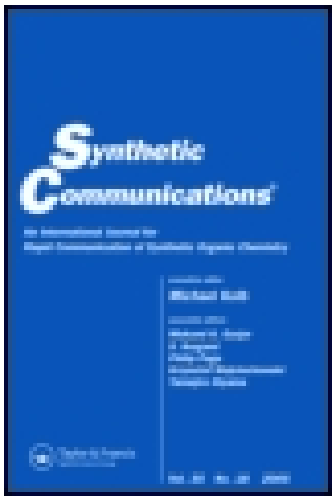

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Ultrasound-Promoted Environment-Friendly Synthesis of 5-(3,3,3-Trifluoro-2-oxopropylidene)pyrrolidin-2-ones

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Ultrasound-Promoted Environment-Friendly Synthesis of 5-(3,3,3-Trifluoro-2-Oxopropylidene)Pyrrolidin-2-Ones

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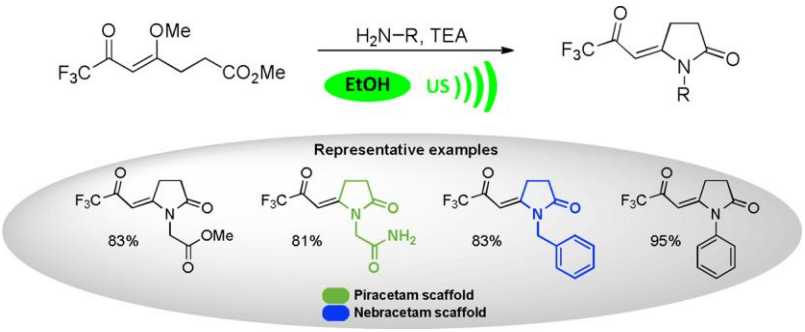
Abstract

A facile one pot ultrasound-promoted synthesis of N-substituted 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-ones from methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate and a wide range of primary alkyl(aryl)amines using ethanol as a green solvent and employing TEA as a base is described.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*



KEYWORDS: Pyrrolidin-2-ones, 5-alkylidenepyrrolidin-2-ones, γ-alkylidene-γ-lactams, [CCCC+N] cyclocondensations, trifluoromethyl, ultrasound

INTRODUCTION

Pyrrolidin-2-one or γ-lactam derivatives have been attracted much attention in the last decade due to the well-established nootropic, post traumatic neuroprotective and anti-epileptic effects of piracetam-like compounds.[1] In nature, the pyrrolidin-2-one core has been found in the structure of natural compounds that possess a wide spectrum of biological activities.[2] The related 5-alkylidenepyrrolidin-2-ones or γ-alkylidene-γ-lactams are important functionalities in natural products chemistry,[2,3] and they are commonly found as building blocks for a wide variety of derivatives including naturally occurring pyrrolidines[4] and other compounds with potential bioactivities.[5] Furthermore, they form the skeleton of biologically important tetrapyrroles such as chlorins, isobacteriochlorins and corrins.[6]

For these reasons, numerous procedures have been reported for the preparation of 5-alkylidenepyrrolidin-2-ones, such as *5-exo-dig* cyclization of alkynylamides,[4a,4b,5b,7] intramolecular cyclization of 4-aminoesters,[3b,5a,8] lactamization of 5-

alkylidenelactones,[9] addition of Grignard reagents to pyrrolidin-2,5-diones[4e,4f,10] and others.[11] However, these methods often involve employment of unsafe solvents, uncommon catalysts as well as time-consuming reaction and work-up steps that can be problematic when planning their application in scaled-up processes. Interestingly, we were surprised to find that environment-friendly methodologies were not employed in the synthesis of 5-alkylidenepyrrolidin-2-ones yet.

Given these precedents, we decided to explore the viability of using ultrasonic irradiation to promote the reaction of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate with primary alkyl(aryl)amines to prepare 5-(3,3,3-trifluoro-2-oxopropylidene)-pyrrolidin-2-ones.

