Asian Journal of Chemistry Vol. 21, No. 9 (2009), 6651-6655

Application of New Blended Catalyst for Synthesizing of Fluoro Intermediate in Herbicide Industries

A. AHMADI
Department of Chemistry, Islamic Azad University, Karaj Branch, P.O. Box: 31485-313, Iran
Fax: (98)(261)4403573; Tel: (98)(21)88339309
E-mail: abbas_ahmady_3957@yahoo.com

Difluoropyridines generally have high thermal stability and are useful agricultural chemicals particularly as pre-emergence herbicides where they are effective in controlling a variety of noxious weeds. For instance, 5-chloro-2,3-difluoro pyridine, can be used for the preparation of pyridinyl-oxyphenoxy alkane carboxylic acid derivatives, which are herbicides with particularly advantageous properties. This compound was synthesized with higher yield in comparison with previous methods, by using new technique and blended catalysts in two blended polar aprotic solvents. After synthesizing, the product was separated from the reaction mixture, by slow fractional distillation with heat sealed cover and vigorous column. This compound is an important starting material for the preparation of agrochemicals and pharmaceuticals compounds.

Key Words: Difluoropyridines, Herbicides, Pharmaceuticals, Pyridinyloxyphenoxy alkane carboxylic acid, Blended catalysts.

INTRODUCTION

The chlorine in certain positions in polychloro-benzenes can be replaced by fluorine using the potassium fluoride exchange reaction[1]. For example, hexachloro-benzene reacts with potassium fluoride to give 1,3,5-trichloro-2,4,6-trifluorobenzene as a major product[2]. This shows that chlorine is not only a strong activating group from the *meta* position as expected in nucleophilic reaction but is also a significant activator even from the *ortho* and *para* positions[3]. Other known methods include fluorination of dichloropyridines using a polar solvent[4] or in a solvent-free medium[5]. In other methods, difluoropyridines were prepared from diaminopyridines by the simultaneous replacement of two amino groups by diazotization in hydrogen fluoride[6]. It is equally well-known that the replacement of chlorine or bromine in the 3-position on pyridine by fluorine using potassium fluoride is much more difficult as reaction of 2,3,5- trichloropyridine (**I**) with 2 moles of potassium fluoride in dimethyl sulfone for 24 h at 200 °C gives only 2-fluoro-3,4-dichloropyridine (**II**), *i.e.* no exchange occurred at the 3-position[4].

The 5-chloro-2,3-difluoro pyridine (**III**), has been known for some times[7,8]. It's useful as intermediate for the preparation of herbicidal 2-[4-((3-fluoro-5-chloro-2-pyridyl)oxy)phenoxy] propionic acid (**IV**) derivatives. This compound has been prepared previously by reaction between some compounds in a solvent[9-11]: (a) A trihalopyridine as a main starting material such as trichloro, tribromo or 3,5-dichloro-2-fluoropyridine (**V**). (b) A fluorinating agent such as anhydrous and finely divided potassium, cesium, mixture of them, sodium, rubidium or tetra alkyl ammonium fluoride. (c) An acid scavenger to consume or inactivation of trace of HCl or HF which may be present or generated during the reaction such as anhydrous K_2CO_3 or Na_2CO_3 or a phase transfer catalyst such as quaternary ammonium or phosphonium chloride or bromide or macrocyclic polyether commonly known as crown ethers. (d) A polar aprotic solvent (or other solvent) to maintain an essentially uniform dispersion of the reactants such as dimethyl sulfoxide, dimethyl formamide, dimethyl acetamide, diethyl acetamide, methyl isobuthyl ketone (MIK), N-methyl pyrrolidinone (NMP), tetramethyl sulfone (sulfolane) and dimethyl propylene urea (DMPU) or other non-polar solvents such as benzonitrile, chloronaphtalene, chloro benzene, dichlorobenzene, xylene or toluene[9-11].

In another process, the mentioned compound (**III**)[12], can be prepared with starting from 2,5-dichloro-3-nitropyridine (**VI**) by hydrogenation of the nitro group, subsequent diazotization and exchange of the diazo group in anhydrous HF in a Monel autoclave and subsequent halex reaction with KF and CsF to introduce the fluorine atom in the 2-position. Better yield had been obtained in this procedure but it also had many steps and accompanied by corrosion problems in handling of anhydrous HF (uneconomical apparatus). Additionally, it could not complete economically the replacement of both fluorine atoms in one step by means of inexpensive alkali metal fluoride.

In another process, the mentioned compound (**III**)[13], can be prepared by nitration of 2,5-dichloropyridine (**VII**) and reduction to 2,5-dichloro-3-aminopyridine (**VIII**), subsequent nitration to the nitramino derivative and treatment therefore by means of boron trifluoride etherates, 2,5-dichloro-3-fluoropyridine (**IX**), being obtained. This can be converted into the desired product by an exchange reaction with KF and/or CsF. This long route has many disadvantageous, inadequate yields, high toxicity and explosiveness of the intermediates and the use of the industrially undesirable reagent boron trifluoride etherates.

