Functionalized 1,2-Dioxetanes as Potential Chemotherapeutic Agents: The Synthesis of Dioxetane-Substituted Carbamates

Waldemar ADAM*, Vidya BHUSHAN**, Thomas DIRNBERGER***, Rainer FUCHS****

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-8700 Würzburg, Federal Republic of Germany

Despite their labile nature[1], 1,2-dioxetanes can be chemically transformed under mild conditions thereby permitting chemical functionalization of these biologically potentially useful substances. For example, it was possible to show[2] that the hydroxydioxetane **1**[3] can be converted in high yields into carboxylic esters using such gentle methods as the Brewster-Ciotti and Mitsunobu esterifications. In these cases, the nucleophilic hydroxy group of the dioxetane can be conveniently derivatized with electrophilic biomolecules, e.g. fatty acids. A broader scope would be achieved, if nucleophilic biomolecules could be attached to dioxetanes. In this manner dioxetane-substituted sugars, steroids, pyrimidine bases, peptides, etc. could be made available as potential chemotherapeutic agents.

In principle two synthetic approaches can be pursued to accomplish such derivatization. In the case of amines, the carbamate linkage is a logical choice to bind such nucleophiles to the nucleophilic hydroxydioxetane **1**. Either the nucleophilic hydroxydioxetane **1** is transformed into the electrophilic carbonochloridate **2** and subsequently converted to the carbamates **3** (Scheme), or the nucleophilic amine is transformed into the electrophilic isocyanate and subsequently treated with the hydroxydioxetane **1**. Presently we report that both synthetic sequences are feasible for derivatizing the hydroxydioxetane **1**, leading to the carbamates **3** in good yields. The results are summarized in the Table.

Table. Yields, Physical Constants, and Spectral Data on the Carbamates **3**

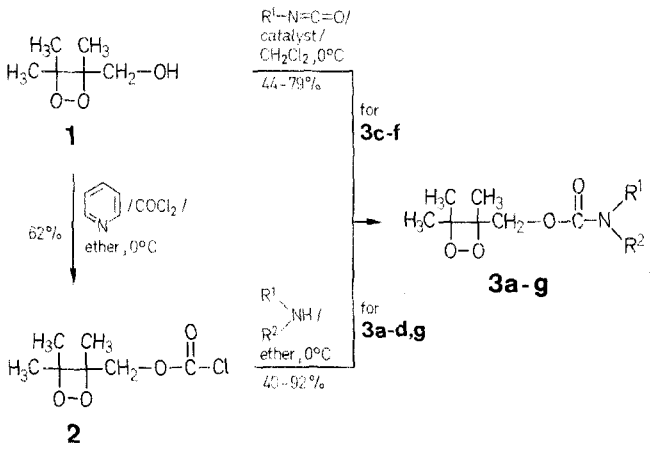
Product	Method[a]	Time [h]	Yields[b] [%]	m.p. [°C] (Solvent)	Molecular Formula[c]	M.S. (70 eV) *m/e* (rel. intens. %)	I.R. ($CDCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. (90 MHz; $CDCl_3$) δ [ppm]	^{13}C-N.M.R. (100.6 MHz; $CDCl_3$) δ [ppm]
3a	B	0.6	40	84–85° (dec.) (pentane/ether)	$C_7H_{13}NO_4$ (175.2)	143 (M^+-O_2, 0.2), 117 (M^+-acetone, 4), 43 ($C_2H_5O^+$, 100)	3555, 3438, 3002, 2980, 2940, 1740, 1585, 1395, 1384, 1375, 1337, 1150, 1105, 1075	1.43 (s, 6H, CH_3); 1.62 (s, 3H, CH_3); AB-pattern ($\delta_A = 4.64$, $\delta_B = 4.50$, $J = 11.7$ Hz, OCH_2); 4.73–5.23 (br. s, 2H, NH_2)	17.55 (q, CH_3); 21.86 (q, CH_3); 23.86 (q, CH_3); 66.31 (t, CH_2O); 89.16 (s, C—OO)[d]; 156.86 (s, C=O)
3b	B	0.6	48	63–64° (pentane/ether)	$C_{12}H_{21}NO_4$ (243.3)	243 (M^+, 0.1), 211 (M^+-O_2, 2), 185 (M^+-acetone, 7), 43 ($C_2H_5O^+$, 100)	3010, 2980, 2940, 2860, 1755, 1470, 1425, 1374, 1350, 1280, 1265, 1235, 1145, 1085, 1025, 855 (in CCl_4)	1.48 (s, 6H, CH_3); 1.53–1.58 [m, 6H, $(CH_2)_3$]; 1.63 (s, 3H, CH_3); 3.36–3.58 (m, 4H, CH_2—N—CH_2); AB-pattern ($\delta_A = 4.48$, $\delta_B = 4.66$, $J = 11.7$ Hz; OCH_2)	17.91 (q, CH_3); 22.13 (q, CH_3); 23.89 (q, CH_3); 24.07 (t, CH_2); 25.29 (t, CH_2); 25.59 (t, CH_2); 44.67 (t, CH_2—N—CH_2)[a]; 66.62 (t, CH_2O); 89.05 (s, C—OO); 89.15 (s, C—OO); 154.56 (s, C=O)

