Short Communication

Selective Formation of 4-Bromo-3-methyl-2(5*H*)-furanone by Solvolysis of 2,2-Dibromo-1-methylcyclopropanecarboxylic Acid

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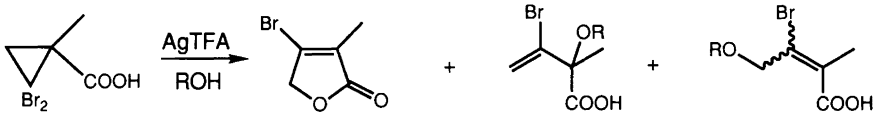
When 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**1**) is solvolyzed in methanol in the dark and in the presence of a silver salt, ring opening of the cyclopropane takes place and a very complex reaction mixture is obtained.[1] One of the products, formed in 25 % yield under the best conditions, is 4-bromo-3-methyl-2(5*H*)-furanone (**2**), a conceivable starting material for the synthesis of various butenolide antibiotics isolated from the red seaweed *Delisea fimbriata* (Bonnemaisoniaceae).[2,3] We therefore wanted to reinvestigate the silver-ion-assisted ring opening of **1** with the aim of improving the yield of butenolide **2**.

Solvolysis of **1** supposedly proceeds via an allylic cation[1,4–6] which furnishes **2** by an intramolecular attack of the carboxy group. When the reaction is carried out in methanol the butenolide formation is inefficient due to solvent trapping of the intermediate. We therefore expected to prevent solvent interference and promote formation of **2** by using a solvent or a solvent mixture considerably less nucleophilic than methanol,[7,8] and this expection was indeed met.

When mixtures of **1** and silver trifluoroacetate (AgTFA) were refluxed in aprotic solvents such as acetonitrile and benzene no reaction occurred. A ring-opening reaction started to take place if some methanol was added, but the progress of the reaction was very slow and the composition of the product mixtures was very similar to that obtained during methanolysis of the same acid.[1] We therefore turned our attention to protic solvents with a lower nucleophilicity than methanol. When the solvolysis was performed in *tert*-butyl alcohol a relatively clean reaction took place to yield **2**, 3-bromo-2-*tert*-butoxy-2-methyl-3-butenoic acid (**3a**) and a 1:1 *E*/*Z* isomer mixture of 3-bromo-4-*tert*-butoxy-2-methyl-2-butenoic acid (**4a**) as the only products (Scheme 1, Table 1). The reaction was much faster than the corresponding methanolysis and could be completed in 3.5 h; this probably reflects the higher temperature reached in refluxing *tert*-butyl alcohol (82 °C) compared with refluxing methanol (64 °C). Furthermore, an extension of the reaction time did not influence the product distribution significantly (Table 1, entry 2).

Solvolysis of **1** in 2,2,2-trifluoroethanol (TFE) (Scheme 1) gave significantly higher yields of **2**, although the temperature prevailing during the reaction (80 °C) was lower than when *tert*-butyl alcohol was used. Under the best conditions butenolide **2** accounted for as much as 90 % of the product mixture (Table 1, entry 5); the other products were 3-bromo-2-(2,2,2-trifluoroethoxy)-2-methyl-3-butenoic acid (**3b**), and a 1:1 *E*/*Z* isomer mixture of 3-bromo-4-(2,2,2-trifluoroethoxy)-2-methyl-2-butenoic acid (**4b**). In a large-scale experiment, **2** was obtained in 90 % isolated yield (Table 1, entry 5), a result which shows the usefulness of the reaction.

Table 1 reveals that the yield of butenolide **2** is much higher in TFE than in *tert*-butyl alcohol. However, the total amount of products **2** and **4**, i.e. products formed by nucleophilic attack of the allylic carbocation intermediate at C-4, relative to the amount of compound **3**, i.e. the product resulting from a C-2 attack, was approximately 85–90 %



1 **2** **3a,b** **4a,b**

a : R = *t*-Bu
b : R = CF_3CH_2

Scheme 1.

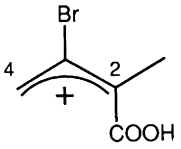
Table 1. Product distribution in reactions of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**1**) with silver trifluoroacetate in *tert*-butyl alcohol (TBA) and 2,2,2-trifluoroethanol (TFE) at reflux in the dark.

Entry	1/M	$[Ag^+]$/M	Solvent	Reaction time/h	Yield (%)[a]		
					2	Other products	
1	0.105	0.161	TBA	3.5	35	20 (**3a**)	45 (**4a**)
2	0.105	0.161	TBA	19.0	38 (33)	17 (**3a**)	45 (**4a**)
3	0.127	0.193	TFE	19.0	69	14 (**3b**)	17 (**4b**)
4	0.070	0.097	TFE	19.0	75 (67)	14 (**3b**)	11 (**4b**)
5	0.070	0.084	TFE	19.0	93 (90)	3 (**3b**)	4 (**4b**)

[a]The yields are determined by a combination of GC and ^{1}H NMR spectroscopy. The yields in parentheses are isolated yields.

irrespective of solvent used. Consequently, the much higher yield of **2** in TFE compared with *tert*-butyl alcohol seems to be related to the lower nucleophilicity of TFE,[9] which allows intramolecular attack at C-4, leading to **2**, to take place at the expense of solvent attack.

