Tetrahedron Letters 55 (2014) 5264–5267

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An easy access to halogenated and non-halogenated spiro-hexadienones

Lucimara J. Martins [a], Bruno R. V. Ferreira [a], Wanda P. Almeida [a], Marcelo Lancellotti [b], Fernando Coelho [a,*]

[a] University of Campinas, Institute of Chemistry, PO Box 6154, 13083-970 Campinas, SP, Brazil
[b] University of Campinas, Institute of Biology, Rua Monteiro Lobato 255, 13083-862 Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 9 July 2014
Revised 26 July 2014
Accepted 26 July 2014
Available online 5 August 2014

Keywords:
Morita–Baylis–Hillman
Spiro-hexadienones
Heck reaction
Hypervalent iodine
Brominated compounds

ABSTRACT

We describe an improved protocol for the synthesis of spiro-hexadienones from Morita–Baylis–Hillman adducts. Solvent modification and temperature resulted in a significant increase in the yield. This protocol was used to synthesize mono- and dibrominated spiro-hexadienones in good overall yields. This report is the first to describe the synthesis of halogenated spiro-hexadienones from Morita–Baylis–Hillman adducts.

Compounds that contain the spiro-hexadienone moiety as part of their structures typically exhibit remarkable biological activities. This structural architecture with varied substitution patterns can be observed in certain natural products.[1] Most often, the biological effects exhibited by these natural products are closely related to the presence of the spiro-hexadienone motif. In Figure 1, some examples of this class of biologically active natural compounds are shown.

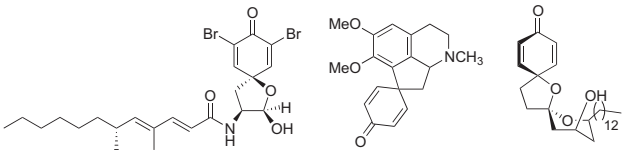
The chemical and biological relevance of spiro-hexadienones has attracted the attention of the chemical community. Therefore, several approaches for the synthesis of this class of compounds have been developed. For example, radical chemistry,[2] electrophilic cyclization,[3] carbene chemistry,[4] multi-component reactions[5] or palladium mediated reactions[6] have been employed to synthesize spiro-hexadienones. Most recently, a sustainable phenol oxidation mediated by $NaNO_2$ was also used for the synthesis of spiro-hexadienones.[7]

However, despite these methodologies, the most commonly employed methods are those based on phenol oxidation mediated by hypervalent iodine.[8]

Due to our interest in the use of Morita–Baylis–Hillman adducts as building blocks for organic synthesis,[9] we have recently developed a new synthetic strategy to prepare spiro-hexadienones.[10] Although it is operationally simple, the yields varied from low (36%) to moderate levels (70%). To circumvent this problem, in this Letter, we describe the optimization of our methodology based on varying key reaction parameters, such as solvent and temperature. Basically, our methodology takes advantage of phenol oxidation mediated by hypervalent iodine reagents. The suitably substituted β-keto esters, which were used as substrates for the key oxidation step, were directly and efficiently prepared from Morita–Baylis–Hillman adducts using the phosphine-free Mizoroki–Heck reaction.[11]

In this communication, we report an improved and efficient protocol for the synthesis of halogenated and non-halogenated spiro-hexadienones from Morita–Baylis–Hillman adducts.

First, a set of Morita–Baylis–Hillman adducts, which were synthesized according to a method developed by our group several years ago, were prepared.[12] In all cases, we observed yields ranging from good to excellent. The adducts were obtained in a straightfor-



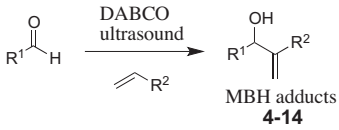
Gimnastatin I (**1**) Pronuciferine (**2**) (-)-Aculeatin A (**3**)

Figure 1. Examples of biologically active natural products that contain the spiro-hexadienone moiety in their structures.

