Synthesis of C, N-diaryl nitrones from the reduction of nitroarene with aromatic aldehydes promoted by metallic samarium

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A mild and facile reduction of nitroarene with aromatic aldehydes promoted by metallic samarium to C, N-diaryl nitrones in moderate yields has been developed.

Keywords: C, N-diaryl nitrone, samarium, aromatic aldehyde, nitroarene

Nitrones are highly versatile synthetic intermediates[1] and spin trapping reagents used in biological systems.[2] Nitrones are an attractive class of 1,3-dipoles, for the synthesis of β-lactams and other biologically interesting compounds.[3] Various methods for the synthesis of nitrones have been reported,[4] including, the condensation of aldehydes with hydroxylamines,[4a] the oxidation of hydroxylamines, secondary amines or imines,[4b-4e] the reaction of secondary amines with selenium dioxide,[4f] and the thiazolium salt-catalysed reduction of nitrobenzene with benzadehyde and triethylamine.[4g] A difficulty with these methods is often the preparation of the starting materials or catalysts. Some methods require expensive reagents or strong oxidising agents.

The use of metallic samarium as a reducing agent in organic synthesis has recently attracted attention.[5] This is due to the fact that metallic samarium is stable in air and has strong reducing power ($Sm^{3+}/Sm = -2.41V$). It is also cheap and easy to handle. Recently, we have reported the reduction and the *C*-acetylation of Baylis–Hillman adducts as well as the acylation of alcohols with acyl chlorides promoted by metallic samarium.[6] We now report a facile reductive coupling of nitroarenes with aromatic aldehydes promoted by metallic samarium to give C, N-diaryl nitrones (Scheme 1).

Our initial experiment was carried out with nitrobenzene (1.1 mmol) and benzaldehyde (1.0 mmol) as model substrates with metallic samarium (2.0 mmol) at room temperature without any other additives. However, no product was observed with various solvents. When a catalytic amount of acetic acid was added, a trace amount of desired nitrone was observed with methanol as solvent. A series of experiments were carried out in order to achieve the optimal conditions. We were pleased to find that samarium (1.6 mmol) and acetic acid (3.2 mmol) were sufficient to promote the present conversion. It was also noteworthy that the reaction proceeded smoothly without the exclusion of moisture or air.

On the other hand, a significant solvent effect was observed in our experiments and methanol was found to be the best choice. When acetonitrile, THF or dichloromethane were used as solvent in this reaction, the desired nitrone was obtained in 10–31% yields. Thus, the optimal reaction conditions were established. A series of aromatic aldehydes were treated with a nitroarene to give the corresponding products (Table 1). All reactions proceeded smoothly and were finished within 0.5 hours.

Table 1 The reduction of nitroarene with aromatic aldehydes promoted by metallic samarium

Entry	R	R′	Isolated yield/%
	nitroarene	aldehyde	
a	H	H	74
b	H	2-Cl	64
c	H	4-Cl	77
d	H	2, 4-Cl_2	67
e	H	4-Me	80
f	H	4-MeO	41
g	H	3-MeO	66
h	H	4-tert-Bu	61
i	H	3, 4-(OCH_2O)	63
j	H	Furan-2-carbaldehyde	76
k	4-Me	H	77
l	4-Me	4-Cl	78
m	4-Me	4-Me	75
n	4-Me	4-MeO	62
o	4-Cl	H	66
p	4-Cl	4-Cl	57

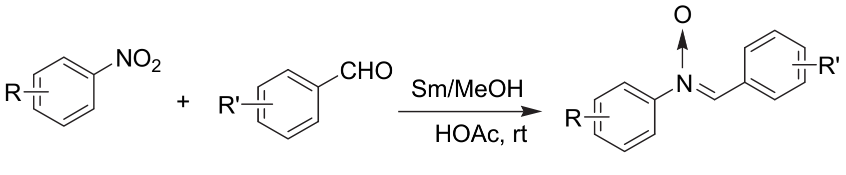
In summary, a mild and facile reduction of nitroarene with aromatic aldehydes promoted by metallic samarium to give C, N-diaryl nitrones in moderate yields has been developed. The advantages of this protocol are single product, simple manipulation, readily available starting materials and mild condition.

