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A NEW AMIDOALKYNYLATION USING ALKYNYLZINC REAGENT

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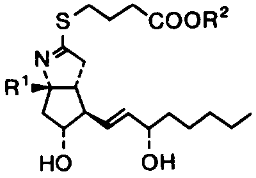
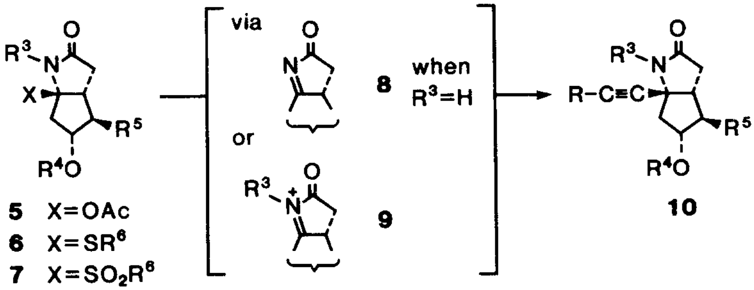
Summary: A new amidoalkynylation using alkynylzinc reagent was developed and successfully applied to various α-thio-lactams including **6**.

Amidoalkynylation plays an important role as a carbon-carbon bond forming reaction like amidoalkylation.[1] A variety of methods are known, which include α-alkynylation of N-alkoxycarbonyl-pyridinium salt,[2] alkynylation of 4-sulfonyl and 4-acetoxyazetidinone using Grignard reagent,[3] or alkali-metal acetylide,[4] and $TiCl_4$ mediated amidoalkynylation.[5]

Recently, in relation to our synthetic studies on 9-substituted β-thiaiminoprostacyclins **2**, **3**, **4**,[6,7] we needed α-alkynylated lactam **10**. We first thought of using acetoxy- **5** or sulfonyloxylactam **7** by known methods but were not able to get these compounds and therefore decided to use the easily available α-thio-lactam **6**[13] and develop a new amidoalkynylation method.



1 R¹=H
2 R¹=alkynyl
3 R¹=alkenyl
4 R¹=alkyl



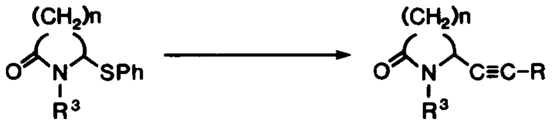
5 X=OAc
6 X=SR⁶
7 X=SO₂R⁶
8
9
10

As the reagent, alkynylzinc[8] was chosen in view of its stability, the controllability of its acidity, and the proper softness of zinc,[9] which we expected would bring about coordination between zinc and sulfur and facilitate formation of acylimine **8** or acyliminium cation **9**, which in turn would lead to the alkynylated product **10**. Alkynylzinc reagents[8] of three different acidity levels were prepared using alkynyllithium[10] and zinc chloride: $(R-C\equiv C-)_2Zn$, weakly basic, pH ~8.5[12]; $(R-C\equiv C-)_2Zn/R-C\equiv C-ZnCl$ = 1/1, neutral, pH ~7.0; $R-C\equiv C-ZnCl$, weakly acidic, pH ~5.5. These reagents were used in the reaction with monocyclic α-thio-γ-lactams **11** and **12**.[13] We found that stronger Lewis acidity enhanced the reaction (Entry 11-13, Table 1) supporting the expected intermediary acylimine or acyliminium cation formation.

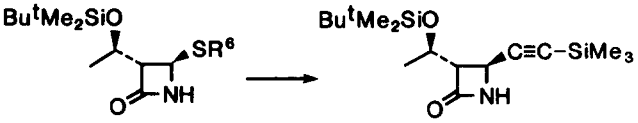
Further screening of the reaction conditions (Table 1) also revealed:

1. Benzene and alkylbenzene were preferable as solvents, although the reagent did not dissolve well in them.
2. The reaction was temperature-dependent (Entry 2, 3 and 10, 11).
3. Substitution on the nitrogen of lactam retarded the reaction (Entry 2, 12).

