J. Chem. Sci., Vol. 117, No. 1, January 2005, pp. 27–32.

Studies on NaI/DMSO induced *retro*-Michael addition (RMA) reactions on some 1,5-dicarbonyl compounds

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MS received 5 August 2004; revised 29 December 2004

Abstract. Studies on the reaction of some 1,5-ketodiesters/1,5-diketones with NaX (X = Cl/Br/I)/ DMSO have shown that under microwave/thermal conditions, facile *retro*-Michael addition (RMA) reaction takes place instead of formation of the expected Krapcho products. Mechanistic studies have shown that the NaI/DMSO system is a better system than NaCl/DMSO or NaBr/DMSO to promote the RMA pathway and DMSO is an essential requirement. The electrophilic halide ion could be involved in this fragmentation reaction.

Keywords. *retro*-Michael addition; microwave-mediated organic reactions; retro reactions.

1. Introduction

Generally two alternative methods are employed for selective mono-dealkoxycarbonylation of *gem*-diesters to the corresponding monoesters. The first one is a straightforward, three-step procedure involving sequentially, (i) base mediated hydrolysis of the diester to the corresponding diacid, (ii) pyrolysis under reduced pressure to affect mono-decaroxylation, (iii) esterification of the resulting mono-acid to the mono-ester.[1] In the alternative one-pot Krapcho procedure, the diester is heated to reflux in DMSO in the presence of sodium chloride to furnish the monoester directly.[2] A few other salts such as potassium cyanide,[3] sodium cyanide,[4] lithium chloride[5] are also found to promote this widely used reaction. We reasoned that as DMSO responds to passing microwaves due to its high dielectric constant (46·45),[6] The Krapcho method could work well under microwave irradiation. Previously Loupy *et al*[7] showed that the mono-decarboethoxylation of selected diesters can be performed readily in the presence of lithium bromide and a phase transfer catalyst. However, there are no studies on microwave-mediated dealkoxycarbonylation of diesters with an inbuilt 1,5-dicarbonyl function. Therefore, in this study we have attempted decarboethoxylation of the diester **1a** using NaCl/ DMSO under microwave irradiation expecting the formation of the monoester **4**. However, surprisingly, the major products formed in the reaction are the *retro*-Michael addition (RMA) product, 1,3-diphenyl-2-propene-2-one (chalcone, 84%) **2a** and diethyl melonate **3** (84%; scheme 1). The expected Krapcho product, the monoester **4**, was the minor product (16%).

The RMA reaction is known to occur readily under biological conditions.[8] However, only a few RMA reactions have taken place in laboratory syntheses.[9] Moreover, studies on the scope of RMA reactions, particularly those involving 1,5-ketodiesters and 1,5-diketones compounds are rare, though the reaction is known to take place for some aromatic 1,5-diketones during mass spectral fragmentation.[10] Albrecht and coworkers[11] studied the RMA reaction of selected 1,5-diketones and showed that the reaction could be improved by using steam distillation in the presence of sodium hydroxide adsorbed on glass wool as catalyst. Li and Wang[12] studied steam-mediated RMA reaction for some 1,5-diketones present in steroid-like molecules.[12]

2. Results and discussion

Since we found an unexpected and facile RMA reaction taking place on **1a** under Krapcho conditions, we set out to study the scope of the reaction. Towards this goal, we have varied reaction conditions such as the salt and the solvent used by taking the transformation of **1a** to **2a** as a test case. The results from

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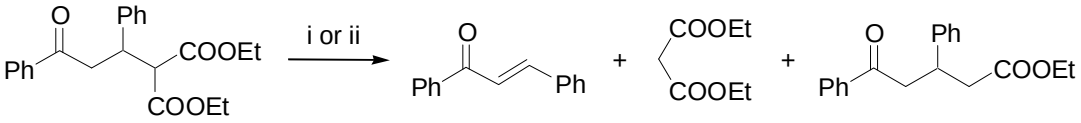


1a **2a** **3** **4**

Scheme 1. Reagents and conditions: (i) NaCl, DMSO, MW, 400 W, 2 min, quantitative, **2a**, **3** : **4** = 84 : 16; (ii) NaCl, DMSO, 160°C, 5 h, 90%, **2a**, **3** : **4** = 81 : 19.

Table 1. Reaction of diesters **1a** under microwave irradiation with different conditions.

