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2011
Vol. 13, No. 7
1750–1753

Metal-Free Halonium Mediated Acetate Shifts of Ynamides To Access α-Halo Acrylamides/Acrylimides

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Received January 27, 2011

ABSTRACT

A metal-free acetate shift of 3-acetoxy ynamides to access α-iodo, bromo, and chloro acrylamides/acrylimides under very mild conditions is demonstrated. The inherent alkyne activation of ynamides is sufficient to ensure the α-halo acrylamides/acrylimides in high yields without the addition of a catalyst. In all cases high *Z*-stereoselectivity is observed.

Acrylamides are commonly used structures in numerous organic reactions.[1] Furthermore, acrylamides are abundant structural motifs in natural products, and many of them display significant biological activities.[2] Access to α-iodo, bromo, and chloro acrylamides is of significant interest as these substrates allow for introduction of further substituents on the acrylamide moiety.[3,4]

Recently, the gold-catalyzed acetate shifts of propargyl acetates to access α-haloenones have been frequently examined.[5] However, these reports do not cover the synthesis of α-halo acrylamides/acrylimides, and furthermore they all utilize homogeneous gold complexes to catalyze

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10.1021/ol200269h
Published on Web 03/08/2011

the reactions along with the stoichiometric halogenation reagent.[6] Although, gold is only used in catalytic amounts it is still an expensive material. Omission of the catalyst by application of the more reactive ynamides would allow for a simple and less expensive protocol and at the same time expand the product scope to include α-halo acrylamides and acrylimides. Based on our recent experiences with ynamides we decided to examine the acetate shifts on these substrates.[7−10]

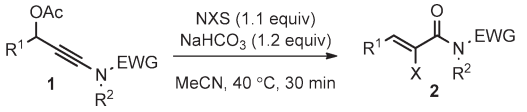
First, the acetate shift on ynamide **1a** with NIS was attempted. We were pleased to see clean conversion to the desired α-iodo acrylamide with only 1.1 equiv of NIS and 1.2 equiv of $NaHCO_3$ at 40 °C in MeCN for 30 min. Thereafter, **1a** was subjected to the same conditions with NBS instead of NIS. In both cases, the desired product was obtained in high yield (Table 1, entries 1 and 2). Under the same conditions the rearrangement with NCS displayed low conversion.

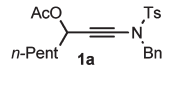
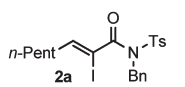
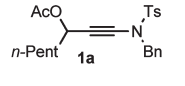
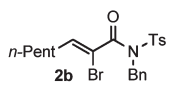
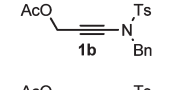
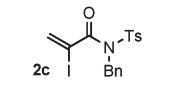
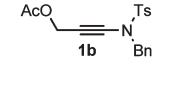
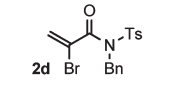
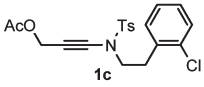
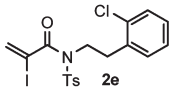
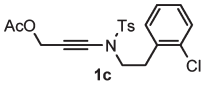
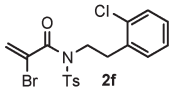
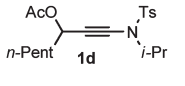
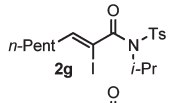
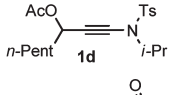
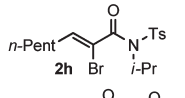
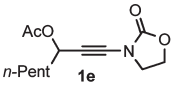
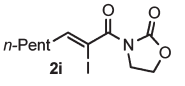
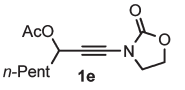
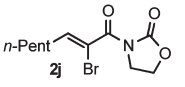
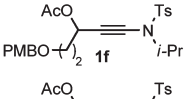
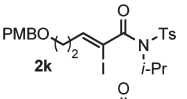
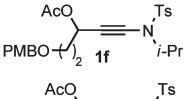
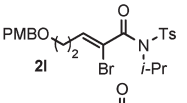
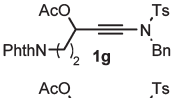
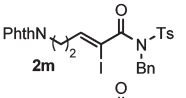
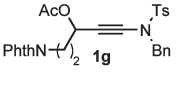
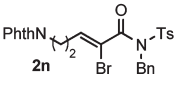
A variety of ynamides were subjected to the iodination/bromination conditions (Table 1). Branched aliphatic chains and benzyl substituents on the nitrogen were tolerated. Also, both alkoxycarbonyl and tosyl groups could be utilized as the electron-withdrawing group. Furthermore, it was demonstrated that chlorides, PMB protected alcohols, and phthalimido protected nitrogens are tolerated.

