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Ceric Ammonium Nitrate Promoted Free Radical Cyclization Reactions Leading to β-Lactams

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Abstract: The reaction of enamides with CAN in methanol affords variously functionalized β-lactams through a 4-*exo-trig* cyclization of α-carbamoylalkyl radicals; in most cases products with *trans* stereochemistry can be obtained. © 1997 Elsevier Science Ltd. All rights reserved.

In the last few years increasing attention has been devoted to the synthesis of four membered rings, particularly β-lactams, by means of radical cyclizations.[1-4] Radicals generated by reductive methods, i.e. by treatment of α-halo N-alkenyl amides either with Bu_3SnH and AIBN,[2,3] or with Ni in acetic acid,[4] have been reported to cyclize in a 4-*exo-trig* mode to afford azeditin-2-ones in variable yields. These methods were used by Ishibashi and coworkers in the synthesis of precursors of pharmacologically important β-lactams such as Thienamicin and PS-5.[3f]

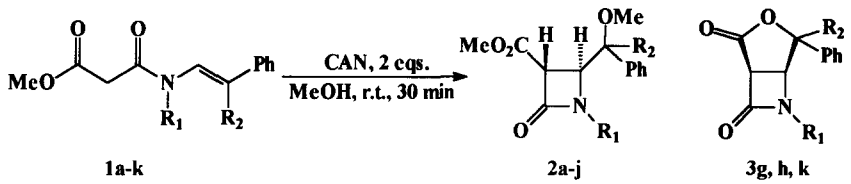
As regards the 4-*exo-trig* cyclization of suitable radicals generated by oxidative methods, we recently reported that α-methoxycarbonyl acetyl enamides, when treated with manganic acetate in acetic acid at 70 °C, afforded the corresponding azetidin-2-ones in modest to good yields. Most of the products showed a relative *trans* stereochemistry of substituents at C-3 and C-4.[5]

As a part of our study on the free radical cyclization of enamides under oxidative conditions, we decided to investigate their reactivity towards ceric ammonium nitrate (CAN).

Although CAN is a reagent commonly employed in the generation of carbon radicals mostly from β-dicarbonyl compounds, most of its applications involve intermolecular radical addition to olefinic double bonds.[6-8] Intramolecular reaction of such radical with double bonds was less studied,[9] and very little is known about the use of CAN to promote the generation of α-carbamoyl alkyl radicals from amides.

Thus, we employed α-methoxycarbonyl acetyl enamides and acetoacetyl enamides, that proved to be satisfactorily reactive towards generation of carbon radicals. On the contrary, other electron-withdrawing groups, such as chloro, cyano, phenylthio or phenylsulphonyl, in the α-position of the amide carbonyl were uneffective to promote the radical reaction. Reactions were all carried out in methanol, that proved to be the best solvent; experiments conducted in acetic acid or acetonitrile led to very poor yields of cyclic products. The choice of the particular substituents on the enamide double bond was dictated by considerations about the stability of the intermediate radicals **5** or **6** (Scheme 1). It could also allow a more direct comparison with the analogous Mn(III)-promoted process. As expected, the reaction of α-methoxycarbonyl acetamides **1** with two equivalents of CAN in MeOH at room temperature afforded the expected β-lactams in short reaction times and good yields (Table 1).[10] The usually isolated products were *trans* β-lactams **2**, as deduced by the small coupling constant of the ring H-3/ H-4 protons (about 2 Hz); in a few cases we isolated also *cis* products of general structure **3** (γ-lactone ring fused to the β-lactam), formed by an oxidative cyclization of the ester group onto the intermediate radical.