Downloaded by: University of Liverpool. Copyrighted material.

3c	B A[e]	0.6 10	60 62	83–84° (pentane/ether)	$C_{13}H_{23}NO_4$ (257.3)	257 (M^+, 0.04), 225 (M^+-O_2, 0.4), 199 (M^+-acetone, 5), 43 ($C_2H_5O^+$, 100)	3440, 3000, 2950, 2875, 1740, 1510, 1450, 1380, 1325, 1260, 1160, 1065, 1055	0.83–2.17 (m, 10H, cyclohexyl); 1.43 (s, 6H, CH_3); 1.60 (s, 3H, CH_3); 3.20–3.66 (m, 1H, CH); AB-pattern (δ_A = 4.42, δ_B = 4.57, J = 11.7 Hz; OCH_2); 4.90–5.25 (m, 1H, NH)	17.67 (q, CH_3); 21.98 (q, CH_3); 23.80 (q, CH_3); 24.66 (t, CH_2); 25.17 (t, CH_2); 33.08 (t, CH_2); 49.78 (d, CH); 65.90 (t, CH_2O); 88.95 (s, C—OO); 89.10 (s, C—OO); 154.95 (s, C=O)
3d	B[f] A[g]	0.06 1	92 72	85–86° (pentane/CH_2Cl_2)	$C_{13}H_{17}NO_4$ (251.3)	251 (M^+, 0.4), 219 (M^+-O_2, 0.6), 193 (M^+-acetone, 18), 43 ($C_2H_5O^+$, 100)	3440, 3000, 2980, 1740, 1600, 1530, 1440, 1310, 1080, 1065, 1030, 910	1.45 (s, 6H, CH_3); 1.60 (s, 3H, CH_3); AB-pattern (δ_A = 4.64, δ_B = 4.56, J = 11.4 Hz; OCH_2); 6.86–7.77 (m, 5H, C_6H_5); 8.80 (br. s, 1H, NH)	17.57 (q, CH_3); 21.91 (q, CH_3); 23.86 (q, CH_3); 66.35 (t, CH_2O); 89.18 (s, C—OO)[d]; 118.29 (d); 123.38 (d); 128.91 (d); 137.36 (s); 152.86 (s, C=O)
3e	A[g]	0.75	70	93–94° (pentane/CH_2Cl_2)	$C_{13}H_{16}ClNO_4$ (286.7)	227 (M^+-acetone, 14), 154 ($C_7H_5ClNO^+$, 23), 153 ($C_7H_4ClNO^+$, 64), 43 ($C_2H_5O^+$, 100)	3440, 3000, 2980, 1740, 1590, 1515, 1495, 1400, 1305, 1150, 1090, 1065, 1010	1.48 (s, 6H, CH_3); 1.70 (s, 3H, CH_3); AB-pattern (δ_A = 4.60, δ_B = 4.72, J = 11.4 Hz; OCH_2); 7.10 (s, 1H, NH); AB-pattern (δ_A = 7.34, δ_B = 7.24, J = 8.0 Hz; C_6H_4)	17.69 (q, CH_3); 22.04 (q, CH_3); 24.02 (q, CH_3); 66.66 (t, CH_2O); 89.25 (s, C—OO)[d]; 119.61 (d); 128.36 (s); 128.99 (d); 135.99 (s); 152.75 (s, C=O)
3f	A[h] A[g]	70 2	44 62	98–99° (pentane/CH_2Cl_2)	$C_{13}H_{15}Cl_2NO_4$ (320.2)	261 (M^+-acetone, 0.3), 43 (100)	3440, 3010, 2980, 2930, 1757, 1590, 1525, 1450, 1413, 1376, 1240, 1205, 1078, 990, 940, 930, 845, (in CCl_4)	1.40 (s, 6H, CH_3); 1.58 (s, 3H, CH_3); AB-pattern (δ_A = 4.60, δ_B = 4.59, J = 12.0 Hz; OCH_2); 6.90–7.40 (m, 4H, NH and C_6H_3)	17.70 (q, CH_3); 22.07 (q, CH_3); 24.03 (q, CH_3); 66.96 (t, CH_2O); 89.19 (s, C—OO)[d]; 116.59 (d); 123.55 (d); 135.27 (s); 139.28 (s); 152.36 (s, C=O)
3g	B[i]	0.25	79	102–103° (pentane/CH_2Cl_2)	$C_{12}H_{16}N_2O_4$ (252.3)	194 (M^+-acetone, 5), 121 ($C_6N_5N_2O^+$, 8), 120 ($C_6H_4N_2O^+$, 5), 43 (100)	3420, 2980, 1750, 1590, 1515, 1495, 1415, 1375, 1335, 1070, 1060, 990	1.47 (s, 6H, CH_3); 1.62 (s, 3H, CH_3); AB-pattern (δ_A = 4.65, δ_B = 4.60, J = 12.0 Hz, OCH_2); AB-pattern (δ_A = 8.37, δ_B = 7.47, J = 6.0 Hz; 4-C_5H_4N); 10.10 (m, 1H, NH)[j]	18.09 (q, CH_3); 22.34 (q, CH_3); 24.19 (q, CH_3); 67.89 (t, CH_2O); 90.16 (s, C—OO)[d]; 113.92 (d); 149.88 (s); 150.55 (d); 154.58 (s; C=O)[j]

