OXIDATIVE COUPLING OF 4-SUBSTITUTED N,N-DIMETHYLANILINES WITH CYCLIC VINYL ETHERS IN THE PRESENCE OF EITHER MANGANESE(II) OR COBALT(II) NITRATE UNDER OXYGEN

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Abstract - The reaction of 4-substituted N,N-dimethylanilines with 2,3-dihydrofuran and 3,4-dihydro-2H-pyran proceeds in the presence of a catalytic amount of manganese(II) or cobalt(II) nitrate under oxygen to give the corresponding hexahydrofuro- and hexahydro-2H-pyrano[3,2-c]quinolines, respectively.

The synthesis of polycyclic compounds involving a quinoline ring is of current interest, since they are expected to exhibit pharmacological effects.[1-3] The [4+2] cycloaddition of benzylidenanilines with 2,3-dihydrofurans using acid catalysts is a useful method for preparation of tricyclic hexahydrofuro[3,2-c]quinoline derivatives,[4-8] some of them being known to exhibit biological activities such as antimalarial effect.[5,6] We have recently reported that N,N-dimethylanilines react with acyclic vinyl ethers in the presence of a catalytic amount of iron(III) chloride under oxygen to give 4-alkoxy-1,2,3,4-tetrahydro-1-methylquinolines.[9] We now report the synthesis of N,O-containing tricyclic compounds, hexahydrofuro- and hexahydro-2H-pyrano[3,2-c]quinolines (4) and (5), by the reactions of 4-substituted N,N-dimethylanilines (1) with 2,3-dihydrofuran (2) and 3,4-dihydro-2H-pyran (3), respectively, in the presence of various transition-metal salts.

Table 1 shows the results for the reaction of N,N-dimethyl-p-toluidine (1a) (2 mmol) with 2 (10 mmol) in acetonitrile under oxygen (1 atm) at 50 °C for 20 h using a variety of metal chlorides and nitrates (0.02 mmol) as the catalysts; 6-28 equivalent of the coupling product, 2,3,3a,4,5,9b-hexahydro-5,8-dimethylfuro[3,2-c]quinoline (4a), per equivalent of catalyst used was produced. Among the metal species tested, Mn(NO$_3$)$_2$•6H$_2$O gave the most satisfactory result in terms of both the product selectivity (93 %) and yield (28 %) which are defined as the yield of 4a based on 1a consumed and charged, respectively. Cobalt(II) nitrate
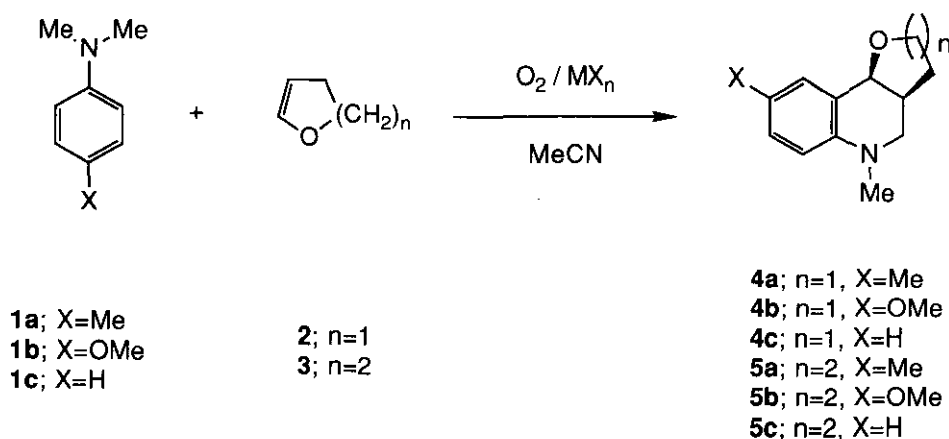
1a; X=Me
1b; X=OMe
1c; X=H

2; n=1
3; n=2

4a; n=1, X=Me
4b; n=1, X=OMe
4c; n=1, X=H
5a; n=2, X=Me
5b; n=2, X=OMe
5c; n=2, X=H

Table 1. Oxidative coupling of N,N-dimethyl-p-toluidine (**1a**) with 2,3-dihydrofuran (**2**)
in the presence of various metal salts.[a]

