Versatile Transformations of α,β-Dibromoesters and Ketones in Basic Media under Microwave Irradiation

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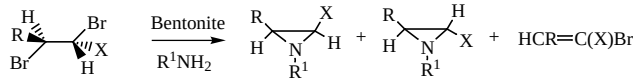
Abstract: Depending on the reaction medium, α,β-dibromoesters under microwave irradiation may selectively lead to α-bromoalkenes, to alkenes or to (*E*)-β-bromostyrenes. The corresponding ketones give selectively the α-bromoketones.

Key words: dehydrobromination, debromination, solvent-free reaction, microwaves

We have previously reported the synthesis of functionalised aziridines[1] starting from α,β-dibromoesters or ketones **1** and primary amines over bentonite as solid support. This first study has shown that coupling of this reaction with microwave irradiation promoted the formation of α-bromoalkenes **4** (Scheme 1).



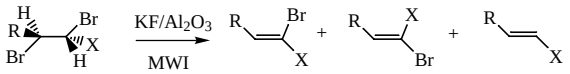
1 **2** **3** **4**

X: ester or ketone

Scheme 1

In order to form selectively the α-bromoalkenes, we studied the behaviour of these α,β-dibromo compounds under various conditions[2] and we found that treatment with KF supported on alumina under microwave irradiation led to an elimination reaction which produced functionalised α-bromoalkenes in fair yields, but at high temperatures the formation of the debrominated alkenes **5** competed (Scheme 2).

These results led us to extend the investigation related to these eliminations in various conditions with the aim of getting better selectivities.



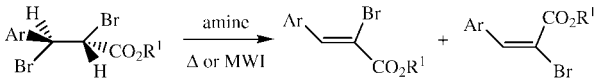
1 **4**(*Z*) **4**(*E*) **5**

X: ester or ketone

Scheme 2

For this purpose, we chose methyl or ethyl-2,3-dibromo-3-phenylpropanoate (*RS,SR*), 2,3-dibromo-4-phenylbutanone (*RS,SR*) and their *p*-substituted phenyl derivatives.

We found that in the presence of piperidine or Et_3N without solvent, under thermal or microwave activation (MWI), the α,β-dibromoesters lead exclusively to α-bromoalkenes **4**-(*Z*) and **4**-(*E*) (Scheme 3) with very good yields in very short times (5–15 min) (Tables 1 and 2).



4(*Z*) **4**(*E*)

Ar: **a**: C_6H_5 **1** : R^1: CH_3
b: $pClC_6H_4$ **2** : R^2: C_2H_5
c: $pMeOC_6H_4$

Scheme 3

All the compounds are already described in the literature resulting from various methods which need longer reaction times, are less straightforward and involve less eco-friendly procedures.[3–7]

Although the yields were quantitative with both amines, it is noteworthy that the *Z* selectivity was higher with piperidine and that higher temperatures promote isomerisation.

We realised a comparison between microwave activation and conventional heating by using an oil bath previously set at the temperature used under irradiation and found no difference between the two activation modes. Nevertheless the microwave experiments are much easier to set up.

We were also interested in the debromination reactions for the synthesis of alkenes. This reaction is known in the literature using DMF coupled with a reducing agent[9–11] or as shown later with DMF alone.[12–14] In the latter case, the temperature was usually 150–160 °C under N_2 during 90 minutes.

We readily achieved the debromination using 8.5 equivalents of DMF under microwave irradiation at a monitored temperature of 150 °C. In these conditions, we could observe the formation of the alkenes **5** in 5–15 minutes in good yields (Scheme 4 and Table 3).

It is noteworthy that an electron-donating substituent on the phenyl group (**1c** and **2c**) leads to a lower yield of **5**

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Table 1 Dehydrobromination with Piperidine