In all cases excellent diastereoselectivity was observed in the ^1H NMR spectrum of the crude product. Single crystal X-ray analysis of compounds **2m** and **2n** in both cases revealed the product to be the *Z*-stereoisomer. Therefore, the other acrylamides were tentatively assigned as the *Z*-configuration.

In order to obtain the acetate shift with NCS, a variety of solvents and temperatures were examined (Table 2). Although, for all the succinimide based electrophiles, the reaction seemed faster in CH_2Cl_2 and dichloroethane, acetonitrile proved to provide a cleaner conversion and superior yields. Despite the fact that NCS is a poorer electrophile than NIS and NBS, almost full conversion was obtained with only a slight increase in the reaction temperature and the number of equivalents of NCS compared to NIS and NBS (Table 2, entry 5).

Table 1. Acetate Shift with NIS or NBS



entry	ynamide	product	yield %[a] (*Z*/*E*)[b]
1			91 (>95:5)
2			95 (95:5)
3[c]			89 (-)
4			87 (-)
5[c]			85 (-)
6[c]			72 (-)
7			91 (95:5)
8[c]			90 (>95:5)
9[c]			88 (>95:5)
10			84 (>95:5)
11			91 (95:5)
12			93 (>95:5)
13			92 (93:7)
14			87 (95:5)

[a] Isolated yield after column chromatography. [b] *Z*/*E* ratio in parentheses based on ^1H NMR of the reaction mixture. [c] Reaction time was 45 min.

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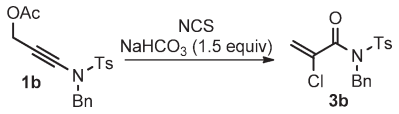
(10) For selected ynamide syntheses, see: (a) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (b) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (c) Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88. (d) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359. (e) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170.

Table 2. Optimization with NCS

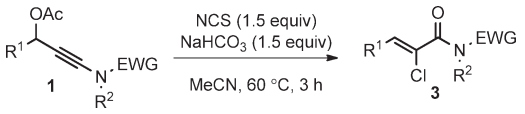


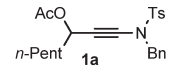
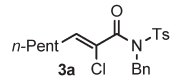
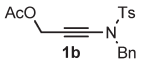
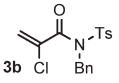
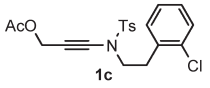
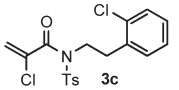
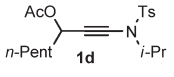
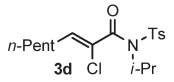
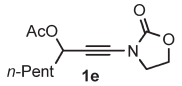
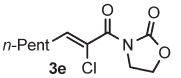
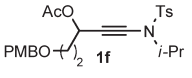
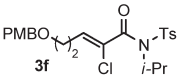
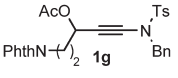
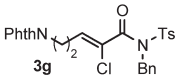
entry	NCS (equiv)	solvent	temp (°C)	time (h)	ratio[a] (**3b**/**1b**)
1	1.1	CH_2Cl_2	40	2	72:28
2	1.1	DCE	60	3	79:21
3	1.1	MeCN	80	3	67:33
4	1.1	MeCN	60	3	66:34
5	1.5	MeCN	60	3	95:5 (71%)

[a] Ratio of product/starting material was determined by ^{1}H NMR of the crude reaction mixture. Isolated yield after column chromatography in parentheses.

