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Acylation of 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{3,11}.0^{5,9}]dodecane

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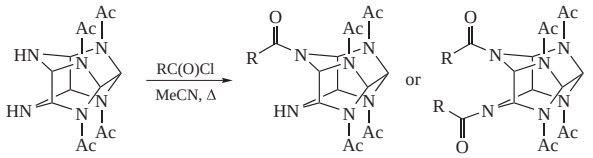
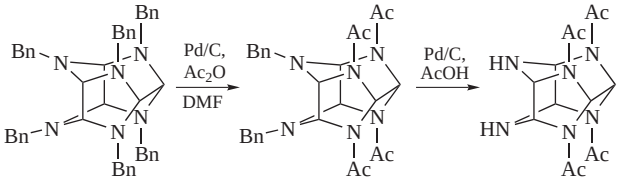
4-Mono- and 4,10-diacyl derivatives of 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{3,11}.0^{5,9}]dodecane were obtained by its treatment with acid chlorides in boiling acetonitrile.



2,4,6,8,10,12-Hexaazatetracyclo[5.5.0.0^{3,11}.0^{5,9}]dodecane (isowurtzitane) tetraacetylated at N^2, N^6, N^8, N^{12} is of interest as a semiproduct in syntheses of high-energy compounds. Its chemical transformations are performed to prepare potently useful materials.[1–6] Condensation of glyoxal with benzylamines is currently the straightforward route to construct isowurtzitane cage with aryl substituents. The use of some other amines does not allow one to obtain the target analogues.[4] This considerably limits the scope of such derivatives that could be synthesized using this approach.

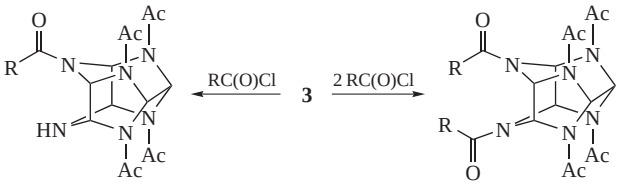
Therefore, the re-functionalization of substituents at nitrogen atoms in starting hexabenzyl compound **1** becomes topical (Scheme 1). Its catalytic hydrogenolysis with application of special acetylation protocol affords 2,6,8,12-tetraacetylisowurtzitane **3**.[4,5] By now, conditions for catalytic hydrogenolysis of 4,10-dibenzyl-2,6,8,12-tetraacetyl intermediate **2** in dilute acetic acid to give product **3** have been optimized. Performing the process in 50% acetic acid at 70–75 °C and a hydrogen pressure of ~5 bar and using 5% Pd/C afford compound **3** in 90–92% yield.[7]



Scheme 1

The structure of compound **3** seems challenging to accomplish acylation of NH groups with some other acyl substituents (Scheme 2).†

The reaction conditions were determined on preparing 4,10-dibenzoyl derivative **5c** with benzoyl chloride. The best results in terms of reaction time and yield were achieved in boiling aceto-



4a R = 2-ClC$_6$H$_4$
4b R = 3-ClC$_6$H$_4$
4c R = 2-HOC$_6$H$_4$

5a R = 3-pyridyl
5b R = 4-pyridyl
5c R = Ph
5d R = 3-O$_2$NC$_6$H$_4$
5e R = 4-O$_2$NC$_6$H$_4$

5f R = 4-MeOC$_6$H$_4$
5g R = 4-ClC$_6$H$_4$
5h R = PhCH$_2$
5i R = 2-ClC$_6$H$_4$CH$_2$
5j R = 4-ClC$_6$H$_4$CH$_2$

Scheme 2

† *General procedure*. 2,6,8,12-Tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo-[5.5.0.0^{3,11}.0^{5,9}]dodecane **3** (0.01 mol) was added to a solution of the corresponding acid chloride (0.025 mol) in acetonitrile (50 ml). The suspension was refluxed until TLC showed full consumption of the reactant **3** at the start of the chromatogram (acetone as the eluent). The resulting precipitate was filtered, washed several times with acetonitrile and dried in air. If required, washing with hot acetonitrile was repeated. In the case of pyridine derivatives, products **5a** and **5b** isolated as hydrochlorides were dissolved in water and treated with sodium carbonate to reach a neutral pH. The resulting suspensions were kept for 24 h at 2–5 °C, then filtered, washed with distilled water and dried in air.

4a: mp 335–337 °C. IR (ν/cm^{-1}): 3320, 3005, 1658, 1414, 1330, 1356, 1292, 1165, 1053, 986, 778, 752, 716, 623, 589. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.98–2.03 (m, 12 H, Me), 4.75–5.02 (m, H, NH), 5.49–5.88 (m, 3 H, CH), 6.24–6.85 (m, 3 H, CH), 7.20–7.53 (m, 4 H$_{Ar}$). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.33, 20.52, 21.76, 22.06, 63.16, 64.58, 65.85, 66.54, 68.17, 71.23, 128.19, 130.19, 131.72, 132.36, 166.89, 167.70.

