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The ferric chloride-catalyzed Ritter amidation of norbornane-type dienes

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The $FeCl_3·6H_2O$ catalyzed Ritter amidation of norbornane dienes with aceto- and propionitriles in the presence of water (145 °C, 6 h) affords the corresponding amides in yields of 35–87%.

Amidation of olefins with nitriles under acid catalysis conditions (the Ritter reaction) is one of the topical methods in organic chemistry.[1,2] Mineral acids, such as H_2SO_4, $PhSO_3H$, HF, oleum and heteropoly acids as well as copper compounds[5] and $NbCl_5$[6] were used as the catalysts.[3,4] On the other hand, compounds containing a norbornane fragment exhibit a broad spectrum of biological activities.[7,8] New types of polymers with unique properties have been obtained by the metathesis and addition polymerization of norbornene and its derivatives.[9,10]

We have recently found that the reaction of norbornene with nitriles in the presence of $FeCl_3·6H_2O$ affords the standard amidation product.[11] In order to clarify whether this reaction is only typical of norbornene or it can also be extended to other relative olefins, we studied the Ritter amidation of bi-, tetra- and pentacyclic dienes of norbornane series with aceto- and propionitriles.

Previously, *N*-(tricyclo[2.2.1.0^{2,6}]hept-3-yl)acetamide was obtained in a small yield (2%) by amidation of norbornadiene **1** with acetonitrile in the presence of HF.[12] When this reaction was carried out in the presence of a fourfold excess of sulfuric acid, the yield of the amide rose to 63%.[13]

In our hands, the reaction of norbornadiene **1** with propionitrile in the presence of $FeCl_3·6H_2O$ ([$FeCl_3·6H_2O$] : [**1**] : [EtCN] : [H_2O] = 0.03 : 1 : 5 : 1, 145 °C, 6 h) occurred smoothly to give a mixture of 3-*exo*-propioamidotricyclo[2.2.1.0^{2,6}]heptane **2a** and 2-*exo*-propioamidobicyclo[2.2.1]hept-5-ene **2b** in 53% overall yield (Scheme 1). A twofold increase in propionitrile concentration allows the total yield of amides **2a**,**b** to be raised to 80%. Other iron compounds, such as $Fe(C_5H_5)_2$, $Fe(OAc)_2·4H_2O$, $Fe(acac)_3$, $Fe(CF_3CO)_3$ and $Fe_2(CO)_9$ showed low catalytic activity. The 2–3 fold increase in the amount of water caused formation of a side product, bicyclo[2.2.1]hept-2-en-5-ol, in up to 50% yield.

Special experiments were performed to clarify the mechanism of the catalytic action of $FeCl_3·6H_2O$. It was found that $FeCl_3·6H_2O$ underwent gradual hydrolysis under the reaction conditions to release HCl (the HCl concentration was 31.5 mg ml^{-1} after 6 h). However, the amidation of **1** with propionitrile under typical conditions in the presence of $FeCl_3·6H_2O$ with HCl additive (3 mol%) resulted in only 16% conversion of diene **1** and occurred non-selectively to afford amides **2a**,**b** along with bicyclo[2.2.1]hept-2-en-5-ol. Thus, though hydrolysis of $FeCl_3·6H_2O$ to give HCl occurs under the reaction conditions, it can be assumed that an iron complex with a complicated composition probably containing HCl, propionitrile and water, is responsible for the whole process.

1 **2a** (69%) **2b** (11%)

Scheme 1 *Reagents and conditions*: i, $FeCl_3·6H_2O$, 145 °C, 6 h.

