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Potassium Fluoride on Alumina—An Efficient Reagent for Isomerization of N-[2-(Alkyl/Arylsulfonyl)Ethyl]-2-Methyl-5-Nitro-1H-Imidazoles

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POTASSIUM FLUORIDE ON ALUMINA - AN EFFICIENT REAGENT FOR ISOMERIZATION OF N-[2-(ALKYL/ARYLSULFONYL)ETHYL] 2-METHYL-5-NITRO-1H-IMIDAZOLES

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Abstract: KF/Al $_2$ O $_3$ has been found to be an efficient reagent for a neat isomerization of 1-[2-(Alkyl/Arylsulphonyl)ethyl]-2-methyl-5-nitro-1H-imidazoles to the corresponding 4-nitro-isomers in more than 90% yields.

N-substituted products from 2-methyl-4(5)-nitro-1Himidazole are of great utility as chemotherapeutic agents. Tinidazole and metronidazole, belonging to the 5-nitro series, have been widely used in the treatment of protozoal infections trichomoniasis^{1,2} like The 4-nitroisomeric compounds pharmacological significance as immunosuppressants 3 aldehyde dehydrogenase inhibitors, potential radio sensitizers, radiotherapy synergists. Normally these nitroimidazoles synthesized by the reactions of 2-methyl-4(5)-nitroimiwith suitable alkyl halides, sulfates or tosylates. Depending on the reaction conditions, especially pH, either N-alkylated 5-nitro-1H-imidazoles or the corresponding 4-nitroor mixtures of both are formed? Extensive work carried out by us on the chemistry of nitroimidazoles has resulted in the development of a new high yielding method for the regio-specific preparation of 4-nitro compounds. We have recently reported isomerization of 1-[2-(ethylsulfonyl) ethyl]-2-methyl-5-nitro-1H-imidazole (Tinidazole) to its 4-nitro isomer. This isomerization has given better insight into the metabolism of Tinidazole and also opened up a new route for the synthesis of 4-nitroisomers of this important class of compounds.

We now wish to report a reaction using KF-Al2O3 where the isomerization is twenty times faster, work-up is simpler and yields are nearly quantitative. The utility of the reagent KF-Al₂O₃ organic synthesis is base in increasing 10 This paper describes the facile isomerization of 1-[2-(alkyl/aryl sulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazoles to the corresponding 4-nitro derivatives using potassium fluoride coated on alumina. The reagent is simply prepared by mixing the support with an aqueous solution of potassium fluoride and This reagent smoothly isomerised 1-[2then removing water. (ethylsulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazole 1-[2to (ethylsulfonyl)ethyl]-2-methyl-4-nitro-1H-imidazole ethanol at 120°C within 15 min. Under the same conditions use of either potassium fluoride or alumina alone failed to effect any isomerisation. To test the generality of reaction a representative set of 1-[2-(alkyl/arylsulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazoles were isomerised and the results have been tabulated.

TABLE

$NO_2 $	KF-Al ₂ O ₃ 120°C, 15 min. O ₂ N CH ₃ CH ₂ CH ₂ SO ₂ R
R	Yield ^{a, b}
-CH ₂ -CH ₃	94%
-(CH ₂) ₃ -CH ₃	93%
-C ₆ H ₅	95%

- a. All yields refer to isolated yields.
- b. Products were characterised using spectral methods ($^{1}\mathrm{H}$ $^{13}\,\mathrm{C-NMR}$).

Experimental

KF-Alumina Reagent

To a stirred solution of potassium fluoride (40 g) in water (300 ml) is added neutral alumina (60-80 mesh, 60 g) and stirred for $\frac{1}{2}$ h. Water is then evaporated under reduced pressure in a rotary evaporator keeping the temperature around 60°C. Then the flask is heated at 130°C-135°C under vacuum (\sim 5 mm) for 6 h, yield 100 g.

Isomerization of 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazole - typical procedure

To a stirred suspension of KF-Al₂O₃ reagent (100 mgs) in

2-ethoxyethanol (10 ml) heated at 120°C was added 1-[2-(ethyl-sulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazole (1 g). The reaction was complete within 15 min. as monitored by TLC. The reaction mixture was cooled, filtered and evaporated to dryness under vacuum to get 1-[2-(ethylsulfonyl)ethyl]-2-methyl-4-nitro-1H-imidazole (0.94 g). m.p. 136-139°C (reported 11 m.p. 130-134°C).

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