A NOVEL ROUTE TO 7-(SUBSTITUTED AMINO)-5,6-DIHYDROBENZ-[*c*]ACRIDINES

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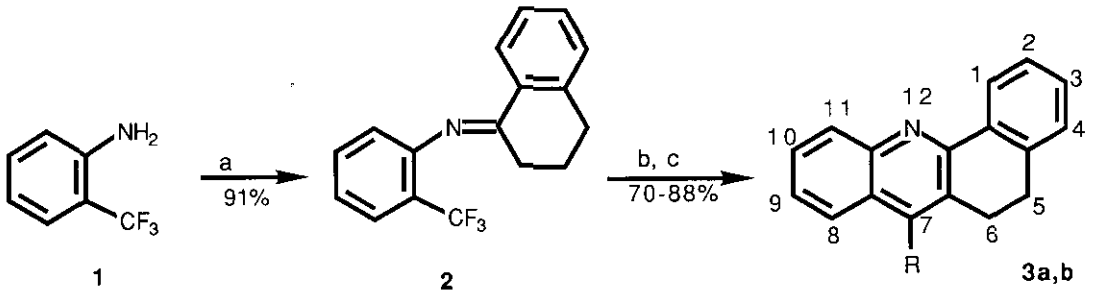
Abstract - The title compounds (**3**) are produced in a novel, lithium alkylamide- and dialkylamide-mediated cyclization of N-(1,2,3,4-tetrahydro-1-naphthylidene)-2-trifluoromethylaniline (**2**). The mechanism of this unusual transformation that involves the trifluoromethyl group is discussed.

In continuation of our studies on the application of the chemistry of the trifluoromethyl group for the synthesis of heterocylic compounds[1] we now describe a facile route to 5,6-dihydrobenz[*c*]acridines of a general structure (**3**)[2] (R=alkylamino or dialkylamino) via lithium alkylamide- and lithium dialkylamide-mediated cyclization of ketimine (**2**)[3] derived from 2-trifluoromethylaniline (**1**) and 1-tetralone (Scheme 1).

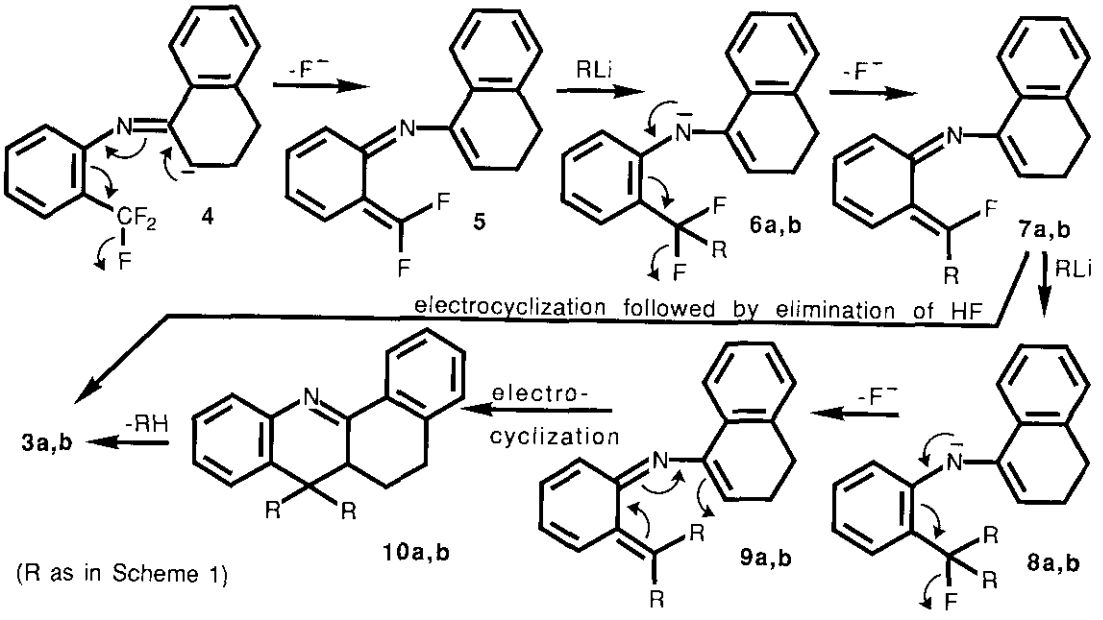
The reaction of **2** with four equivalents of lithium 2-(dimethylamino)ethylamide[4] in ether at



(a) 1-Tetralone, p-TsOH, toluene, reflux for 10 h with removal of H_2O.
(b) Preparation of **3a**: R^1-Li (4 eq.), Et_2O, -10°C, 1 h, then H_2O; preparation of **3b**: R^2-Li (4 eq.), Et_2O, -20°C, 15 min, then aq. HCl. (c) Silica gel chromatography, hexane/Et_3N/EtOH (7:2:1).

