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Combined dealkoxycarbonylation and lactonisation of unsaturated malonates in ionic liquids

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Abstract—Heating unsaturated malonates with LiCl and water in [bmim][Br] or [bmim][BF_4]/[bmim][Br] produces unsaturated esters or lactones, respectively.

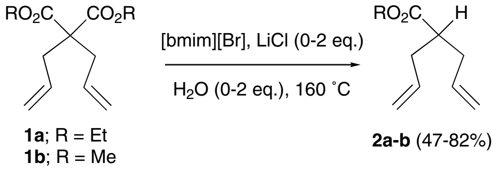
Decarboxylation is an important reaction in organic synthesis. The preparation of many important target molecules, including natural products, involves the removal of unwanted carboxyl groups from carboxylic acids and esters.[1] Of particular synthetic importance is the decarboxylation of malonates, which traditionally requires two steps—basic hydrolysis of the esters is followed by treatment with acid and heating. Alternatively, Krapcho showed that dealkoxycarbonylation is achieved in a single step by heating the malonate with water and inorganic salts in DMSO or DMF.[2] Besides being a single-step procedure, the Krapcho approach is milder than the traditional procedure and acid- or base-sensitive functional groups survive the reaction conditions.[3]

One disadvantage to the Krapcho method is the use of DMSO or DMF as the solvent. DMSO easily penetrates the skin and it serves as a carrier for other chemicals, so increasing their toxic effects, while DMF is toxic to the liver. Industrial grade DMSO and DMF must be handled with particular care and this, together with the problems of removing these solvents from organic products (which generates large quantities of aqueous waste or requires high temperatures), has detracted from the use of these solvents on a large scale.

To overcome the problems of using DMSO or DMF in the Krapcho reaction, this letter reports novel reactions of malonates with water and LiCl in 1-butyl-3-methylimidazolium ([bmim]) ionic liquids.[4] Ionic liquids have recently emerged as a popular alternative to polar organic solvents and they offer a potentially cleaner liquid medium in which to conduct synthesis.[5]

Initial studies concentrated on decarboalkoxylation of diallylmalonates **1a**–**b** in [bmim][Br][6] (Scheme 1). Very slow decarboxylation of **1a** was observed (**2a** was isolated in 82% yield after 5 days) although addition of H_2O and/or particularly LiCl increased the rate of decarboalkoxylation. For example, heating **1a** in [bmim][Br] with LiCl (2 equiv) for ~24 h gave **2a** in 51% yield. Decarboalkoxylation of methyl ester **1b** was generally faster than ethyl ester **1a** (under the same conditions), although **2b** was isolated in only 47% yield after heating for 2 h in [bmim][Br] with LiCl (2 equiv). This was thought to be due to the volatility of **2b** and so decarboalkoxylation to form less volatile esters was investigated.

As shown in Scheme 2 and Table 1, demethoxycarbonylation of various dimethyl malonates proceeded in good to excellent yield in [bmim][Br].[7] Methyl esters **4a**–**d** were isolated in comparable yields to those obtained



Scheme 1.

Keywords: Decarboxylation; Ionic liquid; Lactonisation.

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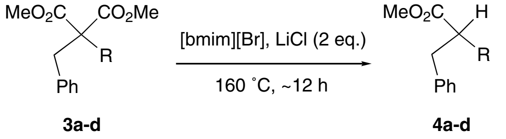


Scheme 2.

Table 1. Demethoxycarbonylation of dimethyl malonates **3a–d**

Precursor	R	Product	Yield (%)
3a	–$CH_2CH{=}CH_2$	**4a**	99
3b	–$CH_2CH{=}CMe_2$	**4b**	82[a]
3c	–CH_2Ph	**4c**	84
3d	–H	**4d**	95

[a] Heating with LiCl (4 equiv) and H_2O (2 equiv) in DMSO for 22 h gave **4b** in 84% yield.

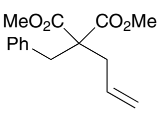
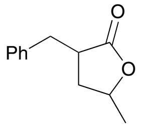
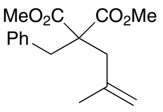
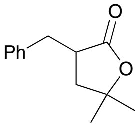
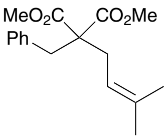
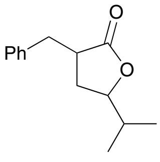
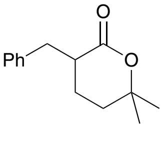
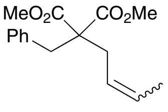
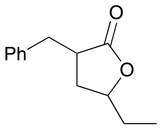
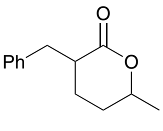
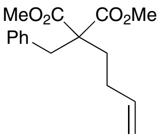
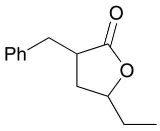
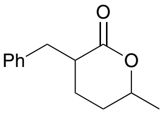
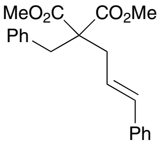
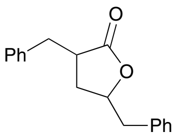
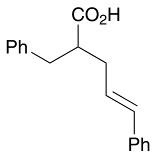
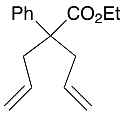
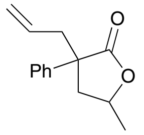
when using the Krapcho method. In all cases, [bmim][Br] was recovered in ~70% yield after workup (and can be reused).