MX$_n$	Conv. of 1a (%)	Yield of 4a (%)[b]	Selectivity of 4a (%)[c]
MnCl$_2$	10	6	60
Mn(NO$_3$)$_2$·6H$_2$O	30	28	93
FeCl$_3$	34	16	47
Fe(NO$_3$)$_3$·9H$_2$O	45	24	53
CoCl$_2$	40	15	38
Co(NO$_3$)$_2$·6H$_2$O	34	28	82
NiCl$_2$	46	17	37
CuCl	66	7	11

(a) The reaction was carried out in acetonitrile at 50 °C under oxygen for 20 h.
[**1a**]:[**2**]:[MX$_n$]= 2:10:0.02. (b) Yield based on **1a** charged was determined by
glc analysis. (c) Yield based on **1a** consumed.

also afforded a fairly good result. Of course, the reaction did not proceed in the absence of the catalysts and
oxygen.

Increase in the amount of Mn(NO$_3$)$_2$ and Co(NO$_3$)$_2$ from 0.02 to 0.2 mmol resulted in the increase in the yield
of **2a** (43 % and 48 % after isolation) (Table 2). However, a further addition of Mn(NO$_3$)$_2$ significantly

decreased the product selectivity, although the conversion of **1a** was increased. Oxygen consumption (1.2 mmol) was observed in the reaction using $Mn(NO_3)_2$ (0.2 mmol) at 30 °C for 22 h; the conversion of **1a** and the yield of **2a** were 60 % (1.2 mmol) and 49 % (1.0 mmol), respectively.

Table 2. Oxidative coupling of N,N-dimethylanilines (**1**) with vinyl ethers (**2**) and (**3**) in the presence of either $Mn(NO_3)_2$ or $Co(NO_3)_2$[a]

Aniline	Ether	Catalyst[b]	Conv. of 1 (%)[c]	Yield of 4 or 5[d]
1a	**2**	A	61	43(48)
1a[e]	**2**	A	82	(32)
1a	**3**	A	46	24(31)
1b	**2**	A	60	47
1b	**3**	A	51	26
1c	**2**	A	59	41
1c	**3**	A	49	20
1a	**2**	B	67	48
1a	**3**	B	48	(32)
1b	**2**	B	65	45
1b	**3**	B	47	27(37)
1c	**2**	B	47	(18)
1c	**3**	B	9	(5)

(a) The reaction was carried out in acetonitrile at 50 °C under oxygen for 20 h. [1]:[2]:[Catalyst]=2:10:0.2. [1]:[3]:[Catalyst]=2:5:0.2. (b) A: $Mn(NO_3)_2 \cdot 6H_2O$, B: $Co(NO_3)_2 \cdot 6H_2O$. (c) Determined by glc analysis. (d) Isolated yield. The value in parentheses indicates yield determined by glc analysis. (e) $[Mn(NO_3)_2]=1$.

Other examples of the coupling reaction are also recorded in Table 2. The reaction of **1a-c** with **3** gave the corresponding hexahydro-2H-pyrano[3,2-c]quinoline (**5a-c**) as well as those with **2** to afford **4a-c**, although the yield of **5** was lower than that of **4**.

The present oxidative coupling reaction, by virtue of the mild conditions using inexpensive reagents, may be complementary to the cycloaddition reaction of benzylidenanilines with vinyl ethers. The reaction mechanism would be similar to that proposed for the formation of tetrahydroquinolines.[9]

EXPERIMENTAL

^{1}H- and ^{13}C-Nmr spectra were obtained with a JEOL JNM-GSX-400 spectrometer for CDCl$_3$ solutions. Ms spectra were obtained with a JEOL JMS-DX-303 spectrometer. Gc analysis was carried out on a Shimadzu GC-8APF gas chromatograph.

The aniline (2b) was prepared by the method reported previously.[10] Other starting materials were commercially available and were purified by standard methods.

General procedure for coupling reaction of N,N-dimethylanilines (1) with either 2,3-dihydrofuran (2) or 3,4-dihydoro-2H-pyran (3): To a flask containing an appropriate metal salt (0.2 mmol) was added a solution of the aniline (1) (2 mmol) and the vinyl ether (2) (10 mmol) or (3) (5 mmol) in acetonitrile (10 ml). The mixture was stirred for 20 h at 50 °C under oxygen (with a balloon). The resulting mixture was poured into water (50 ml) and extracted with ether (50 ml x 2). The organic layer was dried over sodium sulfate and evaporated. The product was isolated with column chromatography on silica gel using ethyl acetate-hexane as eluant. Isolation of the product could also be made by Kugelrohr distillation.

