ORGANIC LETTERS

2013
Vol. 15, No. 24
6246–6249

Syntheses of α-Stannylated and α-Iodinated Enamides via Molybdenum-Catalyzed Hydrostannation

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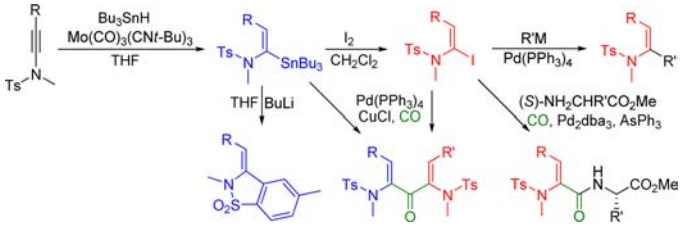
Received October 29, 2013

ABSTRACT



α-Stannylated and α-iodinated enamides can easily be obtained by molybdenum-catalyzed regio- and stereoselective hydrostannation and subsequent tin−iodine exchange. These functionalized enamides are interesting building blocks for a wide range of cross-coupling reactions giving access to various types of α-substituted enamides.

Functionalized enamides are widespread in nature, e.g. as peptide alkaloids such as frangulanin[1] or the zizyphines (Figure 1, **A**).[2] A wide range of biologically active peptides such as tentoxin (**B**)[3] contain dehydroamino acids. Even more unusual structures, such as vinylogous dehydroamino acids, are found in cyclic peptides such as cyclotheonamide C (**C**).[4] The strong phytotoxin tentoxin acts as an inhibitor of ATP synthase,[5] and the family of the cyclotheonamides are found to be strong inhibitors of serine proteases, such as thrombin and trypsin.[4] In addition to their occurrence in natural products, α-substituted enamides are also found in a number of drugs. For example, peptidyl allyl sulfones (**D**) are an interesting class of cysteine protease inhibitors.[6] There is no question that straightforward protocols toward differently substituted enamides are highly welcome. In addition, synthetic protocols should also focus on a stereoselective formation of the enamide double bond, because in general only one isomer shows biological activity, or at least a higher one than the other isomer.

Especially for the synthesis of didehydroamino acids and peptides, various protocols have been developed, mainly based on elimination reactions or olefinations.[7] But in general, control of the olefin geometry is not a trivial issue. Allylic sulfones such as in **D** can be obtained by isomerization of the corresponding vinyl sulfones under basic conditions, but generally also here mixtures of isomers are formed.[6]

Therefore, we were interested in developing a protocol which allows the stereoselective synthesis of most of these enamide structures from the same synthetic intermediates (Scheme 1). α-Substituted enamides should be accessible from α-halogenated enamides *via* cross-coupling chemistry. The required halogen derivatives can be obtained *via*

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10.1021/ol4031028
Published on Web 11/08/2013

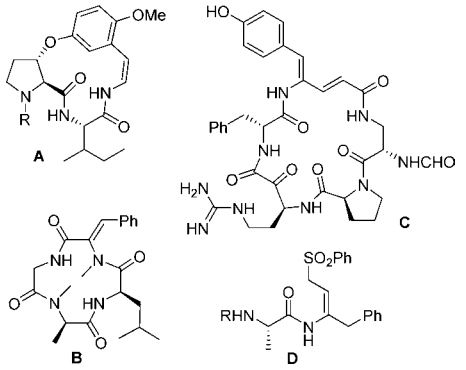
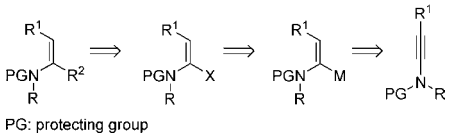


Figure 1. Enamide-containing natural products and drugs.