Interestingly, a different product is formed when dimethyl malonate **3a** is heated with LiCl (4 equiv) and H_2O (2 equiv) in a 1:1 mixture of [bmim][Br]:[bmim][BF_4]. After heating overnight, γ-butyrolactone **6a** was isolated in an excellent 89% yield (as a 1.3:1 mixture of diastereoisomers) after column chromatography (Table 2).[8,9] Similar reactions were observed for malonates **5a–e** and ester **5f**. Lactones were generally isolated in excellent yield and the size of the ring was shown to depend on the position and substitution of the C=C bond—this is consistent with an acid-promoted cyclisation (see later). Lactones were also isolated when unsaturated malonates or esters were heated solely in [bmim][BF_4][10] (although the reactions were generally slower), with varying amounts of LiCl and/or H_2O, and this proved that [bmim][BF_4] plays a crucial role in the formation of the lactones.

Formation of lactones in [bmim][BF_4] is expected to involve acid promoted cyclisation of the unsaturated malonates (Scheme 3). For example, for formation of γ-butyrolactone **6a**, regioselective protonation of the C=C bond in **3a** is expected to form a secondary carbocation and nucleophilic attack by an ester or carboxylic acid group produces the five-membered ring. Cyclisation before and/or after demethoxycarbonylation of the CO_2Me group is possible. (After short reaction times, particularly with diethyl malonates, lactones containing an ester group may be isolated—these lactones undergo dealkoxylation on further heating with LiCl, H_2O in [bmim][BF_4].) It is likely that the acid responsible for lactonisation of the unsaturated malonates is HF, which has recently been shown to be formed on hydrolysis of [bmim] ionic liquids,[11] including [bmim][BF_4].[12]

This novel synthetic approach to lactones compares favourably with other methods. Direct conversion of unsaturated esters into lactones is rare[13] and normally requires two steps—basic hydrolysis forms the unsaturated carboxylic acid, which is subsequently converted

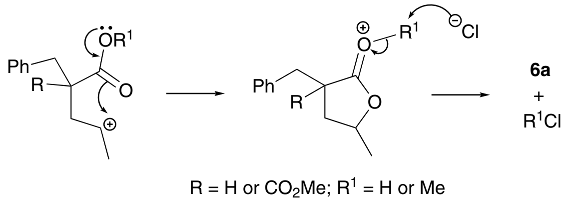
Table 2. Products formed from heating **3a**, **5a–f** with LiCl (4 equiv) and H_2O (2 equiv) in [bmim][BF_4]/[bmim][Br] for ~24 h

Precursor	Product (yield (%)/d.r.)	
 **3a**	 **6a** (89% / 1.3:1)	
 **5a**	 **6b** (93%)	
 **5b**	 **6c** (45% / 1.3:1)	 **7a** (45%)
 **5c** (*E*-:*Z*- = 5:1)	 **6d** (49% / 1:1)	 **7b** (34% / 1.9:1)
 **5d**	 **6d** (55% / 1.1:1)[b]	 **7b** (5% / 1.7:1)
 **5e**	 **6e** (15% / 1.3:1)[c]	 **8** (80%)
 **5f**	 **6f** (67% / 4.1:1)[a]	

[a] After heating for 4 h in [bmim][BF_4] (the ionic liquid was recovered in ~80% yield).

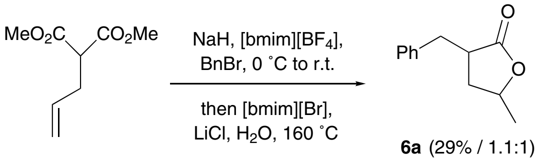
[b] Presumably formed by initial isomerisation of **5d** to give **5c**.

[c] The unexpected formation of the γ-butyrolactone was confirmed by a strong absorption band at 1768 cm^{-1} (C=O) in the IR spectrum.



R = H or CO_2Me; R^1 = H or Me

Scheme 3.



Scheme 4.

into the lactone by selenolactonisation,[14] iodolactonisation,[15] or by heating with strong acids.[16] In comparison, heating in [bmim][BF$_4$]/[bmim][Br] with LiCl and H$_2$O offers a direct and efficient approach to variously substituted lactones from malonates. This is expected to be useful to synthetic chemists because alkylation of malonates followed by decarboalkoxylation is a well-used strategy for regioselective α-alkylation of carbonyls. Indeed, alkylation of dialkyl malonates can be combined with decarboalkoxylation and lactonisation in a one-pot procedure (Scheme 4).

Acknowledgements

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References and notes

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7. Typical procedure: dimethyl allylbenzylmalonate **3a** (131 mg, 0.50 mmol), lithium chloride (42 mg, 1.0 mmol) and [bmim][Br] (0.5 g) were heated at 160 °C for 14 h. After cooling, the mixture was partitioned between water and diethyl ether. The aqueous layer was extracted with further diethyl ether and the combined organic extracts were washed with brine, dried, filtered, evaporated and purified by column chromatography (silica). This gave methyl 2-benzylpent-4-enoate **4a** (101 mg, 99%) as a colourless oil.
8. All new compounds gave consistent spectral and HRMS data.
9. Typical procedure: dimethyl allylbenzylmalonate **3a** (131 mg, 0.50 mmol), lithium chloride (85 mg, 2.0 mmol), water (18 mg, 1.0 mmol), [bmim][Br] (0.5 g) and [bmim][BF$_4$] (0.5 mL) were heated at 160 °C for 22 h. After cooling, the mixture was partitioned between water and diethyl ether. The aqueous layer was extracted with further diethyl ether and the combined organic extracts were washed with brine, dried, filtered, evaporated and purified by column chromatography (silica). This gave 3-benzyl-5-methyl-dihydrofuran-2-one **6a** (85 mg, 89%) as a colourless oil as a 1.3:1 mixture of diastereoisomers (from the ^{1}H NMR spectrum).
10. Similar results were obtained when [bmim][PF$_6$] was used in place of [bmim][BF$_4$].
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