2,3,3a,4,5,9b-Hexahydro-5,8-dimethyl-furo[3,2-c]quinoline (2a): bp 150 °C / 2mmHg. ^{1}H-Nmr δ: 1.72-1.79 (m, 1H), 2.19-2.28 (m, 1H), 2.24 (s, 3H), 2.51-2.57 (m, 1H), 2.72 (dd, J=11.0 and 11.0 Hz, 1H), 2.85 (s, 3H), 2.97 (dd, J=11.0 and 5.1 Hz, 1H), 3.80 (ddd, J=8.7, 8.7, and 6.3 Hz, 1H), 3.94 (ddd, J=8.7, 8.7, and 5.9 Hz, 1H), 4.57 (d, J=5.4 Hz, 1H), 6.63 (d, J=8.3 Hz, 1H), 7.00 (dd, J=8.3 and 2.0 Hz, 1H), 7.17 (d, J=2.0 Hz, 1H). ^{13}C-Nmr δ: 20.18, 30.14, 36.25, 39.51, 52.94, 65.25, 75.86, 112.03, 121.92, 126.74, 129.61, 131.51, 145.11. Ms m/z: 203 (M$^+$). Anal. Calcd for C$_{13}$H$_{17}$NO: C 76.8, H 8.4, N 6.9. Found: C 76.6, H 8.5, N 6.9.

2,3,3a,4,5,9b-Hexahydro-8-methoxy-5-methylfuro[3,2-c]quinoline (2b): bp 180 °C / 2 mmHg. ^{1}H-Nmr δ: 1.73-1.81 (m, 1H), 2.20-2.29 (m, 1H), 2.54-2.61 (m, 1H), 2.68 (dd, J=11.0 and 11.0 Hz, 1H), 2.83 (s, 3H), 2.97 (dd, J=11.0 and 4.9 Hz, 1H), 3.76 (s, 3H), 3.81 (ddd, J=8.5, 8.5, and 6.3, 1H), 3.94 (ddd, J=8.5, 8.5, and 5.9 Hz, 1H), 4.59 (d, J=5.9 Hz, 1H), 6.67 (d, J=8.9 Hz, 1H), 6.81 (dd, J=8.9 and 3.1 Hz, 1H), 6.96 (d, J=3.1 Hz, 1H). ^{13}C-Nmr δ: 30.15, 36.54, 39.86, 53.34, 55.78, 65.44, 76.01, 113.29, 115.52, 115.75, 123.15, 141.85, 152.01. Ms m/z: 219 (M$^+$). Anal. Calcd for C$_{13}$H$_{17}$NO$_2$: C 71.2, H 7.8, N 6.4. Found: C 71.0, H 7.8, N 6.4.

2,3,3a,4,5,9b-Hexahydro-5-methylfuro[3,2-c]quinoline (2c): bp 135 °C / 2 mmHg. ^{1}H-Nmr δ: 1.72-1.80 (m, 1H), 2.20-2.29 (m, 1H), 2.49-2.57 (m, 1H), 2.78 (dd, J=11.1 and 11.1 Hz, 1H), 2.89 (s, 3H), 3.00 (dd, J=11.1 and 4.9 Hz, 1H), 3.80 (ddd, J=8.7, 8.7, and 6.4 Hz, 1H), 3.94 (ddd, J=8.7, 8.7, and 5.9 Hz,

1H), 4.59 (d, J=5.4 Hz, 1H), 6.70 (d, J=8.3 Hz, 1H), 6.76 (dd, J=7.6 and 7.6 Hz, 1H), 7.20 (ddd, J=8.3, 7.6, and 1.8 Hz, 1H), 7.34 (dd, J=7.6 and 1.8 Hz, 1H). ^{13}C-Nmr δ: 30.10, 36.02, 39.35, 52.62, 65.19, 75.90, 111.86, 117.46, 121.74, 129.09, 131.20, 147.21. Ms m/z: 189 (M$^+$). Anal. Calcd for $C_{12}H_{15}NO$: C 76.2, H 8.0, N 7.4. Found: C 75.9, H 8.0, N 7.5.

