A Simple Synthetic Method for 3-Trifluoroacetylated 4-Aminoquinolines from 4-Dimethylaminoquinoline by Novel Trifluoroacetylation and N-N Exchange Reactions

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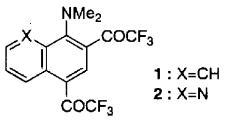
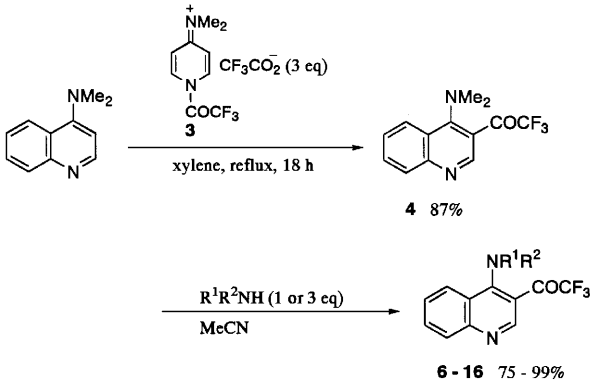
Acylation of 4-dimethylaminoquinoline with 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate proceeded cleanly to give 3-trifluoroacetyl-4-dimethylaminoquinoline, which underwent nucleophilic aromatic substitutions with various amines to afford the corresponding N-N exchanged 3-trifluoroacetyl-4-aminoquinolines in excellent yields.

Malaria remains one of the most important widespread diseases in the world.[1] 4-Aminoquinolines have been greatly used as the basis in the molecular design for synthetic antimalarial compounds.[2] The most important 4-aminoquinoline antimalarials, chloroquine, has remained as a major chemotherapeutic agent for over 40 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 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 1-aminonaphthalenes **1** and 8-aminoquinolines **2** activated by trifluoroacetyl group, the dimethylamino group, which is not generally lost in aromatic systems, actually behaves as an excellent leaving group and undergoes the novel aromatic nucleophilic substitutions with various nucleophiles including amines.[5] This situation prompted strongly us to investigate the design of various novel 4-aminoquinoline derivatives **4** and **6 - 16**, 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 compound, being similar to a phosphine oxide group in behavior.[6]



The present synthetic route is very simple and consists of only two steps, novel trifluoroacetylation of 4-dimethylaminoquinoline and subsequent aromatic nucleophilic N-N exchange reaction. Many heterocycles such as furans, pyrans, thiophenes, pyrroles, and indoles, except for quinolines and pyridines, can be acylated in good yields.[7] 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.[8] Trifluoroacetylation in the pyridine ring of quinolines has not been reported in the past.

Firstly, synthesis of 3-trifluroacetylated 4-dimethylaminoquinoline **4** was attempted. Trifluoroacetylation of 4-dimethylaminoquinoline 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 **3**,[9] which was generated *in situ*, was successfully performed to give 3-trifluoroacetyl-4-dimethylaminoquinoline **4**[10] in 87% yield with the formation of 3-trifluoroacetyl-4-dimethylaminopyridine **5**[11] as a by-product. The yield was nearly optimized under the indicated conditions. For example, the reaction was run for 12 h in refluxing toluene to afford only 21% yield of **4**.



Scheme 1.

Secondly, we examined the aromatic nucleophilic N-N exchange reaction of **4** with various amines to prepare a variety of 3-trifluoroacetylated 4-aminoquinolines and the results are shown in Scheme 1 and summarized in Table 1.[12] Reaction of **4** with ammonia occurred readily at 50 °C for 18 h to give the Me_2N-NH_2 exchanged product **6** 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-aminoquinoline derivatives **7 - 10** in over 93% yields (Entries 2-5). Bulky *tert*-butylamine also reacted cleanly to provide **11** by merely elevating reaction temperature (100 °C) and elongating reaction time (72 h) (Entry 6). More functionalized 4-allylaminoquinolines **12** was easily synthesized in 93% yield from **4** and allylamine (Entry 7). In propargylamine, the reaction was performed in refluxing acetonitrile to obtain exclusively the desired product **13** (Entry 8). While secondary amines showed lower reactivity than primary ones in the present system, pyrrolidine revealed considerable enhanced reactivity to afford **14** 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 corre-

Table 1. N-N Exchange reaction of 3-trifluoroacetyl-4-dimethylaminoquinoline **4** with amines

Entry	Amine (R^1R^2NH)[a]	Molar Ratio[b]	Temp / °C	Time / h	Product	Yield / %[c]
1	NH_3	3	50	18	**6**	81
2	$MeNH_2$	1	rt	4	**7**	96
3	$EtNH_2$	1	rt	4	**8**	93
4	$PhCH_2NH_2$	1	rt	3	**9**	94
5	*i*-$PrNH_2$	3	rt	8	**10**	98
6	*t*-$BuNH_2$	3	100[d]	72	**11**	75
7	$CH_2{=}CHCH_2NH_2$	3	rt	4	**12**	93
8	$CH{\equiv}CCH_2NH_2$	3	reflux	4	**13**	96
9		3	reflux	8	**14**	91
10	*p*-$MeOC_6H_4NH_2$	3	reflux	48	**15**	99
11	$EtO_2CCH_2NH_2$[e]	3	rt	4	**16**	92

[a]Aqueous solutions of ammonia (28%), methylamine (40%), and ethylamine (70%) were used. [b][R^1R^2NH] / [**4**]. [c]Isolated yields. [d]In a sealed tube. [e]Hydrochloride of ethyl glycinate was used in the presence of sodium acetate (3 eq) in MeCN-H_2O.