Table 1



11 n=2, R^3=H **13** n=2, R^3=H
12 n=2, R^3=p-MeO-benzyl **14** n=2, R^3=p-MeO-benzyl
15 n=3, R^3=p-MeO-benzyl **16** n=3, R^3=p-MeO-benzyl



17 R^6=Ph **19**
18 R^6=Et

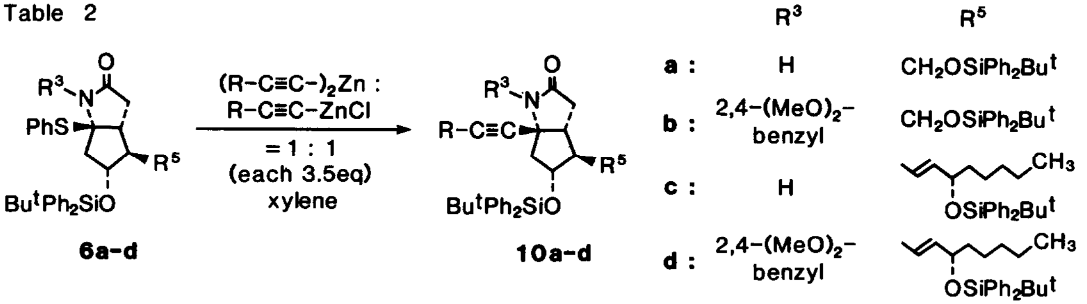
Entry	Starting material	Product	Reag.[a]	Solv.	Temp. (°C)	Time (hr)	Yield (%)
1	11	13 R = $SiMe_3$	B	xylene	60	1	67
2	11	13 R = $SiMe_3$	N	xylene	60	0.5	70
3	11	13 R = $SiMe_3$	N	benzene	r.t.	2.5	74
4	11	13 R = $SiMe_3$	N	THF	60	1	29
5	11	13 R = $SiMe_3$	A	benzene	60	0.5	79
6	11	13 R = CH_3	N	benzene	60	0.5	82
7	11	13 R = C_3H_7	N	benzene	60	0.5	72
8	11	13 R = Ph	N	benzene	60	0.5	78
9	11	13 R = $C\equiv C-SiMe_3$	N	benzene	60	0.5	78
10	12	14 R = $SiMe_3$	B	xylene	140	1	90
11	12	14 R = $SiMe_3$	B	xylene	100	0.5	NR
12	12	14 R = $SiMe_3$	N	xylene	100	2	98
13	12	14 R = $SiMe_3$	A	xylene	100	1	97
14	15	16 R = $SiMe_3$	N	xylene	100	0.5	92
15	17	19	N	xylene	100	2	82
16	18	19	N	xylene	100	2	83 (18, 8)
17	18	19	N	xylene	140	2	90

[a] Reagent, B: $\underset{(5\ eq)}{(R-C\equiv C-)_2Zn}$. N: $\underset{(each\ 3.5\ eq)}{(R-C\equiv C-)_2Zn/R-C\equiv C-ZnCl = 1/1}$, A: $\underset{(5\ eq)}{R-C\equiv C-ZnCl}$

4. Both phenylthio and ethylthio groups could be replaced by an alkynyl group (Entry 15-17).
5. The reaction could be successfully applied not only to γ-lactam, but also to β- (Entry 15-17) and δ-lactams[13] (Entry 14).
6. Various alkynyl groups could be introduced (Entry 1-9).

While experimenting to obtain these basic data, we also tried to obtain the bicyclic α-alkynylated lactams **10a-d**, our main target, from the corresponding α-thio-lactams **6a-d**.[13] We found that the acidic reagent [$R-C\equiv C-ZnCl$] resulted in decomposition of the starting material, while the basic reagent [$(R-C\equiv C-)_2Zn$] was unreactive. However, the neutral reagent

Table 2



Entry	Starting material	Product	Temp. (°C)	Time (hr)	Yield (%)
18	6a	10a $R = SiMe_3$	100	0.5	73
19	6a	10a $R = CH_3$	100	0.5	77
20	6b	10b $R = SiMe_3$	140	0.5	80
21	6b	10b $R = CH_3$	140	0.5	76
22	6c	10c $R = SiMe_3$	140	0.5	86
23	6d	10d $R = SiMe_3$	140	0.5	84
24	6d	10d $R = CH_3$	140	0.5	80

$[R-C\equiv C-)_2Zn/R-C\equiv C-ZnCl = 1/1]$ very smoothly gave the desired products **10a-d**[15] in good to high yield, although a little higher temperature was needed (Table 2).

Our newly developed amidoalkynylation utilizing α-thio-lactam and alkynylzinc reagent should be a widely applicable method, because it can be done under mildly acidic to mildly basic conditions to suit the substrate.

