Influence of phase transfer catalyst structure on the *E* : *Z* ratio in the *O*-alkylation of an enolate†

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Received* (*in Freiburg, Germany*) *20th September 2000, Accepted 23rd January 2001
First published as an Advance Article on the web 14th March 2001

Both C- *vs.* O-alkylations and *Z vs. E* enol ether formation from 2-methyl-1,3-diphenylpropane-1,3-dione (**1**) can be influenced by the structure of the phase transfer catalyst. O-Methylation is the major process in the PTC reaction of **1** with dimethyl sulfate. The *E* : *Z* product ratio can be varied between roughly 1 : 1 and 4 : 96 by use of different catalysts. This is only the fifth type of conversion in which the catalyst structure can exert a decisive influence.

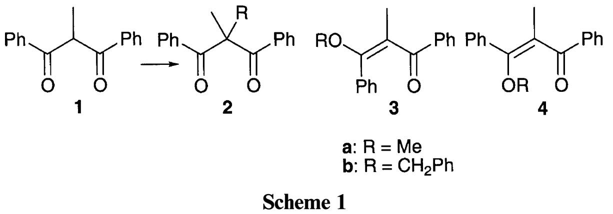
C- *vs.* O-Selectivity in the alkylation of enolates and other ambident anions has been investigated extensively under conventional and phase transfer conditions.[2] The C/O product ratio is known to be influenced by many factors such as the structure of the alkylating agents, the leaving group, solvent, concentrations and presence of water. Twenty years ago, Halpern *et al.* showed that the structure of the phase transfer (PT) catalyst can also have a profound effect on the said C/O product ratio[3] and we were able to enlarge on that in a more systematic fashion.[4] In all this work, little attention was paid to the *E* : *Z* ratio of the enol ether formed. Previous non-PTC studies on alkylation and acylation of ethyl acetoacetate had established, however, that there is a relation between the preferred structure of the intermediate alkali metal enolate and the formation of C, (*E*)-O and (*Z*)-O reaction products.[5–7] Here, we present data for the methylation and benzylation of 2-methyl-1,3-diphenylpropan-1,3-dione (**1**) to yield the C products **2a**,**b** and the *E* (**3a**,**b**) and *Z* (**4a**,**b**) enol ethers (Scheme 1).

Results and discussion

Preliminary experiments were performed with solid potassium carbonate (20 molar excess) as base and toluene as solvent using 5 mol% of the catalysts. After 15 h of equilibration at 110 °C, the alkylating agent, dimethyl sulfate, was added and heating was continued for another 4 h. These runs gave very erratic, irreproducible results, probably due to varying surface conditions of the carbonate.

Deviations of only 0.5 to 1% were observed when both deprotonation and alkylation were executed with sodium hydride in toluene at room temperature. The standard reaction time was chosen to be long enough so that all conversions went to 100%, even the very slow ones in the absence of catalyst.

Table 1 lists these results. It can be seen that the *O*-methyl compounds **3a** and **4a** are the major products in all cases. With most of the catalysts, the C/O product ratio is 0.03 to 0.05, but there is a variation towards C-alkylation (ratios 0.32 to 0.36) for the two 15-membered ring crowns and—to a much lesser extent—for 18-crown-6 (but not so for the dibenzo derivative!), as well as for the sterically shielded ammonium salts, $Hept_4NBr$, Oct_4NBr and $PhCH_2NProp_3Cl$. Turning our attention to the *E* : *Z* (**3a**/**4a**) ratio, we notice a variation between 2 : 98 (no catalyst, very slow process) to 4 : 96 (Me_4NBr) and 56 : 44 (Ph_4AsBr). It is apparent that the 12- and 15-membered crown ethers and onium salt catalysts with a small "sterically accessible" head group [*cf.* ref. 2(*a*)] give much more of the *Z* product **4a**. This trend is seen best in the series of increasing steric bulk around the nitrogen atom: NMe_4 (96% *Z*), cetrimid, $PhCH_2NMe_3$, $PhCH_2NMe_2(C_{16}H_{33})$ (all 86% *Z*), TEBA (75% *Z*), $PhCH_2NProp_3$ (58% *Z*) and $PhCH_2NBu_3$ (57% *Z*).



