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Isolable Pyridinium Trifluoromethoxide Salt for Nucleophilic Trifluoromethoxylation

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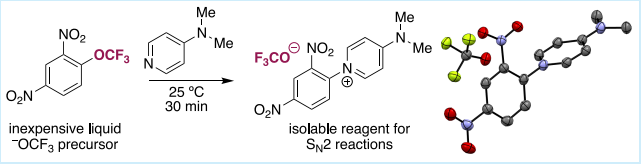
ABSTRACT: An isolable pyridinium trifluoromethoxide salt is prepared from the reaction of 4-dimethylaminopyridine with the commercially available liquid 2,4-dinitro(trifluoromethoxy)-benzene. The salt is an effective trifluoromethoxide source for S_N2 reactions to form trifluoromethyl ethers.



The trifluoromethoxy group (OCF_3) has emerged as an important structural motif in scaffolds relevant to both agrochemical and pharmaceutical development.[1] The introduction of an OCF_3 substituent has been shown to enhance the lipophilicity[2,3] [Hansch parameter (π) = 1.04], bioavailability, and metabolic stability[4,5] of biologically active molecules.[6,7] As a result of the increasing importance of this functional group, considerable recent attention has been focused on developing practical and convenient reagents for introducing OCF_3 groups into organic molecules.[8−11]

Nucleophilic trifluoromethoxide reagents are widely used for the construction of carbon−OCF_3 bonds.[12−17] As one example, S_N2 reactions between alkyl electrophiles and trifluoromethoxide salts serve as an effective route to alkyl trifluoromethyl ethers (Figure 1A).[7,18−20] However, at present, no trifluoromethoxide salts are commercially available.[7,21] Instead, these reagents are typically formed *in situ* through the reaction of fluoride or amine nucleophiles with OCF_3-containing electrophiles (Figure 1B), of which common examples are trifluoromethyl triflate (TFMT),[7,22] trifluoromethyl arylsulfonate (TFMS),[14] trifluoromethyl benzoate (TFBz),[23] or trifluoromethyl methyl ether ($MeOCF_3$).[24] The practicality and scalability of these *in situ* protocols are limited by the OCF_3-containing electrophiles, of which many are gases at room temperature (TFMT and $MeOCF_3$), are expensive/require costly reagents (TFMT and TFMS), and/or require multi-step syntheses (TFMS and TFBz), often involving highly toxic fluorophosgene (TFBz).

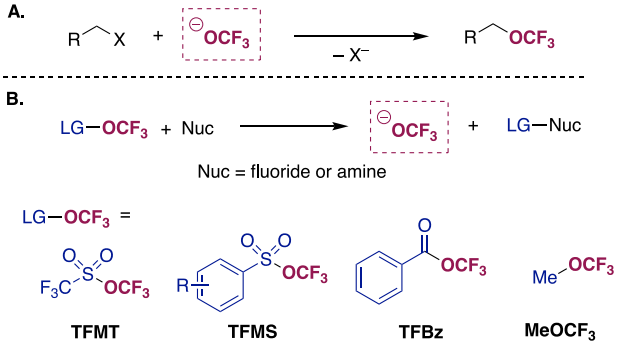


Figure 1. (A) S_N2 reactions using *in situ* generated trifluoromethoxide salts. (B) General procedure for *in situ* activation of trifluoromethoxide electrophiles with nucleophiles to form trifluoromethoxide salts.

Many of these limitations could be addressed by leveraging commercially available 2,4-dinitro(trifluoromethoxy)benzene (DNTFB) as an OCF_3 electrophile. In contrast to the reagents in Figure 1B, DNTFB is a convenient-to-handle high boiling liquid that is relatively inexpensive.[25] In 2010, Langlois and coworkers reported that the S_NAr reaction between DNTFB and tetrabutylammonium triphenyldifluorosilicate (TBAT) releases Bu_4NOCF_3.[19] This *in situ* generated trifluoromethoxide salt was then used as a nucleophile for S_N2 reactions (Scheme 1A). We noted that DNTFB shares the dinitrobenzene moiety with 2,4-dinitrochlorobenzene, which is the reagent used for the formation of pyridinium salts in the Zincke reaction.[26] As such, we hypothesized that pyridine nucleophiles could undergo S_NAr with DNTFB to afford isolable trifluoromethoxide salts with a highly delocalized pyridinium countercation ($PyOCF_3$; Scheme 1B). The advantages of this approach are 2-fold: (1) the trifluoromethoxide salt would be generated from two easy-to-handle, commercially available, and inexpensive precursors, and (2) the isolation of the salt would enable structural characterization as well as deployment under a variety of

