

Abstract:

Dana Herová

Direct N^1 -monosubstitution of piperazine and applications of their products in syntheses

We will report a simplified protocol for the routine direct chemoselective preparation of various piperazines substituted in the 1-position by an electron withdrawing group such as acyl, sulfonyl, carbamoyl group, and for the efficient mono Aza-Michael addition reactions of piperazine to compounds with activated multiple carbon-carbon bonds. These syntheses are based on the formation/reaction of piperazine-1-ium cation with different electrophilic reagents. Piperazine-1-ium cation was chosen because the reactions of piperazine in the free base form with electrophilic reagents in different solvents at usual temperatures are not chemoselective and provide mixtures comprising 1-substituted, 1,4-disubstituted and unsubstituted piperazine as well. Simultaneously, the mono-protonation of piperazine is the simplest synthetic method for its protection/deprotection in comparison with the currently used mono-benylation, mono-Boc-protection, *etc.* Formation of piperazine-1-ium cation ionically supported on weakly acidic cation-exchanger resin in reaction with carboxylic anhydrides or nitrourea is an example of the solid phase synthesis with ionically bonded substrate. Furthermore, utilization of low reactive piperazine-1-ium cation in syntheses was very effectively promoted by catalysis using Cu^+ , Cu^{2+} , Al^{3+} and Ce^{3+} ions supported on weakly acidic cation-exchanger resin as well. The main advantages of our syntheses are great simplicity, one-pot performance, use non-toxic solvents only, mild reaction conditions, no generation of waste, short time of reactions and high yields. This new simplified protocol for direct preparation of N^1 -monosubstituted piperazines opens up new possibilities for the introduction of next piperazine structural motifs in pharmaceutical research and subsequently into clinical practice.

Finally, we will report the new possibility for preparation of quaternary piperazinium salts namely 1-alkyl-1-methylpiperazine-1,4-dium salts where alkyl is benzyl, n-octadecyl, nonyl and methyl, respectively and 1,1-dinonylpiperazine-1,4-dium salt. These compounds were fully determined by several physical methods (FT-IR, FT-Raman, acid-base study, XRD-analysis, and by DFT computational data as well).