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The unusual reaction of 2-isocyanatophenyl acetate with amines and water

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Acetylsalicylic acid and 1-(1-adamantyl)ethan-1-amine hydrochloride were purchased from Sigma-Aldrich. DMF, Et_3N, Et_2O, toluene, conc. HCl (37%), and CH_2Cl_2 were procured from Ruthenia (LLC, Russia). 1-(Aminomethyl)-adamantane and 2-aminoadamantane were obtained by the described method [S1]. NMR spectra were recorded on a DRX-500 (^{1}H: 500.13 MHz, ^{13}C: 125.79 MHz) Bruker spectrometer. The mass spectra were obtained on an Agilent 5975 mass-selective detector coupled with an Agilent 7820 gas chromatograph (HP-5MS quartz capillary column, 30 m; carrier gas helium; oven temperature programming from 80 to 280°C; inlet temperature 250°C). Elemental analysis performed on Perkin-Elmer Series II 2400.

Experimental Procedure for 2-isocyanatophenyl acetate 2: Synthesis of compound **2** was carried out according to a one-step method from acetylsalicylic acid and diphenyl phosphorazidate (DPPA), in toluene, for 3 hours, at 110°C and stirring. Acetylsalicylic acid (27 mmol) was dissolved in toluene, then trimethylamine (1 equiv.), and DPPA (27 mmol) were added. The mixture was stirred at 110°C for 3 hours. The product was purified by extraction with anhydrous diethyl ether, yield 88%. m.p. = 103-105°C; Yield 88%; white solid; MS (EI): *m/z* (%) = 177 (10%) $[M]^+$, 135 (100%) $[M - Acetyl]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (s, 3H), 7.19-7.32 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.96 (s, 1C, CH_3), 121.33 (s, 1C, Ph), 124.57 (s, 3C, Ph), 122.85 (s, 1C, N=C=O), 127.64 (s, 1C, Ph-N), 151.47 (s, 1C, Ph-O), 169.38 (s, 1C, O-C=O). Elemental analysis calc for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91; O, 27.09; found C, 61.04; H, 4.01; N, 7.89; O, 27.06.

General Experimental Procedure for compounds 4a-g: The synthesis of acetamides was carried out by the reaction of amines **3a-e** with 2-isocyanatophenyl acetate 2 (1 equiv.) in DMF and Et_3N at room temperature and constant stirring for 3 hours. The acetamides were isolated by adding 1N HCl, and then by filtration.

***N*-(2-Adamantyl)acetamide 4a:** m.p. = 187-189°C; Yield 78%; white solid; MS (EI): *m/z* (%) = 193 (80%) $[M]^+$, 135 (100%) $[Ad]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (m, 2H, Ad), 1.77 (m, 8H, Ad), 1.87 (m, 2H, Ad), 1.93 (m, 2H, Ad), 2.02 (s, 3H, CH_3), 4.07 (dd, 1H, Ad), 5.80 (m, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.57 (s, 1C, CH_3), 27.17 (s, 2C, Ad), 31.84 (s, 4C, Ad), 37.08 (s, 2C, Ad), 37.48 (s, 1C, Ad), 53.55 (s, 1C, Ad), 169.61 (s, 1C, C=O). Elemental analysis calc for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25; O, 8.28; found C, 74.60; H, 9.93; N, 7.21; O, 8.27.

***N*-(1-Adamantylmethyl)acetamide 4b:** m.p. = 95-97°C; Yield 86%; white solid; MS (EI): *m/z* (%) = 207 (80%) $[M]^+$, 135 (100%) $[Ad]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50(d, 6H, Ad), 1.64 (dt, 6H, Ad), 2.00 (q, 3H, Ad), 2.02 (s, 3H, CH_3), 2.96 (d, 2H, CH_2), 5.55 (s, 1H, NH).^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.62 (s, 1C, CH_3), 28.15 (s, 3C, Ad), 36.67 (s, 1C, Ad), 36.82 (s, 3C, Ad), 40.15 (s, 3C, Ad), 51.61 (s, 1C, CH_2-NH), 171.79 (s, 1C, C=O). Elemental analysis calc for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76; O, 7.72; found C, 75.34; H, 10.23; N, 6.74; O, 7.70.

***N*-[1-(1-Adamantyl)ethyl]acetamide 4c:** m.p. = 112-114°C; Yield 82%; white solid; MS (EI): *m/z* (%) = 221 (80%) $[M]^+$, 135 (100%) $[Ad]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 (d, 3H, CH_3), 1.28 (s, 6H, Ad), 1.56 (m, 6H, Ad), 1.68 (m, 3H, Ad), 2.04 (s, 3H, CH_3), 3.74 (dq, 1H, Ad-CH-), 9.59 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.40 (s, 1C, $H_3\underline{C}$-CH), 23.25 (s, 1C, $H_3\underline{C}$-C=O), 28.25 (s, 3C, Ad), 36.98 (s, 3C, Ad), 38.33 (s, 3C, Ad), 38.49 (s, 1C, Ad), 53.57 (s, 1C, $\underline{C}$H-CH_3), 170.33 (s, 1C, C=O). Elemental analysis calc. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33; O, 7.23; found C, 75.99; H, 10.48; N, 6.32; O, 7.20.