Scheme 1

-10°C was completed within 1h and furnished **3a** after quenching the mixture with water.[5] The ketimine (**2**) reacted even faster in the presence of four equivalents of lithium 4-methylpiperazide.[4] As shown by tlc analysis of the water quenched mixture, compound (**2**) was consumed within 15 min at -20°C. The ^{1}H-nmr spectrum of crude products indicated little of the expected dihydroacridine (**3b**). Treatment of this mixture with acid gave **3b** in a high yield, however.[6] Dihydroacridine (**3b**) was also obtained efficiently when the reaction was continued at 23°C for several hours before quenching with water. These results indicate that **3b** is produced mainly from an intermediate product which decomposes rapidly to **3b** under acidic conditions and slowly in the presence of a strong base. Following chromatographic purification this intermediate product was identified as **10b** (Scheme 2).[7] Similar ratios of **10b/3b** ≈ 9:1 were obtained for varying reaction times up to 15 min at -20°C regardless of the level of conversion of starting ketimine (**2**). These mixtures did not significantly change their composition during aqueous workup and chromatography, as shown by ^{1}H-nmr. It must be concluded, therefore, that in addition to the decomposition of **10b** as



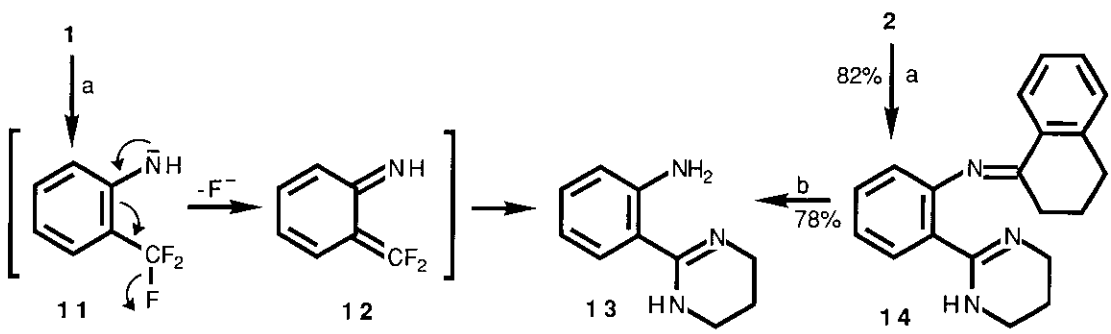
Scheme 2

the major route to **3b**, product (**3b**) is also formed by a different minor pathway.

The mechanism suggested in Scheme 2 for the formation of **3b** is consistent with the above observations. We suggest that deprotonation of **2** to give anion (**4**) is followed by elimination of fluoride with the formation of an intermediate product (**5**). The addition reaction[8] of the piperazide anion with **5** then produces anion (**6b**) which, in turn, undergoes elimination of fluoride to give **7b**. A similar sequence of reactions produces **9b** through the intermediacy of **8b**.[9] Electrocyclization of **9b** then gives **10b**, the major direct precursor to **3b**. The minor pathway to **3b** apparently involves electrocyclization of **7b** followed by fast elimination of HF from the cyclized product.[10] A similar cyclization of **5** is much less likely because the difluoromethylene portion of **5** is not sterically hindered and, as such, undergoes a preferential addition reaction with the 4-methylpiperazide anion.

An essentially similar mechanism may be operative in the reaction of **2** with lithium 2-(dimethylamino)ethylamide, leading to **3a**; however, additional mechanistic pathways are possible for the reactions with a lithium reagent derived from a primary amine.[1,11]

Recently we have shown[1] that anion (**11**) (Scheme 3) generated from **1** in the presence of lithium 3-aminopropylamide undergoes elimination of fluoride to give an intermediate product (**12**), the precursor to a 1,4,5,6-tetrahydropyrimidine (**13**). Since **12** and the postulated **5** are structurally similar, we reasoned that the same chemistry applied to



(a) H_2N〰〰NHLi (4 eq.), Et_2O, -5°C, 1.5 h, then H_2O. (b) MeOH/H_2O (2:1), 1 M HCl, 80°C, 1 h.

Scheme 3

ketimine (**2**) should also result in the transformation of the CF_3 group of **2** into a tetrahydropyrimidine function, provided **5** is formed as the intermediate. Indeed, treatment of **2** with lithium 3-aminopropylamide under the described conditions[1] gave the expected product (**14**).[12] Selective hydrolysis of the ketimine function in **14** furnished **13**.

