Electronic Effects in the Cyclocondensation of Benzil

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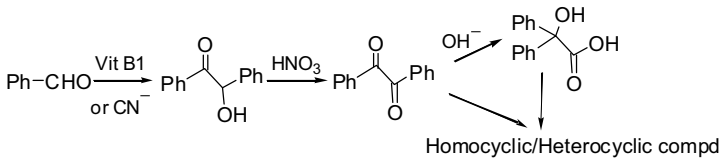
Electronic effects are important directing forces in the course of chemical reactions. Small differences in these effects can bring about considerable changes in the results of very similar reactions. Thus, although the ambident nucleophiles urea, o-phenylenediamine and dibenzyl ketone are expected to take comparable double condensation pathway in their respective reaction with benzil, urea reacts differently by causing benzil-to-benzilic acid type rearrangement. This is attributed to the reduced availability of the lone pair of electrons on nitrogen in urea that is needed for assisting the dehydration of the intermediate.

Introduction

A popular experiment performed in MSc organic chemistry laboratory classes is the following sequence of simple preparations starting from benzaldehyde, which is elaborated schematically in (s1–s6) [1-3].



The exercise provides a good opportunity to teach and learn several preparative procedures and diverse organic reaction mechanisms. It also offers a chance to train students in the application of spectroscopic techniques, particularly IR and UV, to follow structural changes and functional group transformations that accompany the conversion of starting compound to product in each individual reaction. The conversion of benzaldehyde to benzoin (s1) was discussed in some detail in an earlier article (*Resonance*, Vol.13, pp.355–368, 2008), which covered the green chemistry aspect too [3]. In this article three condensation

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Benzil, urea, *o*-phenylenediamine, dibenzyl ketone, condensation, cyclo-condensation, hydantoins, quinoxalines.

reactions of benzil (s4–s6) are taken up for discussion with a view to show how subtle differences in electron shift in the reactant would bring about interesting changes in the reaction course.

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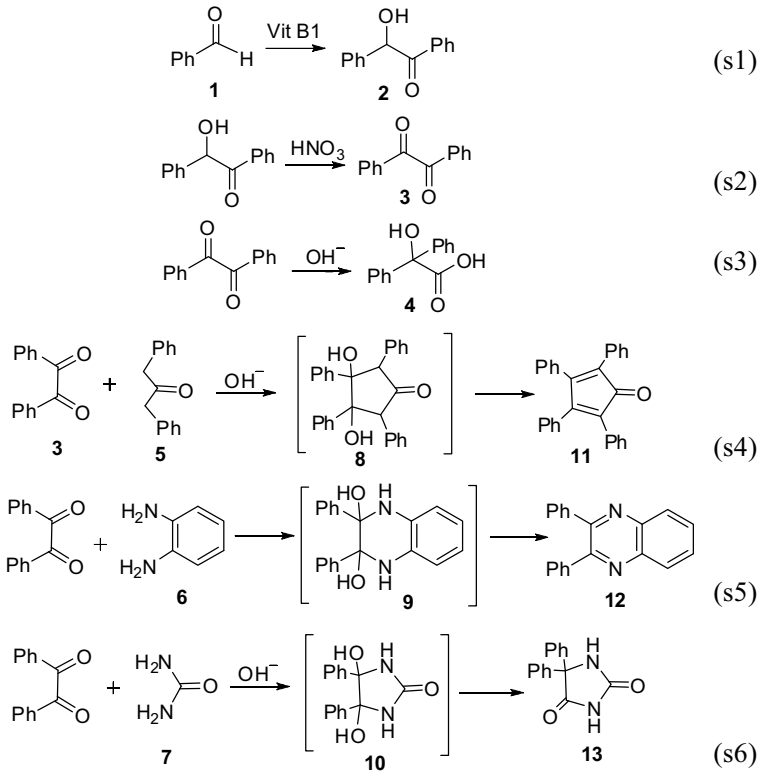

(s1)
(s2)
(s3)
(s4)
(s5)
(s6)

Benzaldehyde – Umpolung and Benzoin Formation

The benzaldehyde-to-benzoin transformation, (s1), is an excellent example of nucleophilic addition of an aldehyde to another aldehyde by charge reversal (umpolung) process catalysed by vitamin B1 or other environmental friendly organo catalysts [3].

