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Reactions of Glycidyl Derivatives with Ambident Nucleophiles. Part 1: Ethyl Acetoacetate

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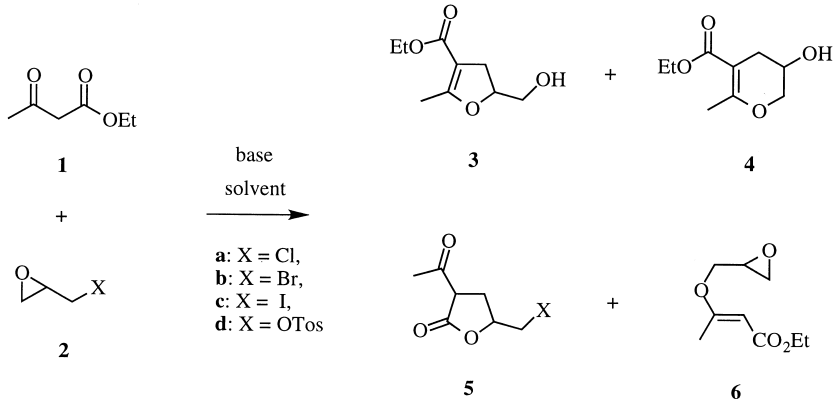
Abstract—The formation of functionalized furans and pyrans from the title reactants is analyzed with regard to the reaction conditions and to the nature of the leaving group.

Ethyl acetoacetate (**1**) as well as glycidyl derivatives **2** such as epichlorohydrin (**2a**)[1a] and glycidyl tosylate (**2d**)[1b] are important industrial chemicals available and regularly applied in bulk quantities. We were surprised to notice that exclusively a furanoid cyclization product of these compounds has been described in literature[2] and no pyranoid product, which we could isolate for the first time. Clearly, a thorough investigation of cyclization reactions of **1** with **2** is missing, a gap we wish to fill with this article.

1 and **2** are both multifunctionalized compounds, which have several opportunities for interaction: up to four nucleophilic and two electrophilic centers can be active in the case of **1**, in the case of **2** one can localize one nucleophilic and three electrophilic centers. Depending on the reaction conditions and especially on the leaving group X we could isolate and identify four types of products (Scheme 1). With epichlorohydrin (**2a**) exclusively lactone **5a** with the chloromethyl side chain was found (Table 1, entry 1: NaOEt as base in ethanol at 50°C), a product already known from an 'Organic Synthesis' procedure.[2] In contrast, applying epibromohydrin (**2b**), epiiodohydrin (**2c**) or glycidyl tosylate (**2d**) let to the formation of a mixture of dihydrofuran **3**[3] and tetrahydropyran **4** (Table 1, entries 2–4). Surprisingly, **4** has never been described before and became the main product when starting from tosylate **2d**. In the case of epibromohydrin (**2b**) changing the base from NaOEt to K_2CO_3 had a minor influence on the yield but no influence on the product ratio (entry 6), whereas the nature of the solvent influenced both yield and product ratio: in the case of the tosylate **2d** applied in DMF the O-alkylation product **6**[4] was identified as the main product.



Scheme 1. Types of products derived from reactions of ethyl acetoacetate (**1**) with glycidyl derivatives **2**.

