Tetrahedron Letters 56 (2015) 3877–3881

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Synthesis of functionalized cyclohexenols via a domino Michael addition–Dieckmann cyclization–isomerization reaction sequence

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ARTICLE INFO

*Article history:*
Received 6 February 2015
Revised 20 April 2015
Accepted 25 April 2015
Available online 29 April 2015

*Keywords:*
Cyclohexenols
Michael addition
Dieckmann cyclization
Enolization
Baylis–Hillman derivatives

ABSTRACT

A simple and new protocol for the synthesis of functionalized cyclohexenols via a domino Michael addition followed by Dieckmann cyclization and enolization reaction sequence has been described. A wide variety of activated olefins were utilized in the domino cyclization along with Baylis–Hillman derivatives to afford libraries of functionalized cyclohexenols in good yields.



Practical and efficient construction of highly functionalized and diversified molecules from readily available starting materials is a great challenge and highly desirable. Recently domino reactions[1a–i] have become very attractive and a useful strategy which minimizes the reaction steps to achieve the target complex organic compounds with high yields. Domino reactions are effectively explored in the Baylis–Hillman (BH) chemistry for the construction of polysubstituted phenols,[2a] 1,2,4,5-tetrasubstituted pyridines,[2c] polysubstituted benzenes, and a variety of other interesting target molecules.[2a–f] These compounds have proven to be good synthons in the synthetic organic chemistry for several manipulations. Among various starting materials available, reactions of Baylis–Hillman bromides or acetates with active methylene compounds have been extensively studied for the synthesis of cyclohexene and its derivatives. Interestingly these types of cyclohexene carboxylates are an important skeleton in many natural products and bioactive molecules. Some of the representative examples containing cyclohexene carboxylates are shown in Figure 1.

The Baylis–Hillman adducts and their derivatives have been demonstrated to be a useful precursor for a myriad of applications leading to the synthesis of heterocycles, drug intermediates, and natural products.[3]

To the best of our knowledge (*E*)-alkyl 2-arylidene-4, 4-dicyanobutanoates have not been utilized for the synthesis of (*E*)-alkyl 3-arylidene-5, 5-dicyano-2-hydroxy cyclohex-1-ene carboxylates. We envisaged that the synthesis of substituted cyclohexenol can be achieved from Baylis–Hillman bromides (**5**) via a Michael reaction followed by Dieckmann cyclization and enolization reaction sequence according to the retrosynthetic strategy shown Scheme 1.

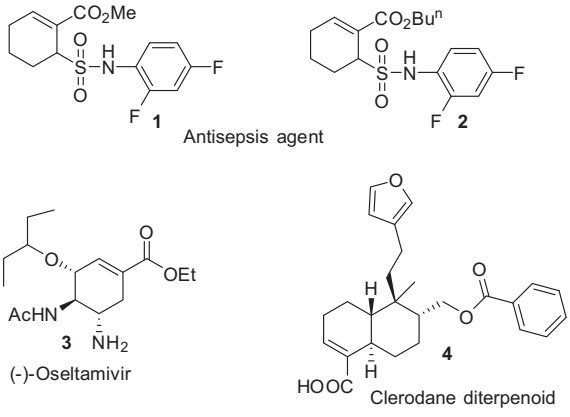


**Figure 1.** Cyclohexene carboxylates containing natural products and bioactive molecules.

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http://dx.doi.org/10.1016/j.tetlet.2015.04.100
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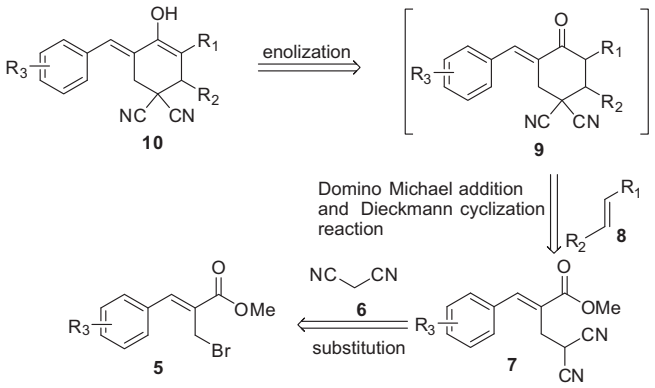
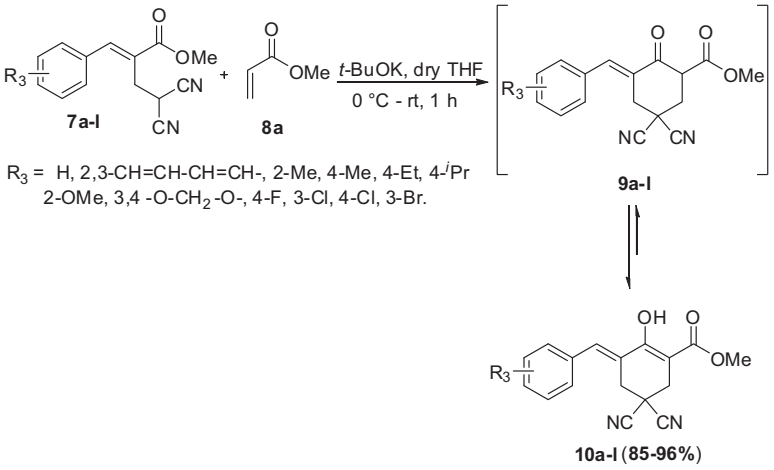



