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Reaction of dianions of acetoacetic esters with epibromohydrin derivatives: a novel synthesis of tetrahydrofuran derivatives and tetrahydropyran derivatives

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Abstract

The dianion of the acetoacetic ester reacts with epibromohydrin derivatives to afford a mixture of (*Z*)-2-alkoxycarbonylmethylidenetetrahydrofuran derivative and (*E*)-2-alkoxycarbonylmethylidenetetrahydropyran derivative. The selective formation of the tetrahydrofuran derivative is achieved by the use of $LiClO_4$ as the additive.

Keywords: acetoacetic ester; dianion; epibromohydrin; epoxide; tetrahydrofuran; tetrahydropyran.

The dianion of the β-diketo compound was first reported by Hauser and Harris,[1] and the dianion of the acetoacetic ester has been a popular reagent in organic synthesis since Huckin and Weiler reported an effective generation method of dianions of acetoacetic esters.[2] The numerous reports and reviews[3] of organic synthesis using the dianion of the acetoacetic ester to date suggest its great utility. Among the many reactions of the dianion of the acetoacetic ester, a very useful one is the construction of cyclic compounds by a one-pot reaction utilizing the property of the dianion.[3,4] Hence, we examined the one-pot reaction of the dianion of the acetoacetic ester with an epibromohydrin derivative and report here the interesting results and the structure of the products possessing a unique functional group.[5]

The reaction of the dianion of the acetoacetic ester with an epibromohydrin derivative has not been examined as far as we know. The dianion **1** is expected to react with the epibromohydrin derivative **2**[6] at its γ position to form the intermediate **3** (Fig. 1), which subsequently cyclizes to afford the *O*-alkylated products and/or the *C*-alkylated products.[3] However, the ratio of these products was expected to be controlled by the choice of the reaction conditions.[2]

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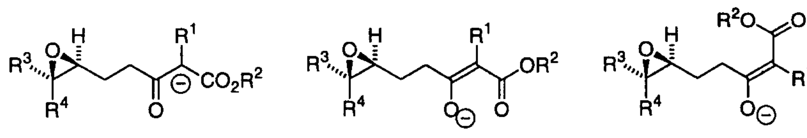
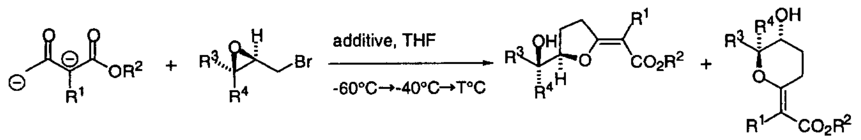

3 **3U (U-shaped)** **3W (W-shaped)**

Figure 1.

First, the dianion **1a** generated by the standard procedure[2] was reacted with the (*E*)-epibromohydrin **2a**. After adding **2a** to the solution of **1a** at −60°C, the reaction mixture was warmed to −40°C and stirred for 6 h. The completion of the alkylation of the dianion **1a** at its γ position was checked by TLC, and further stirring of the reaction mixture at room temperature for 8 h afforded the products, the tetrahydrofuran derivative **4a** and the tetrahydropyran derivative **5a** in 84% combined and isolated yield in the ratio of 1:1.6 (Table 1, entry 1).[7,8] No formation of the *C*-alkylated products was observed.

Table 1

Reactions of dianions of acetoacetic esters **1** with epoxybromides **2**



1a (R^1 = H, R^2 = ${}^tBu$)
1b (R^1 = Me, R^2 = Et)

2a (R^3 = $-CH_2OBn$, R^4 = H)
2b (R^3 = H, R^4 = $-CH_2OBn$)

4a (R^1 = H, R^2 = ${}^tBu$, R^3 = $-CH_2OBn$, R^4 = H)
4b (R^1 = Me, R^2 = Et, R^3 = $-CH_2OBn$, R^4 = H)
4c (R^1 = H, R^2 = ${}^tBu$, R^3 = H, R^4 = $-CH_2OBn$)
4d (R^1 = Me, R^2 = Et, R^3 = H, R^4 = $-CH_2OBn$)

5a (R^1 = H, R^2 = ${}^tBu$, R^3 = $-CH_2OBn$, R^4 = H)
5b (R^1 = Me, R^2 = Et, R^3 = $-CH_2OBn$, R^4 = H)
5c (R^1 = H, R^2 = ${}^tBu$, R^3 = H, R^4 = $-CH_2OBn$)
5d (R^1 = Me, R^2 = Et, R^3 = H, R^4 = $-CH_2OBn$)