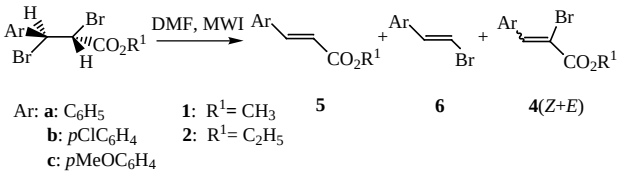
Substrate	T (°C)[a]	t (min)	Yield (%)[b]	**4**-(*Z*) (%)[c]	**4**-(*E*) (%)[c]	Yield **4**[d]	Bp (°C/mbar) or mp (°C)
1a	80	5	89	86	14	85	115/0.07[6,7]
1a	80	15	78	93	07		
1a	100	5	80	85	15		
1a	100	15	78	88	12		
1b	80	5	80	80	20	80	64–66[4,6]
1b	80	15	80	82	18		
1b	100	15	70	77	23		
1c	80	5	90	85	15	80	115/0.06[5–7]
1c	80	15	90	94	06		
1c	100	15	80	89	11		
2a	80	5	99	88	12	90	90/0.06[4,7]
2a	80	15	99	90	10		
2a	100	5	96	82	18		
2a	100	15	99	85	15		
2b	80	5	100	89	11	81	90–95/0.05[8]
2b	80	15	91	93	07		
2b	100	15	82	82	18		
2c	80	5	90	88	12	75	120/0.07[8]
2c	80	15	90	92	08		
2c	100	15	90	90	10		

[a] Temperature monitored by the oven and measured with an IR captor.
[b] Yield of crude reaction mixture.
[c] Ratio estimated by ^{1}H NMR.
[d] Isolated yield.

Table 2 Dehydrobromination with Triethylamine at 80 °C

Substrate	t (min)	Yield (%)[a]	**4**-(*Z*) (%)[b]	**4**-(*E*) (%)[b]
1a	5	90	64	36
1a	15	90	64	36
1b	15	100	67	33
1c	15	100	37[c]	55
2a	5	90	59	41
2a	15	100	59	41
2b	15	82	67	33
2c	15	100	43	57

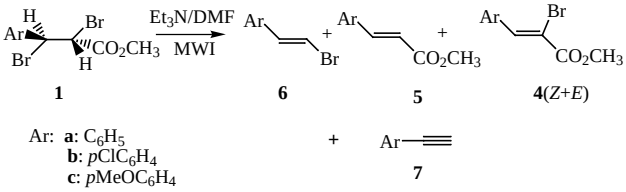
[a] Yield of crude reaction mixture.
[b] Ratio estimated by ^{1}H NMR.
[c] Reaction was not quantitative.



Scheme 4

and favours the formation of **4**-(*Z*,*E*). A longer reaction time or larger excess of DMF does not change the results significantly.

Then our interest was focused on the formation of the (*E*)-β-bromostyrene **6**. These compounds are often used as starting materials for the synthesis of substituted alkenes.[15–21] Although various syntheses are described in the literature,[19,22–26] none to our knowledge starting from α,β-dibromoesters. After some trials, we found out that this could be readily achieved by coupling Et_3N and DMF under irradiation with a monitored temperature of 150 °C (Scheme 5). The results are given in Table 4.



Scheme 5

Starting from the isomeric mixture of **4**-(*Z*,*E*), we could demonstrate that the (*E*)-β-bromostyrene **6** was formed by demethoxycarbonylation of the former by Et_3N according

Table 3 Debromination with DMF Alone

Substrate	T (°C)	t (min)	Yield (%)[a]	**5** (%)[b]	**6** (%)[b]	**4**-(*Z*,*E*) (%)[b]
1a	100	10	[c]	–	–	–
1a	140	5	100	85	–	–
1a	140	7	100	73	16	11
1a	150	5	80	78	13	09
1b	150	5	90	80	10	10
1c	150	7	85	26	–	74
1c	150	15	85	33	–	67
2a	150	5	90	84	–	06
2a	150	7	80	84	06	10
2b	150	7	87	84	05	11
2c	150	7	100	34	–	66
2c	150	10	100	37	–	63

[a] Yield of crude reaction mixture.
[b] Ratio estimated by ^{1}H NMR.
[c] No reaction.

