$J$ = 2.4 Hz), 7.22 (s, 1 H, Ph proton), 10.74 (s, 1 H, CHO); $^{13}$C-NMR ($CDCl_3$) $\delta$ 17.2, 17.3, 20.6, 23.2 ($CH_3$), 131.7, 132.1, 134.3, 134.5, 141.9, 143.8, 145.9 (Ph carbons), 192.7 (CHO); mass $M^+$ = 230; mp 22-23 °C. Anal. Found (calcd): H = 4.76 (4.81); C = 51.80 (52.16).

**11**: IR (KBr) 1680 (CO), 1380, 1195 ($SO_2F$) cm$^{-1}$; $^1$H-NMR ($CDCl_3$) $\delta$ 1.7–2.1 (m, 4 H, $CH_2$), 2.8–3.4 (m, 4 H, $CH_2$), 7.95 (s, 1 H, Ph proton), 8.37 (s, 1 H, Ph proton), 10.05 (s, 1 H, CHO); $^{13}$C-NMR ($CDCl_3$) $\delta$ 21.6, 21.9, 27.2, 30.1 ($CH_2$), 129.1, 129.3, 130.0, 133.8, 136.2, 142.0, 144.6 (Ph carbons), 189.7 (CHO); mass $M^+$ = 242; mp 64–66 °C. Anal. Found (calcd): H = 4.55 (4.58); C = 54.21 (54.53).

**Registry No.** 1 (R = Me), 104-87-0; **3**, 15764-16-6; **4**, 128203-58-7; **5**, 445-15-8; **6**, 5184-75-8; **7**, 139650-04-7; **8**, 139689-26-2; **9**, 139650-06-9; **10**, 139650-07-0; **11**, 139689-27-3; toluene, 108-88-3; *o*-xylene, 95-47-6; *m*-xylene, 108-38-3; *p*-xylene, 106-42-3; mesitylene, 108-67-8; tetralin, 119-64-2; antimony pentafluoride, 7783-70-2; 3,4-dimethylbenzaldehyde, 5973-71-7; 2,5-dimethylbenzaldehyde, 5779-94-2; 2,4,6-trimethylbenzaldehyde, 487-68-3; 6-formyltetralin, 51529-97-6; benzene, 71-43-2; indan, 496-11-7; fluorobenzene, 462-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; benzaldehyde, 100-52-7; 5-formylindan, 30084-91-4; 4-formylindan, 51932-70-8; 5-formyltetralin, 41828-13-1; *p*-fluorobenzaldehyde, 459-57-4; *o*-fluorobenzaldehyde, 446-52-6; *p*-chlorobenzaldehyde, 104-88-1; *o*-chlorobenzaldehyde, 89-98-5; *p*-bromobenzaldehyde, 1122-91-4; *o*-bromobenzaldehyde, 6630-33-7; *o*-tolualdehyde, 529-20-4; 2,3-dimethylbenzaldehyde, 5779-93-1; 2,4,5-trimethylbenzaldehyde, 5779-72-6; 2,6-dimethylbenzenesulfonyl fluoride, 61153-14-8; 2,2′,4,6′-tetramethyldiphenyl sulfone, 139689-28-4; 3-formyl-4-methylbenzenesulfonyl fluoride, 139689-29-5; 5-formyl-2,4-dimethylbenzenesulfonyl fluoride, 128203-58-7; 7-(fluorosulfonyl)-5-formyltetralin, 139689-30-8; fluorosulfonic acid, 7789-21-1.

# α-Alkoxy Ketones from the Nucleophilic Substitution on the Peroxide Bond of 3,3-Disubstituted 1,2-Dioxetanes by Enamines

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The reaction of 1,2-dioxetanes with enamines as π-nucleophiles was investigated. 3,3-Dibenzyl-1,2-dioxetane (**1**) was allowed to react with enamines **2a–c** in methylene chloride to afford after hydrolysis the corresponding α-alkoxylated ketones **4a–c**. Additionally, the reaction of the dimedone-derived enamine **3** with dioxetane **1** yielded the oxidized enamine adduct **4**. Nucleophilic attack of the enamine β-carbon ($S_N2$ reactivity) on the sterically less hindered site of the dioxetane peroxide bond is proposed to constitute the initial step of the reaction.