Entry	Acetoacetic Ester	Substrate[a]	Additive	Time[b] h	T °C	Yield[c] (%)	4 / 5[d]
1	1a	2a	-	8	rt	84	1 / 1.6
2	1a	2a	-	72	rt	63	1 / 2.6
3	1a	2a	$ZnCl_2$ (2.3 eq.)		rt	NR[e]	
4	1a	2a	$MgBr_2$ (2.3 eq.)		rt	NR[e]	
5	1a	2a	$MgClO_4$ (2.0 eq.)		rt	NR[e]	
6	1a	2a	LiCl (2.0 eq.)	8	rt	87	4.4 / 1
7	1a	2a	$LiClO_4$ (2.0 eq.)	5	rt	91	8.4 / 1
8	1a	2a	$LiClO_4$ (2.0 eq.)	48	-10	99	**17 / 1**
9	1a	2b	-	8	rt	83	1.7 / 1
10	1a	2b	$LiClO_4$ (2.0 eq.)	5	rt	86	**22 / 1**
11	1a	2b	$LiClO_4$ (2.0 eq.)	120	-40	79	**1 / 0**
12	1b	2a	-	12	rt	69	5.4 / 1
13	1b	2a	-	72	rt	91	1 / 1.6
14	1b	2a	$LiClO_4$ (2.0 eq.)	5	rt	64	**13 / 1**
15	1b	2b	-	5	rt	67	4.3 / 1
16	1b	2b	$LiClO_4$ (2.0 eq.)	5	rt	82	**135 / 1**

[a] All substrates and products are racemic compounds. [b] The reaction time at T°C. [c] The combined and isolated yield of **4** and **5**. [d] The ratio was determined based on the ^{1}H-NMR analysis. [e] The starting materials were recovered.

It is interesting that the alkene in the products **4** and **5** is (*Z*)-form and (*E*)-form, respectively, and no isomeric product was formed. Prolonged reaction time at room temperature (72 h) resulted in a change in the ratio of **4a**:**5a** to 1:2.6 (entry 2). This change in the ratio was supposed to arise from the isomerization of **4a** to **5a**. To activate the epoxide in the cyclization step, Lewis acid was used as the additive, but no reaction occurred in the case of $ZnCl_2$, $MgBr_2$, $MgClO_4$ (entry 3, 4, 5). On the other hand, the ratio of **4a**:**5a** was improved to 4.4:1 when LiCl was used (entry 6), and by the use of the more acidic $LiClO_4$[9] the reaction time was reduced and the ratio was further improved to 8.4:1 (entry 7). Finally, the products were obtained in 99% yield in the ratio of **4a**:**5a** 17:1 when the reaction was carried out in the presence of $LiClO_4$ at −10°C (entry 8). The effect of $LiClO_4$ was supposed to not only activate the epoxide in the cyclization step, but also inhibit **4a** from isomerizing to **5a** by the formation of a stable chelate complex of **4a** with the metal cation.

In the reaction of the dianion **1a** with the (*Z*)-epibromohydrin derivative **2b**, the same trend as the reaction of (*E*)-derivative **2a** was observed. The addition of $LiClO_4$ was also effective in the selective formation of **4b** over **5b** (entry 9, 10), and **4b** only formed at the low reaction temperature (entry 11). Again, no *C*-alkylated product was observed in this case. Reactions of the dianion **1b**, which possesses a Me group at its α position, were further carried out and the same results as described above were obtained (entries 12–16).

In general, the mono anion of the acetoacetic ester is known to adopt the U-shaped or the W-shaped enolate (Fig. 1). Of these conformations only the U-shaped enolate is capable of serving as a bidentate ligand for association with a metal ion. However, the most stable form of the free enolate anion is expected to be the W-shaped conformer in which dipole–dipole repulsion is minimized.[7,10] Consequently, the mono anion **3** exists primarily as the U-shaped enolate **3U** under the condition in Table 1, but possibly adopts the W-shaped enolate **3W** in part due to the solvation.