RESULTS AND DISCUSSION

The methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) was prepared from levulinic acid, a material derived from wood-processing and agricultural waste,[12] according to published methodology.[8b]

Initially, the reaction of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) with aniline **2k** was carried out in acetonitrile, chloroform, ethanol and water to choose the best solvent (Table I). It was found that acetonitrile and chloroform were not suitable since a mixture of *β*-enaminoketone **3k** and the desired pyrrolidinone **4k** was obtained after 120 min of sonication (Table I, entries 1 and 2). When the same transformation was performed in water for 120 min, only the desired product was observed by GC but the

yield was disappointing (Table I, entry 3). When the reaction was carried out in ethanol the yield of isolated pyrrolidinone **4k** increased substantially although a little amount of the *β*-enaminoketone **3k** was observed by GC after 120 min (Table I, entry 4). Based on these results further examinations were made using ethanol as solvent. An experiment was performed in order to check the importance of the base TEA for the reaction (Table I, entry 5). When the reaction was carried out without base, only the *β*-enaminoketone **3k** was detected by GC. In order to show the beneficial effect of the ultrasonic irradiation in the synthesis, two control experiments were performed in the absence of ultrasonic irradiation: first, the starting material **1** was allowed to react with aniline **2k** for 120 min under room temperature in ethanol; then, the reaction was repeated under reflux for 120 min. Under the former silent condition, the formation of product **4k** was not observed (Table I, entry 6). The reaction conducted under reflux furnished a mixture of **3k** and **4k** in the ratio of 1:1, as determined by GC (Table I, entry 7). These results show that the ultrasonic irradiation plays an important role in the proposed synthesis, mainly in the cyclization of the intermediate **3k**.

To examine the scope of this methodology, the reaction of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) with 1 equivalent of various alkyl(aryl)amines (**2a-t**) in the presence of 1 equivalent of TEA under sonication were studied (Table II).

When **1** was allowed to react with methyl esters of valine **2a** or methionine **2b** only the *β*-enaminoketones **3a** or **3b** were obtained, respectively (Table II, entries 1 and 2). On the other hand, when methyl esters of alanine **2c** or phenylalanine **2d** were used as

nucleophiles, mixtures of *β*-enaminoketones and cyclic products were obtained after sonication for 120 min (Table II, entries 3 and 4). For the less hindered aminoester **2e**, the reaction furnished exclusively the desired cyclic product **4e** after 90 min in 83% of yield (Table II, entry 5). Results of experiments 1-5 show that the success of the reaction of **1** with aminoester derivatives depends on the steric hindrance exerted by the substituent bonded to the nitrogen. Accordingly, by performing the reaction of glycinamide hydrochloride **2f** with **1** for 60 min, only the pyrrolidinone **4f** was isolated in 81% of yield (Table II, entry 6). When methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) was allowed to react under ultrasonic irradiation with *n*-propylamine (**2g**), the pyrrolidinone **4g** was obtained in excellent yield of 94% (Table II, entry 7). Similar results were obtained when 2-chloroethylamine hydrochloride (**2h**) (Table II, entry 8), *n*-butylamine (**2i**) (Table II, entry 9) or benzylamine (**2j**) (Table II, entry 10) were used as nucleophiles. Afterwards, reactions of **1** with several aromatic amines bearing electron-donating groups or electron-withdrawing groups and a variety of substitution patterns were also performed. In general, these reactions were slower than the reactions of alkylamines **2e-j**, moreover the *N*-arylpyrrolidinones were isolated in poorer yields than *N*-alkylpyrrolidinones. As can be seen in Table II, entry 11-20, the electronic effects of the groups attached to the benzene ring did not show a linear response on the reactivity and yields. Finally, the *β*-enaminoketones **3a,b** and the pyrrolidin-2-ones **4e-t** were fully characterized by low and high resolution mass spectrometry as well as ^{1}H and ^{13}C NMR. The spectral data are in accordance with the proposed structures. The structure of the pyrrolidinone **4e** was further confirmed by single-crystal X-ray crystallographic studies. As can be seen in Figure I, the olefinic moiety shows the *E* configuration.

