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ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 931–937
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Synthesis of new 3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfanyl- or phenylsulfonyl-methyl)-1,5-dihydropyrrol-2-ones starting from α,β-unsaturated γ-lactones and primary amines

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Received 6 February 2007; received in revised form 28 March 2007; accepted 29 March 2007
Available online 8 April 2007

Abstract

The paper presents an efficient and straightforward transformation of α,β-unsaturated γ-lactones into 2,2,2-trifluoroethyl substituted γ-lactams, starting from a variety of primary amines. The structures of all new compounds were ascribed using 1D NMR (^{19}F, ^{1}H, ^{13}C), IR, MS. Selected ^{19}F, ^{13}C NMR and IR data of γ-lactams were compared to those of one which was characterized by X-ray diffraction analysis. The possible mechanism for the formation of γ-lactams is also presented.

Keywords: Fluorine; γ-Ketothioester; Heterocycle; γ-Lactam; 1,5-Dihydropyrrol-2-one

1. Introduction

The increasing interest in trifluoromethylated heterocycles [1–3] and the need of new fluorinated scaffolds for parallel synthesis prompted us to investigate the application of γ-ketothioesters towards the synthesis of new heterocycles. It was already shown that S-ethyl 4-oxo-2-(pentafluoroethyl)-pentanethiocarboxylate **1** (R^1 = Me) or aryl substituted analogues (R^1 = Ar) are excellent versatile building blocks for the synthesis of a large variety of trifluoromethyl heterocycles such as γ-lactams, furans, pyrroles, pyridazines, pyridazin-3-ones [4–9]. The γ-ketothioesters **1** were easily obtained in two high yielding steps: substitution of vinylic fluoride of perfluoroketene dithioacetal [10] with potassium enolates of ketones and acidic hydrolysis of dithioacetal intermediates [5]. As it was previously reported, the treatment of γ-ketothioesters **1** with non-nucleophilic diisopropylamine in diethyl ether followed by addition of various primary amines led to α,β-unsaturated γ-lactams **2** as mixtures (∼50/50) of diastereomers (Scheme 1) [7].

More recently, the S-phenyl analogue **3** was easily transformed into the new α,β-unsaturated γ-lactone **4a** (as a mixture of stereomers) by simple treatment with diisopropylamine in ether (Scheme 2) [11].

Continuing our efforts directed toward synthesis of new fluorinated nitrogen-containing heterocycles, we decided to use γ-lactones **4a**, **4b** as precursors for the synthesis of γ-lactams bearing phenylsulfanyl- or phenylsulfonyl-methyl substituent. We report in the present paper on the full investigation of this transformation, especially the influence of the lactone substitution and the nature of the primary amine on the outcome of the reaction.

2. Results and discussion

In the first experiment, compound **4a** was treated with 1.2 equiv. of *n*-pentylamine in diethyl ether at room temperature for 30 h (Scheme 3: Method 1). The crude mixture was

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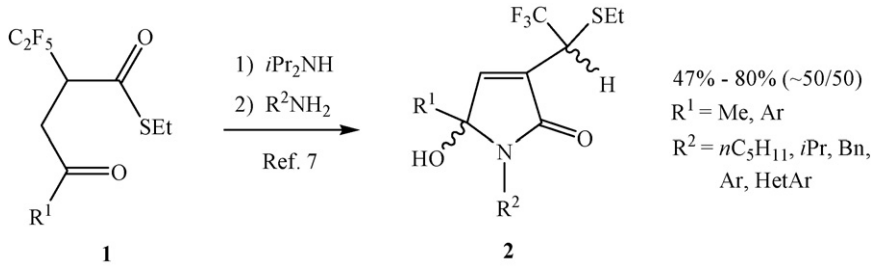
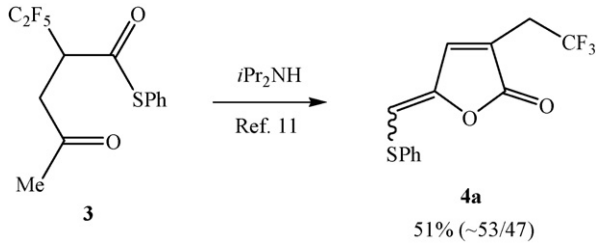
doi:10.1016/j.jfluchem.2007.03.020



Scheme 1.

