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A novel synthesis of tricyclic-fused hydrindene–azetidinone compounds by sequential Mn(III)-promoted 4-*exo-trig* cyclization/radical aromatic substitution

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Abstract

The 2-acyl-*N*-(2,2-diphenyl-1-ethenyl)-*N*-alkylacetamides reacted with excess Mn(III) affording tricyclic fused hydrindene-azetidinones in good yields, through a 4-*exo-trig* radical cyclization process, and further ring closure of the azetidinone via radical aromatic substitution.

Keywords: cyclization; azetidinones; manganese and compounds; radicals and radical reaction; polycyclic heterocyclic compounds.

The synthesis of β-lactams **3** through the 4-*exo-trig* oxidative radical cyclization of enamides **1** has been, for several years, the main feature of our studies concerning transformations mediated by $Mn(OAc)_3$.[1] As previously described, this ring closure was first carried out in an oxidative way by reacting enamides **1a** with 2 equivalents of Mn(III) salt. In this case, the terminal olefinic position has to be substituted in such a way as to provide stabilization of the radical adduct **2a** (Scheme 1). This structural restriction was overcome for either oxidative or reductive methods by using enamides able to fragment after the 4-*exo* cyclization step.[2,3] This approach led to azetidin-2-ones **3b** by treatment of enamides **1b** with a saving of oxidant (only 1 equivalent of Mn(III) was needed).[2]

Most of the enamides we used had the methoxycarbonyl group as the oxidizable β-dicarbonyl moiety.[4] The cyclization of these substrates was selective and high-yielding only at 70°C. Indeed, lower reaction temperatures led to unsatisfactory substrate conversions. Noteworthy, at 70°C no products arising from the further oxidation of the β-lactam products were observed.

With the aim to widen the range of experimental conditions suitable for the reaction, we decided to study the Mn(III) chemistry of the easily obtainable enamides **4** and **5**,[5] which bear an acyl group at C-2. In this communication we report our preliminary results. The acyl group at C-2 in **4** and **5** made

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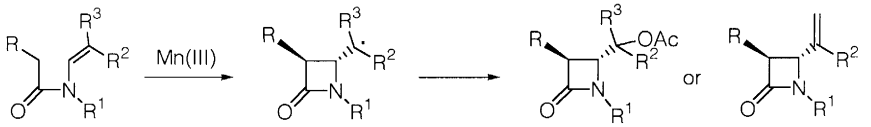


1a R = CO_2CH_3, R^1 = alk, Bz **2a**
R^2 = CH_3, Ph, R^3 = Ph
1b R = CO_2CH_3, R^1 = alk, Bz **2b**
R^2 = CH_3, R^3 = CH_2SPh

3a **3b**

Scheme 1.

the enolization of their β-dicarbonyl system easier than in **1**, as clearly evidenced by their ^{1}H NMR data showing significant amounts of the enol forms. Thus, compounds **4**–**5** could, in principle, be more reactive than enamides **1** at room temperature, since the oxidation mediated by Mn(III) probably involves prior enolization of the carbonyl groups, followed by electron transfer from the enol form to the metal.[6]

To verify the hypothesis of higher reactivity, compound **5b** was treated with 2 equivalents of $Mn(OAc)_3$ dihydrate at room temperature but the oxidation was quite slow, affording compound **7b** in 2 days in 22% yield. Raising the temperature to 70°C made the reaction of enamides **4** and **5** with the same amount of Mn(III) faster, but as shown in Table 1 (condition A) we observed not only the expected compounds **6** and **7**, but also the polycyclic compounds **10** and **11**. A reasonable hypothesis for the formation of these compounds involves a further reaction with Mn(III) of the β-lactams **6** and **7** (Scheme 2) at C-3. The resulting radical **8** could undergo an intramolecular radical aromatic substitution to give **10** and **11** through the intermediacy of radical **9**.

