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A short-cut from 1-acetyl adamantane to 2-(1-adamantyl)pyrroles

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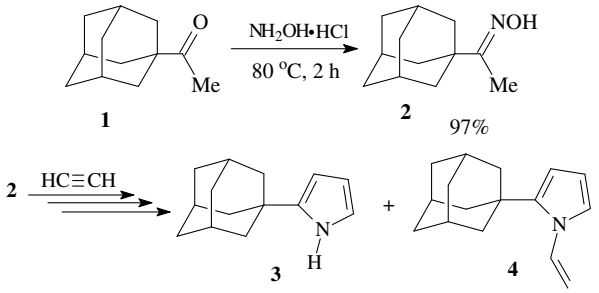
ABSTRACT

The oxime of 1-acetyl adamantane **2** is added to acetylene (KOH/DMSO, 70 °C, initial acetylene pressure 13 atm, 30 min) to afford the corresponding *O*-vinyl oxime **5** in 80% yield. The latter upon heating (DMSO, 120 °C, 1 h) gives 2-(1-adamantyl)pyrrole **3**, 1-acetyl adamantane **1**, and adamantane (6:3:1 mass ratio), the yield of the pyrrole **3** being 83% (based on 1-acetyl adamantane **1** consumed). Under harsher conditions (NaOH/DMSO, 130 °C, atmospheric pressure of acetylene, 4 h) oxime **2** reacts with acetylene to furnish pyrrole **3**, 1-acetyl adamantane **1**, 1-vinyl adamantane **9**, and adamantane (6:7:3:1 mass ratio), with the isolated yield of pyrrole **3** reaching 34%. Under pressure (NaOH/DMSO, 120 °C, initial acetylene pressure 14 atm, 1 h) the same reaction leads to 2-(1-adamantyl)-1-vinylpyrrole **4** and ketone **1** in 48% (based on consumed ketone **1**) and 24% yields, respectively. The pyrrole **4** is easily deprotected to the corresponding 1*H*-pyrrole **3** in 77% yield by treatment (aqueous MeCN) with $Hg(OAc)_2$ and $NaBH_4$.

The chemistry of adamantane continues to attract attention due to the high biological activity of its derivatives. Their hydrophobicity and lypophilicity favor transport of adamantane compounds across biological membranes.[1] Combination of the adamantane structure with heterocyclic compounds modifies their biological activity, often enhancing the effect or imparting a new kind of activity.[2] For example, acylguanidines with an adamantyl–pyrrolyl moiety were shown recently to be β-secretase inhibitors related to Alzheimer's disease.[3] Dipyrromethanes with an adamantane moiety at the bridge exhibit properties of anion receptors.[4] Adamantane–pyrrole ensembles are promising targets in adamantane and pyrrole chemistry as well as for drug design. Pyrroles with bulky substituents such as adamantyl are employed for the construction of new high-performance BODIPY fluorophores with improved fluorescent properties due to prevention of π-stacking.[5] However, until now, adamantane–pyrrole ensembles remain scarcely known. 2-Adamantyl pyrrole was reported (but not characterized) using a multi-step protocol starting from tributyl(vinyl)stannane via the intermediate lithiated dibenzylcyclopropylamine, which further reacted with nitriles.[6] (2-Adamantyl-5-phenylpyrrolyl-1-yl)acetic acid and its guanidine derivative were prepared from 1-adamantyl-4-phenylbutane-1,4-dione and glycine in 57% and 22% yields (final step), respectively, the above diketone being prepared by coupling of 1-adamantylbromomethyl ketone and acetophenone in the presence of $ZnCl_2$ (2–5 days, 44% yield). The poorly characterized (only mp and nitrogen elemental analysis data) 2,5-di(1-adamantyl)pyrrole was synthesized from 1,4-di(adamantyl)butane-1,4-dione and ammonia in 33% total yield (over 4 steps starting from 1-acetyl adamantane).[7] Thus, the synthesis of adamantyl pyrroles still remains a challenge for the development of adamantane–pyrrole chemistry.



Scheme 1.