Table 1. Reactions of α-Methoxycarbonyl Acetyl Enamides With CAN



1a-k 2a-j 3g, h, k

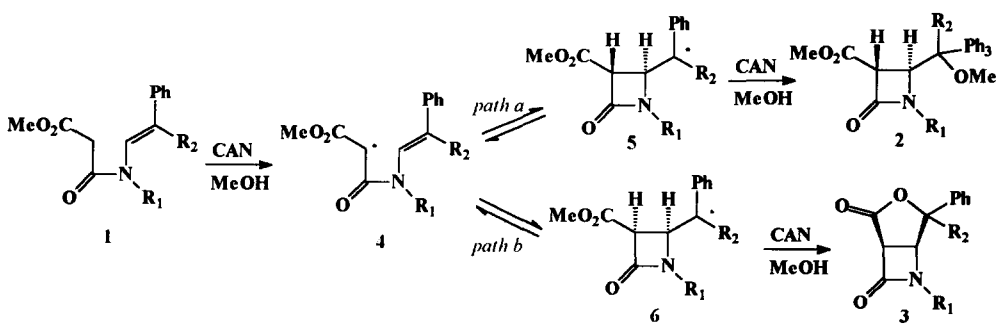
Enamide	R_1	R_2	2 (% yield)[a]	3 (% yield)[a]
1a	n-propyl	Ph	49	-
1b	1-phenethyl	Ph	43[b]	-
1c	cyclopentyl	Ph	48	-
1d	cyclohexyl	Ph	67	-
1e	cycloheptyl	Ph	56	-
1f	cyclooctyl	Ph	52	-
1g	t-butyl	Ph	43	24
1h	n-propyl	Me	55	6
1i	1-phenethyl	Me	65[c]	-
1j	cyclohexyl	Me	47	-
1k	t-butyl	Me	-	32

a: referred to isolated products
b: 1.2 : 1 mixture of diastereoisomers
c: mixture of diastereoisomers

As shown in Table 1, a marked preference for the almost exclusive formation of *trans* β-lactams was observed. In the case of enamide **1g** we could isolate a significative amount of *cis* azetidin-2-one **3g** beside *trans* **2g**. The cyclization of corresponding enamide **1k** with a N-t-butyl group afforded *cis* azetidin-2-one **3k** as the only reaction product, although in low yield. These stereochemical data seem to be in agreement with those we previously reported for Mn(III) promoted cyclizations of enamides.[5] An explanation for the formation of the products is given in Scheme 1.

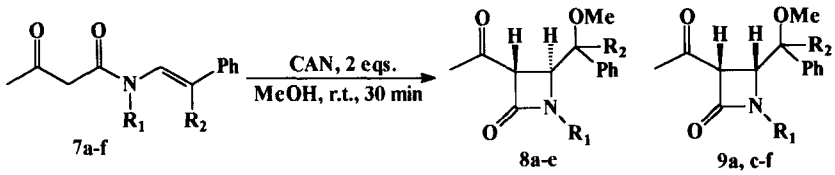
Radical **4**, generated by CAN oxidation of enamide **1**, cyclizes in a 4-*exo*-*trig* mode affording radicals **5** (*path a*) and **6** (*path b*), with *trans* and *cis* stereochemistry respectively, that are further oxidized by another equivalent of CAN to final products **2** and **3**. The final *cis* or *trans* stereochemistry is established at the cyclization stage: a confirmation of this came from the fact that, for example, when we treated separately compounds **2g** and **3g** with CAN in methanol, we did not observe their mutual interconversion.

Scheme 1



To verify the generality of this method and its applicability to the synthesis of valuable intermediates, we reacted under the same conditions acetoacetyl enamides **7a-f**, that could be efficiently prepared by the methodology we recently reported.[11]

Table 2. Reactions of Acetoacetyl Enamides With CAN



7a-f 8a-e 9a, c-f

Enamide	R_1	R_2	8 (% yield)[a]	9 (% yield)[a]
7a	benzyl	Ph	27	21
7b	cyclohexyl	Ph	36	-
7c	t-butyl	Ph	18	22
7d	benzyl	Me	26	34
7e	cyclohexyl	Me	29	17
7f	t-butyl	Me	-	74

a: referred to isolated products

A preferential formation of *trans* β-lactams **8** was still observed for most enamides, while the formation of *cis* azetidin-2-ones **9** was favoured by the presence of N-t-butyl group. Usually mixtures of both isomers were obtained, although some degree of selectivity could be achieved, namely in the case of enamide **7b** that afforded *trans* azetidin-2-one **8b** as the only product in 36% yield, and in the case of enamide **7f** that provided exclusively *cis* β-lactam **9f** in high yield (74%).

