Oxidative fragmentations of some azolyl ketones and related compounds induced by cerium (IV) ammonium nitrate (CAN)

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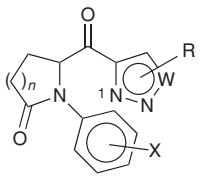
In contrast to simple ketones which are stable to CAN, azolyl ketones **3d–3f, 11a, 11b** and, in part, **3c** and **4c** undergo oxidative fragmentation when treated with cerium(IV) ammonium nitrate (CAN).

Keywords: azolyl ketones, cerium (IV) ammonium nitrate

While azolyl ketones **3a**, **3b** and **4b** were found to undergo oxidative cyclisation to afford the expected tetracyclic products of types **5** and **6** when treated with CAN, the related azolyl ketones **3d** and **3e** underwent fragmentation to yield products of types **7** and **8**, and azolyl ketones **3c** and **4c** afforded mixtures of cyclisation and fragmentation products. Thus, the type of the oxidative transformation depends, as will be rationalised below, on the nature of the substituent X of the group *N*-C_6H_4X of the substrate.

The CAN induced oxidative fragmentation of ketones **3c–3e** and **4c**, leading to products of types **7** and **8** was unexpected since simple ketones are resistant to CAN.[1] Therefore the reactions with CAN of some related ketones (**3f**, **11a–11c** and **12a**) were studied which, except possibly for ketone **3f** and in contrast to ketones **3a–3e**, **4b** and **4c** are, for structural reasons, incapable to undergo oxidative cyclisation.

The reaction of compounds **11a** and **11b** with excess CAN afforded benzophenone, the oxidative fragmentation product,



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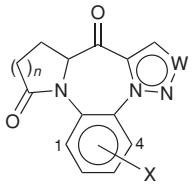
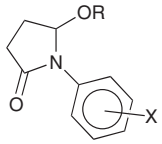
	n	W	R	X
3a	0	N	H	3-OMe
3b	1	N	H	3-OMe
3c	1	N	H	H
3d	1	N	H	4-F
3e	1	N	2-Me	4-F
3f	1	N	1-Me	4-F
4b	1	CH	H	3-OMe
4c	1	CH	H	H



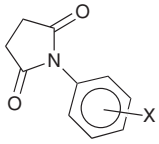
5: *n* = 0, 1; W = N

6: *n* = 1; W = CH



7

	R	X
b	H	3-OMe
c	H	H
d	H	4-F
e	Me	4-F



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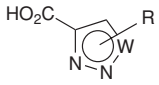
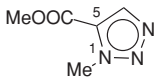
c : X = H

d : X = 4-F



9

	W	R
a	N	H
b	N	2-Me
c	CH	H



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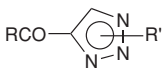

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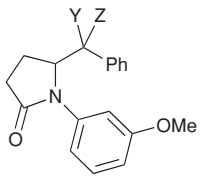
a : R = Ph_2CH, R' = H

b : R = Ph_2CH, R' = 2-Me

c : R = 4-$O_2NC_6H_4$, R' = H



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a : Y+Z=O

b : Y=OH, Z=H

† All chiral compounds described in this paper are racemic.

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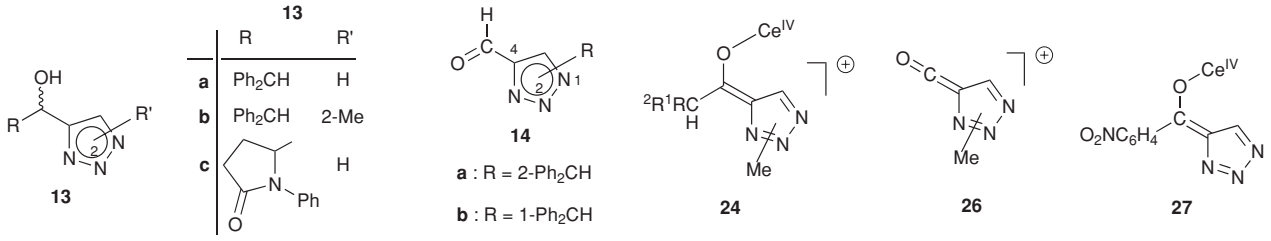

expected in analogy to the case of compounds **3c–3e** and **4c**. Ketones **11c** and **12a** did not react.

From the oxidation mixtures of ketones **3c–3e**, **4c**, **11a** and **11b** only the fragments **7c**, **7d**, **8c**, **8d** and benzophenone, respectively, corresponding to the "left-hand side" of the starting compounds were isolated; the expected fragments (*viz*. azolecarboxylic acids, **9**) corresponding to the "right-hand side" of the starting compounds evaded isolation in all cases (possibly due to their unfavourable physical properties). With the improvement of the physical properties of the right-hand side oxidation product in mind, oxidation with CAN of the *N*-methyl derivative **3f** in methanol was therefore studied and fragments corresponding to both sides of compound **3f**, *viz*. compound **7e** and ester **10** were isolated.

