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ON THE SYNTHESIS AND REACTIVITY OF 1-BENZYL-2-ARYLQUINOLINE-4-THIONES[1]

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Abstract – A panel of 1-benzyl-2-aryl-4-quinolones was synthesized in three steps and converted to the corresponding 4-thione derivatives using Lawesson's reagent. The representative vinylogous thioamide (**5a**) was alkylated to afford a novel series of quinolinium salts.

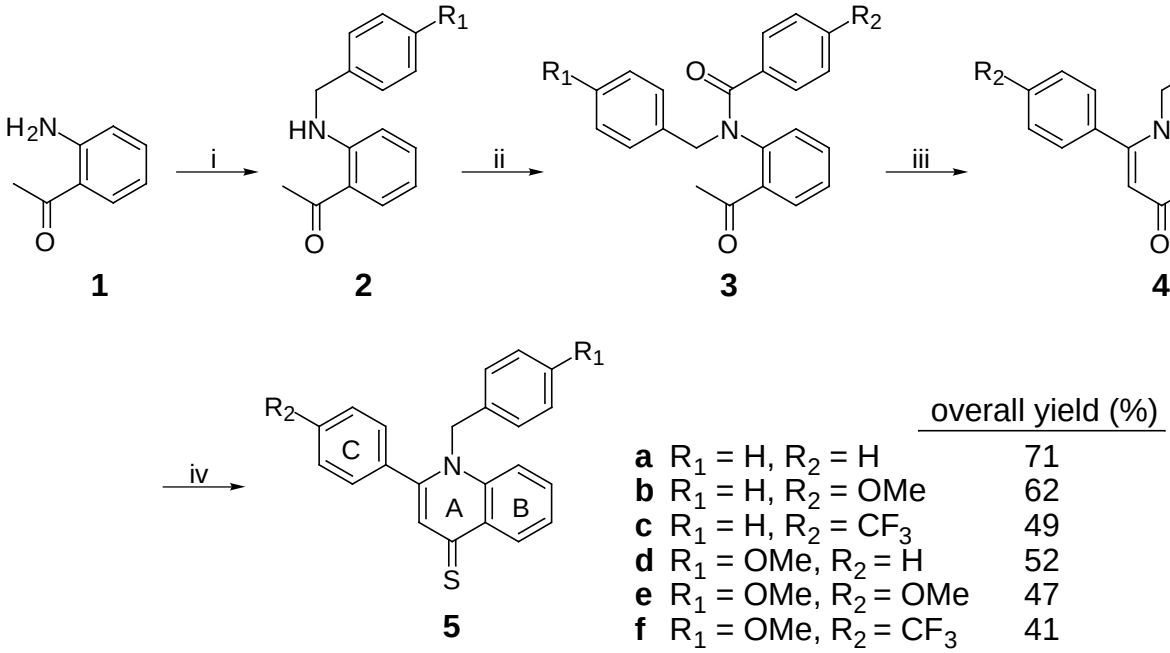
INTRODUCTION

Cystic fibrosis (CF) is an autosomal, recessive genetic disease that afflicts 1 in 2000-2500 Caucasians at birth, annually.[2] Although genetic-based medical approaches such as gene therapy have attempted to alleviate symptoms of the disease, these approaches have suffered serious setbacks.[3] Therefore, the more traditional approach of small molecule therapy once again has become an attractive method for treating patients with CF.[4] Recently, studies by Fischer[5] and others[6] have discovered that flavones are capable of activating the cystic fibrosis transmembrane conductance regulator (CFTR). To explore the potential biological activity of closely related heterocycles, we have synthesized a panel of quinolinium analogs for evaluation as activators of CFTR.[7] We report herein a convenient strategy for the syntheses of 1-benzyl-2-aryl-quinoline-4-thiones and derived quinolinium salts. Our strategy for combinatorial synthesis of these compounds complements previously reported synthetic approaches.[8]

RESULTS AND DISCUSSION

Our synthetic strategy (Scheme 1) was designed to allow the rapid diversification of the quinoline core structure. Reductive amination was used to introduce the first element of diversity. Alkylation of commercially available 2'-aminoacetophenone (**1**) was accomplished by condensation with various aldehydes followed by selective reduction using $NaBH_3CN$.

