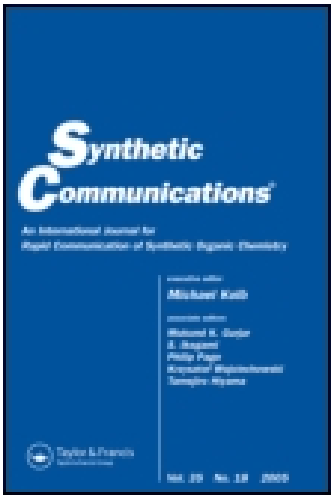

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An Expedient Approach for the Synthesis of 1-Alkyl-4-propionylpyrrolidin-2-ones

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AN EXPEDIENT APPROACH FOR THE SYNTHESIS OF 1-ALKYL-4-PROPIONYLPYRROLIDIN-2-ONES

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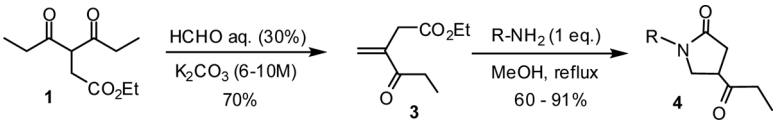
GRAPHICAL ABSTRACT



Abstract *A simple and useful tandem addition–cyclization reaction of primary amines on a prepared α-functionalized propylvinyl ketone* ***3*** *in methanol at reflux is a promising route for the synthesis of a new family of 1-alkyl-4-propionylpyrrolidin-2-ones* ***4****.*

[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 Primary amines; 4-propionylpyrrolidin-2-ones; propylvinyl ketone

INTRODUCTION

The Michael addition reaction, discovered more than a century ago,[1] is one of the most important organic reactions leading to the formation of a new carbon–carbon and carbon–heteroatom bonds. These reactions include nucleophilic reagents (donors) and activated α, β-unsaturated molecules (acceptors)[2] recognized for their great ability to react with various nucleophiles. Aside from single acceptors, we verify that some homologous α-functionalized enones **3**[3–10] are of considerable importance in organic synthesis and can act as intermediates in the synthesis of a wide range of biologically active compounds[11] to skeletal pyrrolidin-2-ones derivatives[12] and γ-butyrolactams.[13,14] Because of the growing importance of some *N*-heterocyclic five-membered rings in the development of synthetic intermediates in medicinal chemistry and their usefulness as pharmacological molecules, much attention has been focused on their synthesis and especially that of γ-lactams.[15–18] In this article, we describe an efficient alternative for the preparation of a new family of 1-alkyl-4-propionylpyrrolidin-2-ones **4** following a tandem Michael-type reaction of primary

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amines in methanol at reflux on enones **3** whose corresponding adducts undergo spontaneous cyclization, giving rise to β-acyl-γ-butyrolactams **4** in good yields.

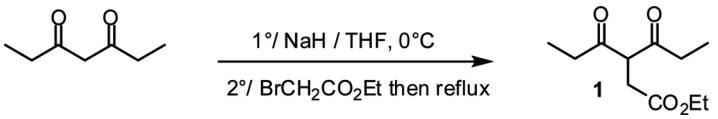
RESULTS AND DISCUSSION

The starting point of this development consisted of a judicious use of commercially available heptane-3,5-dione, alkylated[19–21] as reported in the literature and serving as raw material for the preparation of the enone **3** (Scheme 1).

