DOI: 10.1002/ejoc.201001621

A One-Pot, Three-Component Approach to Functionalised Tetrahydroisoquinolines Using Domino Heck–aza-Michael Reactions

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Keywords: Tetrahydroisoquinoline / Multicomponent reactions / Domino reactions / Heck reaction / Aza-Michael addition / Palladium

A one-pot, three-component method incorporating a domino Heck–aza-Michael reaction has been developed for the rapid synthesis of functionalised tetrahydroisoquinolines. Following the in situ generation of an acrylamide, a domino process involving intermolecular Heck reaction and subsequent intramolecular aza-Michael addition affords tetrahydroisoquinolines bearing C1-acetamide functionality.

Introduction

In recent years, palladium-catalysed domino Heck–aza-Michael reactions have been developed for the synthesis of a range of functionalised N-heterocycles including benzofused sultams,[1] tetrahydro-β-carbolines,[2] tetrahydroisoquinolines,[2b,3] isoindolines[2b] and isoindolinones.[4] These N-heterocyclic scaffolds have been prepared by treating aryl halides with relatively cheap palladium catalysts and are somewhat limited to the range of commercially available acrylate-based starting materials. The ideal domino Heck–aza-Michael process would allow for the use of functionalised electron-deficient terminal alkenes. As such, the scope of these reactions could be dramatically improved if, in one pot, the alkene could be readily generated and then undergo the domino Heck–aza-Michael reaction.

One-pot, multicomponent processes, like domino reactions, are an efficient means of completing multiple synthetic steps without the need for purification of intermediates. Three-component domino Heck–aza-Michael reactions to date have involved variations in the domino precursor, that is, the first step of the multicomponent reaction was the preparation of the aryl halide.[1,3] However, the electron-deficient terminal alkenes employed for these three-component domino reactions have been limited to commercially available ester, carboxylic acid and ketone derivatives. Attempted domino Heck–aza-Michael processes, where the alkene employed has been generated in situ, have not been successful.[1a]

The tetrahydroisoquinoline scaffold is central to a number of naturally occurring alkaloids, some of which exhibit interesting biological activity as antitumor and antibiotic agents.[5] The C1-acetamide tetrahydroisoquinoline core (Figure 1) has also been employed in medicinal chemistry studies,[6] for example compound **1**, which was developed as a ligand for the melanocortin subtype-4 receptor.[7] Further examples include those generated as reversible inhibitors of cysteine proteases,[8] as well as bradykinin 1 antagonists for treating pain and inflammation (compound **2**, Figure 1).[9]

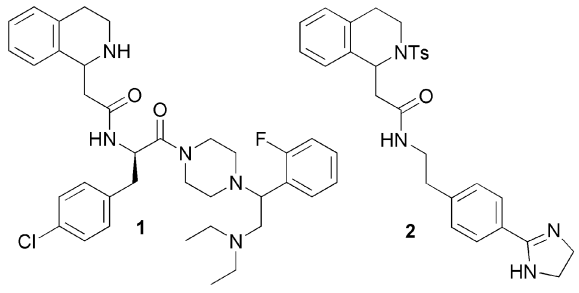

Figure 1. C1-amide substituted tetrahydroisoquinoline medical chemistry agents.

A range of synthetic strategies have been reported to access C1-substituted tetrahydroisoquinoline scaffolds.[3,10] Our group has recently discovered a palladium-catalysed domino Heck–aza-Michael reaction for the synthesis of a series of C1-substituted tetrahydroisoquinolines (Scheme 1).[2b] The domino Heck–aza-Michael process requires a catalytic system that facilitates fast Heck reaction between the domino precursor and an electron-deficient terminal alkene. Following this process aza-Michael cyclisation takes place to form the new N-heterocycle (Scheme 1).

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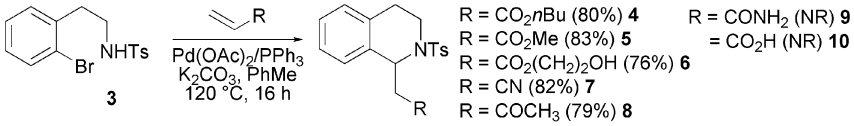
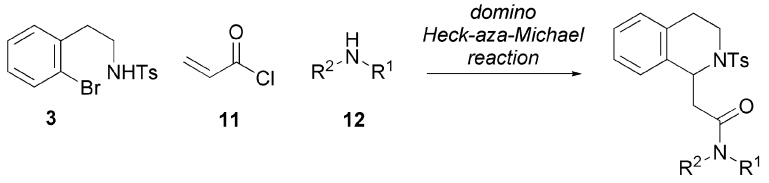
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001621.



Scheme 1. Domino Heck–aza-Michael reaction to access C1-substituted tetrahydroisoquinolines.