In this Letter, we report the first example of an easy, short transformation of 1-acetyl adamantane **1** (via the oxime **2**) to 2-(1-adamantyl)pyrrole **3** and its 1-vinyl derivative **4** through the reaction of the oxime **2** with acetylene in the presence of different superbase catalytic systems (MOH/DMSO, M = Na or K) using a modification of the Trofimov reaction (Scheme 1).[8]

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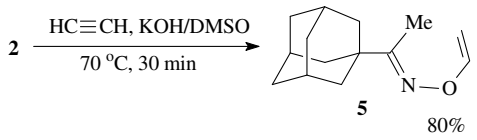
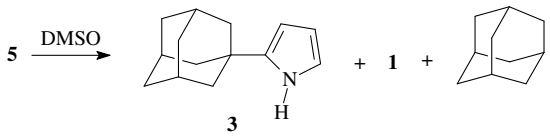
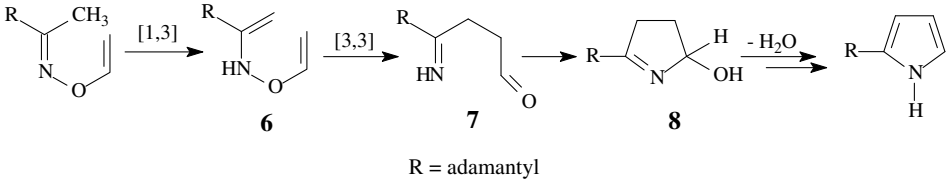


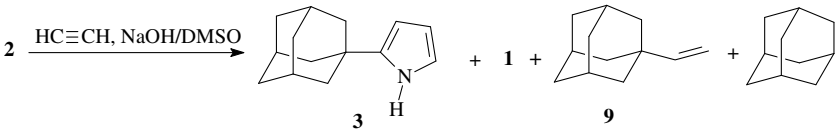
Scheme 2.



Scheme 4.



Scheme 3.



Scheme 5.

Initially, we found that the oxime **2** (prepared from 1-acetyl adamantane **1** in 97% yield)[9] readily reacts with acetylene under pressure[†] in the KOH/DMSO system (70 °C, initial acetylene pressure 13 atm, 30 min) to form exclusively the corresponding *O*-vinyl oxime **5**[10] in 80% isolated yield (Scheme 2).

It is commonly recognized[5,11] that the key step of pyrrole synthesis from an *O*-vinyl ketoxime is the [3,3]-rearrangement of its *O*-vinylhydroxylamine tautomer **6** to an iminoaldehyde **7**, which further ring closes to a hydroxypyrroline **8**, and undergoes dehydration and finally aromatization to the pyrrole (Scheme 3).

Upon heating *O*-vinyl oxime **5** in DMSO (120 °C, 1 h), it rearranged to 2-(1-adamantyl)pyrrole **3**, other products being 1-acetyl adamantane **1** and adamantane (their ratio in the crude product was 6:3:1, as determined by GLC),[13] (Scheme 4). The calculated yield (based on the product ratio) of the pyrrole **3** is 57%, while the isolated yield was 30% because significant amounts of the pyrrole **3** are distributed between other eluted fractions during the chromatographic (column) separation. In fact, since the recovered 1-acetyl adamantane **1** can be returned to the synthesis (Scheme 1), the actual yield of the pyrrole **3** calculated from the mass of 1-acetyl adamantane **1** consumed is higher (in this case, 83% based on the GLC composition of the crude product).

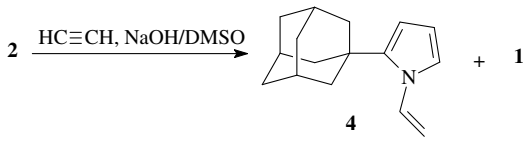
In the NaOH/DMSO system at one atmospheric pressure of acetylene and a higher temperature (130 °C, 4 h), pyrrole **3** was synthesized directly from the oxime **2** in a one-pot procedure, thus avoiding isolation of the intermediate *O*-vinyl oxime **5**. In this case, together with the major products, pyrrole **3** and 1-acetyl adamantane **1**, 1-vinyl adamantane **9** and adamantane were also formed, the mass ratio of the products in the crude being 6:7:3:1 (GLC). From this mixture pyrrole **3**, 1-acetyl adamantane **1**, and adamantane were isolated by column chromatography in 34%, 12% and 3% yields (Scheme 5). The yield of the pyrrole **3** was calculated based on the mass of 1-acetyl adamantane **1** consumed. 1-Vinyl adamantane **9** was identified by ^{1}H NMR[14] and GCMS.

