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A novel synthesis of 1-aryl-3-piperidone derivatives

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ABSTRACT

A novel method to construct the 1-aryl-3-piperidone scaffold is described here. Starting from 3,5-dichloroaniline, a seven-step synthesis, without the use of protecting groups, generates the desired 3-piperidone ring in an overall yield of 30% through a key Morita–Baylis–Hillman reaction and ring-closing metathesis, providing an easy access to diverse and useful heterocycles.

The piperidine ring is an ubiquitous structure present in many natural alkaloids[1] and drug candidates;[2] therefore, its synthesis attracts much interest from organic chemists (Fig. 1). Of the piperidine derivatives, 3-piperidone is an important intermediate because of its easy conversion to other functional groups using various methods for the construction of bioactive heterocycles. For example, the transformation of a 4-carboethoxy-3-piperidone to pyrimidinone RO3203546, a selective α-1 antagonist,[3] and the rearrangement of a 2-methyl-3-piperidone to a 2-acetylpyrrolidine[4] proceed from 3-piperidone intermediates.

A typical procedure to 3-piperidones employs an intramolecular Claisen condensation of two branched esters of a tertiary amine to form a cyclic β-ketoester, followed by decarboxylation.[5] However, the extra deprotection step, as well as the moderate to low yield in the Claisen condensation, limits its application. Herein we report a novel route to construct 1-aryl-3-piperidone-4-carboxylate analogues without the use of protecting groups.

As a part of an ongoing project in our group to discover a therapeutic for amyotrophic lateral sclerosis (ALS),[6] the synthesis of the 3-piperidone, 1-(3,5-dichlorophenyl)-4-carboethoxy-3-piperidone (**6**), was a high priority. Initially we tried diethyl carbonate and Mander's reagent,[7] which was successful in our synthesis of the isomeric 1-aryl-4-piperidone-3-carboxylate **2**, but those reagents gave no β-ketoester from 3-piperidone **5** (Scheme 1). A Dieckmann condensation of diester **3** was shown to be an effective alternative route, but that reaction also failed when applied to **7**. Possibly, the intramolecular enolate attack does not occur because the planar aniline structure (**7**) reduces the flexibility of the ester chain and causes a loss of its ability to condense with the other ester. Several other attempts, including the use of a strong lithium base, intramolecular Claisen condensation between the corresponding Weinreb amide and an ester and a Buchwald amination of the corresponding phenyl bromide and 3-piperidone, also failed.

Since two possible bond-breaking positions around the β-ketoester moiety (**6**, a and b, Fig. 2) were fruitless, our focus shifted to position c. Given the wide utilization of Grubbs catalysts to mediate ring closing metathesis reactions,[8] we decided to replace the single bond at position c with a double bond. The double bond might isomerize from position c to b, which would provide the β-ketoester from the isomeric allylic alcohol in one step. Retrosynthetically, **6** could be derived from **8**, which could come from another key synthon **9** through a Morita–Baylis–Hillman (MBH) nucleophilic addition,[9] and **9** could be made from commercially available **10**.

The selective reactions of ethyl bromoacetate and allyl bromide with the aniline were performed under standard conditions (Scheme 2) in good yields.

Subsequent conversion to **8** was achieved via DIBAL reduction and then the MBH nucleophilic attack of acrylate mediated by DABCO. Standard conditions for ring-closing metathesis with 5% Grubbs II catalyst produced cyclic allyl alcohol **12** in near quantitative yields; the product yield decreased if the loading amount of Grubbs catalyst was reduced (see Supplementary data). With **12** on hand, several redox isomerization reactions of allyl alcohols to carbonyl compounds were explored, including Pd/C, $Ru(PPh_3)_2Cl_2$,[10] and $Cp^*Ru(CH_3CN)_3PF_6$.[11] However, no desired isomeric product was observed. Therefore, **12** was converted to **6** by hydrogenolysis of

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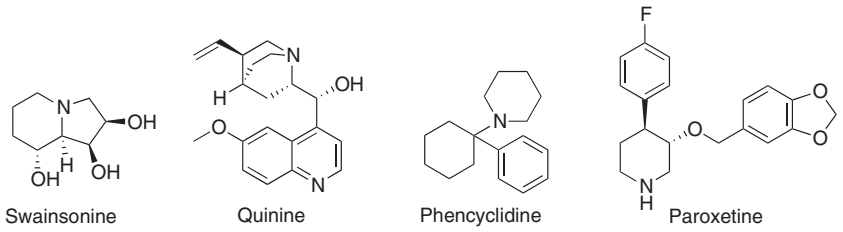
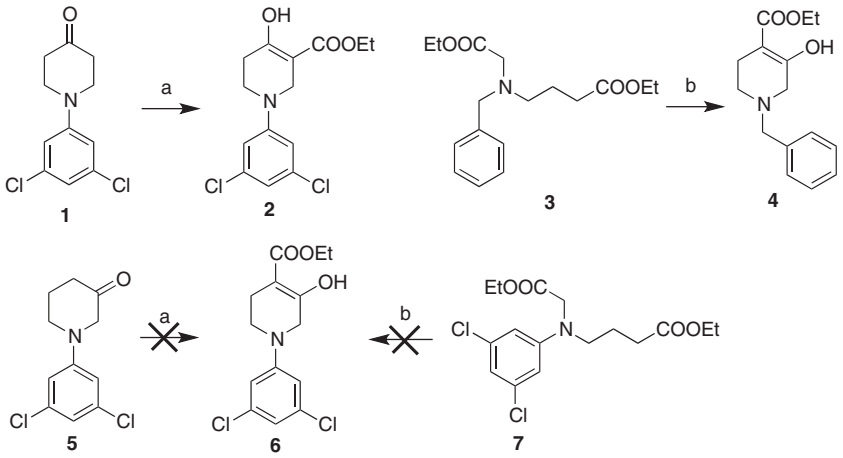