Scheme 1

When extending the methylation experiments to PTC alkylations with NaH and benzyl bromide (Table 2), a higher temperature (15 h at 80 °C) had to be used because of solubility problems. In another set of experiments, the reaction was executed as a solid/liquid phase transfer conversion in dichloromethane at room temperature with solid powdered sodium hydroxide as the base (Table 3).

As expected, the "softer" bromide leaving group (compared to sulfate) and the changed alkyl group, led to a much higher proportion of C-alkylation under both sets of conditions. At the higher temperature in toluene, there was a range between roughly 1 : 1 and 100 : 0 in the C : O product ratios, benzo-15-crown-5 giving *only* **2b**. The *E* : *Z* (**3b** : **4b**) ratio, however, varied only between 35 : 65 and 50 : 50, so that the *E* : *Z* directing effect of the catalysts can be neglected in this case. In the room temperature solid/liquid process, C/O product ratios for different catalysts varied from *ca.* 0.65 (Ph_4AsCl and the phosphoiminium salt) up to 2.7 (cetrimid). Anhydrous conditions were operative in the experiments of Tables 1 and 2, whereas at least one equivalent of water was available to the reactive ion pairs in the third set of experiments (Table 3). It is well known that the presence of even minute quantities of H_2O modifies PTC reactions.[2] Thus, more *E* than *Z* product was formed under the conditions used in Table 3, but again the variation between different catalysts was small.

It is useful to compare the catalyst structure effects observed here with the ones from earlier enolate alkylations (desoxybenzoin,[3,8] 2-naphthol,[9] 1,1-dimethylindan-2-one[10]) and other cases of PT catalyst steered reaction branchings.[4] The main parallel is that certain crown ethers and the "sterically accessible" onium salts behave differently from most of the other salts. The highly delocalized phos-

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† Applications of phase transfer catalysis, part 71. For parts 69 and 70, see ref. 1.

DOI: 10.1039/b100880n

Table 1 Methylation of compound **1** with Me_2SO_4 and dependence on the PT catalyst (base: NaH; solvent: toluene; methylating agent: dimethyl sulfate; room temperature)

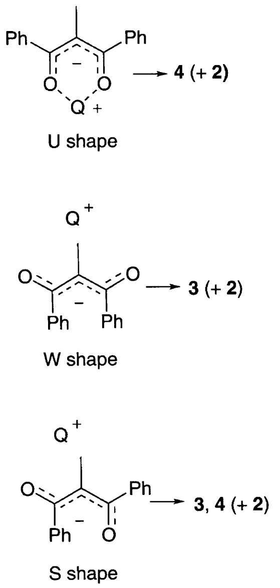
Catalyst	**2a** (%)	**3a** + **4a** (%)	C/O product ratio	*E* : *Z* (**3a** : **4a**) ratio
None	5.5	94.5	0.06	2 : 98
Me_4NBr	5.5	94.5	0.06	4 : 96
Et_4NBr	4.5	95.5	0.05	19 : 81
$Prop_4NBr$	5	95	0.05	39 : 61
Bu_4NBr	4	96	0.04	44 : 56
$Pent_4NBr$	5	95	0.05	48 : 52
Hex_4NBr	4.5	95	0.05	50 : 50
$Hept_4NBr$	7	93	0.08	48 : 52
Oct_4NBr	8	92	0.08	51 : 49
Cetrimid	4.5	95.5	0.05	14 : 86
Bu_4PBr	5	95	0.05	49 : 51
Ph_4PBr	4	96	0.04	10 : 90
Ph_4AsBr	3	97	0.03	56 : 44
$(Ph_3P{=}N{=}PPh_3)Cl$	3	97	0.03	48 : 52
$[(Me_2N)_3P{=}N{=}P(NMe_2)_3]BF_4$	3.5	96.5	0.04	50 : 50
12-Crown-4	5	95	0.05	15 : 85
Benzo-12-crown-4	5.5	94.5	0.05	16 : 84
15-Crown-5	24	76	0.32	11 : 89
Benzo-15-crown-5	26.5	73.5	0.36	14 : 86
18-Crown-6	9	91	0.1	33 : 67
Dibenzo-18-crown-6	4	96	0.04	33 : 67
Kryptofix[2.2.2]	3	97	0.03	51 : 49
$PhCH_2NMe_3Cl$	4	96	0.04	14 : 86
$PhCH_2NEt_3Cl$ (TEBA)	4	96	0.03	25 : 75
$PhCH_2NProp_3Cl$	7.5	92.5	0.08	42 : 58
$PhCH_2NBu_3Cl$	5	95	0.05	43 : 57
$PhCH_2NMe_2(C_{16}H_{33})Cl$	4	96	0.04	14 : 86
$PhCH_2NMe_2(CH_2CH_2OH)Cl$	4	96	0.04	15 : 85

