Preliminary Communication

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Reactions of 3-arylmethylene-3*H*-furan(pyrrol)-2-ones with azomethine ylide: synthesis of substituted azaspirononenes

DOI 10.1515/hc-2016-0124
Received July 26, 2016; accepted August 22, 2016; previously published online September 24, 2016

Abstract: The reaction of arylmethylene derivatives of 3*H*-furan-2-ones or 3*H*-pyrrol-2-ones with N-benzylidenebenzylamine activated with the $AcOAg/Et_3N$ system to form spiropyrrolidynes was carried out for the first time.

Keywords: azaspirononene; 1,3-dipolar cycloaddition; 3H-furan-2-one; 3H-pyrrol-2-one.

1,3-Dipolar addition reaction has recently gained importance in the synthesis of spiroheterocyclic compounds [1–4]. Various heterocyclic systems including biologically active substances can be constructed in one stage [5, 6]. However, the application of this reaction is very limited by a rather weak activation of a multiple bond and unfavorable steric features in the dipolarophilic molecule. Michael's [7, 8] and Friedel-Krafts' reactions by the exocyclic C=C bond [9] and bromation reaction by the heterocyclic double bond [10] have previously been carried out in the 3-arylmethylene-3*H*-furan-2-one series. The reaction of a nucleophilic reagent [9] with diazoacetic ester [11] proceeds through opening of the furanone ring. Spirocompounds from 3-arylmethylene-3*H*-furan-2-ones and pyrrol-2-one analogs have not been obtained previously.

In this work, the synthesis of the spiro compounds by the reaction between 3-arylmethylene-3*H*-furan(pyrrol)-2-one and N-benzylidenebenzylamine was carried out by us for the first time. Azomethine ylide was generated *in situ* by addition of $AcOAg/Et_3N$ to acetonitrile solution of compounds **1a–l** and **2** (Scheme 1). The reaction requires an equimolar ratio of the reagents and is completed at room temperature within 2–3 days.

Starting compounds **1a–l** were synthesized by condensation of 4-oxobutyric acids with aromatic aldehydes by using a general procedure [6]. Products **3a–l** were obtained with yields up to 72–88%. In the ^{1}H NMR spectra of **3a–l** the two doublets for the vicinal protons at 4.01–4.13 ppm and 4.64–4.79 ppm with a coupling constant $J = 14.1–14.5$ Hz are consistent with *trans* orientation of these protons. Another proton at the ternary carbon atom adjacent to the nitrogen atom shows as a singlet within 4.28–4.84 ppm. The signal of the proton at the nitrogen atom resonates within 1.84–2.02 ppm. The protons at the sp^2-hybridized carbon atoms give an unresolved multiplet in the range of 6.87–7.86 ppm. The chemical shift of the proton Ar_2-C-H depends on the substituent type in the adjacent aromatic ring. Electron donating groups, such as 4-OMe, cause a small upfield shift of the signal (4.62–4.65 ppm) while electron withdrawing substituents, such as 2-Cl, and replacement of the benzene ring by a pyridine leads to downfield shift of the signal (4.72–4.79 ppm) in comparison with the similar signal of spiropyrrolidine with no substitution in its benzene ring (4.66–4.68 ppm). The ^{13}C NMR spectra of compounds **3a–l** are also fully consistent with the given structures.

A suggested mechanism for the reaction is presented in Scheme 2.

N-benzylidenebenzylamine is easily deprotonated at one of the methylene groups under the action of triethylamine to form a 2-azaallyl ion stabilized with a silver cation. The metal-organic intermediate keeps its initial spatial structure due to metal coordination and thus provides high stereoselectivity of the process. This reaction is a selective *cis*-addition proceeding by a single-stage synchronous mechanism with the suggested involvement of complex A, in which the maximum stabilization is achieved due to HOMO overlapping in the dipole with LUMO in the dipolarophile, to produce spiropyrrolidine **3**.