Sl. no.	Reagent	Solvent	Power (W)	Time (min)	Yield of **2a** (%)
1	NaCl	DMSO	400	2	84
2	NaCl	DMF	640	5	No reaction
3	NaCl	NMP	640	5	No reaction
4	NaCl	Water	640	5	No reaction
5	NaCl	PEG-200	640	5	No reaction
6	Na_2SO_4	DMSO	640	5	No reaction
7	K10 Clay	–	640	5	No reaction
8	K10 Clay	DMSO	640	5	No reaction
9	K10 + NaCl[a]	–	640	5	No reaction
10	Al_2O_3 + NaCl[a]	–	640	5	No reaction
11	KBr	DMSO	400	2	94
12	NaBr	DMSO	400	2	87
13	NaI	DMSO	400	2	97
14	I_2	DMSO	400	2	20

[a]NaCl coated on K 10/Al_2O_3 (1 : 1)

this study are gathered in table 1. Initially we changed the solvent used in the reaction to evaluate its role and efficacy. The RMA reaction on **1a** was conducted in polar solvents such as DMF (entry 2, table 1), NMP (entry 3, table 1), water (entry 4, table 1) and PEG-200 (entry 5, table 1) apart from DMSO (entry 1, table 1). In all the cases, other than where DMSO was used as a solvent there was no RMA product and the starting diester **1a** was isolated as such. This result indicated that DMSO is essential for the RMA reaction. Next, we changed the salt (NaCl) to evaluate its role in the transformation. There was no RMA product formation when Na_2SO_4/DMSO was used instead of NaCl/DMSO (entry 6, table 1). This result indicates that a halide ion is also a requirement for the RMA reaction. The RMA reaction did not take place when it was conducted under solid-phase conditions using acidic clay, Montmorillonite K10 (entry 7, table 1), Montmorillonite K10 and DMSO (1 : 1 by weight; entry 8, table 1), Montmorillonite K10 and NaCl (1 : 1 by weight; entry 9, table 1) or Al_2O_3 (neutral, 100–200 mesh) and NaCl (1 : 1 by weight; entry 10, table 1), supporting the fact that the reaction takes place only when both NaCl and DMSO are present. In all the cases microwave instrument power was raised from 400 W to 640 W and the reactants were exposed to microwaves for a period of at least 5 min to evaluate formation of a product.

To investigate the role of the counter halide ion on the RMA reaction, the ketodiester **1a** was subjected to microwave irradiation in the presence of KBr/DMSO (entry 11, table 1), sodium bromide in DMSO (entry 12, table 1) or sodium iodide in DMSO (entry 13, table 1). It is clear from table 1 that the maximum yield of the RMA product **2a** could be obtained when the reaction was conducted with NaI/DMSO. From this experiment we concluded that sodium iodide in DMSO is the best to promote the microwave-mediated RMA reaction. Moreover, unlike the NaCl/DMSO system (scheme 1), reaction with NaI/DMSO did not exhibit the formation of Krapcho product even in traces.

To evaluate whether the NaI/DMSO-mediated RMA reaction of **1a** takes place only under microwave irradiation or takes place under thermal conditions also, we conducted the reaction under normal thermal conditions in a pre-heated oil-bath. The transformation of **1a** to **2a** took place smoothly at

160°C but the reaction required 5 h for completion and the yield of **2a** was 96%. The transformation of **1a** to **2a** under thermal conditions (160°C) took place even when NaCl/DMSO was employed but the yield of enone **2a** was marginally lower (90%). From this study, we concluded that there was not much difference between microwave and normal thermal conditions except that the rate of disintegration of **1a** to **2a** under microwave conditions was faster by a factor of $1{\cdot}5 \times 10^2$ compared to that of thermal conditions,

$$2NaI + CH_3SOCH_3 + H_2O \rightarrow I_2 + CH_3SCH_3 + 2NaOH. \quad (1)$$

From the results presented in table 1 it clear that both NaX (X = Cl, Br, I) and DMSO are necessary for inducing the conversion of **1a** to **2a** via the RMA pathway. A possible mechanism for the transformation is given in figure 1. We believe that under microwave/thermal conditions an electrophilic halide ion is generated, which helps to eject diethylmalonate **3** from the substrate in RMA fashion through intermediates **5** and **6**. The electrophilic halide ion may be generated from the halogen molecule formed *in situ*, due to the oxidizing nature of DMSO, (1). Since open vessels were used for conducting the microwave-mediated reaction, we believe that atmospheric or dissolved water plays a role in the generation of electrophilic iodide ion as given in (1). Previously, Watt and Ji[13] reported the use of sodium iodide and chloramine T in DMSO for iodination of phenols. In this transformation, sodium iodide was the source for electrophilic iodine and chloramine T was used as an oxidizing agent. To best of our knowledge, ours is the first report of the formation of an electrophilic halide ion from NaX/DMSO.

