CYCLOADDITION OF LITHIUM YNOLATE TO IMINES: SYNTHESIS OF 3,4-DISUBSTITUTED β-LACTAMS†

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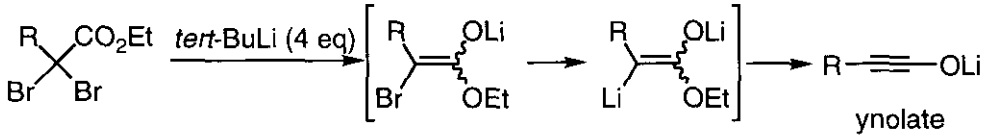
Abstract - Cycloaddition reaction of a lithium ynolate to *N*-sulfonylimines afforded 3,4-disubstituted β-lactams. The *cis*-products were synthesized in high *diastereoselectivity via quenching* of the intermediate, β-lactam enolates, with phenol.

Ynolates having a triple bond in place of a double bond in enolates are ketene anion equivalents and their chemistry should be no less interesting than that of enolates.[1] However, ynolates have received little attention from the synthetic point of view, since methods for generation of the species entailed some limitations. Recently, we reported a new and convenient method for the generation of lithium ynolates *via* the cleavage of ester dianions prepared from readily available α-bromo[2] or α,α-dibromo esters (Scheme 1).[3]

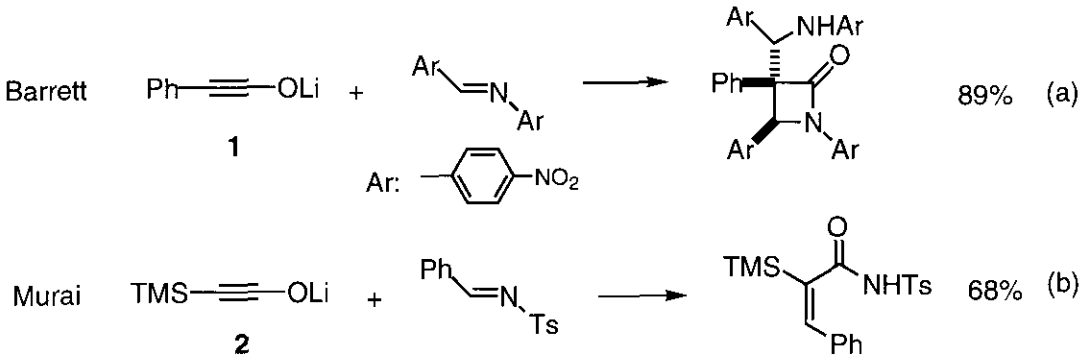


Scheme 1

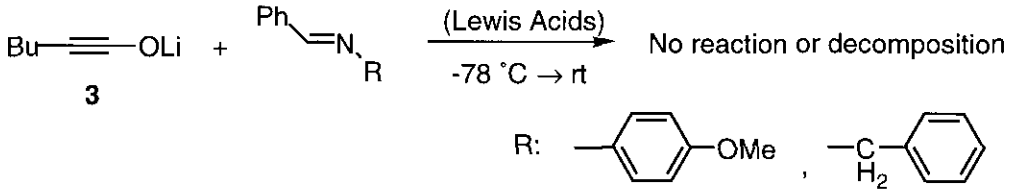
The synthetic utility of ynolates has been demonstrated in our reports on the addition to aldehydes to afford β-lactones[3] and (*E*)-α,β-unsaturated carboxylic acids stereoselectively.[4] The addition of ynolates to imines is expected to give β-lactams. Barrett reported the synthesis of trisubstituted β-lactams (2:1 adducts) *via* the reactions of phenyl-substituted ynolate (**1**) with imines bearing electron-withdrawing groups (Scheme 2(a)).[5] Murai reported that the ynolate (**2**) stabilized by a trimethylsilyl group did not give β-lactams but the α,β-unsaturated amide at room temperature (Scheme 2(b)).[6] Until now, successful reports on an efficient synthesis of disubstituted β-lactams (1:1 adducts) *via* the reaction of ynolates have not been published. Herein, we describe the first examples on synthesis of 3,4-disubstituted β-lactams *via* the reaction of ynolates with *N*-sulfonylimines.

At first, we attempted reactions of butyl-substituted ynolate (**3**), which is assumed to be more reactive than **1** and **2**, with imines having methoxyphenyl or benzyl substituent on nitrogen. However, **3** did not react

with them at all, since the electrophilicity of the imines would not be sufficiently high to react the ynolate. Attempted promotion of the addition reactions by adding various Lewis acids ($TiCl_4$, Me_3Al, BF_3•OEt_2, Me_2AlCl, $ZnCl_2$) in THF or in ether was unsuccessful (Scheme 3).



Scheme 2



Scheme 3

We tried the reactions using imines bearing a strong electron-withdrawing group on the nitrogen. A solution of ynolate, generated by ethyl α,α-dibromocaproate (1.2 mmol) and *tert*-BuLi (4.8 mmol) in THF at -78 °C followed by warming to 0 °C, was treated with *p*-toluenesulfonylimine (**4a**, 1.0 mmol) at -78 °C. After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. After usual workup, followed by purification with column chromatography, the desired β-lactam (**5a**, 1:1 adduct) was obtained in 58% yield along with 11% of the trisubstituted β-lactam (**6a**, 2:1 adduct). In comparison with Murai's result as shown in Scheme 2(b), alkyl ynolate (**3**) was found to be much more reactive than trimethylsilyl ynolate (**2**). As shown in Table 1, sulfonyl imines (**4b**, **4c**, **4d**) also afforded β-lactam (**5**) in preference to **6**, whereas **4e**, **4f** and diphenylphosphinic imine (**4g**) provided **6** predominantly. This selectivity would critically depend upon the nucleophilicity of ynolate (**3**) and that of β-lactam enolates (**7**).