***N*-N-Phenylacetamide 4d:** m.p. = 114-115°C (lit. 111-113 °C); Yield 54%; white solid; MS (EI): *m/z* (%) = 135 (80%) $[M]^+$, 93 (100%) $[Ph\text{-}NH_2]^+$; Coincides with the literature data [S2].

***N*-(4-Fluorophenyl)aceteamide 4e:** m.p. = 149-151°C (lit. 148-150 °C); Yield 45%; white solid; MS (EI): *m/z* (%) = 153 (70%) $[M]^+$, 111 (100%) $[4F\text{-}Ph\text{-}NH_2]^+$; Coincides with the literature data.[2]

***N*-(*n*-Hexyl)acetamide 4f:** colorless liquid; MS (EI): *m/z* (%) = 101 (70%) $[M]^+$, 59 (100%) $[C_3H_7\text{-}NH_2]^+$; Coincides with the literature data [S3].

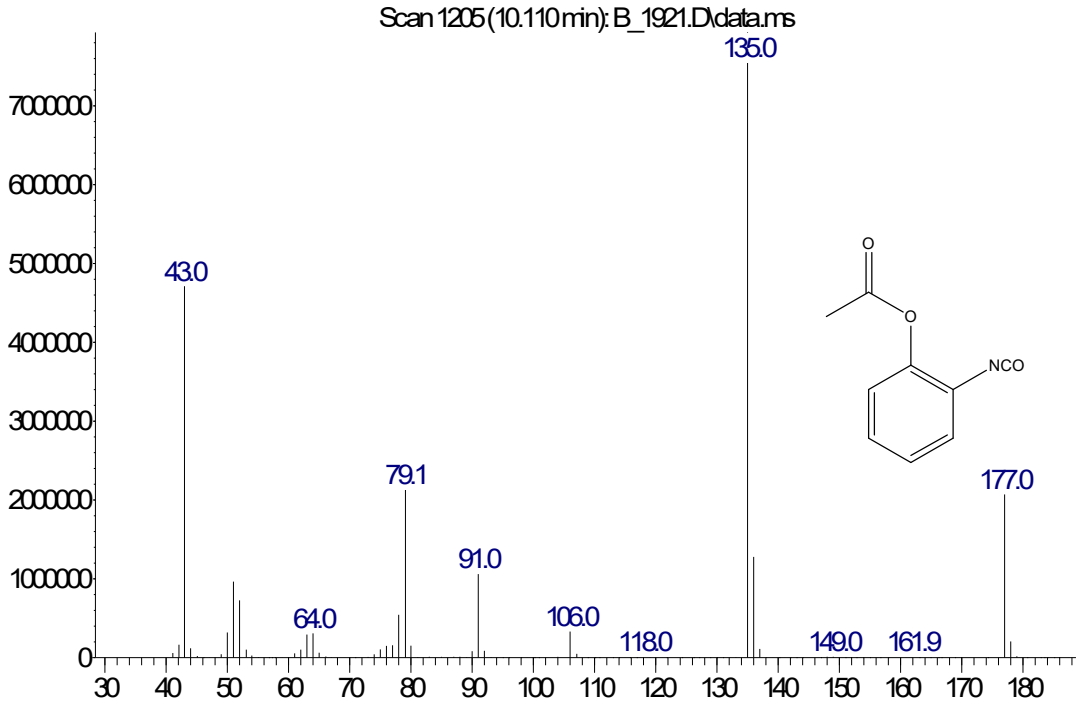
***N*-(*n*-Propyl)acetamide 4g:** colorless liquid; MS (EI): *m/z* (%) = 143 (80%) $[M]^+$, 101 (100%) $[C_6H_{13}\text{-}NH_2]^+$; Coincides with the literature data [S4].

2-Benzoxazolinone 5: Method 1 (acidic medium) The reaction of 2-isocyanatophenyl acetate **2** with concentrated HCl (20 equiv.) was performed in toluene, at room temperature and constant stirring for 12 hours. The product was isolated by filtration. Product yield 92%.

