EFFICIENT SYNTHESIS OF 3-PYRROLIN-2-ONE DERIVATIVES IN AQUEOUS MEDIA

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GRAPHICAL ABSTRACT

Abstract An efficient one-pot, three-component synthesis of 3-pyrroline-2-ones in aqueous media at room temperature is reported. This reaction provides a green and catalyst-free method for generation of 3-pyrroline-2-one derivatives in good yields.

Keywords Aqueous media; 3-pyrroline-2-one; three-component reaction

INTRODUCTION

In recent years, the development of new and clean synthetic routes with simplified workup procedures and reduced use of organic solvents for pharmaceutical compounds has been of great importance.[1–5] Furthermore, because the vast majority of natural products and drug-like compounds possess heterocyclic subunits, the ability to synthesize efficiently diverse heterocyclic compounds is critical.[6] Multicomponent reactions (MCRs) have emerged as a powerful tool for the construction of novel molecular structures, and they are generally much more environmentally friendly and offer rapid access to large compound libraries with diverse functionalities.[7–9]

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3-Pyrrolin-2-ones are important structural units found in pharmacological agents and natural products. Because of their biological significance, the design of new routes to the synthesis of 3-pyrolin-2-ones is currently receiving considerable attention. The most investigated approach to 3-pyrrolin-2-ones rely on multicomponent reactions.

As part of our current studies on the development of new routes in heterocyclic synthesis, here we report a convenient room-temperature, catalyst-free, three-component reaction for the efficient synthesis of 3-pyrrolin-2-ones in aqueous media.

**RESULTS AND DISCUSSION**

Xu and Lu have reported the synthesis of 1-tosyl-5-phenyl-3-methoxy-4-methoxycarbonyl-3-pyrrolin-2-ones 1 via the reaction of dimethyl acetylenedicarboxylate

![Scheme 1](image-url)
with N-tosyl benzaldimine in the presence of 20 mol\% of triphenylphosphine in dry benzene under reflux (Scheme 1). Murthy and coworkers described the synthesis of furan-2-(5H)-ones 2 via the reaction of aromatic aldehydes, aniline derivatives, and diethyl acetylenedicarboxylate in the presence of 10 mol\% of \( \beta \)-cyclodextrin in water at 60–70 °C (Scheme 1). On the other hand, Sarkar and Mukhopadhyay have reported the three-component reaction of acetylenedicarboxylates, arylamines, and aromatic aldehydes under admicellar catalysis by TiO\(_2\) nanoparticles for the synthesis of 3-hydroxy-2-pyrrolidinone derivatives 3. Sun et al. have also described a \( p \)-toluenesulfonic acid–catalyzed, one-pot, two-stage synthesis of 3-hydroxy-2-pyrrolidinones 3 from acetylenedicarboxylates, arylamines, and aromatic aldehydes in ethanol. Furthermore, a three-component reaction of aromatic aldehydes, aniline derivatives, and diethyl acetylenedicarboxylate has been reported for the synthesis of 1,4-dihydropyridine derivatives in absolute ethanol. It can be seen that the molecular diversity of this three-component reaction extremely depends on the reaction conditions. Thus, we performed a catalyst-free, three-component reaction of aromatic aldehydes, anilines, and dialkyl acetylenedicarboxylate in 50% aqueous EtOH at ambient temperature. The spectral data of obtained compounds confirms the formation of 1,5-diaryl-3-hydroxy-4-alkoxycarbonyl-3-pyrrolin-2-ones 3 (Scheme 1, Table 1). The structures of the products were deduced from their elemental analysis and \(^1\)H NMR, \(^{13}\)C NMR, and Fourier transform–infrared (FT-IR) spectral data. In addition, the structure of 3i was determined by x-ray crystallographic study (X-ray data for 3i: C\(_{20}\)H\(_{20}\)ClNO\(_5\), \( M = 389.82 \), monoclinic system, space group \( P2_1/c \), \( a = 17.974(4) \), \( b = 10.689(2) \), \( c = 9.6529(19) \) \( \text{Å} \), \( \beta = 94.33(3) \)^\( \circ \), \( V = 1849.3(7) \) \( \text{Å}^3 \), \( Z = 4 \), \( D_{\text{calc}} = 1.400 \) g cm\(^{-3}\), \( \mu(\text{Mo-K}\alpha) = 0.238 \) mm\(^{-1}\), \( T = 120(2) \) K, crystal size of 0.25 \( \times \) 0.20 \( \times \) 0.10 mm\(^3\). The structure was solved using SHELXS. The structure refinement and data reduction was carried out with SHELXL using the X-STEP32 suite of programs. The nonhydrogen atoms were refined anisotropically by full matrix least-squares on \( F^2 \) values.