The high thermal lability of 1,2-dioxetanes and their cumbersome synthesis are mainly responsible for the limited scope of chemical transformations of these highly reactive and biologically significant molecules.[1] Besides their thermolysis, which yields efficiently triplet-excited carbonyl products, only few reactions of these four-membered ring peroxides have been reported: reduction by lithium aluminum hydride,[2] mercaptans,[3] and biologically relevant reductands,[4] biphilic insertion reactions of phosphines,[5] arsines, and stibines,[6] and the deoxygenation by sulfides[7] and sulfoxylates.[7b]

Recently, we observed the novel $S_N2$-type reactivity of 3,3-disubstituted dioxetanes with π-nucleophiles[8] such as alkenes and enol ethers, with carbanions[9] and with heteroatom nucleophiles,[10] e.g., amines, sulfides and cyanide, thiocyanate, halide, and even hydroxide ions. To extend the $S_N2$ chemistry of electrophilic 3,3-disubstituted dioxetanes, it was of interest to explore their reaction with enamines. These ambident π-nucleophiles should react at their β-carbon to produce after hydrolysis β-keto β′-hydroxy ethers.

## Results and Discussion

The readily available 3,3-dibenzyl-1,2-dioxetane[9,11] **1** was chosen for the $S_N2$ reactions with the three morpholino- and piperidino-substituted enamines **2a–c**. The transformations of **1** with **2** were performed in methylene chloride at low temperature (−20 to 0 °C). The primary reaction products were not isolated but hydrolyzed in situ under acidic conditions. The corresponding β-keto β′-

**Table I. Reaction of Dioxetane 1 with Enamines 2[a]**

| enamine | $T$ (°C) | time (h) | yield[b] (%) adduct[c] | yield[b] (%) ketone[d] |
|---|---|---|---|---|
| **2a** | −20 | 2 | 64 (**4a**) | 11 |
| **2b** | 0 | 3 | 38 (**4b**) | 30 |
| **2c** | −20 | 0.5 | 67 (**4c**) | 6 |

[a] In methylene chloride, up to 10% excess of enamine. [b] Isolated yields of pure products after hydrolysis, column chromatography, and recrystallization. [c] The type of adduct is specified in parentheses. [d] 1,3-Diphenylacetone, isolated together with the ketone derived from enamine hydrolysis.

† Undergraduate research participant, spring 1991.
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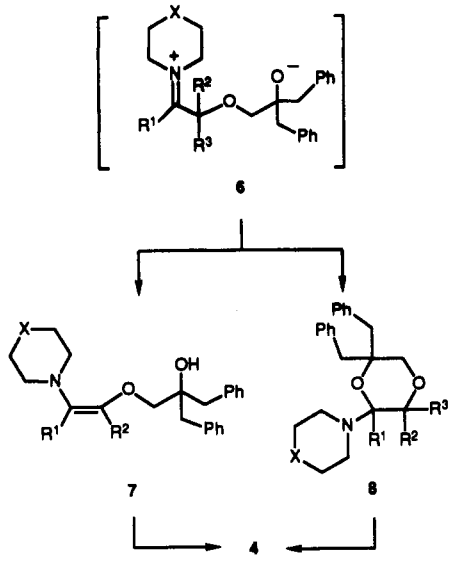
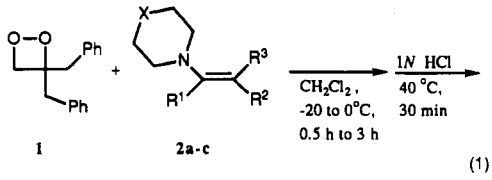
0022-3263/92/1957-2680$03.00/0 

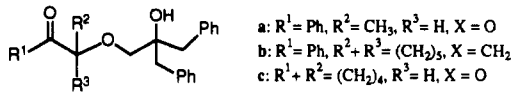
**Scheme I**



hydroxy ethers **4** were isolated in satisfactory yields by column chromatography and were fully characterized (eq 1). As a side product, the dioxetane cleavage product



(1)



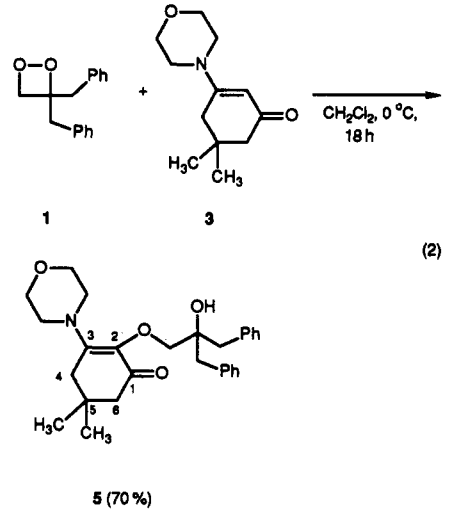
1,3-diphenylacetone was obtained (Table I). Thus, (*Z*)-1-(*N*-morpholino)-1-phenyl-1-propene (**2a**) afforded 79% of the adduct **4a** within 2 h, together with 11% of the cleavage ketone. For the more bulky piperidino-substituted enamine **2b**, the temperature had to be raised to 0 °C and after 3 h, 49% of the adduct **4b** and as much as 30% cleavage ketone were isolated. In contrast, a very fast reaction occurred with enamine **2c** at −20 °C to yield within 0.5 h 79% of adduct **4c** and only 6% cleavage ketone.