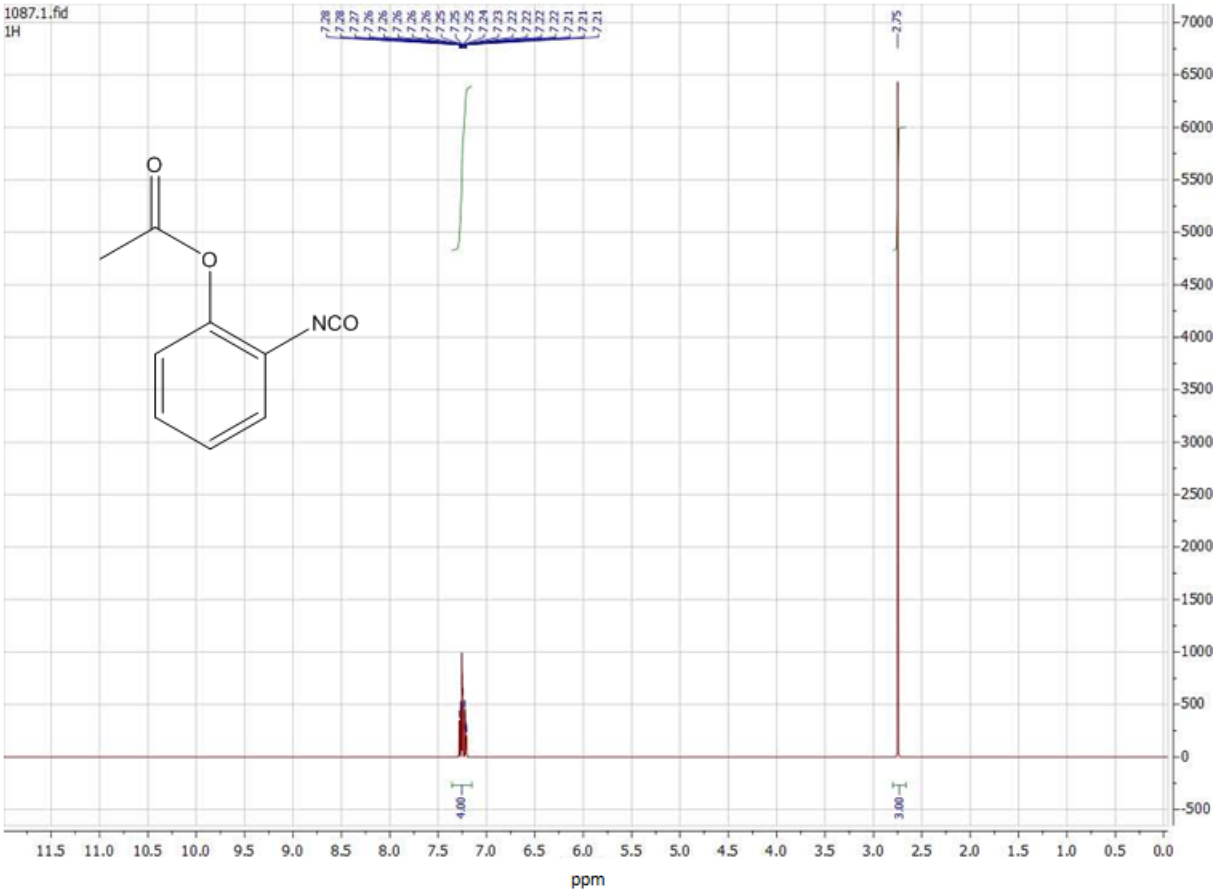
Method 2 (basic medim) The product was isolated from the aqueous solution filtrate by extraction with dichloromethane. m.p. = 137-139°C; Yield 92%; brown solid; MS (EI): *m/z* (%) = 135 (100%) $[M]^+$; 177 (10%) $[Ac\text{-}Ph\text{-}NCO]^+$, 135 (80%) $[HO\text{-}Ph\text{-}NCO]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (m, 4H, Ph), 10.04 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.10 (s, 1C, Ph), 110.33 (s, 1C, Ph), 122.70 (s, 1C, Ph), 129.48 (s, 1C, Ph), 143.88 (s, 1C, Ph), 156.45 (s, 1C, C=O). Elemental analysis calc for $C_7H_5NO_2$: C, 62.22; H, 3.73; N, 10.37; O, 23.68; found C, 61.25; H, 3.74; N, 10.36; O, 23.65.

