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Pseudo Three-Component Synthesis of 1,3-Dioxol Derivatives from the Reaction Between Isocyanides and Aldehydes in Solventless Conditions

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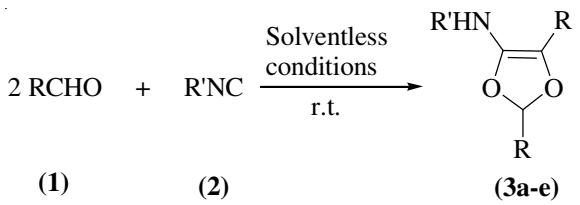
Pseudo three-component reaction between isocyanides and aldehydes in a 1:2 ratio in solventless conditions at room temperature led to 1,3-dioxol derivatives in high yields. The reaction proceeds cleanly under mild conditions and no side reactions were observed. The structures of the products were deduced from their ^{1}H NMR, ^{13}C NMR, mass, IR spectra and elemental analysis.

Key Words: Isocyanide, Multicomponent reactions, 1,3-Dioxol derivatives, Solventless conditions.

INTRODUCTION

1,3-Dioxol derivatives are important heterocycles in medicinal chemistry. Some of these compounds exhibit *in vitro* leishmanicidal activity[1], active inhibitor of phosphodiesterase-4,[2] insecticide activity[3], antitumour and antimicrobial activity[4] and antiinflammatory activity[5]. Nowadays many organic compounds can be synthesized by multicomponent reactions. There are number of advantages that make multicomponent reactions popular for organic chemists such as simple procedures, time saving, superior atom economy, the one-pot character and the high and ever increasing number of accessible backbones[6-15]. In connection with our interest to synthesis of heterocycles[16-19], we report the synthesis of 1,3-dioxol derivatives *via* pseudo three-component reaction between isocyanides (**1**) and aldehydes (**2**) in a 1:2 ratio in solventless conditions at room temperature in high yields (**Scheme-I**).



Scheme-I: Synthesis of 1,3-dioxol derivatives **(3a-e)**

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco FT-IR 6300 spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-rapid analyzer.

Compounds 3a-e: The aldehydes (**1**) (0.2 mmol) and isocyanides (**2**) (0.1 mmol) were added at room temperature to each other in solventless conditions. The mixture was then left at room temperature for 12 h to two weeks. The mixture was connected to vacuum for 0.5 h and the products (**3a-e**) were obtained as white powders without further purification. The characterization data of the products are given below.

***N*-cyclohexyl-*N*-(2,5-dimethyl-1,3-dioxol-4-yl)amine (3a):** White powder, m.p. 71.5-72.8 ºC, yield 93 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3282, 2937, 1747, 1656, 1561, 1235; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.13-1.91 (m,13H, 5CH_2 of cyclohexyl and CH_3), 2.12 (s, 6H, CH_3), 3.73-3.76 (m, 1H, CH of cyclohexyl), 5.13 (q, 1H, *J* = 6.8 Hz, CH of dioxol), 5.95 (s, 1H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 17.92 and 21.12 (2CH_3), 24.75, 25.43 and 32.95 (CH_2 of cyclohexyl), 47.88 (CHN), 70.69 (CH of dioxol), 169.28 and 169.41 (C=C). EI-MS: 132, 115, 88, 82, 49, 43, 41. Anal. calcd. (%) for $C_{11}H_{19}NO_2$ (m.w. 197.27): C 66.97, H 9.71, N 7.10. Found: C 66.93, H 9.65, N 7.16.

***N*-(2,5-diphenyl-1,3-dioxol-4-yl)-*N*-(1,1,3,3-tetramethylbutyl)amine (3b):** White powder, m.p. 91.6-92.9 ºC, yield 97 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3331, 2955, 1730, 1663,

1551, 1264, 1114; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (s, 9H, CMe_3), 1.43 (s, 6H, CMe_2), 1.68 (s, 2H, CH_2), 6.07 (1H, s, CH of dioxol), 6.24 (s, 1H, NH), 7.32-8.11 (m, 10H, aromatic CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.68 (C*Me*$_2$), 28.89 (C*Me*$_3$), 31.42 (*C*Me$_3$), 52.50 (CH_2), 55.59 (*C*Me$_2$), 76.12 (CH of dioxol), 127.32, 128.61, 128.73, 128.84, 129.34, 129.74, 133.59, 135.86 (aromatic carbons), 164.83 and 166.92 (C=C). EI-MS: 206, 156, 57. Anal. calcd. (%) for $C_{23}H_{29}NO_2$ (m.w. 351.48): C 78.59, H 8.32, N 3.99. Found: C 78.67, H 8.28, N 4.02.

