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Communications

An Unusual Base-Mediated Cyclization of Ketimines Derived from 2-(Trifluoromethyl)aniline That Involves the Trifluoromethyl Group: An Expedient Route to 2-Arylquinolines

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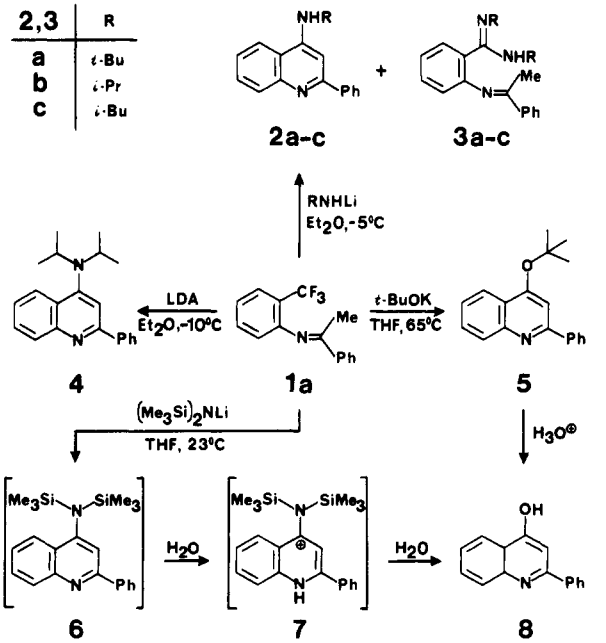
Summary: 6-(Substituted methylene)-*N*-(arylalkylidene)-2,4-cyclohexadien-1-imines, such as **13**, **17**, and **21** (Scheme II) are suggested intermediates in a novel synthetic route to 2-arylquinolines based on the reaction of trifluoromethyl-substituted ketimines, such as **1a**, with strong bases.

The chemistry of organic fluorine compounds is dominated by nucleophilic aromatic substitution and by numerous classical transformations in which fluorine-containing groups are stable substituents.[2] By contrast, examples of a nucleophilic substitution of the trifluoromethyl group and formal nucleophilic displacement of the fluorines of this group, which do not involve a direct nucleophilic attack, are rare.[3,4]

In this paper we describe a facile route to substituted quinolines via anionic cyclization of aralkylketimines **1a** (Scheme I) and **9** (eq 1) derived from 2-(trifluoromethyl)aniline in which each fluorine of the CF_3 group is

Scheme I



successfully displaced by a series of internal nucleophilic processes. The resulting 2-phenylquinolines derived from **1a** contain either an amino or oxygen function in the C-4 position, depending on the nature of the strong base utilized for cyclization, i.e., **2a–c** with lithium alkylamide, **4** with lithium diisopropylamide (LDA), **5** with potassium *tert*-butoxide, and **8** with lithium bis(trimethylsilyl)amide followed by hydrolysis.[5,6] A similar cyclization of ketimine

(1) (a) Georgia State University. (b) University of Florida. (c) University of Canterbury.

(2) See, for example: (a) Hewitt, C. D.; Silvester, M. J. *Aldrichim. Acta* **1988**, *21*, 3. (b) *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH Publishers, Inc.: New York, 1988. (c) Chambers, R. D.; Sargent, C. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1981; Vol. 28, Chapter 1. (d) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis-Horwood: Chichester, 1976.

(3) For a review, see: Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197.

(4) (a) Elsheimer, S.; Slattery, D. K.; Michael, M.; Weeks, J.; Topoleski, K. *J. Org. Chem.* **1989**, *54*, 3992. (b) Elsheimer, S.; Michael, M.; Landavazo, A.; Slattery, D. K.; Weeks, J. *J. Org. Chem.* **1988**, *53*, 6151. (c) Taylor, S. L.; Martin, J. C. *J. Org. Chem.* **1987**, *52*, 4147.

