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SIMPLE SYNTHESES OF 3-TRIFLUOROACETYL-4-QUINOLYL-AMINES, SULFIDES, AND ETHERS STARTING FROM *N*,*N*-DIMETHYL-4-QUINOLYLAMINE

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Abstract – New 3-trifluoroacetyl-4-quinolylamines (**2**), sulfides (**3**), and ethers (**4**) were synthesized in good to high yields by aromatic nucleophilic substitution reactions of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**), which was easily prepared by acylation of *N*,*N*-dimethyl-4-quinolylamine with 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate, with amines, thiols, alcohols, and phenols.

INTRODUCTION

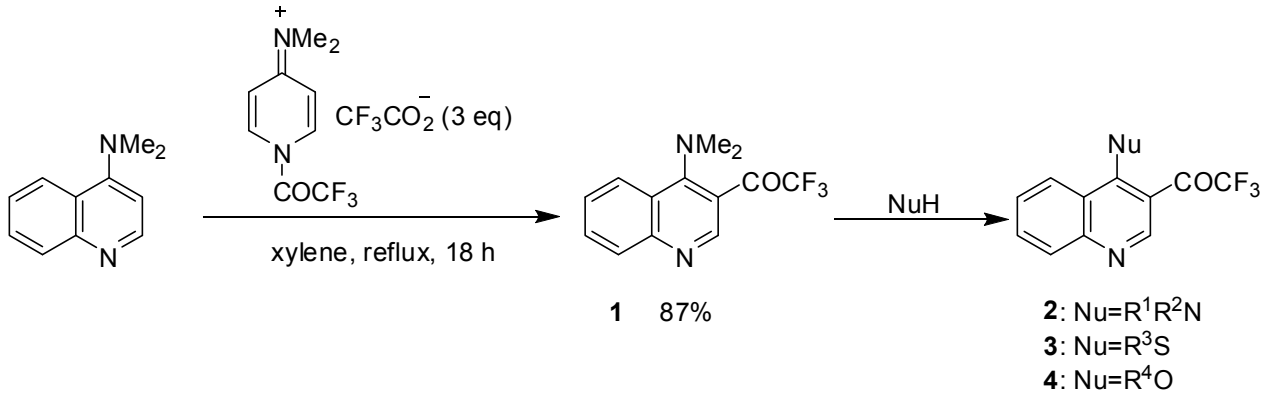
Malaria remains one of the most important widespread infectious diseases and a great public health problem worldwide, particularly in Africa and south Asia.[1] 4-Aminoquinolines and their analogues have been greatly used as the basis in the molecular design for the synthetic antimalarial compounds.[2] The most important 4-aminoquinoline antimalarials, chloroquine, has remains as a major chemotherapeutic agent for over 50 years. However, it has lost much of its value by emergence of chloroquine-resistant *Plasmodium falciparum*. Therefore, there is the necessity for the urgent development of new alternative antimalarial drugs.[3] Moreover, in recent years, considerable attention has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[4] Previously, we have found that in *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthyl-amine and *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-8-quinolylamine activated by trifluoroacetyl group, the dimethylamino group, which is not generally lost in aromatic systems, actually behaves as an excellent

leaving group and undergo the novel aromatic nucleophilic substitutions with various nucleophiles including amines.[5] In this situation, we have reported that the synthesis of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**) and its aromatic nucleophilic *N*-*N* exchange reaction with amines to give the corresponding 3-trifluoroacetyl-4-quinolylamines (**2**) in high yields.[6] Herein we report a full account of our systematic studies on this type of aromatic nucleophilic substitutions, including the new finding of the reactions of **1** with thiols, alcohols, and phenols which are considerably less reactive than amines, to afford various 4-quinoline derivatives (**2**-**4**), substituted with a trifluoroacetyl group at the 3-position. This substituent might regulate important biological functions and might increase the biological activity of this type of heterocyclic compounds, being similar to a phosphine oxide group in behavior.[7]

