The Ritter reaction mechanism: new corroboration in the synthesis of arylsulfonyl(thio)propionic acid *N*-(1-adamantyl)amides

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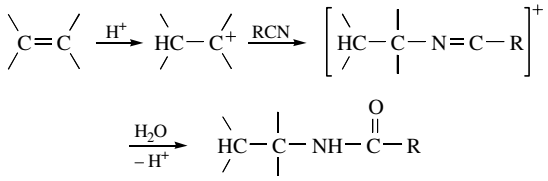
Pure intermediates in the Ritter reactions between adamantan-1-ol and arylsulfonyl(thio)propionitriles were isolated and identified for the first time.

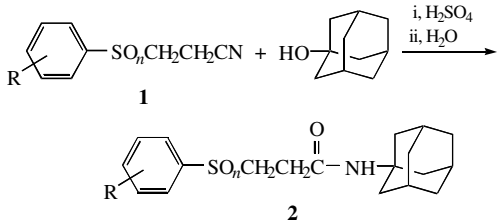
The Ritter reaction is widely used for the laboratory and commercial production of N-substituted carboxylic acid amides.[1,2] It is believed[3–5] that the reaction mechanism includes the formation of a carbocation from an olefin, alcohol or alkyl halide and its interaction with the nucleophilic nitrogen atom of a nitrile followed by the hydrolysis of the intermediate immonium complex (Scheme 1). However, the proposed mechanism was



Scheme 1

experimentally supported only by the isolation and identification of pure immonium intermediates using the alkylation of nitriles with protonated olefins as an example.[6,7] The mechanism of the Ritter reaction was indirectly supported using spectroscopic techniques without isolating pure intermediates[8,9] or by detecting by-products of the reaction.[10]

This study is an application of the Ritter reaction to the synthesis of adamantane derivatives (including the commercial production of the antiviral agent Amantadine).[11–14] With the use of the N-adamantylation of arylsulfonyl(thio)propionitriles **1** (Scheme 2) as an example, we isolated and identified intermediate immonium complexes by spectroscopic and analytical



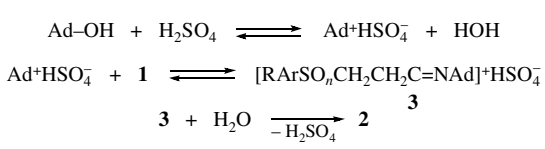
1a–e, **2a–e** $n = 2$
1′a–d, **2′a–d** $n = 0$

a R = H **b** R = 4-Me **c** R = 4-Br **d** R = 4-Cl **e** R = 4-MeO

Scheme 2

techniques. Compounds **1** can be easily prepared by the cyanoethylation of aromatic sulfinic acids and thiols.[15] These latter were chosen as substrates in the Ritter reaction for the synthesis of new derivatives of arylsulfonyl(thio)carboxylic acids[16] including pharmacologically active compounds.[17] It is likely that the mechanism of the test reaction can be represented by Scheme 3.

We found that, in the interaction of 4-bromine-substituted nitriles **1c**, **1′c** with adamantan-1-ol at 70 °C for 16 h under classical Ritter reaction conditions (in a mixture of acetic and concentrated sulfuric acids), intermediate imino sulfates **3c**, **3′c** formed precipitates upon cooling the reaction mixtures. These precipitates were white crystalline compounds with mp 192–



Scheme 3

194 (**3c**) or 173–175 °C (**3′c**) after recrystallization from acetic acid. The yields were 83 and 72%, respectively. The recrystallised products are stable in storage for several months in the absence of moisture.

We failed to isolate pure crystalline intermediate products of adamantan-1-ol reactions with other nitriles (even after solvent removal in a vacuum). However, in all cases, the hydrolysis of reaction mixtures resulted in previously unknown arylsulfonyl(thio)propionic acid *N*-1-adamantylamides **2** in 58–75% yields.†

The IR spectrum of intermediate **3c** or **3′c** exhibited absorption bands at 1670 or 1680 (C=N), 2520, 1180 and 1070 or 3180, 1295 and 1130 cm^{-1} ($HOSO_3^-$), respectively. These absorption bands disappeared after the hydrolysis of these compounds. The IR spectra of resulting products **2c** and **2′c** ex-

† *Synthesis of compounds* **2a–e** *and* **2′a–d**.

A solution of nitrile **1** (0.01 mol) in 15 cm^3 of glacial acetic acid was added to a solution of adamantan-1-ol (1.52 g, 0.01 mol) and concentrated sulfuric acid (0.98 g, 0.01 mol) in 15 cm^3 of glacial acetic acid. The reaction mixture was stirred at 70 °C for 16 h, cooled and poured into ice-cold water. The resulting precipitate was filtered off, dried and recrystallised from ethanol.

^{1}H NMR spectra of 5% sample solutions in [$^2H_6$]DMSO were recorded on a Bruker AC-250 instrument; TMS was used as an internal standard. IR spectra were measured on a Specord 75 R spectrophotometer in the range 300–4000 cm^{-1} using sample suspensions in Vaseline oil.