4b: mp 341–342 °C. IR (ν/cm^{-1}): 3299, 3090, 3037, 1658, 1536, 1402, 1356, 1338, 1160, 1047, 993, 823, 727, 623, 592. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 2.01–2.15 (m, 12 H, Me), 4.89–5.10 (m, H, NH), 5.61–5.91 (m, 3 H, CH), 6.29–6.82 (m, 3 H, CH), 7.80–7.84 (m, H$_{Ar}$), 7.95–7.99 (m, H$_{Ar}$), 8.01–8.38 (m, 2 H$_{Ar}$). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 22.19, 22.21, 22.67, 23.27, 64.64, 66.68, 68.24, 69.08, 71.48, 73.39, 122.80, 125.32, 130.72, 134.56, 136.12, 148.00, 167.83, 169.57.

4c: mp 211–213 °C. IR (ν/cm^{-1}): 3410, 3193, 3053, 3030, 2966, 2882, 1681, 1545, 1401, 1365, 1332, 1262, 1165, 993, 841, 769, 705, 611, 569. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.88–2.06 (m, 12 H, Me), 4.60–4.79 (m, H, NH), 5.44 (br. s, H, OH), 6.16–6.49 (m, 4 H, CH), 6.84–7.00 (m, 2 H, CH), 7.32–7.96 (m, 4 H$_{Ar}$). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 21.15, 21.48, 22.46, 22.69, 63.59, 65.20, 66.46, 67.70, 68.02, 69.85, 117.97, 118.56, 119.16, 167.28, 167.83.

nitrile. If the reaction was carried out in DMF, the reaction time was longer whereas the yield was lower. Moreover, DMF as the solvent makes isolation of the product more difficult due to its higher solubility. It was found in our experiment that the presence of bases for binding hydrogen chloride was not mandatory, as also noted in literature.[8] Organic acid chlorides were good acylating agents, while other ones failed to substitute hydrogen atoms in amino groups.

Thus, the reaction was carried out in boiling acetonitrile, the process time ranged from 2 to 30 h (TLC monitoring). The structures of the compounds obtained were confirmed by NMR and IR spectroscopic data. IR spectra of all disubstituted derivatives **5** show the absence of amino groups, while in the case of mono-substitution (**4**), a signal of NH group is recorded (3300–3180 cm^{-1}).

Mono- or disubstitution course depended on structure of the acyl moiety. Usually, mono-derivatives were preferentially formed when benzoyl chloride bore *ortho*- or *meta*-substituents. In case of mono-substitution, prolongation of the reaction time failed to give disubstituted derivatives.

In conclusion, acylation of 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{3,11}.0^{5,9}]dodecane with acid chlorides can be used to synthesize a new variety of isowurtzitane derivatives. The use of acetonitrile makes it possible to obtain products in high yields without additional isolation and without a need for recrystallization.

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5a: mp 316 °C. IR (ν/cm^{-1}): 3019, 1666, 1590, 1403, 1360, 1318, 1148, 1054, 955, 825, 752, 724, 706, 681, 627, 593. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 2.15 (s, 6H, Me), 2.21 (s, 6H, Me), 6.43–6.46 (dd, 2H, CH), 6.49 (s, 2H, CH), 6.87–6.90 (dd, 2H, CH), 7.45–7.48 (m, 2H_{Ar}), 8.13–8.16 (m, 2H_{Ar}), 8.77 (d, 2H_{Ar}), 8.78 (d, 2H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 21.05, 22.12, 63.52, 69.25, 72.59, 123.63, 128.55, 135.79, 148.67, 152.64, 168.03, 168.44, 169.67.

5b: mp 251–252 °C. IR (ν/cm^{-1}): 3007, 2977, 1667, 1596, 1551, 1407, 1360, 1320, 1155, 1051, 955, 837, 756, 717, 661, 638, 624, 592, 536. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 2.03–2.25 (m, 12H, Me), 5.74 (t, 2H, CH), 6.17–7.13 (m, 4H, CH), 8.26 (d, 4H_{Ar}), 9.03 (d, 4H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.78, 20.84, 22.12, 23.39, 64.60, 65.49, 68.44, 70.55, 72.74, 74.15, 125.33, 125.33, 126.99, 144.33, 146.19, 148.81, 164.81, 167.06, 168.0.

5c: mp 359–361 °C. IR (ν/cm^{-1}): 3102, 3032, 2362, 1687, 1591, 1401, 1359, 1317, 1134, 1090, 956, 847, 758, 724, 646, 622, 587. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.97 (s, 6H, Me), 2.07 (s, 6H, Me), 6.25 (s, 2H, CH), 6.56 (s, 2H, CH), 6.97 (s, 2H, CH), 7.49 (s, 10H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.36, 20.65, 21.85, 23.04, 63.17, 64.88, 68.59, 70.07, 71.17, 72.85, 127.28, 128.83, 129.87, 132.21, 133.84, 167.81, 168.37, 171.31.