For drying the reaction mixture, in some previous papers, it was recommended to distilled off some solvent (azeotropic distillation) for water removing or adding xylene or toluene and azetropic distilled water from the reaction mixture[9-14].

EXPERIMENTAL

2,3,5-Trichloro pyridine, potassium fluoride, cesium fluoride, dimethyl propylene urea (DMPU) and tetramethylene sulfone (sulfolane), tetraethylene glycol dimethyl ether, benzyltriphenylphosphonium chloride, 18-6 crown ether, potassium carbonate and toluene were purchased from Fluka Company.

^{1}H NMR spectra were determined with a Varian XL-400 (400 MHz) instrument in $CDCl_3$ using TMS as the internal standard. ^{19}F NMR spectra were recorded on a Varian XL-400 (400 MHz) instrument using TFA as the internal standard. GC-Mass spectra were performed on a Thermo Finnegan GC 2000 equipped to trace MS. The following chromatographic conditions were used: 60 m × 0.25 mm HP-5 fused silica capillary column. Helium was used as the carrier gas at a flow rate of 1 mL/min. The column temperature was set to 70 ºC for the first 4 min, increased 5 ºC/min to a temperature of 295 ºC and maintained at 295 ºC for 0.5 h. Mass spectral data were obtained with a quadruple analyzer mass selective detector at electron energy of 70 eV over a mass range of 35-500 atomic mass units in the total ion mode.

Drying process: To a 500 mL flask equipped with mantle stirrer, a thermometer, a dean-stark and a water cooler condenser, is charged with 50 mL toluene, 42 g KF + CsF (8:2), 160 g sulfolane, 70 g DMPU, 1 g K_2CO_3, 3 g benzyltriphenyl-ammonium chloride and 1 g 18-6 crown ether. The reaction mixture is heated to azetropic-distilled water for 8 h. Then, toluene is separated from the reaction mixture by vacuum distillation (dried suspension).

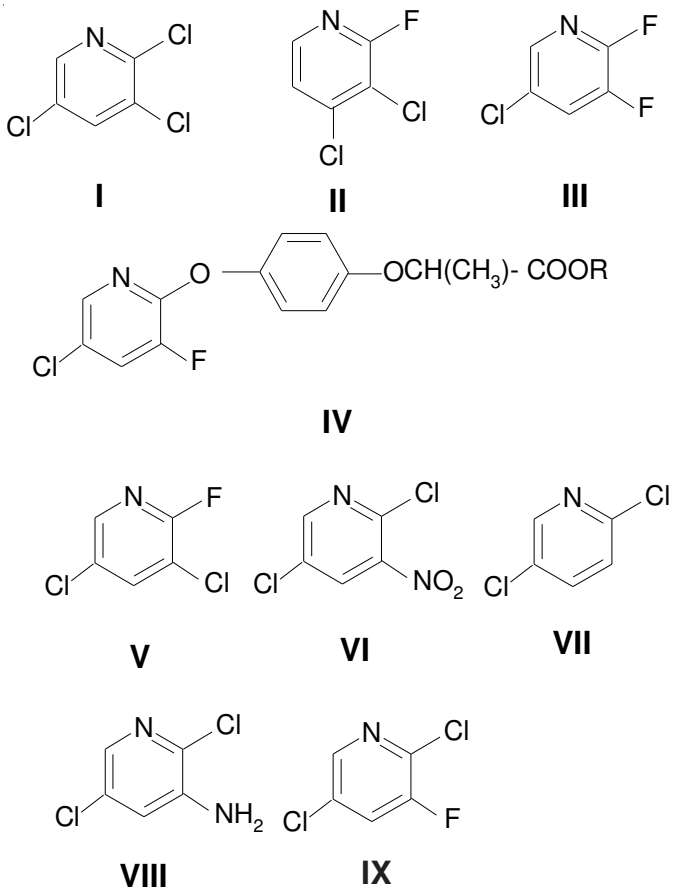
In a same procedure, 41.6 g of 2,3,5-trichloropyridine and 20 mL of toluene in a 250 mL flask equipped with mantle stirrer, a thermometer, a dean-stark and a water cooler condenser, is heated to azetropic distilled water for 8 h. Then, toluene is separated from the reaction mixture by vacuum distillation (dried solution).

Synthesis: To a 500 mL flask equipped with an efficient stirrer, a heating mantle, a thermometer, a temperature controller, a distillation vigroy column, a water cooler condenser, a receiver is charged with dried above suspension and the dried solution is added drop wise to the reaction mixture for 12 h at 220-230 °C. The main product (**III**) with 3,5-dichloro-2-fluoropyridine (**V**) (22.85 g) was collected into the receiver flask by vigroy column distillation for 48 h. The GC-mass spectrum of receiver liquid shows a ratio of (9:1) **III/V** without any impurities. In the last step, these two compounds separated from each other by packed column fractional distillation (18.2 g pure **III**, 70 % yield).