**Table 1.** Synthesis of 1,5-diaryl-3-hydroxy-4-alkoxycarbonyl-3-pyrrolin-2-ones via a three-component reaction

| Entry | \( \text{Ar}^1 \) | \( \text{Ar}^2 \) | R | Product | Reaction time (h) | Yield (%) |
|-------|-----------------|-----------------|---|--------|-----------------|----------|
| 1     | \( \text{C}_6\text{H}_5 \) | \( \text{C}_6\text{H}_5 \) | Me | 3a     | 15              | 87       |
| 2     | \( \text{C}_6\text{H}_5 \) | \( \text{C}_6\text{H}_5 \) | Et | 3b     | 17              | 82       |
| 3     | \( 2-\text{ClC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3c     | 15              | 84       |
| 4     | \( 2-\text{BrC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3d     | 15              | 85       |
| 5     | \( 2-\text{MeC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3e     | 24              | 84       |
| 6     | \( 3-\text{MeC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3f     | 24              | 80       |
| 7     | \( 2-\text{MeOC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3g     | 22              | 85       |
| 8     | \( 3-\text{MeOC}_6\text{H}_4 \) | \( \text{C}_6\text{H}_5 \) | Me | 3h     | 22              | 83       |
| 9     | \( \text{C}_6\text{H}_5 \) | \( 2-\text{ClC}_6\text{H}_4 \) | Me | 3i     | 24              | 80       |
to final $R_1 = 0.0675, wR_2 = 0.1131$, and $S = 1.060$ with 254 parameters using 4973 independent reflections (9 range $= 2.85–29.16^\circ$). Hydrogen atoms attached to oxygen atoms were located in a difference Fourier map and refined isotropically. All other hydrogen atoms were added in idealized positions. The crystallographic information file has been deposited with the Cambridge Data Centre, CCDC 916963.) The structure and the atomic numbering for compound 3i is shown in Fig. 1.

A proposed mechanism for this transformation is shown in Scheme 2. It is conceivable that the initial event is the formation of imine 4 from aldehyde and aniline,
which undergoes nucleophilic attack on the β-carbon of the electron-deficient dimethyl acetylenedicarboxylate to generate the zwitterionic intermediate 5, which trapped by the another component of imine 4, followed by intramolecular nucleophilic addition of the nitrogen atom to the carbonyl group of ester and subsequent elimination of alkoxy group to form intermediate 6. The final products (3a–i) were formed by regenerating the imine 4 upon hydrolysis.

In summary, a more convenient process has been developed for the synthesis of 3-pyrrolin-2-ones in aqueous media. This new, green, three-component method does not require any additive or catalyst for promoting the reaction and gives rise to the target compounds in good yields.

EXPERIMENTAL

Typical procedure for the synthesis of 3-pyrrolin-2-ones 3a–i: A mixture of benzaldehyde (0.1 ml, 1 mmol) and aniline (0.1 ml, 1 mmol) in 50% aq EtOH (2 ml) was stirred for 1 h. Next, dimethyl acetylenedicarboxylate (0.12 ml, 1 mmol) was added. The mixture was stirred until completion of the reaction as indicated by thin-layer chromatography (TLC, 15 h). The sticky precipitated solid was filtered, washed with H2O, and recrystallized from EtOH. Compound 3a was obtained as white crystals (0.27 g, 87% yield). Mp 187–189 °C; IR (KBr) (νmax/cm⁻¹): 3209, 1702, 1679, 1597, 1498, 1381, 1232, 1201, 1135. ¹H NMR (400 MHz, CDCl₃): δ = 3.77 (3H, s, OCH₃), 5.76 (1H, s, CH), 7.11–7.49 (10H, m, CHarom), 8.97 (1H, br s, OH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 52.11 (CH₃ ester), 61.62 (CH), 112.87 (C), 122.39 (CH), 125.97 (CH), 127.47 (CH), 128.61 (CH), 128.71 (CH), 129.01 (CH), 134.97 (C), 136.17 (C), 156.28 (=COH), 162.80 (CO), 165.33 (CO) ppm. Anal. calcd. for C₁₈H₁₅NO₄: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.70; H, 4.89; N, 4.56.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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