Table 4 Formation of the (*E*)-β-Bromostyrene **6** Starting from α,β-Dibromoesters

Substrate	T (°C)	t (min)	Yield (%)[a]	**6** (%)[b]	**5** (%)[b]	**4**-(*Z*,*E*) (%)[b]	**Y**ield **6**[c]
1a	130	45	86	69	3	28	
1a	150	45	57	87	1	12	44[d,26]
1a	150	30	60	82	1	17	
1a	150	15	64	40	4	56	
1b	150	37	83	76	3	10	68[d,15,26]
1c	150	45	80	–	–	–	52[d,26]

[a] Yield of crude reaction mixture.
[b] Ratio estimated by ^{1}H NMR.
[c] Isolated yield.
[d] The alkyne **7** is also formed: **7a** has a bp of 142 °C and is not recovered; **7b** and **7c** (low yield) were characterized by ^{1}H NMR in the crude mixture.

to the mechanism already known.[27] When the mixture **4**-(*Z*,*E*) was placed in the reaction conditions, we got 25% of (*E*)-β-bromostyrene **6** after 30 minutes, together with 61% of remaining **4**-(*Z*,*E*) and 16% of methyl cinnamate (**5**). We repeated this experiment with two drops of bromine and in this case we obtained 61% of **6** after the same time, together with the isomerised mixture of **4**-(*Z*,*E*) (25% *Z* and 5% *E*). It may be concluded that the isomerisation of the mixture **4**-(*Z*,*E*) into the *E*-isomer catalysed by bromine, favours the demethoxycarbonylation as it is the case when the reaction is starting from the dibromoester.

During this synthesis of β-bromostyrene we could observe the formation of small amounts of the corresponding alkynes **7** and the selective formation of **7** is actually under study.

In order to broaden the scope of the debromination reaction by DMF alone, we studied this reaction starting from the α,β-dibromoketones **8** (*SR*,*RS*) (Scheme 6).

The reaction leads to the major formation of the α-bromoketones **9**. The optimal conditions and the results are reported in Table 5.

Compounds **9** are interesting intermediates in the synthesis,[29] which are usually prepared according to two main processes: either by Wittig–Horner reaction of a brominated ylid,[30] or via bromination of an α,β-unsaturated ketone with various brominating agents such as, 2,4,4,6-tetrabromocyclohexa-2,5-dienone,[29] 2-bromo-2-cyano-*N*,*N*-dimethylacetanide (BCDA)[31] or trimethylbromosilane–dimethylsulfoxide (TMBS–DMSO).[32]

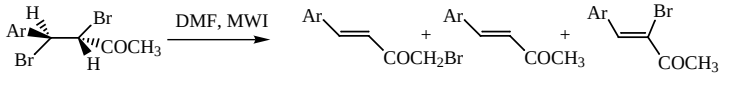
Table 5 Debromination of **8** by DMF Alone under MWI

Substrate	T (°C)	t (min)	Yield (%)[a]	**9** (%)	**10** (%)	**11** (%)	Yield **9**[d]	Bp (°C/mbar) or Mp (°C)
8a	80	5	[b]	–	–	–		
8a	80	15	92	64	28	8		
8a	80	30	92	76	21	3		
8a	80	45	92	83	13	4	83	108–110/0.03[28,32]
8a	150	5	92	58	33	9		
8a	150	15	60[c]	40	35	25		
8b	80	15	90	36	50	14		
8b	80	45	87	85	9	4	64	106
8b	150	5	99	74	19	7		
8b	150	15	86	60	30	10		
8c	80	5	81	49	43	8		
8c	80	15	96	71	19	10		
8c	80	30	66	72	18	10		
8c	80	45	90	80	16	4	63	79–80[27]
8c	150	5	81	69	23	8		
8c	150	15	66[c]	47	35	18		

[a] Yield of crude reaction mixture.
[b] No reaction.
[c] Degradation of crude mixture.
[d] Isolated yield.

It appears that microwave irradiation at 80 °C for 45 min is much more simple. The formation of **9** results from bromination of the alkene **10** via the enolic form and this explains the regioselectivity of bromine as is already demonstrated in the literature[32] in different reaction media. In order to make sure of this, we have realised the following experiments: starting from pure **10**, the addition of bromine in DMF at r.t. leads to **9**–**11**. Under the same conditions (DMF, 80 °C, 45 min), 2,3-dibromo-1,3-diphenylpropanone (which is non-enolisable) remains unchanged.