2a: mp 190–191 °C. ^{1}H NMR, δ: 7.32–7.10 (m, 5H, Ph), 3.08 (t, 2H, CH_2, J 6.5 Hz), 2.35 (t, 2H, CH_2, J 6.5 Hz), 7.10 (s, 1H, NH), 2.03 (s, 3H, 3CH, Ad), 1.95 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). Found (%): C, 65.75; H, 7.19; N, 4.10; S, 9.31. Calc. for $C_{19}H_{25}NO_3S$ (%): C, 65.68; H, 7.25; N, 4.03; S, 9.23.

2′a: mp 120–122 °C. ^{1}H NMR, δ: 7.55–7.87 (m, 5H, Ph), 3.38 (t, 2H, CH_2, J 6.5 Hz), 2.32 (t, 2H, CH_2, J 6.5 Hz), 7.18 (s, 1H, NH), 1.98 (s, 3H, 3CH, Ad), 1.90 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). Found (%): C, 72.41; H, 7.87; N, 4.28; S, 10.21. Calc. for $C_{19}H_{25}NOS$ (%): C, 72.34; H, 7.99; N, 4.44; S, 10.16.

2b: mp 174–176 °C. ^{1}H NMR, δ: 7.78 (d, 2H, H-2, H-6, J 8.1 Hz), 7.40 (d, 2H, H-3, H-5, J 8.1 Hz), 3.35 (t, 2H, CH_2, J 6.6 Hz), 2.35 (t, 2H, CH_2, J 6.6 Hz), 7.25 (s, 1H, NH), 2.23 (s, 3H, Me), 2.00 (s, 3H, 3CH, Ad), 1.85 (s, 6H, 3CH_2, Ad), 1.63 (s, 6H, 3CH_2, Ad). Found (%): C, 66.37; H, 7.59; N, 3.81; S, 8.95. Calc. for $C_{20}H_{27}NO_3S$ (%): C, 66.45; H, 7.53; N, 3.87; S, 8.87.

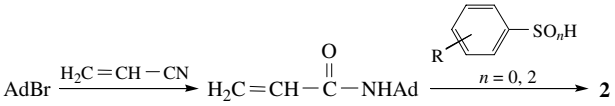
2′b: mp 91–93 °C. ^{1}H NMR, δ: 7.05 (s, 4H), 3.05 (t, 2H, CH_2, J 6.5 Hz), 2.32 (t, 2H, CH_2, J 6.5 Hz), 7.18 (s, 1H, NH), 2.25 (s, 3H, Me), 2.03 (s, 3H, 3CH, Ad), 1.92 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). Found (%): C, 72.79; H, 8.32; N, 4.16; S, 9.79. Calc. for $C_{20}H_{27}NOS$ (%): C, 72.90; H, 8.26; N, 4.25; S, 9.73.

2c: mp 182–184 °C. ^{1}H NMR, δ: 7.82 (s, 4H), 3.48 (t, 2H, CH_2, J 6.9 Hz), 2.42 (t, 2H, CH_2, J 6.9 Hz), 7.23 (s, 1H, NH), 2.00 (s, 3H, 3CH, Ad), 1.85 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). IR (ν/cm^{-1}): 3360 (NH), 1660 (C=O), 1580 (arom.). Found (%): C, 53.58; H, 5.61; N, 3.23; S, 7.61. Calc. for $C_{19}H_{24}BrNO_3S$ (%):C, 53.52; H, 5.67; N, 3.29; S, 7.52.

hibited absorption bands at 3300 and 3360 (NH), 1640 and 1660 (amide I) and 1550 and 1530 cm^{-1} (amide II), respectively, which are characteristic of secondary amines. The ^{1}H NMR spectra of compounds **2c** and **2′c** exhibited singlet signals due to the protons of NH groups at 7.14 and 7.23 ppm, whereas the spectra of intermediates **3c** and **3′c** exhibited signals of acid protons ($HOSO_3^-$) at 7.35 and 7.40 ppm, respectively. Two doublets at 7.85 and 7.80 ppm correspond to the signals of aromatic protons in intermediate **3c**, whereas a singlet at 7.82 ppm corresponds to that of product **2c**.

Along with adamantan-1-ol, we used 1-bromoadamantane for the N-adamantylation of arylsulfonyl(thio)propionitriles **1**; this reagent is commonly used in the commercial and laboratory syntheses of various *N*-(1-adamantyl)amides. Concentrated sulfuric acid, 20% oleum, 90% formic acid, an equimolar mixture of sulfuric acid and boron trifluoride etherate, zinc chloride, aluminium chloride, and a mixture of concentrated sulfuric acid and 50% nitric acid were used for generating the adamantyl carbocation from 1-bromoadamantane. Only in the last-named case, the yield of target *N*-adamantylamide was as high as 45%, whereas the yields were 8–25% in the other cases because the conversion of nitriles into primary amides was the main reaction path.

With the use of the Ritter reaction between 1-bromoadamantane and acrylonitrile, we prepared *N*-1-adamantylacrylamide,[13] which was used for the independent synthesis of arylsulfonyl-(thio)propionic acid *N*-(1-adamantyl)amides in accordance with Scheme 4. The spectroscopic characteristics of the resulting compounds were identical.