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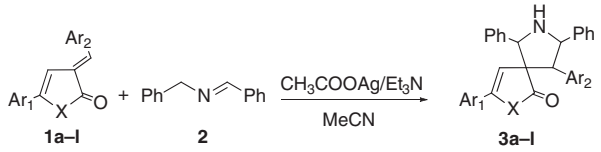
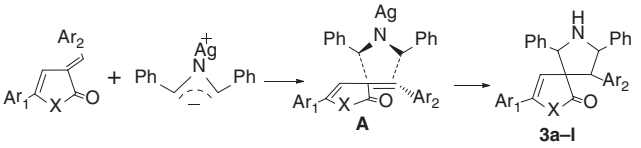


1, 3 a: X=O, Ar_1 = Ph, Ar_2 = Ph; **b:** X=O, Ar_1 = Ph, Ar_2 = 4-$MeOC_6H_4$; **c:** X=O, Ar_1 = Ph, Ar_2 = 2-ClC_6H_4; **d:** X=O, Ar_1 = 4-MeC_6H_4, Ar_2 = 2-Py; **e:** X=O, Ar_1 = 4-MeC_6H_4, Ar_2 = 2-ClC_6H_4; **f:** X=O, Ar_1 = 4-$MeOC_6H_4$, Ar_2 = 2-ClC_6H_4; **g:** X=O, Ar_1 = 4-$MeOC_6H_4$, Ar_2 = Ph; **h:** X=O, Ar_1 = C_4H_9, Ar_2 = Ph; **i:** X=O, Ar_1 = C_4H_9, Ar_2 = 2-Py; **j:** X=NH, Ar_1 = 4-MeC_6H_4, Ar_2 = Ph; **k:** X=NH, Ar_1 = 4-MeC_6H_4, Ar_2 = 2-ClC_6H_4; **l:** X=NH, Ar_1 = Ph, Ar_2 = 2-ClC_6H_4

Scheme 1



Scheme 2

The maximum electronic LUMO density is concentrated near the exocyclic C=C bond of an arylmethylene moiety of 3*H*-furan(pyrrol)-2-one, which favors orbital-controlled cycloaddition of *N*-benzylidenebenzylamine by this bond. The reaction is highly efficient.

Experimental

The ^{13}C NMR (75 MHz) and ^{1}H NMR (400 MHz) spectra were obtained in $CDCl_3$ solution on a Bruker MSL-400 spectrometer. Elemental analysis was performed on an analyzer Vario MicroCube. The IR spectra were obtained in KBr pellets.

General procedure for preparation of azaspiro[4.4]non-3-en-1-ones 3

A solution of 3-arylmethylene-3*H*-furan-2-one (**1**, X = O, 0.18 mmol) or the pyrrol analog (**1**, X = NH, 0.18 mmol), *N*-benzylidenebenzylamine (**2**, 1.8 mmol) and triethylamine (1.8 mmol) in acetonitrile (18 mL) was treated with 15 mol% silver acetate. The mixture was stirred at room temperature for 2–3 days. The excess of silver acetate was filtered out and the solution was neutralized with ammonium chloride. The clear organic layer was separated and concentrated. The resultant crystals of **3** were crystallized from ethanol (**3a,b**) or chloroform (**3c,d**).

3,6,8,9-Tetraphenyl-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3a) Yield 79%; mp 161–163°C; IR: ν_{max} 3194, 3061, 3034, 2923, 1676, 1650, 1445, 1403, 1358, 1263, 1211, 1147, 1070, 1053, 948, 906, 721, 704, 636, 453 cm^{-1}; ^{1}H NMR: δ 2.02 (br s, 1H), 4.07 (d, *J* = 14.4 Hz, 1H), 4.28 (s, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 6.94 (s, 1H), 7.13–7.83 (m, 20H); ^{13}C NMR: δ 34.0, 35.3, 39.5, 85.3, 105.1, 120.5, 121.4, 121.9, 122.8, 123.2, 123.9, 124.4, 124.8, 126.5, 128.4, 129.9, 132.9, 137.3, 138.7, 140.5, 163.4. Anal. Calcd for $C_{31}H_{25}NO_2$: C, 83.95; H, 5.68; N, 3.16. Found: C, 83.69; H, 5.31; N, 3.28.