We have set up selective routes for the debromination and the dehydrobromination/demethoxycarbonylation of α,β-



Ar: **a**: C_6H_5
b: *p*ClC_6H_4
c: *p*$MeOC_6H_4$

Scheme 6

dibromoesters. Starting from α,β-dibromoketones, we were able to prepare α-bromoketones. These various selective methods use very simple reagents and rather short reaction times under microwave irradiation.

NMR spectra were run on a Bruker FTAM 200 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. HRMS (EI) was performed at the Centre de Mesures Physiques de l'Ouest, Rennes on a Varian MAT 311 spectrometer. Microwave irradiations were realised in a Synthewave® 402 oven (Prolabo). The temperatures were measured with a built in IR captor. The maximum power was 300 W and the cylindrical reactors were 1.8 cm diameter for analytic reactions and 4 cm diameter for quantitative reactions (isolation of products). The distillations were carried out in a Kugelröhr (Büchi GKR-50). Unless otherwise stated all the compounds were identified by comparison with literature data.

Dehydrobromination of α,β-Dibromoester by Amines Leading to the α-Bromoesters 4 (*Z* and *E*)

For analytical purpose, amine (2 equiv) [piperidine (0.25 g) or Et_3N (0.3 g)] were added to the α,β-dibromoesters (1 equiv, 1.5 mmol). The mixture was then irradiated in the microwave oven with monitoring of the temperature. According to the reaction time, the assigned temperature was reached after 2–5 min and then maintained for the appropriate time. After cooling, the crude reaction mixture was extracted with CH_2Cl_2 washed with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by distillation. For isolation and purification needs, the quanitities of substrates were multiplied by 10.

Debromination by DMF to form the Alkenes 5

DMF (8.5 equiv, 1 mL) was added to the α,β-dibromoester (1 equiv, 1.5 mmol) and the solution was irradiated in the microwave oven. The monitored temperature of 150 °C was reached in 2 min and maintained for the appropriated time. After cooling, CH_2Cl_2 was added and the solution was washed with water (4 ×) and then dried over $MgSO_4$. After removal of CH_2Cl_2 under vacuum, the crude mixture was analysed by ^1H NMR.

(*E*)-β-Bromostyrene 6 from α,β-Dibromoesters in the Presence of Et_3N in DMF

In the cylindrical reactor (1.8 cm or 4 cm diameter) was placed Et_3N (3 equiv, 0.45 mL) in a mixture of DMF (8.5 equiv, 1 mL) and the dibromoester (1 equiv). With a power of 300 W, the temperature of 150 °C was reached in 5 min and then maintained for 30–45 min. After cooling, CH_2Cl_2 was added and the solution was washed with water (4 ×). After drying over $MgSO_4$ and removal of CH_2Cl_2 under vacuum, the crude mixture was analysed by ^1H NMR and then the product was purified either by distillation or by flash chromatography over SiO_2.

α-Bromoketones 9 Starting from α,β-Dibromoketones

The α,β-dibromoketone (1 equiv, 1.5 mmol) was added to of DMF (8.5 equiv, 1 mL) and irradiated with a monitored temperature of 80 °C which was reached after 5 min and maintained for 45 min. The product was purified as above. Compound **9b** was not found in the literature; mp 106 °C (petroleum ether, bp = 35–60°C).

^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.08 (s, 2 H, CH_2), 6.62 (d, ^2J = 16.02 Hz, 2 H, CH) and 7.64 (d, ^2J = 16.02 Hz, 2 H, CH), 7.37 (d, ^2J = 8.52 Hz, 2 H, CH_{ar}), 7.50 (d, ^2J = 8.52 Hz, 2 H, CH_{ar}).

^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 33.19 (t, ^1J = 151.38 Hz, CH_2), 122.57 (d, ^1J = 158.56 Hz, CH), 129.36 (dd, ^1J = 167.45 Hz, ^2J = 4.95 Hz, CH), 129.79 (dt, ^1J = 161.75 Hz, ^2J = 6.12 Hz, C_m), 132.45 (s, C_q), 137.08 (s, C_q), 143.83 (dt, ^1J = 155.6 Hz, ^2J = 4.72 Hz, C_o), 190.78 (sq, ^2J = 3.47 Hz, CO) ppm.

HRMS: *m*/*z* calcd for $C_{10}H_8OClBr$ (M^+): 257.94470; found: 257.9450.

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