CONCLUSION

In conclusion, a facile and intensified one pot route for the preparation of 5-(3,3,3-trifluoro-2-oxopropylidene)-pyrrolidin-2-ones was developed by applying ultrasound irradiation. The combination of ultrasonic power, short reaction times, use of ethanol as solvent and starting material derived from levulinic acid are features that contribute to the greenness of the process. This simple methodology offers a mild alternative for the synthesis of pyrrolidin-2-ones which are structurally related to known bioactive compounds.

EXPERIMENTAL

The full experimental details and characterization data for the preparation of title compounds are provided in the Supplementary Information, available online. CCDC 1027587 contains the supplementary crystallographic data for **4e**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

Experimental Procedure For The Synthesis Of Methyl 2-(2-Oxo-5-(3,3,3-Trifluoro-2-Oxopropylidene)Pyrrolidin-1-Yl)Acetate (4e)

TEA (101 mg, 1.0 mmol) was added to a solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) (240 mg, 1.0 mmol) and glycine methyl ester hydrochloride (**2e**) (126 mg, 1.0 mmol) in ethanol (15 mL). The mixture was sonicated

for 90 minutes (Table II). Sonication increased the reaction temperature to 55-60ºC after 10 minutes. Ethyl acetate (20 mL) was added and the organic layer was washed with H_2O (3 × 15 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a brownish solid. Purification by silica gel column chromatography (15:7 AcOEt/hexane) afforded the product **4e** as a yellowish solid in 83% of yield.

Characterization Data For Methyl 2-(2-Oxo-5-(3,3,3-Trifluoro-2-Oxopropylidene)Pyrrolidin-1-Yl)Acetate (4e)

Yield: 0.220 g (83%); yellowish solid; mp 111-112°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.69 (s, 1H), 4.37 (s, 2H), 3.80 (s, 3H), 3.44-3.40 (m, 2H), 2.73-2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 178.8 (q, J_{CF} = 34.4 Hz), 176.4, 167.4, 166.2, 116.2 (q, J_{CF} = 293.4 Hz), 91.4, 52.9, 41.8, 27.1, 26.8; MS-EI: *m*/*z* (%) 265 (M, <5), 245 (23), 206 (24), 196 (100), 168 (85), 138 (37), 108 (65), 69 (15); HRMS-ESI: *m*/*z* $[MH]^+$ calcd. for $C_{10}H_{10}F_3NO_4$: 266.0640, found 266.0635.

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SUPPORTING INFORMATION

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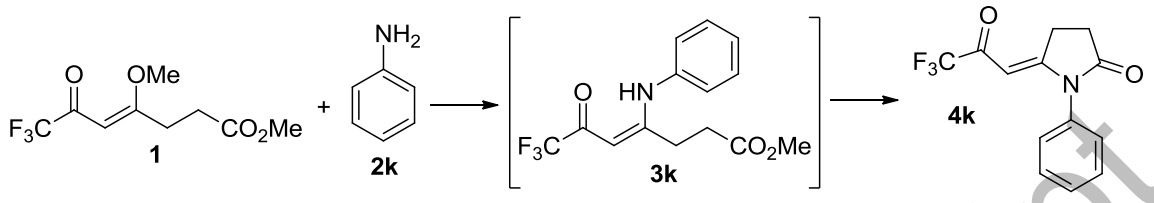
Table 1. Solvent, base and ultrasonic irradiation effects in the reaction of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) with aniline (**2k**).