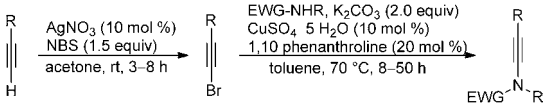
metal−halogen exchange from a suitable α-metalated enamide, which should be available from the corresponding ynamide *via* regioselective transition metal catalyzed hydrometalation.[8]

Scheme 1. α-Substituted Enamides from Ynamides



The ynamides required evolved to an interesting class of functionalized alkynes over recent years, and several practical syntheses toward these compounds have been developed.[9] Some of the most popular approaches are based on Cu-catalyzed or Cu-mediated couplings of amides with bromoalkynes.[10] Especially in the presence of 1,10-phenanthroline as a ligand, a wide range of amide substrates can be coupled under rather mild conditions (Scheme 2).[11] The bromoalkynes required can easily be obtained from the corresponding alkyne and NBS/$AgNO_3$.[12] The ynamides are versatile synthetic building blocks undergoing a wide range of reactions, such as α- or *β*-additions, cycloadditions, cycloisomerizations, or reductions, to name only a few.[9]

Scheme 2. Synthesis of Ynamides



While a variety of α-additions are reported for ynamides, to the best of our knowledge so far only a few examples describe more or less α-regioselective Pd-catalyzed hydrostannations.[13] While high α-selectivities are generally observed in the hydrostannation of alkynyl oxazolidinones, the results obtained with other amides such as tosylated ynamides are significantly worse. Also, the yields are moderate in most cases, depending on the ynamide structure.

Our group is also involved in hydrostannation chemistry. We developed $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$ ($MoBl_3$) as a new highly regioselective catalyst for the α-hydrometalation of terminal propargyl alcohol derivatives.[14] The stannylated allyl alcohol derivatives obtained can be used, e.g., for the synthesis of stannylated amino acids and peptides.[15] Highly α-regioselective reactions are also observed with a variety of terminal alkynes bearing electron withdrawing groups such as sulfones,[16] or phosphonates.[17] So far, the good results obtained were limited to terminal alkynes, and therefore, we were interested to determine if ynamides as disubstituted alkynes are also suitable substrates for our catalyst system. To prove this option, we synthesized a set of tosyl- and Boc-protected ynamides **1** (Table 1) according to Scheme 2.[11] This protocol was suitable for these protecting groups, but failed with *N*-alkyl acetamides or trifluoroacetamides. In this case only a dimerization of the bromoalkyne was observed. But with the ynamides **1** in hand, we investigated the molybdenum-catalyzed hydrostannation (Table 1). The reactions were carried out in a CO atmosphere, because in previous investigations we observed that CO is beneficial for the lifetime of the catalyst, and higher yields are obtained especially with "critical" substrates such as 1,2-disubstituted alkynes.[18] To our complete satisfaction, also with the ynamides **1** the hydrostannation proceeded cleanly in a highly regio- and stereoselective fashion giving rise to the (*E*)-α-stannylation

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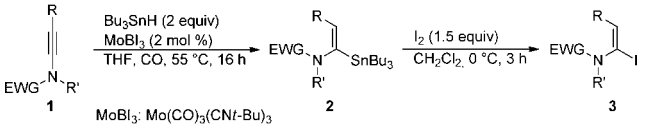
product **2** as the only product in good to high yield. The α-stannylated enamides are stable compounds which could easily be purified by flash chromatography. Subsequent tin−iodine exchange gave access to the corresponding α-iodinated enamides **3**,[19] also in high to excellent yields and with full retention of the olefin geometry. By this protocol two interesting synthetic intermediates (**2** and **3**) became available in a straightforward manner.

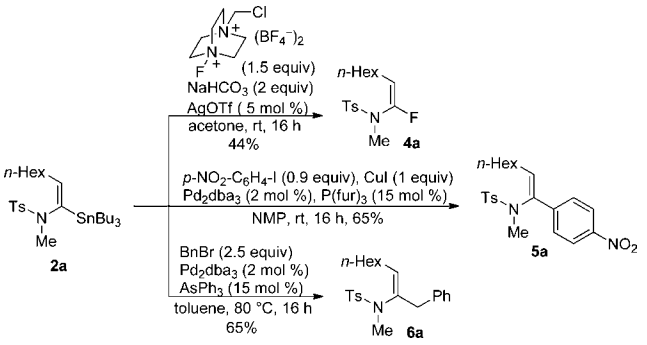
Table 1. Synthesis of α-Stannylated and α-Iodinated Enamides



entry	1	R	R′	EWG	2	yield [%]	3	yield [%]
1	**1a**	*n*-Hex	Me	Ts	**2a**	87	**3a**	96
2	**1b**	*c*-Pr	Me	Ts	**2b**	68	**3b**	96
3	**1c**	$(CH_2)_2OTBDPS$	Me	Ts	**2c**	71	**3c**	87
4	**1d**	Ph	Bn	Boc	**2d**	83	**3d**	98