It is therefore reasonable to assume that the formation of **4** was directly derived from **3U**, and **5** was also derived from **3W**, because the alkene in the products **4** and **5** is (*Z*)-form and (*E*)-form, respectively. However, the reason why **3U** and **3W** afford the corresponding products selectively remains unexplained. Moreover, it is a mystery why only (*E*)-isomers of **5** have been obtained by the isomerization from (*Z*)-isomers of **4** to **5**. Hence, rational explanations are necessary for these phenomena and further study on this reaction has been continued.

In summary, a novel synthesis of (*Z*)-2-alkoxycarbonylmethylidenetetrahydrofuran derivative and (*E*)-2-alkoxycarbonylmethylidenetetrahydropyran derivative has been developed. The selective formation of the tetrahydrofuran derivative was also achieved. The obtained products possessing a unique functional group will be of synthetic value and our progress will be reported in due course.

Acknowledgements

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6. (a) The epibromohydrin derivatives **2a** and **2b** were prepared starting from the commercially available *cis*-1,4-dihydroxybutene as follows. **2a**: (i) BnBr, NaH, TBAI, THF, DMF, rt; (ii) PCC, CH_2Cl_2, rt[6b]; (iii) $NaBH_4$, MeOH, 0°C; (iv) *m*CPBA; (v) PPh_3, CBr_4, CH_2Cl_2, rt (ca. 30% overall yield). **2b**: (i) BnBr, NaH, TBAI, THF, DMF, rt; (ii) *m*CPBA; (iii) PPh_3, CBr_4, CH_2Cl_2, rt (ca. 40% overall yield). (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
7. The concentration of all the reactions in Table 1 was set to 0.1 M because the concentration of the reaction mixture also affects the ratio of **3U/3W**. For the effect of the concentration on the ratio of **3U/3W**, see: (a) Rhoads, S. J.; Holder, R. W. *Tetrahedron* **1969**, *25*, 5443–5450. (b) Miller, B.; Margulies, H.; Drabb Jr., T.; Wayne, R. *Tetrahedron Lett.* **1970**, 3805–3808.
8. The ratio of **4/5** and the structures of **4** and **5** were determined by the ^1H NMR technique including the NOE experiment. For the preparation of **4a** and **5a**; to an agitated suspension of NaH (14.8 mg, 2.3 equiv.) in dry THF (2.2 ml) (2.2 ml) using a magnetic stirring bar and stirrer was added *t*-butyl acetoacetate (0.056 ml, 2.1 equiv.) dropwise at 0°C under Ar atmosphere and the resulted solution was stirred for 10 min. Then *n*-BuLi (0.21 ml, 1.53 M soln in hexane, 2.0 equiv.) was added slowly to the reaction mixture at 0°C and the stirring was continued further for 10 min. The resulted pale yellow dianion solution was cooled to −60°C and to this solution was added first the $LiClO_4$ (34.2 mg in dry THF 2.1 ml), and then **2a** (46.0 mg, 1.0 eq.) in dry THF (0.5 ml) dropwise via a canula. The flask of the solution of **2a** was washed with dry THF (0.5 ml) and the washings were added to the reaction mixture via a canula. After the addition of **2a**, the reaction temperature was raised to −40°C and the reaction mixture was stirred for 12 h. At this point **2a** almost disappeared. Then the reaction mixture was warmed to rt and the stirring was continued for 8 h to complete the reaction. The reaction was quenched with satd NH_4Cl aq. and the aqueous layer was extracted with ether, then CH_2Cl_2 twice. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, concentrated and dried under vacuum. Purification by silica gel chromatography (hexane:EtOAc 2:1) afforded 19.3 mg (32%) of **4a** and 31.3 mg (52%) of **5a**.
9. $LiClO_4$ was dried according to the literature. For the drying method of $LiClO_4$, see: Pocher, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075–2084. For the $LiClO_4$ catalyzed rearrangement of epoxides, see: (a) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693–1700. (b) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321–5334. (c) McMurry, J. E.; Musser, J. H.; Ahmad, M. S.; Blaszczak, L. C. *J. Org. Chem.* **1975**, *40*, 1829–1832. (d) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742–1744. (e) Burge, G. L.; Collins, D. J.; Reitze, J. D. *Aust. J. Chem.* **1982**, *35*, 1913–1925. (f) Kennedy, J. H.; Buse, C. *J. Org. Chem.* **1971**, *36*, 3135–3138.
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