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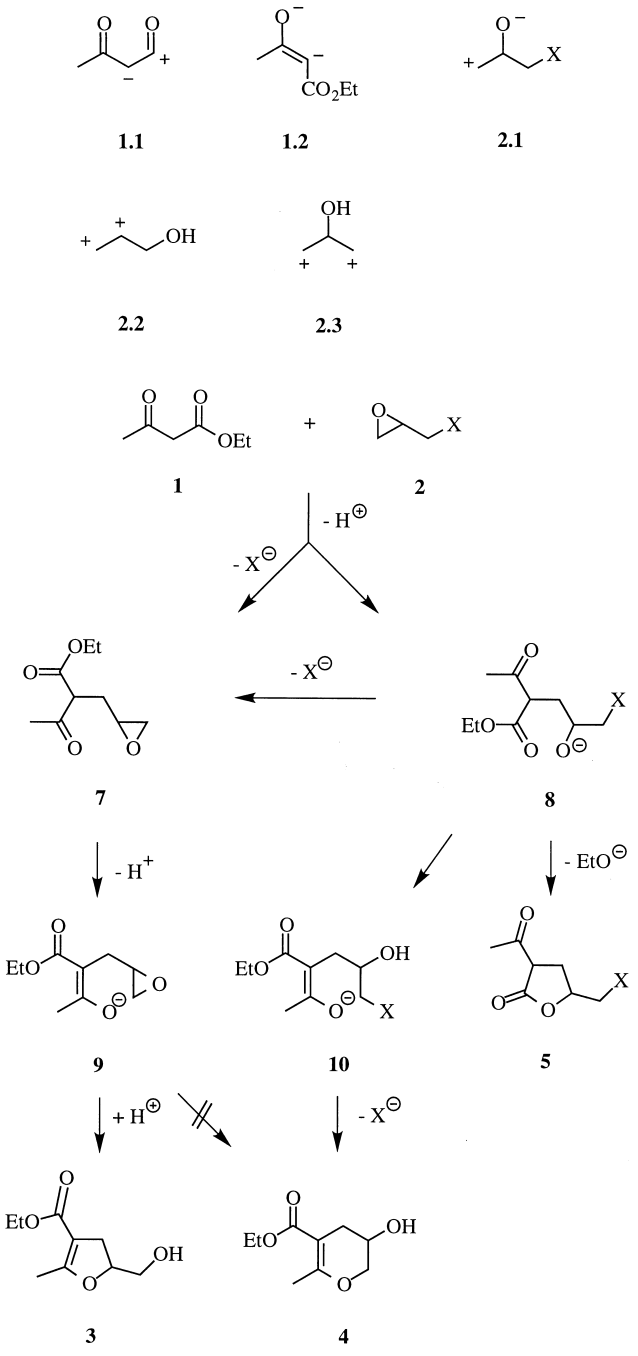
Table 1. Base induced coupling reactions of ethyl acetoacetate (**1**) with glycidyl derivatives **2** (the ratio of **3**:**4** was determined by ^{1}H NMR (500 MHz, $CDCl_3$) of the crude product; diagnostic signals: for **3**: δ=2.20 (t, J=1.6 Hz, 3H, vinyl-CH_3); for **4**: δ=2.26 (t, J=1.5 Hz, 3H, vinyl-CH_3); yield of the purified product after Kugelrohr distillation is given)

Entry	X	Solvent	Base	T [°C]	t [d]	Yield [%]: **3**+**4** (ratio)	**5**	**6**
1	Cl	EtOH	NaOEt	50	1	–	42	–
2	Br	EtOH	NaOEt	50	1	54 (64:36)	–	–
3	I	EtOH	NaOEt	50	1	43 (81:19)	–	–
4	OTos	EtOH	NaOEt	50	1	60 (25:75)	–	–
5	Br	DMF	Li_2CO_3	50	2	44 (100:0)	–	–
6	Br	EtOH	K_2CO_3	50	2	60 (63:37)	–	–
7	Br	DMF	K_2CO_3	50	2	19 (100:0)	–	–
8	Br	DMF	K_2CO_3	20	2	33 (100:0)	–	–
9	Br	DMF	Cs_2CO_3	50	2	13 (88:12)	–	–
10	OTos	DMF	K_2CO_3	20	1	4 (57:43)	–	30



Scheme 2. Mechanistic considerations for heterocyclizations of **1** with **2**.

Formally, the formation of the heterocycles **3**, **4** and **5** is easily understood by appropriate combinations of the synthons **1.1** and **1.2** corresponding to ethyl acetoacetate **1** with the synthons **2.1**, **2.2** and **2.3** corresponding to the glycidyl derivatives **2**; pyran **4** for instance derives from a combination of **1.1** with **2.3**. Obviously, these synthons are useful for classifying cyclization reactions of glycidyl derivatives **2** with various reagents.[5] A mechanistic interpretation, of course, requires a more detailed study: as expected, the O-alkylation product **6** did not cyclize under treatment with NaOEt in ethanol. Therefore it is clear that the formation of the heterocycles **3**, **4** and **5** starts with a C-alkylation, either by nucleophilic attack of the enolate of **1** at the C–X group of **2** directly leading to intermediate **7**, or by attack at the terminal epoxide to give **8**. This key intermediate has several opportunities to cyclize: 1. intramolecular nucleophilic substitution under epoxide formation is an alternative route to **7**; 2. lactone formation gives **5**; 3. enolate formation to **10** and subsequent 6-exo-tet-cyclization is the most feasible pathway to tetrahydropyran **4**. Since the quota of pyran formation is strongly influenced by the nature of the leaving group X, this leaving group should be present in the key intermediates leading to **4**. The structures **8** and **10** fulfil this requirement, but not **7**. Therefore only a minor portion of **4** if at all could be formed via **7**, and indeed, a sample of **7**,[6] independently synthesized by alkylation of **1** with allyl bromide and subsequent epoxidation with dimethyldioxirane, exclusively cyclized to **3** under various reaction conditions (in ethanol at 50°C and also in the presence of NaOEt) (Scheme 2).

