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A new synthesis of pyridinyl trifluoromethanesulfonates via one-pot diazotization of aminopyridines in the presence of trifluoromethanesulfonic acid

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ABSTRACT

The first method for the direct one-pot transformation of aminopyridines into pyridinyl trifluoromethanesulfonates is developed. The procedure involves diazotization of aminopyridines with sodium nitrite in a DMSO paste in the presence of trifluoromethanesulfonic acid.

Pyridinyl trifluoromethanesulfonates contain a triflate as a good leaving group and hence represent compounds of significant value for organic synthesis. For example, substitution of the triflate group can give valuable pyridine derivatives such as bipyridines,[1a] pyridinylpiperazines,[1b] highly functionalized indolizines,[1c] β-carbolines,[1d] arylpyridines,[1e] and pyridyl guanidines,[1f] iodopyridines, quinolines, isoquinolines,[2a–d] pyrrolo-[2,3 *b*]pyridines,[2e] and pyridinyl biosensors.[2f]

Currently, the esterification of hydroxypyridine with trifluoromethanesulfonic acid anhydride and harmful and toxic trifluoromethane sulfonylchloride[1–4] or trifluoromethanesulfonic acid amides[5] in the presence of the base in organic solvents are the only methods for the synthesis of pyridinyl trifluoromethanesulfonates. In general, these methods provide good yields of pyridinyl trifluoromethanesulfonates, but the high cost of reagents, inert atmosphere in some cases, and low temperature (down to −78 °C) make the target products fairly expensive to prepare.

The goal of this work was to develop a one-pot synthesis of pyridinyl trifluoromethanesulfonates from aminopyridines which are often more accessible and cheaper starting materials in comparison with pyridinols. The background for this approach is given in our previous work.[6] We have shown that diazotization of aminopyridines with sodium nitrite in the presence of *p*-TsOH in water paste led to the corresponding pyridinyl tosylates in one step.[6] This differentiated significantly the aminopyridines from other aromatic amines that form stable arenediazonium tosylates[7] after diazotization in the presence of *p*-TsOH. The reason for these differences between aromatic amines and aminopyridines[6,7] is the well-known instability of pyridine diazonium salts compared to arenediazonium salts.[8]

Initially, the approach described in our previous work[6] was utilized. *p*-TsOH was replaced by TfOH (Method A) in the water paste with no desirable effect. It was found that the addition of sodium nitrite to aminopyridines **1a**–**k** in aqueous paste with 3 equiv of TfOH at ambient temperature led to a rapid release of nitrogen oxides and incomplete conversion of the initial aminopyridine. The major products were the corresponding hydroxypyridines and starting aminopyridines **1**, although the desired pyridinyl trifluoromethanesulfonates **2a**–**k** were identified in the reaction mixture. The lower selectivity of diazotization–triflation relative to diazotization–tosylation[6] probably is a reflection of the lower nucleophilicity of TfOH. A more detailed search for suitable conditions was conducted for the synthesis of pyridinyl trifluoromethanesulfonates via diazotization of 2-amino-5-bromopyridine **1a** (Table 1) in the presence of TfOH.

Diazotization of aminopyridine **1a** by grinding with $NaNO_2$ and TfOH under solvent-free conditions (Method B) almost eliminated the side hydroxypyridine formation, however, full conversion of starting substrate **1a** took a long time (36 h). Using *n*-BuONO as the diazotizing agent instead of $NaNO_2$ (Method C) did not give a satisfactory result. Tar formation, a low yield of the desired triflate **2a**, incomplete conversion of the starting amine, and large amounts of the 5-bromo-*N*-butylpyridin-2-amine side product (Table 1) were observed. Apparently, this side product is formed

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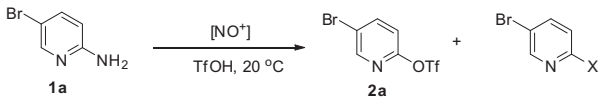
by the alkylation of initial aminopyridine **1a** with *n*-BuOTf or protonated *n*-BuONO, which can appear in the presence of TfOH. A similar side product 5-bromo-*N*-(*tert*-butyl)pyridin-2-amine was formed by diazotization of **1a** in *tert*-butanol (Method D, Table 1); the alkylation process in this case was probably due to *t*-BuOH. Using ethanol instead of *t*-butanol (Method E) led to the formation of significant quantities of the side product, 5-bromo-2-ethoxypyridine (Table 1). Diazotization in acetonitrile (Method F, Table 1), both using $NaNO_2$ and *n*-BuONO, ensured the formation of *N*-(5-bromopyridin-2-yl)acetamide as a side product, probably, via the reactions shown in Scheme 1.

