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Trifluoroethanol as a metal-free, homogeneous and recyclable medium for the efficient one-pot synthesis of α-amino nitriles and α-amino phosphonates

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ABSTRACT

Trifluoroethanol is found to be an efficient and recyclable medium in promoting one-pot, three-component coupling reactions of aldehydes or ketones, amines and trimethylsilyl cyanide or trimethyl phosphite to afford the corresponding α-amino nitriles or α-amino phosphonates in high yields. This protocol does not require the use of an acid or base catalyst.

Fluorous solvents are a class of novel solvents, co-solvents, and additives with very interesting properties in synthetic chemistry and in various catalytic processes.[1] Fluorinated alcohols possess interesting physiochemical properties, which include lower boiling points and higher melting points than their non-fluorinated counterparts, high polarity, strong hydrogen bond donation properties and the ability to solvate water. The electron-withdrawing character of CF_3 confers high acidity to the hydrogen of the hydroxyl group. Besides these properties, fluorinated alcohols are not nucleophiles or hydrogen bond acceptors. Consequently, the degree of auto-association of fluorinated alcohols is low. The main advantage of fluorinated alcohols, for example hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE), is the possibility to carry out, in the absence of promoting agents, reactions that usually require the aid of Lewis acids or catalysts.[2] In addition, they can be easily separated from the reaction mixture for subsequent reuse. In order to take advantage of these properties, we have studied bond cleavage and formation reactions facilitated by the acidic character and strong hydrogen bond donor ability of fluorinated alcohols. We report here in two examples of one-pot, three-component reactions in trifluoroethanol (TFE): Strecker-type and Kabachnik–Fields reactions.

Among three-component condensation reactions, the addition of nucleophiles to in situ generated C=N bonds has become an extremely useful process for the synthesis of various nitrogen-containing molecules such as amines, α-amino nitriles, α-amino phosphonates, and other compounds of interest. However, it is difficult to extend the Lewis acid-catalyzed three-component condensation to the synthesis of amine derivatives because the strong affinity of many Lewis acids for amino groups does not allow regeneration of the Lewis acid during the reaction.[3] It should be noted that when the desired reaction does proceed, because the acids are trapped by the basic nitrogen, more than stoichiometric amounts of the Lewis acids are needed. Moreover, the Lewis acids can be decomposed by the water which is produced during imine formation.[4] On the other hand, many imines are hygroscopic, unstable at high temperatures, and are difficult to purify by distillation or column chromatography. Recently, we found that fluorinated alcohols such as HFIP and TFE activate $(Boc)_2O$ for *tert*-butoxycarbonylation of amines and amine derivatives.[5] These fluorinated alcohols can be recovered after the reactions are complete, and reused. Based on these unique properties of HFIP and TFE, we planned to use TFE as a solvent and catalyst for the one-pot, three-component preparation of α-amino nitriles and α-amino phosphonates from aldehydes and ketones.

α-Amino nitriles are important intermediates in the preparation of natural and unnatural α-amino acids and various nitrogen heterocycles.[6] They are generally prepared by nucleophilic addition of cyanide anion to imines. A variety of cyanating agents such as HCN,[7] KCN,[8] Et_2AlCN,[9] $(EtO)_2P(O)CN$,[10] Bu_3SnCN,[11] and Me_3SiCN[8] have been reported for Strecker-type reactions under various conditions.[12] Trimethylsilyl cyanide is an effective and safe source

