AN ANIONICALLY ACTIVATED TRIFLUOROMETHYL GROUP AS A NOVEL SYNTHON FOR ISOXAZOLES AND 1,3,5-TRIAZINES

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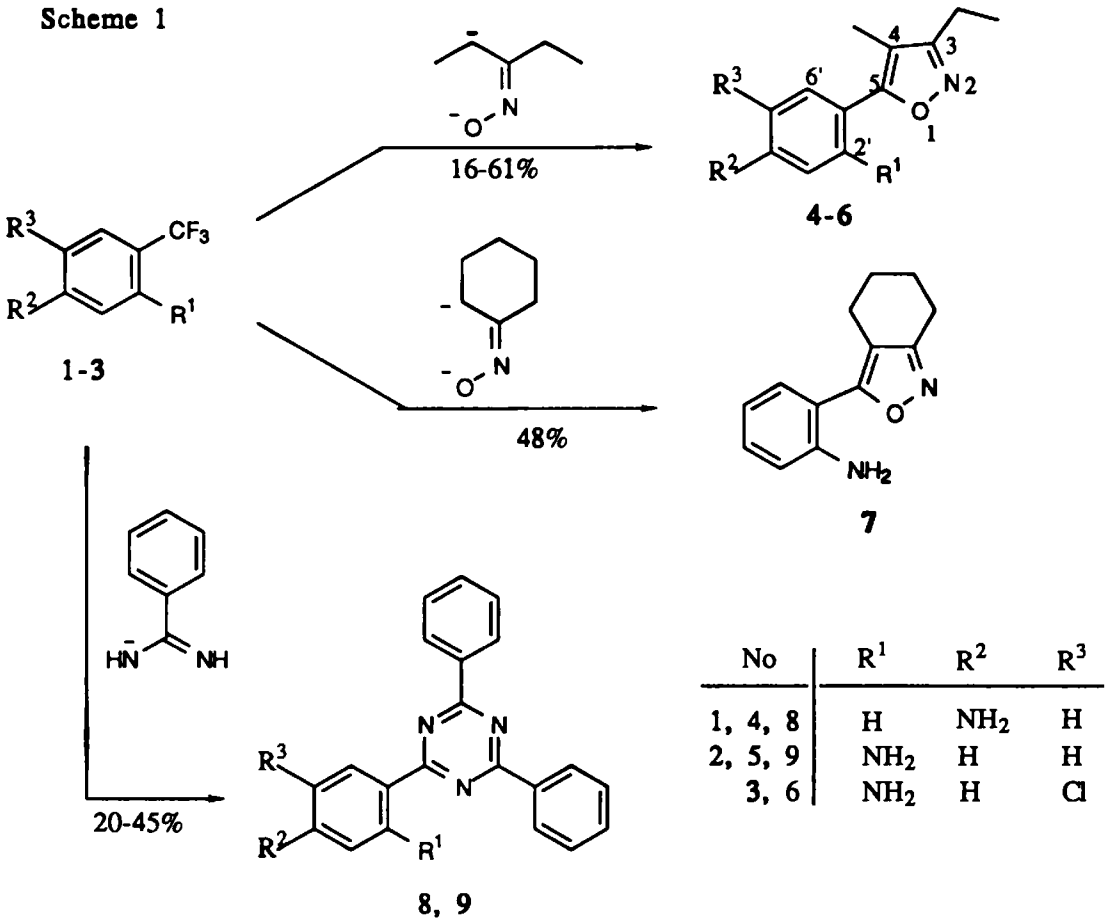
Abstract : A reaction of trifluoromethyl-substituted anilines **1-3** with dianions derived from oximes of 3-pentanon and cyclohexanone provides a facile entry into the corrresponding isoxazoles **4-7**. Triazines **8, 9** are obtained upon treatment of a monoanion derived from benzamidine with the respective substrates **1, 2**.

Anions derived from 4-(trifluoromethyl)aniline **1** , its ortho isomer 2, substituted derivatives such as **3** (Scheme 1) and analogs containing other ionizable groups at ortho or para position to the trifluoromethyl function undergo elimination of fluoride to generate the corresponding intermediate products illustrated by **11** in Scheme 2. The meta isomers are stable under basic conditions. The early chemistry of the anionically activated trifluoromethyl group has been reviewed (1) and another recent review describes synthetic applications of the chemistry of trifluoromethyl-substituted substrates (2). The most recent developments not yet reviewed include one-pot synthesis of 2-(1-alkenyl)anilines (3), naphthalenes (4), fluoro heteroaromatic compounds (5,6), benzothiazoles (7), benzoxazoles (7), and additional examples of 4-amino-quinolines (**8**) obtained by the chemistry already described (2). A strong selective stabilization of the triplex DNA structure in the presence of duplex DNA has been found for certain 4-aminoquinoline products (**9-11**) derived from **2**. The synthetic importance of the chemistry of the activated trifluoromethyl group, thus, is growing rapidly. A large number of substrates including **1-3** are available commercially, and others can easily be prepared by a trifluoromethylation reaction of electron-rich aromatic and heteroaromatic amines (12). In this paper, as part of our fundamental studies on the chemistry o the anionically activated trifluoromethyl group, we describe a novel one-pot preparation of isoxazoles (13) and 1,3,5-triazines (14) (Scheme 1).

