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$CuBr_2$-mediated direct aqueous bromolactonization of 2,3-allenoates. An efficient access to β-bromobutenolides

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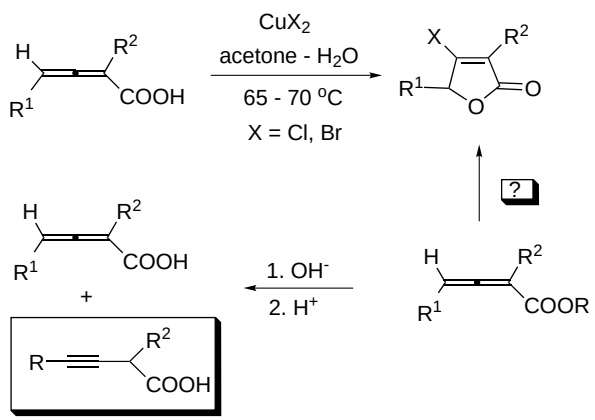
Abstract—An efficient procedure for the synthesis of β-bromobutenolides was developed. 2,3-Allenoates with different substitution patterns react with $CuBr_2$ in aqueous ethanol at 80–85°C to afford the corresponding β-bromobutenolides in moderate to excellent yields (up to 97%).

Butenolides can be found in many natural products with an unusual range of biological activities.[1] Since butenolide-containing compounds have been considered as potential insecticides, bactericides, antibiotics, anticancer agents, anti-inflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors and phospholipase A_2 inhibitors, etc.[2] this unit also represents a structural feature of compounds of pharmaceutical interest. In addition, they appear to be versatile intermediates[3,4] for the synthesis of cyclic and acyclic systems. Recently, much attention has been focused on the efficient and diverse synthesis of these valuable compounds,[4] particularly β-halobutenolides.[5] This is, in large part, due to biologically active natural products[6] isolated from marine sources which have β-halobutenolides as their structural moieties.

During the course of our project aimed at exploration of new synthetic uses of functionalized allenes,[7] we have recently developed a high-yielding procedure for the synthesis of β-halobutenolides from 2,3-allenoic acids and CuX_2 (X = Br or Cl) (Scheme 1).[8] In this transformation, most of the starting materials, i.e. the 2,3-allenoic acids, were obtained from the corresponding esters by hydrolysis. In some cases the yields were low.[9] Furthermore, the concomitant formation of 3-alkynoic acids was often observed, even as the sole products in some cases (Scheme 1).[10] Hence, it was highly desirable to develop new methodologies using the esters of 2,3-allenoic acids directly as the starting materials.

2,3-Allenoates with different substitution patterns are easily available through Wittig-type reactions.[11] As a starting point, the reaction conditions ($CuBr_2$, in a 2:1 mixture of acetone/H_2O, 65–70°C) for the halolactonization of 2,3-allenoic acids established previously[8] were used to cyclize ethyl 2-methyl-2,3-decadienoate (**1a**) to afford the corresponding β-bromobutenolide **2a** in a 62% yield within 12 h, together with recovery of **1a** in a 27% yield. After screening, we found that the reaction carried out in an ethanol/water (3:2) medium at 80–85°C gave better results. The starting material **1a** was consumed completely and β-bromobutenolide **2a** was isolated in an 86% yield (Scheme 2). It is noteworthy that bromolactonization of **1a** with NBS under the conditions described in the literature gave the product **2a** only in 53% yield together with 15% of 3-bromo-4-oxo-2-decenoate.[3a,12]



Scheme 1.

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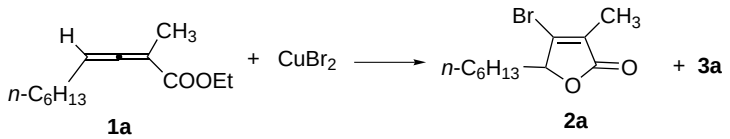
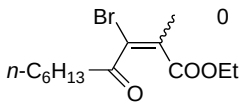


1a 2a

conditions	recovery of **1a**	yield of **2a** +	yield of **3a**
65-70 °C/acetone/H_2O/12 h	27%	62%	0
80-85 °C/ethanol/H_2O/12 h	0	86%	0
NBS/H_2O/rt/14 h	0	53%	15%



3a

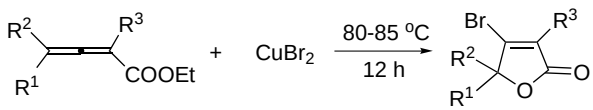
Scheme 2.