Typical procedure: Preparation of compound **10b** ($R = SiMe_3$)

To a solution of trimethylsilyl acetylene (0.75 ml, 5.30 mmol) in dry THF (10 ml) was added 1.64 N n-BuLi in hexane solution (3.2 ml, 5.25 mmol) dropwise at 0°C under nitrogen atmosphere with stirring. After 30 min, 0.68 M $ZnCl_2$ in THF solution (5.1 ml, 3.47 mmol) was added at 0°C and the mixture was stirred for 10 min at room temperature. The solvent was evaporated under diminished pressure and to the resulting residue was added a solution of phenylthio-lactam **6b** (469 mg, 0.518 mmol) in dry xylene (10 ml) under nitrogen atmosphere. The mixture (a slurry) was heated at 140°C for 30 min with stirring. After cooling, aq NH_4Cl was added and the mixture was extracted with EtOAc. The extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give an oily residue (587 mg). Purification by column chromatography (Lobar column B x 2, eluted with n-hexane:EtOAc = 4:1) afforded compound **10b** ($R = SiMe_3$, 372 mg, 80%) as a foamy material. MS: m/z 894 (MH^+), 836 (M^+-Bu), IR ν_{max} ($CHCl_3$): 2170, 1672, 1615, 1590, 1507, 1427, 1112, 842 cm^{-1}, ^{1}H-NMR: (90 MHz, $CDCl_3$, ppm) 0.0 (9H, s), 0.95 (9H, s), 0.99 (9H, s), 3.57 (2H, m), 3.66 (3H, s), 3.73 (3H, s), 4.07 (1H, m), 4.43 (1H, d, $J = 15$ Hz), 4.53 (1H, d, $J = 15$ Hz), 6.33 (2H, m), 7.05-7.7 (21H).

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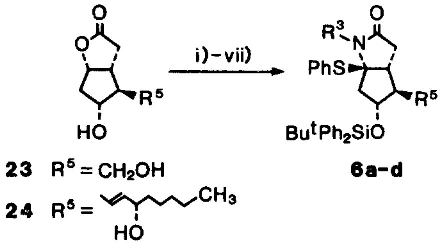
9. a) R. G. Pearson, J. Chem. Educ., 45, 581 (1968). b) We also tried the softer copper (I) acetylide in the reaction with monocyclic α-phenylthio-γ-lactam 11, but the yield was very poor.
10. Alkynyllithium 21 prepared from the corresponding trimethylsilylalkyne 20 and MeLi,[11] is contaminated with alkyllithium 22. When alkynylzinc is prepared from the impure alkynyllithium described above and is used in the amidoalkynylation reaction conducted at a temperature below 100°C, it leads to a low yield or even the absence of the desired alkynylated product.

$$\underset{\textbf{20}}{CH_3-C\equiv C-SiMe_3} \xrightarrow[\text{MeLi / Et}_2\text{O-THF}]{} \underset{\textbf{21}}{CH_3-C\equiv C^{-}Li^{+}} + \underset{\textbf{22}}{CH_2^{-}-C\equiv C-SiMe_3Li^{+}}$$

11. P. A. Aristoff, P. D. Johnson and A. W. Harrison, J. Org. Chem., 48, 5341 (1983).
12. The pH value was measured with pH indicator papers (pH-Box®, E. Merck, West Germany).
13. Preparation of starting materials: Compound 11 was obtained from the corresponding alkoxy-lactam by treatment with PhSH/HCl-Et$_2$O, while compounds 12 and 15 were prepared from the corresponding hydroxy-lactams by sequential treatment with MeOH/HCl and PhSH/HCl-Et$_2$O. Compounds 17 and 18 were prepared from the corresponding 4-acetoxyazetidinone. Compounds 6a-d were prepared from diol-lactones 23, 24, according to the following modified procedure,[6] which was based on that of the Hoechst group.[7]



23 $R^5 = CH_2OH$

24 $R^5 =$

6a-d

i) $^tBuPh_2SiCl$, DMAP/DMF
ii) NH_3/MeOH or 2,4-$(MeO)_2$-benzylamine, 2-hydroxypyridine
iii) Jones oxid. or Collins oxid. or Swern oxid.
iv) DDQ/$CHCl_3$-H_2O (When removal of a methoxy-substituted benzyl group[14] on the nitrogen is necessary.)
v) Me_3SiCl, DMAP/pyridine-CH_2Cl_2
vi) HCl/MeOH
vii) HCl-PhSH/Et$_2$O.

14. Oxidative cleavage of methoxy-substituted benzyl ethers with DDQ reported by Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka and O. Yonemitsu, Tetrahedron Lett., 25, 5393 (1984) was applied to our system.
15. All new compounds, including 13 (R = CH_3, C_3H_7, Ph, $C\equiv C-SiMe_3$), 14 (R = $SiMe_3$), 16 (R = $SiMe_3$), and 19, were characterized by ^{1}H-NMR and IR spectra and gave satisfactory elemental analyses and mass spectra.

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