The reaction of enamides with CAN provides a new, simple access to functionalized azetidin-2-ones, complementary to the Mn(III)-promoted 4-*exo-trig* cyclization of enamides.[5] These preliminar results seem to suggest a dependence of the stereochemical outcome of the reaction from the substituents on both the nitrogen and the double bond, which is matter of our current investigation. The ester or keto groups at the C-3 position of final β-lactams, together with the introduction of an oxygen function in the C-4 side chain, may render these compounds susceptible to further modification into useful synthetic intermediates. Moreover this is the first example, to our knowledge, of the use of amides as substrates in CAN promoted radical generation.

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10. A typical experimental procedure is as follows: to a solution of enamide (0.5 mmol) in dry methanol (5 ml) containing K_2CO_3 (0.25 mmol), CAN (1.0 mmol, 548 mg) is added under inert atmosphere in one portion, and the solution is stirred for 30 minutes; water (50 ml) is then added and extraction with CH_2Cl_2 (3×15 ml) affords, after evaporation, a crude product which is purified by flash column chromatography (silica gel; hexane: EtOAc 4: 1). ^1H NMR data of products (200 MHz, $CDCl_3$, δ): **2a**: 0.88 (3H, t, J= 8.2 Hz); 1.60 (2H, m); 2.78 (1H, dt, J_1= 14.0 Hz, J_2= 5.5 Hz); 3.08 (3H, s); 3.41 (1H, dt, J_1= 14.0 Hz, J_2= 7.5 Hz); 3.68 (1H, d J= 2.2 Hz); 3.78 (3H, s); 4.92 (1H, d, J= 2.2 Hz); 7.2-7.4 (10H, m). **2b**: 1.2:1 mixture of two diastereoisomers: more abundant isomer: 1.62 (3H, d, J= 4.8 Hz); 2.96 (3H, s); 3.58 (1H, d, J= 2.2 Hz); 3.78 (3H, s); 4.35 (1H, q, J= 4.8 Hz); 4.92 (1H, d, J= 2.2 Hz); less abundant isomer: 1.68 (3H, d, J= 4.7 Hz); 2.93 (3H, s); 3.70 (1H, d, J= 2.2 Hz); 3.77 (3H, s); 4.38 (1H, q, J= 4.7 Hz); 4.71 (1H, d, J= 2.2 Hz). **2c**: 1.2-1.8 (8H, m); 2.15 (1H, m); 3.05 (3H, s); 3.58 (1H, d, J= 2.2 Hz); 3.74 (3H, s); 4.87 (1H, d, J=2.2 Hz); 7.2-7.4 (10H, m). **2d**: 1.0-2.0 (10H, m); 2.80 (1H, tt, J_1= 12.0 Hz, J_2= 4.0 Hz); 3.05 (3H, s); 3.62 (1H, d, J= 2.2 Hz); 3.74 (3H, s); 4.87 (1H, d, J= 2.2 Hz); 7.2-7.4 (10H, m). **2e**: 1.1-2.1 (12H, m); 2.94 (1H, m); 3.04 (3H, s); 3.61 (1H, d, J=2.3 Hz); 3.75 (3H, s); 4.66 (1H, d, J= 2.2 Hz); 7.2-7.4 (10H,m). **2f**: 1.2-1.9 (14H, m); 3.03 (3H, s); 3.11 (1H, m); 3.58 (1H, d, J=2.5 Hz); 3.75 (3H, s); 4.87 (1H, d, J=2.5 Hz); 7.2-7.4 (10H, m). **2g**: 1.22 (9H, s); 2.95 (3H, s); 3.50 (1H, d, J= 2.4 Hz); 3.68 (3H, s); 4.88 (1H, d, J=2.4 Hz); 7.2-7.5 (10H, m). **3g**: 0.88 (9H, s); 3.92 (1H, d, J=4.4 Hz); 4.96 (1H, d, J= 4.4 Hz); 7.3-7.6 (10H, m). **2h**: 0.80 (3H, t, J= 8.0 Hz); 1.42 (2H, m); 1.51 (3H, s); 2.85 (1H, dt, J_1=13.7 Hz, J_2= 6.6 Hz); 3.10 (3H, s); 3.38 (1H, dt, J_1= 13.7 Hz, J_2= 7.4 Hz); 3.55 (3H, s); 4.05 (1H, d, J= 2.8 Hz); 7.2-7.5 (5H, m). **3h**: 0.95 (3H, t, J=8.0 Hz); 1.65 (2H, m); 1.80 (3H, s); 2.85 (1H, m); 3.35 (1H, m); 4.05 (1H, d, J= 4.2 Hz); 4.30 (1H, d, J=4.2 Hz); 7.2-7.5 (5H, m). **2i**: mixture of four diastereoisomers in approximately 3.5:2:2:1 ratio; selected data: 3.48-3.72 (four doublets, J= 2.5 Hz); 3.85-4.10 (four doublets, J= 2.5 Hz); 4.25-4.70 (four quartets, J= 5.3 Hz). **2j**: 1.0-2.0 (10H, m); 1.54 (3H, s); 3.08 (3H, s); 3.15 (1H, m); 3.38 (1H, d, J= 2.3 Hz); 3.49 (3H, s); 4.05 (1H, d, J=2.3 Hz); 7.2-7.4 (5H, m). **3k**: 1.48 (9H, s); 1.82 (3H, s); 3.87 (1H, d, J=4.5 Hz); 4.37 (1H, d, J=4.5 Hz); 7.3-7.4 (5H, m). **8a**: 2.25 (3H, s); 2.98 (3H, s); 3.96 (1H, d, J= 12.4 Hz); 4.01 (1H, d, J= 2.4 Hz); 4.83 (1H, d, J=12.4 Hz); 5.03 (1H, d, J=2.4 Hz); 7.1-7.4 (15H, m). **9a**: 1.70 (3H, s); 1.84 (1H, d, J= 15.2 Hz); 2.58 (3H, s); 3.76 (1H, d, J= 3.8 Hz); 4.40 (1H, d, J= 15.2 Hz); 4.77 (1H, d, J= 3.8 Hz); 7.2-7.4 (15H, m). **8b**: 1.0-2.0 (10H, m); 2.21 (3H, s); 2.88 (1H, dt, J_1= 12.0 Hz, J_2= 4.0 Hz); 3.06 (3H, s); 3.82 (1H, d, J= 2.4 Hz); 5.02 (1H, d, J= 2.4 Hz); 7.2-7.4 (10H, m). **8c**: 1.18 (9H, s); 2.15 (3H, s); 2.97 (3H, s); 3.75 (1H, d, J=2.2 Hz); 5.07 (1H, d, J=2.2 Hz); 7.1-7.4 (10H, m). **9c**: 0.78 (9H, s); 1.70 (3H, s); 2.70 (3H, s); 3.65 (1H, d, J= 4.4 Hz); 5.04 (1H, d, J= 4.4 Hz); 7.1-7.5 (10H, m). **8d**: 1.48 (3H, s); 1.98 (3H, s); 3.00 (1H, d, J= 12.9 Hz); 3.08 (3H, s); 3.82 (1H, d, J= 2.4 Hz); 3.90 (1H, d, J= 12.9 Hz); 4.00 (1H, d, J= 2.4 Hz); 7.1-7.4 (10H, m). **9d**: 1.50 (3H, s); 1.55 (3H, s); 2.91 (3H, s); 3.62 (1H, d, J= 4.4 Hz); 4.04 (1H, d, J= 15.0 Hz); 4.46 (1H, d, J= 4.4 Hz); 5.02 (1H, d, J= 15.0 Hz); 7.2-7.4 (10H, m). **8e**: 1.57 (3H, s); 1.90 (3H, s); 3.05 (3H, s); 3.55 (1H, d, J= 2.6 Hz); 4.12 (1H, d, J= 2.6 Hz); 7.2-7.4 (5H, m). **9e**: 1.60 (3H, s); 2.90 (3H, s); 3.52 (1H, d, J= 3.7 Hz); 4.68 (1H, d, J= 3.7 Hz); 7.2-7.5 (5H, m). **9f**: 1.45 (9H, s); 1.52 (3H, s); 1.58 (3H, s); 2.83 (3H, s); 3.55 (1H, d, J=4.3 Hz); 4.75 (1H, d, J= 4.3 Hz); 7.2-7.5 (5H, m).
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