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Selective acylation of 4,5-diamino-9,9′-dimethylxanthene through an aggregation effect

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Dedicated to Professor Yus on the occasion of his 60th birthday

Abstract

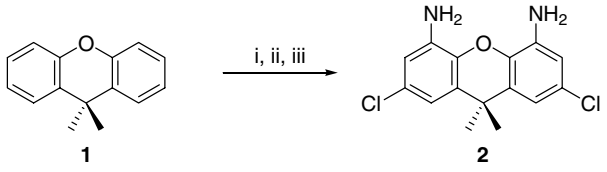
The proximity of the 4,5-diamino groups in a 9,9′-dimethylxanthene skeleton provides unique reactivity due to aggregation effects. While treatment with 1 equiv of an isocyanate yields the diurea and starting material, under similar conditions, Boc_2O provides essentially only the monocarbamoyl derivative.

Keywords: Molecular recognition; Selective acylation; Hydrogen-bond catalysis

Xanthenes are useful building blocks that have been extensively addressed in the recent literature.[1] Interesting applications have been found for them as ligands in metal catalysts[2] in molecular recognition[3] and as chemotherapeutic probes.[4] Since most of the practical synthesis of xanthenes starts from the commercially available xanthone,[5] procedures for the selective functionalization of the aromatic rings of 9,9′-dimethylxanthene **1** are desirable.

4,5-Diamino-9,9′-dimethylxanthene **2** can be obtained through a long sequence that involves a Curtius degradation[6] or the introduction of nitro groups in the 2,7-di-*tert*-butyl-9,9′-dimethylxanthene followed by reduction.[7] These procedures afford low yields owing to the large number of steps or the *ipso* substitution of the *tert*-butyl groups. Nevertheless, when chlorine groups block the reactive positions 2 and 7 diamine **2** can be obtained in high yield (Fig. 1).

Direct monoacylation of diamine **2** tends to be difficult. Addition of an equivalent of several isocyanates (phenyl, butyl, cyclohexyl, *tert*-butyl) in chloroform yielded mixtures of the diurea together with the starting material, in which the monourea was difficult to detect (monourea <5%). To understand this unusual effect, DFT molecular modeling studies were carried out for the reaction of methyl isocyanate with 4,5-diamino-9,9′-dimethylxanthene (see details in Supplementary data) (Fig. 2).



i) SO_2Cl_2, CCl_4, rt, 24 h ii) HNO_3 (fum), CH_2Cl_2, rt, 14 h
iii)$SnCl_2x2H_2O$, EtOH, reflux, 1 h

Fig. 1. Preparation of 4,5-diamino-2,7-dichloro-9,9′-dimethylxanthene.

Transition-state structures were found for the addition of isocyanate to diaminoxanthene **2** and to monourea intermediate **3**. According to the calculations, this second reaction shows a 7.1 kcal/mol lower activation energy than the first acylation, in agreement with the experimental results. H-Bond self-stabilization of the transition states could explain this result (Fig. 3). In both transition states,

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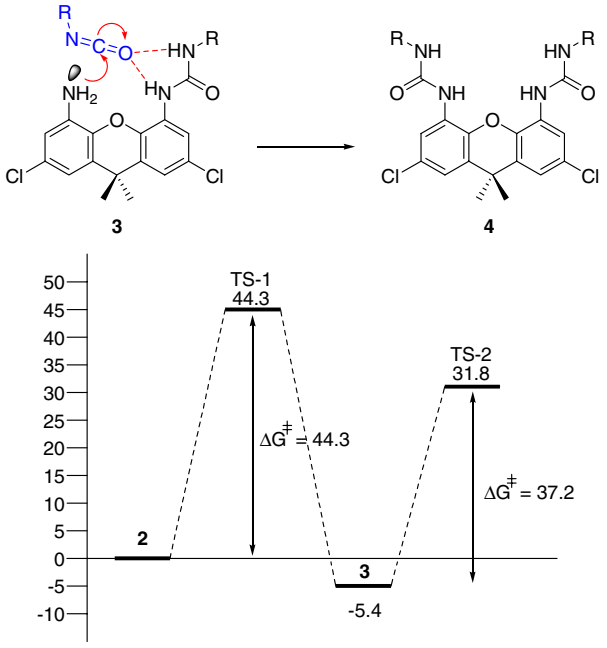

Fig. 2. Reaction of the isocyanate with monourea **3** to form diurea **4** and the energy scheme for the modeling studies on this reaction.

