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Iron(III) chloride promoted Ritter amidation of saturated cyclopropane-containing polycyclic hydrocarbons

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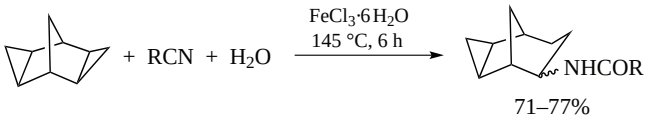
The Ritter-type amidation of cyclopropane-containing norbornane hydrocarbons proceeds *via* cyclopropane ring opening upon treatment with aceto- or propionitrile and water in the presence of $FeCl_3·6H_2O$ as a catalyst.



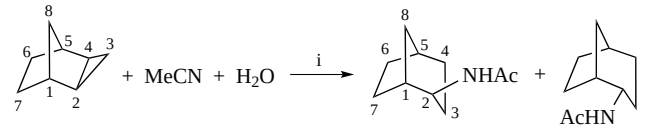
Keywords: amidation, nitriles, cyclopropanes, polycyclic hydrocarbons, norbornane, iron(III) chloride hexahydrate, Ritter reaction.

The Ritter reaction is a classical method for the preparation of *N*-subsituted amides, in which alcohols, halohydrocarbons or olefins react with nitriles and water in the presence of acidic catalysts.[1] Apart from Brønsted acids, this reaction can be catalyzed by transition metal salts like In^{III},[2] Co^{III},[3] Cu^{II},[4,5] Fe^{III},[6–10] and $NbCl_5$.[11] The activity of halohydrocarbons, alcohols and olefins in the Ritter reaction is determined by their ability to form carbocations, which are then attacked by the nitrogen atom of the CN group. There are several published examples of the Ritter reaction of cyclopropane derivatives,[12–14] which originates form partial π-character of the three-carbon ring banana bonds. Amides produced by the Ritter reaction can be used as precursors for pharmacologically promising polycyclic amines.

In our previous work,[10] we have unvestigated the $FeCl_3·H_2O$-catalyzed acetonitrile amidation of four isomeric hexacyclic unsaturated cyclopropane-containing norbornadiene dimers with *exo*,*exo*-, *exo*,*endo*-, *endo*,*exo*- and *endo*,*endo*-configurations with two reaction centers in the molecule, namely double bonds and cyclopropane rings (CPRs). We have found that for *exo*,*exo*-, *exo*,*endo*- and *endo*,*exo*-configured dimers with weakly shielded CPR moiety, the reaction proceeds at the CPR part, whereas the *endo*,*endo*-dimer with more shielded CPR fragment reacts by the double bond. In this regard, it was of interest to examine the amidation of analogous saturated polycyclic hydrocarbons containing di- and trisubstituted CPRs in the molecule.

In fact, amidation of tricyclo[3.2.1.$0^{2,4}$]octane **1** with acetonitrile and water ([**1**]/[MeCN] = 1 : 10) in the presence of 3 mol% $FeCl_3·6H_2O$ resulted in isomeric 2-acetamidobicyclo[3.2.1]octanes *exo*-**2** and *endo*-**2** in 35% total yield (Scheme 1). An increase in acetonitrile concentration to [**1**]/[MeCN] = 1 : 15 results in higher total yield of these amides up to 90%.

Amides *exo*-**2** and *endo*-**2** differed little in their R_f values and therefore were characterized as a mixture by 1D/2D ^1H and ^{13}C NMR spectra. For compound *endo*-**2**, the C^2 carbon atom resonates upfield at 19.90 ppm, which is due to the steric compression induced by the amide group. A corresonding signal of the C^2 carbon atom for compound *exo*-**2** appears at 23.83 ppm. The *exo*/*endo*-**2** ratio 1.25 : 1 was derived from integrated intensities of the characteristic C^2H signals at 3.82 ppm for isomer *exo*-**2** and 3.98 ppm for its counterpart *endo*-**2**.



1 *exo*-**2** *endo*-**2**

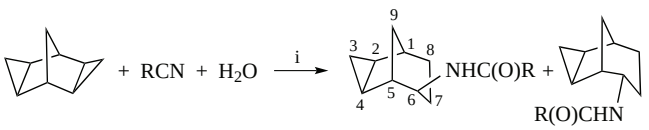
[**1**]/[MeCN] = 1 : 10, total 35%
[**1**]/[MeCN] = 1 : 15, total 90%
exo/*endo* = 1.25 : 1

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

The amidation of *exo*,*exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane **3** with aceto- and propionitriles in the presence of water and $FeCl_3·6H_2O$ afforded the corresponding 6-acylaminotricyclo[3.3.1.$0^{2,4}$]nonanes *exo*/*endo*-**4a**,**b** in good yields (Scheme 2).

