Pergamon

Tetrahedron Letters 43 (2002) 1027–1029

TETRAHEDRON LETTERS

Acyl transfer of 8-acetoxy-2-oxazolinylquinoline assisted by hydrogen bonding formation

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Received 17 October 2001; accepted 6 December 2001

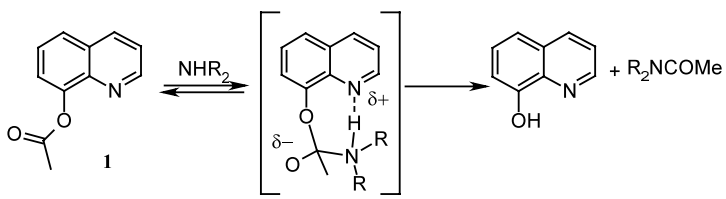
Abstract—A significant acceleration of acyl transfer has been achieved on 8-acetoxy-2-oxazolinylquinoline in the presence of benzylamine. Comparison of the aminolysis by the new acylating reagent with that of 8-acetoxyquinoline and 8-acetoxyquinoline-2-carbonitrile has been carried out. The results of these experiments suggest that the proximity of a supplementary basic atom to the ester group increases the participation effect of the basic site mainly by formation of a possible second hydrogen bond. The association constant of benzylamine into the basic cavity of 8-methoxy-2-oxazolinylquinoline ($K_a = 80\ M^{-1}$) has been measured by ^1H NMR titration experiments.

8-Acetoxyquinolines are well known to catalyse their own ester aminolysis via intramolecular participation of the neighboring basic nitrogen atom, as indicated in Scheme 1.

A large number of kinetic studies have been reported by Bruice and co-workers[1] showing the high reactivity of 8-acetoxyquinoline towards primary and secondary amines. The acetylation of amino acids has also been investigated.[2] 8-Acetoxyquinoline has also displayed high acetylation yields when grafted on a polymer.[3] As discussed in the literature, if the formation of a vicinal hydrogen bonding is responsible for the facile ester aminolysis, then it might be possible to improve the kinetics of the aminolysis by enlarging the basic site. Up until now, no structural modification has been developed to enhance this basic catalytic effect. We herein wish to disclose a novel derivative of the 8-acetoxyquinoline structure able to increase the participation of the quinoline nitrogen atom via an additional basic complexing center.

A molecular modeling study showed that an oxazoline moiety in the 2-position of the 8-acetyloxyquinoline structure was well adapted to display a new basic center close enough to the ester function. Moreover, from this study, we could observe the binding of benzylamine via two hydrogen bonds. The intermolecular complex formed would place the amine nitrogen close to the carbonyl group of the ester function with a distance of roughly 3 Å (Fig. 1).

This new potential acylating agent has been synthesized in only two steps with good yields. In a first step, the oxazoline has been formed in a one-pot reaction,[4] by condensation of (*R*)-phenylglycinol with 8-hydroxyquinoline-2-carbonitrile (**2**) according to Breslow's procedure.[5] In a second step, 8-hydroxy-2-oxa-



Scheme 1.

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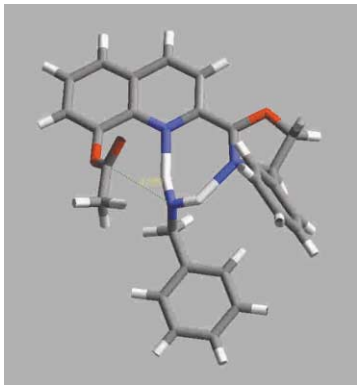


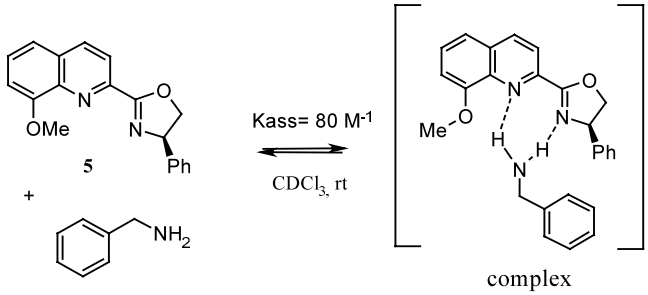
Figure 1. The hydrogen bonding complex between 8-acetoxy 2-oxazolinylquinoline and benzylamine has been minimized using the Cerius[2®] package. The hydrogen bond between NH···N (quinoline) is 2.1 Å long and NH···N (oxazoline) is 1.9 Å long.

zolinylquinoline was further easily acylated with acetic anhydride[6] (Scheme 2).