sponding 4-(*p*-anisidino)quinoline derivative **15** in almost quantitative yield (Entry 10). This reaction can also be applicable to amino acids. For instance, reaction of **4** with ethyl glycinate hydrochloride in the presence of sodium acetate proceeded very readily at room temperature to provide ethyl *N*-[3-trifluoroacetyl-4-quinolyl]glycinate **16** in 92% yield (Entry 11). It seems noteworthy that this type of N-N exchange reaction did not occur under considerably forced conditions in 3-trifluoroacetyl-4-dimethylaminopyridine **5**.[13]

Thus, we have developed a simple and efficient access to 3-trifluoroacetyl-4-aminoquinolines **4** and **6 - 16**, which are not easily accessible by other methods, in two steps, the novel trifluoroacetylation and N-N exchange reactions, starting from 4-dimethylaminoquinoline. Further works on the synthetic application of **4** to the fluorine-containing heterocycles having a quinoline skeleton such as diazepinoquinolines and pyrazoloquinolines are currently continued in our laboratory and the results will be published elsewhere in our forthcoming papers.

References and Notes

1 L. H. Miller, M. F. Good, and G. Milon, *Science*, **264**, 1878 (1994).

2 D. J. Krogstad, I. Y. Gluzman, D. E. Kyle, A. M. J. Oduola, S. K. Martin, W. K. Milhous, and P. H. Schlesinger, *Science*, **238**, 1283 (1987); D. De, J. T. Mague, L. D. Byers, and D. J. Krogstad, *Tetrahedron Lett.*, **36**, 205 (1995).

3 For recent examples: P. M. O'Neill, P. G. Bray, S. R. Hawley, S. A. Ward, and B. K. Park, *Pharmacol. Ther.* , **77**, 29 (1998); D. De, F. M. Krogstad, L. D. Byers, and D. J. Krogstad, *J. Med. Chem.*, **41**, 4918 (1998); T. O. Nguyen, J. D. Capra, and R. D. Sontheimer, *Lupus*, **7**, 148 (1998); D. De, L. D. Byers, and D. J. Krogstad, *J. Heterocycl. Chem.*, **34**, 315 (1997).

4 R. Filler and S. M. Naqvi, in "Biomedicinal Aspects of Fluorine Chemistry," ed by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo (1982), Chap. 1, p.1; J. T. Welch, *Tetrahedron*, **43**, 3123 (1987).

5 M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, **28**, 6199 (1987); M. Hojo, R. Masuda, E. Okada, and H. Miya, *Synthesis*, **1989**, 870; E. Okada, N. Tsukushi, Y. Otsuki, S. Nishiyama, and T. Fukuda, *Synlett*, **1999**, 126; E. Okada and N. Tsukushi, *Synlett*, **1999**, 210.

6 F. Palacios, D. Aparicio, and J. Garcia, *Tetrahedron*, **54**, 1647 (1998).

7 J. March, in "Advanced Organic Chemistry," 4th ed, Wiley-Interscience, New York (1992), Chap. 11 , p. 540; J. F. Begue and D. Bonnet-Delpon, *Tetrahedron*, **47**, 3207 (1991).

8 T. L. Gilchrist, in "Heterocyclic Chemistry," Pitman, London (1985), Chap. 8, p.276; D. L. Comins and S. O'Connor, *Adv. Heterocycl. Chem.*, **44**, 199 (1988).

9 G. Simchen and A. Schmidt, *Synthesis*, **1996**, 1093.

10 Procedure for the synthesis of **4**: 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 **3**.[9] 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 **4** (1167 mg, 87%) and 5[11] (841 mg), respectively. **4**: mp 98-99 °C (*n*-hexane/EtOAc); ^{1}H-NMR ($CDCl_3$) δ 8.97 (q, 1H, J_{HF}=2 Hz, H-2), 8.33-8.00 (m, 2H, H-5, -8), 7.90-7.38 (m, 2H, H-6, -7), 3.17 (s, 6H CH_3); IR (KBr) $\nu_{C=O}$ = 1690 cm^{-1}; Anal Caled 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%.

11 It is now in progress in our laboratbry to study the mechanism for the formation of **5** under the present reaction conditions. **5**: bp 70 °C/4 mmHg (oven temp); ^{1}H-NMR ($CDCl_3$) δ 8.78 (q, 1H, J_{HF}=2 Hz, H-2), 8.31 (d, 1H, J=6.2 Hz, H-6), 6.79 (d, 1H, *J*=6.2 Hz, H-5), 2.97 (s, 6H, CH_3); IR (film) $\nu_{C=O}$=1682 cm^{-1}; Anal Calcd for $C_9H_9F_3N_2O$: C, 49.55; H, 4.16; N, 12.84%. Found: C, 49.64; H, 4.13; N, 12.78%.

12 Typical procedure for the N-N exchange reaction of **4** with amines: To a solution of **4** (268 mg, 1 mmol) in MeCN (7 mL) was added benzylamine (107 mg, 1 mmol) and the mixture was stirred at room temperature for 3 h. Evaporation of the solvent gave **9** (310 mg, 94%); mp 148-149 °C (n-hexane/EtOAc); ^{1}H-NMR ($CDCl_3$) δ 11.10-10.57 (br, 1H, NH), 8.93 (br s, IH, H-2), 8.33-7.13 (m, 9H, H-5, -6, -7, -8, C_6H_5), 5.10 (d, 2H, *J*=5.6 Hz, CH_2); IR (KBr) ν_{NH}=3250-2245, $\nu_{C=O}$=1645 cm^{-1}; 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%.

13 For example, the reaction of **5** with benzylamine (3 eq) in refluxing valeronitrile for 48 h did not take place and almost all of substrate **5** was recovered.