**Scheme 1.** Retrosynthetic strategy for the construction of substituted cyclohexenols.

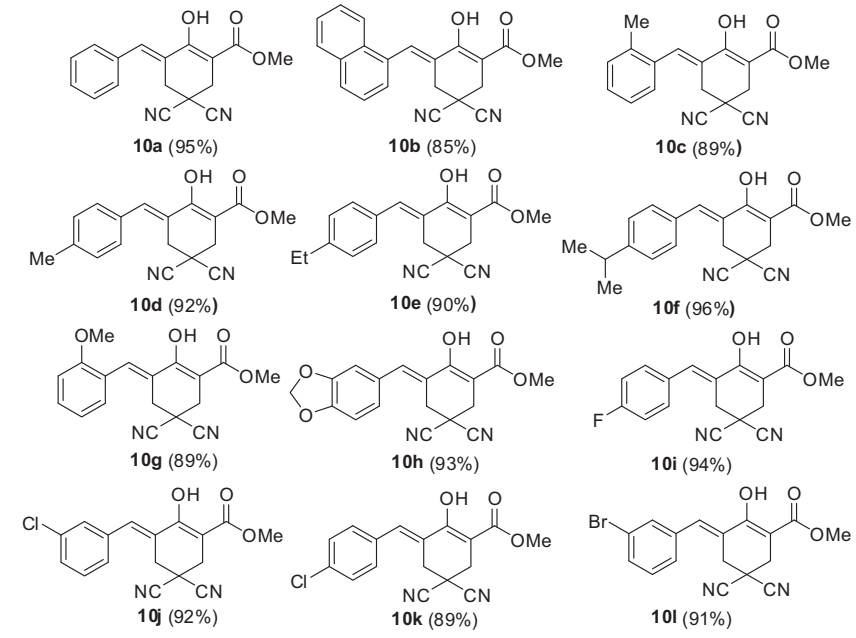
In continuation of our interest in the Baylis–Hillman chemistry,[4] herein we wish to report a new protocol for the synthesis of (*E*)-alkyl 3-aryllidene-5, 5-dicyano-2-hydroxy cyclohex-1-ene carboxylates by using Baylis–Hillman derivatives through tandem Michael addition followed by a Dieckmann cyclization and enolization reaction sequence. It is important to mention that this type of novel domino reaction sequence involves Michael addition, Dieckmann cyclization, and enol isomerization reaction is not known so far in the literature.

To execute our idea, we first treated (*E*)-methyl 2-benzylidene-4,4-dicyanobutanoate (**7a)** with methyl acrylate **8a** under various reaction conditions. The best result was observed when the reaction was conducted in the presence of potassium-*t*-butoxide in dry THF at 0 °C to rt for 1 h which successfully provided the desired (*E*)-methyl3-benzylidene-5,5-dicyano-2-hydroxycyclohex-1-ene carboxylate **10a** in excellent yield (95%) through domino Michael addition followed by Dieckmann cyclization and enolization reaction sequence as shown in Table 1.

**Table 1**
Synthesis of highly substituted cyclohexenol derivatives (**10a–l**)[a,b]




$R_3$ = H, 2,3-CH=CH-CH=CH-, 2-Me, 4-Me, 4-Et, 4-$^i$Pr
2-OMe, 3,4 -O-$CH_2$-O-, 4-F, 3-Cl, 4-Cl, 3-Br.




[a] All reactions were carried out on 1 mmol scale of cyano olefins **7a** with 1.1 mmol of methyl acrylate (**8a**) and 1.1 mmol of *t*-BuOK in dry THF (10 mL) as a solvent at 0 °C to rt for 1 h.
[b] Isolated yield of the pure product after column chromatography (Hexanes/EtOAc 9:1).