Oxidation – Benzoin to Benzil

The oxidation of benzoin to benzil is effected by concentrated nitric acid, (s2), and not by the conventional oxidising agents like permanganate, dichromate or chromic acid, because in these cases benzoin produces benzaldehyde/benzoic acid, but not benzil. Copper sulphate in pyridine also oxidizes benzoin to benzil in

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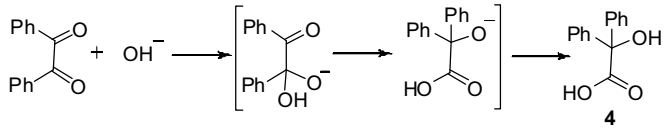
good yield. A green chemical method of oxidation is also known, in which benzoin absorbed on zeolite A is irradiated with microwaves to give benzil. From this the student can meaningfully learn why HNO_3 or $CuSO_4$ in pyridine succeeds while the other oxidising agents produce unwanted products.

Base-Catalysed Reaction of Benzil

Let us analyse the interesting differences in the base-catalysed cyclocondensation reactions of benzil. Benzil, a bis-acceptor synthon with 1,2-diketo function but no α-hydrogen, reacts efficiently with two nucleophilic groups. If the two nucleophilic groups are part of the same molecule, the so-called cyclocondensation takes place, meaning, a cyclic product is formed, as in the three reactions exemplified in (s4–s6). But before taking it up for discussion, it should be kept in mind that benzil, under alkaline conditions, can undergo the so-called benzil-benzilic acid rearrangement involving 1,2-migration of phenyl group to give benzilic acid, (s7).



(s7)

The cyclocondensation of benzil with the two α-methylene groups of dibenzyl ketone gives the homocyclic compound, 2,3,4,5-tetraphenylcyclopentadienone (also known as tetracyclone), (s4). In a comparable manner, 1,2-phenylenediamine and urea, using their two -NH_2 groups, also condense with the two carbonyl groups of benzil to produce the heterocycles, 2,3-diphenylquinoxaline(s5), and 5,5-diphenylhydantoin (s6).

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Mechanism of Cyclocondensation

Looking at the mechanism of these three reactions, one would quickly notice complete resemblance between the reactions of dibenzyl ketone and 1,2-phenylenediamine, while that of urea is strikingly different, as the product formation here is preceded by

rearrangement that is reminiscent of benzil to benzilic acid reaction. Note that this variation occurs despite the fact that the three reactions are subjected to similar reaction conditions. That is, they are carried out in warm or refluxing ethanol under basic conditions. Therefore we have to look elsewhere for explaining the dissimilar outcomes, and so let us consider the possible reasons.

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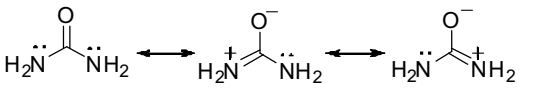
pKa – The Key to Difference in Nucleophilicity

Among the three reactants, *o*-phenylenediamine with pKa > 31 [4] is a good base and a powerful nucleophile and does not need any additional base as catalyst. On the other hand, urea (pKa = 26.8) [4] is a weaker base due to resonance, (s8), and needs the assistance of an added base for enhancing its nucleophilic efficiency and later on for deprotonation during dehydration step. In the case of dibenzyl ketone, which has no such assistance from lone pair of electrons and has pKa = 18.7 [4], a strong base is required to convert it into a good carbanion nucleophile (s9), to initiate the addition to benzil C=O and then for deprotonation led dehydration at the final phase of condensation.



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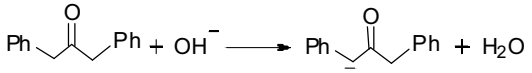

(s9)

The Role of Lone Pair Electrons

To understand what is probably happening while the reactants travel through their individual course to transform into products, let us consider only a few important steps, without going into minute details, in order to keep the discussion short but adequate and clear. To begin with, let us presume that in all three cases similar intermediates **8**, **9** and **10** are formed, (s4–s6). This would be followed by the elimination of proton and -OH groups from the adjacent positions. The removal of proton with the assistance of a base would occur either before or together with the departure of -OH group. In the case of **8**, deprotonation is likely to take place

