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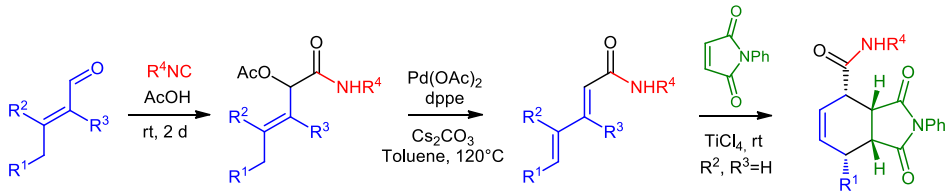

Tetrahedron Letters
journal homepage: www.elsevier.com

A Passerini/Tsuji-Trost Access to Dienamide Derivatives.

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

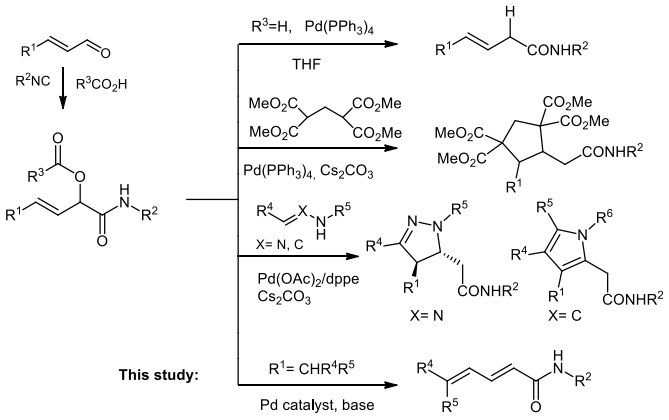
Keywords:
Passerini
Tsuji-Trost
1,3-diene
Diels-Alder
isocyanide

ABSTRACT

The Passerini reaction of α,β-unsaturated aldehydes affords allylic acetates which may be involved in Tsuji-Trost elimations towards conjugated dienamides. The interest of these 2,4-dienamides has been demonstrated in several $TiCl_4$ triggered Diels-Alder reactions with N-phenylmaleimide .

The Ugi and the Passerini reactions constitutes the main representants of the isocyanide based multicomponent reactions (IMCRs).[1] These two old reactions have been the object of an impressive rebirth at the end of the 20th century due to their extensive use for the formation of libraries of heterocycles. While this was particularly true for the Ugi reaction, the Passerini reaction rather benefited from the popularity of the Ugi reaction as its three component nature together with the sensitive ester moieties of its adducts rather prevented chemists in the first years of isocyanide revival to use these adducts for further functionnalisation and formations of heterocycles.[2] Nevertheless proper selection of bases and carboxylic acids could lead to libraries of oxygen based heterocycles such as observed in various Passerini/Knoevenagel tandems.[3] Further studies on Passerini adducts showed that these liabilities could even be turned into assets in transformations involving the fragmentation of the weak C-O bond of esters. Indeed, Passerini adducts could be easily oxidized into α-ketoamides with prior saponification[4] or submitted to various acyl group migrations such as observed in the PADAM strategy[5] or in reduction of the intermediate acyl cyanide Passerini adducts.[6]

Following our interest in palladium chemistry and isocyanide based MCRs,[7] we became recently interested by the Passerini reaction of α,β-unsaturated aldehydes. We first showed that the Passerini adducts between formic acid and cinnamaldehyde derivatives could be easily reduced under Tsuji-Trost type reaction conditions.[8] We next explored the use of various carbon based nucleophiles to trap the intermediate π-allyl palladium complexes and disclosed Tsuji-Trost/Michael addition tandem using bis-nucleophiles such as 1,3-bismalonyles, NH-hydrazones or NH-enamines (Scheme 1).[9] We now wish to report that in the absence of nucleophile, the Tsuji-Trost reaction of α,β-unsaturated aldehydes offers an interesting entry into dienamide derivatives (Scheme 1).



Scheme 1. Tsuji-Trost reactions of Passerini adducts.

Though the formation of dienes in Tsuji-Trost reactions has been documented quite early,[10] most applications of this reaction have

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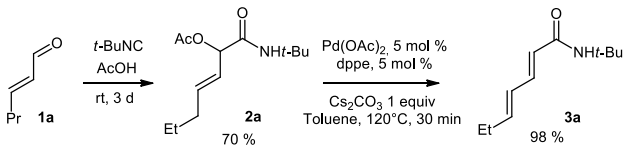
been centered on nucleophilic substitution of allylic acetates leading to new carbon-carbon bond formation.[11] In contrast with the numerous applications of the latter, the related 1,3-diene formation under Tsuji-Trost conditions has been rather neglected being often considered as an unwanted synthetic pathway.[12] Considering the straightforward formation of Passerini adducts form α,β-unsaturated derivatives and our successful use of these allylic acetates in Tsuji-Trost substitution reactions, we surmised that in the absence of nucleophiles, we could settle a fast preparation of 2,4-dienamides. This approach was even more attractive as no synthetic route to these compounds had been reported starting from isocyanides.