Abundance

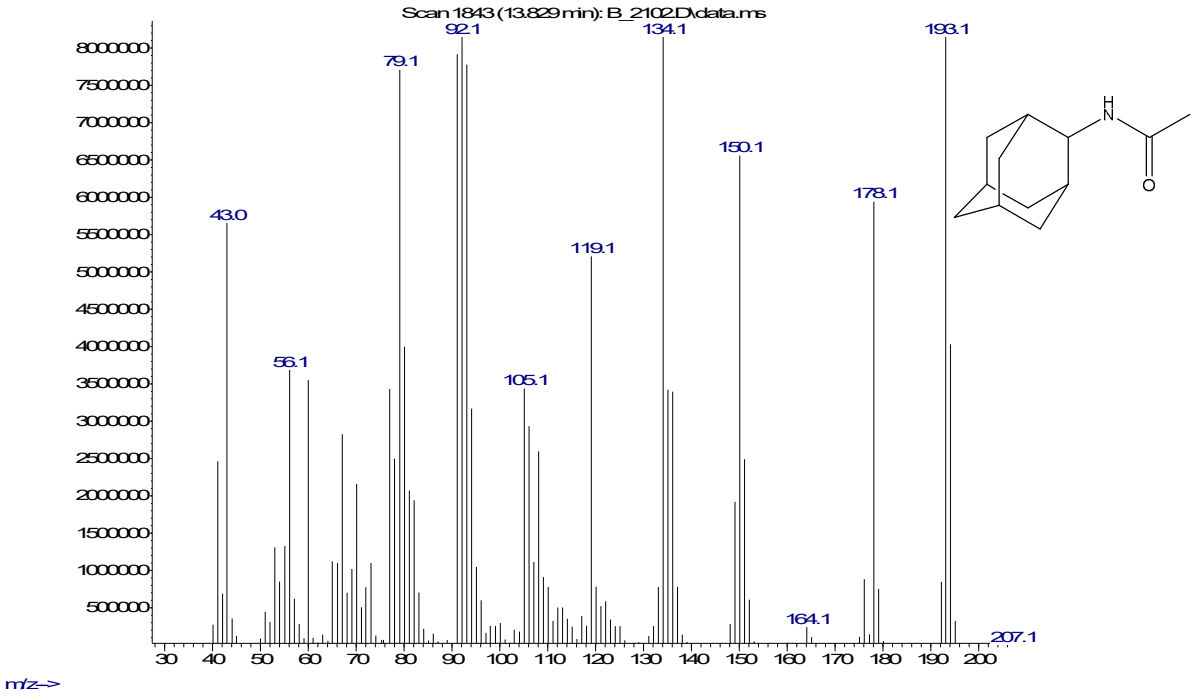
MS 2-isocyanatophenyl acetate (2)