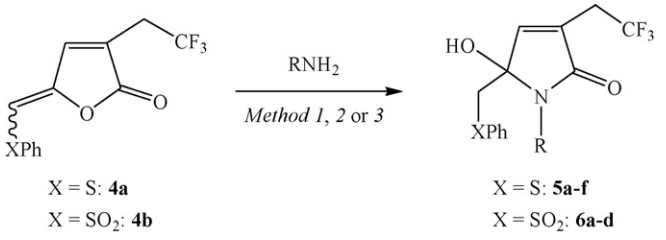


Scheme 2.

checked by ^{19}F NMR to confirm the complete conversion of the starting material. Without further treatment, the solvent was evaporated in vacuo then the residue was purified by silica gel column chromatography to give the new γ-lactam **5a** in 61% yield (Table 1: entry 1). The confirmation of the 1,5-dihydropyrrol-2-one structure will be discussed later.

The reaction was then successfully extended to others amines (Scheme 3). The transformation of **4a** was general and worked well (yields: 61–79%) with a wide variety of primary amines: linear (R = nC_5H_{11} and Bn: entries 1,2), branched (R = *i*Pr: entry 3) and functionalized amines bearing *N*,*N*-(dimethylamino) or hydroxyl groups (R = $(CH_2)_3NMe_2$, $(CH_2)_2OH$: entries 4, 5). It is worth noting that the reaction with 2-aminoethanol was chemoselective, as previously observed for other γ-lactam analogues [7]. Interestingly, the resulting heterocycle **5e** bears an additional nucleophilic hydroxyl group which could be used for further cyclisations.

Unfortunately, the reaction seemed to be more difficult with less nucleophilic amine such as aniline. Indeed, a very low yield of compound **5f** (conversion: <10%) was obtained using Method 1, even in boiling ether for 3 days. The conversion was slightly improved until 60% using boiling 1,4-dioxane as a solvent for 87 h (Scheme 3: Method 2). Nevertheless, we did not obtain a total conversion of the starting material, the yield remaining around 41% (Table 1: entry 6).



Scheme 3. Reagents and conditions—Method 1: Et_2O, rt, 30 h. Method 2: 1,4-dioxane, reflux, 87 h. Method 3: THF, rt, 16 h.

Therefore, we tried to increase the electrophilicity of the carbonyl function by transforming the sulfanyl into a sulfonyl moiety. Indeed, we may expect that the vinylogous conjugation with the electron-withdrawing sulfonyl group will activate the carbonyl making easier the nucleophilic addition of amine (see Scheme 5).

Lactone **4a** was oxidized into the corresponding sulfone **4b** (yield: 76%) by simple treatment with *m*-chloroperbenzoic acid (MCPBA, 3 equiv.) in dichloromethane, at room temperature (Scheme 4). The new heterocycle **4b** was obtained as a single stereomer after careful checking of the crude mixture by ^{19}F and ^{1}H NMR. The stereochemistry of compound **4b** was ascribed by ^{1}H–^{1}H NOE experiments. Irradiation of olefinic proton H_a at $\delta = 6.23$ ppm induced a 11% NOE on proton H_b. Moreover, irradiation of olefinic proton H_b at $\delta = 7.34$ ppm induced a 11% NOE on proton H_a and a 8% NOE on methylenic protons H_c, respectively (Fig. 1). These two observations confirmed the close relationship between H_a and H_b, which are in good agreement with the *Z* configuration between the phenylsulfonyl group and the lactone moiety. Similar results were already observed for a (*p*-chlorophenyl)sulfanyl analogue (Fig. 1) [11].

It was of interest to perform some molecular modeling calculations in order to find the most stable stereomer of **4b** and to try to quantify the difference of reactivity of the carbonyl groups of compounds **4a** and **4b**. The geometry of **4b** was first minimized at the molecular mechanics level using the CVFF force field as implemented in the Cerius2 package. The systematic variation of dihedral angles led to 361 stereomers,

Table 1
Preparation of new α,β-unsaturated γ-lactams **5** and **6**

Entry	Starting compound	R	Method[a]	Conversion (%)	γ-Lactam (%)[b]
1	**4a**	nC_5H_{11}	1	100	**5a** (61)
2	**4a**	Bn	1	100	**5b** (79)
3	**4a**	*i*Pr	1	100	**5c** (55)
4	**4a**	$(CH_2)_3NMe_2$	1	100	**5d** (63)
5	**4a**	$(CH_2)_2OH$	1	100	**5e** (68)
6	**4a**	Ph	2	60	**5f** (41)
7	**4b**	Bn	3	100	**6a** (76)
8	**4b**	*i*Pr	3	100	**6b** (60)
9	**4b**	$(CH_2)_2OH$	3	100	**6c** (79)
10	**4b**	Ph	3	100	**6d** (87)

[a] Method 1: Et_2O, rt, 30 h. Method 2: 1,4-dioxane, reflux, 87 h. Method 3: THF, rt, 16 h.
[b] Isolated yields.