A Simple One-Pot Synthesis of *N*-Alkyl-2,5-diaryl-1,3-dioxol-4-amines

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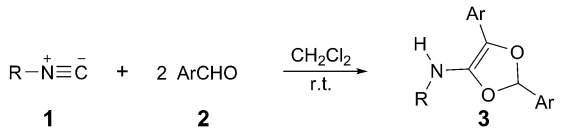
An efficient procedure for the synthesis of *N*-alkyl-2,5-diaryl-1,3-dioxol-4-amines **3** *via* a one-pot reaction of aromatic aldehydes **2** and alkyl isocyanides **1** at room temperature in good yields is described (*Scheme 1*, *Table*).

Introduction. – The 1,3-dioxole moiety is an important substructure found in numerous natural alkaloids [1] (*e.g.*, in hydrastine). Many condensed heterocyclic systems, especially when linked to a 1,3-dioxole ring, play important roles as potent anti-HIV (*e.g.*, AHE) [2][3], anticancer (*e.g.*, podophyllotoxin and etoposide) [4][5], anticonvulsant [6], antidepressive [6], antitumor [7], and antipyretic [6] agents, as well as in the treatment of cardiovascular diseases [8] and lung cancer [9].

A number of synthetic routes for 1,3-benzodioxoles have been reported [7–10], and many syntheses of 1,3-dioxoles *via* the reaction of α-diazo ketones with carbonyl derivatives have been described [11]. As part of our ongoing studies on the development of simple synthetic methods in heterocyclic chemistry, for *e.g.*, the synthesis of iminospiro-γ-lactones, 2*H*-pyrano[2,3-*d*]pyrimidine derivatives, and 2,5-diaminofuran derivatives [12], and our interest in isocyanide-based reactions, we report herein an efficient synthesis of *N*-alkyl-2,5-diaryl-1,3-dioxol-4-amines, starting from simple and readily available precursors. To the best of our knowledge, there are no reports on the synthesis of these compounds *via* isocyanide-based reactions.

Results and Discussion. – The reaction of alkyl isocyanides **1** and aromatic aldehydes **2** proceeds smoothly in dry CH_2Cl_2 in the absence of any catalyst and at room temperature to produce the 1,3-dioxolamines **3** in excellent yields (*Scheme 1*, *Table*). As shown in the *Table*, aromatic aldehydes **2** with electron-withdrawing or donating groups gave excellent yields of the corresponding product **3**.

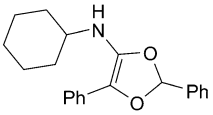
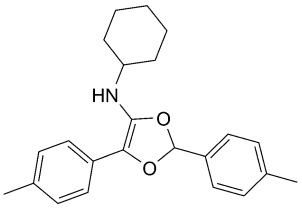
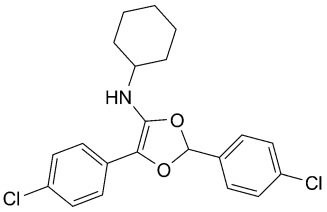
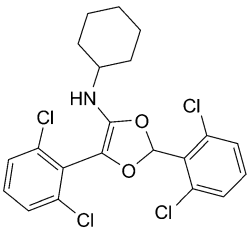
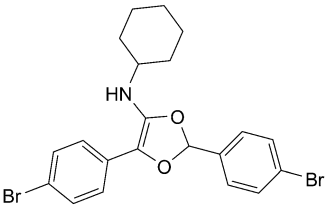
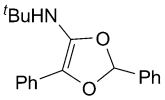
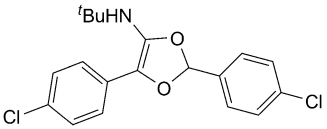
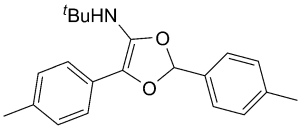
Scheme 1



1 **2** **3**

The structures of the products **3** were deduced from their elemental analyses and IR and ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H- and ^{13}C-NMR spectra of the crude reaction

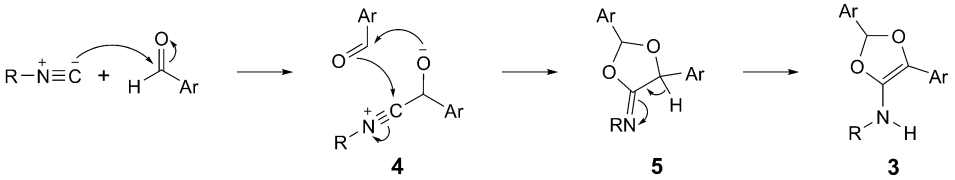
Table. *Synthesis of 1,3-Dioxole Derivatives* **3a** – **3h**