Table 2 Benzylation of compound **1** with $PhCH_2Br$ and dependence on the PT catalyst (base: NaH; solvent: toluene; benzylating agent: benzyl bromide; 80 °C)

Catalyst	**2b** (%)	**3b** + **4b** (%)	C/O product ratio	*E* : *Z* (**3b** : **4b**) ratio
None	77	23	3.35	44 : 56
Me_4NBr	81	19	4.26	42 : 58
Et_4NBr	73	27	2.70	41 : 59
Bu_4NBr	49	51	0.96	35 : 65
$Pent_4NBr$	60	40	1.50	43 : 57
Oct_4NBr	60	40	1.50	40 : 60
$PhCH_2NMe_3Br$	71	29	2.45	41 : 59
$PhCH_2NEt_3Br$	74	26	2.85	50 : 50
Benzo-15-crown-5	100	—	—	—
PBu_4Br	49	51	0.96	39 : 61

Table 3 Benzylation of compound **1** with Me_2SO_4 and dependence on the PT catalyst (base: ground NaOH; solvent: dichloromethane; benzylating agent: benzyl bromide; room temperature)

Catalyst	**2b** (%)	**3b** (%)	**4b** (%)	C/O product ratio	*E* : *Z* (**3b** : **4b**) ratio
None	incomplete conversion				
Me_4NCl	incomplete conversion				
Et_4NCl	64	24	12	1.78	67 : 33
$Prop_4NBr$	57	28	15	1.33	65 : 35
Bu_4NBr	46	36	18	0.85	67 : 33
$Pent_4NBr$	50	33	17	1.0	66 : 34
Hex_4NBr	51	33	16	1.04	67 : 33
$Hept_4NBr$	61	25.5	13.5	1.56	65 : 35
Oct_4NBr	59	27	14	1.44	66 : 34
$CetNMe_3Br$	73	18	9	2.70	67 : 33
$CetNEt_3Cl$	62	25	13	1.63	66 : 34
Ph_4PBr	48	35	17	0.92	67 : 33
Ph_4AsBr	40	40	20	0.67	67 : 33
Bu_4AsBr	62.5	26	11.5	1.67	69 : 31
$(Ph_3P{=}N{=}PPh_3)Cl$	38	46.5	15.5	0.61	75 : 25
Benzo-15-crown-5	71	16	13	2.45	55 : 45
Dibenzo-18-crown-6	65	23	12	1.86	66 : 34
$PhCH_2NMe_3Cl$	65	23	12	1.86	66 : 34
$PhCH_2NEt_3Cl$ (TEBA)	48	35.5	16.5	0.92	68 : 32
$PhCH_2NProp_3Cl$	69	21	10	2.23	68 : 32



Scheme 2

phoiminium and tetraphenylarsonium salts normally direct in the opposite direction from the crowns. This trend is present in Table 3, but non-existent under the conditions of Table 1. In Table 2 these special catalysts behave similarly to other more common ammonium salts.

The evidence put forth in ref. 5–7 made it clear that the anions of β-dicarbonyl compounds can exist in three distinct forms, dubbed "U", "W" and "S" (Scheme 2). Depending on the tightness of the ion pairs, the chelating properties of the counter ion, solvent, and concentrations, the interconversion of the anions might be slower than their trapping of reagents. Even though we do not have direct information on the preferred structures of the ion pairs involved and on the kinetics of their interconversions in the present case, it is obvious that the catalyst structure has a strong influence. Furthermore, the leaving group must be generated and accommodated close to the catalyst cation in the nonpolar solvents. We therefore tentatively suggest that the U-shaped (flat) chelate containing a catalyst with a small "accessible" head group or with a sodium ion/crown complex would lead to either the *Z* product **4** or the C product **2**. Conversely, W- and S-shaped anions might sandwich their counter ions above or below the plane of the anion, giving *E* product **3** (plus **2**) from the W form and either **3** or **4** (and **2**) from the S form (see Scheme 2).