* Corresponding author. Tel.: +55 19 3521 3085; fax: +55 19 3521 3023.
E-mail address: coelho@iqm.unicamp.br (F. Coelho).

http://dx.doi.org/10.1016/j.tetlet.2014.07.114
0040-4039/

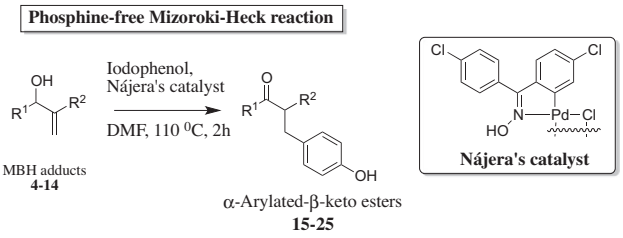
Table 1
Preparation of Morita–Baylis–Hillman adducts



Entry	MBH adducts	Yield[a,b,c] (%)
1	**4**, $R^1 = C_6H_5$; $R^2 = CO_2CH_3$	85
2	**5**, R^1 = 4-NO_2–C_6H_4; $R^2 = CO_2CH_3$	96
3	**6**, R^1 = 2-C_4H_4S; $R^2 = CO_2CH_3$	90
4	**7**, R^1 = 3,4-(OCH_2O)–C_6H_3; $R^2 = CO_2CH_3$	70
5	**8**, R^1 = 3,4,5-CH_3O–C_6H_2; $R^2 = CO_2CH_3$	71
6	**9**, R^1 = 3,4,5-CH_3O–C_6H_2; $R^2 = CO_2C_2H_5$	80
7	**10**, R^1 = 4-CH_3O–C_6H_4; $R^2 = CO_2CH_3$	99
8	**11**, R^1 = 3-CH_3O–C_6H_4; R^2 = CN	77
9	**12**, $R^1 = CH_3CH_2$; $R^2 = CO_2C_2H_5$	85
10	**13**, $R^1 = CH_3(CH_2)_7CH_2$; $R^2 = CO_2CH_3$	85
11	**14**, R^1 = 4-F_3C–C_6H_4; $R^2 = CO_2CH_3$	90

[a] Yields refer to isolated and purified products.
[b] Spectral data (^1H, ^{13}C NMR, IR, HRMS) are all compatible with the proposed structures.
[c] Reaction times varied from 15 min to 96 h.

Table 2
Preparation of α-arylated β-keto esters



Entry	MBH adducts	Yield[a] (%)
1	**4**, $R^1 = C_6H_5$; $R^2 = CO_2CH_3$	**15**, 91
2	**5**, R^1 = 4-O_2N–C_6H_4; $R^2 = CO_2CH_3$	**16**, 71
3	**6**, R^1 = 2-C_4H_4S; $R^2 = CO_2CH_3$	**17**, 90
4	**7**, R^1 = 3,4-(OCH_2O)–C_6H_3; $R^2 = CO_2CH_3$	**18**, 68
5	**8**, R^1 = 3,4,5-$(CH_3O)_3$–C_6H_2; $R^2 = CO_2CH_3$	**19**, 82
6	**9**, R^1 = 3,4,5-$(CH_3O)_3$–C_6H_2; $R^2 = CO_2C_2H_5$	**20**, 65
7	**10**, R^1 = 4-CH_3O–C_6H_4; $R^2 = CO_2CH_3$	**21**, 73
8	**11**, R^1 = 3-CH_3O–C_6H_4; R^2 = CN	**22**, 80
9	**12**, $R^1 = C_2H_5$; $R^2 = CO_2C_2H_5$	**23**, 85
10	**13**, $R^1 = C_9H_{19}$; $R^2 = CO_2CH_3$	**24**, 75

[a] Yields refer to isolated and purified products.

ward manner, and after isolation, only filtration on silica gel was required to achieve a high level of purity (⩾98%). The results are summarized in Table 1.