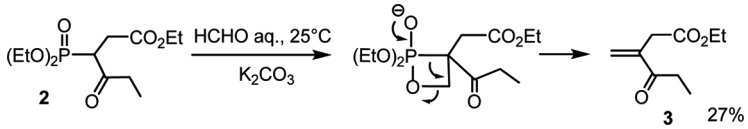
First, 1 equivalent of sodium hydride (60% suspension in mineral oil) was added to a solution of dry tetrahydrofuran (THF) under nitrogen at 0 °C, and then heptane-3,5-dione (1 equiv.) was added dropwise. The mixture was stirred at 0 °C to allow for complete formation of the 3,5-diketone anion and then stirred at room temperature for 1 h. Alkylation of 3,5-dione in the presence of ethyl bromoacetate in THF at reflux for 18 h, offers the ability to isolate, after workup and in good yield, the alkylated diketone **1**. The second approach involved the transformation of the alkylated β-diketone **1** to prepare the desired Michael acceptor **3** used to achieve the expected 5-acyl-3-butyrolactams **4**. In this context, it was decided to adopt a method that combines significant aspects such as easy operation under mild conditions, easy accessibility of reactants and workup procedure, absence of competitive reactions, high atom economy, and the use of water as a green reaction medium. These restrictions are unfavorable to the use of β-alkylated ketophosphonate **2**[22] in the framework of the Wittig–Horner reaction,[23] which leads to the enone **3** in poor yield (27%) (Scheme 2).

These above criteria can be satisfied by using our own protocol[10] based on the deacylative reaction of alkylated 1,3-diketone **1** using 30% aqueous formaldehyde and concentrated (6–10 molar) aqueous solution of potassium carbonate as base in the absent of any solvent and phase transfer agent at 0 °C to isolate α-functionalized α, β-enone **3** in good purity and good yields (Scheme 3).

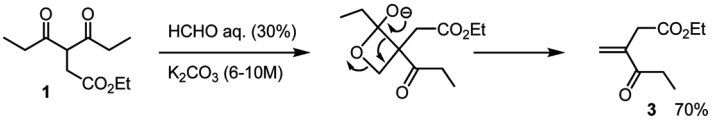
Given the high functional density of the enone **3**, we found it useful to examine its reactivity in a heterocyclization process to obtain a series of 1-alkyl-4-propionylpyrrolidin-2-ones **4** whose one representative has been reported since 1994.[24] In our approach, the construction of the nitrogen heterocycle[25] is based on an efficient coupling of the primary amines and vinyl ketone **3**. The latter Michael acceptor **3**



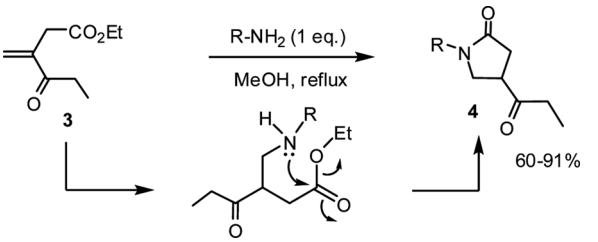
Scheme 1. Alkylation procedure of β-diketone.



Scheme 2. Wittig–Hormer synthesis of α-functionalized enone **3**.



Scheme 3. Synthesis of α-functionalized enone **3** by hydroxymethylation followed by a fragmentation.



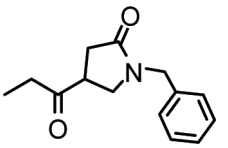
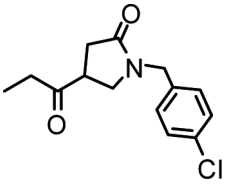
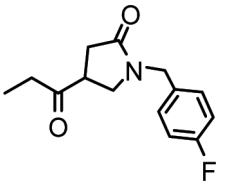
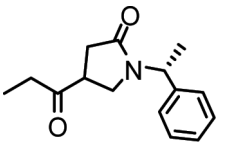
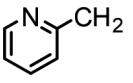
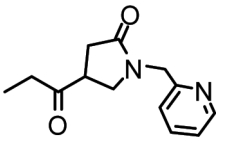
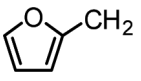
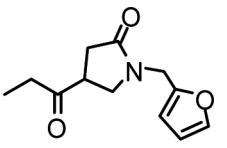
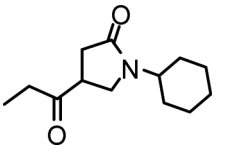
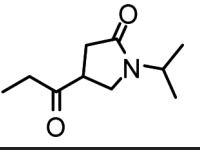
Scheme 4. Synthesis of 1-alkyl-4-propionylpyrrolidin-2-ones **4**.

