Pergamon

Tetrahedron Letters 41 (2000) 5947–5950

TETRAHEDRON LETTERS

# Highly *E*-selective synthesis of α,β-unsaturated amides from *N*-2-methoxyphenyl aldimines via lithium ynolates

Mitsuru Shindo,* Soichiro Oya, Ryoko Murakami, Yusuke Sato and Kozo Shishido

*Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770-8505, Japan*

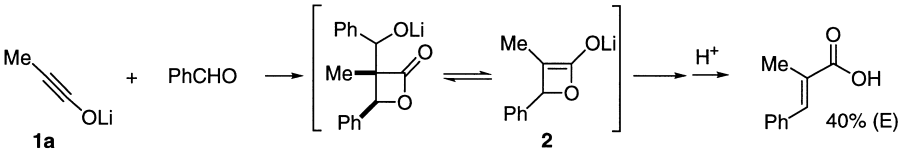
Received 17 May 2000; revised 7 June 2000; accepted 9 June 2000

**Abstract**

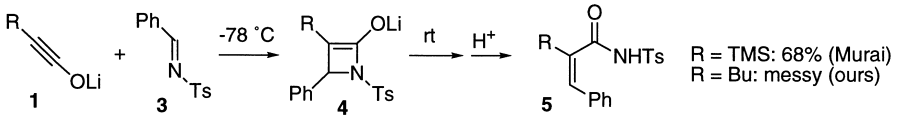
Lithium ynolates reacted with *N*-2-methoxyphenyl (OMP) aldimines to afford α,β-unsaturated amides in excellent *E*-selectivity via a retro-Mannich reaction of the 2:1 adducts (β-lactams), followed by cleavage of the β-lactam enolates. 

*Keywords:* ynolates; imines; olefination; amides.

Kowalski[1] and our group[2] have reported that ynolate anions **1**[3] react with aldehydes to give α,β-unsaturated carboxylates at room temperature with high *E*-selectivity via ring opening of the intermediate β-lactone enolates **2** (Scheme 1). Similarly, aldimines would be expected to react with ynolate anions to afford α,β-unsaturated amides.[4] Murai and co-workers reported one example of a β-lactam enolate **4** generated by the reaction of the *trimethylsilyl*-substituted lithium ynolate **1** (R = TMS) with the *N*-tosyl imine **3** to give the α,β-unsaturated amide **5** (Scheme 2),[5] but there have been no reports of *alkyl*-substituted ynolate reactions.




Scheme 1.




Scheme 2.

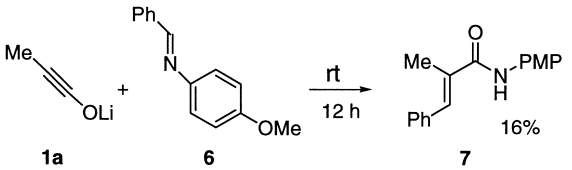
* Corresponding author. Fax: +81-88-633-7294; e-mail: shindo@ph2.tokushima-u.ac.jp

0040-4039/00/$ - see front matter 
PII: S0040-4039(00)00986-2

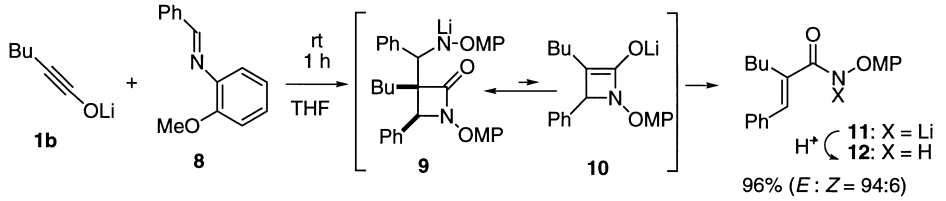
In the preceding paper, we showed that unactivated aldimines having an *N*-2-methoxyphenyl substituent reacted with ynolates to provide β-lactams (2:1 adducts).[6] We report, herein, the reaction of *alkyl*-substituted ynolates with the unactivated imines to give the desired α,β-unsaturated amides with excellent *E*-selectivity via a retro-Mannich reaction of the corresponding 2:1 adducts, followed by cleavage of the β-lactam enolates.

We first attempted the reaction of butyl-substituted lithium ynolate with the *N*-tosyl aldimine **3**. As we reported previously,[7] the ynolate reacted with **3** to give the β-lactam enolate **4** (R = Bu) at –78°C, after which the reaction mixture was warmed to room temperature. However, it gave a complex mixture of products, in contrast to Murai's successful results (Scheme 2).[5] Next, the less electrophilic *N*-4-methoxyphenyl (PMP) aldimine **6**, which would furnish more basic (or nucleophilic) β-lactam enolates, was used, since stabilization of the β-lactam enolate by the tosyl group might inhibit the efficient ring opening.