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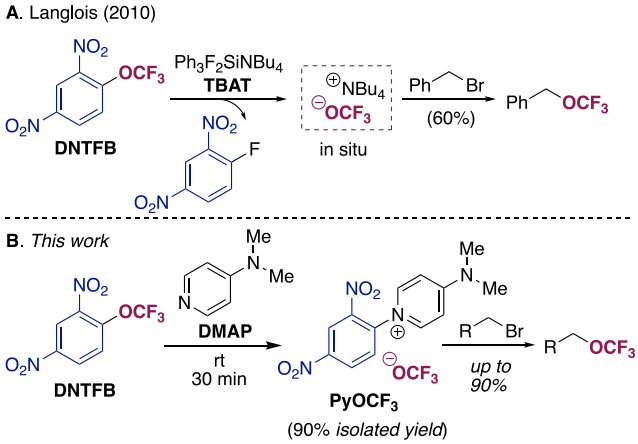
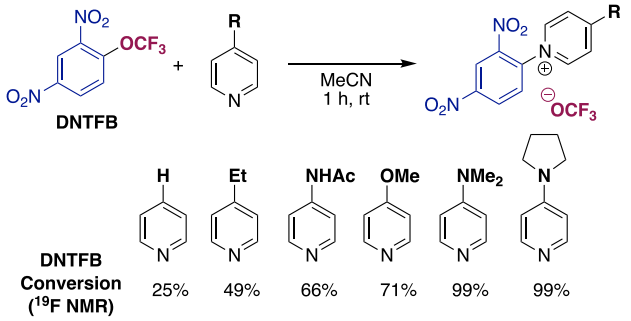
Scheme 1. DNTFB as a Trifluoromethoxide Source



conditions (without limitations to the reaction media required for salt formation).

Our initial studies explored the reaction of 1 equiv of DNTFB with 1 equiv of various pyridine derivatives in MeCN for 1 h at room temperature. As shown in Scheme 2, the

Scheme 2. Conversion of DNTFB Using Different Pyridine Derivatives



percent conversion of DNTFB under these conditions tracks closely with the nucleophilicity of the pyridine. For example, while unsubstituted pyridine affords only 25% conversion, the more nucleophilic 4-dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine result in quantitative conversion of DNTFB. This is accompanied by the formation of a broad ^{19}F nuclear magnetic resonance (NMR) resonance at −22 ppm, which is consistent with the generation of a trifluoromethoxide salt.[17] DMAP was ultimately selected as the optimal activator for DNTFB as a result of its low cost[27] and ease of handling as a free-flowing solid.

The reaction between DNTFB and DMAP proceeds to high (>99%) conversion in a variety of polar aprotic solvents, including *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and *N*,*N*′-dimethylpropyleneurea (DMPU), to afford soluble $PyOCF_3$. In contrast, when the reaction is conducted in tetrahydrofuran (THF), $PyOCF_3$ forms as a yellow precipitate after 30 min at room temperature (Figure 2A). This solid can be collected by filtration and isolated in 90% yield and 94% purity. The major impurities are 1-fluoro-2,4-dinitrobenzene and DMAP. These arise from decomposition of trifluoromethoxide to fluorophosgene and fluoride followed by S_NAr reaction of the latter with the pyridinium cation (Figure S1 of the Supporting Information).