Scheme 2. Proposed three-component domino Heck–aza-Michael reaction to access tetrahydroisoquinolines.

Using this method tetrahydroisoquinolines **4**–**8** were formed by reaction of 2-bromophenethylamine (**3**) with commercial acrylates using either the $Pd(OAc)_2/PPh_3$ or the $Pd(OAc)_2$/DavePhos in K_2CO_3 and toluene catalytic system.

This methodology allowed for the incorporation of various functionalities at R including ester, nitrile and ketone; however, neither the reaction with acrylic acid nor acrylamide was amenable (most likely due to deprotonation under the reaction conditions). As the generation of tetrahydroisoquinolines bearing C1-acetamide functionality was desirable, a modification of the original domino process was sought. To this end, a three-component domino Heck–aza-Michael process that would provide rapid and efficient access to C1-functionalised tetrahydroisoquinolines was devised (Scheme 2). Nucleophilic addition of primary or secondary amines **12** to acryloyl chloride (**11**), prior to the aforementioned domino reaction would afford a vast array of acrylamides. If acrylamide formation occurred under the same mildly basic conditions required for both the Heck and aza-Michael steps in this domino process, a sequential one-pot three-component acylation and domino Heck–aza-Michael reaction for the synthesis of tetrahydroisoquinolines was plausible.

Herein we report the first three-component domino Heck–aza-Michael reaction, for the synthesis of functionalised tetrahydroisoquinolines, where in one pot, the electron-deficient alkene is generated, then subsequently undergoes domino Heck–aza-Michael reaction.

Results and Discussion

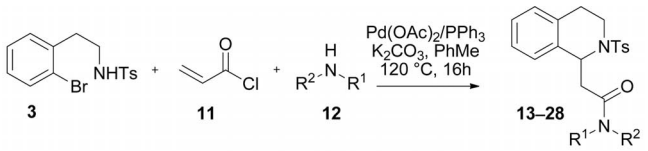
To investigate this one-pot process, benzylamine was initially chosen as the amine nucleophile. This first reaction involved the addition of acryloyl chloride (**11**) to a solution of benzylamine, and potassium carbonate in toluene. After stirring at room temperature for 1 h, $Pd(OAc)_2$, PPh_3 and the 2-bromophenethylsulfonamide substrate **3** were added sequentially and the resultant mixture heated to 120 °C for 16 h. To our delight, a simple workup followed by flash chromatography afforded the desired *N*-benzylacetamidotetrahydroisoquinoline **13** in excellent yield (97%). (As expected, no domino product or Heck adduct was observed when the reaction was repeated by using only acryloyl chloride; attempts to also generate the tetrahydroisoquinolines in a multicomponent manner where all reagents were present from the outset, also failed.) Following this initial success, a range of amines, varying in nucleophilic character were subsequently used in this one-pot process. The amines, including alkyl primary amines (Table 1, Entries 1–7), arylamines (Table 1, Entries 8–10), acyclic secondary amines (Table 1, Entries 11), cyclic secondary amines (Table 1, Entries 12–13), and amino acids (Table 1, entries 14–16), were tested to explore the scope of this reaction sequence.

The first attempt with tryptamine only resulted in trace amounts of the desired tetrahydroisoquinoline. This lack of reactivity appeared to be due to the insolubility of either the initial amine or corresponding acrylamide in toluene. To overcome this, a few drops of DMF were added to the reaction mixture following addition of the amine nucleophile. This approach quickly proved successful with the second attempt using tryptamine to afford tetrahydroisoquinoline **14** in 92% yield (Entry 2, Table 1). During the synthesis of a series of C1-acetamide substituted tetrahydroisoquinolines, a number of other amines also required the addition of DMF to improve solubility.

The one-pot, three-component domino Heck–aza-Michael process proved to be quite general, with high yields (up to 97%) of the C1-acetamide tetrahydroisoquinolines observed when alkylamines, arylamines, secondary amines and amino acids were used. Several of the tetrahydroisoquinolines accessed by using this methodology (**14**, **26**, **27**) resemble a number of the aforementioned medicinal chemistry agents (Figure 1). The only limiting factor in this process appeared to be solubility of the amine and corresponding acrylamide.

For the domino process employing 2-nitrobenzylamine hydrochloride (Table 1, Entry 7), the in situ deprotection of the 2-nitrobenzyl group occurred to afford tetrahydroisoquinoline **19**. The 2-nitrobenzyl group is readily cleaved under photolytic conditions in polar solvents (254–365 nm),[11] As this reaction was carried out in toluene in a dark fumehood, deprotection of the 2-nitrobenzyl group under our reaction conditions was unexpected. However, the basic

Table 1. Formation of functionalised tetrahydroisoquinolines by using a three-component domino Heck–aza-Michael reaction.