***N*-[2,5-*bis*-(4-fluorophenyl)-1,3-dioxol-4-yl]-*N*-(1,1,3,3-tetramethylbutyl)amine (3c):** White powder, m.p. 119.2-120.8 ºC, yield 91 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3435, 3331, 2925, 1731, 1662, 1509, 1261, 1088; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (s, 9H, CMe_3), 1.42 (s, 6H, CMe_2), 1.68 (s, 2H, CH_2), 6.00 (s, 1H, CH of dioxol), 6.17 (s, 1H, NH), 7.07-8.12 (*m*, 8H, aromatic CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.63 (C*Me*$_2$), 28.91(C*Me*$_3$), 31.41 (C*Me*$_3$), 52.44 (CH_2), 55.73 (*C*Me$_2$), 75.50 (CH of dioxol), 115.79 (d, $^2J_{CF}$ = 21.9 Hz), 115.90 (d, $^2J_{CF}$ = 21.9 Hz), 125.43 (d, $^4J_{CF}$ = 2.5 Hz), 129.32 (d, $^3J_{CF}$ =8.1 Hz), 131.60 (d, $^4J_{CF}$ = 3.1 Hz), 132.34 (d, $^3J_{CF}$ = 9.4 Hz), 163.00 (d, $^1J_{CF}$ = 246.9 Hz), 166.1 (d, $^1J_{CF}$ = 253.8 Hz), 163.92 and 166.58 (C=C). EI-MS: 248, 123, 108, 95, 57. Anal. calcd. (%) for $C_{23}H_{27}NO_2F_2$ (m.w. 387.46): C 71.30, H 7.02, N 3.61. Found: C 71.34, H 6.96, N 3.57.

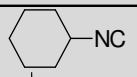
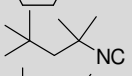
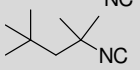
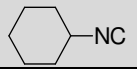
***N*-(*tert*-butyl)-*N*-(2,5-diphenyl-1,3-dioxol-4-yl)amine (3d):** White powder, m.p. 143.7-145.2 ºC, yield 90 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3290, 1721, 1655, 1557, 1268, 1117; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 9H, *t*-Bu), 6.00 (1H, s, CH of dioxol), 6.22 (s, 1H, NH), 7.37-811 (m, 10H, aromatic CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.68 (C*Me*$_3$), 51.58 (*C*Me$_3$), 76.02 (CH of dioxol), 127.42, 128.63, 128.76, 128.89, 129.36, 129.74, 133.58, 135.93 (aromatic carbons), 164.87 and 167.34 (C=C). EI-MS: 212, 194, 105, 77, 57. Anal. calcd. (%) for $C_{19}H_{21}NO_2$ (m.w. 295.38): C 77.26, H 7.17, N 4.74. Found: C 77.30, H 7.22, N 4.76.

***N*-cyclohexyl-*N*-(2,5-diphenyl-1,3-dioxol-4-yl)amine (3e):** White powder, m.p. 137.1-138.4 ºC, yield 93 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3441, 3312, 2935, 1734, 1650, 1449, 1261, 1119; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.12-1.91 (m, 10H, $5CH_2$ of cyclohexyl), 3.77-3.88 (m, 1H, CH of cyclohexyl), 6.11 (d, 1H, NH, *J* = 7.8 Hz), 7.35-8.14 (m, 10H, aromatic CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 24.68, 25.41, 32.85 (CH_2 of cyclohexyl), 48.21 (CHN), 75.91 (CH of dioxol), 127.41, 128.64, 128.76, 128.93, 129.32, 129.78, 133.62, 135.78 (aromatic carbons), 164.93 and 167.32 (C=C). EI-MS: 212, 194, 105, 77. Anal. calcd. (%) for $C_{21}H_{23}NO_2$ (m.w. 321.41): C 78.47, H 7.21, N 4.36. Found: C 78.40, H 7.23, N, 4.30.

RESULTS AND DISCUSSION

The reaction between isocyanides **(1)** and aldehydes **(2)** in 1:2 ratio at room temperature and in solventless conditions led to 1,3-dioxol derivatives **(3a-e)** *via* a pseudo three-component reaction. The reaction proceeded cleanly under mild conditions and the obtained products did not require any purification. The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses. For example the ^{1}H NMR spectrum of **3a** exhibited distinct signals arising from $5CH_2$ of cyclohexyl and CH_3 (δ = 1.13-1.91), CH_3 (δ = 2.12), CH of cyclohexyl (δ = 3.73-3.76), CH of dioxol ring (δ = 5.13) and NH (δ = 5.95). The ^{13}C NMR spectrum of **3a** showed 9 distinct resonances arising from $2CH_3$ (δ = 17.92 and 21.12), CH_2 of cyclohexyl (δ = 24.75, 25.43, 32.95), CHN (δ = 47.88), CH of dioxol ring (δ = 70.69) and C=C carbons of dioxol ring (δ = 169.28 and 169.41).

TABLE-1
SYNTHESIS OF 1,3-DIOXOL DERIVATIVES **(3a-e)**

Entry	RCHO	R'NC	Products	Reaction times
1	CH_3CHO		**3a**	1 week
2	PhCHO		**3b**	1 week
3	4-F-PhCHO		**3c**	2 weeks
4	PhCHO	*t*-BuNC	**3d**	12 h
5	PhCHO		**3e**	12 h

Conclusion

The reported method offers a mild and efficient procedure for the preparation of 1,3-dioxol derivatives (**3a-e**). Ease of work-up, high yields and environment-friendly make it a useful addition to modern synthetic methodologies.

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