Under pressure in the same catalytic system (initial acetylene pressure 14 atm, 120 °C, 1 h), 2-(1-adamantyl)-1-vinylpyrrole **4**[15] and 1-acetyl adamantane **1** were formed in 48% and 24% yields (the former yield is based on the starting ketone **1** consumed) (Scheme 6).

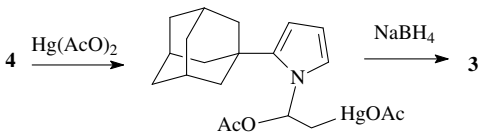
1-Vinyl pyrrole **4** (due to its reactive *N*-vinyl group[8a,16,17]) represents a prospective monomer and promising building block for the design of diverse polymeric and monomeric compounds containing the adamantylpyrrole structural unit. Besides, the pyrrole **4** is in fact protected NH-pyrrole **3**, which augments its synthetic potential further. Indeed, the vinyl group can be readily removed by treatment of pyrrole **4** with mercury acetate and reaction of the intermediate with sodium borohydride (50 °C, 40 min). The yield of the deprotected pyrrole **3**[18] was 77% (Scheme 7).

This modification of the reaction of ketoximes with acetylene exhibits remarkable peculiarities, namely the deoximation forming 1-vinyl adamantane **9** and adamantane.

The deoximation occurs both during *O*-vinyl oxime **5** rearrangement and the direct synthesis of pyrroles **3** and **4** from oxime **2**, the latter proceeding via the intermediate *O*-vinyl oxime **5**. The rearrangement **5**→**1** may be explained by the isomerization of *O*-vinyl oxime **5** to *N*-vinyl nitrone **5a**, which is further transformed to

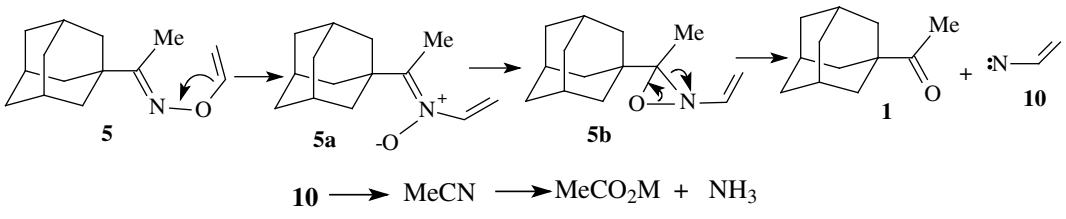


Scheme 6.

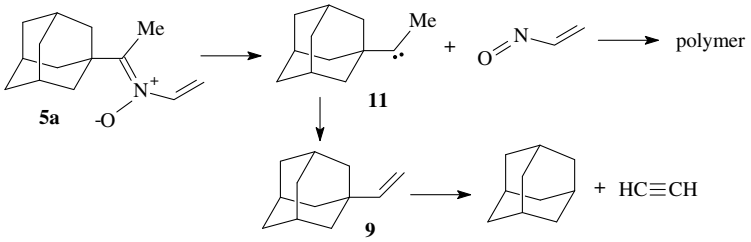


Scheme 7.

[†] The main hazards in handling acetylene at or above atmospheric pressure are comprehensively highlighted in a basic monograph.[12]



Scheme 8.



Scheme 9.

ketone **1** as shown in Scheme 8. Vinyl nitrene **10**, released by the decomposition of the intermediate oxazirane **5b**, isomerizes prototropically to acetonitrile, which is oxidized under the action of alkaline metal hydroxides to sodium or potassium acetates (Scheme 8).

The formation of 1-vinyl adamantane **9** is rationalized by an alternative decomposition of nitrone **5a** to deliver carbene **11** and nitrosoethene (Scheme 9). The carbene **11** rearranges to 1-vinyl adamantane **9**.

Also noteworthy is the fact that the studied reaction allows *O*-vinyl oximes **5** of acyl adamantanes, novel highly reactive derivatives of adamantane, to be synthesized readily in high yield (Scheme 2).

Thus, a short-cut from 1-acetyl adamantane to 2-(1-adamantyl)pyrrole and 2-(1-adamantyl)-1-vinylpyrrole via the isolable intermediate *O*-vinyl oxime of 1-acetyl adamantane through the reaction of the oxime of 1-acetyl adamantane with acetylene in MOH/DMSO superbase systems has been realized. The combination of adamantane and pyrrole chemistry may lead to target compounds such as drugs, fluorophores including BODIPY and other advanced optoelectronic materials.

