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A new one-pot solvent-free synthesis of pyridinyl tosylates via diazotization of aminopyridines

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ABSTRACT

A new, convenient, one-pot method for the synthesis of pyridinyl tosylates is developed. The procedure involves sequential diazotization/tosylation of aminopyridines with sodium nitrite and *p*-toluenesulfonic acid under solvent-free conditions in a water paste at room temperature.

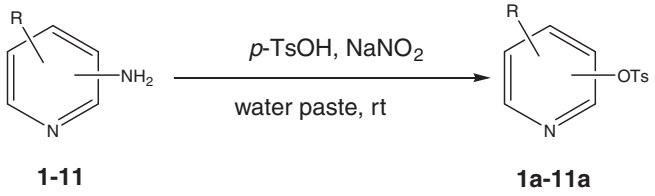
The good leaving ability of tosylate makes aryl and heteroaryl tosylates an important class of compounds with high versatility in organic synthesis. For example, they are useful for carbon–carbon or carbon–heteroatom bond formation.[1] Magnesium derivatives of pyridinyl tosylates serve as convenient precursors for the generation of 3,4-difunctionalized pyridynes,[2] and the tosylate group in some quinolinyl tosylates can be replaced by iodide.[3] Aryl and heteroaryl tosylates are prepared in organic solvents by tosylation of the corresponding hydroxy derivatives with *p*-toluenesulfonyl chloride.[1,2,4,5]

Recently, we reported *p*-toluenesulfonic acid (PTSA) as a mild and efficient reagent for the diazotization/iodination of aromatic amines in solvents or water paste,[6,7] and for the preparation of exceptionally stable arenediazonium tosylates.[8] When trying to apply our diazotization/iodination protocol[6–8] to 2-aminopyridine (**1**), pyridin-2-yl tosylate (**1a**) was isolated as the major product instead of the expected 2-iodopyridine. The reason for these differences between aromatic amines and aminopyridines is the well-known instability of pyridine diazonium salts compared to arenediazonium salts.[9] To the best of our knowledge no precedent for the direct conversion of aminopyridines into pyridinyl tosylates has been reported. This new tosyloxy-dediazotization reaction represents a simple, environmentally friendly alternative approach to pyridinyl tosylates. Furthermore, as a rule, the starting aminopyridines are cheaper and more readily available than the corresponding hydroxypyridines used in traditional syntheses of pyridinyl tosylates.[2,4,5] Herein, we report a new route to pyridinyl tosylates from aminopyridines and sodium nitrite/PTSA under mild reaction conditions.

To demonstrate the scope of this new transformation we chose to study aminopyridines **1–11** and found that the diazotization/tosylation reaction was general, affording the corresponding pyridinyl tosylates **1a–11a** in moderate isolated yields (Scheme 1 and Table 1).[10]

Typically, an aminopyridine (2 mmol), PTSA monohydrate (6 mmol), and water (0.5 mL, 30 mmol) were ground in a mortar for 3–5 min to give a homogeneous mixture. Next, $NaNO_2$ (4 mmol) was added and grinding was continued for another 5 min. The so formed slurry was left for 1–12 h with grinding every 15–20 min. Formation of the intermediate diazonium salts was verified by a positive color test with 2-naphthol and reaction completion was indicated by a negative test with 2-naphthol. Pure products **1a–10a** were isolated simply by sequential washing of the reaction mixture with aqueous sodium carbonate and water.

It was found that the product yields depended on the molar ratio of reagents; a substrate/$NaNO_2$/PTSA ratio of 1:2:3 was optimal. PTSA plays a dual role in the conversion. On one hand, it provides an acidic medium which is necessary for generation of the diazotizing reagent with $NaNO_2$. On the other hand, it participates in the replacement of the diazonium groups resulting in pyridinyl tosylates. This is why at least 2 equiv of PTSA were



Scheme 1. One-pot transformation of aminopyridines **1–11** in pyridinyl tosylates **1a–11a**.

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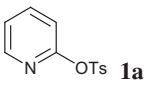
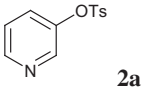
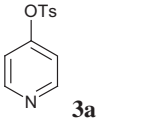
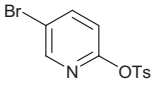
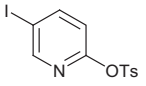
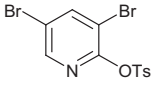
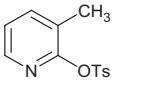
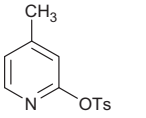
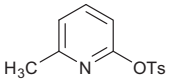
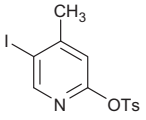
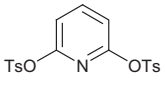
Table 1
Syntheses of pyridinyl tosylates **1a**–**11a** by diazotization of aminopyridines **1**–**11** in a water paste at room temperature (substrate/$NaNO_2$/PTSA, 1:2:3)