RESULTS AND DISCUSSION

Firstly, the synthesis of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**) was attempted. Trifluoroacetylation of *N*,*N*-dimethyl-4-quinolylamine with general electrophilic trifluoroacetylating reagent, trifluoroacetic anhydride, resulted in almost no reactions. Fortunately, as depicted in Scheme 1, the desired acylation with a novel agent, 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate,[8] which was generated *in situ*, was successfully performed to give 3-trifluoroacetylated *N*,*N*-dimethyl-4-quinolylamine (**1**) in 87% yield. Many heterocycles such as furans, pyrans, thiophenes, pyrroles, and indoles, except for quinolines and pyridines, can be acylated in good yields.[9] Electrophilic substitution of quinolines takes place preferentially in the carbocyclic rings because the reactivity of pyridine is much less than that of benzene due to the electron deficiency of the former.[10] Trifluoroacetylation in the pyridine ring of quinolines had never been reported and this became the first example.[6]

Next, we examined the aromatic nucleophilic *N*-*N* exchange reaction of **1** with various amines to prepare a variety of 3-trifluoroacetylated 4-quinolylamines (Scheme 1, Table 1). Reaction of **1** with ammonia occurred readily at 50 °C for 18 h to give the Me_2N-NH_2 exchanged product (**2a**) in 81% yield (Entry 1). The *N*-*N* exchange reactions of aliphatic primary amines such as methyl-, ethyl-, benzyl-, and isopropylamines took place more easily even at room temperature within 8 h to afford the desired 4-quinolylamine derivatives (**2b-e**) in over 93% yields (Entries 2-5). Bulky *tert*-butylamine also reacted cleanly to provide **2f** by merely elevating reaction temperature (100 °C) and elongating reaction time (72 h) (Entry 6). More functionalized *N*-allyl-4-quinolylamines (**2g**) was easily synthesized in 93% yield from **1** and allylamine (Entry 7). In propargylamine, the reaction was performed in refluxing acetonitrile to obtain exclusively the desired product (**2h**) (Entry 8). While secondary amines showed lower reactivity than primary ones in the present system, pyrrolidine revealed considerable enhanced reactivity



Scheme 1

Table 1. *N-N* Exchange reaction of *N,N*-dimethyl-3-trifluoroacetyl-4-quinolylamine **1** with amines

Entry	R^1	R^2	R^1R^2NH (eq)	Temp. (°C)	Time (h)	Solvent	Product	Yield[a] (%)
1[b]	H	H	3	50	18	MeCN	**2a**	81
2[b]	Me	H	1	rt	4	MeCN	**2b**	96
3[b]	Et	H	1	rt	4	MeCN	**2c**	93
4	$PhCH_2$	H	1	rt	3	MeCN	**2d**	94
5	*i*-Pr	H	3	rt	8	MeCN	**2e**	98
6	*t*-Bu	H	3	100[c]	72	MeCN	**2f**	75
7	CH_2=$CHCH_2$	H	3	rt	4	MeCN	**2g**	93
8	CH≡CCH_2	H	3	reflux	4	MeCN	**2h**	96
9	$-(CH_2)_4-$		3	reflux	8	MeCN	**2i**	91
10	*p*-$MeOC_6H_4$	H	3	reflux	48	MeCN	**2j**	99
11[d]	EtO_2CCH_2	H	3	rt	4	MeCN-H_2O	**2k**	92

a) Isolated yields.
b) Aqueous solutions of ammonia (28%), methylamine (40%), and ethylamine (70%) were used.
c) In a sealed tube.
d) Hydrochloride of ethyl glycinate was used in the presence of sodium acetate (3 eq) in MeCN-H_2O.

to afford **2i** in 91% yield (Entry 9). Aromatic amines such as *p*-substituted anilines, for example, *p*-anisidine underwent cleanly the desired dimethylamino–*p*-methoxyphenylamino exchange under not much forced conditions to give the corresponding *N*-(*p*-methoxyphenyl)-4-quinolylamine derivative (**2j**) in almost quantitative yield (Entry 10). This reaction can also be applicable to amino acids. For instance, reaction of **1** with ethyl glycinate hydrochloride in the presence of sodium acetate proceed very readily at room temperature to provide ethyl *N*-(3-trifluoroacetyl-4-quinolyl)glycinate (**2k**) in 92% yield (Entry 11).