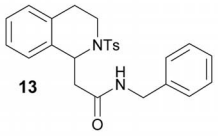
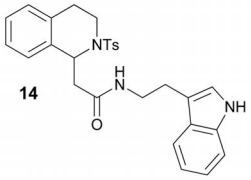
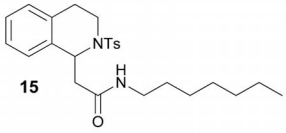
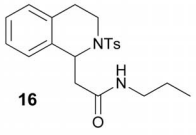
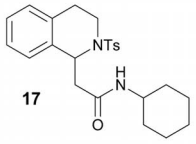
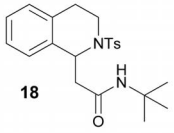
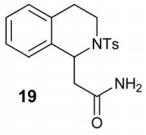
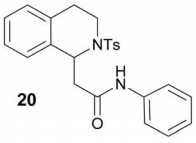
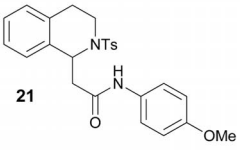
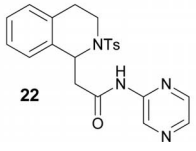
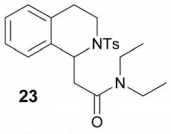
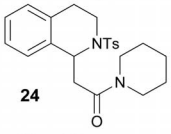
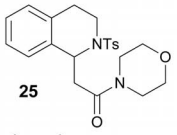
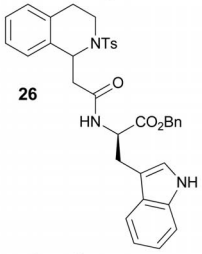
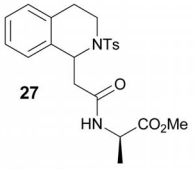
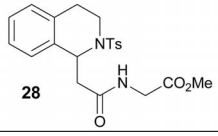
Entry	Amine	Product	Isolated yield [%]
1	benzylamine	 13	97
2	tryptamine[a]	 14	92
3	*n*-heptylamine	 15	89
4	propylamine	 16	42
5	cyclohexylamine	 17	77
6	*tert*-butylamine	 18	93
7	2-nitrobenzylamine hydrochloride[a]	 19	32[b]
8	aniline	 20	83
9	*p*-anisidine	 21	79
10	2-aminopyrazine[a]	 22	28

Table 1. *(Continued)*.

Entry	Amine	Product	Isolated yield [%]
11	diethylamine	 23	57
12	piperidine	 24	88
13	morpholine	 25	78
14	L-tryptophan benzyl ester hydrochloride[a]	 26	96[c]
15	L-alanine methyl ester hydrochloride[a]	 27	54[c]
16	glycine methyl ester hydrochloride[a]	 28	72

[a] A few drops of DMF were added to aid in amine solubility. [b] In situ deprotection of the 2-nitrobenzyl group occurred during reaction, and the product isolated was the tetrahydroisoquinoline acetamide in 32% yield. [c] When chiral amino acids were subject to this domino process (Entries 14–15, Table 1) the resultant tetrahydroisoquinoline was isolated as a mixture of diastereomers in a ratio of 1:1.

conditions and high temperatures employed in this reaction sequence proved sufficient to cleave the 2-nitrobenzyl group.

Multicomponent reactions using a chiral amino acid precursor (Table 1, Entries 14, 15) were carried out to identify whether a stereoselective variant of this one-pot process was achievable. The introduction of a stereogenic centre at the C1-position of the newly formed tetrahydroisoquinoline was monitored by NMR spectroscopy. Unfortunately, in these particular cases where a chiral amino acid was used, the products were determined to be present as a 1:1 mixture of diastereomers, inseparable by standard column chromatography. As such, the presence of a stereocentre in the acrylamide R moiety had no significant induction effects on the stereochemistry at the C1-position of the tetrahydroisoquinoline heterocycle formed during the domino process.

Conclusions

A domino Heck–aza-Michael process has been developed where in one pot, the electron-deficient alkene generated by reaction between acryloyl chloride and an amine, undergoes domino Heck–aza-Michael reaction to afford a series of C1-acetamide tetrahydroisoquinolines. This is the first example of a domino Heck–aza-Michael reaction that allows the electron-deficient terminal alkene to be readily varied in a one-pot process. This multicomponent domino reaction proved to be quite general, by using a range of primary and secondary amines to afford functionalised tetrahydroisoquinolines, in moderate to excellent yields (28–97%). This one-pot process, when employed in a medicinal chemistry setting would facilitate the rapid generation of compound libraries.

Supporting Information (see footnote on the first page of this article): Detailed description of all experimental procedures and analytical data for all compounds.

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Received: December 2, 2010
Published Online: February 8, 2011