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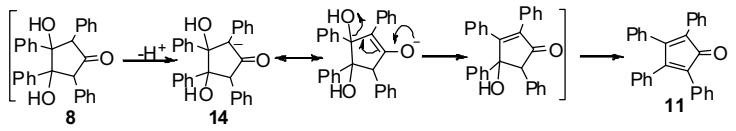
first to form the resonance-stabilized carbanion **14** which will then push off the -OH group, (s10). In the case of **9** and **10,** the lone pair of electrons on the adjacent nitrogen can perform the same task as the carbanion on **14** in helping the exit of -OH group, followed closely by abstraction of proton on nitrogen by base. It is therefore evident that the participation of nonbonded electrons on the adjacent nitrogen is crucial in forcing out the hydroxy group. Herein lies the secret of the difference between the reactions of urea and *o*-phenylenediamine. The nonbonded electrons in urea intermediate **10** are engaged in resonance to considerable extent with the adjacent carbonyl group, (s11), similar to the negative charge on carbanion of **14**, (s10).



(s10)

On the other hand, in the case of *o*-phenylenediamine intermediate **9** the involvement of the nitrogen lone pair of electrons by resonance with benzene ring will be less significant, and these electrons are available to act as the driving force for the departure of -OH group. Because of such subtle differences between them, the intermediates **9** and **10** take different routes in their further transformation. Since the -OH in **10** is not removed quickly by intramolecular process, the intermolecular abstraction of proton (on -OH or -NH-) by base becomes a kinetically preferred process. Because the hydroxy protons (pKa ~16) are much more acidic than the amide protons (pKa ~24), the proton that is removed in **10** is the one from the -OH group, and not from -NH- group. This results in the formation of the alkoxide ion **15**, the consequence of which is the same as in benzil-benzilic acid rearrangement, that is the 1,2-migration of the phenyl group to finally give 5,5-diphenyl-2,4-imidazolidinedione, (s12), also called 5,5-diphenylhydantion or phenytoin.

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Phenytoin is one of the oldest drugs used and still in use in the treatment of seizures (epilepsy) and irregular heart beats or

cardiac arrhythmia in medical parlance [5,6]. Quinoxaline derivatives show a variety of biological activities. They possess anti-HIV activity and are being tested for treating HIV infections. They also find use as herbicides, fungicides and insecticides. Quinoxaline moiety occurs as part of a number of natural products [7,8].

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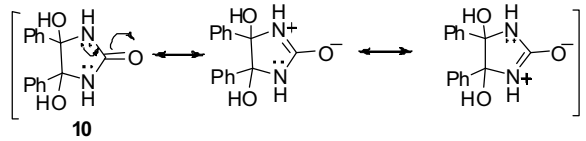

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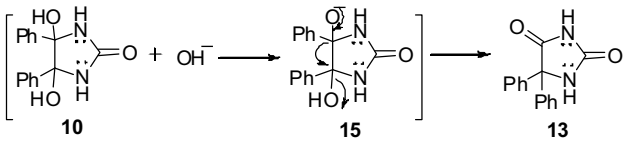
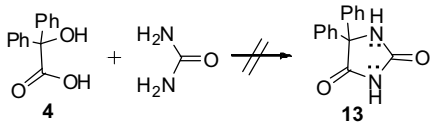


(s12)



(s13)

A Possible Alternative Mechanism

At this stage a question arises, namely, whether the product **13** would have formed by the reaction of urea with benzilic acid (s13), which can initially be formed by the rearrangement of benzil with alkali present in the medium, as in (s7). However, we found in an independent experiment that benzilic acid, when treated with urea under identical experimental conditions, did not react but was recovered without change. This shows that the cyclo-condensation of urea with benzil follows the mechanistic pathway given in (s6) and (s12) taken together, and further indicates that urea reacts faster with benzil than hydroxide ion and therefore it is a better nucleophile.

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An Educative Exercise

This exercise demonstrates how even a small variation in electron distribution can have profound effect on the course of a reaction

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leading to structurally distinct products. Also note that a good knowledge of electron movement and application of pKa data are very useful in the proper understanding of the apparently intriguing reaction mechanism.

The IR spectroscopy can be very effectively employed here to pursue the structural changes occurring through the whole sequence. The carbonyl stretching band is one of the most recognisable absorption frequencies. The C=O peak is sensitive to a variety of electronic and steric effects. Its absence or presence and position are convincing evidence in confirming the structure of the molecule in question. Therefore this absorption peak can serve as a good guidance to track the success of a particular reaction in the sequence. The O-H and N-H stretching bands can provide additional information.

Considering all these points it is evident that this is a highly instructive and worthy set of experiments for MSc classes. The complete exercise may take about 3–4 laboratory hours.

Suggested Reading

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