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Synthesis of 2-substituted 4,5-dihydro-4-oxo-3-furancarboxylates using acylative intramolecular cyclization of sulfonium salts

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ABSTRACT

A simple and efficient synthesis of 4,5-dihydro-4-oxo-3-furancarboxylates using an acylative intramolecular cyclization of sulfonium salts is described. The reaction involved the efficient formation of a mixed anhydride between a linear carboxylic acid and trifluoroacetic anhydride in the presence of *N*-methylimidazole, followed by the sequential conversion into a highly reactive acylammonium species *in situ*. This procedure is easily handled, uses readily available inexpensive reagents, and provides a variety of 2-substituted 4,5-dihydro-4-oxo-3-furancarboxylates.

Introduction

Substituted 3(2*H*)-furanones are important structures present in many natural products and biologically active compounds.[1] These derivatives are known to exhibit a variety of pharmaceutical activities.[2] Therefore, many synthetic methodologies towards polysubstituted 3(2*H*)-furanones have been developed.[3,4] Among substituted 3(2*H*)-furanones, 4,5-dihydro-4-oxo-3-furancarboxylates, which have an alkoxycarbonyl group at the 3-position on the 3(2*H*)-furanone ring are also comprised in various natural products,[5] and are known to exhibit antiallergy, antimalarial, and anticancer activities.[6] In addition, these carboxylates serve as versatile scaffolds to build 1*H*-pyrazole, oxazole, and azepine skeletons.[7] These attractive features of carboxylates have motivated many organic chemists, which has resulted in the development of various synthetic methodologies including the acylation/cyclization of chloroacetyl chloride to 1,3-dicarbonyl compounds,[6a,8] the acylation/cyclization of ethyl α-haloacetoacetates and isocyanates,[6c,8a,9] and the photo-oxidation-intramolecular Michael addition of 2-furyl-1,3-diketones.[10] To date, an efficient and flexible approach for the introduction of various functional groups at the 2-position in 4,5-dihydro-4-oxo-3-furancarboxylates has not been achieved, and therefore the development of a novel synthetic methodology is required.

We have previously reported novel synthetic methodology for the construction of a substituted 3(2*H*)-furanone framework via the intramolecular cyclization of a sulfonium salt (Scheme 1).[11] Thus, the reaction between enolate **A**, generated from sulfonium salt **1** under basic condition, and electrophiles such as alkyl halides or coordination complexes, prepared from an equimolar mixture of *N*-halosuccinimide and 4-(dimethylamino)pyridine (DMAP), produces a variety of 4-substituted 3(2*H*)-furanones. Regarding the reaction mechanism, we believe that using an electrophilic acylating reagent will lead to 2-substituted 4,5-dihydro-4-oxo-3-furancarboxylates **2** and the resulting carboxylate **2** will be used as a versatile substance.[5–7] In this paper, we report the acylative intramolecular cyclization of sulfonium salts as a novel procedure for the preparation of 2-substituted 4,5-dihydro-4-oxo-3-furancarboxylates. This procedure is simple and practical, and use inexpensive commercially available reagents to give the target compounds via a one-pot process under mild conditions.

Results and discussion

We commenced the investigation of acylative intramolecular cyclization with 3-ethoxycarbonyl-2-oxopropyldiphenylsulfonium tetrafluoroborate (**1a**). In order to find acylating agents suitable for this reaction, we screened a variety of acetylating agents, such as acetyl chloride, acetic anhydride, and activated esters derived from acetic acid. Under standard reaction conditions, 1.0 equiv of sulfonium salt **1a** was treated with 1.0 equiv of acetylating agent in the

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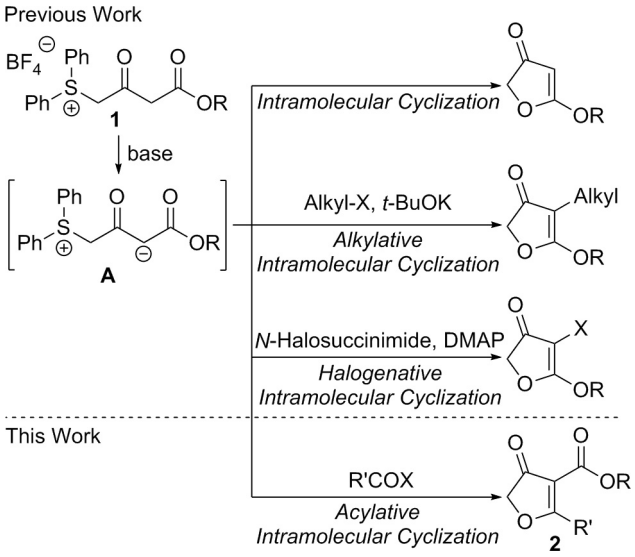