With the optimized conditions in hand a number of ynamides were subjected to these conditions (Table 3). Again, branched aliphatic chains and benzyl substituents on the nitrogen were tolerated. As the electron-withdrawing group, alkoxycarbonyl and tosyl groups were tolerated; however, this time the carbamate (**1e**) provided a lower yield. Also, chlorides, protected alcohols, and protected nitrogens are tolerated.

Table 3. Acetate Shift with NCS

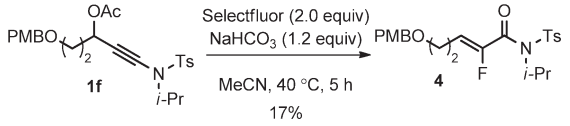


entry	ynamide	product	yield %[a] (*Z*/*E*)[b]
1			70 (>95:5)
2			71 (-)
3			62 (-)
4			62 (>95:5)
5[c]			46 (>95:5)
6			53 (95:5)
7			64 (>95:5)

[a] Isolated yield after column chromatography. [b] *Z*/*E* ratio in parentheses based on ^{1}H NMR of the reaction mixture. [c] 15 h.

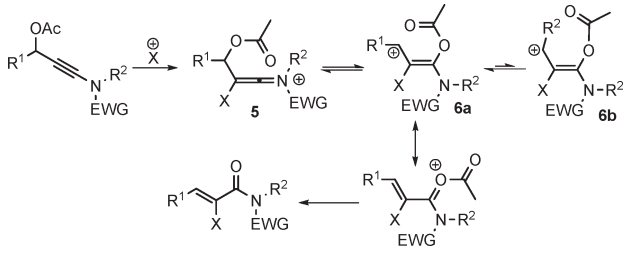
The chlorination reactions also demonstrated high diastereoselectivity, and the *Z*-selectivity was confirmed by single crystal X-ray analysis of compound **3g**.

Scheme 1. Acetate Shift with Selectfluor



Finally, we attempted to make α-fluoro acrylamides using the same approach. Since no succinimide-based fluorinating agent is available, different fluorine sources were examined. Whereas NFSI[11] did not show any conversion, the use of *N*-fluoro-pyridinium tetrafluoroborate only demonstrated proton incorporation. A more promising result was obtained using Selectfluor, which showed almost complete consumption of the starting materal and a high ratio of fluorine to proton incorporation. However, despite significant efforts to optimize the reaction conditions the desired product was obtained in low yield (Scheme 1).[12,13]

Scheme 2. Proposed Mechanism



A mechanistic proposal for the halogenation reactions is outlined in Scheme 2. The halogen electrophile might be attacked by the nucleophilic ynamide forming a ketiminium intermediate (**5**). This inherent nucleophilicity could explain why no metal catalyst is required for the acetate shift/halogenation of 3-acetoxy ynamides. The intramolecular acetate shift onto the ketiminium intermediate generates stable carbenium ion intermediates (**6a** and **6b**) which would enable equilibration to the more stable stereoisomeric allyl cation (**6a**) thus leading to the *Z*-stereoisomer. This would explain the high *Z*-selectivity observed in the halogenation reactions.[14]

In summary, we have demonstrated that the alkyne activation inherent in the ynamide motif is sufficient to

(11) *N*-Fluorobenzenesulfonimide.
(12) See Supporting Information for the optimization.
(13) The *Z*-configuration was confirmed by the proton-fluorine coupling constant.
(14) A concerted [3,3]-rearrangement of **5** would also explain the stereochemical outcome.

ensure that the acetate shift proceeds without the addition of a metal catalyst. This general metal-free protocol grants access to α-iodo, bromo, and chloro acrylamides and acrylimides simply by changing the electrophile and varying the temperature.

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, H. Lundbeck A/S, the OChem graduate school, Ecole Polytechnique, and Aarhus University. Furthermore, we thank Nina Lock and Helle Svendsen at Aarhus University for X-ray structure analysis.

Supporting Information Available. Experimental procedures and characterization data for all the prepared compounds as well as X-ray structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.