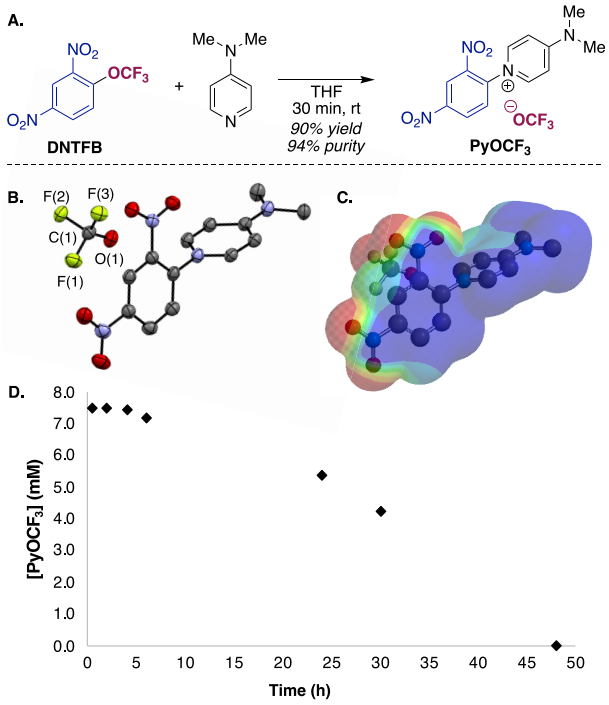


Figure 2. (A) Synthesis of $PyOCF_3$. (B) ORTEP diagram of $PyOCF_3$ (ellipsoids at 50% probability). Selected bond distances (Å): C(1)−O(1), 1.216; C(1)−F(1), 1.406; C(1)−F(2), 1.402; and C(1)−F(3), 1.408 (hydrogen atoms are omitted for clarity). (C) Electrostatic potential map of $PyOCF_3$. (D) Decomposition of an 8.0 mM solution of $PyOCF_3$ in MeCN-d_3 at room temperature. Concentrations determined by ^1H NMR spectroscopy with benzene as an internal standard.

X-ray quality crystals were obtained by slow diffusion of diethyl ether into a MeCN solution of $PyOCF_3$ at −35 °C. An Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram is shown in Figure 2B. The bond distances and angles for $PyOCF_3$ are similar to those reported in the literature for tris(dimethylamino)sulfonium trifluoromethoxide ($TASOCF_3$).[28] In both structures, the C−O single bond is relatively short (1.216 Å in $PyOCF_3$ and 1.227 Å in $TASOCF_3$), which is consistent with significant hyperconjugation. An electrostatic potential map for this salt (Figure 2C) illustrates that the conjugated nature of the cation results in substantial delocalization of the positive charge.[29]

The stability of $PyOCF_3$ was evaluated in two different ways. First, a sample of solid $PyOCF_3$ was stored at −35 °C under nitrogen and periodically assayed by ^{19}F and ^1H NMR spectroscopy. No decomposition of this material was detected over 1 month. Second, the decomposition of an 8.0 mM solution of $PyOCF_3$ in MeCN was monitored via ^1H NMR spectroscopy at room temperature. As shown in Figure 2D, after 30 h, approximately 50% of the salt remained, while full decomposition was observed after 48 h. These data indicate that the solution stability of $PyOCF_3$ is considerably lower than that of the quaternary ammonium trifluoromethoxide salts reported by Friesen and co-workers.[24]

Finally, $PyOCF_3$ was employed as a nucleophilic trifluoromethoxide source for S_N2 reactions (Table 1). We first examined benzyl bromide as the substrate under conditions reported by Langlois and co-workers[19] [using 2 equiv of $PyOCF_3$ (generated *ex situ* from DNTFB and DMAP as a 0.4 M solution in MeCN) at room temperature for 4 days]. This

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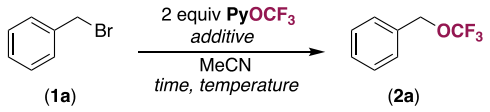
Table 1. Optimization of Nucleophilic Substitution of Benzyl Bromide (1a) with Trifluoromethoxide Salt ($PyOCF_3$)[a]



entry	temperature (°C)	time (h)	additive[b]	yield (%)[c]
1	rt	96	none	38
2	40	24	none	58
3	40	24	AgOTf	70
4	40	5	AgOTf	74
5[d]	40	5	AgOTf	76
6[e]	40	5	AgOTf	20

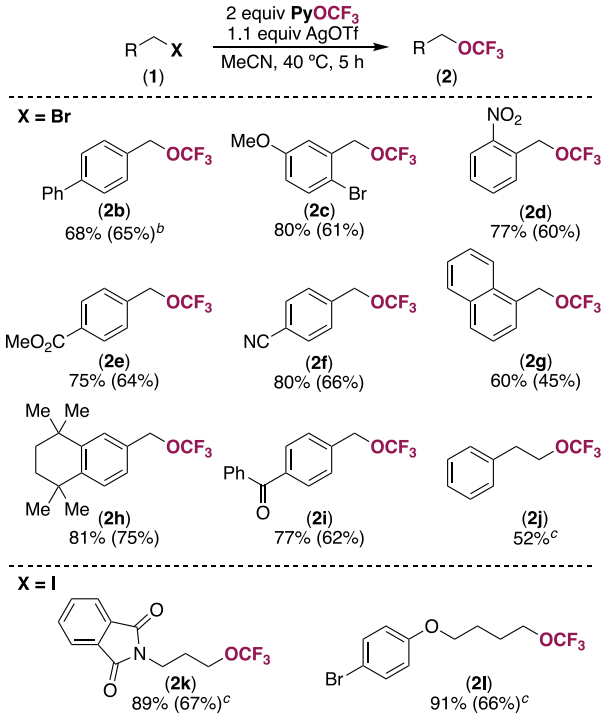
[a]Conditions: 0.05 mmol of compound **1a** and 0.1 mmol of $PyOCF_3$ (generated *ex situ* as a solution in MeCN). [b]A total of 1.1 equiv of silver salt. [c]Yields determined by ^{19}F NMR spectroscopy using trifluorotoluene ($PhCF_3$) as an internal standard. [d]Using isolated $PyOCF_3$. [e]*In situ* generation of $PyOCF_3$ in a single pot.