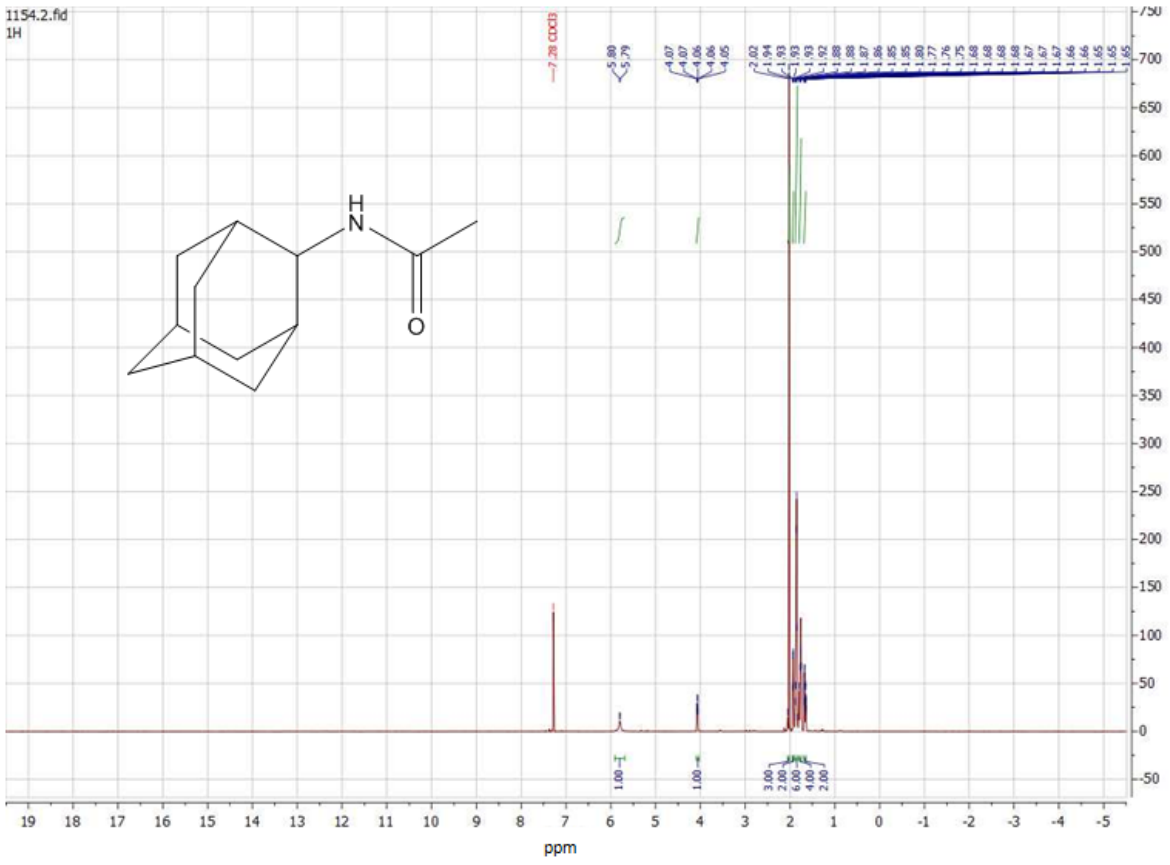


m/z-->

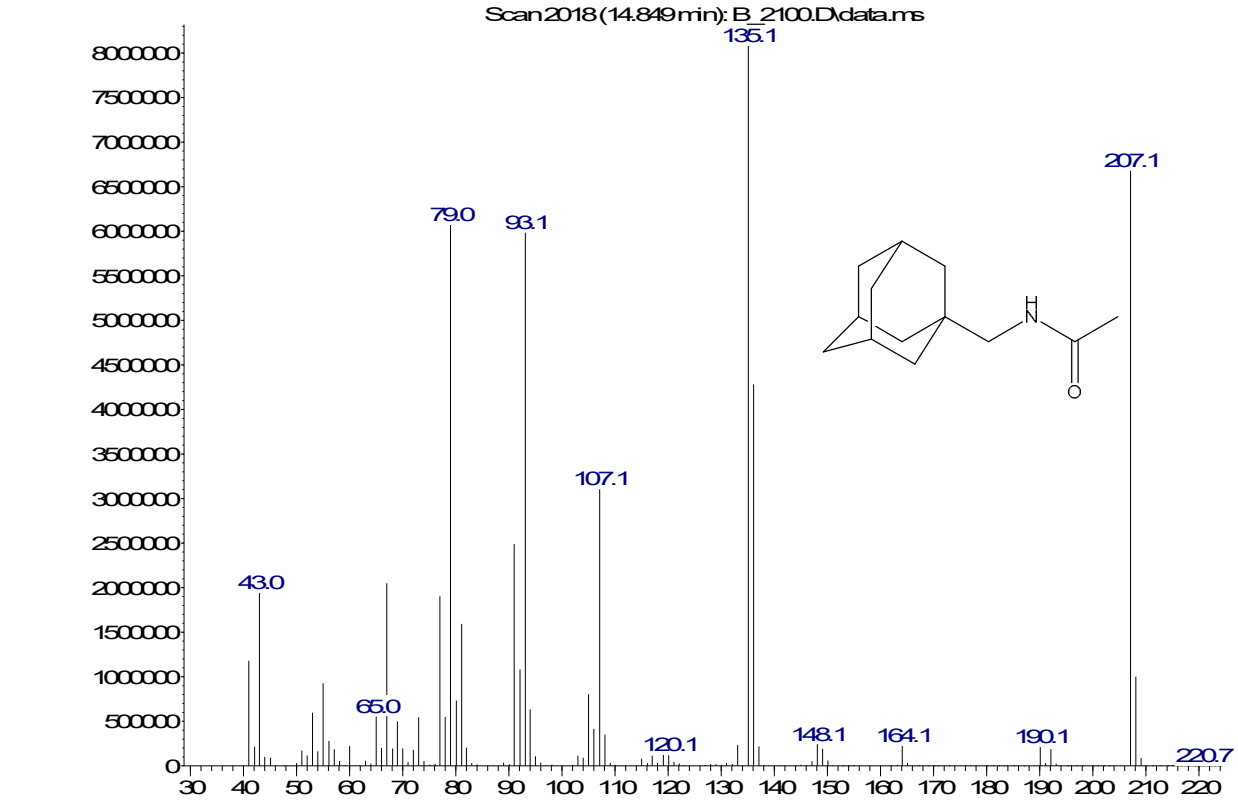


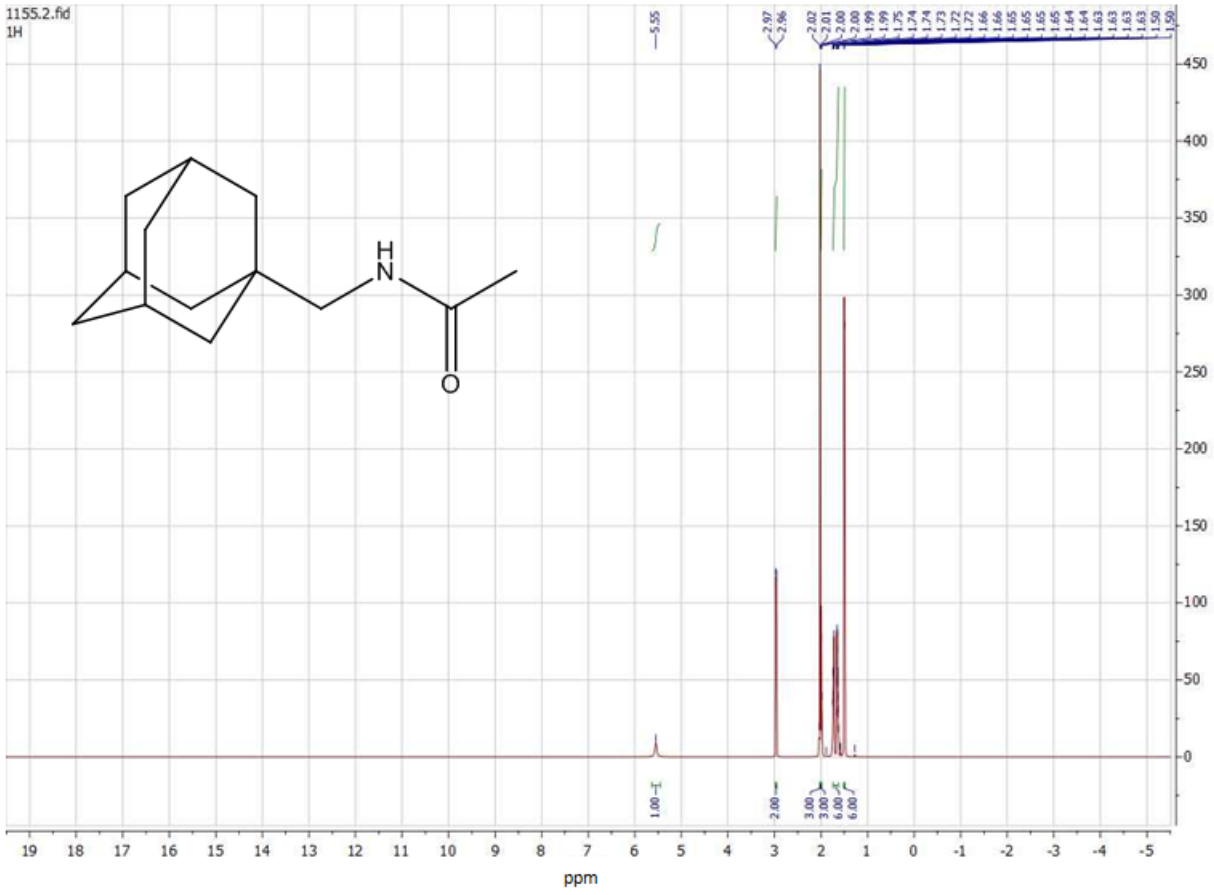
MS *N*-(adamantan-2-yl)acetamide

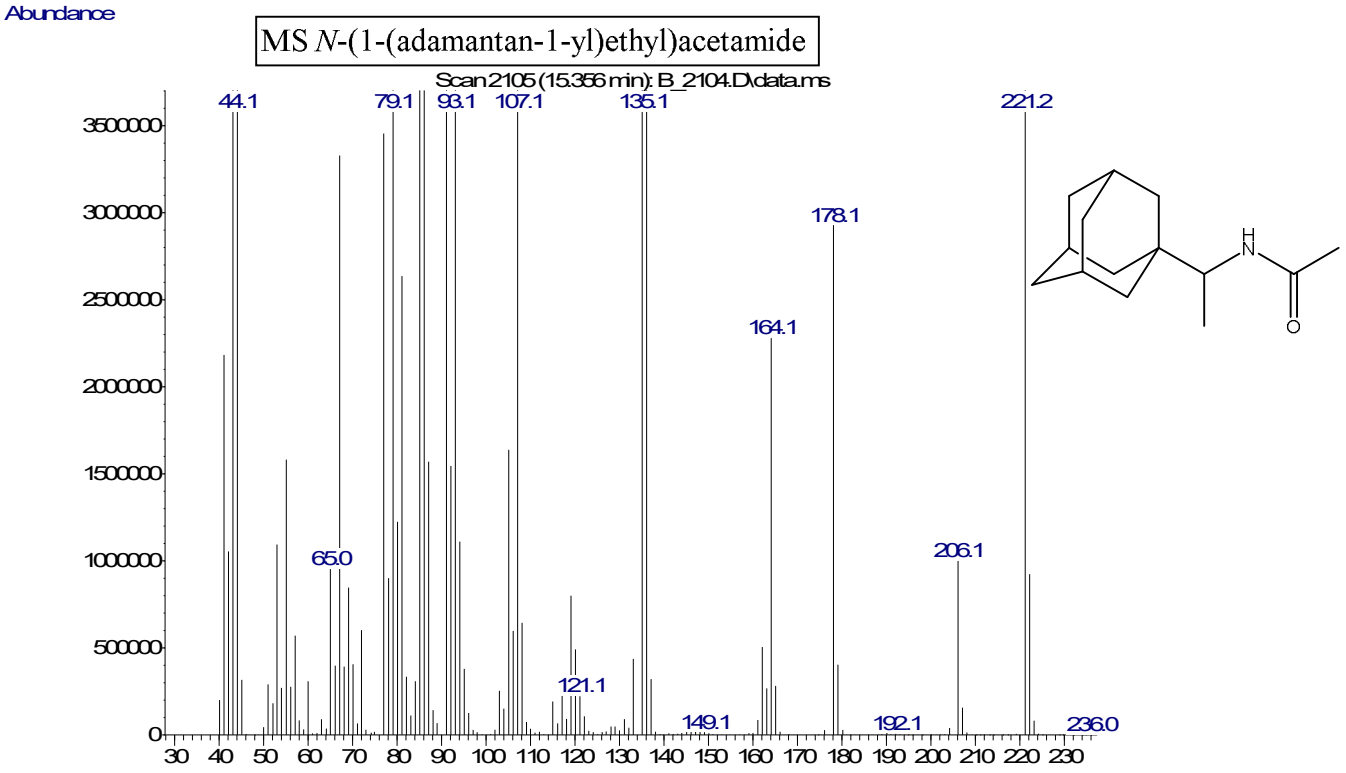




