Pergamon

Tetrahedron Letters 40 (1999) 5643–5646

TETRAHEDRON LETTERS

A novel and highly efficient synthesis of the aza analogs of tacrine

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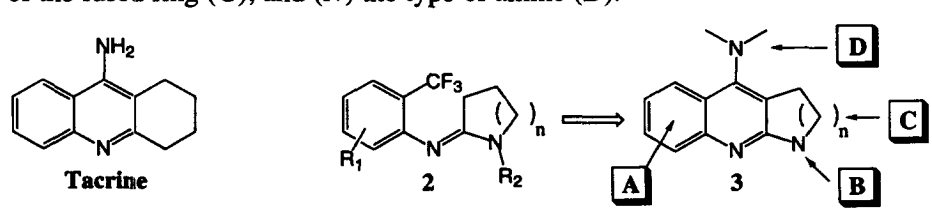
Received 27 April 1999; revised 2 June 1999; accepted 3 June 1999

Abstract

We describe a new and efficient synthesis of the aza analogs of tacrine based upon the chemistry of the anionically activated trifluoromethyl group. We identify four sites (**A–D**) which can be successfully altered to afford the desired fused tricyclic heterocycles in high yield (63–82%). The reaction is believed to proceed through the formation of a quinone methide intermediate.

Keywords: acridines; cyclization.

The utility of the anionically activated trifluoromethyl group in the synthesis of aliphatic, aromatic, and heteroaromatic compounds has been extensively studied.[1,2] In order to expand the synthetic potential of this functionality we attempted synthesis of the aza analogs of tacrine from the corresponding amidines **2** (Scheme 1).[3] The proposed synthetic scheme allows for the introduction of several elements of diversity into the desired heterocyclic compounds using the readily available precursors **2**. These elements of diversity include: (i) the substitution pattern on the aniline (**A**); (ii) the substituent on the *N* atom (**B**); (iii) the size of the fused ring (**C**); and (iv) the type of amine (**D**).



Scheme 1.

Initially, we reacted the easily available amidines **2**[4] with NaHMDS to afford the desired heterocycles **3**. Under the optimized reaction conditions, a solution of the amidine **2** in dry THF was added in one portion to a vigorously stirred solution of NaHMDS (4 molar equivalent) in the same solvent at −78°C. The resultant dark yellow solution was stirred at this temperature for an additional 15 min, and slowly

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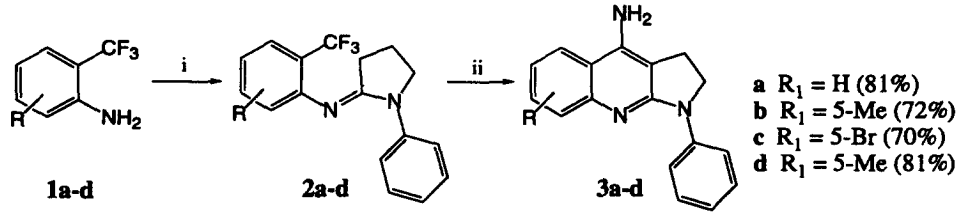
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01122-3

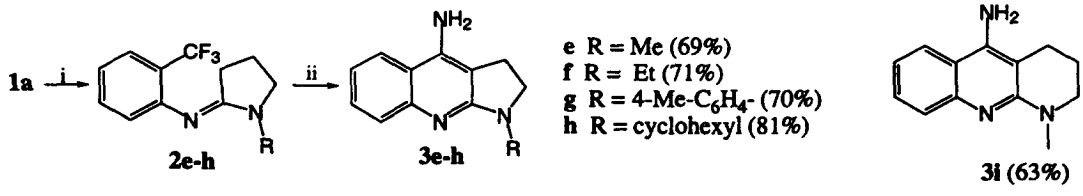
allowed to warm to −20°C (30 min). The dark red mixture was stirred at this temperature for 2 h (dry ice/ethylene glycol/MeCN bath), warmed to room temperature and stirred for another 1.5 h. The mixture was quenched with brine, and extracted three times with 100 mL of EtOAc. The extract was dried over Na_2SO_4, concentrated in vacuo and purified by flash-chromatography (silica gel, eluent hexanes:EtOAc, 2:1) to afford the analytically pure product **3** in excellent yields (Scheme 2).