[a] A = isocyanate, B = carbonochloridate.
[b] Yield of isolated product; not optimized.
[c] The microanalysis for **3a–g** were in satisfactory agreement with the calculated values: C ±0.42, H ±0.27, N ±0.32; exceptions: **3a**: C −0.61; **3c**: C −0.54, H +0.63; **3f**: N −0.69.
[d] Presumably two signals.
[e] One equivalent of CF_3COOH was used as catalyst.
[f] One equivalent of pyridine was used as catalyst.
[g] One equivalent of DABCO was used as catalyst.
[h] No catalyst was used.
[i] 0.2 equivalents of *p-N,N*-dimethylaminopyridine were used as catalyst.
[j] DMSO/$CDCl_3$ used as solvent.

Downloaded by: University of Liverpool. Copyrighted material.



3	R¹	R²
a	H	H
b	—(CH2)5—	
c	c-C6H11	H
d		H
e	Cl	H
f	Cl, Cl	H
g	N	H

3-Chlorocarbonyloxymethyl-3,4,4-trimethyl-1,2-dioxetane (2):

CAUTION! Use an efficiently ventilated hood and carry gas-mask.

A 100-ml, round-bottomed flask, provided with a magnetic spinbar, a 50-ml dropping funnel with drying tube (silica gel), is charged with a solution of phosgene (0.989 g, 10.0 mmol) in anhydrous ether (24 ml). While cooling to ~ 0 °C by means of an ice bath and stirring magnetically is added dropwise over a period of ~ 30 min a solution of 3-hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane **1**; (745 mg, 5.64 mmol) and pyridine (367 mg, 5.64 mmol) in absolute ether (50 ml). After an additional 10 min stirring, the pale yellow reaction mixture is washed with 5 normal hydrochloric acid (15 ml) and with saturated brine (15 ml), dried with magnesium sulfate and the solvent roto-evaporated at 0 °C and 19 torr *(CAUTION: Excess phosgene!)*. The yellow oil (878 mg, 80%) is taken up in dichloromethane (3 ml) and flash-chromatographed over silica gel (5 g; 32–64 μm). The combined peroxidic fractions result in 681 mg (62%) yellowish oil after roto-evaporation of the solvent at 0 °C and 19 torr, peroxide titer (by iodometry) was > 92%. An analytical sample is obtained by additional chromatography as described above.

I.R. (CCl_4): ν = 3000, 2970, 2920, 1780, 1465, 1460, 1440, 1380, 1290, 1140, 960, 875, 845, 680 cm^{-1}.

