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A novel synthesis of 3,4-disubstituted cinnolines from *o*-trifluorophenyl hydrazones

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Abstract

An efficient synthesis of 3-aryl-4-aminocinnolines from *ortho*-trifluoromethylphenyl hydrazones is described. The mechanism of the described transformation is likely to involve the formation of the quinone methide intermediate. The described procedure is easily adaptable to automated solid phase synthesis leading to analytically pure heterocycles. © 1999 Elsevier Science Ltd. All rights reserved.

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Heterocyclic chemistry is an area of ongoing interest for scientists engaged in a broad array of research. Material sciences, total synthesis of natural substances, and medicinal chemistry are representative branches of chemistry, where the design of novel strategies for the synthesis of heterocycles play a pivotal role. Several years ago, we investigated the chemistry of anionically activated trifluoromethyl group.[1] The utility of this functionality in the synthesis of aliphatic, aromatic, and heteroaromatic compounds has been extensively studied.[2] To further explore the synthetic utility of the anionically activated CF_3 group we attempted the synthesis of 3,4-disubstituted cinnolines.[3]

We decided to assemble the desired 3,4-disubstituted cinnolines via the construction of the C3–C4 bond. According to the retrosynthetic scheme indicated below (Scheme 1), the cyclization precursor should possess the easily ionizable NH bond, as well as two leaving groups (L1 and L2) at the C4-carbon. Further analysis led us to the conclusion that the cyclic hydrazones easily accessible from the commercially available *o*-trifluoromethylphenyl hydrazine, and aldehydes are the suitable precursors for the required cinnolines.

In order to validate this synthetic approach, we prepared a series of hydrazones via a previously described procedure.[2] In the next step, the solution of the resultant hydrazones **2a–j** in dry THF were treated with a 4 M excess of NaHMDS to afford the desired 3-aryl-4-aminocinnolines **3a–j** in good yields (63–76%, Scheme 2) after basic workup.[4]

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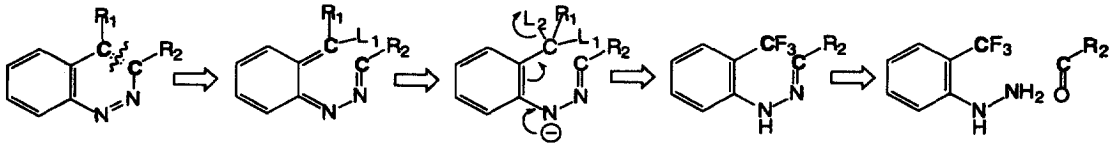
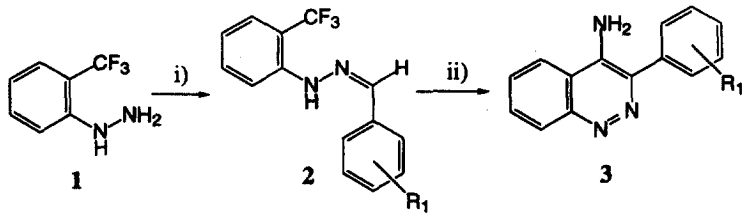


L = Leaving group

Scheme 1.