H-bonds to the oxygen of the isocyanate can be found with both amino and urea groups (H-bond distances: 2.12 for the first addition transition-state, 2.17 and 2.03 Å for the second addition). Nevertheless, the higher acidity of the urea group and the presence of two H-bonds (instead of only one) justify the additional stabilization on the second transition-state.

Indeed, monourea **3** (prepared from the Boc-derivative, vide infra) shows a weak association with the isocyanate. Downfield shifts of the urea NHs were obtained in the presence of cyclohexyl isocyanate.

This hypothesis was further checked by adding to the reaction media guests that are able to compete with the isocyanate for association with monourea **3**. For example, barbital associates the monourea with a $K_{ass} = 55\ M^{-1}$. In the presence of this guest the monourea can be detected in an amount close to that expected for a statistical reaction (diamine **2** 35%, monourea **3** 30%, diurea **4** 35%). Since benzoic acid is expected to be a better guest ($K_{ass} = 220\ M^{-1}$), its presence yields an improved amount of the monourea (25/50/25). Larger guests, such as triphenylacetic acid, could have blocked the free amino group preventing the formation of the diurea but the results were disappointing, probably because triphenylacetic acid can only block one face of diamine **2**. Results with this guest yielded a ratio of 20/60/20.

Other acylating agents, such as phthalic anhydride, yielded the same surprising effect. The addition of 1 equiv of this reactant to a solution of diamine **2** in chloroform led to a precipitate of diamide **4** while in the solution only the starting material could be detected in ^1H NMR.

An almost statistical acylation was obtained with acetic anhydride. The best result was obtained with Boc_2O. In this case, the geometry of diamine **2** almost only produced the monocarbamate.[8] DFT calculations similar to those

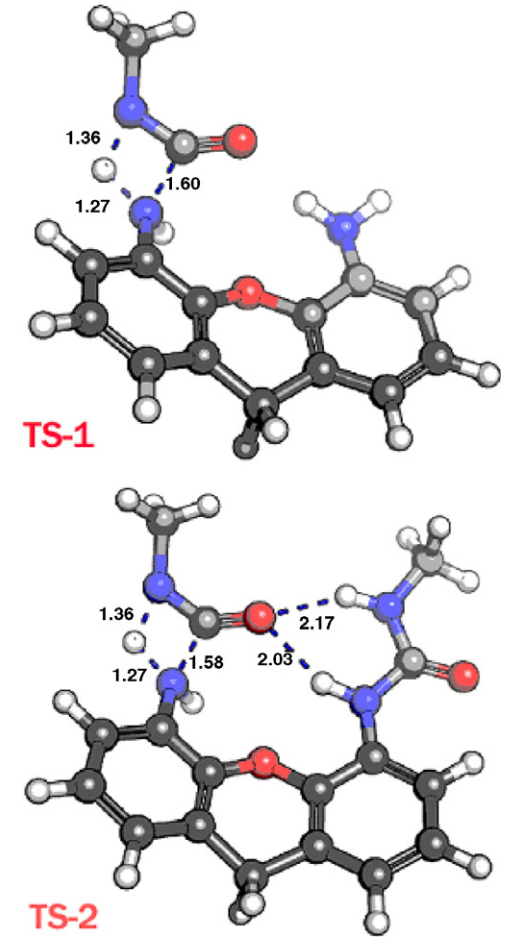

Fig. 3. Transition states of the acylation of compounds **2** and **3**.

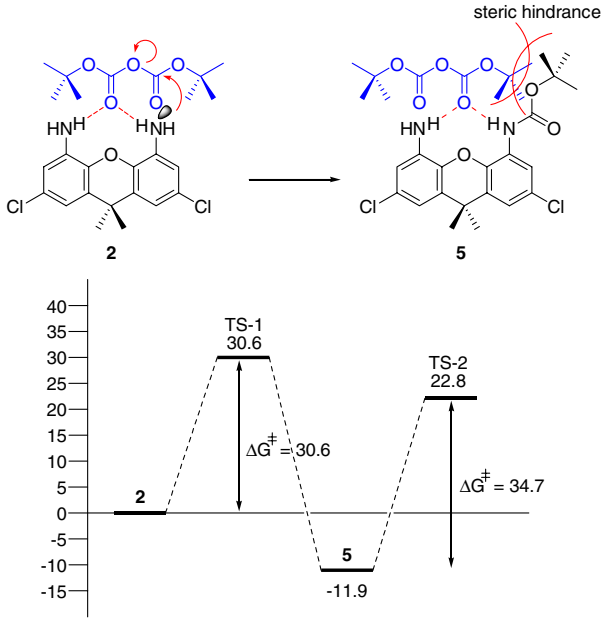

Fig. 4. Mechanism proposed for the reaction of Boc_2O and diamine **2** and the energy scheme of the modeling studies for this reaction.