As expected, the desired α,β-unsaturated amide **7** was generated, but in only 16% yield after 12 h at room temperature, due to the slow cycloaddition step (Scheme 3). Thus, *N*-2-methoxyphenyl (OMP) aldimines, which are much better electrophiles for lithium ynolates due to chelation,[6,8] were examined (Scheme 4). To a THF solution (8 ml) of the lithium ynolate **1b**, generated by the reaction of the α,α-dibromoester (1.2 mmol) and *tert*-BuLi (4.8 mmol),[9] was added the aldimine **8** (1.0 mmol) at room temperature. TLC showed that the 2:1 adducts **9** were immediately generated then slowly converted into other compounds. After 1 h, the α,β-unsaturated amide **12** was obtained in 96% yield in an *E*:*Z* ratio of 94:6. This product is thought to arise from the retro-Mannich reaction, which is the rate-determining step, followed by ring opening of the resulting β-lactam enolate **10**.




Scheme 3.

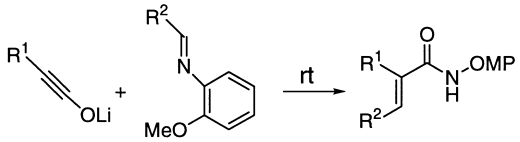



Scheme 4.

The generality of this reaction was examined as shown in Table 1. Aryl aldimines gave the desired amides in good yields with excellent *E*-selectivity. It is noteworthy that, although the retro-Mannich reaction was quite slow, even a small ynolate (R = Me) provided the amides in excellent yields (entries 1–3), while the olefination of aldehydes with the same ynolate resulted in poorer yields.[2a] The aldimine of pivalaldehyde, which did not react with the ynolate at –78°C, also afforded the desired amide with excellent *E*-selectivity (entry 4). In the case of entry 5, only products of decomposition were generated, even at –78°C, followed by gradually warming to

room temperature. The reactions of butyl- and cyclohexyl-substituted ynolates proceeded rapidly to give olefins in good yields (entries 6–9).

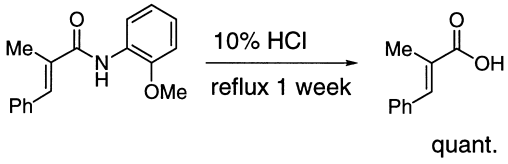
Table 1
Olefination of *N*-2-methoxyphenyl imines with lithium ynolates to give α,β-unsaturated amides[a]




| Entry | $R^1$ | $R^2$ | Time (h) | Yield (%) | *E*:*Z*[b] |
|---|---|---|---|---|---|
| 1 | Me | phenyl | 12 | 88 | >99:1 |
| 2 | Me | 1-naphthyl | 12 | 92 | 95:5 |
| 3[b] | Me | 2-naphthyl | 12 | >99 | 97:3 |
| 4 | Me | *tert*-Bu | 12 | 52 | >99:1 |
| 5 | Me | 4-($MeO_2C$)$C_6H_5$ | 1 | 0 | - |
| 6 | Bu | phenyl | 1 | 96 | 94:6 |
| 7 | Bu | 1-naphthyl | 1.5 | 92 | 91:9 |
| 8 | Bu | 2-naphthyl | 0.5 | 91 | 94:6 |
| 9 | cyclohexyl | phenyl | 1 | 83 | 85:15 |
| 10 | *tert*-Bu | phenyl | 12 | 0 | - |

[a] Conditions: See notes 10.
[b] The stereochemistry was determined by nOe experiments.

The α,β-unsaturated amides were converted into α,β-unsaturated carboxylic acids quantitatively by acidic hydrolysis (Scheme 5).




Scheme 5.

In conclusion, we have found that *N*-2-methoxyphenyl aldimines react with alkyl-substituted ynolates at room temperature to give α,β-unsaturated amides in good yields with good *E*-selectivity.

## Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research on Priority Areas (No. 283, 'Innovative Synthetic Reactions') from the Ministry of Education, Science, Sports and Culture, Government of Japan, and the Eisai Award in Synthetic Organic Chemistry, Japan.

## References


1. Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 321–323.
2. (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857–4860. (b) Shindo, M.; Sato, Y.; Shishido, K., *J. Org. Chem.* in press.
3. For a review, see: Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367–374.
4. A lanthanaid triflate-catalyzed reaction of a silyl ynol ether with *N*-4-methoxyphenyl aldimines giving α,β-unsaturated amides has been reported: Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **2000**, *52*, 545–548. Also see: Ishitani, H.; Nagayama, S.; Kobayashi, S. *J. Org. Chem.* **1996**, *61*, 1902–1903 and references cited therein.
5. Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 7634–7635.
6. Shindo, M.; Oya, S.; Murakami, R.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41, 5943–5946*.
7. Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113–116.
8. (a) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232–233. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049–10053 and references therein.
9. (a) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433–4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411–2422.
10. General procedure for the synthesis of amides: To a solution of 2,2-dibromoester (1.2 mmol) in THF (6 ml) was added *tert*-BuLi (4.8 mmol in pentane) at –78°C. After 3 h, the mixture was stirred at 0°C for 0.5 min. A solution of imine (1.0 mmol) in THF (2 ml) was then added to the ynolate solution at room temperature. The resulting mixture was quenched with satd $NaHCO_3$ aq. and extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. After evaporation, the amides were isolated by $SiO_2$ column chromatography.