocyclization to generate the non-aromatic acridine derivative **64** (*vide infra*). The methyl shift in **64** to generate *N*-methyl derivative **65** concludes the reaction sequence before workup. Quenching the mixture with water followed by oxidation of the resultant dihydroacridine with molecular oxygen generates *N*-methylacridinium intermediate product **66**, which is the direct precursor to the observed acridine **67.** As can be seen from Scheme 8, acridine **67** is formed in an S_N2 nucleophilic attack of hydroxide ion on the methyl group of **66.** The presumed high reactivity of **66** in nucleophilic substitution reaction is expected because the positive charge of the leaving group (acridine **67**) and, therefore, its leaving ability is strongly enhanced by the presence of an electron-withdrawing perfluoroalkyl group. An important result of this analysis is that the mysterious lack of a methyl group in the product is due to removal of this group in the form of a methanol molecule. The reaction leading to 9-arylacridines (Scheme 7) may follow a similar mechanism.

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