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PRELIMINARY NOTE

A Facile Preparation of Fluoropyridines from Aminopyridines via Diazotization and Fluorodediazoniation in HF or HF-Pyridine Solutions

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SUMMARY

Fluoropyridines were prepared in high yields by the diazotization of aminopyridines in HF or HF-pyridine solutions, followed by dediazoniation in situ at 20 - 60 °C.

Although a considerable amount of work has been done to produce aromatic fluorides by the decomposition of aromatic diazonium salts, in only a few cases have fluoropyridines been reported [1,2]. 2- and 3-Fluoropyridines were formed in low yields (10 - 42%) but 4-fluoropyridine was not obtained [3,4]. Other attempts to prepare 4-fluoropyridine from 4-aminopyridine produced poor [5], or only 22% yields [6]. The halogen-exchange fluorination method is an allowed approach for preparing fluoropyridines. Nitro-fluoropyridines were obtained in yields exceeding 50% when heated with KF/DMF for one hour at 100 °C [7]. Recently, spray-dried KF/sulfolane was demonstrated to be an effective reagent for this purpose and produced 2-fluoropyridine in a 75 % yield [8], when heated at a high temperature (240 ° C) for a prolonged time (12 h). However, 4-fluoropyridine was difficult to obtain through the reaction of KF with the corresponding halopyridines [7].

Recently, we have demonstrated an improved procedure for diazotization of anilines and fluoro-dediazoniation in situ to produce

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aromatic fluorides in high yields by using solutions of anhydrous hydrogen fluoride (HF) in organic bases [9]. In the continuation of our work, we have performed the diazotization and fluoro-dediazoniation of aminopyridines to produce fluoropyridines in high yields using HF or HF-organic base solutions. Experimental results are listed in the accompanying Table.

The reaction procedure was in accordance with the method described in our preceding paper [9]. HF without pyridine was employed in the reaction of non-substituted aminopyridines, since these substrates themselves play the part of organic bases in HF. For example, a solution of 1.88 g (20 mmol) of 4-aminopyridine in HF (10 ml) was cooled to -78 °C. After an addition of 1.60 g (23 mmol) of $NaNO_2$, the stirred solution was allowed to react at 0 °C for 30 min (Diazotization). The resulting solution was then allowed to stand at 60 °C for 1 h under stirring (Dediazoniation). The reaction mixture was poured into 50 g of ice/water, followed by the neutralization with cold saturated $NaHCO_3$ (200 ml). After extraction with 100 ml of CH_2Cl_2, the crude product was dried over $MgSO_4$, refluxed in the presence of CaH_2 for 3 h, and evaporated. Distillation (104-105 °C) afforded 1.57 g (16.2 mmol, 81% yield) of 4-fluoropyridine (Lit b.p. 106 °C [6]). 4-Fluoropyridine must be stored in a sealed tube since it is sensitive to moisture changing from colorless to yellow giving polymeric products.

HF-pyridine, which is convenient to handle [10], was also employed in the reaction of 4-aminopyridine. However, in this case, pyridine together with 4-fluoropyridine was inconveniently found in the CH_2Cl_2 extract. On the other hand, in the reaction of aminopyridines with electron withdrawing substituents with relatively low basicity, use of HF containing 40%(w/w) pyridine is recommended in order to prevent undesirable side reactions and facilitate the handling of hydrogen fluoride. Fluoropyridines produced from such substrates were liberated from the HF-pyridine by an addition of a large amount of cold water without neutralization after the completion of the reaction, since their basicity may not be strong enough for solution in the acid layer. Unexpectedly, 2-fluoro-6-methylpyridine, in contrast to 2-, 3-, and 4-fluoropyridines, was also liberated from the acid layer without the neutralization.

Interestingly, although the reaction of anilines having nitro or halogen groups in the ortho position took place very sluggishly, aminopyridines having similar structures to these anilines gave

TABLE

Preparation of Fluoropyridines from Aminopyridines[a]

Substrate	Acid[c]	Dediazoniation[b] temp/°C	Product[d]	Yield/%[e]
2-Aminopyridine	HF	25	2-Fluoropyridine	91
"	HF-40% Pyr.	25	"	94
3-Aminopyridine	HF	40	3-Fluoropyridine	93
"	HF-40% Pyr.	40	"	96
4-Aminopyridine	HF	60	4-Fluoropyridine	90 (81)[f]
"	HF-40% Pyr.	60	"	95
2-Amino-6-methylpyridine	HF-40% Pyr.	0	2-Fluoro-6-methylpyridine	95 (84)
2-Amino-3-nitropyridine	HF-40% Pyr.	20	2-Fluoro-3-nitropyridine	97 (95)
o-Nitroaniline	HF-40% Pyr.	120	o-Fluoronitrobenzene	4
2-Amino-3-chloro-5-trifluoromethylpyridine	HF-40% Pyr.	20	2-Fluoro-3-chloro-5-trifluoromethylpyridine	99 (95)
2-Chloro-4-trifluoromethylaniline	HF-40% Pyr.	130	2-Chloro-4-trifluoromethyl fluorobenzene	trace

[a] Diazotization conditions: Substrate, 5 mmol: $NaNO_2$, 5.2 mmol: temp, 0 °C: time, 30 min. [b] Time: 1 h. [c] HF: 5 ml. HF-40% Pyr.: pyridine(6 g) in HF(9 g). [d] Identified by spectroscopically. [e] Determined by GLPC. Isolated yields in parenthesis. [f] Substrate, 20 mmol: $NaNO_2$, 23 mmol: HF, 10 ml.

corresponding fluorides in very high yields under moderate conditions. The discrepancy observed in the reactions between the heteroaromatics and the usual aromatics is not well understood at present and further work is under way to clarify this.

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