The complexation ability of benzylamine via hydrogen bonding in the basic cavity was confirmed by a proton titration experiment[7] with 8-methoxy-2-oxazolinylquinoline **5**. Indeed, this methylated analogue of **4** permitted blocking of the acylating position, while preserving the basic center. An association constant of 80 M^{-1} was measured. This value of the association constant is in good agreement with a two binding points process[8] with benzylamine (Scheme 3).

The reactivities of this new compound and of 8-acetoxyquinoline (**1**) were compared in order to evaluate their acylating potentialities toward benzylamine. The aminolysis reactions have been carried out at room temperature and the evolution of the reactions monitored by ^1H NMR.[8] As can be seen from Fig. 3, the acylating agent **4** is much more efficient than 8-acyloxyquinoline and no significant evolution of the reaction could be observed with 8-acetoxynaphthalene. The significant acceleration observed is most probably due to the formation of an extra hydrogen bond during the reaction process. However, the electron-withdrawing effect of the oxazoline group in the 2-position cannot be discarded since it would stabilize the phenolate leaving group.

It could be reasonably presumed that the electron-withdrawing effect of a nitrile group is more efficient than that of an oxazolinyl moiety. This assumption was confirmed by an ab initio MO calculation at the HF/



Scheme 3.

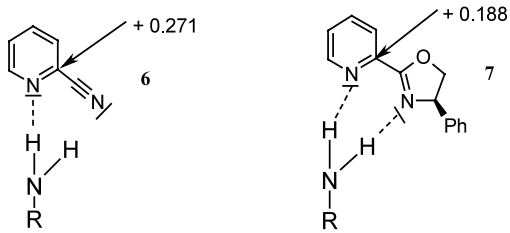


Figure 2. The geometries were first optimized with the Cerius[2®] package. Ab initio calculations were then performed with Gaussian-94 and the STO-6-31G basis set.

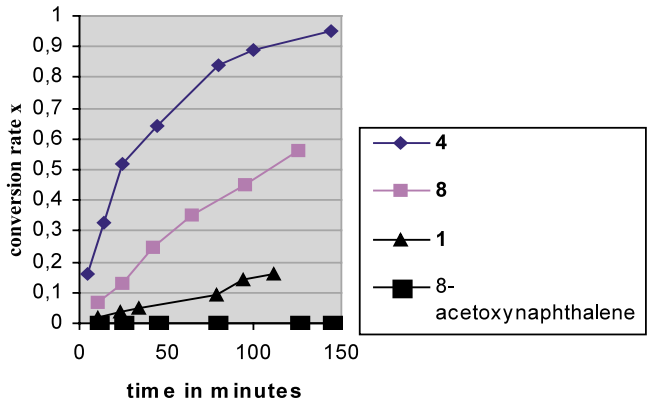
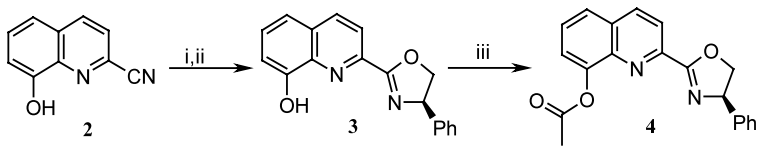
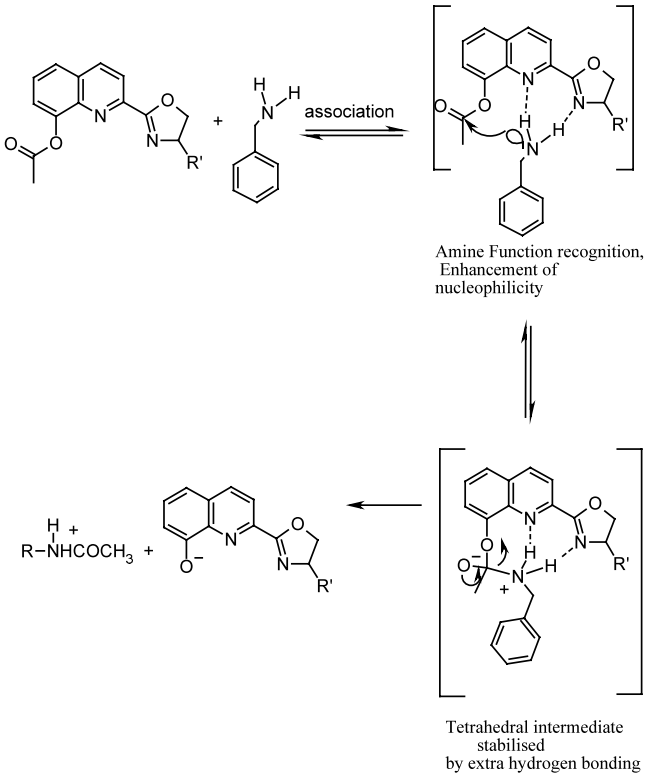