Aldehyde **2**	Isocyanide **1**	Product **3**	Yield [%]
PhCHO	Cy-N≡C		96
4-MeC_6H_4CHO	Cy-N≡C		94
4-ClC_6H_4CHO	Cy-N≡C		92
2,6-$Cl_2C_6H_3CHO$	Cy-N≡C		85
4-BrC_6H_4CHO	Cy-N≡C		92
PhCHO	^{t}BuN≡C		90
4-ClC_6H_4CHO	^{t}BuN≡C		95
4-MeC_6H_4CHO	^{t}BuN≡C		90

mixture, no products other than **3** could be detected. The mass spectra of compounds **3** displayed molecular-ion peaks at appropriate *m*/*z* values, though of low intensity. The ^{1}H-NMR spectrum of **3a** (Ar = Ph, R = cyclohexyl) consisted of a *m* for the cyclohexyl group (δ(H) 1.01 – 2.01), a broad signal for the CH–N group (δ(H) 3.77 – 3.87), a *s* at δ(H) 6.30 for the acetal H-atom and a *d* (δ(H) 6.10 (^3J = 7.5 Hz)) for the NH group, in agreement with the suggested structure. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 17 distinct signals in agreement with the proposed structure. In this case, the molecule is chiral owing to the acetal stereogenic C-atom, consequently the five CH_2 groups of the cyclohexyl moiety are noneqivalent, and they gave separate resonances. The characteristic signal of the acetal C-atom was observed at δ(C) 75.93, and the olefinic C-atoms of the 1,3-dioxole ring appeared at δ(C) 164.95 and 167.37. The ^{1}H- and ^{13}C-NMR spectra of compounds **3b** – **3h** were similar to that of **3a**, except for the signals of the substituted alkyl and aryl moieties, which exhibited characteristic resonances with appropriate chemical shifts (see *Exper. Part*).

A plausible mechanism for the formation of 1,3-dioxolamines **3** is shown in *Scheme 2*. On the basis of the well-established chemistry of isocyanides [13][14], it is reasonable to assume that the reaction between the alkyl isocyanide and the aldehyde involves initial formation of a 1,3-dipolar intermediate **4**, which undergoes addition to the C=O group of another aldehyde molecule to give **5**. This intermediate is converted into product **3** *via* H-atom transfer.

Scheme 2



In conclusion, we have reported a simple method for the synthesis of potentially interesting *N*-alkyl-2,5-diaryl-1,3-dioxol-4-amines from readily available aromatic aldehydes and alkyl isocyanides. The present procedure has the advantage that the reaction occurs under neutral conditions, and, moreover, the substances can be mixed without any further activation or modification.

Experimental Part

General. Alkyl isocyanides, aromatic aldehydes, and solvents used in this work were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. M.p.: *Gallenkamp-9100* electrothermal apparatus; uncorrected. IR Spectra: *Bruker-Tensor-27* spectrometer; KBr; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-DRX-300-Avance* instrument, $CDCl_3$ solns.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Shimadzu-QP-GC-5050* spectrometer; at 70 eV; in *m*/*z* (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

Compounds **3**: *General Procedure.* To a magnetically stirred soln. of benzaldehyde (0.212 g, 2 mmol) in CH_2Cl_2 (3 ml) was added, at r.t. within 10 min *via* a syringe, cyclohexyl isocyanide (= isocyanocyclohexane; 0.109 g, 1 mmol) or *tert*-butyl isocyanide (= 2-isocyano-2-methylpropane; 0.083 g, 1 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at r.t. for 3 d. The solvent was evaporated, and the residue washed with hexane/AcOEt 9 : 1: the product **3**.

N-*Cyclohexyl-2,5-diphenyl-1,3-dioxol-4-amine* (**3a**): Yield 0.308 g (96%). Pale orange solid. M.p. 116–118°. IR: 3440, 3311, 3100, 1733, 1655, 1545, 1256, 1113. ^{1}H-NMR: 1.01–2.01 (*m*, 10 H of Cy); 3.77–3.87 (*m*, CH–N); 6.10 (*d*, ^3J = 7.5, NH); 6.30 (*s*, CH); 7.35–7.64 (*m*, 6 arom. H); 8.10 (*d*, ^3J = 7.4, 4 arom. H). ^{13}C-NMR: 24.68, 24.71, 25.43, 32.85, 32.95 (Cy); 48.24 (CH–N); 75.93 (CH); 127.42, 128.65, 128.77, 130.03, 128.95, 133.63 (10 arom. C); 129.34, 135.78 (arom. C); 164.95, 167.37 (C=C). EI-MS: 321 (1), 273 (2), 82 (4), 58 (44), 42 (100). Anal. calc. for $C_{21}H_{23}NO_2$ (321.41): C 78.47, H 7.21, N 4.36; found: C 78.42, H 7.14, N 4.33.

