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A NOVEL METHOD FOR GENERATION OF ENOLIZABLE N-TRIMETHYLSILYLALDIMINES AND APPLICATION TO β-LACTAM SYNTHESIS

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A new method to generate N-trimethylsilylaldimines has been developed by the combination of bis(trimethylsilyl)formamide and organolithium reagents and applied successfully to β-lactam synthesis.

N-Trimethylsilylaldimines are known as activated imines which react easily with lithium enolates of carboxylic acid esters to give β-lactams in one pot.[1] Aldimines of this type are in situ generated from corresponding aldehydes and lithium hexamethyldisilazide at low temperature.[1-3] This method is also applicable to prepare enolizable aldimines[2] but β-lactams are not always obtained in satisfactory yields. Very recently it has been clarified that enolizable N-trimethylsilylaldimines polymerize even at -10°C.[4] We now report a new method for generation of enolizable N-trimethylsilylimines by the combination of bis(trimethylsilyl)formamide (BSF, **1**) and organolithium reagents and the application to the synthesis of 2-azetidinones (**8**).

In contrast with bis(trimethylsilyl)acetamide, bis(trimethylsilyl)-formamide has the amide structure (1).[5] If an organometallic compound (**2**) adds to the carbonyl of **1**, we can expect two reaction courses from the intermediate (**3**). One is the elimination of lithium hexamethyldisilazide to give the aldehyde (**4**) and the other is the 1,2-elimination like Peterson olefination to give the desired N-trimethysilylaldimine (**6**).

A reaction of BSF and phenyllithium (1 equiv) at -78°C-0°C overnight gave N-trimethylsilylbenzylideneamine (**6**, R=Ph) in excellent yield. Thus, the route from **3** to **6** exists in the case of a non-enolizable stable N-trimethylsilylaldimine.

Treatment of BSF with butyllithium (2 equiv) at 0°C for 3 h gave a 1.3 : 1 mixture of 4-heptanol (**5**, R=n-Bu) and 4-heptylamine (**7**, R=n-Bu) in 92% yield. When the reaction was started at -78°C and the resulting mixture was allowed to warm to 0°C, a 5 : 1 mixture of the alcohol and the amine was obtained in 92% yield. This amine would be formed via the reaction of N-trimethylsilyl-1-pentanimine (**6**, R=Bu) with butyllithium. When a reaction of BSF and butyllithium was carried out at -78°C for 3 h, the formamide was consumed but no remarkable products were isolated after treatment with water. These results seemed to suggest that **6** (R=n-Bu) would be formed at the lower temperature and the addition reaction of butyllithium to **6** (R=n-Bu) would be very slow at -78°C.

In order to confirm formation of enolizable N-trimethylsilylaldimines from BSF, we attempted reactions with ester enolates which should give the corresponding β-lactams. The results are summarized in Table 1.

A solution of BSF in THF was treated with equimolar of butyl lithium at -78°C for 1 h. To this solution was added rapidly a cold solution of the lithium enolate of ethyl isobutyrate (2 equiv) in THF via a cannula and then the mixture was stirred for 1 h below -70°C. To complete β-lactam formation, the mixture was stirred at room temperature for 2 h. The 2-azetidinone (**8a**) was purified by silica-gel chromatography. Preferential formation of **8a** means smooth generation of N-trimethylsilyl-1-pentanimine (**6**, R=n-Bu). An enolizable N-trimethylsilylaldimine now can be generated efficiently from BSF and an alkyllithium.