Due to their close solubility and R_f values, compounds *exo*/*endo*-**4a** and *exo*/*endo*-**4b** were characterized as diastereomeric mixtures by 1D/2D ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of the compounds *exo*/*endo*-**4a** mixture exhibits signals at 3.99 and 3.85 ppm at 4 : 1 ratio for C^6H protons. The signal of the C^6 atom of amide *endo*-**4a** is located at 13.13 ppm and is shifted upfield compared to that of compound *exo*-**4a** at 16.03 ppm due to steric interaction.

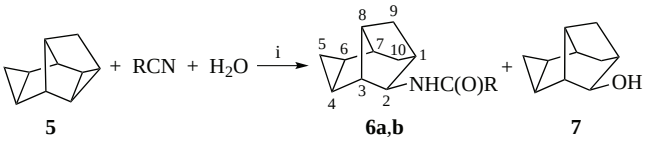
Amidation of pentacyclo[4.4.0.$0^{2,4}$.$0^{3,7}$.$0^{8,10}$]decane **5** containing di- and trisubstituted CPR moieties proceeds regioselectively at the trisubstituted one resulting in the cleavage of the C^2–C^3 bond to give 2-acylaminotetracyclo[5.2.1.$0^{3,8}$.$0^{4,6}$] decanes **6a**,**b** in *exo*-configuration exclusively (Scheme 3, Table 1). Tetracyclo[5.2.1.$0^{3,8}$.$0^{4,6}$]decan-2-ol **7** is formed as a byproduct. The reaction chemoselectivity depends on the molar ratio of reactants. The highest selectivity for acetamide **6a** is



3 *exo*-**4a**,**b** *endo*-**4a**,**b**

a R = Me, *exo*/*endo* = 4 : 1, total 77%
b R = Et, *exo*/*endo* = 3.5 : 1, total 71%

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



a R = Me
b R = Et

Scheme 3 *Reagents and conditions*: i, RCN, H_2O, $FeCl_3 \cdot 6H_2O$, 145 °C, 6–12 h.

Table 1 The amidation of pentacyclo[4.4.0.0^{2,4}.0^{3,7}.0^{8,10}]decane **5** with nitriles catalyzed by $FeCl_3 \cdot 6H_2O$.[a]

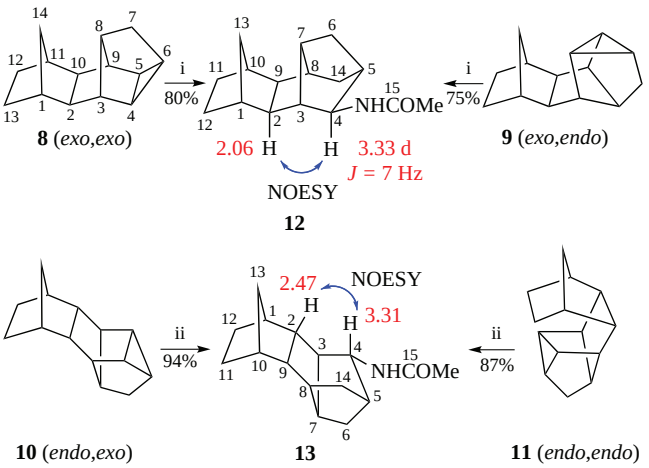
Entry	Nitrile	[**5**]/[RCN] ratio	*t*/h	Yield[b] (%)	
				6a,b	**7**
1	MeCN	1 : 10	6	55	2
2	MeCN	1 : 10	8	60	5
3	MeCN	1 : 10	10	68	7
4	MeCN	1 : 10	12	71	2
5	MeCN	1 : 15	6	69	21
6	EtCN	1 : 10	6	52	41
7	EtCN	1 : 15	6	60	35

[a] Reaction conditions: [$FeCl_3 \cdot 6H_2O$]/[**5**]/[RCN]/[H_2O] = 0.05 : 1 : (10 or 15) : 1, 145 °C, 6–12 h. [b] Isolated yield.

achieved when [**5**]/[MeCN] ratio is 1 : 10 under the optimized conditions, namely 145 °C, 12 h (see Table 1, entry 4). An increase in the MeCN concentration to [**5**]/[MeCN] = 1 : 15, although leads to an improvement in the conversion of compound **5**, results in a lower selectivity and a higher yield of alcohol **7** (see Table 1, entry 5). The reaction with propionitrile proceeds with lower selectivity towards propioamide **6b** (see Table 1, entries 6, 7).