MS *N*-((adamantan-1-yl)methyl)acetamide






Abundance
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93.1
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135.1
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164.1
65.0
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121.1
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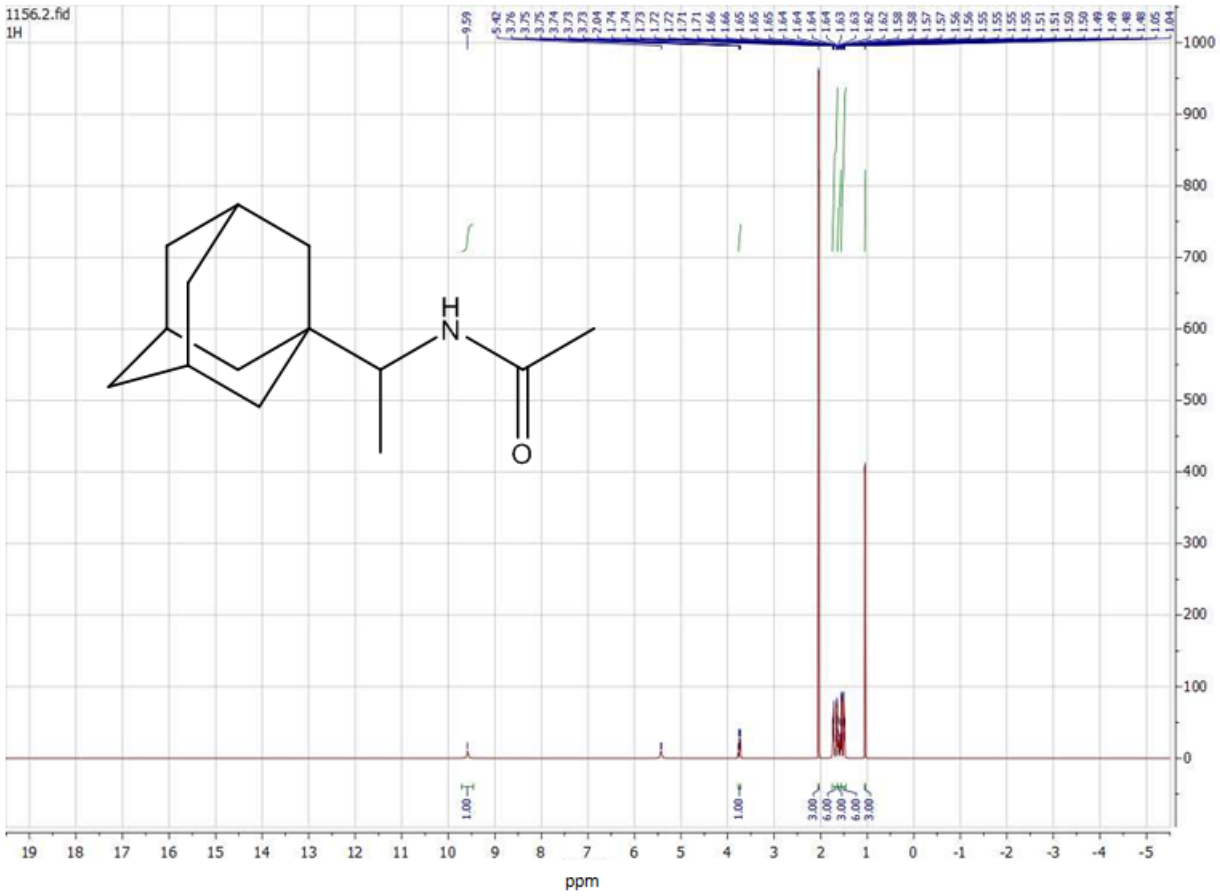
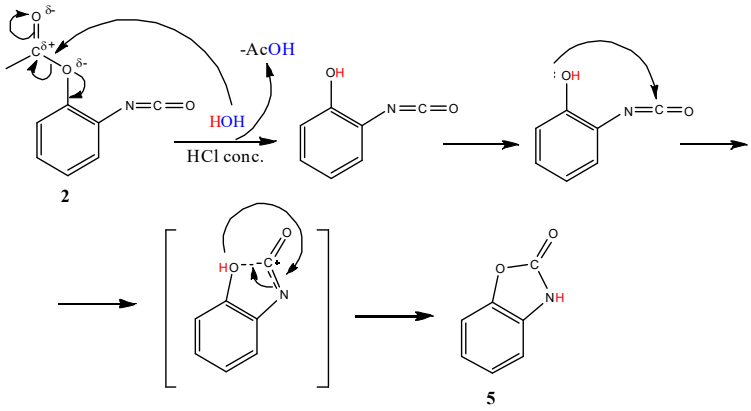
192.1
236.0
m/z-->


