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Unexpected Behavior of Imines Derived from Trifluoromethylaryl Ketones under Basic Conditions: Convenient Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzoxazoles.

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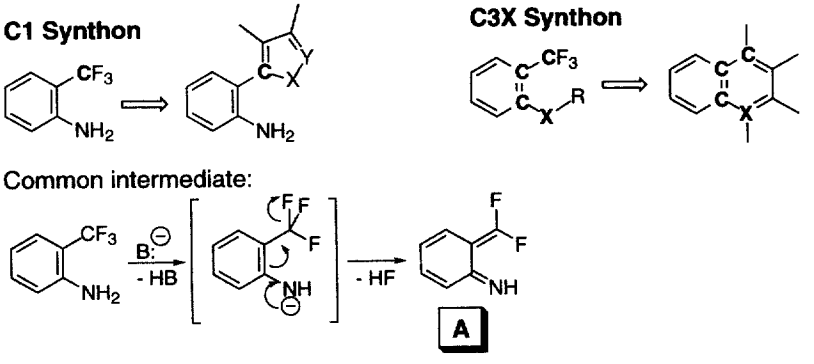
Abstract: Imines derived form trifluoromethylaryl ketones, *ortho*-phenylenediamines or *ortho*-aminophenols undergo intramolecular cyclization with the elimination of the CF_3 group under a variety of basic conditions to afford 2-arylbenzimidazoles and 2-aryloxazoles in good to excellent yields.

Keywords: cyclization; imines; benzimidazoles; benzoxazoles

It has been shown that the anionically activated trifluoromethyl group has great utility in the synthesis of various aromatic, and heteroaromatic compounds.[1] In a majority of cases the literature data suggests that CF_3 can be viewed as a C1 or C_3X (X = N, or CH_2) building block in these transformations (Scheme 1).

Scheme 1.



Syntheses of 2-(substituted 1-alkenyl) anilines,[2] 2-substituted benzothiazoles and benzoxazoles,[3] 4(5)-dihydro-1*H*-imidazole,[4] triazines,[5] and isoxazoles[5] are representative examples of base-promoted heterocyclizations involving the aromatic CF_3 functionality as a C1 building block. On the other hand, the CF_3 group is a C_3X building block in the preparation of 1,3-disubstituted naphthalenes,[6] 2,4-di- or 2,3,4-trisubstituted quinolines,[7] 7-(substituted amino)-5,6-dihydrobenz[c]acridines,[8] 4-fluoroquinolines,[9] and fused fluoronaphthalenes.[10] A relevant synthesis of 3-aryl-4-aminocinnolines has been reported recently.[11] It has been suggested that all

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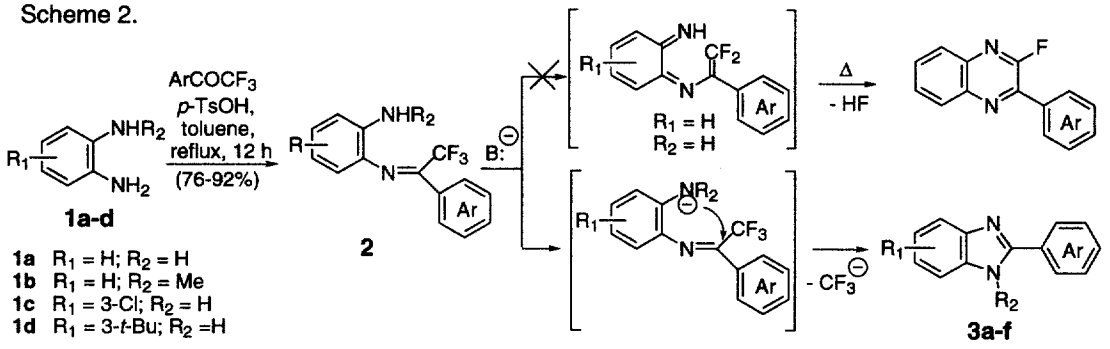
of the above transformations proceed *via* the initial proton abstraction from the anilinic nitrogen, or the methylene group to afford the quinone methide intermediate **A** (Scheme 1). The subsequent reaction of this intermediate with various nucleophiles may lead to the observed array of products. In this paper we report the unusual behavior of imines derived from trifluoromethylaryl ketones under basic conditions. We propose that this reaction proceeds *via the formal elimination of the CF_3 functionality* rather than through the well documented formation of **A**.

