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

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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. © 2000 Elsevier Science Ltd. All rights reserved.

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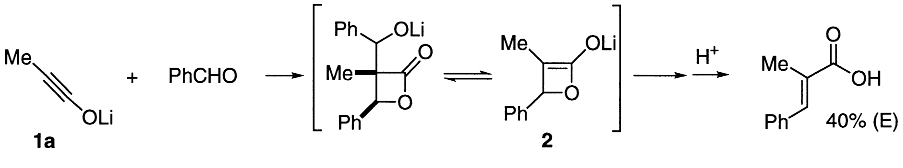
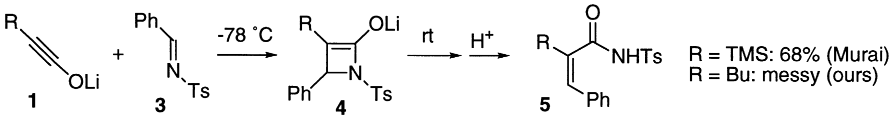
Kowalski[1] and our group[2] have reported that ynolate anions **1**[3] react with aldehydes to give α,β-unsaturated carboxylates at room temperature with high *E*-selectivity via ring opening of the intermediate β-lactone enolates **2** (Scheme 1). Similarly, aldimines would be expected to react with 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.

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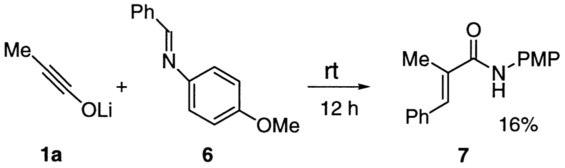
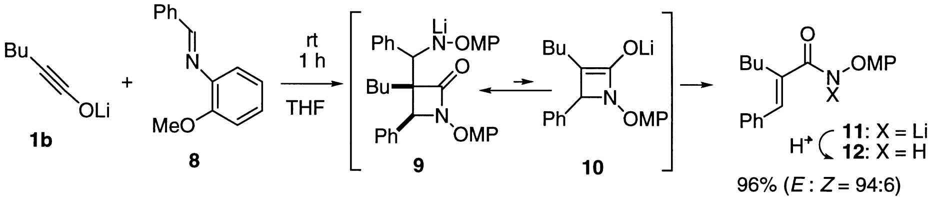
In the preceding paper, we showed that unactivated aldimines having an *N*-2-methoxyphenyl substituent reacted with ynolates to provide β-lactams (2:1 adducts).[6] We report, herein, the reaction of *alkyl*-substituted ynolates with the unactivated imines to give the desired α,β-unsaturated amides with 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**.



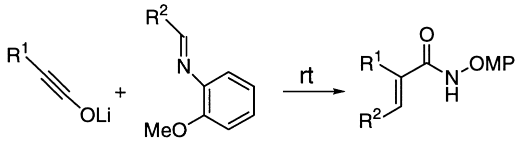
Scheme 3.



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]

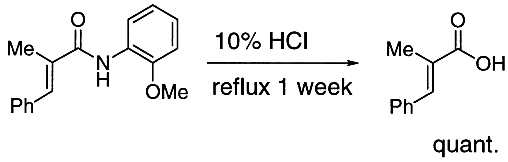


Entry	R^1	R^2	Time (h)	Yield (%)	*E*:*Z*[b]
1	Me	phenyl	12	88	>99:1
2	Me	1-naphthyl	12	92	95:5
3[b]	Me	2-naphthyl	12	>99	97:3
4	Me	*tert*-Bu	12	52	>99:1
5	Me	4-(MeO_2C)C_6H_5	1	0	-
6	Bu	phenyl	1	96	94:6
7	Bu	1-naphthyl	1.5	92	91:9
8	Bu	2-naphthyl	0.5	91	94:6
9	cyclohexyl	phenyl	1	83	85:15
10	*tert*-Bu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

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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.