Support for the proposed mechanism also came from the following observations. We noted that the reaction mixture for the conversion of **1a** to **2a** emitted the pungent smell of dimethyl suphide, even though we could not gather any experimental proof of its formation. We observed the conversion of **1a** to **2a** with I_2/DMSO under microwave conditions (entry 14, table 1), indicating that the electrophilic iodonium ion is indeed responsible for the transformation.

There was no reaction, when the monoester **4** was exposed to microwaves in the presence of sodium iodide in DMSO. The starting material **4** was recovered unchanged even after 10 min (scheme 2). This result is possibly due to the fact that diethyl malonate is a better leaving group compared to ethyl acetate. Similarly, the alcohol **7** did not undergo any change, showing that the keto group in **1a** is necessary for ejecting the diethyl malonate unit.

To test the generality of the reaction, and to evaluate the electronic influence of substituents on the aromatic rings, the diesters **1b–c** were exposed to microwaves in the presence of NaI/DMSO (scheme 3 and table 2). In both the cases the RMA products **2b–c** along with diethyl melonate **3** were obtained in near quantitative yields. The result shows that the electron-withdrawing (Cl, **1b**, entry 2, table 2) or -donating (CH_3, **1c**, entry 3, table 2) nature of the substituents on the aromatic ring of **1a** did not have much effect on the course of the reaction.

When dimethyl 2-(1-benzoyl-3-oxo-3-phenylpropyl) malonate **1d** was subjected to microwave irradiation in the presence of NaI/DMSO the reac-

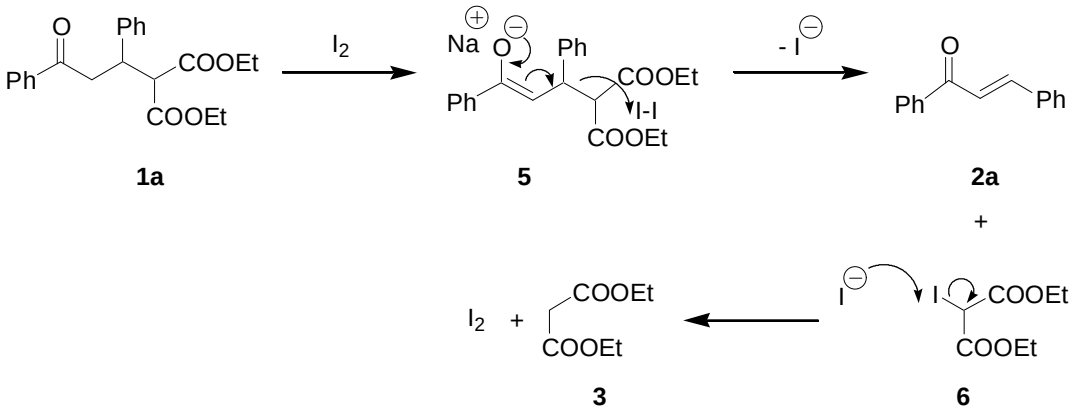
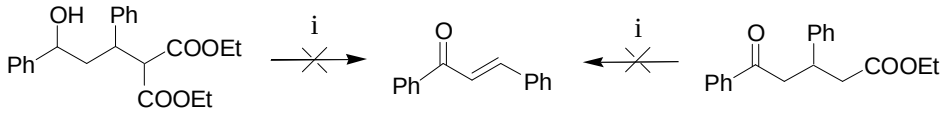


Figure 1. Mechanism for the conversion of 1,5-ketoester **1a** to enone **2a** and diethylmalonate **3**.



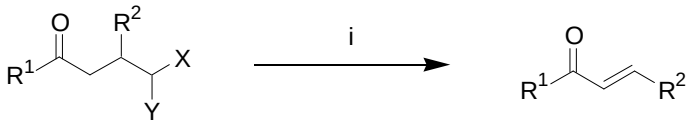
7 **2a** **4**

Scheme 2. Reagents and conditions: (i) NaI, DMSO, MW, 200–400 W, 10 min.

Table 2. Reaction of Michael adducts **1a–h** with NaI in DMSO under microwave irradiation at 450 W at 2 min.