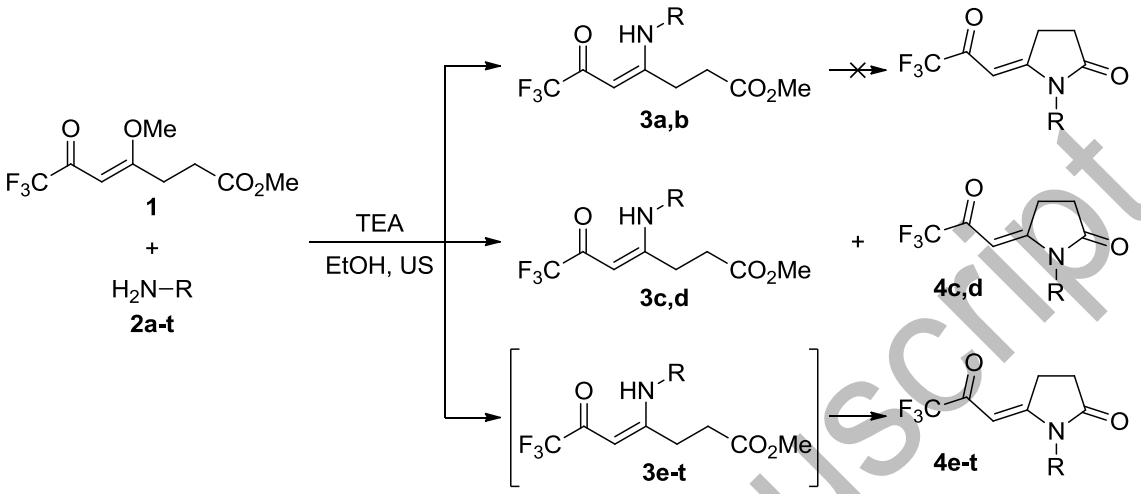
Entry	Solvent	TEA (eq)	Method	Time (min)	Product (%)[a]		Yield of **4k** (%)
					3k	**4k**	
1	MeCN	1	US	120	76	24	-[c]
2	$CHCl_3$	1	US	120	42	58	-[c]
3	H_2O	1	US	120	0	100	16[b]
4	EtOH	1	US	120	1	99	95[b]
5	EtOH	-	US	120	100	0	-[c]
6	EtOH	1	rt	120	91	9	-[c]
7	EtOH	1	reflux	120	53	47	-[c]

[a]Determined by GC.

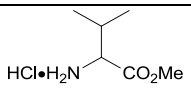
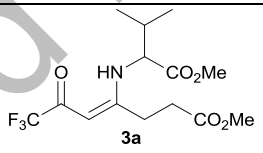
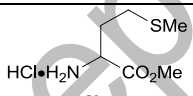
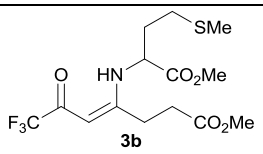
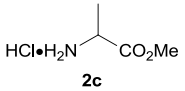
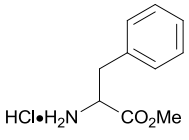
[b]Isolated yield.

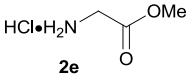
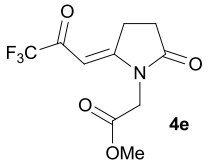
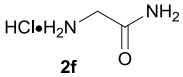
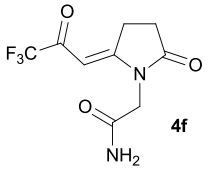
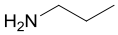
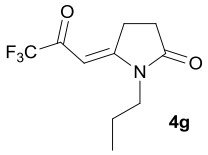
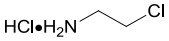
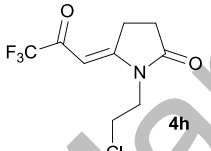
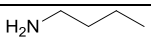
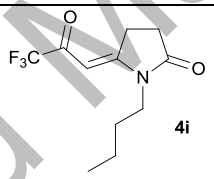
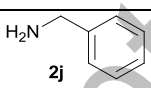
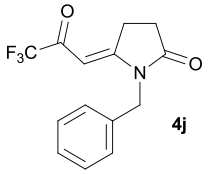
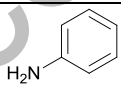
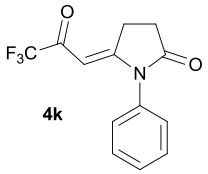
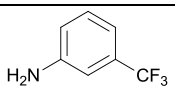
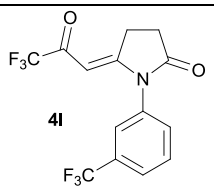
[c]Undetermined yield.