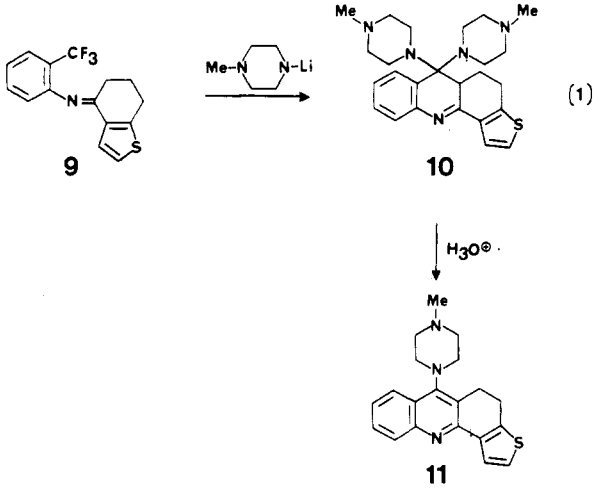
0022-3263/90/1955-4777$02.50/0

Table I. Synthesis of Quinolines 2a–c and Amidines 3a–c

2, 3	R	reagents	2/3[a]
a	*t*-Bu	*t*-BuNHLi[b]	8:1
		t-BuNHLi/*t*-BuNH$_2$ (1:1)[c]	2:1
b	*i*-Pr	*i*-PrNHLi[b]	3:1
		i-PrNHLi/*i*-PrNH$_2$ (1:1)[c]	1:11
c	*i*-Bu	*i*-BuNHLi[b]	2:1
		i-BuNHLi/*i*-BuNH$_2$ (1:1)[c]	1:22

[a] All reactions were carried out in Et_2O at −5 °C for 1 h; total yields (2 + 3) of 80–86%. [b] From 4 equiv of RNH_2 and 4 equiv of *n*-BuLi. [c] From 8 equiv of RNH_2 and 4 equiv of *n*-BuLi.

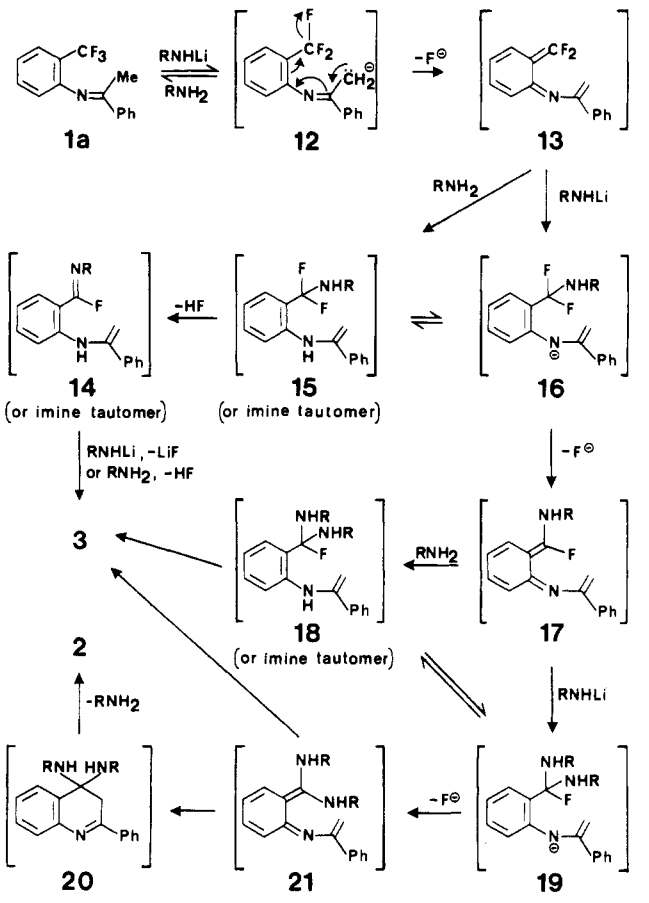
9 with lithium 4-methylpiperazide and followed by acid hydrolysis gave 6-(4-methylpiperazino)-4,5-dihydrothieno[1,2-*c*]acridine (11). The yields of isolated products 2, 4, 5, 8, 11[7] were good to excellent.