Sl. no.	R^1	R^2	X	Y	Michael adduct	Product	Yield (%)
1	C_6H_5	C_6H_5	COOEt	COOEt	**1a**	**2a**[a]	97
2	4-ClC_6H_4	C_6H_5	COOEt	COOEt	**1b**	**2b**[a]	98
3	4-$CH_3C_6H_4$	C_6H_5	COOEt	COOEt	**1c**	**2c**[a]	93
4	C_6H_5	COC_6H_5	COOEt	COOEt	**1d**	**2d**[a]	85
5	C_6H_5	C_6H_5	COOEt	COC_6H_5	**1e**	**2a**	92
6	C_6H_5	C_6H_5	COOEt	CN	**1f**	**2a**	93
7	C_6H_5	C_6H_5	$CO(CH_2)_4$	–	**1g**	**2a**	90
8	C_6H_5	C_6H_5	$CO(CH_2)_5$	–	**1h**	**2a**	89

[a]Reference 15



1b–h **2a–d**

1b: R^1 = 4-ClC_6H_4, R^2 = C_6H_5, X = Y = COOEt
1c: R^1 = 4-$CH_3C_6H_4$, R^2 = C_6H_5, X = Y = COOEt
1d: R^1 = C_6H_5, R^2 = COC_6H_5, X = Y = COOEt
1e: R^1 = R^2 = C_6H_5, X = COOEt, Y = COC_6H_5
1f: R^1 = R^2 = C_6H_5, X = COOEt, Y = CN
1g: R^1 = R^2 = C_6H_5, X = $CO(CH_2)_4$, Y = H
1h: R^1 = R^2 = C_6H_5, X = $CO(CH_2)_5$, Y = H

2a: R^1 = R^2 = C_6H_5
2b: R^1 = 4-ClC_6H_4, R^2 = C_6H_5
2c: R^1 = 4-$CH_3C_6H_4$, R^2 = C_6H_5
2d: R^1 = C_6H_5, R^2 = COC_6H_5

Scheme 3. Reagents and conditions: (i) NaI, DMSO, MW, 450 W, 2 min, 75–98%.

tion resulted in (*E*)-1,4-diphenyl-2-butene-1,4-dione (dibenzoyl ethylene, **2d**), along with diethyl melonate **3**, formed without any event (entry 4, table 2; scheme 3).

Next, we studied the microwave-mediated RMA reaction on the Michael adducts **1e–h** as shown in table 2 (scheme 3). It can be seen from table 2 that excellent yields of RMA product **2a** were obtained in all the cases. Surprisingly, even the adducts **1g** and **1h** underwent RMA reaction under microwave conditions to eject cyclopentanone and cyclohexanone respectively, albeit in lower yields. The results show that apart from diethyl melonate, ethyl benzoylacetate (entry 5, table 2 and **1e** → **2a**), ethyl cyanoacetate (entry 6, table 2 and **1f** → **2a**), cyclohepentanone (entry 7, table 2 and **1g** → **2a**), and cyclohexanone (entry 8, table 2 and **1f** → **2a**) also are good leaving groups under the present conditions.

In conclusion, we have shown that facile RMA reaction on 1,5-ketodiesters/1,5-diketones takes place when adducts are exposed to microwaves in the presence of NaI/DMSO. Mechanistic studies have

shown that NaI/DMSO system is better than NaCl/DMSO and presence of DMSO is necessary to promote the RMA pathway.

3. Experimental section

All reagents and solvents were purchased from E-Merck and Sisco Chemicals, India. Microwave reactions were carried out using Samsung, India; monomode and multi-power microwave oven (power source: 230 V, 50 Hz, microwave frequency: 2450 MHz). The TLC (pre-coated silica gel 60 F_{254}, Merck) method was used to monitor the progress of the reaction. Melting points were noted using a Gallenkamp melting point apparatus. IR spectra were recorded as KBr pellets using a Bomem MB104 spectrometer. The frequencies at which the ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 300 MHz NMR instrument are noted in the spectral data. TMS was used as internal standard. GC analysis was performed on a Systronic (Model: 5700; detector: FID). All starting materials **1a–h** and products **2a–d** are known.[14,15] The authenticity of the starting materials and the products were ensured on the basis of spectroscopic, and analytical data and by comparison with authentic samples.

3.1 *General procedure for microwave-mediated RMA reaction: Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate* **1a** *with NaI/DMSO*

A 25-mL conical flask, charged with Michael adduct **1a** (500 mg, 1·33 mmol) and sodium iodide (408 mg, 2·71 mmol) in DMSO (2 mL) was irradiated in the microwave oven at 450 W for 2 min. After completion of the reaction (TLC), it was cooled (rt), the reaction mixture was transferred into water (10 mL) and the aqueous layer was extracted with dichloromethane (2 × 10 mL). GC analysis showed the formation of diethyl malonate and chalcone in equal proportions. Removal of solvent after drying with anhydrous Na_2SO_4 resulted in crude product, which was purified on a short column of silica (1 cm × 10 cm) by eluting with increasing percentage of ethyl acetate in hexane (1% → 3%). Removal of solvent from pooled fractions resulted in the separation of (*E*)-1,3-diphenyl-2-propen-1-one **2a** and diethyl malonate **3**. Analytically pure sample of **2a** (275 mg, 97%) was obtained by recrystallization from DCM/hexanes (2 : 98).