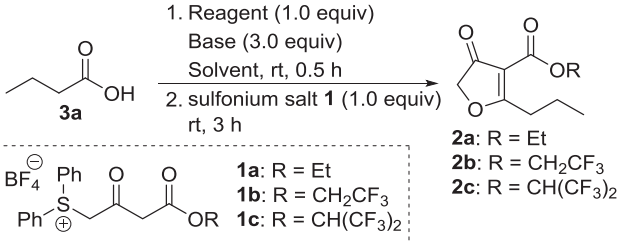
Scheme 1. Intramolecular cyclization of sulfonium salt **1.**

presence of 1.0 equiv of DMAP in acetonitrile (MeCN). Among the acetylating agent used, the most reactive acetyl chloride gave 4-chloroacetoacetate as a major product. This result suggested that substitution reaction between sulfonium salt and eliminated chloride ion should be faster than acylation. Finally, only acetic anhydride underwent acylative intramolecular cyclization with moderate yield (Table S1).

Bearing these results in mind, we then used a mixed anhydride generated *in situ* from readily available carboxylic acids and electrophilic activating agents to simplify the experimental procedure. The examination of electrophilic activating agents for the acylative intramolecular cyclization was carried out with butyric acid in the presence of 3.0 equiv of *N*-methylimidazole (NMI) in MeCN (Table 1). To our satisfaction, when sulfonic anhydrides such as *p*-toluenesulfonic anhydride (Ts_2O) and trifluoromethanesulfonic anhydride (Tf_2O) were used, expected 2-substituted product **2a** was obtained in moderate yields (entries 1 and 2), but base-induced unsubstituted cyclized product, 5-ethoxy-3(2*H*)-furanone, was detected as a byproduct.[11b] Among other electrophilic activating agent tested, i.e. pivalic anhydride (Piv_2O), 2-methyl-6-nitrobenzoic anhydride (MNBA), and trifluoroacetic anhydride (TFAA), TFAA was the most efficient, generating **2a** in 49% yield (entry 5).

Next, we investigated the effect of the solvent on this reaction (entries 6–10). The results revealed that the use of polar aprotic solvents facilitates the reaction and DMF was found to be the most suitable solvent among those tested. With the best conditions in hand, we then screened different bases. Poor nucleophilic amines, such as triethylamine (Et_3N), or inorganic bases prevented the acylative intramolecular reaction and only the intramolecular cyclization product[11b] was obtained (entries 11 and 12). Using aromatic nucleophilic amines, yields increased corresponding to

Table 1
Optimized conditions.[a]



Entry	Reagent	Solvent	Base	1	Yield/%[b]
1	Ts_2O	MeCN	NMI	**1a**	36
2	Tf_2O	MeCN	NMI	**1a**	42
3	Piv_2O	MeCN	NMI	**1a**	35
4	MNBA	MeCN	NMI	**1a**	34
5	TFAA	MeCN	NMI	**1a**	49
6	TFAA	CH_2Cl_2	NMI	**1a**	37
7	TFAA	THF	NMI	**1a**	40
8	TFAA	DMF	NMI	**1a**	56
9	TFAA	DMA	NMI	**1a**	54
10	TFAA	NMP	NMI	**1a**	52
11	TFAA	DMF	Et_3N	**1a**	n.d.[d]
12	TFAA	DMF	K_2CO_3	**1a**	n.d.[d]
13	TFAA	DMF	pyridine	**1a**	n.d.[d]
14	TFAA	DMF	imidazole	**1a**	7
15	TFAA	DMF	4-MeOPy	**1a**	10
16	TFAA	DMF	DMAP	**1a**	55
17	TFAA	DMF	PPY	**1a**	50
18[c]	TFAA	DMF	NMI	**1a**	59
19[c]	TFAA	DMF	NMI	**1b**	72
20[c]	TFAA	DMF	NMI	**1c**	48

[a] All reactions were performed using butyric acid **3a** (0.2 mmol), reagent (1.0 equiv), base (3.0 equiv), and sulfonium salt **1** (1.0 equiv) in solvent (2.0 mL). Ts_2O = *p*-toluenesulfonic anhydride, Tf_2O = trifluoromethanesulfonic anhydride, Piv_2O = pivalic anhydride, MNBA = 2-methyl-6-nitrobenzoic anhydride, TFAA = trifluoroacetic anhydride, MeCN = acetonitrile, DMF = *N*,*N*′-dimethylformamide, DMA = *N*,*N*′-dimethylacetamide, DMP = *N*-methylpyrrolidone, NMI = *N*-methylimidazole, 4-MeOPy = 4-methoxypyridine, PPY = 4-pyrrolidinopyridine.

[b] Isolated yield based on **1**.

[c] Step1) 0 °C, 0.5 h.

[d] n.d. = not detected.