In conclusion, we have proven that not only furanoid heterocycles but also the equally interesting tetrahydropyran moiety is accessible by simple cyclization reactions of ethyl acetoacetate **1** with glycidyl derivatives **2**.

Experimental

General

Mp (uncorrected): Reichert Thermovar. IR: Perkin–Elmer 983. UV: Perkin–Elmer 554. NMR: Bruker DRX 500; ^{1}H NMR spectra (500 MHz) were recorded in $CDCl_3$ (if not mentioned otherwise) with TMS as the internal standard. ^{13}C NMR spectra (126 MHz) were measured by using $CDCl_3$ as the solvent and the internal standard. MS: MAT 311A (70 eV). For analytical TLC precoated plastic sheets

'POLYGRAM SIL G/UV254' from 'Macherey-Nagel' were used. Epiiodohydrin (**2c**)[7] and glycidyl tosylate (**2d**)[8] were synthesized according to literature procedures.

Ethyl 4,5-dihydro-5-hydroxymethyl-2-methylfuran-3-carboxylate (3) and ethyl 5,6-dihydro-5-hydroxy-2-methyl-4H-pyran-3-carboxylate (4). A solution of sodium ethoxide in ethanol was prepared from 575 mg (25.0 mmol) of sodium and 40 ml of ethanol. 3.25 g (25.0 mmol) of ethyl acetoacetate (1) and 5.71 g (25.0 mmol) of glycidyl tosylate (**2d**) were added and the resulting reaction mixture was stirred at 50°C for 1 d. After hydrolyzation with 80 ml of water the solution was extracted three times with 30 ml of diethyl ether. The combined organic layers were concentrated and the residue was distilled in the Kugelrohr oven at 150°C/0.02 mbar to give 2.79 g (60%) of a mixture of the regioisomers 3 and 4 in the ratio 1:3 according to the ^{1}H NMR spectrum (the same ratio was determined for the crude product before distillation). TLC (silica, petroleum ether/methy *tert*-butyl ether 1:1): R_f=0.23 (4), 0.21 (3). Analytically pure samples of the regioisomers were obtained by flash chromatography. First fraction: dihydropyran 4 as a colorless oil. IR (film): ν=3437 cm^{-1} (m, br, OH), 2979 (w), 2934 (w), 1701 (s), 1687 (s), 1624 (s), 1380 (m), 1258 (s), 1227 (m), 1106 (s), 1066 (m), 1047 (m). ^{1}H NMR: δ=1.28 ppm (t, J=7.1 Hz, 3H), 2.26 (t, J=1.5 Hz, 3H), 2.37 (s, br, 1H, OH), 2.38 (m, 1H), 2.59 (m, 1H), 3.94 (m, 2H), 4.13 (m, 1H), 4.16 (q, J=7.1 Hz, 2H). ^{13}C NMR: δ=14.38 ppm (q), 19.92 (q), 30.36 (t), 59.90 (t), 62.43 (d), 69.68 (t), 98.87 (s), 164.40 (s), 168.30 (s). MS (70 eV, 120°C); *m/z* (%): 187 (4), 186 (33, M^+), 168 (16), 143 (22), 141 (42), 140 (9), 139 (27), 115 (17), 97 (100), 71 (10), 69 (12), 55 (37), 44 (11), 40 (13). $C_9H_{14}O_4$ (186.2): calcd C 58.05, H 7.58; found C 58.22, H 7.56.

Second fraction: dihydrofuran **3** as a colorless oil, whose spectroscopic data are in accord with literature.[3a] IR (film): ν=3438 cm^{-1} (m, br, OH), 2981 (m), 2936 (m), 2875 (m), 1692 (s), 1641 (s), 1444 (m), 1384 (s), 1328 (m), 1264 (s), 1228 (s), 1146 (s), 1091 (s), 1056 (m), 1020 (m), 967 (m), 825 (m), 765 (m). ^{1}H NMR: δ=1.27 ppm (t, J=7.1 Hz, 3H), 1.99 (s, br, 1H, OH), 2.20 (t, J=1.6 Hz, 3H), 2.62 (m, 1H), 2.92 (m, 1H), 3.68 (dd, J=12.1, 6.6 Hz, 1H), 3.72 (dd, J=12.1, 3.6 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 4.73 (m, 1H). ^{13}C NMR: δ=14.08 ppm (q), 14.44 ppm (q), 31.38 (t), 59.59 (t), 64.99 (t), 82.39 (d), 102.26 (s), 166.11 (s), 167.47 (s). MS (70 eV, 120°C); *m/z* (%): 186 (24, M^+), 155 (9), 141 (26), 140 (9), 139 (16), 126 (12), 108 (9), 97 (21), 95 (10), 85 (8), 83 (28), 69 (9), 57 (9), 55 (12), 42 (100), 41 (8), 38 (8).