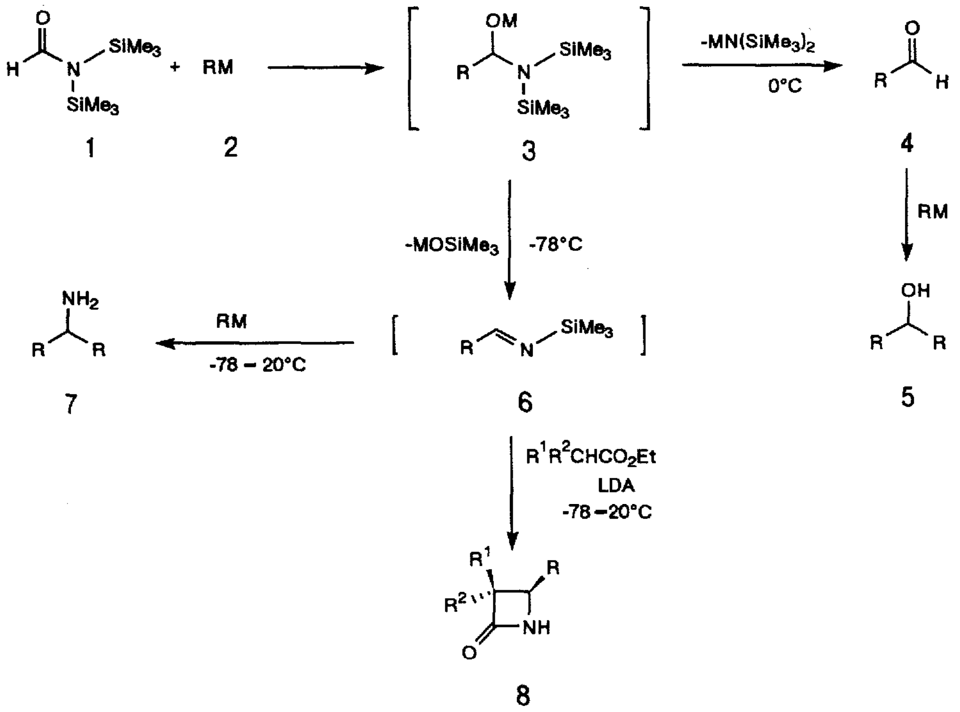
When ethyl isovalerate was employed instead of ethyl isobutyrate, only the 3,4-cis disubstituted 2-azetidinone (**8b**) was derived. A reaction with the lithium enolate of ethyl butyrate gave a 10 : 1 mixture of the cis- and trans isomers (**8c** and **8d**, respectively). Formation of the 3,3,4-trimethyl-2-azetidinone (**8e**) indicates that N-trimethylsilylethanimine (**6**, R=Me) was generated in an excellent yield. N-Trimethylsilylbenzylideneamine generated in situ was also useful to prepare the 2-azetidinone (**8f**). Even the α-branched enolizable aldimine (**6**, R=s-Bu) could be generated and converted into 2-azetidinones (**8g**) and (**8h**) in good yields. Benzyloxymethyllitium and methoxymethyllithium, functionalized lithium reagents, were also useful to prepare 2-azetidinones (**8i**) and (**8j**), respectively. A reaction of BSF with 1-methoxyvinyllithium followed by treatment with the lithium enolate of ethyl butyrate gave a 10 : 7 mixture of cis and trans 2-azetidinones (**8k**) and (**8l**), respectively, in 46 % yield. Ozonolysis of this mixture and treatment of the resulting ozonides with dimethyl sulfide gave a 10 : 7 mixture of cis- and trans-3-ethyl-4-methoxycarbonyl-2-azetidinones in 66% yield. Hydrolysis of the mixture of **8k** and **8l** in acidic aqueous acetone gave cis- and trans-3-ethyl-4-(1'-oxoethyl)-2-azetidinones in a ratio of 10 : 7 in 67% yield.

In conclusion, enolizable N-trimethylsilylaldimines, as well as non-enolizable derivatives, are prepared easily by treating of BSF with organolithium reagents.

Table 1. β-Lactam synthesis *via* N-trimethylsilylaldimines, derived from BSF and alkyllithiums, and ester enolates.

RM	Ester	2-Azetidinones	Yield
BuLi	Me_2CHCO_2Et	**8a** (R^1=R^2=Me)	98%
BuLi	$Me_2CHCH_2CO_2Et$	**8b** (R^1=*i*-Pr, R^2=H)	99%
BuLi	$Me(CH_2)_2CO_2Et$	**8c** (R^1=Et, R^2=H), **8d** (R^1=H, R^2=Et)[a]	93%
MeLi	Me_2CHCO_2Et	**8e** (R^1=R^2=Me)	94%
PhLi	Me_2CHCO_2Et	**8f** (R^1=R^2=Me)	86%
s-BuLi	Me_2CHCO_2Et	**8g** (R^1=R^2=Me)	60%
s-BuLi	$Me_2CHCH_2CO_2Et$	**8h** (R^1=*i*-Pr, R^2=H)	73%
$PhCH_2OCH_2Li$	Me_2CHCO_2Et	**8i** (R^1=R^2=Me)	67%
$MeOCH_2Li$	Me_2CHCO_2Et	**8j** (R^1=R^2=Me)	58%
CH_2=C(OMe)Li	$Me(CH_2)_2CO_2Et$	**8k** (R^1=Et, R^2=H), **8l** (R^1=H, R^2=Et)[b]	46%

a) The ratio of **8c** to **8d** was 10. b) The ratio of **8k** to **8l** was 1.4.



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