The alkylation products (**2**) were then readily acylated using different benzoyl chlorides under standard conditions to provide amides (**3**). The availability of a wide variety of substituted benzoyl chlorides ensures that the acylation step can serve as a simple means for structural diversification. By modification of a procedure initially disclosed by Lee *et al.*,[9] amides (**3**) were cyclized by treatment with *t*-BuOK in *t*-BuOH. The two-step sequence of acylation-cyclization delivered 1-benzyl-2-aryl-4-quinolones (**4**) in moderate to good yields (61 - 89%).[10] Quinolones (**4**) were treated with Lawesson's reagent[11] in refluxing toluene for six hours to yield thiones (**5**).[12] The four-step sequence afforded the panel **5a**-**f** in overall yields of 41-71%. We were gratified to find these synthetic transformations were accomplished with either electron withdrawing or donating groups in the *para*-position of the quinolone C-ring.



		overall yield (%)
a	R_1 = H, R_2 = H	71
b	R_1 = H, R_2 = OMe	62
c	R_1 = H, R_2 = CF_3	49
d	R_1 = OMe, R_2 = H	52
e	R_1 = OMe, R_2 = OMe	47
f	R_1 = OMe, R_2 = CF_3	41

Scheme 1. Synthesis of 1-benzyl-2-aryl-quinoline-4-thiones. i. a. PhCHO, C_6H_6 b. $NaCNBH_3$, PPTS, MeOH ii. PhC(O)Cl, Et_3N, CH_2Cl_2 iii. *t*-BuOK, *t*-BuOH iv. Lawesson's reagent, toluene.

Amides (**3**) generally were used directly without purification in the preparative procedure; however, purification and characterization of representative members revealed a unique spectroscopic property. For example, the ^{13}C NMR of compound (**3e**) shows twenty signals, the expected number of signals for a rotationally restricted amide.[13] Furthermore, the ^{1}H NMR signals for the benzylic protons in **3e** appear as a single *AX* quartet (Figure 1), suggesting not only restriction to a single amide isomer but also a conformational restriction. The restricted rotation about the benzylic C-N bond places these protons in a single diastereotopic environment. Hence, the benzylic protons appear as doublets due to the atropisomerism.[14] On cyclization to amides (**4e**) these signals coalesce to a 2H singlet at δ 5.25 ppm.