^{1}H-N.M.R. (90 MHz; $CDCl_3$): δ = 1.43 (s, 3 H, CH_3); 1.47 (s, 3 H, CH_3); 1.66 (s, 3 H, CH_3); AB-pattern (δ_A = 4.84, δ_B = 4.74 ppm, J = 11.4 Hz; OCH_2).

^{13}C-N.M.R. (100.6 MHz; $CDCl_3$): δ = 17.64 (q, CH_3); 21.98 (q, CH_3); 23.87 (q, CH_3); 72.42 (t, CH_2O); 88.28 (s, C—OO); 89.07 (s, C—OO); 150.67 ppm (s, C=O).

MS (70 eV): m/e = 135.9 (M^+-acetone, 0.8); 43 (100%).

Carbamates 3:

Method A: Reaction of carbonochloridate **2** with amines: A 50-ml round-bottomed flask, provided with a magnetic spinbar and dropping funnel, is charged with carbonochloridate **2** (357 mg, 1.83 mmol) in anhydrous ether (30 ml) and cooled to 0 °C by means of an ice bath. Within ~ 30 min a solution of the corresponding amine (1.83 mmol) in anhydrous ether (10 ml) is added dropwise with vigorous magnetic stirring and cooling at 0 °C. After complete addition the reaction mixture is stirred for additional time (cf. Table for details), 2 normal hydrochloric acid (5 ml) is added, the organic layer separated, and washed with saturated aqueous sodium hydrogen carbonate (1 ml) and with water (5 ml). After drying with magnesium sulfate, the solvent is roto-evaporated at 0 °C and 19 torr and the residue flash-chromatographed on silica gel (32–64 μm) at −25 °C. Subsequent recrystallization at low temperature (~ −30 °C) gives the pure carbamate **3** (cf. Table for details). Iodometric titration gives > 97% peroxide content.

Method B: Reaction of isocyanates with hydroxydioxetane **1**: A 50-ml, round-bottomed flask, provided with a magnetic spinbar and dropping funnel, is charged with the isocyanate (1.5 mmol) in dry dichloromethane (5 ml) containing either DABCO (112 mg, 1.0 mmol) or trifluoroacetic acid (114 mg, 1.0 mmol) as catalyst. The solution is cooled to 0 °C by means of an ice bath and a solution of the hydroxydioxetane **1** (92 mg, 0.7 mmol) in dichloromethane (2 ml) is added dropwise while stirring vigorously magnetically and cooling at 0 °C. Reaction progress is monitored by T.L.C. (silica gel / dichloromethane). After completion of the reaction, the mixture is diluted with dichloromethane (20 ml), the organic phase is separated and washed with water (15 ml), the aqueous phase extracted with dichloromethane (2 × 20 ml), and the combined organic phases are washed with water (20 ml); in the case of trifluoroacetic acid as catalyst 5% aqueous sodium hydrogen carbonate (20 ml) followed by saturated brine (20 ml) are used as wash. The organic layer is dried with magnesium sulfate and the solvent roto-evaporated (< 0 °C at 15 torr). The crude product is purified by flash chromatography over silica gel (32–64 μm) at −35 °C, using 1:9 ether/dichloromethane as eluant. The crude product is recrystallized from dichloromethane/petroleum ether (30–50 °C) at −20 °C.

Acknowledgements are made to the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich no. 172 "Molekulare Mechanismen kanzerogener Primärveränderungen"), the Stiftung Volkswagenwerk, the Alexander von Humboldt Stiftung, and the Fonds der Chemischen Industrie. For helpful discussions with Professor G. Cilento (São Paulo) we are especially thankful.

Received: August 9, 1985

* Address for correspondence.
** Alexander von Humboldt postdoctoral fellow, 1984–1985.
*** Undergraduate research participant, spring 1985.
**** Doctoral research assistant in the Sonderforschungsbereich No. 172, sponsored by the Deutsche Forschungsgemeinschaft, 1985–1986.

[1] Adam, W., Cilento, G., Eds. *Chemical and Biological Generation of Excited States*, Academic Press, New York, 1982.
[2] Adam, W., Babatsikos, C., Cilento, G. *Z. Naturforsch. Teil B* **1984**, 39, 679.
[3] Leclerq, D., Bats, J.-P., Picard, P., Moulines, J. *Synthesis* **1982**, 778.

Downloaded by: University of Liverpool. Copyrighted material.