i) $R_1C_6H_4CHO$, toluene, reflux, 2h; ii) NaHMDS (4 eq), THF, -78°C to RT, 4 h

Yields of hydrazones **2a-j** and quinazolines **3a-j**

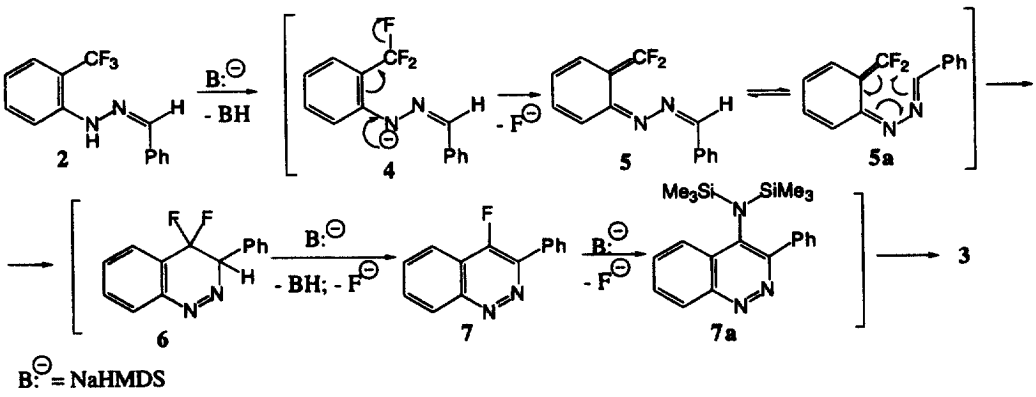
	R_1		Yield of **2**, %	Yield of **3**, %			R_1		Yield of **2**, %	Yield of **3**, %
1	H	**a**	84	68		5	3-Cl	**e**	92	70
2	4-F	**b**	87	73		6	3,4-diCl	**f**	93	68
3	3-Me	**c**	78	65		7	3,4-OCH_2O	**g**	86	72
4	4-OMe	**d**	83	63		8	3-Pyridine	**h**	79	64

Scheme 2.

We found that hydrazones **2** derived from the *o*-substituted aldehydes did not afford the desired cinnolines **3** under a variety of experimental conditions. Attempts to use a variety of bases, namely LDA, Li(morpholide), or Li(piperidide) were not successful. However, the cyclization step proceeded smoothly with hydrazones **2** derived from *m*- and/or *p*-substituted aldehydes. We found that neither the electronic, nor the steric nature of the substituent(s) affected the outcome of the cyclization. Dry degassed THF was found to be the optimal solvent for the reaction. Application of Et_2O, dioxane, or 2-methyltetrahydrofurane as solvents afforded considerably lower yields of the desired 3-aryl-4-aminocinnolines. The temperature was also found to have a pronounced effect upon the cyclization. We did not observe a reaction, when a mixture of the substrate **2** and fourfold excess of NaHMDS was incubated at temperatures between –78 to –60°C. The optimal range for the cyclization temperatures was found to be –35 to –15°C. The nature of the base counter anion did not affect the outcome of the reaction significantly. For example, both LiHMDS (THF as a solvent), and KHMDS (mixture THF:toluene, 3:1 as a solvent) were used successfully as substitutes for NaHMDS. Attempts to use less equivalents of base were not successful. The targeted heterocycles **3** were isolated in considerably lower yields (by ca. 30–35%).

The proposed mechanism for the discussed transformation is outlined in Scheme 3.[5] The initial base-induced proton abstraction from **2** leads to the formation of the corresponding anion **4**. The anion **4** undergoes HF abstraction to afford the quinone methide intermediate **5/5a**. The existence of similar species in related transformations has been postulated earlier.[6] The quinone methide undergoes

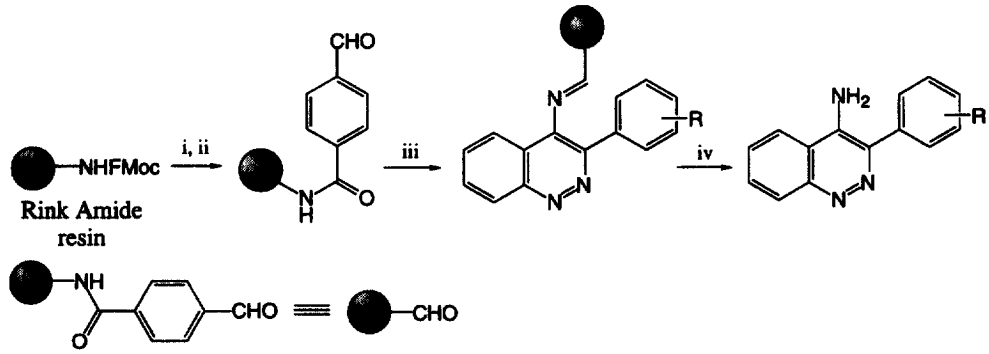
intramolecular cyclization to afford **6**. This intermediate undergoes rapid elimination of HF under basic conditions to afford the fluorinated cinnoline **7**. The nucleophilic aromatic substitution of fluorine with excess of NaHMDS in **7** affords **7a**, which upon the basic hydrolysis, yields the observed cinnoline **3**.