Moreover, we attempted to carry out the *N-S* exchange reactions of **1** with various thiols (Table 2). Reactions of **1** with phenylmethanethiol took place in refluxing acetonitrile within 24 h to afford the desired benzyl 3-trifluoroacetyl-4-quinolyl sulfide (**3a**) in 83% yield (Entry 1). In the case of

Table 2. *N-S* Exchange reaction of *N,N*-dimethyl-3-trifluoroacetyl-4-quinolylamine **1** with thiols

Entry	R^3	R^3SH (eq)	Temp. (°C)	Time (h)	Solvent	Product	Yield[a] (%)
1	$PhCH_2$	1	reflux	24	MeCN	**3a**	83
2	*n*-Bu	5	100	96	PrCN	**3b**	62
3	*p*-$MeOC_6H_4$	1	reflux	48	toluene	**3c**	97
4	*p*-MeC_6H_4	1	reflux	48	toluene	**3d**	95
5	Ph	3	reflux	48	toluene	**3e**	90
6	*p*-ClC_6H_4	3	reflux	48	toluene	**3f**	100
7	*p*-$NO_2C_6H_4$	3	reflux	48	toluene	**3g**	81

a) Isolated yields.

n-butanethiol, the reaction was easily performed with a larger amount of reagent (5 eq), at a higher temperature (100 °C) and for an extended time (96 h) to provide **3b** in 62% yield (Entry 2). Aromatic thiols, *p*-substituted benzenethiols, also underwent cleanly the dimethylamino-arylthio exchanges for 48 h in refluxing toluene to give the corresponding aryl 3-trifluoroacetyl-4-quinolyl sulfides (**3c-g**) in excellent yields (Entries 3-7).

Lastly, the present aromatic nucleophilic substitutions were applied to alcohols and phenols (Table 3). In spite of the fairly low reactivities of alcohols, compared with the corresponding amines and thiols, the *N-O* exchange reaction of **1** with them, e. g. *n*-butyl, phenethyl and 2-phenoxyethyl alcohols, proceeded cleanly without the aid of base at reflux temperature in xylene to provide the corresponding 3-trifluoroacetyl-4-quinolyl ethers (**4b-d**) in good to high yields (Entries 2-4). In the case of *n*-propyl alcohol, however, the desired *N-O* exchange reaction could barely proceed in refluxing xylene. The attempted alcoholysis of **1** under reflux was successful and the desired ether (**4a**) was prepared in 72% yield (Entry 1). *p*-Substituted phenols such as *p*-methoxyphenol and *p*-cresol also underwent easily the dimethylamino-aryloxy exchanges under relatively mild conditions to give the corresponding aryl 3-trifluoroacetyl-4-quinolyl ethers (**4e** and **4f**) in 77% and 59% yields, respectively (Entries 5 and 6).

Table 3. *N-O* Exchange reaction of *N,N*-dimethyl-3-trifluoroacetyl-4-quinolylamine **1** with alcohols and phenols

Entry	R^4	R^4OH (eq)	Temp. (°C)	Time (h)	Solvent	Product	Yield[a] (%)
1	*n*-Pr	98	reflux	168	*n*-PrOH	**4a**	72
2	*n*-Bu	10	reflux	72	xylene	**4b**	89
3	$PhCH_2CH_2$	10	reflux	48	xylene	**4c**	88
4	$PhOCH_2CH_2$	10	reflux	72	xylene	**4d**	77
5	*p*-$MeOC_6H_4$	5	reflux	96	xylene	**4e**	77
6	*p*-MeC_6H_4	5	reflux	96	xylene	**4f**	59

a) Isolated yields.

Thus, we succeeded in extending the novel aromatic nucleophilic substitutions of **1** with amines to those with thiols, alcohols, and phenols and in providing an efficient synthetic method for various 3-trifluoroacetyl-4-quinolylamines, sulfides, and ethers, which are not easily accessible by other methods. The present synthetic route is very simple and consists of only two steps, novel trifluoroacetylation of *N*,*N*-dimethyl-4-quinolylamine and subsequent aromatic nucleophile *N*-*N*, *N*-*S*, and *N*-*O* exchange reactions. Further work is currently being continued in our laboratory.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra was obtained with JEOL PMX 60SI and Bruker Avance 500 spectrometers; TMS was used as an internal standard. IR spectra were recorded on Hitachi EPI-G3 and PerkinElmer Spectrum ONE spectrophotometers. Microanalyses were obtained with a Yanaco CHN-Coder MT-5 analyzer.