Figure 3. Benzylacetamide formation monitored by proton NMR spectroscopy.

STO-6-31G level of theory (Fig. 2) on pyridine-2-carbonitrile (**6**) and 2-pyridyloxazoline **7**.[9] Moreover, we could verify by a molecular modeling study on quinoline-2-carbonitrile that the nitrile group, because of its linear geometry, did not allow any additional hydrogen bonding. So, in order to evaluate the actual role of the above-mentioned electronic effect, the aminolysis of 8-acyloxyquinoline-2-carbonitrile (**8**) was performed under the same experimental conditions. The corresponding results are depicted in Fig. 3.



Scheme 2. *Reagents and conditions*: (i) *R*-Phenylglycinol, cat. $CuCl_2$, 100°C/1 h, 90%; (ii) EDTA/K_2CO_3; (iii) Ac_2O/reflux/1 h, 100%.



Scheme 4.

The reaction has been run in $CDCl_3$ using an excess of 5 equivalent (Ci = 0.085 M) of benzylamine for 1 equivalent (Cr = 0.017 M) of acylating agent. Conversion rate x was determined by integration of the methyl protons of benzylacetamide formed and methyl ester consumed.

Calculation of the rate constants shows that, in spite of the stronger electron withdrawing power of the nitrile group, 8-acetyloxy-2-oxazolinylquinoline **4** ($k = 0.21$ mol^{-1} l min^{-1}) still reacts five times faster than **8** ($k = 0.04$ mol^{-1} l min^{-1}). This last result suggests that the formation of a second hydrogen bond is more important than an electron-withdrawing effect in the 2-position of quinoline.

From the topology of that new acylating agent, displaying a neighboring complexing center to the ester group, we could explain this substantial acceleration by taking into account two types of considerations.

Firstly, by facilitating attack of the primary amine by pre-complexation via hydrogen bonding into the basic pocket, as shown by the above molecular modeling study and the value of the association constant. This type of complexation could enhance the nucleophilicity of the amine nitrogen, as recently demonstrated by Philp et al.[9]

Secondly, by increasing the stability of the tetrahedral intermediate as proposed in Scheme 4.

To conclude, the synthesis and the aminolysis study of a new kind of acylating agent has been performed. This agent exhibited higher reactivity towards benzylamine than 8-acetoxyquinoline and 8-acetoxyquinoline-2-carbonitrile.

The results of aminolysis studies tend to prove that the formation of an additional hydrogen bond is mainly responsible for the high acceleration observed. A complementary study using an NMR titration method suggested that benzylamine can be pre-complexed via hydrogen bonding into the basic pocket with an association constant of about 80 M^{-1}. We are presently studying the chiral discrimination properties of receptor **5** by hydrogen bonding complexation of chiral amines with the view to developing a new resolution process of primary amines using this class of acylating agents and quinoline analogues.

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