3,4,4a,5,6,10b-Hexahydro-6,9-dimethyl-2H-pyrano[3,2-c]quinoline (3a): bp 170 °C / 2 mmHg. ^{1}H-Nmr δ: 1.41-1.47 (m, 1H), 1.70-1.81 (m, 2H), 1.85-1.94 (m, 1H), 2.10-2.18 (m, 1H), 2.22 (s, 3H), 2.86 (s, 3H), 2.90 (dd, J=11.5 and 3.9 Hz, 1H), 3.47 (dd, J=11.5 and 11.5 Hz, 1H), 3.66 (ddd, J=10.8, 10.8, and 2.6 Hz, 1H), 3.95-3.97 (m, 1H), 4.38 (d, J=2.4 Hz, 1H), 6.56 (d, J=8.3 Hz, 1H), 6.97 (dd, J=8.3 and 2.0 Hz, 1H), 7.03 (d, J=2.0 Hz, 1H). ^{13}C-Nmr δ: 20.14, 22.57, 25.67, 32.63, 39.29, 51.28, 67.47, 74.24, 111.75, 121.85, 125,71, 129.97, 131.09, 144,50. Ms m/z: 217 (M$^+$). Anal. Calcd for $C_{14}H_{19}NO$: C 77.4, H 8.8, N 6.4. Found: C 77.4, H 8.9, N 6.6.

3,4,4a,5,6,10b-Hexahydro-9-methoxy-6-methyl-2H-pyrano[3,2-c]quinoline (3b): bp 190 °C / 2mmHg. ^{1}H-Nmr δ: 1.44-1.50 (m, 1H), 1.66-1.92 (m, 3H), 2.10-2.17 (m, 1H), 2.84 (s, 3H), 2.91 (ddd, J=10.8, 3.8, and 1.1 Hz, 1H), 3.39 (dd, J=10.8 and 10.8 Hz, 1H), 3.65 (ddd, J= 7.9, 6.7, and 2.7 Hz, 1H), 3.75 (s, 3H), 3.90-3.95 (m, 1H), 4.43 (d, J=3.4 Hz, 1H), 6.60 (d, J=8.9 Hz, 1H), 6.79 (dd, J=8.9 and 3.1 Hz, 1H), 6.84 (d, J=3.1 Hz, 1H). ^{13}C-Nmr δ: 22.76, 25.47, 32.76, 39.71, 51.79, 55.88, 67.00, 74.07, 113.00, 115.36, 115.92, 122.82, 141.36, 151.43. Ms m/z: 233 (M$^+$). Anal. Calcd for $C_{14}H_{19}NO_2$: C 72.1 H 8.2 N 6.0. Found: C 71.7, H 8.2, N 6.1.

3,4,4a,5,6,10b-Hexahydro-6-methyl-2H-pyrano[3,2-c]quinoline (3c): bp 155 °C / 2 mmHg. ^{1}H-Nmr δ: 1.42-1.48 (m, 1H), 1.72-1.82 (m, 2H), 1.85-1.94 (m, 1H), 2.11-2.18 (m, 1H), 2.90 (s, 3H), 2.95 (ddd, J=11.0, 3.9, and 1.0 Hz, 1H), 3.53 (dd, J=11.0 and 11.0 Hz, 1H), 3.67 (ddd, J=10.9, 10.9, and 2.6 Hz, 1H), 3.93-3.98 (m, 1H), 4.42 (d, J=2.8 Hz, 1H), 6.62 (d, J=8.3 Hz, 1H), 6.66 (dd, J=7.4 and 7.4 Hz, 1H), 7.15 (ddd, J=8.3, 7.4, and 1.6 Hz, 1H), 7.20 (dd, J=7.4 and 1.6 Hz, 1H). ^{13}C-Nmr δ: 22.59, 25.56, 32.39, 39.06, 51.13, 67.41, 74.21, 111.42, 116.47, 121.71, 129.41, 130.68, 146.52. Ms m/z: 203 (M$^+$). Anal. Calcd for $C_{13}H_{17}NO$: C 76.8, H 8.4, N 6.9. Found: C 76.4, H 8.5, N 7.0.

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