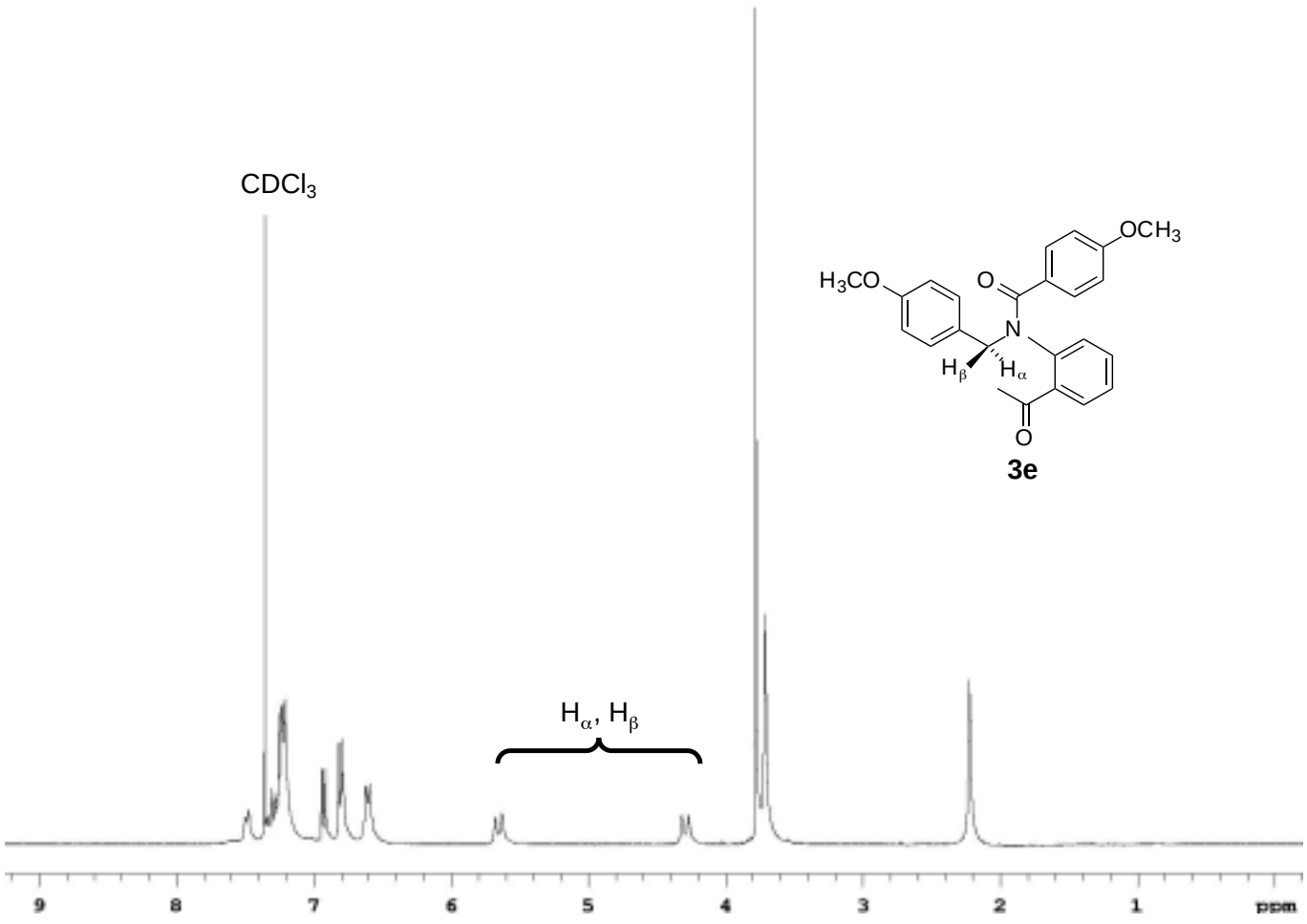
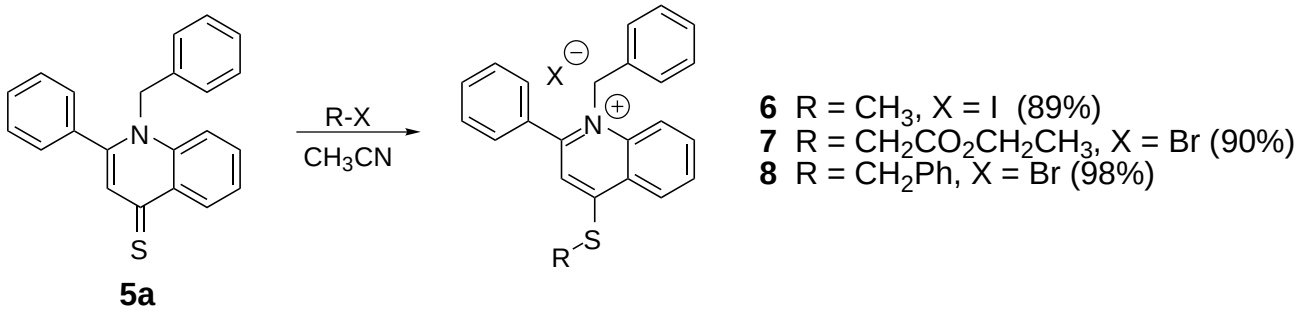


Figure 1. ^{1}H-NMR of *N*-(2-Acetylphenyl)-*N*-(4-methoxybenzyl)-4-methoxybenzamide

To diversify the thioquinoline panel, we examined alkylation of the vinylogous thioamide functionality. Although *S*-alkylation of thioamides by treatment with alkyl halides has been demonstrated,[15] little is known about alkylation of vinylogous thioamides.[8] We envisioned that A-ring aromatization would facilitate *S*-alkylation of the vinylogous thioamide. Indeed, thioquinoline (**5a**) was alkylated readily under mild conditions by reaction with representative alkyl halides, yielding quinolinium salts (**6** - **8**) in 89-98% yields (Scheme 2).[16]



Scheme 2. Alkylation of 1-benzyl-2-phenylquinoline-4-thiones.

CONCLUSION

In conclusion, we have presented a new route to substituted quinoline-4-thiones. Our four-step synthetic approach facilitates structural diversification in two stages. In addition, we have demonstrated that the vinylogous thioamide functionality is readily alkylated by simple electrophiles. En route to the title compounds, we observed that *N,N*-disubstituted benzamides **3** demonstrated peculiar atropisomerism. A full account outlining the activities of these and analogous heterocycles in chloride conductance studies will be reported elsewhere.

