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Reaction of triflyl-imidazole with aldoximes: facile synthesis of nitriles and formation of novel aldoxime-bis(*N*-triflyl)-imidazole adducts

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ABSTRACT

The synthetic utility of *N*-triflylimidazole as an in situ reagent for facile, high yielding, synthesis of various aliphatic, aromatic, and heteroaromatic nitriles from the corresponding aldoximes has been demonstrated. With benzaldoximes, in the presence of certain substitutents (2-F; 2-OMe; 3-CF₃; 2-Me-5-F) a different course of reaction was observed, leading instead to novel 1:1 aldoxime-bis(*N*-triflyl)imidazole covalent adducts, in which the aldoxime oxygen atom is bonded to the imidazole C-2 ring carbon. For these aldoximes, conversion to nitrile could be effected by reaction with Tf₂O in the absence of imidazole. The molecular structure of the adduct formed from 2-methyl-5-fluoro-benzaldoxime was confirmed by X-ray analysis. Plausible mechanisms for the formation of 1:1 covalent adducts have been considered. Various attempts to isolate such adducts via the reaction of an authentic sample of bis(*N*-triflyl)imidazolium trifate with aldoxime were unsuccessful. Remarkably, whereas isolated benzaldoxime adducts undergo deprotonation/methylation with NaH/Mel, an authentic sample of bis(*N*-triflyl)imidazolium triflate did not undergo H/Me exchange under these conditions. These transformations are discussed.

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Due to its widespread presence in natural products, pharmaceuticals, and functional materials, and its high versatility for conversion to other functional groups, the cyano moiety occupies a position of paramount importance in chemistry. The –CN group can be synthesized from a wide range of precursors using a large number of methods and reagents that have been discussed and summarized earlier in several authoritative reviews.^{1a-g} Among these, one of the most extensively studied methods is by dehydration of aldoximes. Some of the more recently reported synthetic methods/reagents for the preparation of nitriles from aldoximes include bromodimethylsulfonium bromide,² Pd(OAc)₂/PPh₃,³ Ru(Ph₃P)₃(CO)H₂/Xantphos,⁴ ClSO₃H/toluene,⁵ (EtO)₂POCl/toluene,⁶ dry or wet alumina,⁷ CuCl₂/MeCN/ultrasound,⁸ silica sulfate/acetone,⁹ enzymatic method,¹⁰ NH₂OH·HCl/red-mud/ microwave,¹¹ Ph₃P/Tf₂O,¹² 1-pentyl-3-methylimidazolium tetrafluoroborate,¹³ 2,4,6-trichloro[1,3,5]triazine in DMF,¹⁴ and BOP/ DBU or Bt-OTS/DBU.¹⁵

In a short Letter published in 1970, Effenberger and Mack¹⁶ introduced a new reagent trifluoromethanesulfonic imidazolide (triflylimidazole) **1**, by reacting imidazole with Tf_2O (in 2:1 ratio), and isolated this compound as a low boiling liquid (Scheme 1). The utility of **1** as a triflyl-transfer reagent was briefly shown in reaction with phenols, forming aryl triflates, but its potential to effect other transformations remained unexplored.



convenient, high yielding, method for the synthesis of various nitriles, and on the formation of novel 1:1 aldoxime-bis(*N*-triflyl) imidazole adducts with certain substituted benzaldoximes. Structure of these adducts and the mechanistic implications of this transformation are discussed.

Given the potential of triflylimidazole as a triflyl transfer agent, we reasoned that it might serve as a convenient reagent for the dehydration of aldoximes according to Scheme 2. Initial studies sought to employ isolated **1**, but the isolated yields proved to be rather low despite the fact that the reaction proceeded efficiently and in good yields, judging from the amount of the imidazolium triflate byproduct that was formed and isolated. Subsequent work focused on employing this reagent in situ without isolation, and this proved successful.

A variety of aliphatic, aromatic, and heteroaryl oximes were converted to nitriles in respectable isolated yields at room temperature.¹⁷ The results are summarized in Table 1. Given the mild





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Scheme 2. Aldoxime to nitrile conversion via the in situ generated triflylimidazole.