N-*Cyclohexyl-2,5-bis(4-methylphenyl)-1,3-dioxol-4-amine* (**3b**): Yield 0.328 g (94%). Yellow solid. M.p. 164–166°. IR: 3444, 3292, 2928, 1728, 1658, 1256, 1107. ^{1}H-NMR: 1.09–1.98 (*m*, 10 H of Cy); 2.34, 2.42 (2 *s*, 2 Me); 3.78–3.88 (*m*, CH–N); 6.03 (*d*, ^3J = 7.5, NH); 6.26 (*s*, CH); 7.18 (*d*, ^3J = 7.8, 2 arom. H); 7.27 (*d*, ^3J = 7.8, 2 arom. H); 7.40 (*d*, ^3J = 8.1, 2 arom. H); 7.97 (*d*, ^3J = 8.1, 2 arom. H). ^{13}C-NMR: 21.13, 21.63 (2 Me); 24.63, 24.67, 25.34, 32.67, 32.79 (Cy); 48.10 (CH–N); 75.55 (CH); 126.59 (arom. C); 127.27, 129.21, 129.27, 129.71 (arom. C); 132.95, 138.58, 144.26 (arom. C); 165.07, 167.58 (C=C). EI-MS: 349 (0.6), 315 (1), 240 (10), 119 (100), 104 (19), 91 (27), 58 (23), 42 (65). Anal. calc. for $C_{23}H_{27}NO_2$ (349.47): C 79.07, H 7.79, N 4.01; found: C 79.11, H 7.76, N 4.08.

2,5-Bis(4-chlorophenyl)-N-*cyclohexyl-1,3-dioxol-4-amine* (**3c**): Yield 0.358 g (92%). White solid. M.p. 199–201°. IR: 3446, 3279, 2930, 2358, 1732, 1657, 1253, 1100. ^{1}H-NMR: 1.10–1.98 (*m*, 10 H of Cy); 3.76–3.85 (*m*, CH–N); 5.95 (*d*, ^3J = 8.1, NH); 6.22 (*s*, CH); 7.36 (*d*, ^3J = 8.4, 2 arom. H); 7.47–7.53 (2*d*, ^3J = 8.2, 4 arom. H); 8.10 (*d*, ^3J = 8.4, 2 arom. H). ^{13}C-NMR: 24.67, 24.70, 25.39, 32.86, 32.96 (Cy); 48.40 (CH–N); 75.39 (CH); 128.85, 129.06, 129.10, 131.14 (arom. C); 129.48, 134.03, 135.13, 140.36 (arom. C), 164.11, 166.69 (C=C). EI-MS: 390 (0.9), 363 (1), 273 (2), 139 (100), 111 (46), 57 (34), 42 (52). Anal. calc. for $C_{21}H_{21}Cl_2NO_2$ (390.30): C 64.62, H 5.42, N 3.59; found: C 64.55, H 5.34, N 3.62.

N-*Cyclohexyl-2,5-bis(2,6-dichlorophenyl)-1,3-dioxol-4-amine* (**3d**): Yield 0.390 g (85%). Pale orange paste. IR: 3430, 2931, 2854, 1650, 1529, 1489, 1090. ^{1}H-NMR: 1.11–1.97 (*m*, 10 H of Cy); 3.76–3.86 (*m*, CH–N); 5.91 (*d*, ^3J = 7.4, NH); 6.22 (*s*, CH); 7.38 (2*t*, ^3J = 7.6, 2 arom. H); 7.46 (*d*, ^3J = 7.6, 2 arom. H); 8.02 (*d*, ^3J = 7.2, 2 arom. H). ^{13}C-NMR: 24.66, 24.70, 25.39, 32.87, 32.95 (Cy); 48.49 (CH–N); 76.59 (CH); 128.85, 129.07, 129.11, 131.14 (arom. C); 129.42, 130.08, 130.45, 140.35 (arom. C); 164.11, 166.69 (C=C). EI-MS: 459 (3), 370 (11), 281 (6), 212 (30), 185 (38), 105 (100), 83 (33), 57 (70). Anal. calc. for $C_{21}H_{19}Cl_4NO_2$ (459.19): C 54.93, H 4.17, N 3.05; found: C 54.85, H 4.27, N 3.12.