Summing up then, we have demonstrated here that the structure of a PT catalyst may have a strong influence on the *E* : *Z* ratio in the alkylation of a β-dicarbonyl compound, but the extent of this influence can vary widely. Altogether, there are now five types of reactions in which the catalyst structure has a directing influence on reaction channel branching: (i) enantioselective reactions (chiral catalysts); (ii) generation of mixed dihalocarbenes CXY from haloforms HCX_2Y;[4] (iii) competitive trapping of halocarbenes CX_2 and anions CX_3^-;[4] (iv) position selectivity of alkylations of various ambident anions[4] and (v) the present formation of *E* and *Z* enol ethers.

Experimental

Methylation

3 g of a 10% NaH suspension in paraffin (about 10 mmol) were washed three times with 5 ml of toluene, then combined with a solution of 1.19 g (5 mmol) of **1** in 50 ml of toluene and stirred for 2 h at room temperature until the evolution of hydrogen stopped. Thereafter 0.25 mmol of catalyst and 5 ml (50 mmol) of dimethyl sulfate were added and the mixture was stirred for 15 h at room temperature. Excess Me_2SO_4 was destroyed by addition of 40 ml of dilute ammonia. The phases were separated and the organic one was washed three times with 50 ml of water, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was dissolved in chloroform and analyzed by integration of the relevant peaks of the ^1H NMR spectrum. **2a**: δ 1.66 (s, 6 H), 7.26–7.41 (m, 6 H), 7.81–7.86 (m, 4 H). **3a**: δ 2.15 (s, 3 H), 3.46 (s, 3 H), 7.07–7.95 (m, 10 H). **3b**: δ 1.90 (s, 3 H), 3.03 (s, 3H), 7.07–7.95 (m, 10 H).[11]

To test for the relative rate of the uncatalyzed reaction, two runs were executed in the absence of a catalyst and with NBu_4Br for 1 h only. Conversions of 45 and 100%, respectively, were observed.

Benzylation

NaH as base. The sodium salt of **1** in toluene was prepared as described above. The catalyst (0.25 mmol) and 8.55 g of benzyl bromide were then added and the mixture was stirred for 15 h at 80 °C. An aqueous 10% $NaHCO_3$ (40 ml) solution was added and the organic phase was separated, washed with water and dried (Na_2SO_4). Solvent and excess benzyl bromide were removed *in vacuo* and the mixture was analyzed by integration of the relevant ^1H NMR signals in $HCCl_3$. **2b**: δ 1.57 (s, 3 H), 3.60 (s, 2 H), 6.84–6.87 (m, 2 H), 7.15–7.46 (m, 9 H), 7.84–7.89 (m, 4 H). **3b**: δ 2.09 (s, 3 H), 4.65 (s, 2 H), 7.07–7.96 (m, 15 H). **4b**: δ 1.91 (s, 3 H), 4.28 (s, 2 H), 7.09–8.09 (m, 15 H).[11]

Solid NaOH as base. Powdered NaOH (2.0 g) and 1.19 g (5 mmol) of **1** were suspended/dissolved in 15 ml of CH_2Cl_2. Then 0.5 mmol of catalyst in 15 ml of CH_2Cl_2 and 1.71 g (10 mmol) of benzyl bromide were added. The mixture was stirred for 15 h at room temperature, then diluted with water. Phases were separated and the organic phase was extracted three times with 30 ml of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2, treated with a little silica gel, filtered, and the silica gel was washed with more CH_2Cl_2. Removal of the solvent was followed by NMR analysis in chloroform solution as above.

Acknowledgements

This work was supported in part by Deutsche Forschungsgemeinschaft (project De 173/20-1/2) and Fonds der Chemischen Industrie.

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11 *E*/*Z* structural assignments are in line with the fact that a *cis* alkoxy group shifts the methyl signal to lower field. According to ref. 5, *E*- and *Z*-1-methoxy-1,2-diphenylpropenes have the following methyl and methoxy signals. *E*: 3.29 and 2.08; *Z*: 1.91 and 3.13 ppm.