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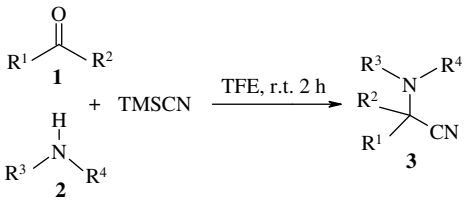
of cyanide anions.[13] Many catalysts have been used to promote the Strecker reaction using TMSCN, for example, lithium perchlorate,[14] scandium triflamide,[15] vanadyl triflate,[16] nickel(II) chloride,[17] zinc halides,[18] ruthenium(III) chloride,[19] ytterbium triflate,[20] bismuth(III) chloride,[21] and Montmorillonite KSF.[22] However, many of these catalysts are expensive, moisture sensitive, non-recyclable, and require extended reaction times and harsh conditions. Moreover, some of the Lewis acids used are toxic. In view of the emerging importance of the use of environmentally friendly and reusable reagents, we herein describe a simple and efficient protocol for the three- component coupling reactions of aldehydes (ketones), amines (both primary and secondary), and TMSCN or trimethyl phosphite to produce α-amino nitriles or α-amino phosphonates using TFE under mild reaction conditions.

Treatment of benzaldehyde and aniline with TMSCN in TFE afforded the corresponding α-amino nitrile in 97% yield at ambient temperature. This method is equally effective with electron-withdrawing 4-chlorobenzaldehyde and 2-cyanoaniline. Furthermore, the reaction conditions are mild enough to perform these reactions with acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde,[23] without any decomposition or polymerization, and with enolizable aldehydes such as cyclohexanecarboxaldehyde. This method is also effective with ketones. No cyanohydrin trimethylsilyl ether (an adduct between an aldehyde and trimethylsilyl cyanide) was obtained under these reaction conditions. This is due to rapid formation and activation of the imines or iminium salts by TFE. In this reaction, the molar ratio of aldehyde or ketone: amine: TMSCN was 1:1:1. After the reaction was complete, the solvent was evaporated, and the products were isolated with acceptable purity (by NMR). The recovery of TFE by fractional distillation below 80 °C with 98% purity was sufficient for its reuse. For example, the reaction of benzaldehyde, aniline, and trimethylsilyl cyanide gave the corresponding α-amino nitrile (Scheme 1, entry 1) in 97%, 97%, and 95% yields over three cycles.

Due to a broad spectrum of biological activity, α-amino phosphonates have received significant attention in organic synthesis,[24] and various methods have been developed for their synthesis.[25] However, many of the catalysts employed have drawbacks, for example, reactions require a long time[25d,25e,25n] when the carbonyl compounds are ketones, and when the starting materials contain aliphatic amines, some reactions gave uncharacterizable products.[25j] In addition, some of these catalysts are costly, moisture sensitive, and are difficult to prepare. Furthermore, α-amino phosphonates formed from aliphatic aldehydes are typically obtained in moderate yields, and the reported methods do not work well with electron-deficient amines such as nitroanilines. Thus, we explored the effectiveness of TFE as a reusable catalyst for the generation of α-amino phosphonates. Reaction of trimethyl phosphite with the in situ generated imine from benzaldehyde and aniline in TFE at room temperature afforded the corresponding α-amino phosphonate in a very good 97% yield (Scheme 2).

Under optimized conditions, the reaction of aniline with a variety of aromatic aldehydes containing electron-withdrawing groups (entries 2 and 3) or with aliphatic aldehydes such as butyraldehyde and trimethyl phosphite funished the corresponding α-amino phosphonates in very high to excellent yields. For generalization of this method, we also screened *p*-chloroaniline, *p*-methoxyaniline, dibenzylamine, and morpholine in reactions with various aldehydes and ketones and obtained the desired α-amino phosphonates in very good yields.

In summary, we have described simple, convenient and practical methods for the synthesis of α-amino nitriles and α-amino phosphonates through the one-pot, three-component coupling of aldehydes or ketones, amines (primary and secondary), and trimethylsilyl cyanide or trimethyl phosphite using TFE as a reusable solvent and catalyst.