4-Dimethylamino-3-trifluoroacetylquinoline (1): To a solution of 4-dimethylaminopyridine (1833 mg, 15 mmol) in xylene (30 mL) was added trifluoroacetic anhydride (3150 mg, 15 mmol) and the solution was stirred at room temperature for 0.5 h to generate 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate. To the stirred suspension was added the solution of 4-dimethylaminoquinoline (862 mg, 5 mmol) in xylene (10 mL) and the mixture was refluxed for 18 h. After removal of the solvent under reduced pressure, CH_2Cl_2 (100 mL) was added to the residue. The solution was washed with 20% aq Na_2CO_3 (50 mL), dried (Na_2SO_4) and evaporated to give the crude mixture, which was purified by chromatography on silica gel using *n*-hexane/EtOAc (3:1) and EtOAc to afford **1** (1167 mg, 87%). **1**: mp 98-99 °C (*n*-hexane/EtOAc); IR (KBr): 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.97 (q, J = 2.0 Hz, 1H, H-2), 8.33-8.00 (m, 2H, H-5, H-8), 7.90-7.38 (m, 2H, H-6, H-7), 3.17 (s, 6H, CH_3); Anal Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.27; H, 4.31; N, 10.20.

***N*-*N* Exchange Reaction of 1 with Amines; General Procedure**

To a solution of **1** (268 mg, 1 mmol) in MeCN (7 mL) was added the appropriate amines (1-3 mmol) and the mixture was stirred at room temperature-reflux temperature for 3-48 h. The solvent was evaporated in vacuo to give the practically pure products **2b-e**, **h**, **j**, **k**. In the case of **2a**, **g**, **i**, the crude product was chromatographed using *n*-hexane:EtOAc, 4:1 for **2a**, **i** and *n*-hexane:EtOAc, 6:1 for **2g**, as eluent.

Using tert-Butylamine: To a solution of **1** (268 mg, 1 mmol) in MeCN (7 mL) was added *tert*-butylamine (219 mg, 3 mmol) and the mixture was heated in a sealed tube at 100 °C for 72 h. The solvent was evaporated in vacuo and the crude product was chromatographed using EtOAc as eluent to give **2f**.

1-(4-Aminoquinolin-3-yl)-2,2,2-trifluoroethanone (2a): mp 240-241 °C (*n*-hexane/EtOAc); IR (KBr): 3400, 3300, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.10-8.85 (m, 1H, H-2), 8.17-7.47 (m, 4H, H-5, H-6, H-7, H-8). Anal. Calcd for $C_{11}H_7F_3N_2O$: C, 55.01; H, 2.94; N, 11.66. Found: C, 55.06; H, 3.24; N, 11.85.

2,2,2-Trifluoro-1-(4-(methylamino)quinolin-3-yl)ethanone (2b): mp 127-128 °C (*n*-hexane/EtOAc); IR (KBr): 3120, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.17-10.13 (br, 1H, NH), 9.19-8.86 (br, 1H, H-2), 8.43-8.25 (m, 1H, H-8), 8.03-7.25 (m, 3H, H-5, H-6, H-7), 3.62 (d, J = 6.0 Hz, 3H, CH_3). Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.92; H, 3.60; N, 11.40.

1-(4-(Ethylamino)quinolin-3-yl)-2,2,2-trifluoroethanone (2c): mp 100-101 °C (*n*-hexane/EtOAc); IR (KBr): 3230, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.90-10.10 (br, 1H, NH), 8.90 (br s, 1H, H-2), 8.23 (d, J = 8.0 Hz, 1H, H-8), 8.00-7.16 (m, 3H, H-5, H-6, H-7), 3.97, 3.90 (dq, J = 7.0, 7.0 Hz, 2H, CH_2), 1.47 (t, J = 7.0 Hz, 3H, CH_3). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.24; H, 4.38; N, 10.14.

1-(4-(Benzylamino)quinolin-3-yl)-2,2,2-trifluoroethanone (2d): mp 148-149 °C (*n*-hexane/EtOAc); IR (KBr): 3165, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.10-10.57 (br, 1H, NH), 8.93 (br s, 1H, H-2), 8.33-7.13 (m, 9H, H-5, H-6, H-7, H-8, Ph), 5.10 (d, J = 5.6 Hz, 2H, CH_2). Anal. Calcd for $C_{18}H_{13}F_3N_2O$: C, 65.45; H, 3.97; N, 8.48. Found: C, 65.37; H, 4.19; N, 8.33.