With these conditions in hand, this halolactonization reaction was examined for differently substituted 2,3-allenoates, and the results are summarized in Table 1. In all cases, the starting allenoates **1** reacted completely, and the reaction proceeded smoothly and cleanly to give the corresponding β-bromobutenolides **2** in moderate to excellent yields, the highest being 97%. Generally, the yields of 3,5-dialkyl bromobutenolides are higher than those of 3,5,5-trialkyl bromobutenolides (compare entries 1–7 with 8–9). On the other hand, it was previously reported that the bromolactonization of ethyl 2,4-dimethyl-2,3-pentadienoate **1i** with molecular Br_2 afforded the corresponding bromobutenolides **2i** in only a 58% yield.[13] Of special interest to us was that the allenic ester **1k**, which bears an allyl group at the 2-position, reacted with $CuBr_2$ also to give the β-bromobutenolide **2k** in a moderate yield (entry 10). Dibromination of the allylic C=C bond[14] was not observed. Products like **2k**, having different types of functional groups at the 3- and 4-positions should provide efficient access to other butenolide derivatives via further elaboration.

In an attempt to bromolactonize ethyl 4-aryl-2,3-butedienoates under these reaction conditions, rather disappointing results were obtained. For example, from ethyl 2-methyl-4-phenyl-2,3-butedienoate **1l**, the reaction afforded **2l** in 40% yield together with an unidentified product. Nevertheless, when the benzyl ester **1l′** was used instead of the ethyl ester **1l**, the yield of **2l** was improved to 67%. Similarly, bromolactonization of benzyl 2-methyl-4-phenyl-2,3-hexadienoate **1m′** afforded **2m** in 66% yield (Scheme 3).

In conclusion, we have developed a convenient and efficient method for the synthesis of β-bromobutenolides, i.e. the reaction of easily available 2,3-allenoates with $CuBr_2$ in aqueous ethanol. This reaction opens up

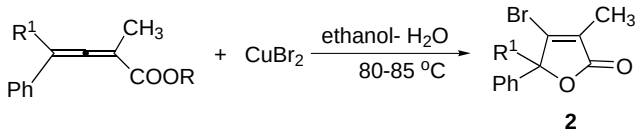
Table 1. Bromolactonization of allenoates with $CuBr_2$[a]



1 2

Entry	**1**			Product	Yield (%)
	R^1	R^2	R^3		
1	n-C_6H_{13}	H	n-C_3H_7 (**1b**)	**2b**	95
2	n-C_6H_{13}	H	$C_6H_5CH_2$ (**1c**)	**2c**	97
3	n-C_3H_7	H	$C_6H_5CH_2$ (**1d**)	**2d**	78
4	n-C_3H_7	H	n-C_3H_7 (**1e**)	**2e**	68
5	n-C_3H_7	H	CH_3 (**1f**)	**2f**	86
6	CH_3	H	CH_3 (**1g**)	**2g**	72
7	CH_3	H	n-C_3H_7 (**1h**)	**2h**	84
8	CH_3	CH_3	CH_3 (**1i**)	**2i**	68
9	CH_3	CH_3	n-C_3H_7 (**1j**)	**2j**	66
10	n-C_3H_7	H	Allyl (**1k**)	**2k**	54

[a] The reaction was carried out using **1** (0.5 mmol), $CuBr_2$ (4 equiv.), and ethanol:H_2O (4 mL, 3:2).



2

1l (R^1 = H, R = C_2H_5) **2l** 40% + unidentified product

1l' (R^1 = H, R = $CH_2C_6H_5$) **2l** 67%

1m' (R^1 = C_2H_5, R = $CH_2C_6H_5$) **2m** 66%

Scheme 3.

new possibilities for the synthesis of optically active butenolides due to the easy availability of optically active 2,3-allenoates.[10] Further studies on the scope and synthetic application of this methodology are being carried out in our laboratory.

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