Isoxazoles **4-6** are obtained by the reaction of dianion derived from 3-pentanone oxime with the respective trifluoromethyl-substituted anilines **1-3**. The cyclization involves the CF_3 group, the carbon atom of which becomes C-5 o the isoxazole system. In a typical experiment a solution of LDA (20 mmol) and n-BuLi (20 mmol) prepared by the addition of n-BuLi (40 mmol, 2 M in cyclohexane) to a solution of diisopropylamine (20 mmol) in THF (20 mL) is treated dropwise at -75 °C under a nitrogen atmosphere with 3-pentanone oxime (20 mmol) (15,16). The mixture is stirred at +23 °C for 30 mir cooled to -75 °C and then treated with a solution of **1-3** (4 mmol) in THF (2 mL). The mixture is stirred at -75 °C for 30 min and then at +23 °C for 2 h. A standard workup is followed by chromatography on silica gel with pentanes/ether (1:1) as an eluent to give the corresponding isoxazole **4-6**. A similar treatment of dianion of cyclohexanone oxime with 2 gave the

Scheme 1



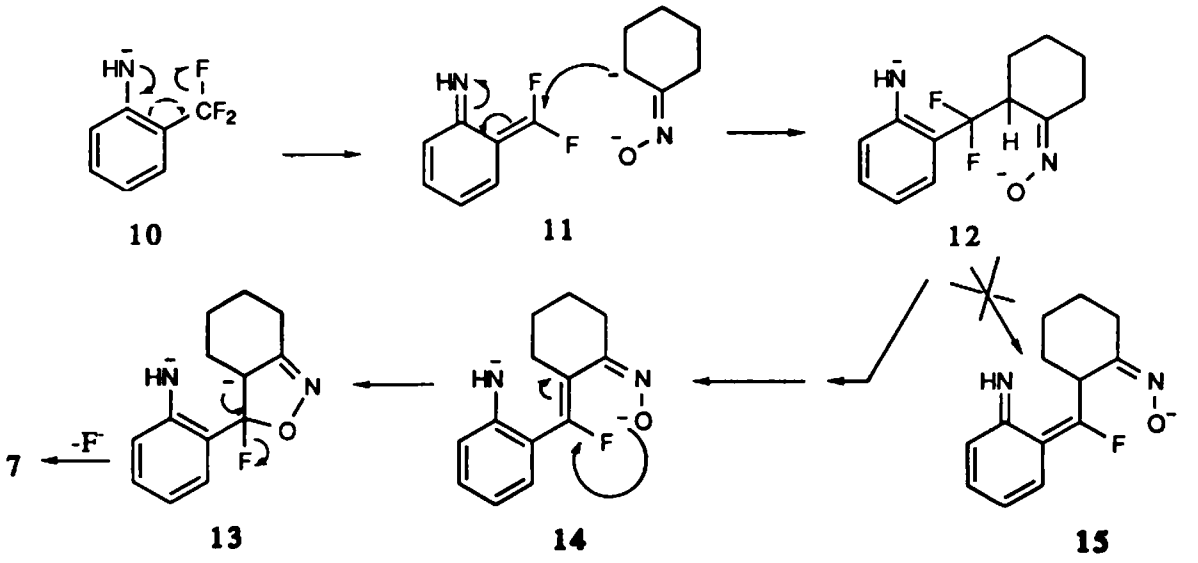
No	R^1	R^2	R^3
1, 4, 8	H	NH_2	H
2, 5, 9	NH_2	H	H
3, 6	NH_2	H	Cl

expected isoxazole **7** (17). On the other hand, an attempted reaction of **2** with dianion derived from cyclopentanone oxime failed to yield any identifiable product.

In the preparation of triazines **8, 9** a solution of benzamidine (20 mmol) in DME (10 mL) is treated dropwise at -20 °C with n-BuLi in cyclohexane (20 mmol). The mixture is stirred at 0°C for 10 min, treated with a solution of **1** or **2** (5 mmol) in DME (5 mL), and then heated under reflux under a nitrogen atmosphere for 12 h. Quenching with water followed by concentration on a rotary evaporator gives a triazine which is purified by sublimation and then crystallization (17). Compound **8** had spectral characteristics virtually identical with those of a sample of **8** obtained by an independent method (18). It should be noted, however, that our one-pot preparation is much simpler and yields a purer product than the literature method.