2,2,2-Trifluoro-1-(4-(isopropylamino)quinolin-3-yl)ethanone (2e): mp 101-102 °C (*n*-hexane/EtOAc); IR (KBr): 3210, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.95-10.38 (m, 1H, NH), 9.38-8.65 (m, 1H, H-2), 8.32-7.28 (m, 4H, H-5, H-6, H-7, H-8), 4.88-4.48 (m, 1H, CH), 1.52 (d, J = 6.0 Hz, 6H, CH_3). Anal. Calcd for $C_{14}H_{13}F_3N_2O$: C, 59.57; H, 4.64; N, 9.93. Found: C, 59.74; H, 4.69; N, 9.70.

1-(4-(*tert*-Butylamino)quinolin-3-yl)-2,2,2-trifluoroethanone (2f): mp 136-137 °C (*n*-hexane/EtOAc); IR (KBr): 3080, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.62-10.05 (m, 1H, NH), 8.99 (br s, 1H, H-2), 8.35-7.30 (m, 4H, H-5, H-6, H-7, H-8), 1.58 (s, 9H, CH_3). Anal. Calcd for $C_{15}H_{15}F_3N_2O$: C, 60.81; H, 5.10; N, 9.46. Found: C, 60.88; H, 5.07; N, 9.41.

1-(4-(Allylamino)quinolin-3-yl)-2,2,2-trifluoroethanone (2g): mp 146-147 °C (*n*-hexane/EtOAc); IR (KBr): 3096, 1628 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.12-10.18 (br, 1H, NH), 8.91 (q, J = 2.0 Hz, 1H, H-2), 8.28-7.23 (m, 4H, H-5, H-6, H-7, H-8), 6.43-5.30 (m, 3H, $CH=CH_2$), 4.63-4.45 (m, 2H, CH_2). Anal. Calcd for $C_{14}H_{11}F_3N_2O$: C, 60.00; H, 3.96; N, 10.00. Found: C, 60.31; H, 4.04; N, 10.25.

2,2,2-Trifluoro-1-(4-(prop-2-ynylamino)quinolin-3-yl)ethanone (2h): mp 167-168 °C (*n*-hexane/EtOAc); IR (KBr): 3195, 3080, 2115, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.95-10.05 (br, 1H, NH), 8.96 (q, J = 2.0 Hz, 1H, H-2), 8.50-8.30 (m, 1H, H-8), 8.10-7.30 (m, 3H, H-5, H-6, H-7), 4.63 (dd, J = 2.0, 6.0 Hz, 2H, CH_2), 2.55 (t, J = 2.0 Hz, 1H, CH). Anal. Calcd for $C_{14}H_9F_3N_2O$: C, 60.44; H, 3.26; N, 10.07. Found: C, 60.19; H, 3.47; N, 10.13.

2,2,2-Trifluoro-1-(4-(pyrrolidin-1-yl)quinolin-3-yl)ethanone (2i): mp 123-124 °C (*n*-hexane/EtOAc); IR (KBr): 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.88 (q, J = 2.0 Hz, 1H, H-2), 8.15-7.18 (m, 4H, H-5, H-6, H-7, H-8), 3.75-3.52 (m, 4H, CH_2), 2.15-1.88 (m, 4H, CH_2). Anal. Calcd for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.13; H, 4.43; N, 9.77.

2,2,2-Trifluoro-1-(4-(4-methoxyphenylamino)quinolin-3-yl)ethanone (2j): mp 150-151 °C (*n*-hexane/EtOAc); IR (KBr): 3087, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.61 (br s, 1H, NH), 9.07 (q, *J* = 2.0 Hz, 1H, H-2), 8.02-7.50 (m, 3H, H-5, H-7, H-8), 7.23-6.83 (m, 5H, H-6, C_6H_4), 3.85 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.25; H, 3.83; N, 8.08.

Ethyl 2-(3-(2,2,2-trifluoroacetyl)quinolin-4-ylamino)acetate (2k): mp 151-152 °C (*n*-hexane/EtOAc); IR (KBr): 3044, 1728, 1648 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.13-10.60 (m, 1H, NH), 8.97 (br s, 1H, H-2), 8.23-7.10 (m, 4H, H-5, H-6, H-7, H-8), 4.68 (d, *J* = 4.0 Hz, 2H, CH_2), 4.33 (q, *J* = 7.0 Hz, 2H, $C\underline{H_2}CH_3$), 1.33 (t, *J* = 7.0 Hz, 3H, CH_3). Anal. Calcd for $C_{15}H_{13}F_3N_2O_3$: C, 55.22; H, 4.02; N, 8.59. Found: C, 55.26; H, 3.99; N, 8.58.