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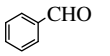
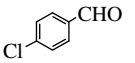
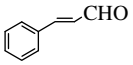
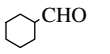
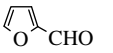
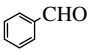
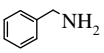
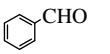
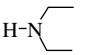
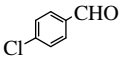
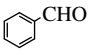
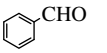
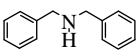
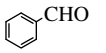
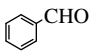
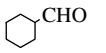
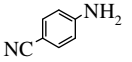
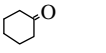
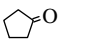
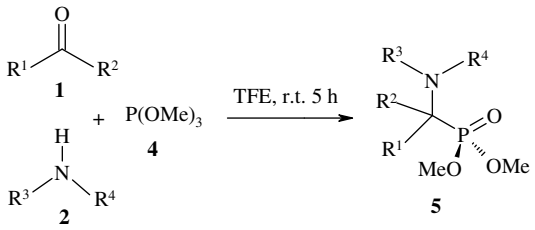
1			97 [22]
2			97 [22]
3			96 [22]
4			98 [27]
5			95 [22]
6			93 [17]
7			96 [27]
8			98 [28]
9			95 [16]
10			96 [14]
11			95 [17]
12			95 [27]
13			90 [16]
14			97 [26]
15			97 [26]

[a] The spectral data (^{1}H, ^{13}C NMR) of known compounds were found to be identical with those reported in the literature.

Scheme 1.

General procedure for the preparation of α amino nitriles: A mixture of amine (1 mmol), aldehyde (1 mmol), and trimethylsilyl cyanide (1 mmol) in TFE (1 mL) was stirred at ambient temperature for the appropriate amount of time (2 h). After completion of the reaction as indicated by TLC, the TFE was separated by distillation and the crude product was purified by recrystallization from diethyl ether (solid products) or by chromatography using silica gel and mixtures of hexane/ethyl acetate of increasing polarity. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature.[14,16,17,22,26–28]

General procedure for the preparation of α amino phosphonates: A mixture of amine (1 mmol), aldehyde (1 mmol), and trimethyl-



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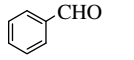
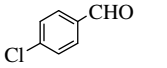
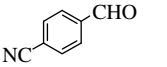
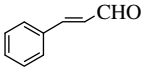
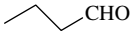
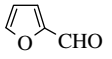
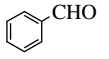
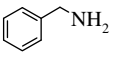
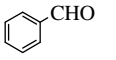
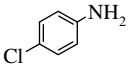
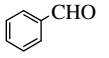
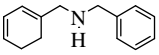
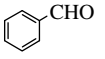
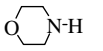
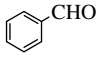
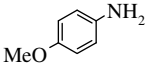
1			97 [25h]
2			93 [25l]
3			85 [28]
4			93 [25l]
5			95 [25h]
6			95 [25l]
7			90 [25l]
8			82 [28]
9			80 [25h]
10			90 [25l]
11			92 [28]
12			95 [25l]
13			85 [25l]

[a] The spetral data (^{1}H, ^{13}C NMR) of known compounds were found to be identical with those reported in the literature.

Scheme 2.

phosphite (1 mmol) in TFE (1 mL) was stirred at ambient temperature for the appropriate amount of time (5 h). After completion of the reaction as indicated by TLC, the TFE was separated by distillation and the crude product was purified by recrystallization from diethyl ether (solid products) or by chromatography using silica gel and mixtures of hexane/ethyl acetate of increasing polarity. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature.[25h,25l,28] Spectroscopic data for a selected example: (Scheme 2, entry 12)[25l]: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.50 (m, 6H), 1.54–2.10 (4H, m), 3.64 (d, J = 10.4 Hz, 3H), 3.66 (d, J = 10.4 Hz, 3H), 4.84 (br s, 1 H), 7.00 (t, J = 7.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.16 (t, J = 8.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 52.2 (d, $^2J_{P-C}$ = 7.4 Hz, OCH_3), 53.2 (d, $^2J_{P-C}$ = 7.4 Hz, OCH_3), 65.2 (d, J_{P-C} = 155.1 Hz, C), 118.2 (CH), 118.3 (CH), 129.1 (CH), 145.5 (C).

Acknowledgment

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References and notes

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