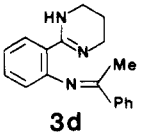


(1)

The formation of the 4-(alkylamino)quinolines **2a–c** on treatment of **1a** with primary alkylamides is accompanied by varying amounts of amidines **3a–c**[7] (Scheme I). The ratio of **2**/**3** (Table I) decreases with decreasing steric bulk of the alkyl group in the lithium reagent and in the presence of an excess of the amine used for the preparation of the lithium reagent. Consistent with this pattern is the high yield (82%) of amidine **3d** and lack of a quinoline formation for the reaction of **1a** with lithium (3-aminopropyl)amide.[8]

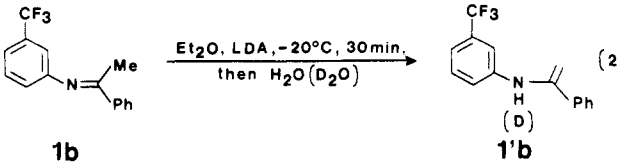
Scheme II





3d

Treatment of **1a** with 4 equiv of LDA gave quinoline **4** in an 85% yield. A similar reaction of **1a** with 1 equiv of LDA gave **4** (30%) in addition to recovered **1a** (65%). When the mixture of **1a** with 4 equiv of LDA was quenched with D_2O after a short period of time, neither the resultant quinoline **4** nor the recovered Schiff's base **1a** were labeled with deuterium. In a control experiment the meta isomer **1b** was allowed to react with LDA followed by quenching of the mixture with water to give the enamine tautomer **1'b** as the sole product[9] (eq 2). Sub-



(2)

1b 1'b

(5) A similar treatment of **1a** with methyllithium resulted in an addition reaction with C=N of **1a** to give a corresponding secondary amine.

(6) For an efficient nonrelated synthesis of 4-aminoquinolines unsubstituted at the amino group, see: (a) Strekowski, L.; Kong, S.-B.; Cegla, M. T.; Harden, D. B. *Heterocycles* **1989**, *29*, 539. (b) Reference 13b.

(7) Satisfactory microanalyses were obtained and molecular ion peaks were observed in the mass spectra for all new compounds **2–5**, **9**, **11**. Melting points and NMR ($CDCl_3$/Me_4Si, 60 MHz) follow. **1a**: mp 22–25 °C (oil: Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1980**, *102*, 4464). **1b**: oil (Bellus, D. Ger. Offen., 1973, DE 2259222; *Chem. Abstr.* **1973**, *79*, 78787n). **2a**: mp 151–153 °C; NMR δ 1.59 (s, 9 H), 5.30 (br s, 1 H), 7.12 (s, 1 H), 7.4–7.7 (m, 6 H), 8.05 (m, 3 H). **2b**: mp 179–181 °C; NMR δ 1.40 (d, *J* = 6, 6 H), 3.98 (sept, *J* = 6, 1 H), 4.85 (br s, 1 H), 6.88 (s, 1 H), 7.4–7.7 (m, 6 H), 8.07 (m, 3 H). **2c**: mp 114–116 °C; NMR δ 1.10 (d, *J* = 6, 6 H), 2.11 (m, 1 H), 3.23 (t, *J* = 6.5, 2 H), 5.05 (br s, 1 H), 6.87 (s, 1 H), 7.4–7.8 (m, 6 H), 8.08 (m, 3 H). **3a**: mp 79–81 °C; NMR δ 1.16 (s, 18 H), 2.26 (s, 3 H), 6.63 (d, *J* = 8, 1 H), 7.0–7.4 (m, 6 H), 7.95 (m, 2 H). **3b**: mp 115–117 °C; NMR δ 1.02 (d, *J* = 6, 12 H), 2.25 (s, 3 H), 3.51 (br s and sept, *J* = 6, 3 H), 6.71 (d, *J* = 8, 1 H), 7.1–7.5 (m, 6 H), 7.94 (m, 2 H). **3c**: oil; NMR δ 0.83 (d, *J* = 6, 12 H), 1.75 (sept, *J* = 6, 2 H), 2.23 (s, 3 H), 2.95 (d, *J* = 6, 4 H), 6.74 (d, *J* = 8, 1 H), 7.1–7.4 (m, 6 H), 7.90 (m, 2 H). **3d**: mp 201–203 °C; NMR δ 1.75 (m, 2 H), 1.84 (s, 3 H), 3.13 (m, 2 H), 3.85 (m, 2 H), 4.30 (br s, 1 H), 6.6–6.8 (m, 2 H), 7.2–7.9 (m, 7 H). **4**: oil; NMR δ 1.11 (d, *J* = 6, 12 H), 3.78 (sept, *J* = 6, 2 H), 7.4–7.7 (m, 5 H), 7.70 (s, 1 H), 8.12 (m, 3 H), 8.42 (d, *J* = 8, 1 H). **5**: mp 49–51 °C; NMR δ 1.68 (s, 9 H), 7.38 (s, 1 H), 7.4–7.7 (m, 5 H), 8.0–8.2 (m, 4 H). **8**: mp 258–259 °C (lit.[11] mp 258–260 °C). **9**: mp 90–92 °C; NMR δ 2.02 (m, 2 H), 2.34 (t, *J* = 6.5, 2 H), 2.96 (t, *J* = 6, 2 H), 6.75 (d, *J* = 8, 1 H), 7.1–7.6 (m, 5 H). **11**: mp 130–131 °C; NMR δ 2.45 (s, 3 H), 2.67 (m, 4 H), 3.2 (m, 8 H), 7.19 (d, *J* = 5.2, 1 H), 7.5 (m, 2 H), 7.83 (d, *J* = 5.2, 1 H), 8.1 (m, 2 H).