In addition to ketones **11a**, **11b** and **12a**, the reactions of their reduction products, the secondary alcohols **13a**, **13b** and **12b**, respectively, with CAN were also studied. Alcohol **13a** afforded two isomeric oxidative rearrangement products, **14a** and **14b** (which are similar to those obtained from compound **13c**[2] on similar treatment), together with benzophenone, an oxidative fragmentation product corresponding to the left-hand side of the substrate. Alcohol **13b** afforded benzophenone and diphenylmethanol, the two possible oxidative fragmentation products of the left-hand side of the substrate, but no oxidative rearrangement products were isolated. Alcohol **12b** afforded compound **7b**, an oxidative fragmentation product.

The formation of oxidative fragmentation products on treatment with CAN of ketones **3c–3f**, **4c**, **11a**, and **11b** clearly points to the activating effect of an azole ring adjacent to the carbonyl group, enabling ketones of this structural type to undergo CAN induced oxidative fragmentations. The explanation of this activating effect appears to be that, in the presence of azole groups adjacent to the carbonyl group, the oxidant is able to attack the carbonyl oxygen atom to afford intermediates of type **18** (Scheme 2).

As mentioned above, the course of the CAN induced oxidative transformation (cyclisation, fragmentation or both) of ketones **3** and **4** is determined by the nature of the substituent X of the *N*-C_6H_4X group of the substrate. While fragmentation has never been observed for X = 3-MeO (**3a**, **3b**, **4b**), exclusive fragmentation occurs for X = 4-F (**3d–3f**), and fragmentation and cyclisation take place competitively for X = H (**3c**, **4c**). Thus, these substituents facilitate fragmentation in the order 4-F > H > 3-MeO. This is also the order of decreasing electron withdrawing powers of these substituents which appears to mean that fragmentation takes place the easier the less prone is the *N*-C_6H_4X substituent to oxidation, while the opposite is true for cyclisation. The most obvious explanation for such a behaviour is the assumption that if the *N*-C_6H_4X group is sufficiently susceptible to oxidation (X = 3-MeO) the initial site of attack will be this group and oxidative cyclisation will take place therefore (*cf.* ref. 2) while, for X = 4-F, the *N*-C_6H_4X group is more resistant to oxidation so that the oxidant will attack the molecule at a different site and oxidative fragmentation takes place. The unsubstituted phenyl group is intermediate between the 3-methoxy- and the 4-fluorophenyl groups; therefore either site may be attacked by the oxidant and oxidative cyclisation and oxidative fragmentation take place competitively.

The *N*-methyl derivatives **3e**, **3f** and **11b** may be assumed to react similarly with CAN, with intermediates **24** and **26** replacing intermediates **18** and **21**, respectively. When the reaction of compound **3f** with CAN is conducted in methanol, rather than in aqueous acetonitrile cations **22** and **26** react with methanol to afford ether **7c** and ester **10**.

The insensitivity of ketone **12a** to CAN is the result of the absence of any activating azole group. The case of ketone **11c**, however, is different. Here formation of intermediate **27** should be possible; however, one of the products of its fragmentation would be the 4-nitrophenyl radical which is considerably less stable[4] than the radicals of type **20**; therefore fragmentation of **27** does not take place, and this intermediate is recovered, after heterolysis of its O–Ce^{IV} bond in form of the unchanged starting ketone **11c**.

The mechanism of formation of the oxidative rearrangement products **14a** and **14b** from alcohol **13a** and of the oxidative fragmentation products (diphenylmethanol and benzophenone) from alcohol **13b** should be analogous to the mechanism of formation of the corresponding products from alcohol **13c** (= **7c** in ref. 2).[2] The mechanism of the oxidative fragmentation of alcohol **12b** to afford compound **7b** could be similar, with the cationic oxidation product of the left-hand side of the substrate reacting only with water but not with benzaldehyde, the oxidation product of the right-hand side of the substrate.

Techniques used: flash chromatography, HRMS, ^{1}H- and ^{13}C-NMR, IR

References: 21

Scheme 1 Alternative mechanisms suggested for the oxidation of compounds **3a**–**3c**, **4b** and **4c**.

Scheme 2 Suggest mechanism of the oxidative fragmentation of ketones **3c**, **3d**, **4c** and **11a**.

Scheme 3 Mechanisms of oxidative rearrangement and oxidative fragmentation of compounds **13a** and **13b**.

Scheme 4 Preparation of compounds **3a**–**3f**, **4b** and **4c**.

Scheme 5 Synthesis (a) of the starting ketones **11a**–**11c** and alcohols **13a**, **13b** of starting ketone **12a** and alcohol **12b**.

Table 1 Oxidation of compounds **3a**–**3d**, **4b** and **4c** with CAN

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