Scheme 3.

In the optimized experimental procedure, a solution of 1 mmol of hydrazone **2** in 2 mL of dry degassed THF was added in one portion to a solution of 4 mmol of NaHMDS in the same solvent at –78°C under Ar. The resultant dark yellow solution was stirred at this temperature for 10 min, and slowly warmed up to –30°C (water/ethylene glycol/dry ice bath). The resulting dark solution was stirred for an additional 4 h while the temperature of the mixture was maintained between –30 and –20°C. The reaction mixture then was slowly brought up to room temperature (2 h), and quenched with a saturated solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc. The EtOAc extract was dried, concentrated in vacuo, and purified by flash chromatography (silica gel, eluent: hexanes:EtOAc, 6:1).

In the alternative purification procedure the EtOAc extract was diluted with dry trimethyl orthoformate (ratio EtOAc:$HC(OMe)_3$=1:5). The commercially available Rink amide resin modified with 4-carboxybenzaldehyde (Scheme 4) was added to the resulting mixture.[7] The slurry was carefully stirred for 6 h at room temperature, washed with DMF, dioxane, and CH_2Cl_2. The resultant resin was dried, and treated with MeOH/KOH (0.01 M). The solution was collected, concentrated, and treated with EtOAc. The EtOAc extract was collected, concentrated, and triturated with Et_2O to afford the analytically pure cinnolines **3**. The solid phase extraction procedure was automated, and successfully applied toward the purification of a cinnoline library generated via the described approach.



Scheme 4. Reagents and conditions: (i) 20% piperidine in DMF; (ii) (*p*-CHO-C_6H_4-$COO)_2O$, DMF:CH_2Cl_2, 1:1, rt, 8 h; (iii) reaction mixture in EtOAc:TMOF, 1:5, rt, 6 h; (iv) MeOH:KOH, 0.01 M, rt, 30 min

In summary, we have devised an efficient synthesis of 3-aryl-4-aminocinnolines from *ortho*-trifluoromethylphenyl hydrazides. The mechanism of the described transformation is likely to involve the formation of the quinone methide intermediate. The described procedure is easily adaptable to automated solid phase synthesis allowing for analytically pure heterocycles.

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4. Selected experimental data: **3g**: m.p. 159–161°C; ^{1}H NMR ($CDCl_3$): δ 3.54 (s, 2H), 6.02 (s, 2H, exch. D_2O), 6.83 (m, 2H), 7.04 (d, *J*=8.0 Hz, 1H), 7.35 (s, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H); EIMS: *m/z* 265 (M^+); ESIMS: *m/z* 266 (M+1); Elemental analysis: calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.72; H, 4.33; N, 15.66; HRMS: exact mass calcd for $C_{15}H_{11}N_3O_2$: 265.0851. Found: 265.0853. **3h**: m.p. 171–172°C; ^{1}H NMR ($CDCl_3$): δ 6.71 (t, *J*=7.6 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 7.26 (s, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 7.45 (m *J*=8.0 Hz, 2H), 7.56 (t, *J*=8.0 Hz, 1H), 7.95 (s, 2H, exch. D_2O), 8.33 (d, *J*=2.4 Hz, 1H); EIMS: *m/z* 222 (M^+); ESIMS: *m/z* 223 (M+1); Elemental analysis: calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.11; H, 4.69; N, 25.05; HRMS: exact mass calcd for $C_{13}H_{11}N_4$ (M+1): 223.0984. Found: 223.0986.
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