 Table 1

 Conversion of aldoximes to nitriles with *N*-triflylimidazole

Entry	Oximes	Product	Oxime:Tf ₂ O ratio	Time (h)	Isolated yield ^{c} (%)
1	H)=N OH	——————————————————————————————————————	0.7	16	61
2		N	0.5	12	70
3	N-OH	√N	1	18	78
4			0.5	12	65
5	O ₂ N-V-OH	0 ₂ N-(=)-=N	0.75	12	76
6	о- N-он		1	4	83 ^a
7	ОН М-ОН	, N	1	4.3	67 ^{b,19}
8	о- М-он	`0-√N	0.55	12	88
9	к К	F N	1	6	82ª
10	F ₃ C	F ₃ C	1	12	71 ^a
11	N_OH	N	1	12	74
12	€ N-OH	€ O D N	0.66	12	78
13	N-OH H	[∑N H H	0.4	12	84
14	€ S ^{N−OH}	∑N	1	12	72
15	E,E isomer	CN	0.7	2.5	87
16	E, Z isomer	CN	0.7	2.5	85

^a Product obtained in the absence of imidazole.

^b Benzisoxazole¹⁹ was obtained both with and without imidazole.

^c Reported yields are based on quantity of aldoximes taken.

conditions and absence of high boiling solvents, the method is superior to a recently reported method using *N*-tosylimidazole/DBU in refluxing DMF or DMSO.¹⁸ With substituted benzaldoximes variable

outcomes were observed depending on the substituents. Thus whereas the 2-NO₂, 4-NO₂, and 4-OMe derivatives gave nitriles, unexpected products were isolated from 2-F, 2-OMe, 2-Me/5-F,



R = 2-F (**a**), 2-OMe (**b**), 2-Me-5F (**c**), 3-CF₃ (**d**)

Scheme 3. Formation of covalent adducts (3a-d).



Figure 1. X-ray structure, ORTEP diagram of compound **3c** (thermal ellipsoid plot; ellipsoids are drawn at the 30% level. H atoms are omitted for clarity).

and $3-CF_3$ benzaldoximes (**2a–d**). However by excluding imidazole from the reaction, and in DCM as solvent, these benzaldoximes reacted 'normally' to give nitriles (Table 1; entries 6, 9, and 10).

To gauge the influence of aldoxime stereochemistry on the ease of dehydration, and in concert with the work of Singh and Lakshman,¹⁵ we studied the reaction of *E*,*E*- and *E*,*Z*-cinnamaldoximes with **1** in side-by-side experiments. TLC monitoring the progress of the reactions indicated that both isomers reacted to the same extent, forming *E*-nitrile in near equal overall yields, suggesting that aldoxime stereochemistry did not influence the ease of dehydration.

Turning our attention to the adducts, suitable crystals were obtained from 2-Me/5-F derivative (**3c**) for X-ray analysis, establishing the formation of novel 1:1 aldoxime-bis(*N*-triflyl)imidazole covalent adducts, in which the aldoxime oxygen atom is bonded to the imidazole C-2 ring carbon (see Scheme 3). The ORTEP plot for **3c** is shown in Figure 1. The ArCH=N, CHN–O, and the CHNO–CH bond length are 1.278, 1.447, and 1.381 Å, respectively. The molecular structures of all four compounds were fully established by multinuclear 1D (¹H, ¹³C, ¹⁹F) and by 2D NMR correlation (HMQC; see experimental and Supplementary data).

As depicted in Scheme 4, formation of the covalent adducts **3** may be explained by equilibrium formation of *N*-heterocyclic carbene (NHC) derived from bis(triflyl)imidazolium triflate as a key intermediate. Alternatively, the imidazolium triflate may undergo nucleophilic attack by the conjugate base of benzaldoxime.

Subsequent studies focused on gathering information in connection to the mechanistic hypothesis outlined in Scheme 4. The proposed bis(*N*-triflyl)imidazolium triflate **4** was independently synthesized and isolated in good yield by further reaction of **1** with Tf₂O. With **4** at hand, several reactions, employing various bases, were performed in an effort to synthesize covalent adducts with benzaldoximes, but no such adducts could be isolated and the aldoximes remained unreacted (Scheme 5).

In a recent report from Beller et al.²⁰ BuLi/Mel was used to introduce a methyl at C-2 in diphenyl-substituted imidazolium salts. Contrary to our expectation that presence of -Tf groups should lower the pK_a of salt **4** allowing a milder base to be used for deprotonation, in a control experiment, **4** could not be methyl-ated with NaH/Mel to give **5** (Scheme 5).