The same regiochemistry was observed for all adducts **4**; i.e., exclusively the regioisomer from attack of the enamine at the sterically less hindered oxygen atom of the dioxetane was produced, which is consistent with the traditional $S_N2$ reactivity. The structural assignment of adducts **4** rests on their characteristic $^1H$ and $^{13}C$ resonances, which matched those of similar compounds, derived from the reaction of dioxetane **1** with related nucleophiles.[9]

In the present reactions of the dioxetane **1** with the ambident enamines **2**, exclusively C-oxidation is preferred; no N-oxidized products were detected. A precedent for this reaction pathway is the formation of $\alpha$-acyloxy ketones when diacyl peroxides were allowed to react with enamines and subsequent hydrolysis.[12]

For the reaction of the dioxetanes **1** with enamines **2** we propose, analogous to electron-rich olefins[8] and heteroatom nucleophiles,[10] a $S_N2$ mechanism with the 1,7-dipole **6** as the primary adduct (Scheme I). In the case of the enamines **2a,c** this intermediate may abstract a proton to yield the oxidized enamine **7** or undergo ring closure to give the cyclic adduct **8**, both of which on in situ hydrolysis are converted to the $\alpha$-alkoxy ketones **4**. No efforts were made to isolate and characterize these labile primary adducts **7** and **8**. Alternatively, the primary dipolar intermediate may also fragment to the enamine and to carbonyl products (Grob fragmentation[13]), which would explain the formation of the dioxetane cleavage product, namely 1,3-diphenylacetone.

The isolation of a stable, primary dioxetane–enamine adduct was achieved in the reaction of **1** with the dimedone-derived enamine **3**, which yielded 70% of the oxidized enamine adduct **5** (eq 2). Adduct **5** was characterized on



(2)

the basis of its $^{13}C$ NMR data, which exhibited singlets at $\delta$ 134.6 and $\delta$ 152.0 for the N- and O-substituted carbon atoms of the double bond. Furthermore $^1H$ NMR, IR, and MS data and elemental analysis are in support of the proposed structure. An analogous adduct was reported[14] for the reaction of benzoyl peroxide with cyclic acyl enamines such as **3**.

To summarize, the reaction of dioxetane **1** with enamines constitutes a novel transformation for 3,3-disubstituted dioxetanes, which provides a convenient one-step synthesis of $\beta$-keto $\beta'$-hydroxy ethers. Nucleophilic attack of the enamine $\beta$-carbon ($S_N2$ mechanism) on the exposed oxygen atom of the dioxetane peroxide affords, after hydrolysis of the resulting dipolar intermediate, regioselectively the final $\alpha$-alkoxy ketone product.

## Experimental Section

**General Aspects.** For analytical instruments and spectral calibrations cf. ref 15a. Column chromatography: silica gel (63–200 $\mu$m) from Woelm as stationary phase with an absorbance/substrate ratio of about 80:1. Enamines **2a,b**,[15b] **2c**,[16] **3**[17] were prepared according to literature procedures. A convenient

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synthesis for dioxetane 1 was recently published by us.[9]

**General Procedure for the Reaction of Dioxetane 1 with Enamines 2.** The dioxetane 1 (0.8–1.0 mmol) in 10 mL of methylene chloride was cooled to −20 °C under argon gas atmosphere, and equimolar amounts of enamines **2** in 2 mL of $CH_2Cl_2$ were added. Depending on the reactivity of the enamine, the solution was eventually allowed to warm to 0 °C. After complete conversion of the dioxetane (negative KI test), 20 mL of 1 M HCl were added and the reaction mixture was warmed to 40–50 °C for 30 min under vigorous stirring. The phases were separated, and the aqueous layer was extracted with methylene chloride (3 × 20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (1 × 20 mL). Drying over $MgSO_4$ was followed by evaporation of the solvent at 20 °C (15 Torr). The products were separated and purified by column chromatography.