A first step of the transformations discussed above involve ionization of trifluoromethyl-substituted anilines **1-3** at the amino group, which is followed by elimination of fluoride from the resultant anion. The latter process is illustrated in Scheme 2 by the reaction **10**→**11**. In the pathway leading to **7** the intermediate product **11** undergoes a nucleophilic addition of the carbon-centered anion, the more nucleophilic site of the bidentate ketoxime dianion (15), to give an aromatic adduct **12**. It is proposed that intramolecular cyclization by the sequence **12**→**14**→**13** followed by aromatization of **13** produces the isoxazole **7**. The alternative pathway which would give **15** is less likely because it would result in loss of aromaticity and, as such, would be a higher energy process. The proposed pathway **12**→**14**→**13** is consistent with the experimental results that an isoxazole was not obtained in an attempted reaction of

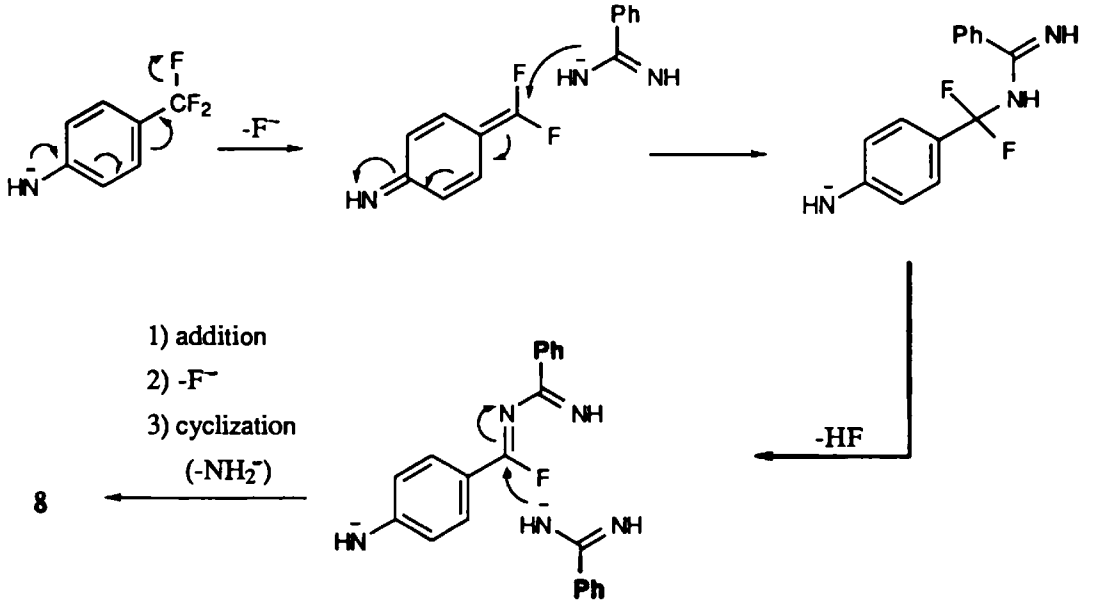
Scheme 2



dianion derived from cyclopentanone oxime, but, in contrast, the isoxazole **7** was prepared in a good yield starting with the cyclohexanone derivative. It can be hypothesized that the intermediate product **14** undergoes intramolecular cyclization as shown in Scheme 2. By contrast, a similar cyclization of an analog of **14** derived from cyclopentanone oxime does not occur for geometric reasons.

A similar mechanism, which requires a loss of aromaticity in the first step only, is proposed for 1,3,5-triazines, as briefly outlined in Scheme 3 for the particular case of a triazine **8**. This reaction involves two equivalents of benzamidine anion as required for the construction of a triazine system.

Scheme 3



In summary, we have described two novel unconventional syntheses of heterocyclic compounds. The modest efficiency is outweighed by ready availability of starting materials and facility of a one-pot procedure. It appears that the amino group in **1-3** can be replaced by other ionizable groups such as hydroxy or methyl for a similar anionic activation of the trifluoromethyl group. The scope and limitations of these novel chemistries will be published in due course.

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(16) Dilithiation of ketoximes with n-BuLi alone or LDA alone followed by the reaction with 1-3 resulted in lower yields of **4-7** in comparison to the use of a mixture n-BuLi/LDA for the dilithiation as described.

(17) Products **4-6**, 9 gave satisfactory elemental analyses (C, H, N) and analytically pure **7**, **8** were characterized by HRMS. Molecular ion peaks were observed in the mass spectra of all compounds **4-9**. ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) and ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) spectra were fully consistent with the given structures. In particular, for compound **4** an irradiation at δ 2.12 (C4-Me) gave a strong proton NOE signal at δ 7.50 (C2'-H/C6'-H) as expected. **4**: yield 16%, mp 88-90 °C ; **5**: yield 56%, an oil; **6**: yield 61%, an oil; **7**: yield 48%, an oil; **8**: yield 45%, mp 270-272 °C (from decalin) [reported (18) mp 273 °C]; 9: yield 20%, mp 188-190 °C (from ethanol)

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