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Lithium perchlorate-, acetic anhydride-, and triphenylphosphine-assisted multicomponent syntheses of 4-unsubstituted 2,5-dioxooctahydroquinoline-3-carboxylates and 3-carbonitriles

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ABSTRACT

Lithium perchlorate and acetic anhydride were the key additives for the multi-component reaction between 3-aminocyclohex-2-enones, formaldehyde, and malonates yielding adducts that were annulated under acidic conditions to afford bicyclic 2,5-dioxooctahydroquinoline-3-carboxylates. When methyl cyanoacetate was subjected to the same reaction conditions in the presence of a catalytic amount of triphenylphosphine, the bicyclic 2,5-dioxooctahydroquinoline-3-carbonitriles were obtained in a one-flask reaction.

1. Introduction

1,4-Dihydropyridines, 1,4-dihydropyridine-2-pyridones, pyridines, and piperidines are closely related structural motifs found in many natural products and bioactive molecules. 1,4-Dihydropyridines are considered to be privileged structures, because they bind to multiple ion channels and receptors.[1] For example, the 4-aryl-1,4-dihydropyridine moiety is a component of the cardiovascular drug nifedipine (**1**, Fig. 1), which is a calcium channel antagonist.[2,3] The annulated 1,4-dihydropyridine analogue **2** (Fig. 1) initiates cardiac differentiation in mouse embryonic stem cells by inhibiting TGFβ signaling—a mechanism unrelated to calcium channel blockade.[4] These analogues represent a new class of agents for potential use in cardiac regenerative medicine.[5] The structurally related 1,4-dihydropyridine-2-pyridone scaffold is also of medicinal interest. The 2-pyridone moiety is a component of clinically used phosphodiesterase-3 (PDE3) inhibitors, such as milrinone (**3**, Fig. 1) and related derivatives,[6,7] including the annulated PDE3 inhibitor **4** (Fig. 1).[8] 2-Pyridones are also found as structural elements in a variety of other bioactive compounds

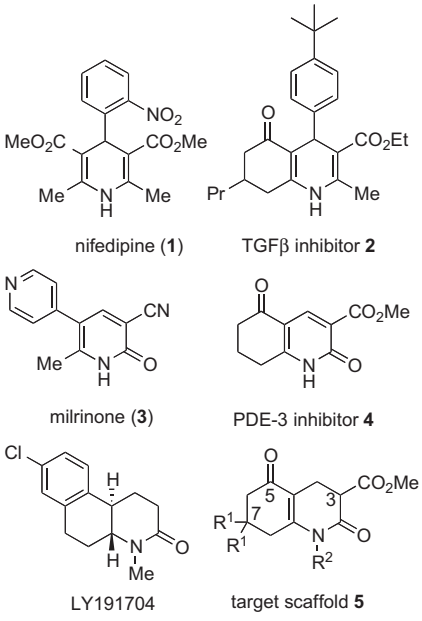

Fig. 1. Representative structures of cardiovascular drugs, 1,4-dihydropyridine nifedipine (**1**), a calcium channel blocker, TGFb inhibitor **2**, milrinone (**3**), annulated 2-pyridone phosphodiesterase-3 inhibitor **4**, human type I steroid 5-α-reductase inhibitor LY191704, and target scaffold **5**.

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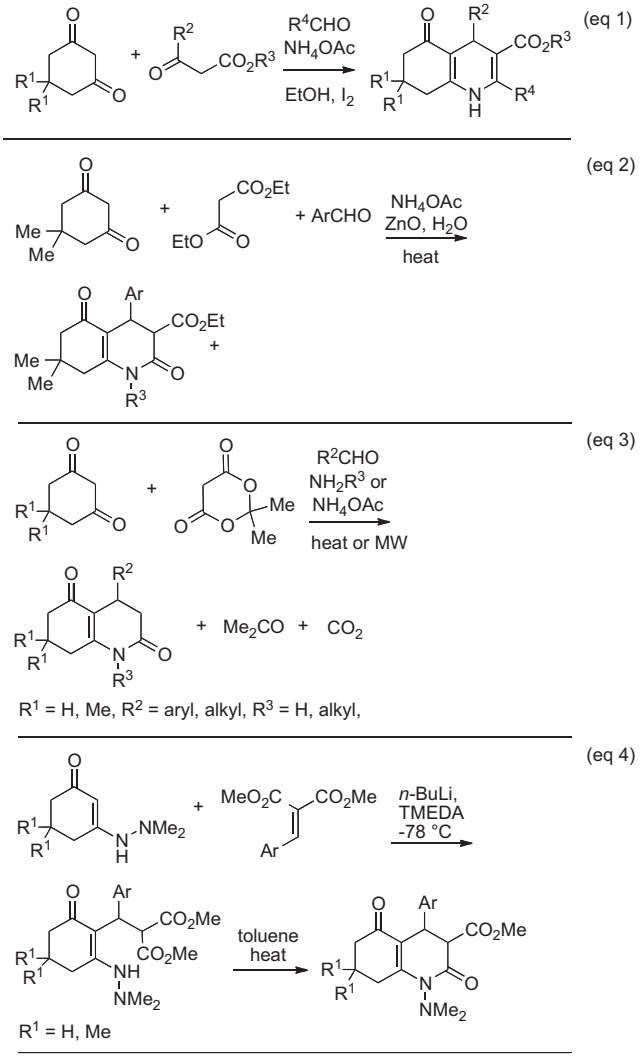
including natural products.[7,9] Octahydro-2-pyridones, such as LY191704 and the related tetrahydro analogues were found to be specific inhibitors of human type I steroid 5-α-reductase.[10–12] Despite the fact that these structural types have displayed interesting bioactivities, 3,4-dihydropyridinones and their annulated analogues, 2,5-dioxooctahydroquinoline-3-carboxylates **5** (target scaffold **5**, Fig. 1) have not been examined extensively yet in terms of synthesis, biological activity, and structure–activity relationships.