**Enamine 2a.** According to the general procedure, dioxetane 1 (200 mg, 0.833 mmol) was mixed with enamine **2a** (175 mg, 0.861 mmol) at −20 °C, and the reaction mixture was allowed to warm to 0 °C within 2 h. Hydrolysis and chromatography ($CH_2Cl_2$ as eluent) afforded first 44 mg of a mixture of 1,3-diphenylacetone (11%) and propiophenone (22%). As a second fraction, there was obtained 246 mg (79%) of **4a** as a colorless oil, which crystallized on treatment with petroleum ether (bp 30–50 °C) to give 199 mg (64%) colorless needles, mp 74–75 °C.

**2-(2′-Benzyl-2′-hydroxy-3′-phenylprop-1′-oxy)-1-phenyl-1-propanone (4a):** TLC ($CH_2Cl_2$) $R_f$ = 0.13; $^1$H NMR ($CDCl_3$) $\delta$ 1.51 (d, $J$ = 6.9 Hz, $CH_3$), 2.15 (br s, OH), AB pattern ($\delta_A$ = 2.82, $\delta_B$ = 2.89, $J$ = 13.7 Hz, 2 H, $CH_2Ph$), AB pattern ($\delta_A$ = 2.84, $\delta_B$ = 2.92, $J$ = 13.7 Hz, 2 H, $CH_2Ph$), AB pattern ($\delta_A$ = 3.16, $\delta_B$ = 3.19, $J$ = 12.3 Hz, 2 H, $CH_2O$), 4.68 (q, $J$ = 6.9 Hz, 1 H, CH), 7.20 (m, 10 H, arom H), 7.50 (m, 3 H, arom H), 7.95 (m, 2 H, arom H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.7 (q, $CH_3$), 43.3 and 43.7 (t, $CH_2Ph$), 73.3 (t, $CH_2O$), 73.9 (s), 78.6 (d, CH), 126.4 (d), 128.2 (d), 128.7 (d), 130.7 (d), 133.4 (d), 134.0 (d), 134.8 (s), 137.0 (s), 200.2 (s, C=O); IR (KBr) 3460, 3060, 3020, 2920, 1675, 1590, 1490, 1440, 1400, 1220 cm$^{-1}$. Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 79.90; H, 7.04.

**Enamine 2b.** Following the above procedure, dioxetane 1 (300 mg, 1.38 mmol) was allowed to react with enamine **2b** (352 mg, 1.38 mmol) at 0 °C for 3 h. Hydrolysis and chromatography ($CH_2Cl_2$ as eluent) gave as a first fraction 118 mg of a mixture of 1,3-diphenylacetone (30%) and phenylcyclohexyl ketone (22%). The second fraction afforded 260 mg (49%) of **4b** as a colorless oil, which was crystallized from petroleum ether (bp 30–50 °C)/$CH_2Cl_2$ to yield 202 mg (38%) of colorless plates, mp 106–108 °C.

**2-(2′-Benzyl-2′-hydroxy-3′-phenylprop-1′-oxy)-2,2-pentamethylene-1-phenyl-1-ethanone (4b):** TLC ($CH_2Cl_2$) $R_f$ = 0.52; $^1$H NMR ($CDCl_3$) $\delta$ 1.20–2.00 (m, 11 H, cyclohexyl-H and OH), AB pattern ($\delta_A$ = 2.65, $\delta_B$ = 2.75, $J$ = 13.6 Hz, 4 H, $CH_2Ph$), 3.01 (s, 2 H, $CH_2O$), 7.05–7.45 (m, 13 H, arom H), 7.95 (m, 2 H, arom H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.7, 25.3, 32.7 (all t, cyclohexyl-C), 43.6 (t, $CH_2Ph$), 68.1 (t, $CH_2O$), 73.8 (s, COH), 83.9 (s, $C$ C(O)Ph), 126.4 (d), 138.0 (d), 128.3 (d), 129.3 (d), 130.6 (d), 132.5 (d), 135.8 (s), 137.0 (s), 203.8 (s, C=O); IR (KBr) 3530, 3020, 2940, 2860, 1670, 1595, 1490, 1210, 1080. Anal. Calcd for $C_{29}H_{32}O_3$: C, 81.27; H, 7.52. Found: C, 81.46; H, 7.57.

**Enamine 2c.** According to the above procedure, dioxetane 1 (200 mg, 0.833 mmol) was allowed to react with enamine **2c** (146 mg, 0.875 mmol) at −20 °C for 30 min. Hydrolysis and chromatography ($CH_2Cl_2$ followed by 5:1 $CH_2Cl_2$/ethyl acetate as eluent) gave first 11.0 mg (6%) of 1,3-diphenylacetone. As second fraction, 223 mg (79%) of **4c** was obtained as a colorless solid, which was recrystallized from petroleum ether (bp 30–50 °C)/$CH_2Cl_2$ to afford 189 mg (67%) colorless needles, mp 110–112 °C.