(8) Analysis of the mass balance of the crude product mixture revealed, in addition to **3d** (82%), polymeric materials (15%) and two unidentified low molecular products (<2% each), the ^1H NMR (400 MHz) spectra of which lacked signals characteristic for a quinoline system.

(9) Compound **1'b**: oil%; NMR δ 4.80 and 4.88 (2 s, $=CH_2$, *J* = 0), 5.60 (br s, NH), 6.7–7.7 (m, 7 H), 8.00 (m, H2 and H6 of Ph). On standing in $CDCl_3$ solution the enamine **1'b** tautomerized quantitatively (half-life of 3 h at 23 °C) into imine **1b**. For similar tautomerizations, see: ref 13b.

stitution of deuterium oxide for water gave **1'b** deuterated at the nitrogen atom. Moreover, the rate of consumption of **1a** to give quinoline **4** and that of **1b** to give enamine **1'b** after quenching were similar under the same conditions.

These results suggest that both **1a** and **1b** are lithiated with a similar rate, which is consistent with similar steric hindrance[10] about the methyl group in these two isomers. The two lithiated species, however, differ strikingly in stability.

A *tert*-butyl derivative **5** was obtained in an 83% yield. It was hydrolyzed to a 4-hydroxyquinoline **8** (96% yield), which was identical with an authentic sample of **8** prepared using an independent method.[11] Interestingly, the same quinoline **8** (64% yield) was obtained upon treatment of **1a** with lithium bis(trimethylsilyl)amide followed by the usual aqueous workup. A driving force for this rather unexpected outcome is apparently a facile protonation of the initially formed quinoline **6** to give a nitrogen- and silicon-stabilized cation **7**, which is then hydrolyzed.

Treatment of ketimine **9** with lithium 4-methylpiperazide in Et_2O at −10 °C for 30 min gave the dipiperazino derivative **10**[12] in a 77% yield accompanied by **11** (10%). Compound **10** decomposed slowly under basic conditions and rapidly on treatment with acid to give dihydroacridine **11** quantitatively.