Experimental

Melting points were determined on a capillary melting point apparatus and were uncorrected. All reagents were commercially purchased and used without further purification. All ^1H NMR spectra were measured in $CDCl_3$ and recorded on Bruker AC – 500 (500 MHz) spectrometer with TMS as the internal standard. ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on Bruker AC – 125(125 MHz) spectrometer with TMS as the internal standard. IR spectra were measured with a Perkin Elmer FT-IR-1600 spectrometer. Mass spectra were determined with a HP 5989A mass spectrometer. Purification of products was accomplished by preparative TLC.

General procedure

Nitroarene (1.1 mmol), aromatic aldehyde (1.0 mmol), methanol (5 ml), acetic acid (3.2 mmol) and samarium powder (1.6 mmol) were added successively to a round bottom flask containing a magnetic stirrer bar. After being stirred at room temperature for 0.5 h, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried



Scheme 1

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over $NaSO_4$. The solvent was removed under reduced pressure and the residue was purified by preparative TLC on silica gel eluting with petroleum ether/ethyl acetate to afford the corresponding C, N-diaryl nitrones in moderate yields. The products were identified by m.p., IR, ^1H NMR, ^{13}C NMR, IR and mass spectra.

a: 111.2–111.5°C (lit.[4d] 112–113°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.47–7.49 (m, 6H), 7.77–7.79 (m, 2H), 7.93 (s, 1H), 8.39–8.40 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ: 121.8, 128.7, 129.1, 129.2, 129.9, 130.7, 130.9, 134.6, 149.1; IR (KBr) ν: 3058, 1590, 1567, 1547, 1487, 1457, 1402, 1193, 1071, 843, 766 cm^{-1}; MS (EI): *m/z* (rel. intensity): 197 (M^+, 10), 181 (5), 105 (16), 91 (100), 77 (43).

b: 82.1–82.5 (lit.[7] 81–82°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.32–7.49 (m, 6H), 7.77–7.79 (m, 2H), 8.41 (s, 1H), 9.52–9.54 (dd, J = 2.0, 8.0 Hz, 1H); IR (KBr) ν: 3057, 1590, 1572, 1547, 1486, 1460, 1446, 1396, 1191, 1067, 889, 770 cm^{-1}.

c: 154.9–155 (lit.[8] 156–158°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.45 (d, J = 9.0 Hz, 2H), 7.47–7.51 (m, 3H), 7.76–7.78 (m, 2H), 7.91 (s, 1H), 8.36 (d, J = 9.0 Hz, 2H); IR (KBr) ν: 3059, 1592, 1574, 1548, 1485, 1461, 1445, 1397, 1192, 1068, 888, 771 cm^{-1}.

d: 69.5–70.2 (lit.[9] 72°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.39–7.53 (m, 5H), 7.77–7.79 (m, 2H), 8.38 (s, 1H), 9.54 (d, 1H); IR (KBr) ν: 3069, 2922, 1627, 1598, 1580, 1537, 1484, 1385, 1189, 1089, 854, 749 cm^{-1}.

e: 89.8–90.5 (lit.[10] 91–93°C); ^1H NMR ($CDCl_3$, TMS) δ: 2.42 (s, 3H), 7.29–7.49 (m, 5H), 7.77–7.79 (m, 2H), 7.89 (s, 1H), 8.30 (d, 2H); IR (KBr) ν: 2921, 1618, 1597, 1549, 1484, 1455, 1400, 1184, 1067, 841, 755 cm^{-1}.

f: 117.1–118.2°C (lit.[11] 116.6–117.8°C); ^1H NMR ($CDCl_3$, TMS) δ: 3.89 (s, 3H), 7.0 (d, J = 9.0 Hz, 2H), 7.43–7.50 (m, 3H), 7.76–7.79 (m, 2H), 7.86 (s, 1H), 8.41 (d, J = 9.0 Hz, 2 H); IR (KBr) ν: 2923, 1613, 1600, 1507, 1458, 1396, 1256, 1175, 1063, 846, 755 cm^{-1}.

g: Oil;[12] ^1H NMR ($CDCl_3$, TMS) δ: 3.85 (s, 3H), 6.99–7.02 (m, 2H), 7.01–7.03 (m, 1H), 7.33–7.37 (m, 1H), 7.44–7.45 (m, 3H), 7.66 (d, 1H), 7.74–7.76 (m, 2H), 7.91 (s, 1H), 8.37 (s, 1H); IR (KBr) ν: 2924, 1611, 1601, 1506, 1456, 1398, 1253, 1172, 1060, 843, 756 cm^{-1}.

