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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

A. K. S. Bhujanga Rao [a] , C. Gundu Rao [a] & B. B. Singh [a]
[a] R&D Centre , Reckitt & Colman of India Limited , Plot 176, SIPCOT Industrial Complex, Hosur, 635 126, Tamil Nadu, India
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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

A K S Bhujanga Rao, C Gundu Rao and B B Singh*

R&D Centre, Reckitt & Colman of India Limited,
Plot 176, SIPCOT Industrial Complex,
Hosur-635 126, Tamil Nadu, India

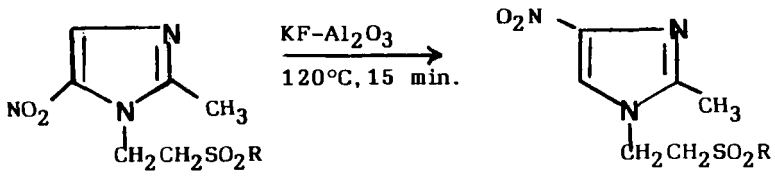
Abstract : KF/Al_2O_3 has been found to be an efficient reagent for a neat isomerization of 1-[2-(Alkyl/Arylsulphonyl)ethyl]-2-methyl-5-nitro-1H-imidazoles to the corresponding 4-nitro-isomers in more than 90% yields.

N-substituted products from 2-methyl-4(5)-nitro-1H-imidazole 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 like trichomoniasis[1,2] The 4-nitroisomeric compounds are gaining pnarmacological significance as immunosuppressants[3], aldehyde dehydrogenase inhibitors[4], potential radio sensitizers[5], and radiotherapy synergists[6]. Normally these nitroimidazoles are synthesized by the reactions of 2-methyl-4(5)-nitroimi-dazoles with suitable alkyl halides, sulfates or tosylates. Depending on the reaction conditions, especially pH, either N-alkylated 5-nitro-1H-imidazoles or the corresponding 4-nitro-isomers or mixtures of both are formed[7]. 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.[8] We have recently reported isomerization of 1-[2-(ethylsulfonyl) ethyl]-2-methyl-5-nitro-1H-imidazole (Tinidazole) to its 4-nitro isomer.[9] 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-Al_2O_3 where the isomerization is twenty times faster, work-up is simpler and yields are nearly quantitative. The utility of the reagent KF-Al_2O_3 as a base in organic synthesis is steadily 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 then removing water. This reagent smoothly isomerised 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazole to 1-[2-(ethylsulfonyl)ethyl]-2-methyl-4-nitro-1H-imidazole in ethoxy 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 this 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



R	Yield[a,b]
$-CH_2-CH_3$	94%
$-(CH_2)_3-CH_3$	93%
$-C_6H_5$	95%

a. All yields refer to isolated yields.

b. Products were characterised using spectral methods (^1H ^{13}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 ½ 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 (~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-Al_2O_3 reagent (100 mgs) in

2-ethoxyethanol (10 ml) heated at 120°C was added 1-[2-(ethylsulfonyl)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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