5d: mp 236–238 °C. IR (ν/cm^{-1}): 3085, 3038, 2336, 1659, 1531, 1394, 1355, 1309, 1285, 1149, 1055, 967, 899, 773, 724, 706, 636, 584. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.97 (s, 6H, Me), 2.09 (s, 6H, Me), 6.11–6.43 (m, 2H, CH), 6.62 (s, 2H, CH), 6.87–7.07 (m, 2H, CH), 7.73–7.83 (m, 2H_{Ar}), 7.98–8.06 (m, 2H_{Ar}), 8.33–8.44 (m, 4H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 21.30, 21.50, 22.37, 22.60, 64.35, 65.62, 67.34, 69.29, 72.10, 73.56, 123.29, 126.18, 130.94, 134.73, 135.09, 135.24, 147.88, 148.07, 168.21, 168.55, 169.63.

5e: mp 277–280 °C. IR (ν/cm^{-1}): 3110, 3033, 2361, 1679, 1602, 1525, 1402, 1355, 1316, 1142, 1053, 954, 859, 768, 720, 707, 648, 622, 599. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 2.11 (s, 6H, Me), 2.16 (s, 6H, Me), 6.30–6.32 (dd, 2H, CH), 6.43 (s, 2H, CH), 6.78–6.81 (dd, 2H, CH), 7.87 (d, 4H_{Ar}), 8.36 (d, 4H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.91, 20.25, 21.25, 21.47, 62.60, 64.32, 68.17, 69.84, 71.82, 73.51, 123.29, 128.33, 130.04, 137.83, 149.65, 168.26, 170.01.

5f: mp 288–291 °C. IR (ν/cm^{-1}): 3077, 2988, 2936, 2843, 2558, 1660, 1606, 1514, 1398, 1358, 1325, 1256, 1175, 1160, 1028, 955, 844, 764, 711, 646, 623, 610. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.95–2.06 (m, 12H, Me), 3.76 (s, 6H, Me), 6.20–6.25 (dd, 2H, CH), 6.55 (s, 2H, CH), 6.67–6.73 (dd, 2H, CH), 6.96 (d, 4H_{Ar}), 7.53 (d, 4H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.57, 20.75, 21.84, 23.08, 55.20, 56.59, 57.98, 63.59, 65.24, 70.35, 71.21, 113.51, 115.13, 125.75, 129.58, 131.08, 161.84, 167.73, 168.67, 171.15.

5g: mp 346–349 °C. IR (ν/cm^{-1}): 3102, 3032, 2362, 1667, 1591, 1401, 1359, 1317, 1284, 1145, 1134, 1090, 956, 847, 758, 724, 646, 623, 587. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.95 (s, 6H, Me), 2.06 (s, 6H, Me), 6.22 (s, 2H, CH), 6.58 (t, 2H, CH), 6.95 (s, 2H, CH), 7.56 (s, 8H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.39, 20.57, 21.73, 23.04, 63.36, 65.01, 68.41, 70.06, 71.25, 72.89, 128.35, 129.33, 129.98, 130.93, 132.46, 136.33, 167.98, 168.56, 170.56.

5h: mp 238–239 °C. IR (ν/cm^{-1}): 3042, 2930, 2332, 1662, 1403, 1359, 1287, 1163, 1049, 975, 954, 865, 792, 732, 702, 654,627, 602, 585, 553. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 2.04 (s, 6H, Me), 2.16 (s, 6H, Me), 4.03–4.28 (q, 2H, CH_2), 6.39 (s, 2H, CH), 6.58 (s, 4H, CH), 7.28–7.33 (m, 10H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 21.04, 21.72, 39.34, 40.29, 61.04, 63.04, 63.85, 66.30, 72.28, 74.49, 127.54, 128.47, 129.43, 133.51, 167.83, 168.61, 170.01.

5i: mp > 360 °C. IR (ν/cm^{-1}): 3051, 2929, 1672, 1407, 1360, 1287, 1166, 1050, 979, 951, 864, 797, 758, 737, 718, 634, 582. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.90–2.07 (m, 12H, Me), 4.11–4.53 (m, 4H, CH_2), 6.53 (s, 2H, CH), 6.71 (s, 2H, CH), 6.94 (s, 2H, CH), 7.26 (d, 6H_{Ar}), 7.40 (s, 2H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 20.67, 21.82, 37.53, 63.16, 64.72, 65.71, 71.36, 83.80, 84.20, 126.90, 128.51, 130.41, 133.50, 133.88, 134.82, 167.83, 168.25, 169.39.

5j: mp 250–253 °C. IR (ν/cm^{-1}): 3033, 2931, 1670, 1408, 1363, 1285, 1162, 1092, 981, 859, 808, 745, 710, 635, 561. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.98–2.14 (m, 12H, Me), 3.98–4.09 (m, 4H, CH_2), 6.36 (s, 2H, CH), 6.48–6.51 (dd, 2H, CH), 6.66–6.69 (dd, 2H, CH), 7.02 (d, 2H_{Ar}), 7.24–7.29 (m, 4H_{Ar}). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 19.69, 20.70, 21.87, 23.02, 37.81, 63.15, 63.98, 64.54, 65.62, 85.99, 87.03, 127.94, 129.61, 130.74, 131.39, 131.98, 134.26, 167.83, 168.51, 170.61.