To evaluate the synthetic potential of these building blocks, we investigated the reaction behavior of the stannylated ynamides **2**. As shown in Table 1, the tin−iodine exchange proceeds in almost quantitative yield and the corresponding bromine and chlorine exchange can be performed in analogous manner using the corresponding halogens or *N*-halosuccinimides.[20] While these reactions are well established, in comparison, the introduction of fluorine is not a trivial issue. In principle, F_2,[21] $CsSO_4F$,[22] and $XeF_2/AgPF_6$[23] can be used as fluorination reagents, but these reagents are not easy to handle and are very expensive. The most suitable fluorination reagent probably is selectfluor,[24] especially in the presence of Ag-catalysts. This protocol was optimized for the synthesis of fluorinated aromatic ring systems by Ritter et al.[25] It is proposed that, in this case, the aryl stannane used is transmetalated to the corresponding arylsilver derivative which on oxidation by the selectfluor and reductive elimination provides the required aryl fluoride. We were interested to see if such a protocol might also be suitable for the synthesis of α-fluorinated enamides. Therefore, we subjected exemplarily one of our stannylated enamides (**2a**) to the optimized reaction conditions for aryl stannane. And indeed, the required α-fluorinated enamide **4a** could be obtained, although in moderate yields (Scheme 3). Classical Stille coupling reactions,[26] e.g. with benzyl and aryl halides, proceeded well and gave access to α-alkylated and arylated enamides with clean (*Z*)-olefin geometry.

Scheme 3. Fluorination and Cross-Coupling of Stannylated Enamide **2a**



Comparable cross-coupling reactions could also be carried out with the α-iodinated enamides **3** (Scheme 4). An excellent yield was obtained in the Sonogashira coupling with phenyl acetylene, and also Suzuki and Stille couplings gave rise to the desired products in acceptable yields. If vinyl stannane was used as a coupling partner, an amide-substituted 1,3-diene was formed, which could be subjected to further modifications such as Diels−Alder reactions.

Because our group is mainly interested in the development of new protocols for the synthesis of unusual amino acids and peptides,[27] we wanted to also apply the α-iodinated enamides in the synthesis of α,β-unsaturated amino acids and peptides (Table 2).

The corresponding dehydroamino acid esters could easily be obtained from the iodides under carbonylative conditions in alcohol as solvent. Good results were obtained with the tosyl-protected enamides. But in many cases the *N*-tosyl group is not easily removable, and therefore we also investigated the reaction of *N*-Boc-protected ynamide **3d**. Unfortunately, in this case the yield was lower (entry 4).

To prove if our protocol is also suitable for the synthesis of dehydrodipeptides, we reacted some of the iodides with amino acid esters as nucleophiles in the carbonylation reaction. DMF was used as solvent in this case to avoid side reactions of the solvent. The yields obtained were comparable to the analogous esterifications.

(19) α-Iodinated enamides are also accessible by hydroiodination of ynamides: Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547–1550.