In summary, all these results strongly suggest that (i) the intermediate compound (**5**) is generated from **2** in the presence of lithium alkylamide and dialkylamide reagents, and (ii) this intermediate is an early precursor to dihydroacridines (**3**).

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

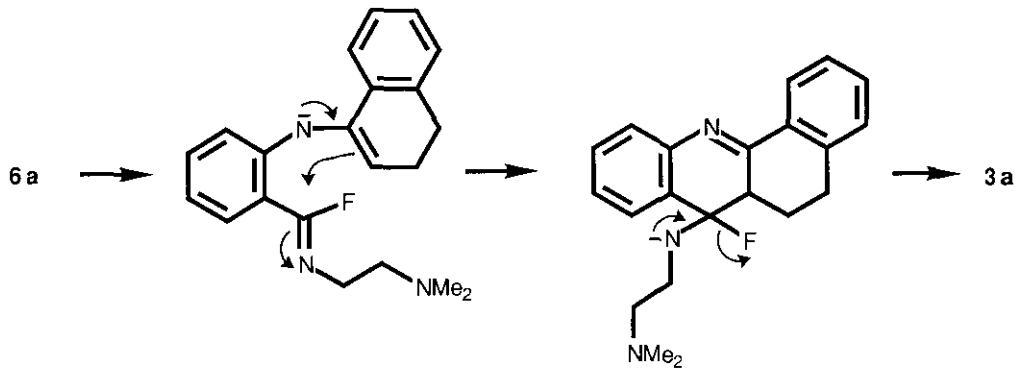
1. R. L. Wydra, S. E. Patterson, and L. Strekowski, J. Heterocycl. Chem., 1990, **27**, 803.
2. For a classical method, see: J. S. Bindra, S. N. Rastogi, G. K. Patnaik, N. Anand, K. G. G. Rao, P. C. Dwivedi, and C. N. R. Rao, Indian J. Chem., 1987, **26B**, 318.
3. **2**: mp 95-97°C; ir (neat) υ 1638 cm^{-1}.
4. The amide reagents were generated from the corresponding amines and n-butyllithium.
5. **3a**: an oil; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 2.49 (m, 2H), 2.96 (m, 2H), 3.07 (m, 2H), 3.99 (m, 2H), 5.25 (br s, 1H, exchangeable with D_2O), 7.26 (d, J = 8 Hz, 1H), 7.34 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.42 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.47 (d, J = 8 Hz, 1H); ms, m/z 58 (100), 259 (35), 317 (52, M^+). **3a•2HBr•1/2H_2O**: mp 275-277°C (from EtOH/H_2O).
6. **3b**: mp 130-131°C; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.67 (m, 4H), 2.94 (m, 2H), 3.16 (m, 2H), 3.40 (m, 4H), 7.26 (d, J = 8 Hz, 1H), 7.35 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 8.11 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H), 8.45 (d, J = 8 Hz, 1H); ms, m/z 257 (66), 329 (100, M^+).
7. **10b**: ^{1}H-nmr (400 MHz, $CDCl_3$) δ 2.13 (s + m, 5H), 2.34 (s, 3H), 2.45 (m, 6H), 2.72 (m, 4H), 2.90 (m, 6H), 3.03 (m, 2H), 3.53 (dd, J = 1.6, 7.6 Hz, 1H, H6a), 7.18 (d, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H) 7.51 (d, J = 8 Hz, 1H), 8.52 (d, J = 8 Hz, 1H); ir (neat) υ 1630 cm^{-1}.

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

9. This suggested mechanism is consistent with previous studies on the chemistry of the activated trifluoromethyl group. For a review, see: Y. Kobayashi and I. Kumadaki, Acc. Chem. Res., 1978, **11**, 197.

10. In agreement with the two suggested reaction pathways the treatment of **3b** with lithium 4-methylpiperazide under the general conditions did not produce **10b**.

11. For example, as pointed out by a reviewer, the formation of **3a** from **6a** may involve the additional pathway shown below.



This suggested pathway is quite feasible because it does not require transformation of the low-energy aromatic systems of **6a** and **8a** into the respective higher-energy cyclohexadiene systems of **7a** and **9a**. It should also be noted that attempts to isolate the expected intermediate product (**10a**) failed. This result indicates that either (i) **3a** and **3b** are formed by different mechanisms or (ii) the suggested intermediate product (**10a**) is much less stable than **10b**.

12. **14**: mp 190-192°C.

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