9-(4-Methoxyphenyl)-3,6,8-triphenyl-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3b) Yield 72%; mp 167–169°C; IR: ν_{max} 3238, 3032, 2957, 2931, 2837, 1691, 1639, 1600, 1442, 1413, 1358, 1305, 1261, 1174, 1074, 1030, 1006, 964, 833, 736, 707, 613, 455 cm^{-1}; ^{1}H NMR: δ 1.99 (br s, 1H), 3.87 (s, 3H), 4.03 (d, *J* = 14.1 Hz, 1H), 4.64 (d, *J* = 14.1 Hz, 1H), 4.84 (s, 1H), 6.43 (s, 1H), 6.87–7.64 (m, 19H); ^{13}C NMR: δ 33.7, 35.8, 40.2, 55.9, 87.7, 103.9, 120.7, 121.8, 122.3, 122.9, 123.5, 124.1, 124.6, 125.3, 127.8, 128.9, 130.2, 132.1, 136.4, 139.5, 156.0, 165.1. Anal. Calcd for $C_{32}H_{27}NO_3$: C, 81.16; H, 5.75; N, 2.96. Found: C, 80.99; H, 5.46; N, 2.64.

3,6,8-Triphenyl-9-(2-chlorophenyl)-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3c) Yield 85%; mp 180–181°C; IR: ν_{max} 3165, 3033, 2943, 1674, 1651, 1437, 1410, 1355, 1227, 1213, 1156, 1070, 1032, 923, 887, 777, 712, 692, 677, 461, 453 cm^{-1}; ^{1}H NMR: δ 1.91 (br s, 1H), 4.11 (d, *J* = 14.5 Hz, 1H), 4.52 (s, 1H), 4.73 (d, *J* = 14.5 Hz, 1H), 7.01 (s, 1H), 7.13–7.88 (m, 19H); ^{13}C NMR: δ 34.3, 38.7, 41.9, 87.0, 107.3, 121.5, 121.9, 122.3, 122.8, 123.7, 124.9, 125.2, 125.9, 126.8, 129.0, 130.9, 134.5, 133.4, 138.1, 141.6, 169.1. Anal. Calcd for $C_{31}H_{24}ClNO_2$: CC, 77.90; H, 5.06; N, 2.93; Cl, 7.42. Found: C, 77.72; H, 5.21; N, 3.18; Cl, 7.07.

3-(4-Methylphenyl)-6,8-diphenyl-9-(2-pyridinyl)-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3d) Yield 88%; mp 174–175°C; IR: ν_{max} 3283, 3052, 3027, 2943, 1668, 1641, 1603, 1584, 1468, 1431, 1418, 1384, 1217, 1211, 1110, 1024, 1006, 953, 914, 817, 785, 698, 609, 517 cm^{-1}; ^{1}H NMR: δ 1.84 (br s, 1H), 2.33 (s, 3H), 3.50 (s, 1H), 4.03 (d, *J* = 14.4 Hz, 1H), 4.77 (d, *J* = 14.4 Hz, 1H), 7.03 (s, 1H), 7.10–7.65 (m, 17H), 8.55 (d, 1H); ^{13}C NMR: δ 20.9, 24.3, 41.4, 44.0, 91.2, 107.1, 122.3, 125.6, 125.9, 127.1, 128.3, 128.8, 129.1, 133.7, 136.2, 138.2, 138.9, 139.4,149.6, 154.8, 168.9. Anal. Calcd for $C_{31}H_{26}N_2O_2$: C, 81.20; H, 5.72; N, 6.11. Found: C, 81.12; H, 5.32; N, 6.19.

3-(4-Methylphenyl)-6,8-diphenyl-9-(2-chlorophenyl)-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3e) Yield 75%; mp 166–167°C; IR: ν_{max} 3285, 3045, 3027, 2936, 1669, 1652, 1603, 1584, 1454, 1408, 1364, 1212, 1115, 1024, 1006, 953, 914, 817, 785, 698, 609, 517 cm^{-1}; ^{1}H NMR: δ 1.86 (br s, 1H), 2.35 (s, 3H), 3.51 (s, 1H), 4.04 (d, *J* = 14.3 Hz, 1H), 4.78 (d, *J* = 14.3 Hz, 1H), 7.02 (s, 1H), 7.12–7.79 (m, 18H); ^{13}C NMR: δ 20.9, 24.4, 41.3, 44.2, 90.8, 106.9, 124.3, 125.7, 125.9, 127.5, 128.3, 128.9, 129.4, 133.7, 137.3, 138.2, 138.5, 139.7, 141.6, 148.6, 152.4, 169.3. Anal. Calcd for $C_{32}H_{26}ClNO_2$: C, 78.12; H, 5.33; N, 2.85. Found: C, 78.32; H, 5.32; N, 3.19.