Ethyl *trans*-3-oxiranylmethoxy-2-butenoate (6). A mixture of 1.00 g (7.68 mmol) of ethyl acetoacetate (**1**), 1.75 g (7.68 mmol) of glycidyl tosylate (**2d**), 1.06 g (7.68 mmol) of potassium carbonate and 30 ml of dry DMF was stirred for at 50°C for 1 d. After addition of 60 ml of water the solution was extracted three times with 30 ml of diethyl ether. The combined organic layers were concentrated in vacuo and the residue was fractionated by flash chromatography; TLC (silica, petroleum ether/methy *tert*-butyl ether 1:1): R_f=0.57 (**6**), 0.25 (**3**+**4**), 0.22 (**2d**). Besides 57 mg (4%) of a mixture of **3** and **4** in the ratio 57:43 and 420 mg (24%) of recovered starting material **2d** 430 mg (30%) of enol ether **6** were obtained as a colorless oil, identified by comparison of the NMR spectra with published data[4] of the corresponding methyl ester. IR (film): ν=2983 cm^{-1} (m), 2932 (m), 2403 (w), 2243 (w), 1706 (s), 1624 (s), 1446 (m), 1367 (m), 1342 (m), 1277 (s), 1145 (s), 1054 (s), 963 (m), 915 (m), 947 (m), 819 (m), 773 (m), 665 (m). ^{1}H NMR: δ=1.27 ppm (t, J=7.2 Hz, 3H), 2.33 (s, 3H), 2.69 (dd, J=4.9, 2.6 Hz, 1H), 2.89 (dd, J=4.9, 4.2 Hz, 1H), 3.29 (m, 1H), 3.70 (dd, J=11.1, 6.1 Hz, 1H), 4.05 (dd, J=11.1, 2.9 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 5.00 (d, J=0.4 Hz, 1H). ^{13}C NMR: δ=14.38 ppm (q), 18.84 (q), 44.54 (t), 49.37 (d), 59.45 (t), 68.74 (t), 91.96 (d), 167.61 (s), 171.71 (s). MS (70 eV, 75°C); *m/z* (%): 187 (6), 186 (49, M^+), 141 (75), 140 (11), 130 (15), 115 (10), 103 (10), 102 (15), 87 (11), 85 (66), 84 (28), 83 (17), 69 (20), 58 (10), 57 (100), 43 (59). $C_9H_{14}O_4$ (186.2): calcd C 58.05, H 7.58; found C 57.97, H 7.55.

Ethyl 2-acetyl-4,5-epoxypentanoate (7). To a solution of 100 mg (0.587 mmol) of ethyl 2-acetyl-4-pentenoate[9] in 10 ml of acetone 17.6 ml (1.76 mmol) of a 0.1 M solution of dimethyldioxirane in acetone was added within 10 min. The solvent was removed at room temperature under reduced pressure (at first 16 mbar, finally 0.25 mbar) to give 98 mg (90%) of epoxide **7** as a mixture of diasteroisomers in the ratio 53:47 according to the ^{1}H NMR spectrum. – ^{1}H NMR: δ=1.29 ppm (m, 3H), 1.88 (m, 1H), 2.28 (m, 1H), 2.28 and 2.30 (s, 3H of diasteroisomers A and B), 2.51 (m, 1H), 2.77 (m, 1H), 2.97 (m, 1H), 3.67 ('q', 1H), 4.16 (q, J=7.1 Hz, 2H). ^{13}C NMR: δ=13.88 ppm (q), 29.31 (q), 30.42 (t), 47.03 (t), 49.71 (d), 55.87 (d), 61.54 (t), 169.05 (s), 202.04 (s).

Heating epoxide **7** in ethanol in the presence of potassium carbonate at 50°C let exclusively to the formation of dihydrofuran **3**; its regioisomer **4** was not detected.

Acknowledgements

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