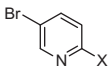
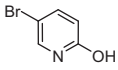
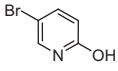
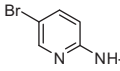
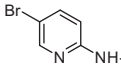
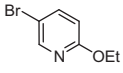
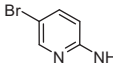
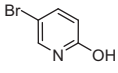
The formation of *N*-(5-bromopyridin-2-yl)acetamide as a side product in the diazotization–iodination of **1a** in acetonitrile in the presence of *p*-TsOH has been also observed previously.[9]

A relatively high yield of the target product **2a** was obtained by diazotization with *n*-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–halogenation of aromatic amines, 2-amino-5-nitropyridine, and amino-derivatives of quinoline, isoquinoline, and anthraquinone.[10]

However, even in those cases complete conversion of amine **1a** was not achieved. Furthermore, 5-bromopyridin-2-ol appeared as a side product due to the presence of residual water in DMSO. In addition, there were problems with preparative separation of highly soluble pyridines from DMSO solution. To reduce the amounts of DMSO and water we performed the diazotization by grinding aminopyridine **1a**, $NaNO_2$, and TfOH in DMSO and allowing the slurried mixture to stand for 5.5 h without further grinding (Method H). This method showed the optimal selectivity and efficiency with the GC yield of **2a** being more than 90% (Table 1), a preparative yield of 70% was obtained (Table 2). The optimal approach **H** was used to obtain a series of pyridinyl trifluoromethanesulfonates **2a–k**[11] (Table 2). It is important to mention that Method H in all cases ensures complete conversion of initial aminopyridines **1a–k**, and gives no side pyridinols. In general, the yields of pyridyl triflates **2a**, **2c**, **2g**, **2h**, and **2i** were comparable, and for compounds **2b** and **2d** they were higher than obtained using traditional hydroxypyridine esterification.[1–5] Moreover, Method H allowed

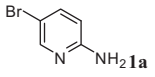
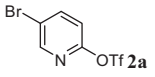
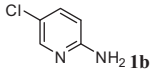
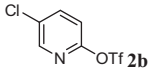
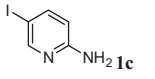
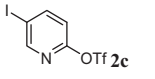
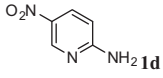
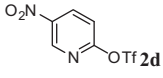
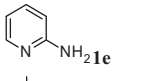
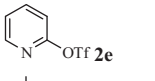
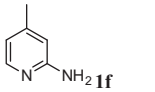
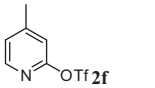
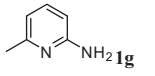
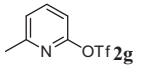
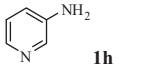
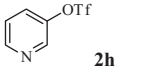
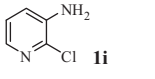
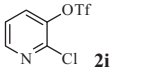
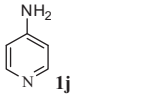
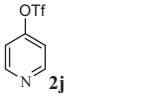
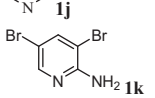
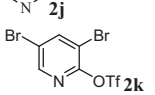
Table 1
The diazotization of 2-amino-5-bromopyridine **1a** via Methods A–H

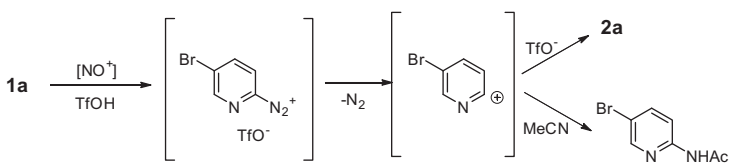


Method[a]	Solvent	Source of [NO+]	The reaction mass composition (GC) (%)			
			2a			**1a**
A	Water paste	$NaNO_2$	21		27	52
B	None	$NaNO_2$	93		4	0
C	None	*n*-BuONO	35		20	30
D	*t*-BuOH	*n*-BuONO	34		12	54
E	EtOH	*n*-BuONO	18		22	60
F	MeCN	*n*-BuONO	30		35	13
G	DMSO	*n*-BuONO	83		7	10
H	DMSO paste	$NaNO_2$	93	Not detected		Not detected

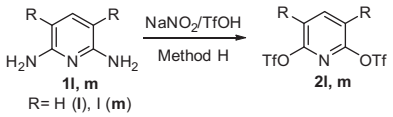
[a] Mole ratio of **1a**: [NO+]: TfOH and the reaction time: 1:2:3, 5 h (Method A); 1:2:3, 36 h (Method B); 1:2:3, 4 h (Method C); 1:2:3, 4 h (Method D); 1:2.5:3, 4 h (Method E); 1:2:3, 4 h (Method F); 1:2.5:3, 4 h (Method G); 1:2.5:3, 5.5 h (Method H).