3-(4-Methoxylphenyl)-6,8-diphenyl-9-(2-chlorphenyl)-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3f) Yield 79%; mp 198–199°C; IR: ν_{max} 3293, 3032, 2855, 1672, 1654, 1601, 1592, 1457, 1402, 1372, 1215, 1110, 1024, 1011, 958, 905, 812, 783, 699, 613, 513 cm^{-1}; ^{1}H NMR: δ 1.80 (br s, 1H), 3.53 (s, 1H), 3.86 (s, 3H), 4.05 (d, *J* = 14.6 Hz, 1H), 4.73–4.79 (d, *J* = 14.6 Hz, 1H), 7.10 (s, 1H), 7.19–7.68 (m, 18H); ^{13}C NMR: δ 34.9, 42.9,

55.9, 58.9, 70.2, 104.3, 114.2, 122.7, 126.0, 126.1, 126.7, 127.4, 128.2, 128.6, 128.9, 133.5, 138.7, 140.5, 142.6, 159.9, 169.9. Anal. Calcd for $C_{32}H_{26}ClNO_3$: C, 75.66; H, 5.16; N, 2.76. Found: C, 75.39; H, 5.22; N, 3.01.

3-(4-Methoxyphenyl)-6,8,9-triphenyl-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3g) Yield 77%; mp 182–184°C; IR: ν_{max} 3291, 3035, 2853, 1670, 1651, 1603, 1586, 1461, 1405, 1369, 1210, 1103, 1027, 1009, 947, 908, 815, 787, 687, 614, 519 cm^{-1}; ^1H NMR: δ 1.97 (br s, 1H), 3.54 (s, 1H), 3.87 (s, 3H), 4.06 (d, *J* = 14.7 Hz, 1H), 4.74–4.79 (d, *J* = 14.7 Hz, 1H), 7.01 (s, 1H), 7.09–7.62 (m, 19H); ^{13}C NMR: δ 35.1, 43.6, 55.8, 59.9, 70.2, 102.3, 114.2, 122.6, 126.0, 126.3, 126.7, 127.6, 128.3, 128.7, 128.9, 133.7, 139.2, 140.6, 143.1, 159.9, 169.9. Anal. Calcd for $C_{32}H_{27}NO_3$: C, 81.16; H, 5.75; N, 2.96. Found: C, 81.33; H, 5.59; N, 3.12.

3-Butyl-6,8,9-triphenyl-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3h) Yield 73%; mp 132–134°C; IR: ν_{max} 3311, 2985–2962, 1673, 1648, 1601, 1577, 1463, 1402, 1369, 1225, 1111, 1045, 1012, 947, 903, 815, 787, 679, 623 cm^{-1}; ^1H NMR: δ 0.85 (t, 3H), 1.26-1.86 (m, 6H), 2.01 (br s, 1H), 3.52 (s, 1H), 4.03 (d, *J* = 14.4 Hz, 1H), 4.73 (d, *J* = 14.4 Hz, 1H), 6.97 (s, 1H), 7.07–7.41 (m, 15H); ^{13}C NMR: δ 14.3, 22.5, 26.3, 34.5, 38.1, 43.4, 57.8, 66.2, 107.7, 126.0, 126.1, 128.2, 128.6, 128.9, 138.7, 140.5, 147.0, 170.6. Anal. Calcd for $C_{29}H_{29}NO_2$: C, 82.24; HH, 6.90; N, 3.31. Found: C, 81.98; H, 6.79; N, 3.42.

