1902 *J. Org. Chem.* **1996,** *61,* 1902−1903

Communications

A New Reaction of Imines with Alkynyl Sulfides Affording α,*β*-Unsaturated Thioimidates

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Received October 31, 1995

The α,*β*-unsaturated thioimidates are useful intermediates,[1] and a preparation was reported that uses imidoyltriphenylphosphonium methylides.[2] Recently, we found that lanthanide triflates (Ln(OTf)$_3$) are stable Lewis acids in water and are very effective for the activation of imines.[3,4] Most Lewis acids are trapped by the nitrogen atoms of imines or tertiary amines (products), and therefore more than stoichiometric amounts of the acids are required to complete the reactions.[5] However, it was found that Ln(OTf)$_3$ promotes the reaction of imines with some nucleophiles catalytically. For example, the reactions of imines with ketene silyl acetals[3] and dienes or dienophiles[4] proceeded smoothly in the presence of a catalytic amount of Ln(OTf)$_3$ to afford the corresponding *β*-amino esters or imino Diels−Alder adducts, respectively, in high yields. In the course of our program to develop useful synthetic reactions using Ln(OTf)$_3$ as a catalyst, we discovered a new reaction, that of imines with alkynyl sulfides, which provides α,*β*-unsaturated thioimidates. In this paper, we report the preliminary results of this study.

Previously,[4] we reported that in the presence of a catalytic amount of Ln(OTf)$_3$ some imines behave as aza dienes and react with alkenes such as vinyl ethers and vinyl sulfides to afford tetrahydroquinoline derivatives.[6] In subsequent investigations, we found that imines react with alkynyl sulfides to afford the corresponding quinoline derivatives in high yields under nearly identical reaction conditions.[7]

We then examined the reaction of *N*-benzylidene-*p*-toluenesulfonamide (**1**) with 1-(methylthio)-1-propyne in dichloromethane, under the influence of 20 mol % of ytterbium triflate (Yb(OTf)$_3$). The starting materials disappeared after 15 h at room temperature, and a new adduct was detected by TLC. The adduct was found to be stable under usual aqueous workup conditions and could be purified by silica gel column chromatography. The IR, ^{1}H NMR, ^{13}C NMR, and MS spectra of the adduct suggested that it was the α,*β*-unsaturated thioimidate (**3**), which was finally confirmed by X-ray analysis.[8] To our knowledge, this type of reaction has not been previously reported.[9,10] The reaction does not proceed in the absence of the Lewis acid or under thermal conditions.

Several combinations of imines and alkynyl sulfides were tested, and the results are summarized in Table 1.[11] *N*-Benzylidenebenzylamine reacted slowly with 1-(methylthio)-1-propyne to give an adduct in moderate yield. Several *N*-tosylimines reacted with alkynyl sulfides smoothly in the presence of Yb(OTf)$_3$, Sc(OTf)$_3$, or BF$_3$·OEt$_2$ to afford the corresponding α,*β*-unsaturated thioimidates in high yields. When Ln(OTf)$_3$ was used as a catalyst, better results were obtained in acetonitrile than in dichloromethane. In the reactions of aliphatic *N*-tosylimine (R^1 = alkyl), the imines were prepared *in situ* from the corresponding dimethyl acetals[12] and were used directly in the same pot. While BF$_3$·OEt$_2$ was effective in some reactions, a distinct advantage of using Ln(OTf)$_3$ is that the catalyst can be recovered and reused.[13]

The reactions are assumed to proceed via a [2 + 2] cycloaddition and successive fragmentation. The [2 + 2] cycloaddition of imines with alkynyl sulfides proceeds smoothly in the presence of a Lewis acid to form azetine intermediates (**12**),[14] which are unstable and immediately fragment to the α,*β*-unsaturated thioimidates. Several attempts to isolate the azetine intermediates or to detect them by NMR failed.

