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ORIGINAL ARTICLE

Synthesis of pyrrole and furan derivatives in the presence of lactic acid as a catalyst

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KEYWORDS

Lactic acid;
Pyrrole;
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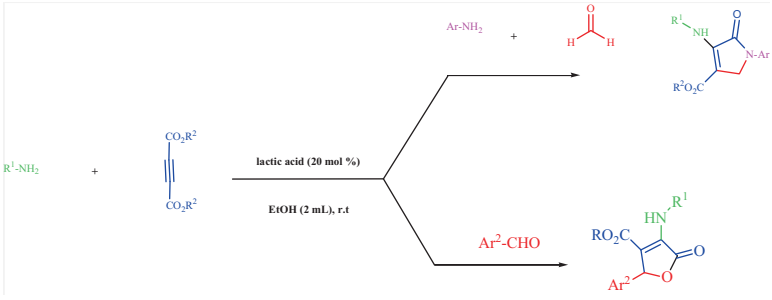
Ambient temperature

Abstract



For the first time lactic acid was applied as an efficient and green catalyst for the one-pot synthesis of pyrrole and furan derivatives at ambient temperature in EtOH. This methodology includes a number of advantages such as: short reaction time, clean work-up, use of non toxic and expensive catalyst and high yield.

1. Introduction

In recent years, growing attention has been paid to the synthesis of N-heterocycles due to diverse biological and pharmaceutical applications [1–3]. In this respect, the presence of pyrrol-2-ones (5-lactams or g-lactams) in pharmaceuticals and natural products has continued to stimulate a great deal of interest in the development of new methodologies for their synthesis [4–6]. There are several bioactive natural molecules with a pyrrol-2-one moiety, such as holomycin and thiolutin [7], thiomarinol A4 [8], oteromycin [9], pyrrocidine A [10], quinolactacin C [11], and ypaoamide [12]. On the other hand, dihydropyrrol-2-ones have been successfully used as peptidomimetic [13], HIV integrase [14], herbicidals [15], DNA polymerase inhibitors [16], caspase-3 inhibitors [17] cytotoxic and antitumor agents [18], antibiotics [19], and also inhibitors

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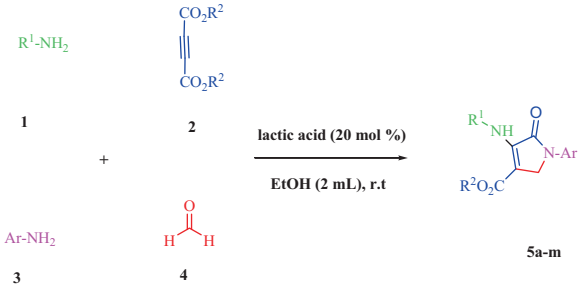


Scheme 1 Synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates.

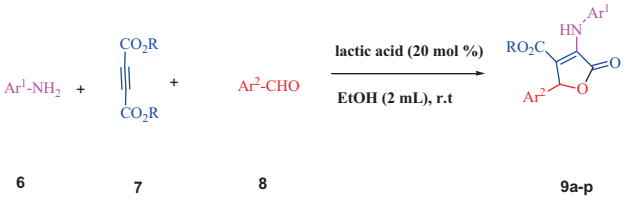
of the annexin A2-S100A10 protein interaction [20]. Recently, a few methods have been reported for the synthesis of highly substituted dihydropyrrol-2-ones using one-pot, four-component reactions in the presence of catalyst, such as AcOH, I2, benzoic acid, TiO_2 nanopowder or $Cu(OAc)_2\_H_2O$ [21–25]. However, some of these methods have drawbacks, such as high temperature and utilize a chlorinated solvent. Therefore, the development of a milder and more efficient route for one-pot synthesis of these important heterocycles is still in demand.

