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# Ultrasound promoted facile synthesis of some pentafluoropyridine derivatives at ambient conditions

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ABSTRACT

Some pentafluoropyridine derivatives have been synthesized by the reaction of pentafluoropyridine with appropriate mono and bidentate nucleophile under ultrasonic irradiation. This new methodology provides good to excellent yields in short reaction times (25–120 min) at room temperature.



## 1. Introduction

The use of ultrasound to promote chemical reactions is called sonochemistry. What makes sonochemistry unique is cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles (cavities), leading to turbulent flow of the liquid and enhanced mass transfer [1–5]. The effect of ultrasound on different reactions is widely studied during the last two decades [6–8]. Increasing the yields of reactions and in some cases the ratio of formed products has mostly showed the effect of ultrasound. Nano-sized of organic and inorganic compounds have been prepared very really by this methods [9].

Synthesis of polyfunctional heterocyclic fused ring systems with low molecular weight are important in life science industries [10,11]. Pentafluoropyridine has attracted considerable interest due to its synthetic utility. Various multi-functional pyridine derivatives and construction of new heterocyclic and macrocyclic systems could be accessed from simple reaction conditions [12–19]. These include reaction of various bifunctional nucleophiles with pentafluoropyridine. All five fluorine atoms in pentafluoropyridine may be substituted by an appropriate nucleophile due to its highly electron efficient aromatic ring system. The site-reactivity order of pentafluoropyridine is well known [20–22] that, the order of activation towards nucleophilic attack follows the sequence 4-fluorine > 2-fluorine > 3-fluorine. Reactions of pentafluoropyridine with various nucleophiles are summarized and discussed in detail [23]. Previously we reported the use of ultrasound irradiation for electrophilic fluorination of CH and $CH_2$ groups attached to the heterocycle and nitro function [24]. In this report we aimed at exploring and establishing new methodologies for selective preparation of some substituted pentafluoropyridine by reaction of appropriate nucleophile with pentafluoropyridine under ultrasonic irradiation.

## 2. Experimental

### 2.1. Apparatus

A multiwave ultrasonic generator (Bandlin Sonopuls Gerate-Typ: UW 3200, Germany) equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 45 kHz with a maximum power output of 780 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. Melting points were determined in open capillary tubes by an Electrothermal IA 9000 melting point apparatus. The reactions were carried out under an atmosphere of argon unless otherwise specified. The elemental analyses for C, H, and N were performed using Heraeus CHN-O-Rapid analyzer. The $^{13}C$ NMR spectra were recorded at 125 MHz. The $^{19}F$ NMR spectra were recorded at 470 MHz. In the $^{19}F$ NMR spectra, upfield shifts were quoted as negative and referenced to $CFCl_3$. Mass spectra were taken by a Micromass Platform II: EI mode (70 eV). Column

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chromatography was performed using silica (Merck #60). Silica plates (Merck) were used for TLC analysis.

### 2.2. Typical procedure for preparation of 4-substituted 2,3,5,6-tetrafluoropyridine

To a solution of pentafluoropyridine (0.1 mmol) in acetonitrile (2 mL), was added nucleophile (0.1 mmol) and sodium hydrogen carbonate (0.15 mmol).This reaction mixture was sonicated at 45 kHz. After the completion of reaction as indicated by TLC, the reaction mixture was filtered and dil. sodium hydrogen carbonate solution (15 mL) was added. The organic products were extracted into dichloromethane (2 × 30 mL), dried ($MgSO_4$) and vaporated to give the product which was purified by recrystallisation from ethyl acetate/*n*-hexane. The authenticity of the reproduced products (Table 1) was established by comparing their melting points, $^{19}F$ and $^{13}C$ NMR with the data in the literature [27,29]. Other new products were confirmed by their spectra (Table 3).

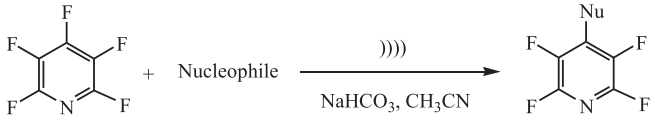
### 2.3. Typical procedure for preparation of bis tetrafluoropyridyl bridged compounds

To a solution of pentafluoropyridine (0.2 mmol) in THF (2 mL), was added diamine (0.05 mmol) and sodium hydrogen carbonate (0.15 mmol). This reaction mixture was sonicated at 45 kHz. After the completion of reaction as indicated by TLC, the reaction mixture was filtered and dil. sodium hydrogen carbonate solution (15 mL) was added. The organic products were extracted into dichloromethane (2 × 30 mL), dried ($MgSO_4$) and vaporated to give the product which was purified by recrystallisation from ethyl acetate/*n*-hexane. The authenticity of the reproduced products (Table 2) was established by comparing their melting points, $^{19}F$ and $^{13}C$ NMR with the data in the literature [30]. Other new products were confirmed by their spectra (Table 3).

### 2.4. Typical procedure for preparation of trifluoropyridopyrazine compounds

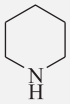
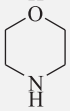
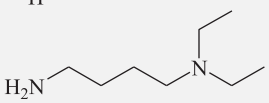
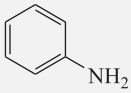
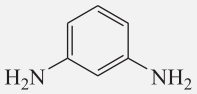
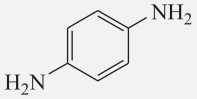
To a solution of pentafluoropyridine (0.1 mmol) in acetonitrile (7 mL), was added diamine (0.5 mmol) and sodium hydrogen carbonate (0.15 mmol).This reaction mixture was sonicated at 45 kHz for 120 min. After the completion of reaction as indicated by TLC, the reaction mixture was filtered and dil. sodium hydrogen carbonate solution (15 mL) was added. The organic products were extracted into dichloromethane (2 × 30 mL), dried ($MgSO_4$) and vaporated to give the product which was purified by recrystallisation from ethyl acetate/*n*-hexane. The authenticity of the reproduced products (Scheme 1) was established by comparing their

**Table 1**
Reaction of pentafluoropyridine with various nucleophiles under ultrasonic irradiation.




**1** **2a-j**

.

| Entry | Nucleophile | Product | %Yield (time/min)[a] | %Yield (time/h)[c] | M.P. (°C) |
|---|---|---|---|---|---|
| 1 | $NaSO_2Ph$ | **2a** | 93 (30) | 67 (22)[d] | 149–150[d] |
| 2 | $NH_2Me$ | **2b** | 92 (30) | 85(12)[e] | 56–57 |
| 3 | $NHMe_2$ | **2c** | 94 (25) | 82 (20)[g] | 24–26[g] |
| 4 | $NHEt_2$ | **2d** | 93 (25) | 90 (12)[e] | Oil[f] |
| 5 |  | **2e** | 92 (30) | 88 (12)[e] | Oil[f] |
| 6 |  | **2f** | 90 (35) | 85 (12)[e] | 71–73 |
| 7 |  | **2 g** | 94 (30) | 90 (12)[e] | Oil |
| 8 |  | **2 h** | 72 (90)[b] | 60 (12)[e] | 98–100 |
| 9 |  | **2i** | 70 (60)[b] | 65 (12)[e] | 147–149 |
| 10 |  | **2j** | 72 (65)[b] | 65 (12)[e] | 154–156 |

[a] With sonication.
[b] The reaction was performed at 60 °C.
[c] Without sonication.
[d,f,g] According to Refs. [27], [29] and [35] respectively.
[e] The reaction was performed in $CH_3CN$ at reflux temperature for 12 h.