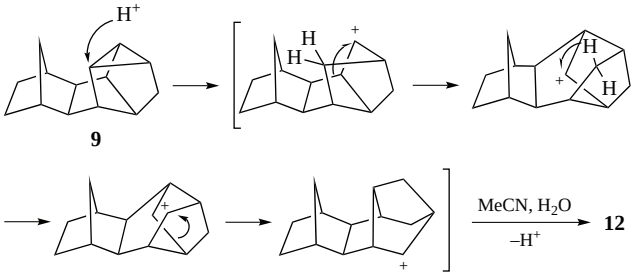
The amidation of four isomeric hexacyclo-[9.2.1.0^{2,10}.0^{3,8}.0^{4,6}.0^{5,9}]tetradecanes **8**–**11** which represent hydrogenated 4 + 2 dimers of norbornadiene, with acetonitrile follows an unusual pathway (Scheme 4) affording amides **12** and **13** resulting from selective cleavage of the C^4–C^5 bond in the CPR moieties of the starting compounds. Hydrocarbons **8** and **9** are transformed into the same amide **12**, while the second pair **10** and **11** is converted into another isomer **13** (see Scheme 4).

Note, that amides **12** and **13** are formed from hydrocarbons **8** and **10**, respectively, without skeletal isomerization. Contrary to that, hydrocarbons **9** and **11** with more shielded CPR moieties undergo skeletal rearrangement during their transformation into



Scheme 4 *Reagents and conditions*: i, MeCN, H_2O, $FeCl_3 \cdot 6H_2O$, 145 °C, 12 h; ii, MeCN, H_2O, $FeCl_3 \cdot 6H_2O$, 145 °C, 6 h.

the corresponding amides **12** and **13**.[15] Apparently, $FeCl_3$ is partially hydrolyzed in the course of reaction affording HCl, which acts acting as protonating agent (Scheme 5) causing the sequential carbocationic rearrangement with driving force originated from a decrease in internal strain of the molecule. However, treatment of hydrocarbons **8** and **9** with 35% aqueous HCl in the presence of MeCN afforded only the corresponding alcohol rather than amide **12**. Therefore, although $FeCl_3$ can be hydrolyzed with HCl evolution under the reaction conditions, one may suggest that a complicated iron complex, probably containing HCl, acetonitrile and water is responsible for the whole process. The conversion of hydrocarbon **11** into amide **13** followed the similar pathway, which was confirmed by the identity of amide obtained from hydrocarbon **10**.



Scheme 5

The structures of stereoisomers **12** and **13** were confirmed by one-dimensional (^{1}H, ^{13}C) and two-dimensional (COSY, NOESY, HSQC, HMBC) NMR experiments. The presence of the Nuclear Overhauser Effect between the signals of *exo*-oriented C^{2}H proton at δ 2.47 and AcNHC^4*H* proton at δ 3.31 in the spectrum of compound **13** indicates *endo*,*exo* configuration of the norbornane and brendane cycles. In contrast to compound **13**, the NOESY spectrum of amide **12** contains the cross peak between C^{2}H proton at δ 2.06 and AcNHC^4*H* proton at δ 3.33, which indicates *endo* configuration of the proton at C^2. Thus, according to the NOESY data for amides **12** and **13**, C^{4}H protons have *endo* configuration and, consequently, the acetamide substituent has exclusively *exo* configuration. This was ultimately confirmed by X-ray diffraction examination of 4-*exo*-acetamido pentacyclo[8.2.1.1^{5,8}.0^{2,9}.0^{3,7}]tetradecane **12**. (Figure 1).[†]

Compound **12** forms triclinic crystals in space group $P\bar{1}$. According to the X-ray diffraction data, an asymmetric cell includes two independent molecules with similar geometry linked by N–H···O hydrogen bond with the length of 2.15(4) Å. The structure of product **12** consists of *exo*,*exo*-coupled brendane and norbornane moieties. All five-membered rings are in the *envelope* conformations. The *exo*-orientation of the acetamide substituent is characterized by torsion angles C(3)–C(4)–N(1)–C(15) [C(3′)–C(4′)–N(1′)–C(15′)] and

[†] *Crystal data for* **12**. $C_{16}H_{23}NO$, M = 245.35, triclinic, space group $P\bar{1}$, a = 9.6178(9), b = 11.7641(10) and c = 13.2023(3) Å, α = 77.274(8)°, β = 69.349(9)° and γ = 79.321(7)°, V = 1353.9(2) Å^3, Z = 4, d_{calc} = 1.204 g cm^{-3}, F(000) = 536.0, μ = 0.074 mm^{-1}, the final R_1 = 0.0827, wR_2 = 0.2096 and S = 0.992 for 3104 observed reflections with $I > 2\sigma(I)$. The measurements were performed using an Agilent XCalibur diffractometer with an Eos detector and graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved with the SHELXS[16] structure solution program using direct methods and refined with the SHELXL[17] refinement package using the least squares minimization. All hydrogen atoms are generated using the proper HFIX command and refined isotropically as riding ones.