Finally, an intramolecular version of this reaction for the synthesis of cycloalkene derivatives was investigated. 1-(Methylthio)-7,7-dimethyl-1-heptyne (**13**), which has acetal and alkynyl sulfide functions in the same molecule, was treated with 2 equiv of TsNH$_2$ in the presence of 20 mol % of Yb(OTf)$_3$ in benzene. The mixture was refluxed

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[1] (a) *The Chemistry of the Amidines and Imidates;* Patai, S., Ed.; John Wiley and Sons: New York, 1975. (b) Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179.

[2] Yoshida, H.; Ogata, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3315.

[3] (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

[4] (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.

[5] Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis;* Academic Press: London, 1987.

[6] Cf. Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801.

[7] Unpublished results. Similar reactions were reported using BF$_3$·OEt$_2$ as a catalyst. Narasaka, K.; Shibata, T. *Heterocycles* **1993**, 35 1039.

[8] The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

[9] Arens and Bos *et al.* reported that the reactions of aldehydes or ketones with alkynyl ethers or alkynyl sulfides afforded α,*β*-unsaturated esters or α,*β*-unsaturated thioesters in the presence of a stoichiometric amount of a Lewis acid. (a) Vieregge, H.; Schmidt, H. M.; Renema, J.; Bos, H. J. T.; Arens, J. F. *Rec. Trav. Chim.* **1966**, *85*, 929. (b) Bos, H. J. T.; Boleij, J. *Rec. Trav. Chim.* **1969**, *88*, 465 and references cited therein. See also: (c) Hayashi, A.; Yamaguchi, M.; Hirama, M. *Synlett* **1995**, 195. (d) Fischer, H.; Tiriliomis, A.; Gerbing, U.; Huber, B.; Müller, G. *J. Chem. Soc., Chem. Commun.* **1987**, 559. (e) Elferink, V. H. M.; Visser, R. G.; Bos, H. J. T. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 414.

[10] It was reported that ynamines added to imines in moderate yields in the absence of Lewis acids. Fuks, R.; Viehe, H. G. *Chem. Ber.* **1970**, *103*, 573.

[11] A typical experimental procedure is described for the reaction of *N*-benzylidene-*p*-toluenesulfonamide (**1**) with 1-(methylthio)-1-propyne using Sc(OTf)$_3$ as a catalyst: To a suspension of Sc(OTf)$_3$ (49.2 mg, 0.10 mmol, 20 mol %) in CH$_3$CN (1.0 mL) were added *N*-benzylidene-*p*-toluenesulfonamide (129.5 mg, 0.50 mmol) in CH$_3$CN (1.0 mL) and 1-(methylthio)-1-propyne (64.5 mg, 0.75 mmol) in CH$_3$CN (0.5 mL) at rt. After the mixture was stirred for 15 h, water was added and the product was extracted with ethyl acetate. After the organic layer was dried (Na$_2$SO$_4$) and evaporated, the crude product was chromatographed on silica gel to afford the corresponding α,*β*-unsaturated thioimidate **3**. The catalyst was quantitatively recovered from the aqueous layer and could be reused for further runs.

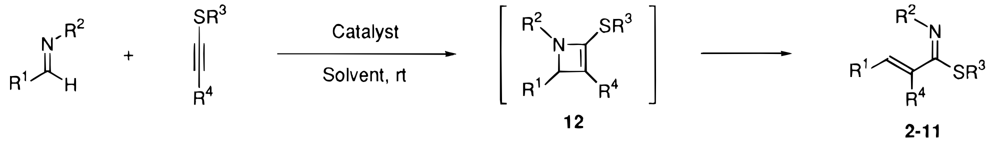
[12] Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *97*, 1483.

[13] Kobayashi, S. *Synlett* **1994**, 689.

[14] Cf. (a) Warreher, R. N.; Kretschmer, G. *J. Chem. Soc., Chem. Commun.* **1977**, 806. See also: (b) Friedrich, L. E.; Bower, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6869. (c) Friedrich, L. E.; Lam, D. Y.-S. *J. Org. Chem.* **1981**, *46*, 306. (d) Martino, P. C.; Shevlin, P. B. *J. Am. Chem. Soc.* **1980**, *102*, 5429 and references cited therein.