Table 1
Reaction of enamides **4** and **5** with $Mn(OAc)_3$ in AcOH

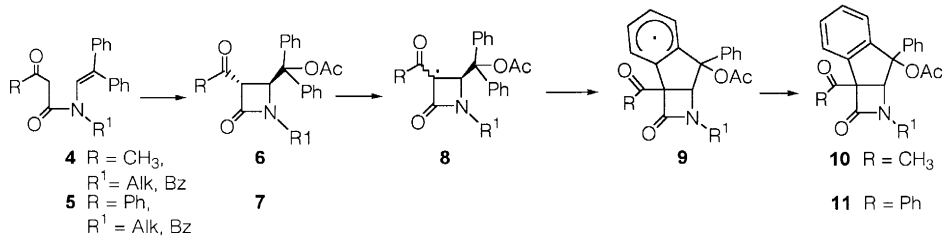
Entry	Substrate	R	R^1	Conditions[a]	Product (yield %)[b]		Reaction time (h)
1	**4a**	CH_3	Bz	A	**6a** (43)	**10a** (14)	0.3
2	"	"	"	B		**10a** (22)	2
3	**4b**	"	Cyclohexyl	A	**6b** (53)	**10b** (18)	0.3
4	"	"	"	B		**10b** (80)	2
5	**4c**	"	*i*-Pr	A	**6c** (26)	**10c** (28)	0.3
6	"	"	"	B		**10c** (53)	2
7	**5a**	Ph	Bz	A	**7a** (20)	**11a** (21)	1
8	"	"	"	B		**11a** (45)	2
9	**5b**	"	Cyclohexyl	A	**7b** (24)	**11b** (23)	1
10	"	"	"	B		**11b** (82)	2
11	**5c**	"	*i*-Pr	A	**7c** (75)		1
12	"	"	"	B		**11c** (83)	2
13	**5d**	"	(*R*)- CH (Me) Ph	"		**11d** (65)[c]	"
14	**5e**	"	(*S*)-CH(CO_2Me)Ph	"		**11e** (86)[d]	"

a) Conditions (A) and (B) refer to reactions carried out using two and four eqs. of Mn(III) respectively (see experimental in ref. 7; b) Isolated yield; c) **11d**: 1:1 d.r.; **11e:** 5.2 : 1 d.r. (determined by ^{1}H-NMR).

This was proved by reacting pure **6a** with Mn(III) at 70°C; the expected product **10a** was formed in 3 hours in 81% yield. Thus, we planned to obtain the products **10** and **11** in the highest possible yields by treating enamides **4** and **5** with an excess of $Mn(OAc)_3$ (4 equivalents).

Indeed, the skeleton of **10**/**11** was interesting since analogous compounds **12** and **13** have been patented as promoters in the polymerization of pyrrolidones[8] and in the preparation of polyurethanes (Fig. 1).[9]

As we expected, in the presence of an excess of Mn(III) at 70°C (conditions B), **10** and **11** were obtained in good to high yields and in short times. In two examples (entries 13 and 14) the chiral



Scheme 2.

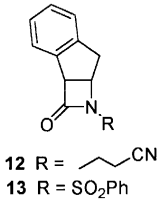


Fig. 1.

enamides **5d** and **5e** were reacted under the same conditions to investigate the stereoselectivity of the reaction. Indeed, we had previously reported that a chiral amino acid-derived group on the enamidic nitrogen atom could have a good effect on the diastereoselectivity of the 4-*exo-trig* ring closure to β-lactams.[10] The same behaviour was also confirmed in these reactions, and the product **11e** was obtained from **5e** in a 5.2:1 diastereomeric ratio, which is the highest value that we have obtained at present in the 4-*exo-trig* ring closures. Unfortunately, the absolute configurations of the stereogenic centers of the prevalent, oily diastereomer could not be determined by the usual spectral or X-ray diffraction methods.

In conclusion, the Mn(III)-promoted synthesis of polycyclic compounds **10**–**11** in one step from enamides **4**–**5** is a significant result either in the light of the industrial use of their analogues or the possibility of achieving a spread of the backbones obtainable by Mn(III)-mediated 4-*exo-trig* ring closure of enamidic systems.

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5. Compounds **4** and **5** were easily prepared through the reaction of a suitable imine with commercially available 2,2,6-trimethyl-1,3-dioxin-4-one[11] or its 6-phenyl analogue, obtainable by literature methods.[12]
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7. Experimental procedure: To a solution of **4** or **5** (0.5 mmols) in glacial acetic acid (15 ml), $Mn(OAc)_3$ dihydrate (1.0 mmols in condition A, 2.0 mmols in condition B) was added at 70°C under an argon atmosphere. The resulting brown solution was stirred until the colour of the mixture turned pale yellow. The mixture was poured into water (100 ml) and extracted

with CH_2Cl_2 (4×50 ml). The organic phase was washed with saturated $NaHCO_3$, then with water, and finally dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a residue that was chromatographed on a silica gel column, eluted with Et_2O and light petroleum ether to give pure **10** or **11**. Representative spectral data; compound **10c**: ^{1}H NMR, 200 MHz (δ, $CDCl_3$): 1.37 (3H, d, *J*=6.7 Hz), 1.41 (3H, d, *J*=6.7 Hz), 2.20 (3H, s), 2.39 (3H, s), 3.59 (1H, septuplet, *J*=6.7 Hz), 4.95 (1H, s), 7.10–7.50 (9H, m); ^{13}C NMR: 20.56, 20.82, 28.59, 48.44, 65.67, 79.80, 80.61, 124.42–129.96, 135.31, 142.94, 162.89, 168.83, 199.96.

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