Acknowledgments

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9. A mixture of **1** (1.00 g, 5.6 mmol), $H_2NOH{\cdot}HCl$ (2.90 g, 7.0 mmol) and pyridine (15 mL) was heated (80 °C) for 2 h and then poured into water (80 mL). The crystalline precipitate was filtered off, washed with water and dried in vacuo to afford 1.05 g (yield 97%) of **2** as a white powder, mp 182–184 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.82 (s, 1H, OH), 2.01 (m, 3H, H3, H5, H7), 1.82 (s, 3H, Me), 1.75 (m, 6H, H4, H6, H10), 1.67 (m, 6H, H2, H8, H9). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 164.6 (C=N), 39.3 (C2, C8, C9), 38.3 (C1), 36.8 (C4, C6, C10), 28.1 (C3, C5, C7), 9.2 (Me). IR (KBr) ν_{max}: 3227 (OH), 1659 (C=N), 1446, 1359, 1342, 1270, 1010, 984, 936, 859, 771, 732, 665, 554, 459 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO$ (193.29): C, 74.57; H, 9.91; N, 7.25. Found: C, 74.78; H, 9.98; N, 7.25.
10. A mixture of **2** (2.00 g, 10.3 mmol) and $KOH{\cdot}0.5H_2O$ (0.84 g, 12.9 mmol) was dissolved under heating (70 °C) in DMSO (50 mL). The solution of potassium oximate thus obtained was placed into a 0.25 L steel rotating autoclave. Then acetylene gas was transferred to the autoclave to remove air and the autoclave was charged with acetylene again from a cylinder at room temperature (initial pressure 13 atm). The autoclave was heated upon rotating (70 °C) for 30 min. The reaction mixture, after being cooled to room temperature, was extracted with pentane (10 mL × 7). The pentane extracts were washed with cold water (10 mL × 3) to remove dissolved DMSO. The mixture was dried over K_2CO_3 overnight and the pentane was removed to yield a residue (1.93 g). After column chromatography (basic Al_2O_3, hexane–ether 3:1) pure **5** was obtained (1.81 g, 80%) as white crystals (mp 113–114 °C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.88 (dd, 1H, $^3J_{BX}$ = 14.2 Hz, $^3J_{AX}$ = 6.8 Hz, H_X), 4.55 (dd, 1H, $^3J_{BX}$ = 14.2 Hz, $^2J_{AB}$ = 1.4 Hz, H_B), 4.04 (dd, 1H, $^3J_{AX}$ = 6.8 Hz, $^2J_{AB}$ = 1.4 Hz, H_A), 2.01 (m, 3H, H3, H5, H7), 1.82 (s, 3H, Me), 1.77 (m, 6H, H4, H6, H10), 1.72 (m, 6H, H2, H8, H9). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 166.6 (C=N), 152.8 (C_α), 87.0 (C_β), 39.3 (C2, C8, C9), 38.3 (C1), 36.6 (C4, C6, C10), 28.0 (C3, C5, C7), 10.2 (Me). IR (KBr) ν_{max}: 2903, 2849, 1640, 1614, 1449, 1376, 1344, 1275, 1253, 1168, 1006, 985, 953, 888, 863, 831, 649. Anal. Calcd for $C_{14}H_{21}NO$ (219.33): C, 76.67; H, 9.65; N, 6.39. Found: C, 77.00; H, 9.71; N, 6.69.
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13. A solution of **5** (1.35 g, 6.2 mmol) in DMSO (20 mL) was heated at 120 °C for 1 h. The mixture was diluted with water (50 mL), extracted with diethyl ether (10 mL × 5), and the combined organics were washed with water (5 mL × 3) and dried over K_2CO_3 overnight. Evaporation of the solvent gave 1.17 g of crude product with the **3**:**1**:adamantane ratio being 6:3:1 (GLC), corresponding to a 57% yield of **3**. Column chromatography (basic Al_2O_3, hexane–diethyl ether = 10:1) afforded 0.37 g (30% yield) of **3**, 0.30 g (27% yield) of **1**, and 0.09 g (11% yield) of adamantane.
14. Compound **9**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.72 (dd, 1H, $^3J_{BX}$ 17.5 Hz, $^3J_{AX}$ 10.8 Hz, H_X), 4.86 (d, 1H, $^3J_{BX}$ 17.5 Hz, H_B), 4.84 (d, 1H, $^3J_{AX}$ 10.8 Hz, H_A), 2.00 (m, 3H, H3, H5, H7), 1.70 (m, 6H, H4, H6, H10), 1.60 (m, 6H, H2, H8, H9). GCMS (ES) *m/z* 162.
15. A mixture of **2** (1.00 g, 5.2 mmol) and NaOH (0.21 g, 5.2 mmol) was dissolved under heating (80–90 °C) in DMSO (50 mL). The solution of sodium oximate thus obtained was placed into a 0.25 L steel rotating autoclave. Then acetylene