3.2 *(E)-1-(4-chlorophenyl)-3-phenyl-2-propen-1-one* (**2b**) *and diethyl malonate*

Following the above general procedure, Michael adduct, diethyl 2-[3-(4-chlorophenyl)-3-oxo-1-phenylpropyl]malonate, **1b** (100 mg, 0·25 mmol), was transformed to **2b** with sodium iodide (75 mg, 0·5 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min. Yield of **2a**: 60 mg (98%).

3.3 *(E)-1-(4-methylphenyl)-3-phenyl-2-propen-1-one* (**2c**) *and diethyl malonate*

Following the above general procedure, Michael adduct, diethyl 2-[3-(4-methylphenyl)-3-oxo-1-phenylpropyl]malonate **1c** (100 mg, 0·26 mmol) was transformed to **2c** with sodium iodide (78 mg, 0·52 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min. Yield of **2a**: 54 mg (93%).

3.4 *(E)-1,4-diphenyl-2-butene-1,4-dione (dibenzoyl ethylene,* **2d***) and diethyl malonate*

Following the above general procedure, Michael adduct, diethyl 2-(1-benzoyl-3-oxo-3-phenylpropyl) malonate **1d** (100 mg, 0·22 mmol) was transformed to **2d** with sodium iodide (67 mg, 0·44 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min. Yield of **2a**: 55 mg (85%).

3.5 *(E)-1,3-diphenyl-2-propen-1-one (***2a***) and ethyl 3-oxo-3-phenylpropanoate*

Following the above general procedure, Michael adduct, ethyl 2-benzoyl-5-oxo-3,5-diphenylpentanoate **1e** (100 mg, 0·26 mmol) on treatment with sodium iodide (76 mg, 0·5 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min was transformed to **2a** and ethyl 3-oxo-3-phenylpropanoate. Yield of **2a**: 48 mg (92%); yield of ethyl 3-oxo-3-phenylpropanoate: 42 mg (88%).

3.6 *(E)-1,3-diphenyl-2-propen-1-one (***2a***) and ethyl cyanoacetate*

Following the above general procedure, Michael adduct, Ethyl 2-cyano-5-oxo-3,5-diphenylpentanoate **1f** (100 mg, 0·30 mmol) was transformed to **2a** with sodium iodide (100 mg, 0·66 mmol) in DMSO (1 mL)

under microwave irradiation at 450 W for 2 min. Yield of **2a**: 60 mg (93%); formation of ethyl cyanoacetate was detected by GC.

3.7 *(E)-1,3-diphenyl-2-propen-1-one (**2a**) and cyclopentanone*

Following the above general procedure, Michael adduct, 2-(3-oxo-3-phenylpropyl)-1-cyclopentanone **1g** (100 mg, 0·33 mmol) was transformed to **2a** with sodium iodide (100 mg, 0·67 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min. Yield of **2a**: 64 mg (90%); yield of cyclopentanone: 25 mg (86%).

3.8 *(E)-1,3-Diphenyl-2-propen-1-one (**2a**) and cyclohexanone*

Following the above general procedure, Michael adduct, 2-(3-oxo-3-phenylpropyl)-1-cyclohexanone **1h** (100 mg, 0.33 mmol) was transformed to **2a** with sodium iodide (100 mg, 0·67 mmol) in DMSO (1 mL) under microwave irradiation at 450 W for 2 min. Yield of **2a**: 61 mg (89%); yield of cyclohexanone: 28 mg (87%).

3.9 *General procedure for RMA reaction under thermal condition: (E)-1,3-diphenyl-2-propen-1-one (**2a**) and diethyl malonate*

A 10 mL round-bottom flask, charged with Michael adduct, diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate **1a** (100 mg, 0·27 mmol) and sodium iodide (40·7 mg, 0·27 mmol) in DMSO (2 mL) was heated to 160°C for 5 h. After completion of the reaction (TLC), it was cooled (rt), and the reaction mixture was transferred into water (20 mL). After due work up and chromatographic purification as described previously, the reaction furnished **2a**. Analytically pure sample of **2a** (54 mg, 96%) was obtained by recrystallization from DCM/hexanes (2 : 98).

Acknowledgments

SJ thanks Council of Scientific and Industrial Research, New Delhi for a fellowship. HSPR thanks the UGC-SAP programme and the CSIR for financial support. We thank Prof A Srikrishna of the Indian Institute of Science for spectra and helpful discussions.

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