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S47

Synthesis of Novel Leflunomide Analogues as Antirheumatic Agents

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Leflunomide, 5-methyl-N-[4-(trifluoromethyl)phenyl]-4-isoxazolecarboxamide, is a dihydroorotate dehydrogenase inhibitors which is used in the treatment of rheumatoid artritis. In this project we replaced methylisoxazolyl moiety in leflunamide with bioisoesteric group 2-alkylthio-1-benzyl-5-imidazolyl.
Starting from benzylamine hydrochloride (1) and dihydroxyacetone, 1-benzyl-2-mercapto-5-hydroxymethylimidazole (2) was synthesized. Compound 2 was alkylated with RX to give 2-alkylthio-1-benzyl-5-hydroxymethylimidazole (3). Oxidation of 3 with MnO_2 gave aldehyde (4). Further oxidation of 4 with silver oxide gave corresponding carboxylic acid (5). Compound 5 was converted to its acid halide (6) with thionyl chloride, which was reacted with 4-trifluoromethylaniline to give the title 1-alkylthio-2-benzyl-N-[4-(trifluoromethyl)phenyl]-5-imidazolecarboxamide (7).
All the title compounds and intermediates were determined by spectroscopic methods including NMR and IR.