h: Oil;[13] ^1H NMR ($CDCl_3$, TMS) δ: 1.36 (s, 9H), 7.45–7.49 (m, 3H), 7.51 (d, J = 8.5 Hz, 2H), 7.76–7.78 (dd, J = 2.0, 8.5 Hz, 2H), 7.90 (s, 1H), 8.34 (d, J = 8.5 Hz, 2H); IR (KBr) ν: 2922, 1615, 1596, 1547, 1482, 1458, 1401, 1180, 1065, 840, 753 cm^{-1}.

i: 134.5–135 (lit.[14]135°C); ^1H NMR ($CDCl_3$, TMS) δ: 6.05 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.44–7.49 (m, 3H), 7.69 (d, J = 8.0 Hz, 1H), 7.75–7.77 (m, 2H), 7.83 (s, 1H), 8.31 (s, 1H); IR (KBr) ν: 3057, 2893, 1655, 1617, 1595, 1550, 1486, 1452, 1393, 1266, 1192, 1106, 1073, 841, 761 cm^{-1}.

j: 81.4–82.1 (lit.[8] 78–80°C); ^1H NMR ($CDCl_3$, TMS) δ: 6.64–6.66 (m, 1H), 7.46–7.51 (m, 3H), 7.59–7.81 (m, 3H), 8.01 (d, J = 3.5 Hz, 1H), 8.16 (s, 1H); IR (KBr) ν: 3097, 3055, 2926, 1654, 1595, 1568, 1543, 1473, 1388, 1296, 1156, 1070, 873, 769 cm^{-1}.

k: 123–124 (lit.[15]122.8–123.5°C); ^1H NMR ($CDCl_3$, TMS) δ: 2.42 (s, 3H), 7.27 (d, J = 8.5 Hz, 2H), 7.46–7.48 (m, 3H), 7.67 (d, J = 8.5 Hz, 2H), 7.91 (s, 1H), 8.38–8.40 (m, 2H); IR (KBr) ν: 3048, 2923, 1637, 1598, 1549, 1500, 1443, 1416, 1389, 1294, 1189, 1064, 815, 750 cm^{-1}.

l: 167–167 (lit.[16]166.4–167.1°C); ^1H NMR ($CDCl_3$, TMS) δ: 2.42 (s, 3H), 7.27 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 8.35 (d, J = 8.5 Hz, 2H); IR (KBr) ν: 3051, 2920, 1665, 1592, 1545, 1502, 1482, 1419, 1399, 1193, 1075, 842, 820, 782 cm^{-1}.

m: 143–145 (lit.[17] 145.3–146.2°C); ^1H NMR ($CDCl_3$, TMS) δ: 2.42 (s, 6H), 7.26 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.87 (s, 1H), 8.29 (d, J = 8.5 Hz, 2H); IR (KBr) ν: 3039, 2844, 1637, 1601, 1547, 1503, 1448, 1415, 1389, 1177, 1072, 841, 815, 751 cm^{-1}.

n: 129 (lit.[18] 128.6–129.8°C); ^1H NMR ($CDCl_3$, TMS) δ: 2.41 (s, 3H), 3.88 (s, 3H), 6.99 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.84 (s, 1H), 8.40 (d, J = 9.0 Hz, 2H); IR (KBr) ν: 3045, 2922, 2852, 1645, 1600, 1557, 1507, 1460, 1417, 1392 1253, 1169, 1069, 826, 749 cm^{-1}.

o: 164–166 (lit.[16]165.7–166.4°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.46 (d, J = 9.0 Hz, 2H), 7.48–7.50 (m, 3H), 7.75 (d, J = 9.0 Hz, 2H), 7.90 (s, 1H), 8.37–8.39 (m, 2H); IR (KBr) ν: 3048, 2925, 1632, 1591, 1548, 1482, 1444, 1417, 1385, 1191, 1065, 819, 751 cm^{-1}.

p: 137–138 (lit.[19] 137.9–138.8°C); ^1H NMR ($CDCl_3$, TMS) δ: 7.45–7.47 (m, 4H), 7.30 (d, J = 9.0 Hz, 2H), 7.89 (s, 1H), 8.35 (d, J = 9.0 Hz, 2H); IR (KBr) ν: 3092, 2923, 1633, 1588, 1544, 1485, 1417, 1399, 1172, 1073, 828 cm^{-1}.

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