Entry	Product	Time (h)	Isolated yield (%)
1	 **1a**	3.5	52
2	 **2a**	1.0	50
3	 **3a**	1.0	80
4	 **4a**	2.5	79
5	 **5a**	4.5	69
6	 **6a**	1.5	66
7	 **7a**	1.0	55
8	 **8a**	1.0	55
9	 **9a**	12	47
10	 **10a**	10	75
11	 **11a**	2.0	20

needed for the conversion to occur. We found that either increasing or decreasing the optimal 1:3 substrate to PTSA molar ratio led to a decrease in the product yields. For example, the use of either 1:1 or 1:5 ratios of **2** to PTSA led to a lower yield of pyridin-3-yl tosylate (**2a**). The amount of water present in the reaction mixture was very important for successful diazotization/tosylation. Diazotization of aminopyridines **1–11** in aqueous solutions in the presence of PTSA led predominantely to the corresponding hydroxypyridines, whereas pyridinyl tosylates **1a–11a** were formed only in trace quantities. In the absence of water, diazotization of aminopyridines **1–11** and formation of products **1a–11a** did not occur at all. An increase to 0.1–0.15 mL (5–8 mmol) of water was not enough to provide full conversion of the aminopyridines. Use of 0.5 mL (30 mmol) of water per 2 mmol of substrate led to predominant formation of the corresponding pyridinyl tosylates. However, even when using the given conditions, hydroxypyridines were detected as side products. This contributed to an overall decrease of products **1a–10a** yields despite full conversion of the starting compounds. Fortunately, hydroxypyridine impurities were easily removed by washing the reaction mixtures with aqueous sodium carbonate. Products **1a–10a**, after simple aqueous washing, had high GS–MS and NMR purity and did not need any additional purification. It should be noted that conventional tosylation of hydroxypyridines with *p*-toluenesulfonyl chloride provides known pyridinyl tosylates **1a–3a** in low to moderate 55%, 75%, and 20% yields, respectively,[4] and in 42% yield for compound **3a** in another example.[5]

The yield of 2,6-ditosyloxypyridine **11a** was lower due to tar formation during the diazotization. Attempts at selective tosyloxy-dediazotization of only one amino group were not successful leading to a mixture of starting diamine **11** and pyridinyl tosylate **11a** being obtained.

In general, we did not observe any clear correlation between reaction time or electronic and steric effects of substituents on the pyridine ring and the product yields. This situation is rather common for the diazotization–dediazotization reactions of aromatic amines in which substituents may often produce opposite effects at different stages of the reaction mechanism.[11] However, aminopyridines bearing strong electron-withdrawing groups such as nitro (e.g., in 2-amino-5-nitropyridine and 3-amino-2-nitropyridine) could not be diazotizated with $NaNO_2$ in water paste. Thus, the diazotization/tosylation presented is general for aminopyridines bearing moderate electron-donating and withdrawing substituents.

In summary, we have described a new method for the direct transformation of aminopyridines into the corresponding pyridinyl tosylates by diazotization of aminopyridines with sodium nitrite and PTSA in a water paste at room temperature. The advantages of this approach are operating simplicity and an aqueous reaction medium. The yields of the pyridinyl tosylates were comparable with those obtained using classic procedures (tosylation of hydroxypyridines with *p*-toluenesulfonyl chloride in organic solvents).

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 doi:10.1016/j.tetlet.2010.10.163.

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10. *3,5-Dibromopyridin-2-yl 4-methylbenzenesulfonate* (**6a**). Yield 66%, mp 98–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.5 (s, 3H), 7.4 (d, J = 7.5, 2H), 7.9 (d, J = 7.8, 2H), 8.1 (s, 1H), 8.2 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 112.1, 118.0, 128.9, 129.8, 133.7, 145.3, 145.8, 147.3, 153.2. MS m/z: 407 (1, M^+), 343 (45), 262 (2), 124 (5), 194 (4), 155 (38), 121 (5), 91 (100), 77 (3), 65 (21), 51 (3), 39 (4). Anal. Calcd for $C_{12}H_9Br_2NO_3S$: C, 35.41; H, 2.23; Br, 39.26; N, 3.44. Found: C, 35.04; H, 2.34; Br, 39.52; N, 3.38.
Pyridin-2,6-diyl bis(4-methylbenzenesulfonate) (**11a**). Yield 20%, mp 81–82 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.5 (s, 6H), 7.0 (d, J = 7.8 Hz, 2H), 7.3 (d, J = 8.1 Hz, 4H), 7.8 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 114.2, 128.7, 129.8, 133.1, 143.4, 145.6, 154.8. MS m/z: 355 (6, M^+-SO_2), 327 (2), 291 (3), 274 (2), 263 (2), 200 (25), 184 (3), 165 (2), 155 (59), 139 (5), 129 (1), 107 (2), 91 (100), 77 (2), 65 (16), 39 (5). Anal. Calcd for $C_{19}H_{17}NO_6S_2$: C, 54.40; H, 4.08; N, 3.34. Found: C, 54.60; H, 3.97; N, 3.50.
A typical experimental procedure is as follows: A mixture of an aminopyridine (2 mmol), PTSA (1.14 g, 6 mmol), and H_2O (0.5 mL, 30 mmol) was ground for 3–5 min in an agate mortar until a homogeneous paste formed. Next, $NaNO_2$ (0.28 g, 4 mmol) was added and the mixture was ground for 5 min and then left in the open air for 1–4.5 h with grinding every 15–20 min. With longer reaction times, partial drying of the H_2O pastes occurred, so to compensate, 0.1–0.2 mL of H_2O was added. The crude pastes were treated with 20 mL of 3% aqueous Na_2CO_3, and the solid products **2a**–**11a** were filtered, washed with H_2O, and dried. Compound **11a** was additionally purified by recrystallization from hexane. Liquid product **1a** was extracted with CH_2Cl_2 (3×15 mL), the extract dried over Na_2SO_4, and the solvent evaporated in vacuum.
CAUTION! Although arenediazonium tosylate salts are stable in the dry state,[8] the operation needs to be conducted carefully. Diazonium salts may decompose violently upon heating.
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