The mechanism suggested in Scheme II for the formation of quinolines **2a–c** is consistent with the above observations. We suggest that the anion **12** undergoes spontaneous elimination of fluoride to give an intermediate product **13** which can be aromatized in the addition reaction with either amine or amide anion.[13] The corresponding adducts **15** and **16** are in an amine/amide-mediated quasi-equilibrium, as are other postulated intermediate products, **18** and **19**, derived from **16** by elimination of fluoride and followed by the amine/amide nucleophilic additions with the resultant intermediate product **17**. The addition of amine to the mixture would result in a decreased concentration of **21**, the major postulated intermediate, which cyclizes to a dihydroquinoline **20** and increased concentrations of **15** and **18**, the apparent precursors to amidine **3**. Thus the effect of excess amine would be to increase the yield of the amidine at the expense of quinoline, as observed. On the other hand, the increased steric bulk in the primary amine and its lithium derivative appears to strongly hinder elimination of HF from **15** and **18** leading to amidine **3**, but it would not be expected to have a large effect on the electrocyclization of **21**. The overall effect would be an increased yield of the quinoline, also as observed.

An unusual conclusion is that the intermediate product **13** does not cyclize[14] to a quinoline system but, instead, undergoes aromatization in an intermolecular addition reaction with amine or its lithium derivative.[13] It is the cyclization of the diamino derivative **21** and its secondary amino and oxy analogues as the major reaction in the postulated mechanistic pathway that leads to the quinoline formation.[15]

Acknowledgment. This work was supported by the NIH NIAID Grant UO1 AI27196.

(10) Imines **1a** and **1b** are *E* diastereomers, as shown by NOE experiments. In this geometry the *C*-phenyl is coplanar and the *N*-aryl is approximately perpendicular to the C=N plane, due to conjugation with the C=N bond and sp^2 nitrogen atom, respectively: Strekowski, L.; Cegla, M. T.; Harden, D. B.; Kong, S.-B. *J. Org. Chem.* **1989**, *54*, 2464 and references cited therein. The *E* stereochemistry does not change after lithiation: (a) Houk, K. N.; Stozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chauqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426. (b) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1983**, *105*, 4396.

(11) Ogata, Y.; Kawasaki, A.; Tsujimura, K. *Tetrahedron* **1971**, *27*, 2765.

(12) **10**: an oil; NMR ($CDCl_3$/Me_4Si, 400 MHz) δ 2.15 (s, 3 H), 2.3–3.5 (m + s at δ 2.33, 24 H), 7.11 (d, *J* = 5.2, 1 H), 7.20 (t, *J* = 8, 1 H), 7.28 (t, *J* = 8, 1 H), 7.45 (d, *J* = 8, 1 H), 7.47 (d, *J* = 8, 1 H), 7.68 (d, *J* = 5.2, 1 H).

(13) For addition reactions of LDA with unsaturated systems, see: (a) Shen, C. C.; Ainsworth, C. *Tetrahedron Lett.* **1979**, 89. (b) Strekowski, L.; Patterson, S.; Cegla, M. T.; Wydra, R. L.; Czarny, A.; Harden, D. B. *Tetrahedron Lett.* **1989**, *30*, 5197.

(14) Cyclization of **13** followed by base-mediated elimination of hydrogen fluoride from the resultant dihydroquinoline would give 4-fluoro-2-phenylquinoline. A nucleophilic substitution with the latter compound would produce **2**: Smalley, R. K. In *Quinolines*; Jones, G., Ed.; Wiley: London, 1977; Part 1. The results presented in ref 8 demonstrate that this is not the case. The same results show that the anion **12** does not undergo cyclization through intramolecular substitution of fluoride.

(15) The formation of **10** (eq 1) as the major product shows that a possible cyclization of **17** and analogues is not a major reaction that leads to a quinoline. It is interesting to note the results of MNDO computations on **13**, **17**, and **21** using a frontier orbital approach. The geometries of these postulated intermediates are similar as are their HOMO–LUMO energy gaps (8.2 ± 0.4 eV). Accordingly, all these intermediates should cyclize with similar efficiency in the absence of the competing addition reactions.