**2-(2′-Benzyl-2′-hydroxy-3′-phenylprop-1′-oxy)-1-cyclohexanone (4c):** TLC (5:1 $CH_2Cl_2$/ethyl acetate) $R_f$ = 0.38; $^1$H NMR ($CDCl_3$) $\delta$ 1.70, 1.98, 2.28 and 2.50 (all m, 8 H, cyclohexyl-H), 2.85 (s, 1 H, OH), AB pattern ($\delta_A$ = 2.90, $\delta_B$ = 2.96, $J$ = 10.5 Hz, 4 H, $CH_2Ph$), AB pattern ($\delta_A$ = 3.17, $\delta_B$ = 3.24, $J$ = 9.20 H, 2 H, $CH_2O$), 3.75 (dd, $J$ = 9.3, 5.7, Hz, 1 H, CH), 7.26 (m, 10 H, arom. H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.4, 27.4 and 34.6 (all t, cyclohexyl-C), 40.7 (t, $CH_2$C=O), 43.3 and 43.8 (t, $CH_2Ph$), 74.0 (t, $CH_2O$), 75.6 (s), 83.5 (d, CH), 126.3 (d), 126.4 (d), 128.0 (d), 128.0 (d), 130.7 (d), 130.7 (d), 137.2 (s), 1374 (s), 210.1 (s, C=O); IR (KBr) 3520–3480, 3110, 3090, 3060, 2970, 2950, 2880, 1720, 1610, 1590 cm$^{-1}$. Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.08; H, 7.74. Found: C, 77.90; H, 8.08.

**Reaction of Dioxetane 1 with Enamine 3.** To a solution of dioxetane 1 (295 mg, 1.23 mmol) in 5 mL of $CH_2Cl_2$ was added the enamine **3** in 3 mL of $CH_2Cl_2$. The solution was allowed to warm to 0 °C and kept at this temperature for 18 h until the dioxetane was completely consumed (negative KI test). The solvent was evaporated at 20 °C (15 Torr) and the residue taken up to 10 mL of petroleum ether (bp 30–50 °C), whereby the product **5** precipitated. Recrystallization from ethyl acetate affoded 380 mg (70%) of adduct **5** as colorless needles, mp 143–145 °C.

**2-(2′-Benzyl-2′-hydroxy-3′-phenylprop-1′-oxy)-5,5-dimethyl-3-(*N*-morpholino)-1-cyclohexanone (5):** $^1$H NMR ($CDCl_3$) $\delta$ 1.01 (s, 6 H, $CH_3$), 2.20 (s, 2 H, 4-H), 2.25 (s, 2 H, 6-H), AB pattern ($\delta_A$ = 2.82, $\delta_B$ = 2.92, $J$ = 13.7 Hz, 4 H, $CH_2Ph$), 3.43 (s, 2 H, $CH_2O$), 3.50 (m, 4 H, $CH_2NCH_2$), 3.65 (m, 4 H, $CH_2OCH_2$), 6.00 (s, 1 H, OH), 7.25 (m, 10 H, arom H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.5 (q, $CH_3$), 31.8 (s, C-5), (t, C-6) 43.6 (t, $CH_2Ph$), 48.8 (t, $CH_2NCH_2$), 49.4 (t, C-4), 67.2 (t, $CH_2OCH_2$), 74.0 (s, COH), 79.6 (t, $CH_2O$), 126.0 (d), 127.8 (d), 130.7 (d), 134.6 (s, C-2), 137.9 (s), 152.0 (s, C-3), 192.4 (s, C-1); IR (KBr) 3300–3200, 3090, 3070, 3030, 2980, 2960, 2850, 1605, 1540, 1495, 1445; MS (70 eV) $m/z$ = 449 (1) [M$^+$], 225 (10), 209 (13), 166 (13), 96 (14), 91 (17), 61 (11), 55 (19), 45 (16), 43 (100). Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.11. Found: C, 74.94; H, 7.70; N, 3.12.

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**Registry No.** 1, 40814-69-5; **2a**, 66217-92-3; **2b**, 139608-40-5; **2c**, 670-80-4; **3**, 13297-58-0; **4a**, 139608-41-6; **4b**, 139608-42-7; **4c**, 139608-43-8; **5**, 139608-44-9; 1,3-diphenylacetone, 102-04-5.