Returning to the isolated 1:1 covalent adducts, we reasoned that deprotonation may trigger the break-up of the C–O bond, forming an NHC which could possibly be trapped with RX. Remarkably reaction with NaH/MeI resulted in H/Me exchange and this was shown with three different adducts (Scheme 6). Attempts to install R groups larger than methyl were unsuccessful, and reactions with adamantly-, isopropyl- and ethyl bromide as well as ethyl iodide resulted in the recovery of intact adducts.

In summation, the present study has demonstrated interesting new applications for triflylimidazole **1**, a reagent first reported by Effenberger and Mack¹⁶ in 1970 for the synthesis of ArOTf from phenols. Whereas the in-situ formed **1** proved efficient for nitrile synthesis from a variety of aldoximes under mild conditions in respectable isolated yields, more remarkable was the formation of novel covalent adducts with certain substituted benzaldoximes. Although formation of covalent adducts via the corresponding NHC or by direct nucleophilic attack of benzaldoxime seems plausible, our attempts to independently generate covalent adducts by reacting the bis(*N*-triflyl)imidazolium triflate **4** with benzaldoximes in the presence of various bases have been unsuccessful. The isolated adducts undergo H/Me exchange with NaH/MeI to give the methylated analogs in good yields but this reaction appears to be highly



Scheme 4. Suggested mechanisms for the formation of covalent adducts (3a-d).



Scheme 5. Exploring adduct formation from 4.



R = 2-OMe, 3-CF₃, 2-Me-5-F

Scheme 6. Synthesis of methylated adducts (6b-d).

sensitive to steric affects, since R groups larger than CH_3 could not be installed by this method.

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Supplementary data

Supplementary data (X-ray data collection parameters, (excluding structure factors) for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 822706. Copies of the data can be obtained, free of charge, via http://www.pubs.acs.org or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033; or e-mail: deposit@ccdc.cam.ac.uk) associated with this article can be found, in the online version, at doi:10.1016/ j.tetlet.2011.07.135.

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- 17. General procedure for synthesis of nitriles from oximes (1-16): A mixture of aldoximes (1 mmol) and imidazole (3 mmol) in anhydrous DCM (10-15 mL) was charged into an oven-dried round-bottom flask under nitrogen and the reaction mixture was stirred at r.t. for 20 min, after which triflic anhydride (0.4-1.0 mmol) was added dropwise via syringe under nitrogen, and the reaction mixture was allowed to stir at r.t. for a specific time (Table 1). Progress of the reaction was monitored by TLC and/or by GC-MS. Upon completion, the reaction mixture was quenched with dilute NaHCO₃ solution and the product mass was extracted in DCM. The solvent was removed under reduced pressure to yield the crude product which was purified by prep TLC (ethyl acetate–hexane mixture) (80:20), to give the corresponding nitrile (61–88% yield). The structure of the products was confirmed by comparison of their mp or bp, TLC, IR, GC-MS, ¹H NMR and ¹³C NMR data with authentic samples obtained commercially or prepared by literature methods.

General procedure for the synthesis of adducts (**3a**–**d**): A mixture of aldoximes (**2a**–**d**) (1 mmol) and imidazole (3 mmol) was added to anhydrous DCM (10– 15 mL) in an oven-dried round bottom flask under nitrogen and stirred at r.t. for 20 min. Triflic anhydride (0.4–1 mmol) was then introduced dropwise via syringe under nitrogen and the reaction mixture was allowed to stir at r.t. overnight. The progress of reaction was monitored by TLC and by GC–MS. Upon completion the reaction mixture was quenched with dilute NaHCO₃ solution, and the product mass was extracted in DCM, removal of solvent gave the crude product, which was purified by Prep-TLC (ethyl acetate–hexane mixture) (80:20) and column chromatography (ethyl acetate–hexane mixture) (80:20) to give the corresponding adducts (65–90% yield), whose structures were confirmed by NMR (¹H, ¹³C and HMQC; see below), and by X-ray analysis in the case of **3c**. GC–MS analysis of adducts **3** consistently exhibited an intense *m*/*z* 333 ion corresponding to the bis(*N*-triflyl)imidazolium cation, and the intact molecular ions were not detected even at 20 eV.

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