It is well known that 1,3-diketones, including cyclic ketones,[13] react via enamine formation (Scheme 1, Eq. 1) to produce substituted 1,4-dihydropyridines (Hantzsch reaction). Similar to the Hantzsch-type reaction that is used to synthesize annulated 1,4-dihydropyridines (Scheme 1, Eq. 1), formal [3+3] cycloaddition reactions were employed to construct dihydro-2-pyridones including annulated core structures.[9,14–17] In these multi-component reactions 1,3-cyclohexanediones, malonates or Meldrum's acid, aldehydes, and amines or ammonia are reacted in one flask, as is depicted in Scheme 1, Eq. 2. In the example shown in Eq. 2, ZnO serves as an efficient catalyst to effect the reaction with aromatic aldehydes in excellent yields, but apparently does not work with formaldehyde or aliphatic aldehydes.[18] When Meldrum's acid is used in the multicomponent reaction, formaldehyde and aliphatic aldehydes can be employed, but the reaction products lack the 3-carboxylic acid moiety (Scheme 1, Eq. 3), which is lost by decarboxylation.[17] In related chemistry (Scheme 1, Eq. 4), hydrazinyl enamines of 1,3-cyclohexanediones, and the arylidenemalonates are preformed and then reacted in the presence of butyl lithium to form the Michael addition products that are subsequently cyclized to yield 4-aryl-2,5-dioxooctahydroquinoline-3-carboxylates.[19]

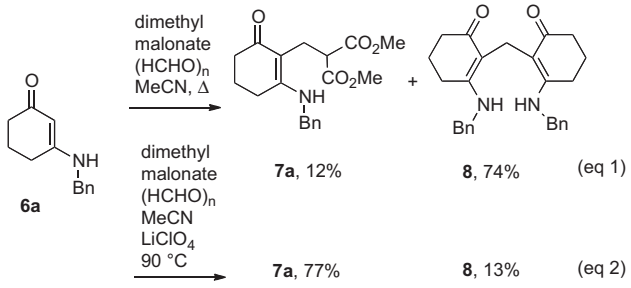


Scheme 1. Multicomponent literature methods for the synthesis of 5-oxohexahydroquinoline-3-carboxylates (Eq. 1), 2,5-dioxooctahydroquinoline-3-carboxylates (Eqs. 2 and 3) and a step-wise reaction to form 2,5-dioxooctahydroquinoline-3-carboxylates (Eq. 4).

2. Results and discussion

In our efforts to prepare structurally diverse and novel nitrogen-containing heterocyclic compounds with privileged structures for biological screening, we targeted the synthesis of bicyclic 1,4-dihydropyridine-2-pyridones **5** (Fig. 1) that do not contain a substituent at C4 but an ester moiety at C3 (2,5-dioxooctahydroquinoline-3-carboxylates). While aromatic aldehydes have been employed in the multicomponent reaction shown in Eq. 2 in Scheme 1, the reaction apparently did not take place when formaldehyde was used.[18] The availability of a method that provides the target compounds **5** without a substituent at C4 is of importance to expand the scope of this chemistry. Once an aryl or aliphatic group is present at C4 it will require multiple steps for removal if unsubstituted analogues are desired for biological investigations.

We started our investigations by carrying out a one-flask reaction similar to the one shown in Scheme 1, Eq. 3, by following a reported procedure[17] using 1,3-cyclohexanedione, formaldehyde, dimethyl malonate, and benzylamine, but failed to obtain the desired bicyclic reaction product. We then decided to explore the possibility of synthesizing the target molecule in a step-wise manner in order to simplify the reaction system. 3-(Benzylamino) cyclohex-2-enone (**6a**), easily prepared by condensation of 1,3-cyclohexanedione and benzylamine,[20] paraformaldehyde, and dimethyl malonate, were envisaged to form an adduct, followed by a subsequent cyclization to yield the target molecule. Yet, when a mixture of the enaminone, formaldehyde, and dimethyl malonate were heated in a reaction vessel, only little of adduct **7a** formed and instead bis-addition of the enaminone to formaldehyde took place and **8a** was isolated as the major product in 74% (Scheme 2, Eq. 1). Clearly, this side reaction needed to be suppressed in order to allow the desired multi-component reaction to become the major reaction pathway and yield the desired adduct **7a**. Since $LiClO_4$ has been introduced as a useful reagent to facilitate Mannich-type reactions,[21–25] we tested this Lewis acid as an additive in the reaction (Scheme 2, Eq. 2). The reaction was heated to 90 °C in acetonitrile in the presence of 1 equiv of $LiClO_4$, and the desired adduct **7a** was isolated as the major product in 77%, along with the bis-addition side product **8** in 13% as the minor product.



Scheme 2. Multi-component reactions of 3-(benzylamino)cyclohex-2-enone (**6a**) with and without $LiClO_4$ as additive.

Optimization of the reaction conditions (Table 1) showed that an equimolar amount of $LiClO_4$ was crucial to obtain good yields (Table 1, entries 1–3) and that excess $LiClO_4$ was unnecessary (entries 4 and 5). In an attempt to annulate the adduct in the same flask,