Scheme 2. Reagents and conditions: (i) *N*-phenyl-2-pyrrolidone (**2**), $POCl_3$, $CHCl_3$, 60°C, 4 h; (ii) NaHMDS (1 M in THF), −78°C–rt, 4 h

The optimal solvent for the reaction was found to be dry, degassed THF. Application of Et_2O, dioxane, or 2-methyltetrahydrofuran as solvents resulted in considerably lowered yields of the desired heterocycles. Temperature also was found to have a pronounced effect upon the cyclization. We did not observe a reaction if the mixture of the substrate **2** and a fourfold excess of NaHMDS was incubated at temperatures between −78 and −60°C. Additionally, the yields of the desired heterocycles were somewhat lower (by ca. 10–15%) if the reaction mixture was allowed to warm to room temperature rapidly (20–25 min). The optimal range for the cyclization temperature was found to be −35 to −15°C. The nature of the base counteranion did not affect the outcome of the reaction significantly. For example, both LiHMDS (THF as a solvent), and KHMDS (mixture of THF:toluene, 3:1 as a solvent) were used successfully as substitute for NaHMDS. Attempts to use less than 4 equivalents of base were not successful. In this case, the targeted heterocycles **3** were isolated in considerably lowered yields (by ca. 30–35%). The nature of the substituents (mildly electron donating versus mildly electron withdrawing groups) in trifluoromethylanilines **1a–d** did not affect the outcome of the reaction (Scheme 1, site **A**).

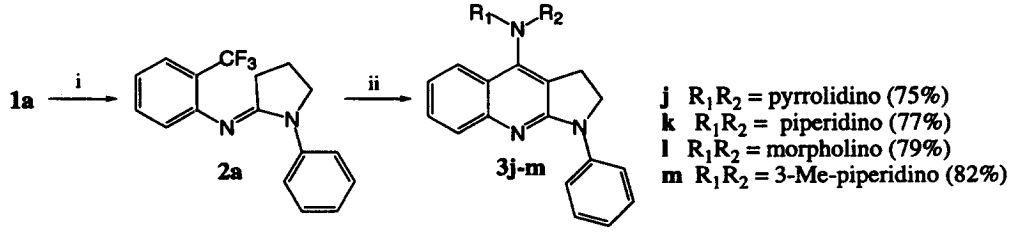
In the next step, we varied the substituent on the nitrogen atom (Scheme 1, site **B**). A series of amidines **2e–h** were prepared using the above protocol. NaHMDS promoted cyclization in dry THF afforded the desired heterocycles **3e–h** (69–81% yield) (Scheme 3). The substitution pattern of the amidines **2e–h** did not affect the outcome of the reaction. Products **3g** and **3h** were successfully isolated from the reaction mixtures by precipitation of cold EtOAc extract with ether. These products were additionally purified by recrystallization from EtOH. The cyclization product **3i** was isolated in a 63% yield when the amidine derived from *N*-methyl-2-piperidone and **1a** was treated with NaHMDS under the same experimental conditions (Scheme 1, site **C**).



Scheme 3. Reagents and conditions: (i) *N*-*R*-2-pyrrolidone, $POCl_3$, $CHCl_3$, 60°C, 4 h; (ii) NaHMDS (1 M in THF), −78°C–rt, 4 h

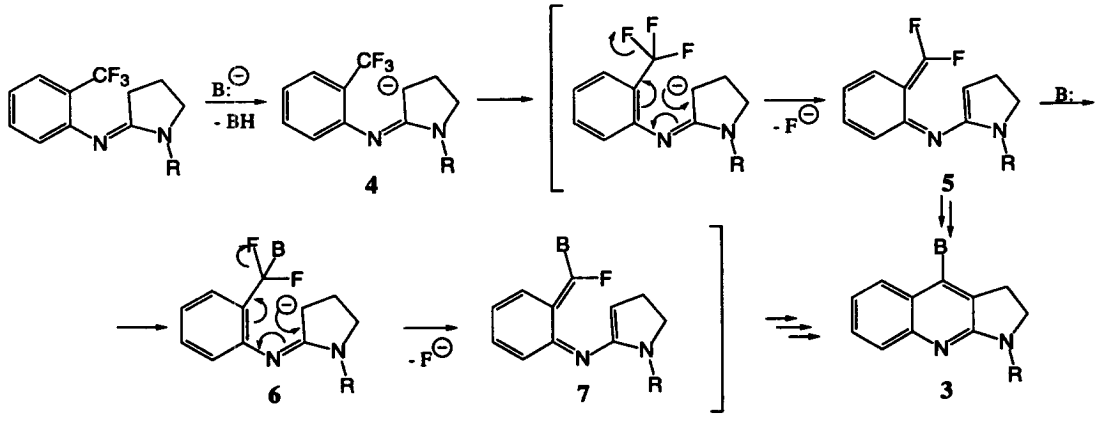
An additional set of experiments was conducted to examine the effect of the base on the cyclization (Scheme 4). Amidine **2a** was treated with lithium salts of secondary amines prepared from the corresponding amines and *n*-BuLi in dry THF. The cyclization in all cases proceeded smoothly to afford the