reaction afforded compound **2a** in 38% yield (entry 1 in Table 1). Increasing the temperature to 40 °C and lowering the reaction time to 24 h resulted in a 58% yield of compound **2a**. The addition of 1.1 equiv of AgOTf led to a further enhancement in the yield to 70%, likely driving the reaction by the precipitation of AgBr[7,24] (entries 2 and 3 in Table 1). Under the optimal conditions (1 equiv of benzyl bromide, 2 equiv of *ex situ* generated $PyOCF_3$ as a 0.4 M solution in MeCN, and 1.1 equiv of AgOTf at 40 °C for 5 h), product **2a** was formed in 74% yield (entry 4 in Table 1) and only traces (<5%) of benzyl fluoride were detected.[30] Notably, benzyl fluoride is a common byproduct in other S_N2 reactions with trifluoromethoxide, and it derives from decomposition of trifluoromethoxide to fluorophosgene and fluoride, followed by S_N2 by the latter.[7] We hypothesize that the high chemoselectivity with $PyOCF_3$ is due to the cation serving as a fluoride sponge via S_NAr (see the Supporting Information for further details). Consistent with this proposal, the reaction of $PyOCF_3$ with 1 equiv of anhydrous NMe_4F afforded 1-fluoro-2,4-dinitrobenzene in 63% yield.[31]

We evaluated the scope of this reaction with respect to the alkyl halide electrophile (Scheme 3).[32] A variety of functionalities, including methoxy, nitro, ester, amide, and nitrile groups, were well-tolerated. We note that the yields with $PyOCF_3$ under these conditions are comparable to or slightly lower than those reported with other trifluoromethoxide salts.[33] However, the practicality and synthetic accessibility of $PyOCF_3$ render it an attractive alternative. In addition, only traces of benzyl and alkyl fluorides were observed in these systems, which demonstrates a higher selectivity for trifluoromethoxylation over nucleophilic fluorination.

In conclusion, this report describes the synthesis and characterization of a new pyridinium trifluoromethoxide salt that is easily prepared from inexpensive and readily available starting materials. This salt serves as an effective reagent for S_N2 reactions, and we anticipate that it should find broader use as a practical trifluoromethoxide source for other transformations.

Scheme 3. Trifluoromethoxylation of Benzyl and Alkyl Bromides with $PyOCF_3$[a]



[a]Conditions: 1.0 equiv of alkyl halide, 2.0 equiv of $PyOCF_3$ (0.4 M solution in MeCN), 1.1 equiv of AgOTf, 40 °C, and 5 h. [b]A 1.0 mmol scale reaction. [c]Reaction time = 20 h. Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene ($PhCF_3$) as an internal standard and represent an average of three runs. Isolated yields are in parentheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01664.

Experimental procedures, optimization details, X-ray crystallographic data, and NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1k**, **1l**, **2b**–**2i**, **2k**, **2l**, and $PyOCF_3$ (ZIP)

Accession Codes

CCDC 2080854 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(31) The reaction of 0.05 mmol of $PyOCF_3$ with 0.05 mmol of anhydrous Me_4NF in MeCN-d_3 at room temperature for 1 h resulted in complete decay of the trifluoromethoxide signal, and the formation of 1-fluoro-2,4-dinitrobenzene as the major product in 63% yield, as determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

(32) Secondary alkyl bromides, including bromodiphenylmethane, 1-bromoethylbenzene, and 2-bromopentane, were also evaluated as substrates for this transformation and yielded trifluoromethoxylated products **2m**, **2n** and **2o** in 58, 51, and 40% ^{19}F NMR yield, respectively. The isolation of these products proved difficult as a result of their volatility and the modest stability of the products to the isolation conditions (see the Supporting Information for details).

(33) For example, product **2e** was formed in 87% yield using $AgOCF_3$ (generated from TFMT; ref 22a), 78% yield using TFMS (ref 15), and 73% yield using 1,1-dimethylpyrrolidinium trifluoromethoxide (generated from $MeOCF_3$; ref 24).

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