3-Butyl-9-(2-pyridinyl)-6,8-diphenyl-2-oxa-7-azaspiro[4.4]non-3-en-1-one (3i) Yield 79%; mp 139–140°C; IR: ν_{max} 3308, 2987–2969, 1670, 1647, 1610, 1571, 1465, 1403, 1367, 1220, 1110, 1037, 1015, 943, 905, 817, 785, 679, 623 cm^{-1}; ^1H NMR: δ 0.86 (t, 3H), 1.26–1.84 (m, 6H), 2.00 (br s, 1H), 3.55 (s, 1H), 4.03 (d, *J* = 14.4 Hz, 1H), 4.74 (d, *J* = 14.4 Hz, 1H), 6.96 (s, 1H), 7.07–7.45 (m, 14H), 8.65 (d, 1H); ^{13}C NMR: δ 14.2, 22.9, 26.2, 34.3, 38.6, 43.4, 57.2, 66.4, 107.4, 122.7, 123.9, 126.1, 128.2, 128.6, 136.6, 138.7, 140.5, 147.8, 148.3, 170.9. Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.48; H, 6.69; N, 6.47.

3-(4-Methylphenyl)-6,8,9-triphenyl-2,7-diazaspiro[4.4]non-3-en-1-one (3j) Yield 51%; mp 171–173°C; IR: ν_{max} 3192, 3064, 3030, 2924, 1681, 1647, 1444, 1407, 1361, 1259, 1208, 1150, 1068, 1052, 950, 907, 719, 705, 632, 449 cm^{-1}; ^1H NMR: δ 2.02 (br s, 1H), 4.06 (d, 1H), 4.28 (s, 1H), 4.67 (d, 1H), 6.94 (s, 1H), 7.13–7.83 (m, 20H); ^{13}C NMR: δ 34.0, 34.9, 39.4, 85.3, 104.8, 119.2, 121.6, 122.2, 122.8, 123.5, 124.1, 124.9, 125.3, 126.8, 127.8, 130.2, 133.1, 136.8, 139.2, 140.1, 162.4. Anal. Calcd for $C_{32}H_{28}N_2O$: C, 84.18; H, 6.18; N, 6.14. Found: C, 84.29; H, 6.21; N, 6.18.

3-(4-Methylphenyl)-6,8-diphenyl-9-(2-chlorophenyl)-2,7-diazaspiro[4.4]non-3-en-1-one (3k) Yield 72%; mp 165–167°C; IR: ν_{max} 3236, 3029, 2961, 2927, 2836, 1687, 1641, 1600, 1443, 1408, 1358, 1311, 1261, 1178, 1069, 1028, 1003, 967, 829, 741, 710, 614, 460 cm^{-1}; ^1H NMR: δ 1.99 (br s, 1H), 3.87 (s, 3H), 4.03 (d, 1H), 4.64 (d, 1H), 4.84 (s, 1H), 6.43 (s, 1H), 6.87–7.64 (m, 19H); ^{13}C NMR: δ 33.6, 36.3, 41.2, 56.4, 88.1, 104.5, 120.2, 121.6, 122.5, 123.4, 123.9, 124.8, 125.6, 126.3, 127.8, 128.5, 130.4, 133.1, 135.4, 140.2, 156.1, 164.1. Anal. Calcd for $C_{32}H_{27}ClN_2O$: C, 78.27; H, 5.54; N, 5.71. Found: C, 78.25; H, 5.60; N, 5.44.

3,6,8-Triphenyl-9-(2-chlorophenyl)-2,7-diazaspiro[4.4]non-3-en-1-one (3l) Yield 56%; mp 162–164°C; IR: ν_{max} 3163, 3043, 2947, 1669, 1648, 1440, 1408, 1351, 1230, 1215, 1161, 1074, 1038, 932, 878, 778, 717, 689, 675, 460, 448 cm^{-1}; ^1H NMR: δ 1.91 (br s, 1H), 4.11 (d, 1H), 4.52 (s, 1H), 4.73 (d, 1H), 7.01 (s, 1H), 7.13–7.88 (m, 19H); ^{13}C NMR: δ 34.1, 37.7, 42.2, 86.7, 108.3, 120.5, 121.7, 122.1, 122.7, 123.4, 124.3, 124.9, 125.3, 127.6, 129.8, 131.9, 134.5, 136.4, 137.6, 142.6, 171.1. Anal. Calcd for $C_{31}H_{24}ClNO_2$: C, 78.06; H, 5.28; N, 5.87. Found: C, 77.98; H, 5.21; N, 5.68.

Acknowledgments: This project was supported by the Russian Science Foundation (project № 15-13-10007).

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