With the purified adducts in hand, the β-keto esters can be prepared. α-Substituted β-keto esters are classically prepared by Claisen condensation following by alkylation or via a Knoevenagel reaction between β-keto esters and aldehydes followed by hydrogenation of a double bond. Although these approaches are very simple, they present some drawbacks. Di-alkylation can occur, requiring additional purification. Otherwise, depending on the substituents present in the alkylating agent or in the aldehyde, a step involving a protecting group could also be required with both reactions (alkylation or Knoevenagel). In both cases, substituted β-keto esters can be obtained in 2 or 3 steps, if no protecting step is involved.

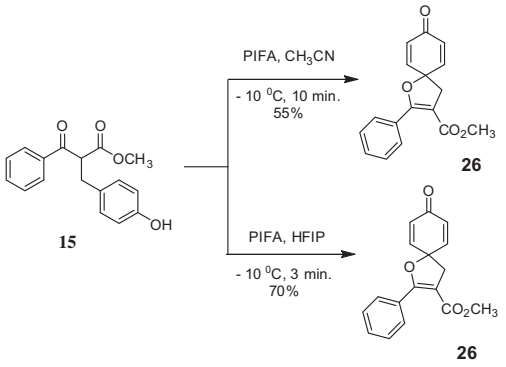
Several years ago, Alonso et al.[13] described a Mizoroki–Heck reaction using new oxime-derived palladacycle catalysts. Based on this catalyst, which provides an in situ source of palladium(0) nanoparticles, we have developed a phosphine-free method to prepare mono-α-arylated β-keto esters in good yields and high selectivity using the Mizoroki–Heck reaction and the MBH adducts as substrates.[11] This approach provides the required β-keto esters in one step from a MBH without the need of any protecting group. Therefore, a solution of the MBH adduct in DMF was treated with iodophenol in the presence of a catalytic amount (0.5 mol %) of the oxime-derived palladacycle (Nájera's catalyst) to afford the required α-arylated-β-keto esters in good yields, low reaction times and good selectivity. The results are summarized in Table 2.

In our previous communication,[11] the key phenolic oxidation step, which is mediated by a hypervalent iodine reagent, exhibited only moderate yields, which decreased the overall yields of our synthetic sequence. Initially, we decided to optimize this experimental condition by changing the solvent used in the oxidative step. Dohi et al.[14] reported the use of hexa-fluoroisopropanol (HFIP) in phenolic oxidation mediated by hypervalent iodine reagents. Due to its particular physical and chemical characteristics (i.e., low nucleophilicity, high polarity and high hydrogen-bond donor ability), this solvent increases the yield of this oxidative step. We decided to carry out a phenolic oxidation with HIFP and PIFA [phenyliodine bis(trifluoroacetate)] and compare this reaction to the one carried out in acetonitrile. The β-keto ester **15** was used as a model for both reactions. The results are shown in Scheme 1.

The change in the solvent results in a net increase in the yield and rate of the reaction. The yield increased from 55% to 70%, and the reaction medium was cleaner than when acetonitrile was used. We also observed a net effect on the rate of reaction. After only 3 min, the substrate was completely transformed to the reaction product based on TLC analysis. Therefore, we decided to test this experimental protocol with the entire set of β-keto esters. The results are summarized in Table 3.

For some cases, we observed a net increase in the yield of the reaction (Table 3, entries 6, 8 and 9). For other cases, no changes were observed (Table 3, entries 2–6). In all of the cases, no decrease in the yield was observed. Apparently, the increase in the yields is substantial for those β-keto esters substituted by alkyl groups (entries 8 and 9, Table 3). However, for all of the cases, the reaction times substantially decreased from 10 to 3 min. These results are due to the high polarity of HFIP. This solvent stabilizes the cationic intermediate formed in this oxidative process, which contributes to an increase in the yield and rate of the reaction.[14]

To increase the structural pattern diversity of our spiro-hexadienones, we decided to evaluate the feasibility of this methodology for the preparation of brominated spirohexadienones due to the biological potential exhibited by this particular class of spiro-hexadienones.[1] Bromine atoms can be incorporated into our sequence using two different approaches. First, the bromination



Scheme 1. Testing a fluorinated solvent for the phenolic oxidation of substituted β-keto esters.