CCDC 1897723 contains 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.

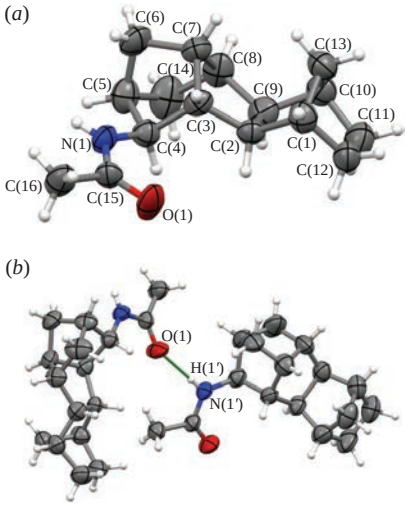


Figure 1 (*a*) Crystal structure of compound **12** determined from X-ray diffraction data. The atoms are shown as thermal ellipsoids at the 50% probability level. (*b*) Asymmetric cell of crystal **12**.

C(5)–C(4)–N(1)–C(15) [C(5′)–C(4′)–N(1′)–C(15′)] equal to –75.0(4)° [71.5(4)°] and 170.0(3)° [174.4(3)°], respectively.

In summary, we have carried out the $FeCl_3 \cdot 6H_2O$-catalyzed selective Ritter amidation of cyclopropane-containing norbornane-derived hydrocarbons, namely, tricyclo[3.2.1.$0^{2,4}$]-octane, *exo*,*exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane, pentacyclo [4.4.0.$0^{2,4}$.$0^{3,7}$.$0^{8,10}$]decane,andhexacyclo[9.2.1.$0^{2,10}$.$0^{3,8}$.$0^{4,6}$.$0^{5,9}$]-tetradecane by treatment with aceto- and propionitriles. The reaction proceeds most easily involving the trisubstituted cyclopropane ring. The yields of the corresponding amides are independent on spatial factors and reach 94%.

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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.2020.05.036.

References

1 J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc*., 1948, **70**, 4045.
2 D. Posevins, K. Suta and M. Turks, *Eur. J. Org. Chem*., 2016, 1414.
3 M. Mukhopadhyay and J. Iqbal, *J. Org. Chem*., 1997, **62**, 1843.
4 G.-R. Qu, Y.-W. Song, H.-Y. Niu, H.-M. Guo and J. S. Fossey, *RSC Adv*., 2012, **2**, 6161.
5 N. Zhu, T. Wang, L. Ge, Y. Li, X. Zhang and H. Bao, *Org. Lett*., 2017, **19**, 4718.
6 M. M. Lakouraj, B. Movassagh and J. Fasihi, *Synth. Commun*., 2000, **30**, 821.
7 B. Anxionnat, A. Guérinot, S. Reymond and J. Cossy, *Tetrahedron Lett*., 2009, **50**, 3470.
8 C. Feng, B. Yan, G. Yin, J. Chen and M. Ji, *Synlett*, 2018, **29**, 2257.
9 H. R. F. Karabulut and M. Kacan, *Synth. Commun*., 2002, **32**, 2345.
10 R. I. Khusnutdinov, T. M. Egorova, R. I. Aminov, Yu. Yu. Mayakova and E. S. Mescheryakova, *Synth. Commun*., 2020, **50**, 564.
11 K. Yasuda and Y. Obora, *J. Organomet. Chem*., 2015, **775**, 33.
12 H. Huang, X. Ji, F. Xiao and G.-J. Deng, *RSC Adv*., 2015, **5**, 26335.
13 H. Huang, X. Ji, W. Wu and H. Jiang, *Chem. Commun*., 2013, **49**, 3351.
14 Y. D. Vankar, G. Kumaravel and C. T. Rao, *Synth. Commun*., 1989, **19**, 2181.
15 R. I. Khusnutdinov, R. I. Aminov, T. M. Egorova, E. S. Mescheryakova, L. M. Khalilov and U. M. Dzhemilev, *ChemistrySelect*, 2018, **3**, 9600.
16 G. M. Sheldrick, *Acta Crystallogr., Sect. A*: *Found. Adv*., 2008, **64**, 112.
17 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem*., 2015, **71**, 3.

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