***N*-*S* Exchange Reaction of 1 with Thiols; General Procedure**

To a solution of **1** (268 mg, 1 mmol) in toluene (7 mL) was added the appropriate thiols (1-5 mmol) and the mixture was stirred at 100 °C-reflux temperature for 24-96 h. The solvent was evaporated in vacuo and the crude product was chromatographed using *n*-hexane:EtOAc, 15:1 for **3a**, **b** and *n*-hexane:EtOAc, 5:1 for **3c-f** and EtOAc for **3g**, as eluent. In the case of **3a**, **b**, MeCN and PrCN were used as solvents, respectively.

1-(4-(Benzylthio)quinolin-3-yl)-2,2,2-trifluoroethanone (3a): mp 59-60 °C (*n*-hexane/EtOAc); IR (KBr): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.86 (s, 1H, H-2), 8.53-8.40 (m, 1H, H-8), 8.30-8.07 (m, 1H, H-5), 8.05-7.50 (m, 2H, H-6, H-7), 7.33-6.83 (m, 5H, Ph), 4.07 (s, 2H, CH_2). Anal. Calcd for $C_{18}H_{12}F_3NOS$: C, 62.24; H, 3.48; N, 4.03. Found: C, 62.25; H, 3.61; N, 3.97.

1-(4-(Butylthio)quinolin-3-yl)-2,2,2-trifluoroethanone (3b): bp 150 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.83 (s, 1H, H-2), 8.63-8.40 (m, 1H, H-8), 8.23-8.03 (m, 1H, H-5), 7.95-7.53 (m, 2H, H-6, H-7), 3.13-2.80 (m, 2H, SCH_2), 1.80-0.73 (m, 7H, $CH_2CH_2CH_3$). Anal. Calcd for $C_{15}H_{14}F_3NOS$: C, 57.50; H, 4.50; N, 4.47. Found: C, 57.10; H, 4.65; N, 4.71.

2,2,2-Trifluoro-1-(4-(4-methoxyphenylthio)quinolin-3-yl)ethanone (3c): bp 175 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.90 (s, 1H, H-2), 8.57-8.33 (m, 1H, H-8), 8.30-8.07 (m, 1H, H-5), 8.00-7.40 (m, 2H, H-6, H-7), 7.60-6.55 (m, 4H, C_6H_4), 3.87 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{12}F_3NO_2S$: C, 59.50; H, 3.33; N, 3.86. Found: C, 59.37; H, 3.58; N, 3.73.

2,2,2-Trifluoro-1-(4-(*p*-tolylthio)quinolin-3-yl)ethanone (3d): bp 170 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.97 (s, 1H, H-2), 8.50-8.10 (m, 2H, H-5, H-8), 7.96-7.41 (m, 2H, H-6, H-7), 7.07 (s, 4H, C_6H_4), 2.27 (s, 3H, CH_3). Anal. Calcd for $C_{18}H_{12}F_3NOS$: C, 62.23; H, 3.48; N, 4.03. Found: C, 62.07; H, 3.82; N, 4.26.

2,2,2-Trifluoro-1-(4-(phenylthio)quinolin-3-yl)ethanone (3e): mp 63-64 °C (*n*-hexane/EtOAc); IR (KBr): 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.93 (s, 1H, H-2), 8.50-8.03 (m, 2H, H-5, H-8), 7.97-7.50 (m, 2H,

H-6, H-7), 7.17 (br s, 5H, C_6H_5). Anal. Calcd for $C_{17}H_{10}F_3NOS$: C, 61.26; H, 3.02; N, 4.20. Found: C, 61.28; H, 3.09; N, 4.12.

1-(4-(4-Chlorophenylthio)quinolin-3-yl)-2,2,2-trifluoroethanone (3f): mp 57-58 °C (*n*-hexane/EtOAc); IR (KBr): 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.97 (s, 1H, H-2), 8.40-8.07 (m, 2H, H-5, H-8), 8.00-7.40 (m, 2H, H-6, H-7), 7.30-6.93 (m, 4H, C_6H_4). Anal. Calcd for $C_{17}H_9ClF_3NOS$: C, 55.52; H, 2.47; N, 3.81. Found: C, 55.15; H, 2.72; N, 3.93.

