Regioselective Alkylation of Quinolin-2-ones by Chloroacetic Acid Amides

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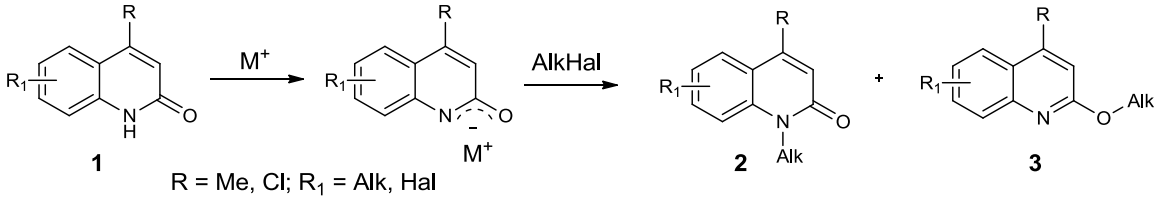
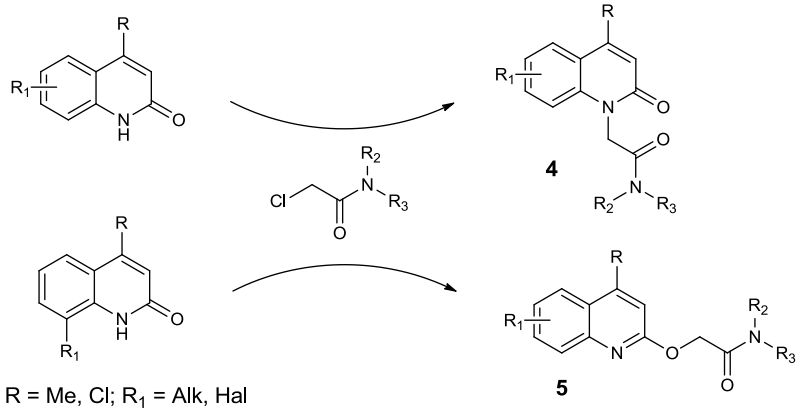
N-alkylated quinolin-2-ones are the prominent pharmacophores because of the N-alkyl quinoline-2-one skeleton that is present in large number of natural products, as well the synthetic alkyl derivatives of quinolone have a wide range of biological activity. However, the simplest synthesis of these compounds by direct alkylation of N-unsubstituted quinolin-2-ones using alkyl halides in presence of inorganic bases involves a competitive alkylation leading to the mixture of N- and O- alkylated products (Scheme 1). The ratio of N-alkylation *versus* O-alkylation is highly dependent on the nature of substituents and the nature of inorganic base.

Scheme 1



It was found, that in the case of using chloroacetic acid amides as alkylating agents in the presence of potassium carbonate the alkylation takes place regioselectively in N- (compounds **4**) or O- position (**5**) of quinolones (Scheme 2). This selectivity is connected with the presence or absence of substituents at the 8-position of quinolone cycle.

Scheme 2



A plausible mechanism of regioselective alkylation of quinoline-2-ones is proposed on the basis of the quantum chemical calculations and NMR spectroscopy data. The nature of metal in inorganic base and intermolecular hydrogen bonds formed between the reactants play the key roles in this possible mechanism.