Scheme 4

2′c: mp 134–136 °C. ^{1}H NMR, δ: 7.42 (d, 2H, H-3, H-5, *J* 8.2 Hz), 7.35 (d, 2H, H-2, H-6, *J* 8.2 Hz), 3.08 (t, 2H, CH_2, *J* 7.3 Hz), 2.32 (t, 2H, CH_2, *J* 7.3 Hz), 7.14 (s, 1H, NH), 2.02 (s, 3H, 3CH, Ad), 1.90 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). IR (ν/cm^{-1}): 3300 (NH), 1640 (C=O), 1560 (arom.). Found (%): C, 57.86; H, 6.17; N, 3.66; S, 8.23. Calc. for $C_{19}H_{24}BrNOS$ (%): C, 57.87; H, 6.13; N, 3.55; S, 8.13.

2d: mp 181–183 °C. ^{1}H NMR, δ: 7.78 (d, 2H, H-2, H-6, *J* 8.3 Hz), 7.15 (d, 2H, H-3, H-5, *J* 8.3 Hz), 3.32 (t, 2H, CH_2, *J* 6.5 Hz), 2.35 (t, 2H, CH_2, *J* 6.5 Hz), 7.25 (s, 1H, NH), 2.00 (s, 3H, 3CH, Ad), 1.85 (s, 6H, 3CH_2, Ad), 1.63 (s, 6H, 3CH_2, Ad). Found (%): C, 59.69; H, 6.30; N, 3.72; S, 8.45. Calc. for $C_{19}H_{24}ClNO_3S$ (%): C, 59.75; H, 6.33; N, 3.67; S, 8.40.

2′d: mp 125–127 °C. ^{1}H NMR, δ: 7.32 (s, 4H), 3.08 (t, 2H, CH_2, *J* 6.5 Hz), 2.35 (t, 2H, CH_2, *J* 6.5 Hz), 7.15 (s, 1H, NH), 2.03 (s, 3H, 3CH, Ad), 1.92 (s, 6H, 3CH_2, Ad), 1.65 (s, 6H, 3CH_2, Ad). Found (%): C, 65.28; H, 6.96; N, 4.07; S, 9.23. Calc. for $C_{19}H_{24}ClNOS$ (%): C, 65.22; H, 6.91; N, 4.00; S, 9.16.

2e: mp 165–166 °C. ^{1}H NMR, δ: 7.78 (d, 2H, H-2, H-6, *J* 8.3 Hz), 7.15 (d, 2H, H-3, H-5, *J* 8.3 Hz), 3.76 (s, 3H, OMe), 3.32 (t, 2H, CH_2, *J* 6.5 Hz), 2.35 (t, 2H, CH_2, *J* 6.5 Hz), 7.25 (s, 1H, NH), 2.00 (s, 3H, 3CH, Ad), 1.85 (s, 6H, 3CH_2, Ad), 1.63 (s, 6H, 3CH_2, Ad). Found (%): C, 63.55; H, 7.15; N, 3.77; S, 8.40. Calc. for $C_{20}H_{27}NO_4S$ (%): C, 63.63; H, 7.21; N, 3.71; S, 8.49.

3c: mp 192–194 °C. ^{1}H NMR, δ: 7.85 (d, 2H, H-2, H-6, *J* 8.3 Hz), 7.80 (d, 2H, H-3, H-5, *J* 8.3 Hz), 3.45 (t, 2H, CH_2, *J* 6.5 Hz), 2.35 (t, 2H, CH_2, *J* 6.5 Hz), 7.40 (s, 1H, $HOSO_3^-$), 1.93 (s, 3H, 3CH, Ad), 1.80 (s, 6H, 3CH_2, Ad), 1.55 (s, 6H, 3CH_2, Ad). IR (ν/cm^{-1}): 1670 (C=N), 1560 (arom.), 3180, 1295, 1130, 850 ($HOSO_3^-$). Found (%): C, 45.21; H, 4.84; N, 2.75; S, 12.73. Calc. for $C_{19}H_{24}BrNO_6S_2$ (%): C, 45.06; H, 4.78; N, 2.77; S, 12.66.

3′c: mp 173–175 °C. ^{1}H NMR, δ: 7.48 (d, 2H, H-3, H-5, *J* 7.7 Hz), 7.32 (d, 2H, H-2, H-6, *J* 7.7 Hz), 3.08 (t, 2H, CH_2, *J* 6.6 Hz), 2.34 (t, 2H, CH_2, *J* 6.6 Hz), 7.35 (s, 1H, $HOSO_3^-$), 1.95 (s, 3H, 3CH, Ad), 1.85 (s, 6H, 3CH_2, Ad), 1.58 (s, 6H, 3CH_2, Ad). IR (ν/cm^{-1}): 1680 (C=N), 1560 (arom.), 2520, 1180, 1070, 870 ($HOSO_3^-$). Found (%): C, 48.18; H, 5.03; N, 2.90; S, 13.57. Calc. for $C_{19}H_{24}BrNO_4S_2$ (%): C, 48.10; H, 5.10; N, 2.95; S, 13.52.

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