In our attempt to further utilize the rich synthetic potential of the aromatic anionically activated CF_3 functionality, we attempted the synthesis of substituted quinoxalines (Scheme 2). The starting materials for the synthesis were the corresponding imines **2,** which were easily available from trifluoromethylaryl ketones,[12] and aromatic *ortho*-diamines **1a-d**. We rationalized that the treatment of the imine with a strong base (NaHMDS, 1M in THF) would produce the quinone methide intermediate,[2,3,9] which would cyclize to afford, after elimination of HF, the desired quinoxalines. However, the only product detected in the reaction mixtures by both GC, and LCMS were 2-aryl-substituted-benzimidazoles **3a-f**.

Scheme 2.



Yield of benzimidazoles **3a-f**:

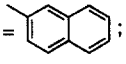
3a: Ar = Ph; R_1 = 4-H; R_2 = H (74%)

3b: Ar = Ph; R_1 = 4-H; R_2 = Me (77%)

3c: Ar = Ph; R_1 = 3-Cl; R_2 = H (79%)

3d: Ar = Ph; R_1 =3-*t*-Bu; R_2 = H (67%)

3e: Ar =  ; R_1 = H; R_2 = H (66%)

3f: Ar =  ; R_1 = H; R_2 = H (76%)

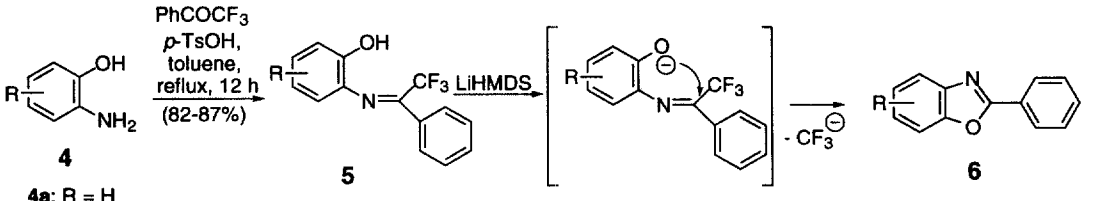
The starting imines were prepared in 76-92% yield *via* the conventional protocol from the diamines **1a-d** and the corresponding trifluoromethyl ketones by reflux in toluene (Dean-Stark trap) in the presence of catalytic TsOH for 4 hrs.[13] The solution of the resultant imine **2** (10 mmol) in 5 mL of dry THF was added in one portion to a solution of NaHMDS (40 mmol) in 40 mL of dry THF under Ar at -78°C. The mixture was stirred at this temperature for 1 h., slowly warmed up to room temperature (3 h.), and stirred for an additional 2 h. The resulting dark red solution was diluted with 200 mL of ether, washed with brine, and the pH was adjusted to 5 with AcOH. The extract was concentrated, redissolved in EtOAc, and purified by flash chromatography to afford the analytically pure benzimidazoles **3a-g** in 62-79% yield.[14]

Several other bases afforded similar results. In a case study, the imine derived from **1a** and trifluoromethyphenyl ketone was treated with a 4 fold molar excess of base under the conditions presented above to afford the benzimidazole **3a** in various yields as follows: KO*t*-Bu (69%); LDA (42%),[15] Li(piperidide) (58%), and Li(morpholide) (61%). Only nonreacted starting material was recovered from the reaction mixtures when NaOH in MeOH or NaOMe in MeOH were used as the base. The outcome of the reaction was affected by neither the nature of diamines **1a-d** nor the nature of the trifluoromethylaryl ketones.

We rationalized the outcome of the described reaction in terms of the intramolecular nucleophilic attack of the imine carbon with the nitrogen of the diamine followed by the elimination of the CF_3 functionality. It is worth noting that reports dealing with CF_3 as a leaving group are scarce.[16]

In a similar manner, imines **5** available from the *ortho*-aminophenols **4a-c**, and trifluoromethylphenyl ketone were treated with a 4 fold excess of LiHMDS in THF (the procedure was analogous to the one described above for the synthesis of **3**) to afford the substituted benzoxazoles **6a-c** in a 66-71% yield (Scheme 3).

Scheme 3.



4

4a: R = H
4b: R = 3-Cl
4c: R =3-*t*Bu

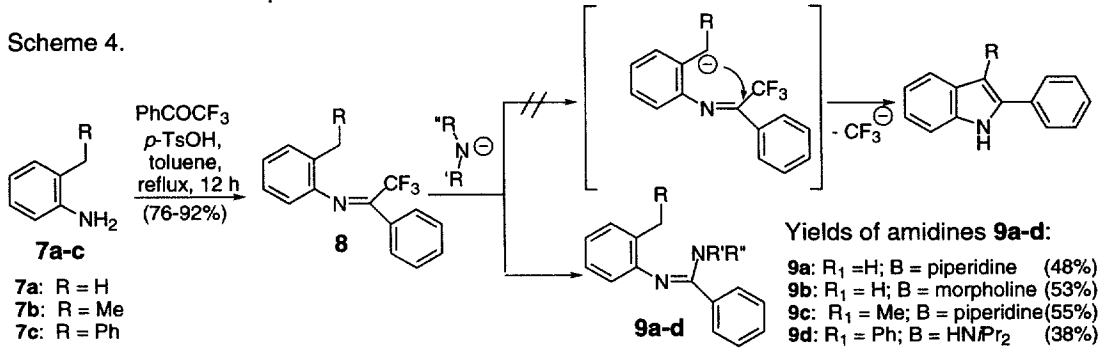
5

6

Yield of benzoxazoles **6**: **6a**: R = H (66%)
6b: R = 3-Cl (71%)
6c: R =3-*t*Bu (68%)