Figure 1. Examples of piperidine-containing alkaloids and drugs.



Scheme 1. Reagents and conditions: (a) $(EtO)_2CO$ or CNCOOMe, NaH, MeOH, toluene, 80 °C, 3 h, 24%; (b) NaH, toluene, reflux, 4 h, 52%.[3]

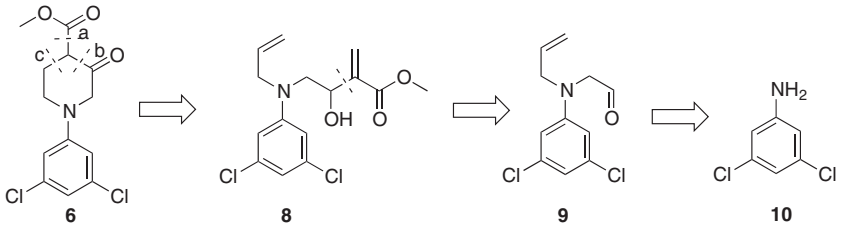
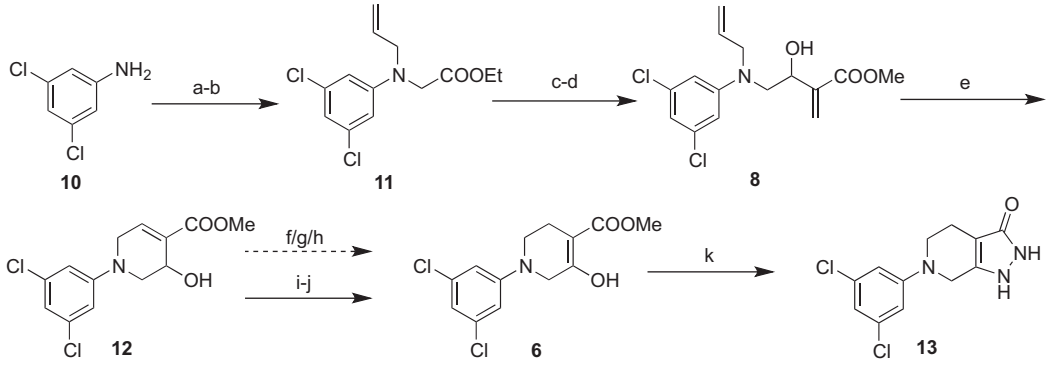


Figure 2. Retrosynthetic analysis of 3-piperidone analogue.



Scheme 2. Reagents and conditions: (a) $BrCH_2COOEt$, DIPEA, 90 °C, 24 h, 88%; (b) K_2CO_3, NaI, allyl bromide, CH_3CN, reflux, 2 days, 83%; (c) DIBAL, DCM, −78 °C, 1 h, 86%; (d) DABCO, methyl acrylate, room temp, 3 days, 71%; (e) 5 mol % Grubbs II, DCM, reflux, 5 h, 96%; (f) 5 mol % Pd/C, MeOH, reflux, 16 h; (g) 5 mol % $Ru(PPh_3)_2Cl_2$ toluene, K_2CO_3, 100 °C, 16 h; (h) $Cp^*Ru(CH_3CN)_3PF_6$, K_2CO_3, CH_3CN, 80 °C, 1 h; (i) Pd/C, EtOAc, 1 atm H_2, room temp, 16 h; (j) Dess-Martin periodinane, DCM, room temp, 1 h, 70% for two steps; (k) NH_2NH_2, EtOH, room temp, 16 h, 74%.

the double bond followed by Dess–Martin periodinane oxidation of the alcohol in good yields, giving **6** in an overall yield of 30% for the seven steps. Compound **6** was readily converted to our desired pyrazolone analogue **13** with hydrazine.

The 3-piperidinone analogue (**6**) is a useful intermediate for the synthesis of a variety of heterocycles, such as pyrimidinones,[3] quinuclidinones,[12] cyclohexanediamines[13] and benzomorphans.[14] Furthermore, medium size ring derivatives, such as azepanone and azocanone analogues, could be attainable from homoallylic or γ-propionate anilines using standard RCM conditions.[15]

In conclusion, a novel synthesis of 1-aryl-3-piperidone-4-carboxylates has been accomplished without the need for protecting groups. This method should be highly applicable for the synthesis of a variety of diverse heterocyclic compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.085.

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