Table 2
The synthesis of pyridinyl trifluoromethanesulfonates **2a–l** using Method H

Substrate	Product	Time (h)	Isolated yield (%)
		5.5	70
		2.5	89
		6.5	78
		2.5	86
		7.0	65
		6.5	90
		6.0	80
		4.0	70
		5.0	75
		6.0	60
		18	56



Scheme 1. Plausible reaction pathways for the diazotization of **1a** in acetonitrile.



Scheme 2. Diazotization of diaminopyridines **1l**,**m** in the presence of TfOH.

the synthesis of novel 5-iodopyridin-2-yl trifluoromethanesulfonate **2c**, pyridin-4-yl trifluoromethanesulfonate **2j**, and 3,5-dibromopyridin-2-yl trifluoromethanesulfonate **2k**.

Thus, unlike a number of well-established methods, the procedure presented in this Letter can be broadly applied to the synthesis of 2-, 3-, and 4-pyridine triflates in one step starting from readily available aminopyridines.

Also we tried to apply Method H on pyridine-2,6-diamine **1l** and 3,5-diiodopyridine-2,6-diamine **1m** with 6 equiv of TfOH, but the results were ambiguous. In both cases the diazotization reactions occurred much more slowly than for monoaminopyridines **1a**–**k** (up to 30–38 h), and with incomplete conversion of the diaminopyridines **1l**,**m**. At the same time, the reaction mixtures contained products of substitution only of both amine groups to triflates **2l**,**m** (GC–MS data) (Scheme 2).

In the case of the diazotization of **1m** we were able to isolate product **2m** in 35% preparative yield. Compound **2m** represents a rare example of a pyridine with two triflate groups and possesses interesting synthetic potential because it has four active sites. As far as we know, only one pyridine with two triflate substituents was described before.[12]

In summary, an efficient and economic method for the synthesis of pyridinyl trifluoromethanesulfonates via one-pot diazotization of aminopyridines with sodium nitrite in the presence of trifluoromethanesulfonic acid in DMSO paste has been presented for the first time. It differs from the known methods in the use of easily available reagents, and employs mild conditions and a simple synthetic procedure.

Acknowledgments

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Supplementary data

Supplementary data (the synthetic procedure and spectral and analytical data for all compounds are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.052.

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11. *A typical experimental procedure is as follows:* Trifluoromethanesulfonic acid, DMSO, and $NaNO_2$ were used without further purification and drying. All operations were performed in air using normal wet. A mixture of an aminopyridine **1** (2 mmol) and $NaNO_2$ (5 mmol) was ground with a pestle in an agate mortar until a homogeneous mixture formed. The mixture was added to solution of TfOH (6 mmol, 0.54 mL) and DMSO (1.3 mmol, 0.1 mL) cooled to 5 °C, and ground once again. The resulting homogenous paste was left in open to air for 2.5–18 h (Table 2) at room temperature during which gradual evolution of N_2 took place. The crude paste was suspended in H_2O (40 mL), stirred, and treated with 25% aqueous Na_2CO_3 (4 mL) until pH = 10, and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with H_2O (2 × 15 mL), dried over anhydrous Na_2SO_4, and the solvent evaporated in vacuum. The products **2a**–**k**,**m** were purified by silica gel flash chromatography, eluent CH_2Cl_2.
*5-Bromopyridin-2-yl trifluoromethanesulfonate (**2a**).*[3g] Yield 70%, oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.1 (d, J = 8.7 Hz, 1H), 7.99 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 8.5 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.8, 118.5 (q, J = 300 Hz), 120.5, 143.6, 149.7, 154.5. MS (EI): m/z 307 (15) [^{81}Br, M]$^+$, 243 (4), 213 (62), 174 (4), 144 (29), 117 (46), 96 (10), 69 (100), 38 (46).
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