Spectroscopic data

5-Chloro-2,3-difluoropyridine (III): ^{1}H NMR ($CDCl_3$, internal standard: TMS): 7.61 [ddd, 1H, J = 2.24 Hz (H-6), 7.89 Hz (F-2), 8.41 Hz (F-3), H-4], 7.97 [dd, 1H, J = 2.24 Hz (H-4), 1.8 Hz (F-2), H-6]. ^{19}F NMR ($CDCl_3$, internal standard: $CFCl_3$): -88.80 (ddd, iF, J = 1.80 Hz (H-6), 7.89 Hz (H-4), 25.67 Hz (F-3), F-2], -136.51 (dd, iF, J = 8.41 Hz (H-4), 25.67 Hz (F-2), F-3]. MS: m/e (%): 50.2 (4), 64.2 (25), 69.2 (7), 87.2 (9), 94.2 (3), 114.2 (63), 122.2 (11), 124.2 (2), 149.2 (100), 151.2 (34).

3,5-Dichloro-2-fluoropyridine (V): ^{1}H NMR ($CDCl_3$, internal standard: TMS): 7.83 [dd, 1H, J = 2.32 Hz (H-6), 7.63 Hz (H-6), 7.63 Hz (F-2), H-6], 8.07 [dd, 1H, J = 2.32 Hz (H-4), 1.47 Hz (F-2), H-6]. ^{19}F NMR ($CDCl_3$, internal standard: $CFCl_3$): 73.77 [dd, 1F, J = 1.47 Hz (H-6), 7.63 Hz (H-4), (F-2]. MS: m/e (%): 49.2 (9), 68.2 (9), 75 (3), 84.1 (8), 94.1 (8), 103.1 (13), 110.1 (13), 130.2 (50), 132.2 (15), 138.1 (3), 165.2 (100), 167.1 (63), 169.2 (10).



Structures of fluorine compounds

RESULTS AND DISCUSSION

In the previous methods, only the synthesis of these compounds with low purity of desired compound (**III**) were mentioned and no discussion was reported about separating them. Here, we synthesized 5-chloro-2,3-difluoropyridine (**III**) and 3,5-dichloro-2-fluoropyridine (**V**) with high purity (90 %) in comparison with the previous methods (maximum: 58 %) and separated from each other by packed column fractional distillation as pure compounds (**III**, b.p: 135 ºC; V, b.p: 174 ºC). In this procedure for production of **III**, we can use the mixture of **III/V** (9:1) for the preparation of pyridinyloxyphenoxy alkane carboxylic acid derivatives, as herbicidal and pharmaceutical activity in industry, because this mixture have a good ratio of **III/V** (9:1) and could be used as a main starting material with low cost and commercial procedure. In this method, by using the best ratio of fluorinating agents (KF + CsF) and mixture of catalysts (benzyltriphenyl ammonium chloride + 18-6

crown ether) and aprotic solvents (Sulfolane + DMPU), drying procedure with toluene and drop wise adding of **I** to the reaction mixture and slow distilled it, we could obtain **III** with 90 % purity and could be separated from **V**, by packed column fractional distillation.

ACKNOWLEDGEMENTS

This work was done as a research project in Islamic Azad University, Department of Science, School of Chemistry. The author would like to thank Research Management of Tehran University for their assistance in this project.

REFERENCES

1. G.C. Finger, C.W. Kruse, R.H. Shiley, R.H. White and H.A. Whaley, Abstract, Organic Chemistry Division, XVIth International congress of Pure and Applied Chemistry, Paris, p. 303 (1957).
2. J.T. Maynard, *J. Org. Chem.*, **28**, 112 (1963).
3. J.F. Bunnett and R.E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
4. G.C. Finger, L.D. Starr, D.R. Dickerson, H.S. Gutowsky and J. Hamer *J. Org. Chem.*, **28**, 1666 (1963).
5. M.M. Boudakian, *J. Hetrocycl. Chem.*, **5**, 683 (1968).
6. M.M. Boudakian, J. Pittsford and J. Stanely, US Patent, 3,798,228 (1974).
7. M. Abromovitch, Pyridine and It's Derivatives, Part 2, p. 439 (1955).
8. P.L. Coe, A.G. Holton and J.C. Tatlow, *J. Fluorin Chem.*, **21**, 171 (1982).
9. J. Venugopal, C. Balakrishnan and B. Rouge, Eur. Patent, 710,649 (1995).
10. J. Little, A. Charles and C. Wilson, US Patent, 4,822,887 (1989).
11. J. Little, A. Charles and C. Wilson, Eur. Patent, 146,924 (1984).
12. R. Schurter and U. Siegrist, Eur. Patent, 178,260 (1986).
13. K. Hoegerle, DE, 3,700,764 (1987).
14. A.E. Tschitschibabin and A.F. Egorov, *J. Russ. Phys. Chem. Soc.*, **60**, 683 (1983).

(*Received*: 26 June 2008; *Accepted*: 8 July 2009) AJC-7672