ACKNOWLEDGMENTS

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10. Representative Acylation-Cyclization Procedure. To a solution of *N*-benzyl-2'-aminoacetophenone (250 mg, 1.11 mmol) in dry CH_2Cl_2 (4 mL) at room temperature was added triethylamine (0.184 mL, 1.22 mmol). The resulting yellow mixture was cooled to 0 °C and benzoyl chloride (0.14 mL, 1.2 mmol) was added dropwise by syringe. On complete addition, the solution was allowed to warm to room temperature. After stirring at room temperature for 16 h, the reaction mixture was diluted with CH_2Cl_2 and then washed with an equal volume of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with an equal volume of CH_2Cl_2. The combined organic extract was dried using anhydrous Na_2SO_4 and followed by

concentration *in vacuo*. The residue was dissolved in *t*-BuOH (2.2 mL) and treated with potassium *t*-butoxide (560 mg, 5.50 mmol). The mixture was heated to reflux for 16 h, after which the reaction mixture was cooled and diluted with saturated aqueous NH_4Cl. The resultant solution was extracted with CH_2Cl_2 (3x). The combined organic extract was dried using anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was chromatographed (SiO_2), eluting with a solvent gradient (CH_2Cl_2 to 1:99 MeOH: CH_2Cl_2) to afford 1-benzyl-2-phenyl-4-quinolone (**4a**, 280 mg, 81%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.21 (s, 2H), 6.29 (s, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 7.46-7.19 (m, 13H), 8.45 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.1, 112.3, 117.2, 123.7, 125.3, 126.6, 127.0, 127.5, 128.0, 128.6, 128.9, 129.6, 132.2, 135.4, 136.2, 140.6, 155.0, 177.5; IR (neat) 1546, 1583, 1622, 3001 cm^{-1}.

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12. Representative Thiolation Procedure. To 1-benzyl-2-phenyl-4-quinolone (74 mg, 0.24 mmol) in toluene (1.2 mL) at room temperature was added Lawesson's reagent (53 mg, 0.13 mmol). The reaction mixture was heated for 16 h at reflux and followed by solvent removal *via* vacuum distillation. The product was purified by chromatography (SiO_2), eluting with a gradient (1:4 EtOAc:hexane to 1:1 EtOAc:hexane), to afford 1-benzyl-2-phenylquinoline-4-thione (**5a**, 74 mg, 95%) as an orange oil; ^{1}H NMR ($CDCl_3$) δ 5.41 (s, 2H), 6.98 (d, *J* = 6.5 Hz, 2H), 7.58-7.24 (m, 11H), 7.59 (s, 1H), 9.07 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.1, 117.9, 125.3, 125.4, 127.8, 128.1, 128.3, 128.7, 129.0, 130.0, 130.6, 132.8, 133.7, 134.4, 135.4, 137.0, 147.7; IR (neat) 1162, 1254, 1493, 1538, 1577, 1734, 2923, 3062 cm^{-1}.
13. ^{13}C NMR ($CDCl_3$) of **3 e**: δ 28.7, 53.4, 55.0 (2), 112.6, 113.4, 113.5, 127.1, 127.7, 129.4, 130.2, 130.6, 131.9, 132.0, 136.0, 141.7, 158.7, 160.3, 169.4, 198.9.
14. For an example of atropisomerism in benzamides, see: J. Clayden, M. Helliwell, C. McCarthy, and N. Westlund, *J. Chem. Soc., Perkin Trans. I*, 2000, 3232.
15. For a review see: R. N. Hund and O. DeLaMater, *Chem. Rev*., 1961, **6 1**, 45.
16. Vinylogous Thioamide Alkylation. To 1-benzyl-2-phenylquinoline-4-thione (28 mg, 0.084 mmol) in acetonitrile (0.4 mL) at room temperature was added benzyl bromide (0.1 mL of a 0.84 M acetonitrile solution, 0.084 mmol). After stirring for 6 h at room temperature, the suspension was diluted with ether and the precipitates were collected to yield 1-benzyl-4-benzylsulfanyl-2-phenylquinolinium bromide (**8**, 41 mg, 98%) as a yellow solid, mp = 181-182 °C; ^{1}H NMR ($CDCl_3$) δ 4.71 (s, 2H), 6.36 (br s, 2H), 7.04 (d, *J* = 4.5Hz, 2H), 7.29-7.28 (m, 3H), 7.40-7.38 (m, 3H), 7.62-7.51 (m, 5H), 7.68 (s, 1H), 7.79-7.72 (m, 2H), 7.96 (t, *J* = 4.5Hz, 1H), 8.34 (t, *J* = 6Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 39.0, 56.9, 118.7, 122.0, 125.0, 125.6, 126.0, 128.3, 128.6, 128.7, 129.2 (2), 129.3 (2), 129.4, 131.7, 132.4, 132.7, 134.4, 135.8, 137.1, 157.0, 163.2; IR (neat) 1121, 1164, 1492, 1536, 1580, 2946, 3027 cm^{-1}; HRMS m/z calcd for $[M - Br]^+$ 418.1629, found 418.1641.