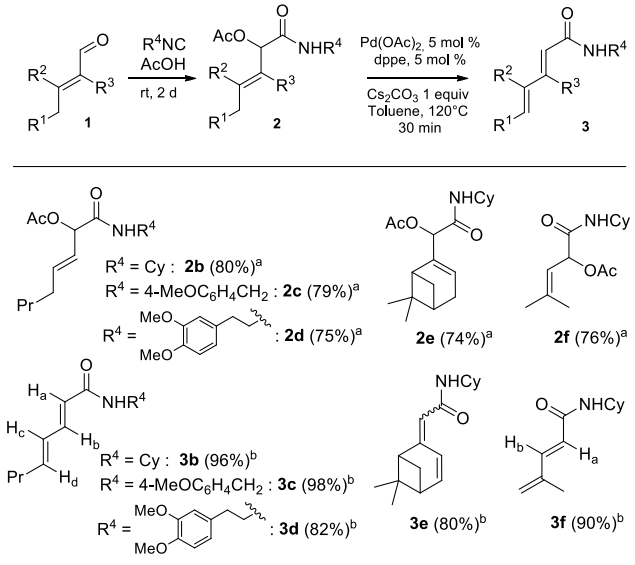
n-Hexenal was selected for our first trials and used together with acetic acid and *t*-butyl isocyanide to afford Passerini ester **2a** in 70% isolated yield after letting the compounds react for three days at room temperature without solvent. When **2a** was heated in toluene in conditions previously settled for our pyrrole synthesis from enamines and Passerini adducts (heating under microwave with palladium acetate, dppe and cesium carbonate), we were delighted to observe the expected formation of diene **3a** obtained in 98% isolated yield (Scheme 2).



Scheme 2. Passerini/Tsuji-Trost tandem towards diene **2a**.

Satisfied with these conditions, we prepared a set of Passerini adducts **2** from commercially available α,β-unsaturated aldehydes **1** and converted them into 2,4-dienamides **3**. The results are summarized in Table 1.

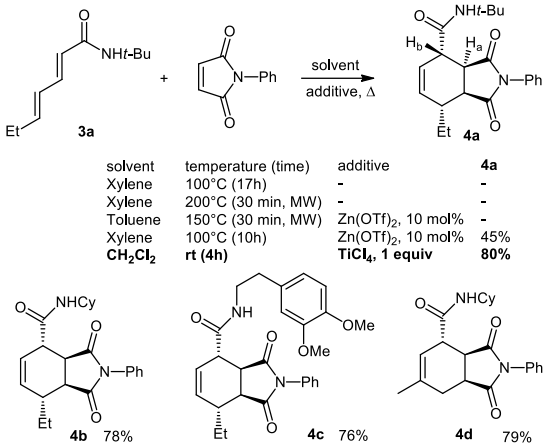
Table 1. Dienes **2** from Passerini adducts **1**.



[a] Isolated yields of Passerini adduct 2. [b] Isolated yields of diene 3 from 2.

Dienamides **3a**, **3b**, **3c** and **3d** all displayed trans,trans configuration for their two conjugated double bonds as shown by their characteristic $^3J_{Ha\text{-}Hb}$ and $^3J_{Hc\text{-}Hd}$ coupling constants close to 15 Hz between ethylenic hydrogens.[13] Diene **3e** was obtained as a mixture of two diastereomers whereas the double bond of **3f** tethered to the amide moiety possesses a trans configuration ($^3J_{Ha\text{-}Hb}$ = 17 Hz).

The preparation of 1,3-dienes have been the object of important research activities due to the presence of this motive in many natural products and their particular reactivity in both catalyzed and uncatalyzed processes leading to cyclic derivatives (cycloadditions, transition metal triggered cascades…).[14] To demonstrate further the interest of this Passerini/Tsuji-Trost elimination sequence, we decided to engage some of the resulting dienes in cycloaddition reactions to reach more complex bicyclic derivatives. Conjugated dienamides **3a**-**3d** can be considered as sorbic ester analogues, compounds which have been well described as Diels-Alder partners with both electron-rich and electron-poor alkenes such as maleimides.[15] Thus, N-phenylmaleimide (NPM) was selected to react with **3a** under thermal as well as Lewis acid catalyzed conditions (Scheme 3).



Scheme 3. Diels-Alder reaction of diene **3a**.

We could not observe any coupling between NPM and **3a** under thermal conditions without any additive. However, cycloadduct **4a** could be isolated in moderate yield under heating in the presence of a catalytic amount of zinc triflate. Best conditions were obtained using stoichiometric amount of titanium tetrachloride in dichloromethane at room temperature. Similar conditions were previously described in various Diels-Alder reactions with electron-deficient alkenes.[16] Endo adduct **4a** was selectively obtained in agreement with a typical $^3J_{Ha\text{-}Hb}$ coupling constant of 7.8 Hz. These conditions were used for the following reactions of **3b**, **3d** and **3f** with NPM to afford **4b**, **4c** and **4d** respectively in similar yields (Scheme 3). In terms of diversity, when analyzing the whole sequence, the Diels-Alder step restores the three-component nature of the process. Its efficiency could be further improved performing the Diels-Alder step without isolating the intermediate Tsuji-Trost dienamide. Indeed, after palladium triggered formation of diene **3a** from acetate **2a**, evaporation of the solvent followed by addition of dichloromethane and $TiCl_4$ directly afforded **4a** in 60% isolated yield.

In conclusion, following our first reports on the use of cinnamaldehyde Passerini adducts in Tsuji-Trost allylic substitutions, we have demonstrated that a similar approach

could be settled to form 2,4-dienamides derivatives. The loss of diversity associated with the elimination of the carboxylate moiety may be counterbalanced by the formation of cycloadducts with dienophiles. This Passerini/Tsuji-Trost/Diels-Alder cascade enrich the family of Diels-Alder reactions performed on IMCRs adducts, a strategy pioneered by Paulvanan in the late 1990s.[16]

Acknowledgments

We wish to thank the Ministry of Higher education and Scientific Research (Algeria) for their financial support to S.D. Youcef. We wish to thank ENSTA Paristech for financial support.

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