Substituted furan derivatives are fundamentally important heterocyclic molecules and are present in many natural and medicinal structures [26,27]. They can be used as valuable intermediates for the construction of heterocycles in organic synthesis. Thus, efforts for the synthesis of furan scaffolds are in demand by organic chemists. Among the various furan derivatives, butenolides have appeared in the literature as interesting components for the construction of natural and pharmacological compounds. These skeletons show a wide range of biological activities such as antimicrobial [28], antifungal [29], anti-inflammatory [30], anticancer [31] and anti-viral HIV-1 [32] activities. Due to this wide range of abundance and applicability, various approaches toward substituted butenolides have been developed, which involve the use of organo-lithium [33], boronic acids [34,35], transition-metal catalysts such as $Pd(OAc)_2$ [36], Ru [37], Cu(II) [38], AuCl [39], secondary amines [40] and b-cyclodextrin [41] and $SnCl_2$ [42]. In spite of the merits of these procedures, each of them suffers at least from one of the following limitations: low yields, unavailability of the catalyst, long reaction times, effluent pollution, harsh reaction conditions, and tedious work-up. In continuation of our ongoing program on multi-component reactions [43–48], an efficient and convenient synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxy lates and 3,4,5-trisubstituted furan-2(5H)-ones has been accomplished using lactic acid as an efficient catalyst in EtOH at ambient temperature, with good yields (Schemes 1 and 2).

2. Experimental

2.1. Chemicals and apparatus

Chemicals were purchased from Merck (Darmstadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification. Melting points were taken on an Electrothermal 9100 apparatus. IR spectra were obtained on a JASCO FT/IR-460 plus spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a



Scheme 2 Synthesis of 3,4,5-trisubstituted furan-2(5H)-ones.

Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent and using TMS as internal reference at 400 MHz and 100 MHz, respectively.

2.2. General procedure for the synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates 5

A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in EtOH (2 mL) was stirred for 25 min. Next, amine **3** (1 mmol), formaldehyde **4** (37% solution, 1.5 mmol) and lactic acid (20 mol%) were added in successively. The reaction mixture was allowed to stir at ambient temperature for appropriate time. After completion of the reaction (monitored by TLC), water was added to produce solid precipitate, and the precipitate was filtered off and washed with ethanol (3×2 mL) to give the pure product **5**. The structures of the synthesized compounds were characterized by their IR, ^1H NMR and ^{13}C NMR spectra and were found to be identical with data described in the literature [21,22].

2.3. General procedure for the synthesis of 3,4,5-trisubstituted furan-2(5H)-ones

A mixture of amine **6** (1 mmol) and dialkyl acetylenedicarboxylate **7** (1 mmol), aromatic aldehyde **8** (1 mmol) and lactic acid (20 mol%) in EtOH (2 mL) was stirred at ambient temperature for appropriate time. After completion of the reaction (monitored by TLC), water was added to produce solid precipitate, and the precipitate was filtered off and washed with ethanol (3×2 mL) to give the pure product **9**. The structures of the synthesized compounds were characterized by their IR, ^1H NMR and ^{13}C NMR spectra and were found to be identical with data described in the literature [43].

2.4. Characterization data of selected compound

2.4.1. Methyl-2,5-dihydro-2-(4-bromophenyl)-5-oxo-4-(phenylamino)-furan-3-carboxylate Colorless solid (9p)

IR (KBr, cm^{-1}): δ 3215 (NH), 1697 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, CH_3) 5.72 (s, benzylic), 7.04–7.70 (m, aromatic), 9.01 (s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 162.7 (CO of carbonyl), 156.0, 142.1, 135.8, 134.2, 133.6, 132.2, 131.9, 129.7, 129.13, 129.12, 126.1, 125.7, 124.8, 122.57, 122.3 and 112.4 (C aromatic C and vinylic), 61.0 (benzylic), 52.1 (methoxy).

3. Results and discussion

Formaldehyde, aniline, and dimethyl acetylenedicarboxylate were taken as model compounds for the optimization of the