2,2,2-Trifluoro-1-(4-(4-nitrophenylthio)quinolin-3-yl)ethanone (3g): bp 175 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H, H-2), 8.33-7.03 (m, 8H, H-5, H-6, H-7, H-8, C_6H_4). Anal. Calcd for $C_{17}H_9F_3N_2O_3S$: C, 53.97; H, 2.40; N, 7.40. Found: C, 53.99; H, 2.44; N, 7.45.

***N-O* Exchange Reaction of 1 with Alcohols; General Procedure**

To a solution of **1** (268 mg, 1 mmol) in xylene (7 mL) was added the appropriate alcohols (5-98 mmol) and the mixture was stirred at reflux temperature for 48-168 h. The solvent was evaporated in vacuo and the crude product was chromatographed using *n*-hexane:EtOAc, 30:1 for **4a**, **b** and *n*-hexane:EtOAc, 5:1 for **4c-f**, as eluent. In the case of **4a**, *n*-PrOH was used as solvent.

2,2,2-Trifluoro-1-(4-propoxyquinolin-3-yl)ethanone (4a): bp 140 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.03 (s, 1H, H-2), 8.33-7.27 (m, 4H, H-5, H-6, H-7, H-8), 4.23-4.00 (m, 2H, OCH_2), 2.23-1.67 (m, 2H, CH_2), 1.23-0.99 (m, 3H, CH_3). Anal. Calcd for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.08; H, 4.39; N, 5.12.

1-(4-Butoxyquinolin-3-yl)-2,2,2-trifluoroethanone (4b): mp 67-68 °C (*n*-hexane/EtOAc); IR (KBr): (hydrate form) 3421 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.07 (q, J = 2.0 Hz, 1H, H-2), 8.38-7.48 (m, 4H, H-5, H-6, H-7, H-8), 4.17 (t, J = 6.0 Hz, 2H, OCH_2), 2.13-0.83 (m, 7H, $CH_2CH_2CH_3$). Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 60.60; H, 4.75; N, 4.71. Found: C, 60.24; H, 4.99; N, 4.85.

2,2,2-Trifluoro-1-(4-(phenethyloxy)quinolin-3-yl)ethanone (4c): bp 135 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.04 (q, J = 2.0 Hz, 1H, H-2), 8.17-7.27 (m, 9H, H-5, H-6, H-7, H-8, Ph), 4.36 (t, J = 7.0 Hz, 2H, OCH_2), 3.22 (t, J = 7.0 Hz, 2H, CH_2). Anal. Calcd for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09; N, 4.06. Found: C, 65.79; H, 4.42; N, 4.03.

2,2,2-Trifluoro-1-(4-(2-phenoxyethoxy)quinolin-3-yl)ethanone (4d): mp 104-106 °C (*n*-hexane/EtOAc); IR (KBr): (hydrate form) 3440 cm^{-1}; ^1H NMR ($CDCl_3$ and CD_3CN): δ (hydrate form) 9.10 (br s, 1H, H-2), 8.53-6.79 (m, 9H, H-5, H-6, H-7, H-8, Ph), 4.77-4.30 (m, 4H, CH_2CH_2), 2.90-1.83 (br, 2H, OH). Anal. Calcd for $C_{19}H_{16}F_3NO_4$ (hydrate form): C, 60.16; H, 4.25; N, 3.69. Found: C, 59.16; H, 4.25; N, 3.67.

2,2,2-Trifluoro-1-(4-(4-methoxyphenoxy)quinolin-3-yl)ethanone (4e): bp 150 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1737 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H, H-2), 8.21-7.29 (m, 4H,

H-5, H-6, H-7, H-8), 6.77 (s, 4H, C_6H_4), 3.70 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03. Found: C, 62.06; H, 3.84; N, 3.86.

2,2,2-Trifluoro-1-(4-(*p*-tolyloxy)quinolin-3-yl)ethanone (4f): bp 150 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.20 (br s, 1H, H-2), 8.32-6.70 (m, 8H, H-5, H-6, H-7, H-8, C_6H_4), 2.28 (s, 3H, CH_3). Anal. Calcd for $C_{18}H_{12}F_3NO_2$: C, 65.26; H, 3.65; N, 4.23. Found: C, 65.06; H, 3.70; N, 3.99.

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