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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 easy access to diverse and useful heterocycles.

Keywords

3-Piperidone; Synthesis; Morita-Baylis-Hillman; Ring-closing metathesis; Heterocycles

The piperidine ring is a ubiquitous structure present in many natural alkaloids¹ and drug candidates;² therefore, its synthesis attracts much interest from organic chemists (Figure 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-acetylpyrrolidine⁴ 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. Here we report a novel route to construct 1-aryl-3-piperidone-4-carboxylate analogues without the use of protecting groups.

As 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

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Supplementary data

Supplementary data associated with this article can be found in the online version at XXX.

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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, Figure 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 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** in hand, several redox isomerization reactions of allyl alcohols to carbonyl compounds were explored, including Pd/C, Ru(PPh₃)₂Cl₂,¹⁰ and Cp*Ru(CH₃CN)₃PF₆.¹¹ However, no desired isomeric product was observed. Therefore, **12** was converted to **6** by hydrogenolysis of 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,¹² quinuclidinones,¹³ cyclohexanediamines,¹⁴ and benzomorphans.¹⁵ Furthermore, medium size ring derivatives, such as azepanone and azocanone analogues, could be attainable from homoallylic or γ -propionate anilines using standard RCM conditions.¹⁶

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 to the synthesis of a variety of diverse heterocyclic compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of piperidine-containing alkaloids and drugs

Figure 2.
Retrosynthetic analysis of 3-piperidone analog.

Scheme 1.

Reagents and conditions: (a) $(\text{EtO})_2\text{CO}$ or CNCOOMe , NaH , MeOH , toluene, 80°C , 3 h, 24%; (b) NaH , toluene, reflux, 4 h, 52%.³

Scheme 2.

Reagents and conditions: (a) $\text{BrCH}_2\text{COOEt}$, 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% $\text{Ru}(\text{PPh}_3)_2\text{Cl}_2$ toluene, K_2CO_3 , 100 °C, 16 h; (h) $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$, 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%.