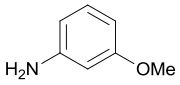
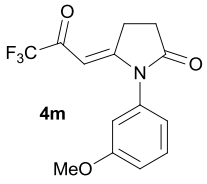
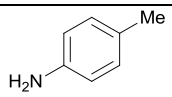
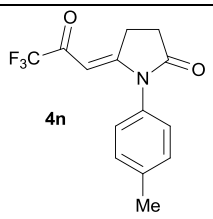
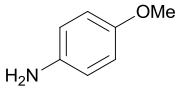
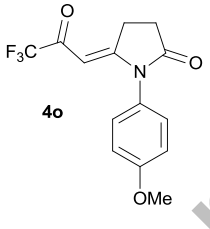
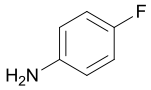
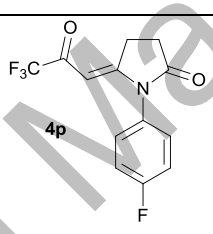
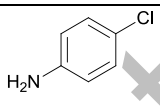
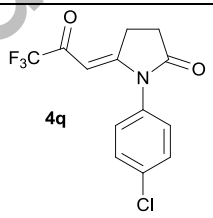
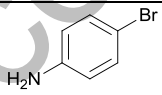
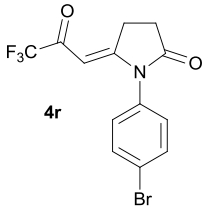
Table 2. Selected experimental data for the reaction of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate (**1**) with alkyl(aryl)amines (**2a-t**) under ultrasonic irradiation.

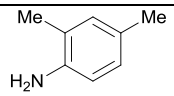
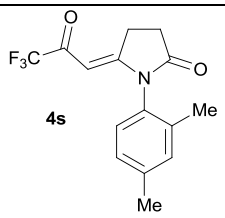
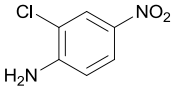
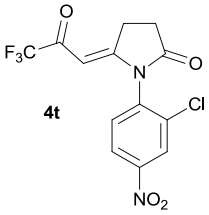


R = CH(*i*-Pr)CO_2Me (**a**), CH(CH_2CH_2SMe)CO_2Me (**b**), CH(Me)CO_2Me (**c**), CH(Bn)CO_2Me (**d**), CH_2CO_2Me (**e**), CH_2CONH_2 (**f**), *n*-Pr (**g**), CH_2CH_2Cl (**h**), *n*-Bu (**i**), Bn (**j**), C_6H_5 (**k**), 3-(CF_3)C_6H_4 (**l**), 3-MeOC_6H_4 (**m**), 4-MeC_6H_4 (**n**), 4-MeOC_6H_4 (**o**), 4-FC_6H_4 (**p**), 4-ClC_6H_4 (**q**), 4-BrC_6H_4 (**r**), 2,4-$Me_2C_6H_3$ (**s**), 2-Cl,4-(NO_2)C_6H_3 (**t**)

Entry	Amine (**2a-t**)	Product	Time (min)	Yield (%)[a]
1	 **2a**	 **3a**	60	85
2	 **2b**	 **3b**	60	86
3	 **2c**	**3c** + **4c** (1.1:1)[b]	120	-[c]
4	 **2d**	**3d** + **4d** (9:1)[b]	120	-[c]

5	 **2e**	 **4e**	90	83
6	 **2f**	 **4f**	60	81
7	 **2g**	 **4g**	30	94
8	 **2h**	 **4h**	30	88
9	 **2i**	 **4i**	45	65
10	 **2j**	 **4j**	60	83
11	 **2k**	 **4k**	105	95
12	 **2l**	 **4l**	60	59

13	 **2m**	 **4m**	90	61
14	 **2n**	 **4n**	120	55
15	 **2o**	 **4o**	60	64
16	 **2p**	 **4p**	120	45
17	 **2q**	 **4q**	60	60
18	 **2r**	 **4r**	90	59

19	 **2s**	 **4s**	120	51
20	 **2t**	 **4t**	120	25

[a]Isolated yield.

[b]Determined by GC.

[c]Undetermined yield.

Figure 1. ORTEP diagram of **4e**.