The relative configuration of the *cis* and *trans* diastereomers of **5a** was determined by NOE experiments. The ratio of these diastereomers was dependent on the quenching method of the reaction. When **7a** was quenched with saturated aqueous NH_4Cl solution, **5a** was obtained in the *cis-trans* ratio of 3:1 (Table 2, Entry 1). This means that the kinetically controlled protonation to the β-lactam enolate leads to preferential *anti* introduction of the proton to the phenyl substituent at the C-4 position. Acetic acid as a proton donor gave **5a** in the slightly better ratio of 4:1 (Table 2, Entry 2). A dramatic improvement in the

stereoselectivity (11:1) was realized by using phenol as a sterically bulky proton donor (Table 2, Entry 3). More hindered proton donors, 2,6-dimethylphenol and 2,6-di-*tert*-butyl-4-methoxyphenol, however, did not give good stereoselectivity (Table 2, Entries 4, 5).

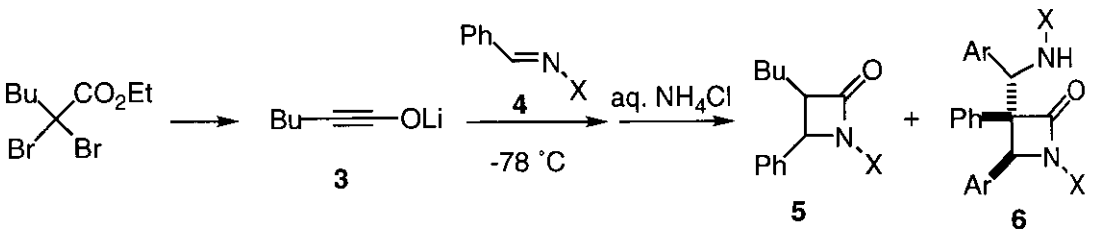
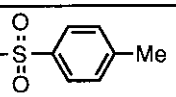
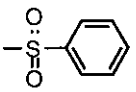
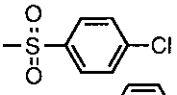
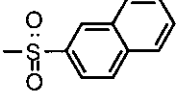
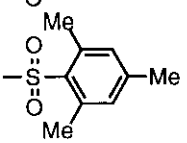


Table 1. The reactions of ynolate (**3**) with imines (**4**) to form β-lactams.

Entry	Imine (X)[a]		**5** (%)	**6** (%)
1	**4a**		58[b]	11
2	**4b**		64[b]	18
3	**4c**		44[b]	12
4	**4d**		33[b]	19
5	**4e**		18[c]	30
6	**4f**		6[c]	30
7	**4g**		12[c]	72

a) Imines were prepared according to the references.[7] b) The ratio of *cis-trans* isomers was 3:1. c) Minor isomers were not detected.

In conclusion, we have developed the synthesis of β-lactams *via* cycloaddition of a lithium ynolate to imines. The high diastereoselectivity was achieved via quenching of the intermediate, β-lactam enolate, with phenol. The results described herein also demonstrate the synthetic utility of ynolate anions.

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Synthetic Reactions") from the Ministry of Education, Science, Sports and Culture, Government of Japan, and Eisai Award in Synthetic Organic Chemistry, Japan.

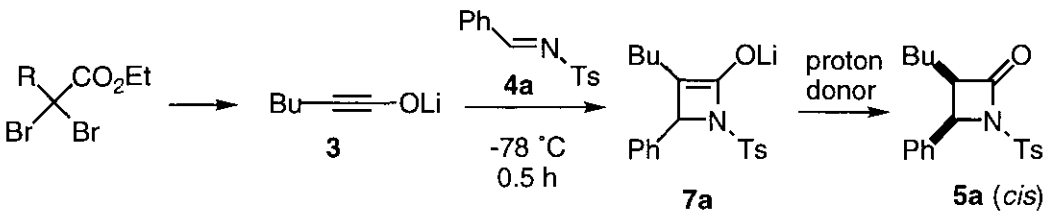
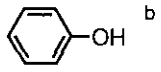
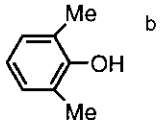
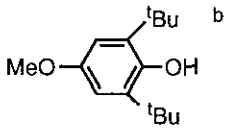


Table 2. Protonation of the β-lactam enolates.

Entry	Proton Donor	Conditions	*cis*/*trans*	Yield (%)
1	sat. aq. NH_4Cl[a]	-78 °C → rt	3/1	58
2	CH_3CO_2H[b]	-78 °C → rt	4/1	73
3	 [b]	-78 °C, 10 min then sat. aq. NH_4Cl	11/1	68
4	 [b]	-78 °C, 10 min then sat. aq. NH_4Cl	6/1	54
5	 [b]	-78 °C, 10 min then sat. aq. NH_4Cl	4/1	69

a) Excess amount. b) 3 eq.

REFERENCES AND NOTES

†Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

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