To further expand the utility of this transformation, we attempted to prepare polysubstituted indoles from the imines **8** prepared from toluidines **7a-c**, and trifluoromethylphenyl ketone. We reasoned that the anion derived from **8** may undergo an intramolecular cyclization similar to the described above to yield the indole system (Scheme 4). However, this reaction afforded amidines (**9a-d**, 38-55% yield) as the major products. Compounds **9a-d** probably resulted from the formal nucleophilic displacement of the CF_3 group with the lithium amides. The outcome of the reaction did not depend upon the nature of the amide.

Scheme 4.



7a-c

7a: R = H
7b: R = Me
7c: R = Ph

8

9a-d

Yields of amidines **9a-d**:
9a: R_1 =H; B = piperidine (48%)
9b: R_1 = H; B = morpholine (53%)
9c: R_1 = Me; B = piperidine(55%)
9d: R_1 = Ph; B = HN*i*Pr$_2$ (38%)

An indole system was not formed when higher concentrations, and/or higher ratios of base/substrate were applied. Attempts to use a 4-fold excess of *n*-BuLi as a base to form indoles were not successful. The only products detected under these conditions were the products of the formal addition of *n*-BuLi to the imines.[17]

In summary, we found that imines derived form trifluoromethyaryl ketones, and *ortho*-diamines or ortho-aminophenols undergo intramolecular cyclization with the elimination of the CF_3 group under basic conditions to afford 2-arylbenzimidazoles, and 2-arylbenzoxazoles respectively in good yields. The outcome of this reaction was affected by neither the nature of the base used nor

the imine. A similar reaction of the imines derived from toluidines, and trifluotomethylphenyl ketone afforded the corresponding amidines as the sole product.

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10. Kiselyov, A.S.; Strekowski, L. *Tetrahedron Lett.* **1994**, *35*, 7597.
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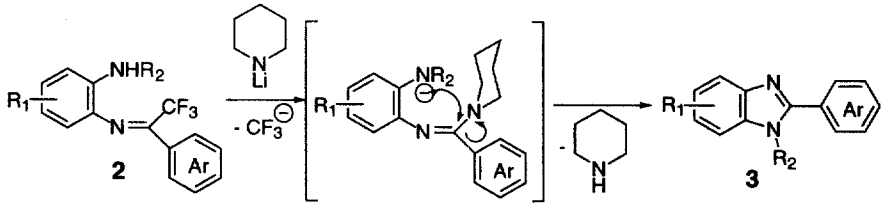
12. Prepared according to the procedure previously reported: Kiselyov, A.S.; Harvey, R.G. *Tetrahedron Lett.* **1995**, *36*, 4005.
13. Formation of *bis*-imines from the diamines **1a**, **1c**, and**1d** have not been detected.
14. The authenticity of the isolated benzimidazoles has been confirmed by comparison of their melting points (uncorrected), 1H NMR, and mass-spectra with the data reported.
15. Major isolated product. Reaction resulted in a complex mixture of compounds.
16. An alternative to the proposed mechanism is the initial displacement of the CF_3 group with the nucleophile (Li(piperidide) is shown) followed by the intramolecular attack of the anilinic nitrogen on the carbon of the imine, and elimination of the secondary amine:



For examples of nucleophilic displacement of a perfluoroalkyl substituent see : a) Chambers, R.D.; Sargent, C.R. In: *Advances in Heterocyclic Chemistry*; Ed. by Katritzky, A.R. and Boulton, A.J. ; Academic Press: New York-London-Toronto-Sydney-San Francisco, 1981, Vol. 28, 1; b) Bergman, J.; Bergman, S. *J.Org.Chem.* **1985**, *50*, 1246; c) Kobayashi, Y.; Kumadaki, I. *Chem.Rev.* **1978**, *11*, 197.

17. A similar behavior of the imines towards *n*-BuLi, and Grignard reagents was documented, see for example: Strekowski, L.; Cegla, M.T.; Harden, D.B.; Mokrosz, J.L.; Mokrosz, M.J. *Tetrahedron Lett.***1988**, *29*, 4265.