2,5-Bis(4-bromophenyl)-N-*cyclohexyl-1,3-dioxol-4-amine* (**3e**): Yield 0.440 g (92%). Yellow oil. IR: 3449, 3268, 2932, 2354, 1731, 1659, 1249, 1123. ^{1}H-NMR: 1.08–1.95 (*m*, 10 H of Cy); 3.75–3.85 (*m*, CH–N); 5.93 (*d*, ^3J = 7.2, NH); 6.20 (*s*, CH); 7.39 (*d*, ^3J = 8.4, 2 arom. H); 7.52 (*d*, ^3J = 8.4, 2 arom. H); 7.63 (*d*, ^3J = 6.8, 2 arom. H); 7.93 (*d*, ^3J = 6.8, 2 arom. H). ^{13}C-NMR: 24.67, 24.71, 25.39, 32.86, 32.95 (Cy); 48.40 (CH–N); 75.45 (CH); 123.34, 127.97 (arom. C); 129.12, 131.24, 132.02, 132.10 (arom. C); 132.46, 134.51 (arom. C); 164.25, 166.59 (C=C). EI-MS: 479 (1), 370 (14), 316 (4), 199 (8), 183 (66), 97 (34), 83 (50), 71 (53), 57 (100). Anal. calc. for $C_{21}H_{21}Br_2NO_2$ (479.20): C 52.63, H 4.42, N 2.29; found: C 52.55, H 4.48, N 2.36.

N-*(*tert-*Butyl)-2,5-diphenyl-1,3-dioxol-4-amine* (**3f**): Yield 0.266 g (90%). Yellow solid. M.p. 144–145°. IR: 3435, 3290, 1724, 1655, 1555, 1450, 1263, 1113. ^{1}H-NMR: 1.37 (*s*, *Me*$_3$C); 6.02 (br. *s*, NH); 6.23 (*s*, CH); 7.35–7.63 (*m*, 8 arom. H); 8.08 (*d*, ^3J = 8.1, 2 arom. H). ^{13}C-NMR: 28.71 (*Me*$_3$C); 51.61 (Me$_3$*C*); 76.06 (CH); 127.45, 128.65, 128.78, 128.91, 129.76 (8 arom. C); 129.39, 135.96 (2 arom. C); 133.60 (2 arom. C); 164.90, 167.38 (C=C). EI-MS: 295 (0.8), 212 (34), 190 (8), 162 (9), 105 (100), 77 (28), 57 (18). Anal. calc. for $C_{19}H_{21}NO_2$ (295.38): C 77.26, H 7.17, N 4.74; found: C 77.29, H 7.18, N 4.71.

N-*(*tert-*Butyl)-2,5-bis(4-chlorophenyl)-1,3-dioxol-4-amine* (**3g**): Yield 0.345 g (95%). White solid. M.p. 148–150°. IR: 3450, 3291, 1725, 1656, 1555, 1258, 1103. ^{1}H-NMR: 1.36 (*s*, *Me*$_3$C); 5.89 (br. *s*, NH); 6.14 (*s*, CH); 7.30 (*d*, ^3J = 8.2, 2 arom. H); 7.82 (*d*, ^3J = 8.2, 2 arom. H); 7.83 (*d*, ^3J = 8.4, 2 arom. H); 8.00 (*d*, ^3J = 8.4, 2 arom. H). ^{13}C-NMR: 28.76 (*Me*$_3$C); 51.80 (Me$_3$*C*); 75.71 (CH); 128.86, 129.07, 129.38, 131.11 (8 arom. C); 127.60, 134.20, 135.08, 140.32 (4 arom. C); 164.09, 166.72 (C=C). EI-MS: 307 (1), 280 (12), 141 (45), 139 (100), 11 (16), 57 (40). Anal. calc. for $C_{19}H_{19}Cl_2NO_2$ (364.27): C 62.65, H 5.26, N 3.85; found: C 62.64, H 5.32, N 3.83.

N-*(*tert-*Butyl)-2,5-bis(4-methylphenyl)-1,3-dioxol-4-amine* (**3h**): Yield 0.290 g (90%). Pale yellow solid. M.p. 127–128°. IR: 3480, 3291, 1720, 1656, 1555, 1113. ^{1}H-NMR: 1.36 (*s*, *Me*$_3$C); 2.34, 2.42 (2 Me); 6.00 (br. *s*, NH); 6.18 (*d*, ^3J = 7.8, 2 CH); 7.26 (*d*, ^3J = 7.8, 2 arom. H); 7.40 (*d*, ^3J = 7.8, 2 arom. H); 7.96 (*d*,

$^3J = 7.8$, 2 arom. H); 8.00 (*d*, $^3J = 8.4$, 2 arom. H).^{13}C-NMR: 21.21, 21.70 (2 Me); 28.71 (Me_3C); 51.50 (Me_3C); 75.81 (CH); 127.89, 127.41, 129.18, 129.31, 129.78 (arom. C); 126.74, 133.16, 138.70, 144.34 (arom. C); 164.95, 167.67 (C=C). EI-MS: 273 (0.7), 240 (22), 119 (100), 104 (15), 91 (18), 42 (20). Anal. calc. for $C_{21}H_{25}NO_2$ (323.43): C 77.98, H 7.79, N 4.33; found: C 78.06, H 7.82, N 4.31.

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Received February 2, 2011