We are currently employing the methodology reported here to prepare 2-bromobutenolides with alkyl substituents attached to C-3 and C-5.



Scheme 2.

Experimental

GC analysis was performed using a Carlo Erba 4160 gas chromatograph equipped with a Supelco SPB-5 (25 m×0.25 mm i.d.) capillary column. ^{1}H NMR spectra were recorded on a Jeol FX 90 Q (89.55 MHz) instrument. Combined GC/MS analysis was carried out on a Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 5799 mass selective detector.

General procedure for the synthesis of 4-bromo-3-methyl-2(5H)-furanone (**2**). A solution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid[10] (**1**) in an alcoholic solvent was refluxed in the presence of silver trifluoroacetate. When the reaction was complete the solvent was removed under reduced pressure and a saturated, aqueous solution of sodium chloride (aq. NaCl:reaction mixture = 1:1 v/v) was added. The precipitate was removed by suction filtration and was washed well with ether. The organic phase of the filtrate was separated and the aqueous phase was extracted with ether (4×15 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The product mixture was analyzed by ^{1}H NMR spectroscopy and GC prior to work-up.

Solvolysis in tert*-butyl alcohol.* A solution of the acid **1** (0.41 g, 1.58 mmol) and silver trifluoroacetate (0.53 g, 2.42 mmol) in *tert*-butyl alcohol (15 ml) was refluxed for 19 h. After extractive work-up, an oil (0.30 g) consisting of 4-bromo-3-methyl-2(5*H*)-furanone (**2**), 3-bromo-2-*tert*-butoxy-2-methyl-3-butenoic acid (**3a**), and (*E*)- and (*Z*)-3-bromo-4-*tert*-butoxy-2-methyl-2-butenoic acid (**4a**) in a 38:17:23:22 ratio was obtained. Lactone **2** (0.092 g, 33 %) was easily separated from **3a** and **4a** by washing the organic phase with aqueous sodium bicarbonate. The spectral data for **2** were in accordance with those reported in the literature.[1] **3a**: ^{1}H NMR ($CDCl_3$): δ 1.26 (9 H, s), 1.72 (3 H, s), 5.76 (1 H, d, *J* 3.0 Hz), 6.09 (1 H, d, *J* 3.0 Hz), 9.9 (1 H, br s). (*E*)-**4a**: ^{1}H NMR ($CDCl_3$): δ 1.26 (9 H, s), 2.16 (3 H, m), 5.15 (2 H, m), 9.9 (1 H, br s); MS [*m/z* (% rel. int.)]: 196 (33), 194 (36), 179 (28), 177 (33), 151 (21), 149 (23), 133 (4), 131 (4), 115 (57), 97 (100). (*Z*)-**4a**: ^{1}H NMR ($CDCl_3$): δ 1.26 (9 H, s), 2.14 (3 H, m), 4.53 (2 H, m), 9.9 (1 H, br s); the mass spectrum was indistinguishable from that of compound (*E*)-**4a**.

Solvolysis in 2,2,2-trifluoroethanol. A solution of **1** (0.27 g, 1.05 mmol) and silver trifluoroacetate (0.36 g, 1.63 mmol) was refluxed in 2,2,2-trifluoroethanol for 19 h. After extraction an oil (0.32 g) containing **2**, 3-bromo-2-(2,2,2-trifluoroethoxy)-2-methyl-3-butenoic acid (**3b**), and the (*E*)- and (*Z*)- isomers of 3-bromo-4-(2,2,2-trifluoroethoxy)-2-methyl-2-butenoic acid (**4b**) in a 75:14:6:5 ratio was obtained. Butenolide **2** (0.125 g, 67 %) was isolated by preparative column chromatography (SiO_2, chloroform:hexane = 5:1). **3b**: ^{1}H NMR ($CDCl_3$): δ 1.75 (3 H, s), 3.88 (2 H, q, *J* 8.9 Hz), 5.98 (1 H, d, *J* 3.1 Hz), 6.17 (1 H, d, *J* 3.1 Hz), 10.9 (1 H, br s); MS [*m/z* (% rel. int.)]: 233 (96), 231 (100), 179 (22), 177 (23), 151 (35), 133 (15), 131 (13), 97 (10). (*Z*)-**4b**: ^{1}H NMR ($CDCl_3$): δ 2.19 (3 H, m), 3.89 (2 H, q, *J* 8.9 Hz), 4.79 (2 H, m), 10.4 (1 H, br s); MS [*m/z* (% rel. int.)]: 278 (M^+, 4), 276 (M^+, 4), 197 (17), 179 (5), 177 (5), 151 (25), 133 (4), 131 (3), 97 (100). (*E*)-**4b**: ^{1}H NMR ($CDCl_3$): δ 2.19 (3 H, m), 3.89 (2 H, q, *J* 8.9 Hz), 5.54 (2 H, m), 10.4 (1 H, br s); the mass spectrum was indistinguishable from that of (*Z*)-**4b**.

Preparative synthesis of 4-bromo-3-methyl-2(5H)-furanone (**2**). A solution of **1** (2.70 g, 10.4 mmol) and silver trifluoroacetate (3.60 g, 16.3 mmol) was refluxed in 2,2,2-trifluo-

roethanol (150 ml) for 19 h. After extractive work-up butenolide **2** (1.67 g, 90 %) was obtained.

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