gas was transferred to the autoclave to remove air and the autoclave was charged with acetylene again from a cylinder at room temperature (initial pressure 14 atm). The autoclave was heated upon rotating (120 °C) for 1 h. The reaction mixture, after cooling to room temperature, was extracted with diethyl ether (15 mL × 5). The ether extracts were washed with cold water (15 mL × 3) to remove dissolved DMSO and dried over K_2CO_3 overnight. Column chromatography (basic Al_2O_3, hexane) of the residue (1.51 g) after evaporation of the diethyl ether gave 0.44 g (yield 48% based on 1-acetyl adamantane **1** consumed) of **4** as white crystals (mp 106–108 °C) and 0.22 g of **1** (yield 24%). Compound **4**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 (dd, 1H, $^3J_{BX}$ = 15.8 Hz, $^3J_{AX}$ = 8.6 Hz, H_X), 6.87 (m, 1H, H5pyr), 6.08 (m, 1H, H3pyr), 5.92 (m, 1H, H4pyr), 5.05 (d, 1H, $^3J_{BX}$ = 15.8 Hz, H_B), 4.69 (d, 1H, $^3J_{AX}$ = 8.6 Hz, H_A), 2.04 (m, 3H, H3, H5, H7), 2.00 (m, 6H, H4, H6, H10), 1.74 (m, 6H, H2, H8, H9). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 142.0 (C2pyr), 134.0 (C_α), 119.0 (C5pyr), 108.3 (C4pyr), 106.4 (C3-pyr), 99.8 (C_β), 42.1 (C2, C8, C9), 36.6 (C4, C6, C10), 34.4 (C1), 28.7 (C3, C5, C7). IR (KBr) ν_{max}: 3445, 2904, 2848, 1635, 1476, 1449, 1420, 1281, 1101, 862, 711. Anal. Calcd for $C_{16}H_{21}N$ (227.35): C, 84.53; H, 9.31; N, 6.16. Found: C, 84.58; H, 9.12; N, 6.19.

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18. Procedure for the synthesis of **3** by deprotection of **4**. Mercury acetate (2.12 g, 6.6 mmol) in 25 mL of 10% aqueous acetonitrile was added to **4** (0.50 g, 2.2 mmol) in 25 mL of acetonitrile under stirring. The reaction mixture was stirred for 40 min at 50 °C, then $NaBH_4$ (0.38 g, 8.2 mmol) was added in small portions. After gas evolution was complete, the residue was filtered off. The filtrate was diluted with brine (50 mL), extracted with diethyl ether (15 mL × 3), and the combined ether extracts were dried over E_2CI_3 overnight. The ether was removed to give 0.34 g (yield 77%) of **3** as white crystals (mp 100–102 °C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.01 (br s, 1H, NH), 6.66 (m, 1H, H5pyr), 6.13 (m, 1H, H4pyr), 5.91 (m, 1H, H3pyr), 2.04 (m, 3H, H3, H5, H7), 1.88 (m, 6H, H4, H6, H10), 1.74 (m, 6H, H2, H8, H9). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 135.7 (C2pyr), 115.7 (C5pyr), 107.9 (C3pyr), 101.8 (C4pyr), 43.0 (C2, C8, C9), 36.9 (C4, C6, C10), 36.8 (C1), 28.7 (C3, C5, C7). IR (KBr) ν_{max}: 3387, 2905, 2845, 1563, 1470, 1450, 1419, 1365, 1341, 1317, 1125, 1001, 1028, 782, 724, 712, 570. Anal. Calcd for $C_{14}H_{19}N$ (201.31): C, 83.53; H, 9.51; N, 6.96. Found: C, 83.68; H, 9.23; N, 7.11.