1156.2.fid
1H
ppm

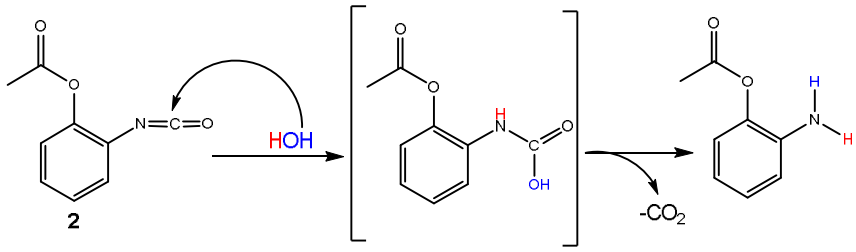
Proposed pathways and reaction mechanism

In the first case, the hydrolysis of the ester bond probably takes place, with the formation of 2-isocyanatophenol followed by its transformation into 2-benzoxazolinone **5**. The proposed mechanism of 2-benzoxazolinone formation under acidic conditions is shown in scheme 1.



Scheme S1

Another route involves the addition of water to an isocyanate group to form a carbamic acid intermediate (Scheme 2). However, the occurrence of this reaction is unlikely, due to the fact that carbamic acid is instantly decarboxylated with the formation of an amine, which was not detected in the crude reaction product mixture even in trace amounts.



Scheme S2

It should also be noted that the redistribution of the electron density in the ester bond makes it more polarized and less strong, which will accelerate the acid hydrolysis, primarily through this bond.

Calculated basicities of the starting amines

Below are the calculated basicities of the starting amines and their ability to enter into the acylation reaction (Figure S1) (Calculated using the ChemAxon/Chemicalize: an online platform for chemical calculations. https://chemaxon.com/products/chemicalize [S5].

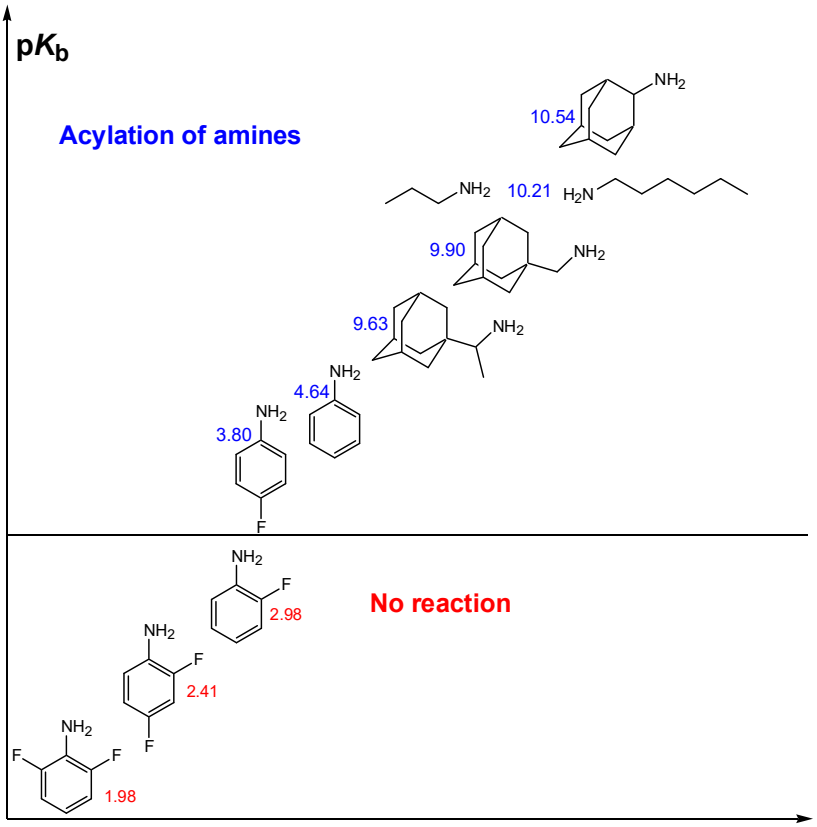


Figure S1 pK_b values of starting amines

References

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