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Scheme 4. Cross-Coupling of α-Iodinated Enamide **3a**

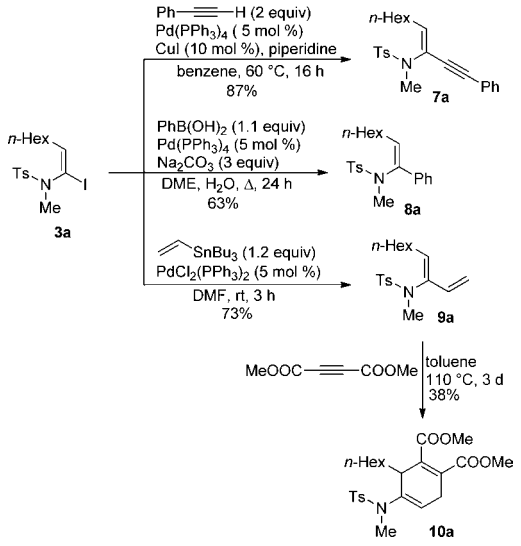
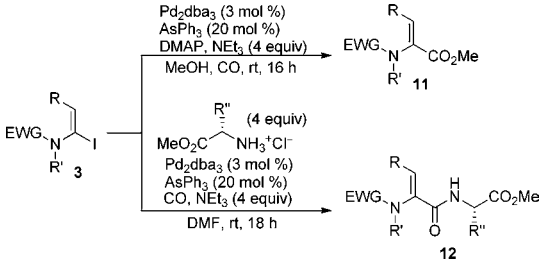


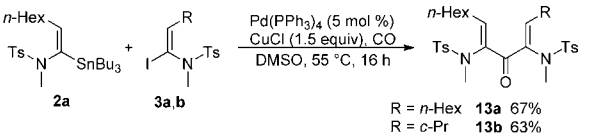
Table 2. Synthesis of α,β-Dehydroamino Acids and Peptides



entry	3	R	R′	EWG	R″	product	yield [%]
1	**3a**	*n*-Hex	Me	Ts		**11a**	78
2	**3b**	*c*-Pr	Me	Ts		**11b**	67
3	**3c**	$(CH_2)_2$OTBDPS	Me	Ts		**11c**	69
4	**3d**	Ph	Bn	Boc		**11d**	35
5	**3b**	*c*-Pr	Me	Ts	*i*-Bu	**12b**	85
6	**3c**	$(CH_2)_2$OTBDPS	Me	Ts	*i*-Bu	**12c-1**	63
7	**3c**	$(CH_2)_2$OTBDPS	Me	Ts	*i*-Pr	**12c-2**	64
8	**3c**	$(CH_2)_2$OTBDPS	Me	Ts	Bn	**12c-3**	71

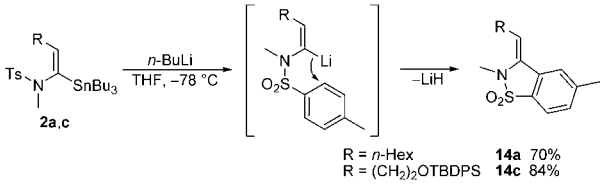
To enlarge the structural diversity, we also used the building blocks **2** and **3** in carbonylative Stille couplings, giving rise to tosylamide substituted divinyl ketones **13**, which might be interesting building blocks for further modifications (Scheme 5).

Scheme 5. Cross-Couplings of Enamides **2** and **3**



Last but not least we subjected some of our stannylated enamides **2** to a tin−lithium exchange by treatment with *n*-BuLi. Our initial plan was to treat the vinyl lithium species formed with electrophiles such as aldehydes or α,β-unsaturated carbonyls. But none of these coupling products were obtained; we were not even able to trap the vinyl lithium intermediate with D_2O. The lithiated intermediate was too reactive and underwent an intramolecular attack on the electron-poor aromatic ring system of the tosyl protecting group. The corresponding benzo-fused sultames **14** were obtained in good to high yield (Scheme 6).

Scheme 6. Synthesis of Benzosultames **14**



In conclusion, we could show that α-stannylated and iodinated enamides can easily be obtained from ynamides by molybdenum-catalyzed regio- and stereoselective hydrostannation and subsequent tin−iodine exchange. These functionalized enamides are interesting building blocks for a wide range of cross-coupling reactions, giving access to various types of functionalized enamides. Further investigations, especially concerning synthetic applications, are currently in progress.

Acknowledgment. Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Supporting Information Available. Experimental procedures as well as analytical and spectroscopic data for all new compounds, as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.