made for the isocyanate reaction explain the experimental results. The second addition reveals an activation barrier that is 4.1 kcal/mol higher for the second addition (Fig. 4).

Self-H-bonding in the transition states is also observed, but unlike the isocyanate reaction, the same number of H-bonds is present in the transition-state structures corresponding to the first and second transition states. In this reaction, the stronger H-bond with a carbamate group is not able to compensate the higher reactivity of diaminoxanthene **2** (Fig. 5). Additionally, steric interactions hinder H-bond stabilization in this transition state.

The formation of a weak associate between diamine **2** and Boc_2O can be observed in ^1H NMR, since in the presence of the acylating agent upfield shifts of the aromatic protons of the diamine can be measured (protons H-3/H-6 move from 6.763 in the free diamine to 6.725 in the associate). From these shifts it is possible to evaluate the association constant around 1.9 M^{-1}. Easy access to compound **5** allowed the preparation of the previous monourea **3**. Simple treatment with cyclohexyl isocyanate followed by deprotection under acidic conditions afforded this compound (Fig. 6).

The monocarbamoylation of compound **2** is an interesting way to improve the construction of new building blocks based on an 9,9′-dimethylxanthene skeleton.

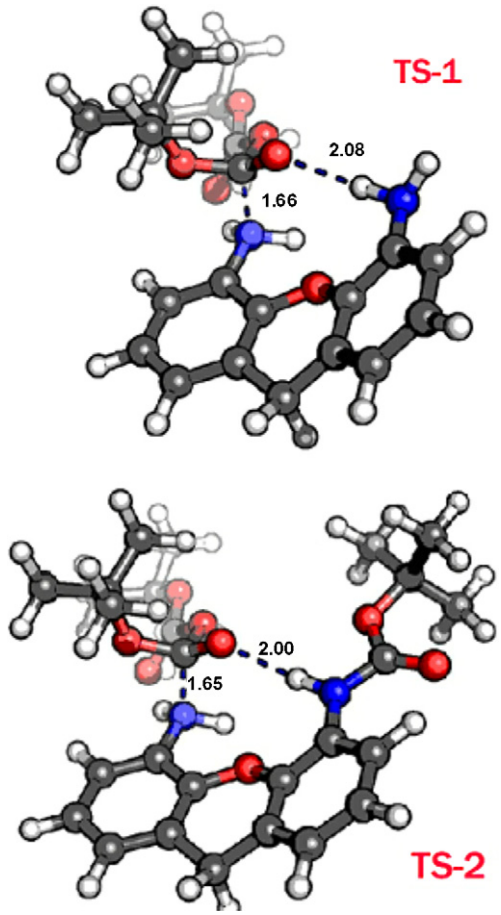

Fig. 5. Transition states of the reaction of **2** and **5** with Boc_2O.

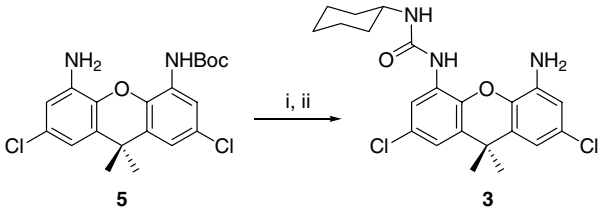

Fig. 6. Synthesis of compound **3**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.189.

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8. Compound **2** (42.0 g, 135 mmol) was dissolved in $CHCl_3$ (840 ml). Boc_2O (29.8 g, 137 mmol) and AcOH (1.0 ml, 17 mmol) were added. The flask was evacuated and filled with argon and the reaction was allowed to proceed at room temperature for seven days. The reaction mixture was washed with a carbonate solution. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Compound **5** was purified by chromatography with CH_2Cl_2 as eluent, affording 51.2 g (125 mmol, 92% yield).