2-Chlorobicyclo[2.2.1]hepta-2,5-diene **3** rather readily reacts with propionitrile in the presence of $FeCl_3$ and water giving thus a mixture of 3-*exo*- and 2-*exo*-propioamido-1-chlorotricyclo[2.2.1.0^{2,6}]heptanes **4a** and **4b**, respectively, in 3 : 1 ratio in 82% overall yield (Scheme 2). The reaction of diene **3** with acetonitrile and water in the presence of $FeCl_3·6H_2O$ results in a single product, *i.e.*, 3-*exo*-acetamido-1-chlorotricyclo[2.2.1.0^{2,6}]heptane **4′a**, in 35% yield. The structure of amide **4′a** was confirmed by single crystal X-ray diffraction data (Figure 1).[†] The single crystals of compound **4′a** were obtained from acetonitrile solution by slow evaporation. The structure consists of one three-membered ring and three five-membered rings that have envelope conformations.

3
4a Alk = Et (62%)
4′a Alk = Me (35%)
4b (20%)

Scheme 2 *Reagents and conditions*: i, $FeCl_3·6H_2O$, 145 °C, 6 h.

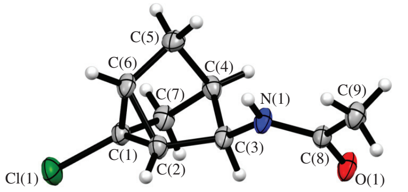

Figure 1 Molecular structure of compound **4′a**. Atoms are represented by thermal displacement ellipsoids at the 30% probability level.

[†] *Crystal data for* **4′a**. $C_9H_{12}ClNO$ (M = 185.65), orthorhombic, space group *Pbca*, a = 10.6925(6), b = 9.6385(7) and c = 17.2215(13) Å, V = = 1774.8(2) Å^3, Z = 8, d_{calc} = 1.390 g cm^{-3}, μ = 0.379 mm^{-1}, $F(000)$ = 784, 5267 reflections were measured and 2110 independent reflections (R_{int} = = 0.0243) were used in a further refinement. The refinement converged to wR_2 = 0.1608 and GOF = 1.112 for all reflections [R_1 = 0.0686 was calculated against F for 1432 observed reflections with $I > 2\sigma(I)$].

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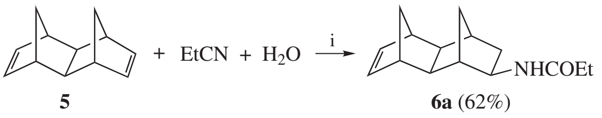


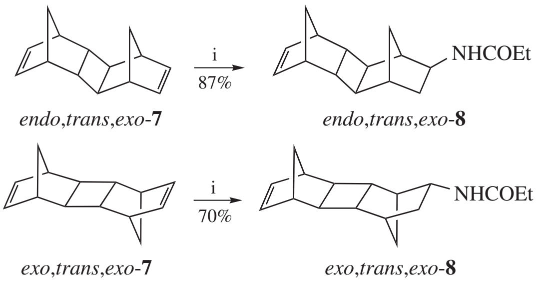
5 **6a** (62%)

Scheme 3 *Reagents and conditions*: i, $FeCl_3 \cdot 6H_2O$, 145 °C, 6 h.

The acetamide group acquires an *exo*-position; the C(1)–C(2)–C(3)–N(1) torsion angle is 153.3(3)°.

The amidation of *exo*,*exo*-tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene **5** with propionitrile in the presence of water and $FeCl_3 \cdot 6H_2O$ occurs rather smoothly. Though the double bonds are remote from each other, only one of them participates in the reaction (Scheme 3).

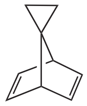
1,7-Dienes such as pentacyclic [2+2]-dimers of norbornadiene **1**, *viz*., *endo*,*trans*,*exo*- and *exo*,*trans*,*exo*-pentacyclo-[8.2.1.1^{4,7}.0^{2,9}.0^{3,8}]tetradeca-5,11-dienes **7**, behave similarly in reactions with nitriles (Scheme 4). The amidation of dimers **7** with propionitrile catalyzed by $FeCl_3 \cdot 6H_2O$ in the presence of water (145 °C, 6 h) occurs at one double bond to give the corresponding isomeric amides **8**.