offers the possibility to react with 1 equivalent of primary amine in methanol as solvent, involving as expected a two-step sequence: conjugate addition of the amine on the terminal ethylenic carbon leading the γ-amino-ester intermediate, which spontaneously undergoes an intramolecular cyclization via 5-exo-trig process[26] to provide the corresponding functionalized γ-lactam **4** (Scheme 4, Table 1).

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium–benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo. All reactions were monitored by thin-layer chromatography (TLC) on silica-gel plates (Fluka Kieselgel 60 F254, Merck) and series of lactams was eluted in (AcOEt/hexane, 1:1) as solvent visualized with a 254-nm UV lamp, aqueous potassium permanganate solution, and iodine. Crude products were purified using column chromatography on silica gel; Fluka Kieselgel (70–230 mesh) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 300 spectrometer working at 300, 282, and 75 MHz respectively for ^{1}H, ^{19}F, and ^{13}C with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) and coupling constants (*J*) are, respectively, expressed in parts per million (ppm) and hertz (Hz). All NMR spectra were acquired at room temperature. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintuplet; sept, septuplet; m, multiplet. Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with NH_3 gas. High-resolution mass spectrometry (HRMS) analyses were performed at the Centre Commun de Spectrométrie de Masse in Lyon (France), on a Micro-TOFOII Thermofischer Scientific for electrospray ionization (ESI) measurements. Melting points (mp) were determined on a System Kofler type WME apparatus.

Table 1. Synthesis of 1-alkyl-4-propionylpyrrolidin-2-ones **4a–h**

Entry	R	Time (h)	Pyrrolidin-3-one **4**	Yield[a] (%)
a	$PhCH_2$	15		91
b	$p\text{-}ClC_6H_4CH_2$	20		80
c	$p\text{-}FC_6H_4CH_2$	48		85
d	$Ph(CH_3)CH$	72		75
e		45		65
f		34		70
g	[c]C_6H_{14}	40		60
h	[i]Pr	60		70

[a]Yields refer to the pure isolated products after chromatography.

Typical Procedure for the Preparation of Ethyl 3-Methylene-4-oxohexanoate 3

A mixture of ethyl 4-oxo-3-propionylhexanoate **1** (20 mmol), 30% aqueous formaldehyde (4 mL), and solution of potassium carbonate (6–10 M) (40 mmol) was stirred at room temperature for 4 h and then quenched with water (60 mL) and extracted with diethyl ether (4×50 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed to leave an oil residue, which was distilled at reduced pressure, affording the corresponding enone **3**. Full experimental detail and ^1H and ^{13}C NMR spectra of **3** can be found via the Supplementary Content section of this article's webpage.

General Procedure for the Synthesis of 1-Alkyl-4-propionylpyrrolidin-2-ones 4a-H

Primary amine (1.76 mmol, 1 equiv.) was added dropwise to a solution of ethyl 3-methylene-4-oxohexanoate **3** (0.3 g, 1.76 mmol) in 6 mL of methanol. The mixture was stirred at reflux for 15 to 72 h. The reaction mixture was concentrated under reduced pressure to remove methanol, and then the crude product was purified by chromatography on silica gel. Full experimental detail and ^1H and ^{13}C NMR spectra of **4a–h** can be found via the Supplementary Content section of this article's webpage.

CONCLUSION

In summary, we successfully developed through a valuation of a functionalized enone **3**, an expedient and single-step synthetic way to prepare 1-alkyl-4-propionyl-pyrrolidin-2-ones **4** using commercially available reagents and inexpensive methodology, and the prepared 4-functionalized γ-lactams **4** may find some applications in the development of active compounds.

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