0022-3263/96/1961-1902$12.00/0

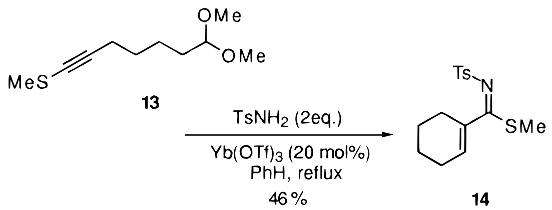
Table 1. Reactions of Imines with Alkynyl Sulfides



entry	R^1	R^2	R^3	R^4	thioimidate	catalyst (mol %)	solvent	condns[a]	yield (%)
1	Ph	$PhCH_2$	Me	Me	**2**	$Sc(OTf)_3$ (20)	CH_3CN	A	40
2	Ph	Ts (**1**)	Me	Me	**3**	$Yb(OTf)_3$ (20)	CH_3CN	A	80
3	Ph	Ts (**1**)	Me	Me	**3**	$Sc(OTf)_3$ (20)	CH_3CN	A	95
4	Ph	Ts (**1**)	Me	Me	**3**	$BF_3{\cdot}OEt_2$ (20)	CH_2Cl_2	A	66
5	Ph	Ts (**1**)	Me	Me	**3**	$BF_3{\cdot}OEt_2$ (100)	CH_2Cl_2	A	85
6	Ph	Ts (**1**)	Me	Me	**3**	$Sc(OTf)_3$ (20)	CH_3CN	B	94
7	p-MeOPh	Ts	Me	Me	**4**	$Sc(OTf)_3$ (20)	CH_3CN	A	75
8	p-ClPh	Ts	Me	Me	**5**	$Sc(OTf)_3$ (20)	CH_2Cl_2	A	80
9	p-ClPh	Ts	Me	Me	**5**	$BF_3{\cdot}OEt_2$ (100)	CH_2Cl_2	A	quant
10	2-furyl	Ts	Me	Me	**6**	$Sc(OTf)_3$ (20)	CH_3CN	A	73
11	PhC≡C	Ts	Me	Me	**7**	$Sc(OTf)_3$ (20)	CH_3CN	B	65
12	c-C_6H_{11}	Ts	Me	Me	**8**	$BF_3{\cdot}OEt_2$ (20)	CH_2Cl_2	B	80
13	$Ph(CH_2)_2$	Ts	Me	Me	**9**	$Sc(OTf)_3$ (10)	CH_3CN	B	62
14	Ph	Ts	Me	Bu	**10**	$Sc(OTf)_3$ (20)	CH_2Cl_2	A	90
15	$Ph(CH_2)_2$	Ts	Bu	H	**11**	$Yb(OTf)_3$ (10)	CH_3CN	B	8

[a] A: isolated imine was used. B: imine was prepared *in situ*.

Scheme 1



for 5 h to give the desired cyclohexene thioimidate (**14**) in 46% yield (Scheme 1).

In summary, we have developed a new reaction of imines with alkynyl sulfides to afford α,*β*-unsaturated thioimidates, which is catalyzed by $Ln(OTf)_3$ or $BF_3{\cdot}OEt_2$. [2 + 2] cycloaddition and successive fragmentation mechanisms are suggested, and the reaction was successfully applied to an intramolecular case for the synthsis of cycloalkane derivatives. Further studies to survey the scope and limitations of this reaction as well as to examine the reactivities of the produced α,*β*-unsaturated thioimidates are in progress.

Acknowledgment. The authors are grateful to Dr. Yukihiko Hashimoto, University of Tokyo, for the X-ray analysis. This work was partially supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Science and Culture, Japan. H.I. thanks the JSPS fellowship for Japanese Junior Scientists.

Supporting Information Available: Experimental procedures and IR, NMR, MS, and X-ray crystallographic data. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, and tetramethylsilane (TMS) served as internal standard (3 pages).

JO951924L