heterocycles **3j–m** (Scheme 1, site **D**) in 75–82% yields. Substitution of the Li salts of amines by the corresponding Na or K salts did not affect the outcome of the reaction. Unfortunately, attempts to utilize lithium salts of primary amines for similar cyclizations were not successful. The GC–MS analysis of the reaction mixtures revealed the presence of the desired heterocycles (10–15% yield) along with a number of unidentified products.[2]



Scheme 4. Reagents and conditions: (i) *N*-phenyl-2-pyrrolidone, $POCl_3$, $CHCl_3$, 60°C, 4 h; (ii) $LiNR_1R_2$, –78°C–rt, 4 h

The proposed mechanism for the described transformation of amidines **2** is outlined in Scheme 5.[5,6] The initial proton abstraction from **2** results in the formation of **4**. We believe that the anion **4** is stable at –78°C, however at temperatures above –55°C it undergoes elimination of the fluoride anion to afford the quinone methide intermediate **5**.



Scheme 5.

In order to test this hypothesis, we treated the amidine **2a** with NaHMDS (4 equiv.) at –78°C. The mixture was stirred at this temperature for 20 min, and immediately quenched with saturated NH_4Cl. The only detectable compound in the reaction mixture (LC–MS) was the nonreacted starting compound **2a**. Chromatography of the mixture (silica gel, eluent $CHCl_3$:MeOH, 99:1) afforded **2a** in 84% yield. Similar species were proposed as intermediates in a series of relevant transformations involving the anionically activated trifluoromethyl group.[1,2] The intermediate **5** undergoes electrocyclization, followed by aromatization via the loss of HF. Subsequent displacement of fluorine with an excess of amine affords the observed product **3**. Alternatively, attack of **5** with base generates anion **6**, which eliminates a second equivalent of fluoride. The resulting **7** can cyclize to afford **3** after aromatization with loss of HF.[7]

In summary, we described an efficient synthesis of the aza analogs of tacrine based on the chemistry of the anionically activated trifluoromethyl group. We identified four sites on tacrine which can be successfully modified to afford a diverse array of aza analogs in high yield (63–82%). The reaction is believed to proceed through the formation of the quinone methide intermediate.

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5. All isolated compounds were completely characterized by elemental analysis, HPLC, ^{1}H NMR, and mass spectroscopy. Melting points of previously reported compounds are uncorrected. Selected experimental data: **3m**: isolated in 82% yield, yellow oil, ^{1}H NMR ($CDCl_3$): δ 0.97 (d, *J*=6.0 Hz, 3H), 1.14 (m, 1H), 1.87 (m, 2H), 1.96 (m, 2H), 2.68 (m, 1H), 3.01 (m, 1H), 3.27 (m, 2H), 3.34 (t, *J*=8.0 Hz, 2H), 4.04 (t, *J*=8.0 Hz, 2H), 7.03 (t, *J*=7.4 Hz, 1H), 7.19 (t, *J*=7.4 Hz, 1H), 7.35 (m, 2H), 7.46 (t, *J*=7.4 Hz, 1H), 7.74 (d, *J*=8.0 Hz, 1H), 7.92 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=8.0 Hz, 2H); ESIMS: *m/z* 344 (M+1). Elemental analysis: calcd for $C_{23}H_{25}N_3$: C, 80.43; H, 7.34; N, 12.23. Found: C, 80.22; H, 7.56; N, 12.12.
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