Scheme 4 *Reagents and conditions*: i, EtCN, H_2O, $FeCl_3 \cdot 6H_2O$ ([$FeCl_3 \cdot 6H_2O$] : [**7**] : [EtCN] : [H_2O] = 0.03 : 1 : 10 : 1), 145 °C, 6 h.

The structure of amide *endo*,*trans*,*exo*-**8** was confirmed by single crystal X-ray diffraction data (Figure 2).[†] The unit cell of its monoclinic crystals contains two crystallographically independent molecules [Figure 2(*b*)] connected by a strong N–H···O hydrogen bond [length 2.095(2) Å, symmetry code *x*, *y*, *z*]. These molecules have an identical conformation, as well as similar bond angles and bond lengths. The crystal consists of *exo*,*trans*,*endo*-linked norbornane moieties [Figure 2(*a*)] when all the five-membered rings acquire an envelope conformation. The position of the propionamide moiety is described by the C(4)–C(5)–N(1)–C(15) and C(6)–C(5)–N(1)–C(15) torsion angles of 163.0(3) and –81.3(4)°, respectively.

Under the conditions we chose, spiro[bicyclo[2.2.1]hepta-2,5-diene-7,1′-cyclopropane] **9** and 2,3-bis(methoxycarbonyl)-norbornadiene **10** do not undergo the transformation. It may be assumed that the inactivity of compound **9** results from the spatial hindrance created by the cyclopropane ring, while that of **10** is caused by the catalyst deactivation due to the formation of a strong complex with two CO_2Me substituents.



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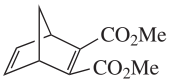

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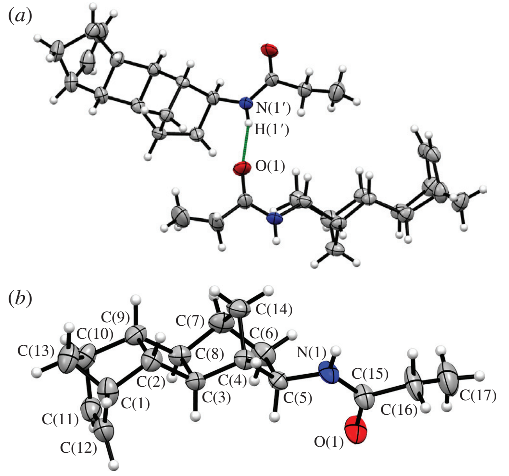

Figure 2 Molecular structures of (*a*) unit cell and (*b*) individual molecule of *endo*,*trans*,exo-**8**. Atoms are represented by thermal displacement ellipsoids at the 30% probability level.

In summary, the Ritter reaction of norbornadiene, 2-chloro-norbornadiene, *exo*,*exo*-tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene, *endo*,*trans*,*exo*- and *exo*,*trans*,*exo*-pentacyclo[8.2.1.1^{4,7}.0^{2,9}.0^{3,8}]-tetradeca-5,11-dienes with aceto- and propionitriles in the presence of iron(III) chloride hexahydrate affords the products of amidation of only one double bond.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.007.

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[†] *Crystal data for endo,trans,exo*-**8**. $C_{17}H_{23}NO$ (M = 257.36), monoclinic, space group $P2_1/c$, a = 9.4127(6), b = 15.7092(14) and c = 19.6191(16) Å, β = 92.115(7)°, V = 2899.0(4) Å^3, Z = 8, d_{calc} = 1.179 g cm^{-3}, μ = = 0.072 mm^{-1}, $F(000)$ = 1120, 13282 reflections were measured and 6681 independent reflections (R_{int} = 0.0633) were used in a further refinement. The refinement converged to wR_2 = 0.2134 and GOF = 0.876 for all reflections [R_1 = 0.0775 was calculated against F for 2167 reflections with $I > 2\sigma(I)$].

CCDC 1847560 and 1853228 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.